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Synthesis of Novel 4-(5′-Pyrrolidinyl)-β-Lactams

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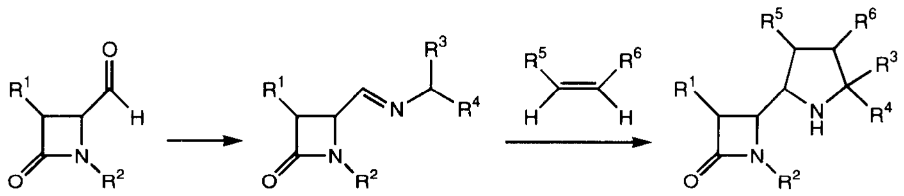
Abstract: The synthesis of novel 4-(5′-pyrrolidinyl)-β-lactams from imines derived from 4-formyl-β-lactams and α-amino esters *via* cascade imine→azomethine ylide→1,3-dipolar cycloaddition reactions is described. These cascades are *endo*-specific, exhibit facial stereoselectivity and occur in good to excellent yields.

Keywords: β-lactams, azomethine ylide, cycloaddition, cascade reaction.

The biological activity of β-lactams continues to foster strong interest in β-lactam chemistry. Our interest in 1,3-dipolar cycloaddition reactions of imines,[1] including those derived from 7-aminocephalosporins,[2] identified 4-formyl-β-lactams as versatile building blocks for the synthesis of novel 4-(5′-pyrrolidinyl)-β-lactams *via* 1,3-dipolar cycloaddition reactions of their imines (**Scheme 1**).



Scheme 1

The *cis*-stereospecific synthesis of 3-substituted-4-formyl β-lactams was achieved *via* a diimine route (**Scheme 2**)[3,4] and employed *N,N′*-bis-(4-methoxyphenyl)ethylenediimine **2** which was obtained in 75% yield when 40% aqueous glyoxal reacted with *p*-anisidine[5] in methanol. *Cis*-3-substituted-4-formyl-β-lactams were then obtained by a one-pot procedure involving treatment of acid chlorides **1** with triethylamine in toluene at room temperature to generate the corresponding ketenes which underwent *in situ* [2+2]-cycloaddition with imine **2** to afford *cis*-4-imino β-lactams **3**. Hydrolysis of **3** using 5% aqueous HCl for 1.5 h gave the desired *cis*-3-substituted-4-formyl β-lactams **4a-d** in good yield.

Enantiopure 3-substituted-4-formyl β-lactams were obtained from imines **5**, which were prepared from (*R*)-glyceraldehyde acetonide,[6] followed by [2+2] ketene-imine cycloaddition at −20°C to room temperature which produced the β-lactams **6a-c** as *cis*-diastereomers.[7] Deprotection with 1 N HCl in THF gave diols **7a-c**,

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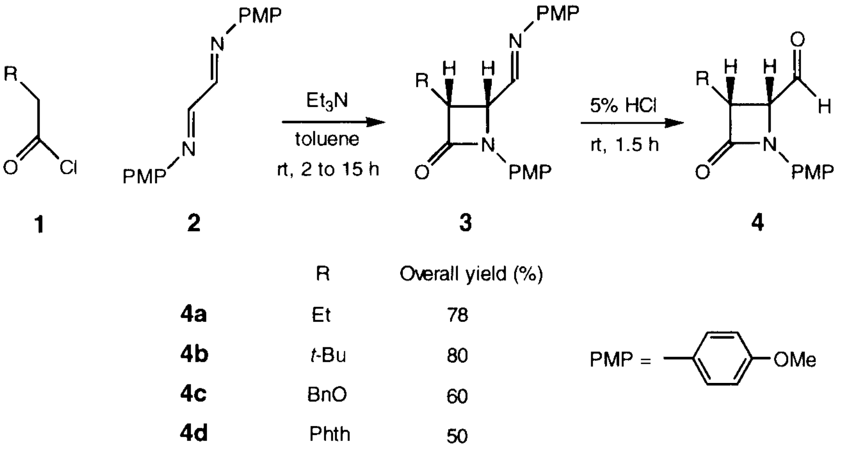
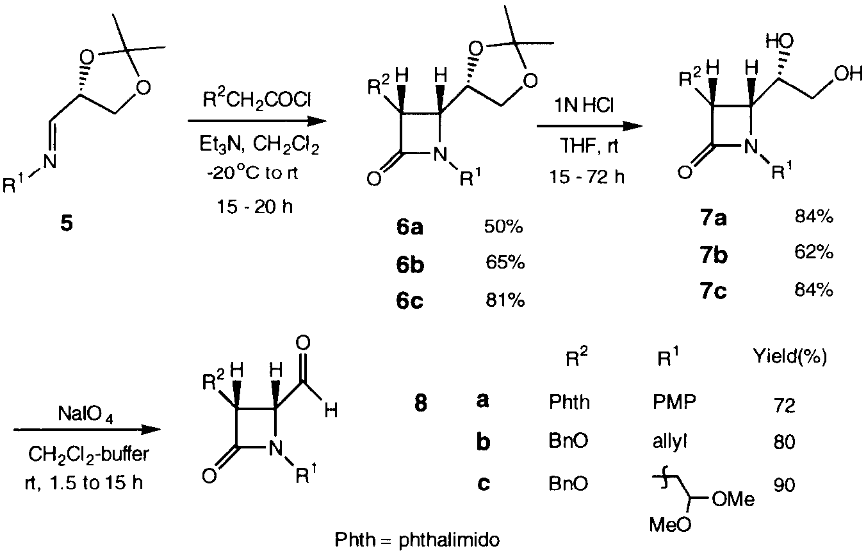
and subsequent oxidation with $NaIO_4$ afforded enantiopure 3-substituted-4-formyl-β-lactams **8a-c** (**Scheme 3**). When methanol,[8] or methanol and water,[9] were used as the solvent, the oxidation was often not complete and as a consequence low yields of **8** were obtained. However, when **7** reacted with 1.25 equiv of $NaIO_4$ in a 3:1 mixture of CH_2Cl_2 and buffer (0.05 M potassium dihydrogen phosphate-sodium hydroxide buffer, pH 7), good results were obtained. The absolute configuration of **6a** has been determined by Bose[6] and we assume **6b** and **6c** have analogous stereochemistry to **6a**.



	R	Overall yield (%)
4a	Et	78
4b	*t*-Bu	80
4c	BnO	60
4d	Phth	50

Scheme 2



6a	50%
6b	65%
6c	81%

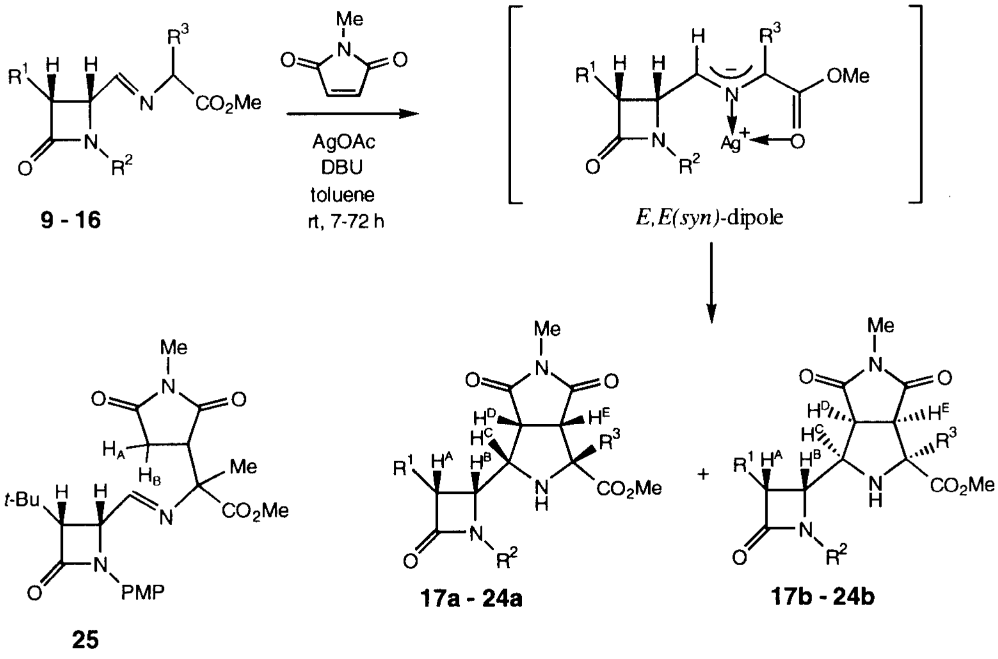
7a	84%
7b	62%
7c	84%

		R^2	R^1	Yield(%)
8	**a**	Phth	PMP	72
	b	BnO	allyl	80
	c	BnO	OMe MeO	90

Phth = phthalimido

Scheme 3

4-(5'-Pyrrolidinyl)-β-lactams were generated *via* 1,3-dipolar cycloaddition reactions of β-lactam imines with dipolarophiles. Depending on the type of dipolarophile [*N*-methylmaleimide (NMM) or methyl acrylate] used the product of 1,3-dipolar cycloaddition can contain up to six chiral centres – two chiral centres from the β-lactam starting material and three or four new chiral centres generated in the pyrrolidine. Consequently, structural assignment of the diastereomeric reaction products was anticipated to be a difficult task. It was hoped that the stereochemical outcome of the 1,3-dipolar cycloaddition could be understood on the basis of previous work[1] and that the β-lactam centres would not undergo epimerisation under the reaction conditions. Therefore, we specifically focused on the relative stereochemistry of the β-lactam and pyrrolidine ring systems which is a consequence of the facial selectivity of the cycloaddition. The imines **9-16** were obtained in almost quantitative yields by the condensation of 4-formyl-β-lactams with α-amino esters in DCM at room temperature in the presence of 4 Å molecular sieves. Importantly, the β-lactam ring configuration was unaffected by this process. The cycloaddition of the imines **9-16** with *N*-methylmaleimide in toluene in the presence of AgOAc and base (DBU or Et_3N) afforded mixtures of two diastereomeric cycloadducts **17-24** in good yield (**Scheme 4**) (**Table 1**). Much poorer cycloaddition stereoselectivity was observed when the reactions were carried out in polar solvents (*e.g.* DMSO and MeCN). For example, **19a** and **19b** were obtained as a 1:1.2 mixture in 90% combined yield when DMSO was used as solvent and triethylamine as base whereas in toluene with triethylamine as base the reaction afforded a 9:1 mixture (89%) of **19a** and **19b** (compare these ratios with **Table 1**, entry 3).



Scheme 4

In this process four new chiral centres are formed from a *cis*-β-lactam ring possessing two chiral centres. In each case mixtures of two cycloadducts were formed. The formation of only two, not four, cycloadducts could occur *via endo*-specific cycloaddition on the both faces of the *E,E* (*syn*)-dipole (**Scheme 4**). ^{1}H NMR analysis of proton coupling constants, $J_{CD} \approx J_{DE} \approx J_{ER^3}$ (when R^3=H) ≈ 7-8, is consistent with an all *cis* relationship for these protons in all the stereoisomeric cycloadducts *i.e. endo* diastereoisomerism. The *endo* diastereoisomerism of **17b** was established by its X-ray crystal structure (**Figure 1**) whilst the relative stereochemistry of the pyrrolidine ring of **17a** was determined by NOE experiments. Irradiation of Me (R^3) of **17a** caused enhancement of the signals for H^C (2.9%) and H^E (3.4%). Another set of NOE experiments was carried out on **18a** and **18b** and are summarised in the experimental. The X-ray crystal structures of **19a** and **19b** are shown in **Figure 2** whilst those of **20a** and **20b** are shown in **Figure 3**. The cycloaddition reaction of imine **14** and NMM in toluene with DBU as base afforded an approximately 4:1 mixture of the cycloadduct **22** and the Michael adduct **25**. The latter was identified by the presence of a doublet at δ 8.14 (*J* 6.6 Hz, CH=N) and two double doublets at δ 2.52 (*J* 5.4 and 18.1 Hz) and 2.79 (*J* 9.3 and 18.1 Hz) for the methylene protons H_A/H_B. When the reaction was repeated in cyclohexane the product was composed of a 9 : 1 mixture of **22a** and **25**.

Table 1. Synthesis of Cycloadducts 17 – 24[a]

Imine	R^1	R^2	R^3	Product	Yield (%)	a : b[b]
9	Et	PMP	Me	**17**	92	2 : 1
10	BnO	PMP	Me	**18**	57	1 : 3
11	Phth	PMP	Me	**19**	88	> 30 : 1
12	BnO	PMP	H	**20**	80	1 : 7
13	Phth	PMP	H	**21**	86	24 : 1
14	t-Bu	PMP	Me	**22**	57	9 : 1(c)
15	BnO	Allyl	Me	**23**	83	1.5 : 1(d)
16	BnO	$CH_2CH(OMe_2)$	Me	**24**	71	2 : 1(d)

(a) The reactions were carried out in toluene at room temperature in the presence of AgOAc (1.2 mol eq) and DBU (1.2 mol eq) as base for 7 h – 3 d. (b) Isomer ratios determined from ^{1}H NMR spectra of the crude products by integration of the H^B proton signal (*vide infra*). (c) The reaction was carried out in cyclohexane and afforded a 9 : 1 mixture of **22a** and Michael adduct **25**. (d) Et_3N as base.

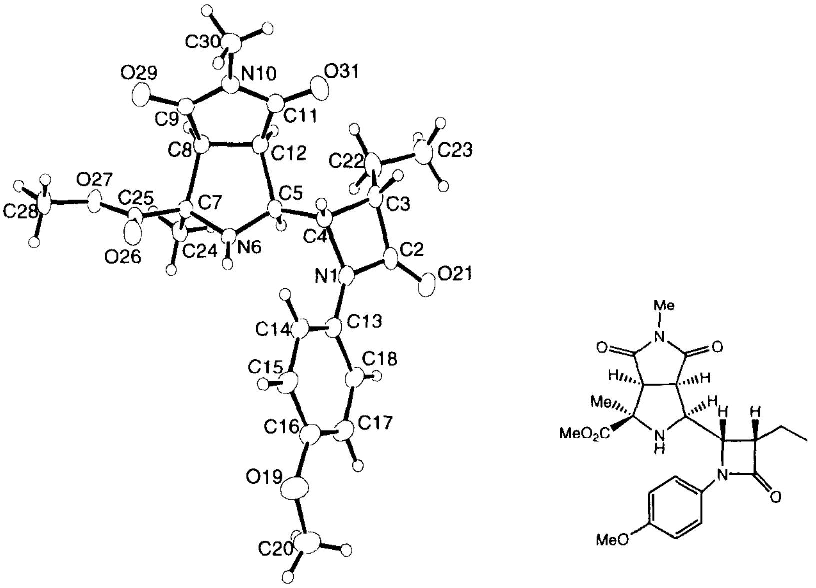
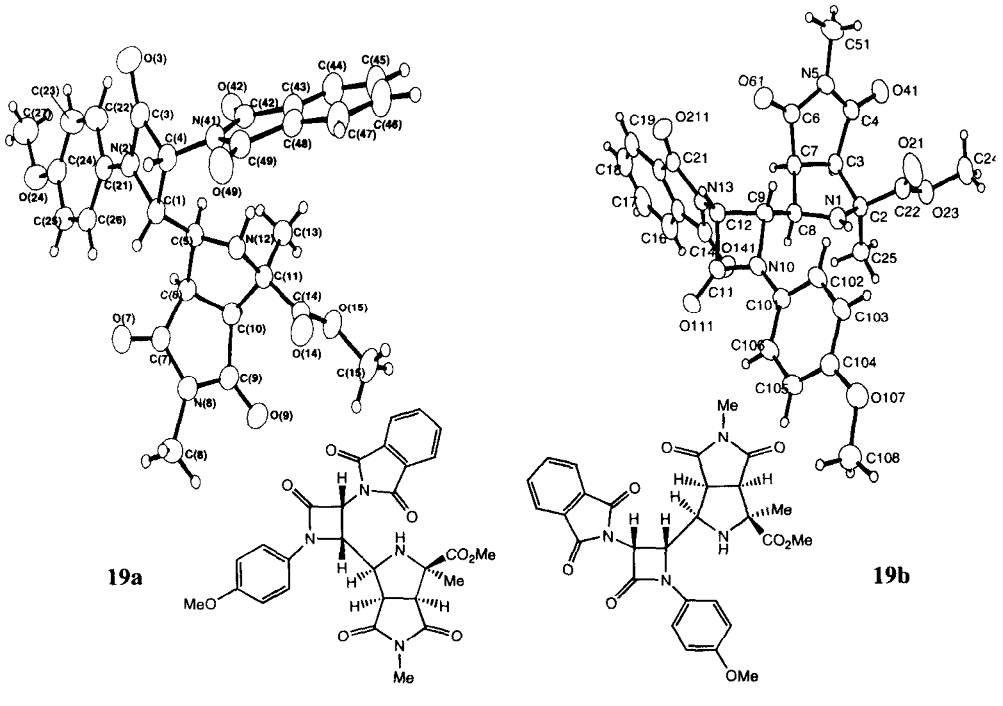


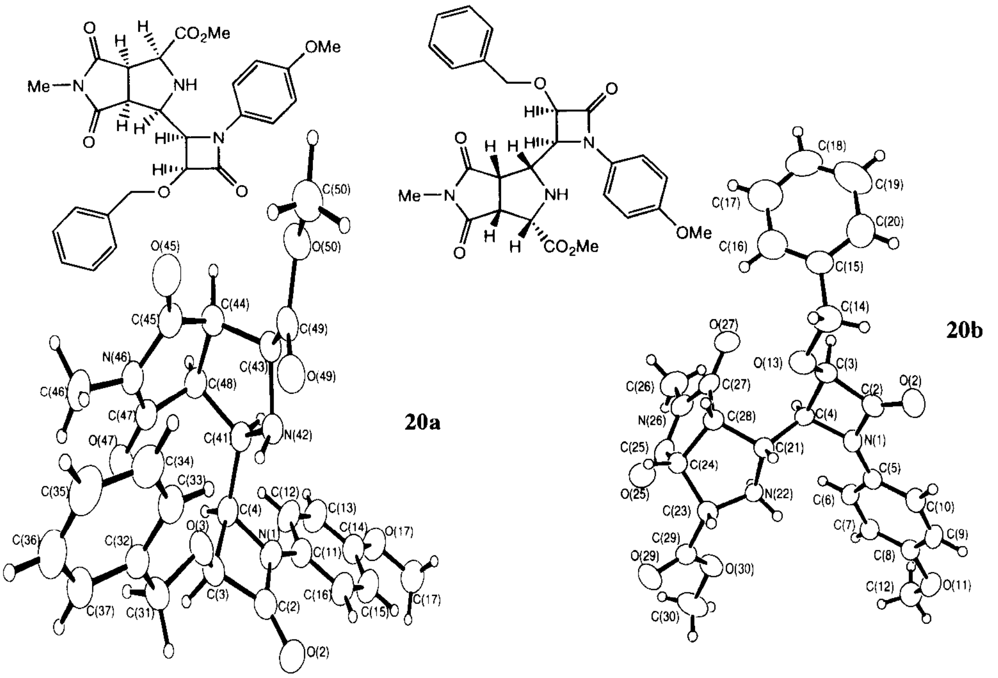
Figure 1. The X-Ray Crystal Structures of 17b



19a

19b

Figure 2. The X-Ray Crystal Structures of 19a and 19b

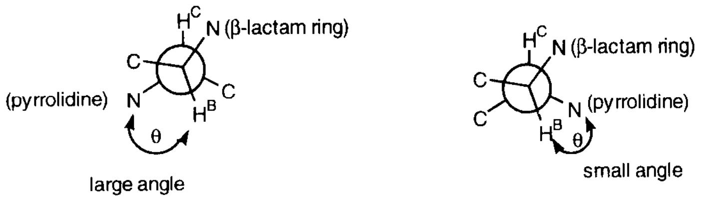


20a

20b

Figure 3. The X-Ray Crystal Structures of 20a and 20b

The remaining stereochemical problem was the cycloaddition facial selectivity. The NOE experiments cannot distinguish the relative configurations of the β-lactam and pyrrolidine ring systems due to the connection between the two rings through a single bond. The coupling constants of H^B and H^C, the two protons located at the single bond connecting the two rings, in the two types of adduct vary between 6.1 and 9.9 Hz, but are not diagnostic of the '**a**' or '**b**' series. However, the chemical shift of H^B in the **b** isomer is always smaller than the chemical shift of H^B in the **a** isomer for a pair of diastereoisomers (**Table 2**). There is a 0.4 - 0.7 ppm difference between each pair of diastereoisomers. A plausible explanation for this difference is that it reflects the through space shielding interaction of the neighbouring pyrrolidine nitrogen atom on H^B (**Figure 4**). The X-ray data does indeed show that in the **a** isomers the dihedral angle θ between H^B and the pyrrolidine nitrogen is significantly larger than the corresponding angle in the **b** isomers (**Table 2**). Thus this trend correlates with the solution chemical shift date although the role of crystal packing forces is unclear.



a-isomer

b-isomer

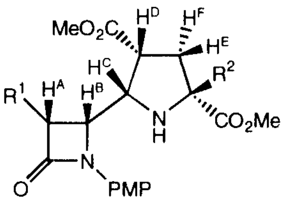
Figure 4

Table 2. ^{1}**H NMR Chemical Shifts of** H^B **and** $N(1)/H^B$ **Dihedral Angle in Cycloadducts (17 - 24)**

Isomer	δ value of proton H^B (ppm) and $N(1)/H^B$ dihedral angle θ (°)[a]							
	17	**18**	**19**	**20**	**21**	**22**	**23**	**24**
A	4.9	5.0	5.3 (89)	5.0 (172)	5.2	5.0	4.2	4.3
B	4.2 (55)	4.3	4.6 (53)	4.4 (62)	4.7	–	3.8	3.9

a. From X-ray data.

A brief study was made of cycloadditions employing methyl acrylate as the dipolarophile with imines **9**, **11** and **13**. Cycloaddition occurred in a regio- and *endo*-specific manner in toluene with AgOAc and base, at room temperature overnight to afford mixtures of two diastereoisomers **26-28** (**Table 3**). The coupling constants of the protons on the pyrrolidine ring were compatible with *endo* products. NOE experiments on a pair of diastereoisomers, **28a**, **b**, are shown in the experimental. The facial diastereoselectivity results from an identical approach of the dipolarophile to that discussed for *N*-methylmaleimide. The assignment of stereochemistry was achieved by consideration of the H^B chemical shifts and was confirmed by an X-ray crystal structure of **26b** (**Figure 5**). The facial selectivities for **27** and **28** were lower compared to the corresponding reactions with NMM especially for R^2 = H (**Table 3**) when no selectivity was observed and additionally more than one other inseparable isomer was observed by ^{1}H NMR spectroscopy. The best stereoselectivity was observed with imine **11** (R^1 = phthalimido, R^2 = Me), when a 9:1 mixture of **27a** and **27b** was obtained in 87% yield. The cycloadduct ratio obtained from **9** is the reverse of that observed with NMM.



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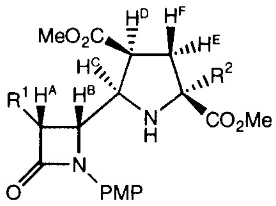


26a - 28a

26b - 28b

Table 3. 1,3-Dipolar Cycloadducts of 9, 11 and 13 with Methyl Acrylate[a]

Imine	$\mathbf{R^1}$	$\mathbf{R^2}$	**Base**	**Product**	**Yield(%)**	**a : b**
9	Et	Me	DBU	**26**	76	1 : 2
11	Phth	Me	Et_3N	**27**	87	9 : 1
13	Phth	H	DBU	**28**	73	1 : 1

(a) The reactions were carried out in toluene at room temperature in the presence of AgOAc (1.2 mol eq) and DBU/Et_3N (1.2 mol eq) for 15 h – 24 h.

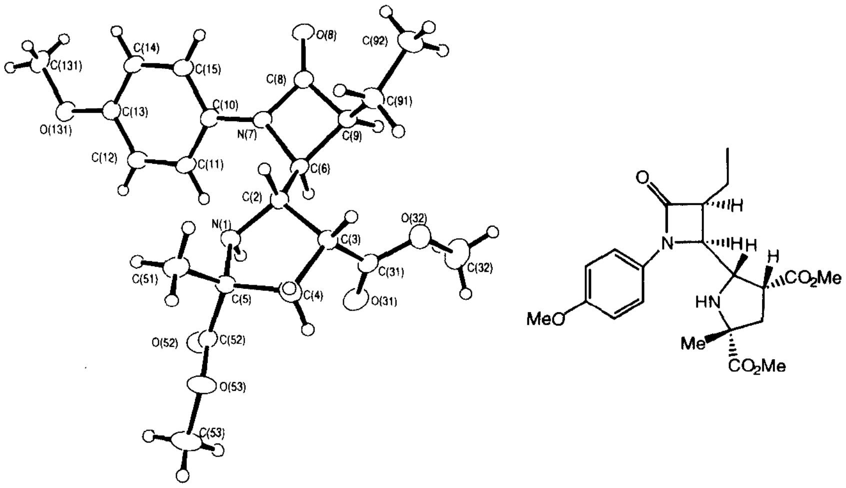
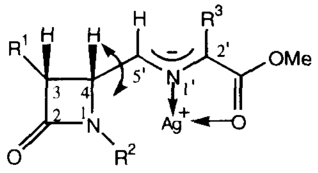
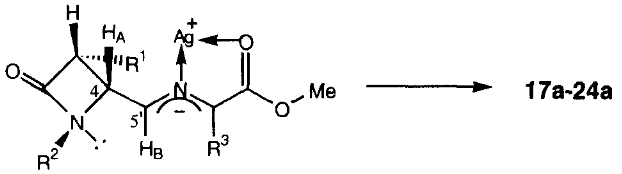


Figure 5. The X-Ray Crystal Structure of 26b

Origin of the Facial Selectivity: Metalloazomethine ylides arising from aldimines of α-amino esters give rise to the *E,E*-dipoles **29** under kinetic control and these invariably undergo *endo*-specific cycloaddition to NMM and methyl acrylate.[1a] In the current context the β-lactam moiety comprises a large substituent with a relatively conformationally inflexible ring.



29



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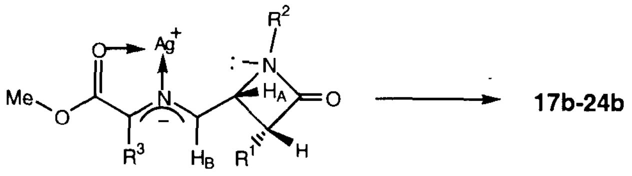


31

Rotation of the planar metalloazomethine ylide moiety (numbering as for the pyrrolidine product) about the C(4)-C(5') bond in **29** is affected by the size and orientation of the flanking substituents on N(1) and C(3) of the β-lactam. Assuming the reactive conformations are those which have either a *trans*-relationship between the N(1) substituent and the C(4)-C(5') bond [N(1) sp^3 hybridised] or in which the N(1)-R^2 bond is coplanar with

N(1)/C(2)/C(4) [as apparent from the foregoing X-ray crystal structures] (N(1) sp^2 hybridised) the two reactive azomethine ylide conformations are **30** and **31** with approach of the dipolarophile from the front face (*trans* to R^1) in both cases.

In both **30** and **31** the H_A/H_B dihedral angle is sensitive to the buttressing effect of the R^1 substituent, the hybridisation of N(1) and the effect of R^2. In both metallodipoles the back face is shielded by the R^1 substituent. Inspection of molecular models in which the β-lactam was taken to be planar (the X-ray structures show the ring to be planar or to fold across the C(2)-C(4) axis with an angle of 5-10°) informs the following comments.

In the case of **30** (R^2=PMP) if N(1) is sp^2 hybridised it blocks the front face *endo* attack unless the plane of the aryl ring is orthogonal to the plane of the β-lactam ring. When N(1) is sp^3 hybridised and the PMP substituent is *trans* to the C(4)-C(5′) bond there is no untoward steric impediment to front face *endo* attack. Depending, in addition, on the effective steric bulk of the Ag(I) (solvation, counterion) the H_A/H_B dihedral angle can vary from approximately 120-180° while still allowing front-side access of the dipolarophile. This metalloazomethine ylide gives rise to the **a** isomers.

In the case of metalloazomethine ylide **31** analogous factors to those discussed above influence the cycloaddition transition state geometry. In this metallodipole the steric interactions permit the H_A/H_B dihedral angle to vary from approximately 45-90° (molecular models) while allowing front-side access of the dipolarophile. A dihedral angle of *ca.* 90° with N(1) sp^2 hybridised and bearing a PMP substituent orthogonal to the β-lactam plane allows interaction of the Ag(I) with the aryl π-system, a potentially stabilising influence. Alternatively if N(1) is sp^3 hybridised and the PMP group is *trans* to the C(4)-C(5′) bond interaction of the N(1) lone pair with the Ag(I) become possible. This metalloazomethine ylide gives rise to the **b** isomers.

The precise reason for the selectivity for *endo*-addition *via* **30** compared to *endo*-addition *via* **31** in the majority of examples in **Table 1** may be related to an increase ease of access of the dipolarophile to the metallodipole in **30** consequent on the somewhat wider variation of H_A/H_B dihedral angle that permits *endo*-cycloaddition. The smaller the size of the R^1 substituent the greater the variation of dihedral angle accessible in **31** and the consequent decrease in selectivity between **30** and **31**.

In summary novel 4-(5′-pyrrolidinyl)-β-lactams containing up to six chiral centres have been prepared *via* *endo*-specific 1,3-dipolar cycloaddition reactions of imines. The reactions exhibit variable facial selectivity depending on steric effects arising from dipole and dipolarophile in the transition state. Enantiopure cycloadducts were also obtained.

Experimental. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. ^1H Nuclear magnetic resonance spectra were recorded at 300 MHz on a Bruker DPX 300 instrument, at 400 MHz on a Bruker WP 400 instrument or at 500 MHz on a Bruker DRX 500 instrument. ^{13}C Nuclear magnetic resonance spectra were recorded at 100 MHz on a Bruker WP 400 instrument. Deuterochloroform was used as solvent unless stated otherwise, and chemical shifts are given in parts per million (δ) downfield from tetramethylsilane. ^{1}H Spectra are referenced to tetramethylsilane or residual protonated solvent and ^{13}C spectra are referenced to deuterochloroform. Assignments of ^{1}H signals were made with the aid of 2D COSY spectra where necessary. Assignment of ^{13}C signals were made with the aid of APT spectra. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument. Mass spectra were recorded on a VG-AutoSpec spectrometer using electron impact (EI) operating at 70 eV or by fast atom bombardment (FAB), as specified. Accurate molecular weights were determined using perfluorokerosene as an internal standard. Optical rotations were recorded on an AA1000 Polarimeter. X-ray analysis was performed on a Stoe STADI 4-circle machine or a Nonius Kappa CCD area-detector diffractometer. Flash column chromatography employed silica gel 60 (Merk 230-400 mesh). Ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40-60°C. All reagents and solvents were purified according to literature procedures.[10] Compounds **4a**,[11] **4c**, **4d**, **5a** and **6a** were prepared by the literature methods.[3,7]

***cis*-3-*t*-Butyl-4-formyl-1-(4-methoxyphenyl)azetidin-2-one 4b.** 3,3-Dimethylbutyryl chloride (538 mg, 4 mmol) in toluene (70 ml) was added dropwise to a vigorously stirred suspension of triethylamine (0.61 ml, 4.4 mmol) and *N,N'*-bis(4-methoxyphenyl) ethylenediimine **2** (536 mg, 2 mmol) in toluene (150 ml) under a nitrogen atmosphere at room temperature. The mixture was stirred for 2.5 h, and then 10% HCl (100 ml) was added, and stirring continued for 1.5 h. The organic layer was separated and washed with 1 N HCl, brine and dried ($MgSO_4$). Filtration followed by evaporation of the solvent afforded a residue which was purified by column chromatography (20:1 v/v CH_2Cl_2-ethyl acetate) to afford the **product 4b** (420 mg, 80%) as colourless rods from Et_2O/hexane, m.p. 99 -101°C. (**Found**: C, 68.8, H, 7.45, N, 5.3. **$C_{15}H_{19}O_3N$ requires**: C, 68.95, H, 7.35, N, 5.35 %); δ 1.12 (s, 9H, 3 × Me), 3.62 (d, *J* 6.3 Hz, 1H, β-lactam ring CH), 3.79 (s, 3H, OMe), 4.48 (dd, *J* 3.9 and 6.3 Hz, 1H, β-lactam ring NCH), 6.87 and 7.24 (2 × d, *J* 8.8 Hz, 2 × 2H, ArH) and 10.06 (d, *J* 3.9 Hz, 1H, CHO); **m/z (%)**: 261 (M^+, 57), 204 (61), 176 (13), 149 (37), 134 (100), 107 (10), 92 (9), 77 (13), 57 (12) and 41 (24).

Imine 5b. D-glyceraldehyde acetonide[6] (1.66 g, 12.8 mmol) in CH_2Cl_2 (5 ml) was added dropwise at 0°C under N_2 to a stirred mixture of allylamine (0.97 ml, 13 mmol) and $MgSO_4$ (5 g) in CH_2Cl_2 (20 ml). The resulting mixture was stirred for 2.5 h and filtered through Celite. The solvent was evaporated under reduced pressure to give the imine **5b** (2.16 g) in quantitative yield as a pale yellow syrup which was unstable to chromatography and therefore used in the next reaction without further purification. δ 1.41 and 1.46 (2 × s, 2 × 3H, 2 × Me), 3.95 (dd, *J* 6.3 and 8.5 Hz, 1H, $OC\underline{H}H$), 4.07 (m, 2H, NCH_2), 4.21 (dd, *J* 6.8 and 8.5 Hz, 1H, $OCH\underline{H}$), 4.61 (m, 1H, OCH), 5.16 (m, 2H, $C{=}CH_2$), 5.96 (m, 1H, $C\underline{H}{=}CH_2$) and 7.67 (d, *J* 5.0 Hz, 1H, N=CH); **m/z (%)**: 169 (M^+, 1), 154 (19), 136 (26), 124 (17), 121 (22), 112 (25), 105 (21), 101 (21), 97 (7), 91 (10), 85 (17), 82 (29), 71 (22), 68 (45), 59 (22) and 43 (100).

Imine 5c. The same procedure was followed as for the preparation of **5b** starting from D-glyceraldehyde acetonide (130 mg, 1 mmol) in CH_2Cl_2 (2 ml), aminoacetaldehyde dimethyl acetal (105 mg, 1 mmol) and

$MgSO_4$ (500 mg) in CH_2Cl_2 (4 ml) with a reaction time of 2.5 h to give the imine **5c** (208 mg, 96%) as a colourless syrup which was unstable to chromatography and therefore used in the next reaction without further purification. δ 1.41 and 1.46 (2 × s, 2 × 3H, 2 × Me), 3.38 (s, 6H, 2 × OMe), 3.59 (m, 2H, NCH_2), 3.95 (dd, *J* 6.2 and 8.5 Hz, 1H, $OC\underline{H}H$), 4.20 (dd, *J* 6.8 and 8.5 Hz, 1H, $OCH\underline{H}$), 4.58 (m, 2H, 2 × CH) and 7.68 (d, *J* 5.0 Hz, 1H, N=CH); **m/z (%)**: 218 (M^++1, <1), 202 (5), 172 (5), 128 (12), 116 (7), 84 (10), 75 (100), 59 (11), 47 (13) and 43 (24).

General Procedure for the Synthesis of Enantiopure β-Lactams 6b, c. A solution of acid chloride (1.2 - 1.5 mmol) in DCM (0.5 - 1 ml) was added dropwise to a stirred solution of triethylamine (2 - 2.5 mmol) and imine **5** (1 mmol) in DCM (5 – 10 ml) under a nitrogen atmosphere at −20 °C. The mixture was stirred overnight at room temperature and then washed successively with a saturated solution of $NaHCO_3$ and brine. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography to afford the product.

(+)-*cis*-1-Allyl-3-(*R*)-benzyloxy-4-(*S*)-(2,2-dimethyl-[1,3]dioxolan-4-(*S*)-yl)-azetidin-2-one 6b. Prepared by the general procedure from benzyloxyacetyl chloride (2.99 ml, 19 mmol) in CH_2Cl_2 (5 ml), imine **5b** (2.16 g, 12.8 mmol) and Et_3N (3.3 ml, 24 mmol) in CH_2Cl_2 (50 ml) with a reaction time of 18 h. Flash chromatography (1:3 to 1:1 v/v EtOAc-petroleum ether) afforded the **product 6b** (3.62 g, 65%) as a colourless syrup, $[\alpha]_D$ = + 29.5 (0.61, $CHCl_3$); (**Found**: C, 67.95, H, 7.1, N, 4.15. $C_{18}H_{23}O_4N$ **requires**: C, 68.15, H, 7.25, N, 4.4%); δ 1.33 and 1.41 (2 × s, 2 × 3H, Me), 3.62 - 3.79 (m, 3H, $NC\underline{H}H$, $OC\underline{H}H$ and β-lactam ring NCH), 4.11 – 4.20 (m, 2H, $NCH\underline{H}$ and $OCH\underline{H}$), 4.35 (m, 1H, OCH), 4.62 (d, *J* 5.0 Hz, 1H β-lactam ring CH), 4.64 and 4.91 (2 × d, *J* 11.8 Hz, 2 × 1H, $PhCH_2O$), 5.21 (m, 2H, $C{=}CH_2$), 5.77 (m, 1H, $\underline{H}C{=}CH_2$) and 7.30 (m, 5H, ArH); **m/z (%)**: 318 (M^++1, 2), 302 (8), 219 (8), 204 (10), 176 (54), 163 (24), 143 (48), 132 (9), 113 (31), 107 (20), 105 (19), 101 (20), 91 (100), 85 (48), 72 (71), 70 (19), 65 (37), 59 (21) and 43 (69).

(+)-*cis*-3-(*R*)-Benzyloxy-1-(2,2-dimethyloxyethyl)-4-(*S*)-(2,2-dimethyl-[1,3]dioxolan-4-(*S*)-yl)-azetidin-2-one 6c. Prepared by the general procedure from benzyloxyacetyl chloride (886 mg, 4.8 mmol) in CH_2Cl_2 (5 ml), imine **5c** (847 mg, 3.9 mmol) and Et_3N (1.37 ml, 9.75 mmol) in CH_2Cl_2 (25 ml) with a reaction time of 17 h. Flash chromatography (1:1 v/v EtOAc-petroleum ether) afforded the **product 6c** (1.15 g, 81%) as a colourless syrup, $[\alpha]_D$ = + 56.9 (0.85, $CHCl_3$); (**Found**: C, 62.35, H, 7.4, N, 3.8. $C_{19}H_{27}O_6N$ **requires**: C, 62.45, H, 7.4, N, 3.85%); δ 1.33 and 1.43 (2 × s, 2 × 3H, 2 × Me), 3.33 - 3.39 (m, 7H, 2 × OMe and $NC\underline{H}H$), 3.62 (m, 2H, $NCH\underline{H}$ and $OC\underline{H}H$), 3.74 (dd, *J* 5.1 and 9.1 Hz, 1H, β-lactam ring NCH), 4.14 (dd, *J* 6.7 and 8.7 Hz, 1H, $OCH\underline{H}$), 4.32 (m, 1H, OCH), 4.64 (m, 3H, $NCH_2C\underline{H}$, $PhC\underline{H}H$ and β-lactam ring CH), 4.90 (d, *J* 11.8 Hz, 1H, $PhCH\underline{H}$) and 7.32 (m, 5H, ArH); **m/z (%)**: 366 (M^++1, 3), 250 (7), 176 (9), 143 (9), 107 (15), 91 (100), 75 (84) and 43 (21).

General Procedure for the Synthesis of β-Lactam Glycols 7a-c. A solution of **6** (1 mmol) in THF (10 ml) was added to 1 N HCl (10 ml) at room temperature with stirring and stirring was continued for 1 - 3 d under a nitrogen atmosphere. The solvent was then removed under the reduced pressure, and the residue was taken up in DCM and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$), filtered, and the filtrate was evaporated. The residue was purified by column chromatography to afford the product.

(−)-*cis*-4-(*R*)-[1(*S*),2-Dihydroxyethyl]-1-(4-methoxyphenyl)-3-(*R*)-phthalimidyl-azetidin-2-one 7a. Prepared by the general procedure from **6a** (323 mg, 0.76 mmol) and 1 N HCl (10 ml) in THF (10 ml) with a reaction time of 3 d. Flash chromatography (1:6 v/v THF-CH_2Cl_2) afforded the **product 7a** (244 mg, 84%) as colourless prisms from Et_2O/petroleum ether, m.p. 178 - 179°C, $[\alpha]_D = -58.4$ (1.0, $CHCl_3$); (**Found**: C, 62.55, H, 4.9, N, 7.2. $\mathbf{C_{20}H_{18}O_6N_2}$ **requires**: C, 62.8, H, 4.75, N, 7.3%); δ 2.27 and 3.07 (2 × br s, 2 × 1H, 2 × OH), 3.50 (m, 2H, CH_2), 3.78 (s, 3H, OMe), 4.07 (m, 1H, CH), 4.53 (dd, *J* 5.7 and 7.1 Hz, 1H, β-lactam ring NCH), 5.51 (d, *J* 5.7 Hz, 1H, β-lactam ring CH), 6.86 and 7.55 (2 × d, *J* 8.9 Hz, 2 × 2H, ArH) and 7.77 and 7.86 (2 × m, 2 × 2H, ArH); **m/z (%):** 382 (M^+, 36), 293 (11), 235 (15), 202 (8), 174 (11), 160 (23), 149 (100), 134 (52), 104 (30), 92 (8), 76 (25) and 50 (9).

(+)-*cis*-1-Allyl-3-(*R*)-benzyloxy-4-(*S*)-[1-(*S*),2-dihydroxyethyl]-azetidin-2-one 7b. Prepared by the general procedure from **6b** (2.6 g, 8.2 mmol) and 1 N HCl (50 ml) in THF (50 ml) with a reaction time of 3 d. Flash chromatography (1:1 v/v EtOAc-Et_2O) afforded the **product 7b** (1.4 g, 62%) as a colourless syrup, $[\alpha]_D = +44.0$ (1.0, $CHCl_3$). (**Found**: C, 64.75, H, 7.0, N, 4.8. $\mathbf{C_{15}H_{19}O_4N}$ **requires**: C, 65.0, H, 6.85, N, 5.05%); δ 2.74 and 3.12 (2 × br s, 2 × 1H, 2 × OH), 3.59 - 3.80 (m, 4H, CHOH, CHHOH, NCHH and β-lactam ring NCH), 3.98 (m, 1H, CHHOH), 4.14 (m, 1H, NCHH), 4.67 (d, *J* 5.0 Hz, 1H, β-lactam ring CH), 4.69 and 4.93 (2 × d, *J* 11.6 Hz, 2 × 1H, $PhCH_2$), 5.22 (m, 2H, C=CH_2), 5.75 (m, 1H, HC=CH_2) and 7.34 (m, 5H, ArH); **m/z (%):** 278 (M^++1, 4), 186 (71), 163 (81), 149 (34), 117 (15), 105 (8), 91 (100), 89 (15), 85 (12), 77 (14), 73 (15), 71 (18), 65 (56), 63 (13), 57 (14), 51 (15), 43 (26) and 41 (81).

(+)-*cis*-3-(*R*)-Benzyloxy-1-(2,2-dimethyloxyethyl)-4-(*S*)-[1-(*S*),2-dihydroxyethyl]-azetidin-2-one 7c. Prepared by the general procedure from **6c** (1.1 g, 3 mmol) and 1 N HCl (25 ml) in THF (25 ml) with a reaction time of 1 d. Flash chromatography (EtOAc) afforded the **product 7c** (815 mg, 84%) as a colourless syrup, $[\alpha]_D = +94.5$ (0.88, $CHCl_3$); (**Found**: C, 59.0, H, 7.1, N, 4.05. $\mathbf{C_{16}H_{23}O_6N}$ **requires**: C, 59.1, H, 7.1, N, 4.3%); δ 2.47 (br s, 1H, OH), 3.38 - 3.50 (m, 8H, 2 × OMe and NCH_2), 3.65 and 3.75 (2 × m, 2 × 1H, CH_2OH), 3.82 (dd, *J* 5.1 and 6.5 Hz, 1H, β-lactam ring NCH), 3.93 - 4.01 (m, 2H, CHOH), 4.56 (dd, *J* 4.2 and 6.0 Hz, 1H, MeOCHOMe), 4.69 (m, 2H, PhCHH and β-lactam ring CH), 4.92 (d, *J* 11.7 Hz, 1H, PhCHH) and 7.31 - 7.36 (m, 5H, ArH); **m/z (%):** (Fab) 326 (M^++1, 7), 312 (8), 294 (7), 280 (42), 262 (13), 234 (6), 163 (6), 105 (21), 91 (100) and 75 (32).

General Procedure for the Synthesis of 4-Formyl β-Lactams 8a-c. A suspension of $NaIO_4$ (2.5 – 3.5 mmol) in buffer solution (0.05 M KH_2PO_4-NaOH, pH 7) (2 –3 ml) was added dropwise to a solution of diol **7** (1 mmol) in CH_2Cl_2 (6 – 9 ml), at room temperature. The mixture was stirred for 1 to 15 h under a nitrogen atmosphere. Anhydrous Na_2SO_4 was added, the mixture filtered, and the filter cake washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, evaporated and the residue purified by column chromatography to afford the product.

(+)-*cis*-3-(*R*)-Phthalimidyl-4-(*R*)-formyl-1-(4-methoxyphenyl)-azetidin-2-one 8a. Prepared over 1.5 h by the general procedure from **7a** (240 mg, 0.63 mmol) and $NaIO_4$ (428 mg, 2 mmol) with buffer solution (2 ml) and CH_2Cl_2 (6 ml). Flash chromatography (1:10 v/v EtOAc-CH_2Cl_2) afforded the **product 8a** (157 mg, 72%) as colourless needles from CH_2Cl_2/ Et_2O, m.p. 214 - 216°C, $[\alpha]_D$ = + 246.0 (1.0, $CHCl_3$). (**Found**: C, 65.15, H, 4.05, N, 8.25. **$C_{19}H_{14}O_5N_2$ requires**: C, 65.15, H, 4.0, N, 8.0%); δ 3.82 (s, 3H, OMe), 4.76 (dd, *J* 2.6 and 6.3 Hz, 1H, β-lactam ring NCH), 5.80 (d, *J* 6.3 Hz, 1H, β-lactam ring CH), 6.94 and 7.39 (2 × d, *J* 8.9 Hz, 2 × 2H, ArH), 7.80 and 8.70 (2 × m, 2 × 2H, ArH) and 9.90 (d, *J* 2.6 Hz, 1H, CHO); **m/z (%):** 350 (M^+, 38), 293 (15), 160 (12), 149 (100), 134 (57), 104 (28), 92 (11), 76 (31), 64 (7) and 50 (8).

(+)-*cis*-1-Allyl-3-(*R*)-benzyloxy-4-(*R*)-formyl-azetidin-2-one 8b. Prepared over 6 h by the general procedure from **7b** (1.08 g, 3.9 mmol) and $NaIO_4$ (2.1 g, 10 mmol) with buffer solution (3 ml) and CH_2Cl_2 (9 ml). Flash chromatography (1:1 v/v EtOAc-CH_2Cl_2) afforded the **product 8b** (763 mg, 80%) as a colourless syrup, $[\alpha]_D$ + 41.2° (1.0, $CHCl_3$); (**Found**: C, 68.45, H, 6.05, N, 5.65. **$C_{14}H_{15}O_3N$ requires**: C, 68.55, H, 6.1, N, 5.7%); δ 3.96 (m, 2H, NCH_2), 4.14 (dd, *J* 2.5 and 5.0 Hz, 1H, β-lactam ring NCH), 4.62 and 4.76 (2 × d, *J* 11.7 Hz, 2 × 1H, $PhCH_2$), 4.92 (d, *J* 5.0 Hz, 1H, β-lactam ring CH), 5.21 (m, 2H, $C{=}CH_2$), 5.70 (m, 1H, $\underline{C}\underline{H}{=}CH_2$), 7.32 (m, 5H, ArH) and 9.54 (d, *J* 2.5 Hz, 1H, CHO); **m/z (%):** 245 (M^+, <1), 128 (7), 91 (100), 84 (28), 77 (13), 65 (20), 51 (25), 49 (49) and 41 (29).

(+)-*cis*-3-(*R*)-Benzyloxy-1-(2,2-dimethyloxyethyl)-4-(*R*)-formyl-azetidin-2-one 8c. Prepared over 15 h by the general procedure from **7c** (570 mg, 1.75 mmol) and $NaIO_4$ (1.28 g, 6 mmol) with buffer solution (3 ml) and CH_2Cl_2 (9 ml). Flash chromatography (1:2 v/v EtOAc-CH_2Cl_2) afforded the **product 8c** (463 mg, 90%) as a colourless syrup, $[\alpha]_D$ + 49.5° (0.97, $CHCl_3$); (**Found**: C, 61.3, H, 6.7, N, 4.55. **$C_{15}H_{19}O_5N$ requires**: C, 64.1, H, 6.5, N, 4.8%); δ 3.28 - 3.42 (m, 7H, $NC\underline{H}H$ and 2 × OMe), 3.63 (dd, *J* 4.1 and 14.5 Hz, 1H, $NCH\underline{H}$), 4.17 (dd, *J* 3.7 and 5.1 Hz, 1H, β-lactam ring NCH), 4.42 (dd, *J* 4.1 and 5.2 Hz, 1H, $MeOC\underline{H}OMe$), 4.62 and 4.72 (2 × d, *J* 11.6 Hz, 2 × 1H, $PhCH_2$), 4.91 (d, *J* 5.1 Hz, 1H, β-lactam ring CH), 7.32 (m, 5H, ArH) and 9.53 (d, *J* 3.7 Hz, 1H, CHO). Somewhat surprisingly this compound proved highly unstable in the mass spectrometer using EI or FAB and it was not possible to obtain to its mass spectrum.

General Method for the Preparation of β-Lactam Imines. α-Amino methyl ester (1.05 - 1.1 mmol) was added under N_2 at room temperature to a stirred mixture of β-lactam aldehyde (1 mmol) and 4 Å molecular sieves (*ca.* 2 g) in CH_2Cl_2 (*ca.* 10 ml). The resulting mixture was stirred at room temperature for 2 - 24 h and filtered through Celite. The solvent was evaporated under reduced pressure to give the β-lactam imines which were unstable to chromatography and therefore the lactams that were not solids were used in subsequent reactions without further purification.

β-Lactam imine 9. The general method was applied to **4a** (233 mg, 1 mmol), alanine methyl ester (114 mg, 1.1 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (10 ml) for 2 h. Work up afforded a 1:1 mixture of inseparable diastereoisomers **9** (305 mg, 96%) as a colourless syrup. δ 1.07 (t, 2 × 3H, 2 × Me), 1.48 (m, 2 × 3H, 2 × Me), 1.70 and 1.88 (2 × m, 2 × 2H, 2 × CH_2), 3.48 (m, 2H, 2 × CH), 3.74 - 3.78 (m, 12H, 4 × OMe), 4.08 and 4.66 (2 × m, 2 × 2H, 4 × β-lactam ring CH), 6.85 (d, *J* 9.0 Hz, 2 × 2H, ArH), 7.32 (m, 2 × 2H, ArH) and 7.80 (m, 2 × 1H, HC=N); **m/z (%)**: 318 (M^+, 28), 289 (81), 259 (14), 243 (11), 231 (100), 216 (8), 203 (22), 189 (67), 176 (27), 160 (14), 149 (42), 134 (55), 123 (6), 107 (14), 72 (11), 77 (19) and 56 (18).

β-Lactam imine 10. The general method was applied to **4c** (311 mg, 1 mmol), alanine methyl ester (114 mg, 1.1 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (10 ml) for 2 h. Work up afforded a 1:1 mixture of inseparable diastereoisomers **10** (375 mg, 96 %) as a pale yellow gum. δ 1.44 and 1.46 (2 × d, *J* 6.8, 2 × 3H, 2 × Me), 3.71 and 3.73 (2 × s, 2 × 3H, 2 × OMe), 3.78 (s, 2 × 3H, 2 × OMe), 4.07 (m, 2 × 1H, 2 × β-lactam ring NCH), 4.75 (m, 2 × 3H, 2 × CH_2 and 2 × CH), 4.98 (d, *J* 5.2 Hz, 2 × 1H, 2 × β-lactam ring CH), 6.85 (d, *J* 8.4 Hz, 2 × 2H, ArH), 7.35 (m, 2 × 7H, ArH) and 7.80 (m, 2 × 1H, 2 × HC=N); **m/z (%)**: 396 (M^+, 9), 298 (73), 261 (19), 231 (8), 217 (14), 189 (26), 175 (7), 160 (13), 149 (25), 143 (15), 107 (6), 91 (100), 77 (9), 65 (12) and 55 (7).

β-Lactam imine 11. The general method was applied to **4d** (350 mg, 1 mmol), alanine methyl ester (114 mg, 1.1 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (10 ml) for 15 h. Work up afforded a 1:1 mixture of inseparable diastereoisomers **11** (451 mg) in quantitative yield as colourless prisms from CH_2Cl_2/petroleum ether. (**Found**: C, 63.15, H, 4.8, N, 9.7. **$C_{23}H_{21}O_6N_3$ requires**: C, 63.45, H, 4.85, N, 9.65%); δ 1.03 and 1.39 (2 × d, *J* 7.2 Hz, 2 × 3H, 2 × Me), 3.18 and 3.66 (2 × s, 2 × 3H, 2 × OMe), 3.82 (s, 2 × 3H, 2 × OMe), 3.92 (m, 2H, 2 × CH), 5.04 (m, 2H, 2 × β-lactam ring CH), 5.80 (m, 2H, 2 × β-lactam ring CH), 6.92 (d, *J* 8.9 Hz, 2 × 2H, ArH), 7.41 and 7.79 (m, 2 × 4H, ArH) and 7.89 (m, 6H, 2 × HC=N and 4ArH); **m/z (%)**: 435 (M^+, 58), 376 (25), 348 (20), 335 (8), 313 (17), 305 (8), 293 (9), 285 (8), 261 (13), 227 (39), 201 (13), 189 (32), 160 (27), 149 (100), 134 (51), 130 (23), 123 (12), 104 (57), 92 (16), 76 (50) and 59 (25).

β-Lactam imine 12. The general method was applied to **4c** (311 mg, 1 mmol), glycine methyl ester (98 mg, 1.1 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (10 ml) for 15 h. Work up afforded the imine **12** in quantitative yield as a pale yellow syrup. δ 3.75 and 3.77 (2 × s, 2 × 3H, 2 × OMe), 4.27 (s, 2H, CH_2), 4.70 (m, 2H, PhC$\underline{H}$H and β-lactam ring NCH), 4.79 (d, *J* 11.7, 1H, PhCH$\underline{H}$), 4.98 (d, *J* 5.0 Hz, 1H, β-lactam ring CH), 6.85 (d, *J* 8.9 Hz, 2H, ArH), 7.35 (m, 7H, ArH) and 7.76 (d, *J* 7.0, 1H, HC=N); **m/z (%)**: 382 (M^+, 12), 275 (49), 247 (18), 203 (10), 175 (32), 164 (8), 160 (8), 149 (38), 134 (21), 107 (9), 91 (100), 84 (10), 77 (14), 65 (12) and 51 (7).

β-Lactam imine 13. The general method was applied to **4d** (700 mg, 2 mmol), glycine methyl ester (196 mg, 2.2 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (20 ml) for 15 h. Work up afforded imine **13** (822 mg, 98%) as colourless plates from CH_2Cl_2/petroleum ether, m.p. 153 - 155°C. (**Found**: C, 62.4, H, 4.6, N, 9.75. **$C_{22}H_{19}O_6N_3$ requires**: C, 62.7, H, 4.55, N, 9.95%); δ 3.44 and 3.81 (2 × s, 2 × 3H, 2 × OMe), 4.03 and 4.24 (2 × d, *J* 15.7 Hz, 2H, CH_2), 5.05 (t, *J* 5.7, 1H, β-lactam ring NCH), 5.80 (d, *J* 5.7 Hz, 1H, β-lactam ring CH), 6.91 and 7.42 (2 × d, *J* 8.7 Hz, 2 × 2H, ArH) and 7.75 - 7.92 (m, 5H, HC=N and 4ArH); **m/z (%)**: 421 (M^+, 100), 362 (11), 348 (16), 333 (9), 305 (7), 275 (6), 247 (17), 213 (15), 199 (16), 187 (11), 175 (40), 160 (21), 149 (76), 134 (41), 104 (40), 92 (11), 76 (30) and 45 (9).

β-Lactam imine 14. The general method was applied to **4b** (172 mg, 0.66 mmol), alanine methyl ester (72 mg, 0.70 mmol) and 4 Å molecular sieves (1.5 g) in CH_2Cl_2 (5 ml) for 15 h. Work up afforded a 1:1 mixture of inseparable diastereoisomers **14** (220 mg, 98%) as a colourless syrup. δ 1.12 (s, 2 × 9H, 6 × Me), 1.50 (m, 2 × 3H, 2 × Me), 3.53 (m, 2H, 2 × CH), 3.72 - 3.77 (m, 2 × 6H, 4 × OMe), 4.09 and 4.75 (2 × m, 2 × 2H, 4 ×β-lactam ring CH), 6.85 and 7.30 (2 × m, 2 × 4H, ArH) and 7.97 (m, 2 × 1H, 2 × HC=N); **m/z (%)**: 346 (M^+, 5), 289 (14), 261 (38), 231 (21), 204 (25), 189 (15), 176 (14), 163 (15), 149 (21), 134 (100), 122 (5), 107 (10), 92 (7), 77 (13), 57 (9) and 41 (13).

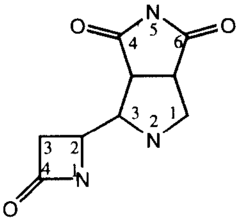
β-Lactam imine 15. Alanine methyl ester (115 mg, 1.1 mmol) was added to a stirred mixture of β-lactam aldehyde **8b** (245 mg, 1 mmol) and 4 Å molecular sieves (1 g) in CH_2Cl_2 (10 ml) under N_2 at room temperature. The resulting mixture was stirred for 15 h and filtered through Celite. The solvent was evaporated under reduced pressure to give a 1:1 mixture of inseparable diastereoisomers **15** (322 mg, 98%) as a pale yellow syrup. δ 1.40 and 1.43 (2 × d, *J* 6.0 Hz, 2 × 3H, 2 × Me), 3.69 and 3.73 (2 × s, 2 × 3H, 2 × OMe), 3.88 - 4.06 (m, 6H), 4.28 - 4.33 (m, 2H), 4.61 - 4.75 (m, 4H), 4.87 (m, 2H), 5.21 (m, 4H, 2 × $C=CH_2$), 5.71 (m, 2H, 2 × $C\underline{H}=CH_2$), 7.29 - 7.35 (m, 10H, ArH) and 7.69 (m, 2H, 2 × CH=N). **m/z (%)**: 330 (M^+, <1), 132 (25), 122 (13), 108 (29), 105 (21), 102 (6), 91 (68), 86 (22), 79 (31), 72 (46), 65 (10), 59 (12), 51 (19) and 44 (100).

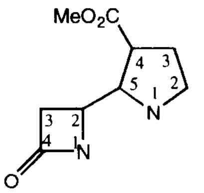
β-Lactam Imine 16. The same procedure was followed as for the preparation of **15** starting from alanine methyl ester (103 mg, 1.0 mmol), β-lactam aldehyde **8c** (240 mg, 0.82 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (10 ml) for 4 h. Work up afforded a 1:1 mixture of inseparable diastereoisomers **16** (303 mg, 98%) as a colourless syrup. δ 1.41 and 1.46 (2 × d, *J* 6.7 Hz, 2 × 3H, 2 × Me), 3.33 (s, 12H, 4 × OMe), 3.40 (d, *J* 5.2 Hz, 2 × 2H, 2 × NCH_2), 3.67 and 3.73 (2 × s, 2 × 3H, 2 × OMe), 4.04 (q, *J* 6.7 Hz, 2 × 1H, 2 × $MeC\underline{H}$), 4.35 - 4.40 and 4.46 - 4.55 (2 × m, 2 × 2H), 4.61 - 4.72 (m, 4H), 4.87 (m, 2H), 7.29 - 7.37 (m, 10H, ArH) and 7.69 - 7.72 (m, 2H, 2 × CH=N); **m/z (%)**: (Fab) 379 (M^++1, 14), 347 (13), 271 (17), 256 (13), 248 (10), 243 (8), 225 (7), 197 (9), 167 (7), 136 (9), 91 (100) and 75 (49).

General Procedure for 1,3-Dipolar Cycloaddition Reactions of the Imines. AgOAc (1.2 eq) was added at room temperature in the dark with stirring to a solution of imine (1 eq) in toluene or DMSO followed *N*-methylmaleimide (or methyl acrylate) (1.5 eq). Finally the base (DBU or Et_3N) (1.2 eq) was added and the resulting mixture was stirred overnight, then diluted with EtOAc or CH_2Cl_2, washed with a saturated solution of

NH_4Cl and then water. The organic layer was separated, dried ($MgSO_4$), and the solvent evaporated. The residue was purified by column chromatography to afford the cycloadducts.

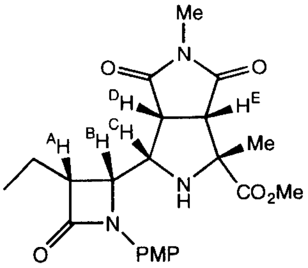
* All the cycloadducts have been named using the Autonom-1.0 program which assigned the numbering noted.





***endo*-Methyl 3-(*S*,*R*)-[*cis*-3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*R*,*S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 17a** and ***endo*-Methyl 3-(*R*,*S*)-[*cis*-3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*R*,*S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 17b.** Prepared by the general procedure from imine **9** (154 mg, 0.485 mmol), AgOAc (100 mg, 0.6 mmol), *N*-methylmaleimide (83 mg, 0.75 mmol) and DBU (91 mg, 0.6 mmol) in toluene (10 ml) for 15 h. Flash chromatography (1:1 v/v EtOAc-petroleum ether) afforded the separated stereoisomers **17a** and **17b** (192 mg, 92% combined yield) in a 2:1 ratio.

Major isomer **17a**: obtained as colourless prisms from AcOEt/hexane, m.p. 209 - 211°C. (**Found**: C, 61.55, H, 6.1, N, 9.5. $C_{22}H_{27}O_6N_3$ **requires**: C, 61.55, H, 6.35, N, 9.8%); δ 1.17 (t, *J* 7.3 Hz, 3H, Me), 1.49 (s, 3H, Me), 1.81 – 2.05 (m, 2H, CH_2), 2.4 (br s, 1H, NH), 2.84 (s, 3H, NMe), 3.07 (d, *J* 7.0 Hz, 1H, CH^E), 3.20 (t, *J* 7.0 Hz, 1H, CH^D), 3.35 (m, 1H, β-lactam ring CH^A), 3.61 (t, *J* 7.0 Hz, 1H, NCH^C), 377 and 3.78 (2 × s, 2 × 3H, 2 × OMe), 4.86 (dd, *J* 5.8 and 7.0 Hz, 1H, β-lactam ring NCH^B) and 6.87 and 7.52 (2 × d, *J* 8.9 Hz, 2 × 2H, ArH); δ (^{13}C) 175.3 (CO), 175.2 (CO), 172.5 (CO), 168.8 (CO), 157.3 (ArC), 129.5 (ArC), 123.3 (2 × ArC), 114.2 (2 × ArC), 68.3 ($\underline{C}CO_2Me$), 60.1, 56.5, 55.4, 55.3, 54.4, 53.0, 49.2, 25.0, 23.8, 19.2 (CH_2) and 13.0; **m/z** (%): 429 (M^+, 100), 300 (21), 225 (88), 205 (57), 177 (64), 165 (93), 149 (52), 134 (50), 108 (49) and 80 (21).



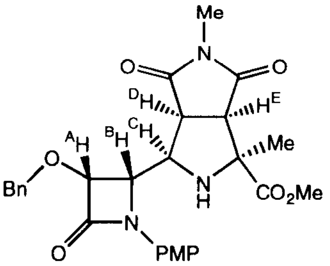
NOE ($CDCl_3$, 400 MHz)

proton irradiated	H^A	H^B	H^C	H^D	H^E	Me
H^A		7.8				
H^B	6.9					
H^C		5.3		2.4	1.5	2.8
H^D		4.6	4.2			
H^E						4.1
Me			2.9		3.4	

Minor isomer **17b**: obtained as colourless rhombs from CH_2Cl_2/hexane, m.p. 148 - 150°C. (**Found**: C, 61.2, H, 6.35, N, 9.5. **$C_{22}H_{27}O_6N_3$ requires**: C, 61.55, H, 6.35, N, 9.8%); δ 1.29 (t, *J* 7.3 Hz, 3H, Me), 1.43 (s, 3H, Me), 1.85 (br s, 1H, NH), 2.0 (m, 2H, CH_2), 2.99 (s, 3H, NMe), 3.16 (d, *J* 7.7 Hz, 1H, CH^E), 3.5 (m, 2H, CH^D and β-lactam ring CH^A), 3.23 (m, 1H, NCH^C), 378 and 3.80 (2 × s, 2 × 3H, 2 × OMe), 4.19 (dd, *J* 5.7 and 9.4 Hz, 1H, β-lactam ring NCH^B), 6.86 and 7.40 (2 × d, *J* 9.1 Hz, 2 × 2H, ArH); δ (^{13}C): 175.3 (CO), 174.8 (CO), 172.1 (CO), 168.7 (CO), 156.6 (ArC), 130.5 (ArC), 120.9 (2 × ArC), 114.1 (2 × ArC), 67.5 (<u>C</u>CO_2Me), 59.8, 58.0, 55.3, 54.7, 53.7, 52.5, 46.5, 25.2, 23.7, 19.3 (CH_2) and 12.5; **m/z (%)**: 429 (M$^+$, 100), 300 (28), 225 (83), 205 (51), 177 (66), 165 (90), 149 (38), 134 (41), 108 (44) and 80 (20).

***endo*-Methyl 3-(*S,R*)-[*cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*R,S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 18a** and ***endo*-Methyl 3-(*R,S*)-[*cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*R,S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 18b.** Prepared by the general procedure from imine **10** (200 mg, 0.5 mmol), AgOAc (100 mg, 0.6 mmol), *N*-methylmaleimide (83 mg, 0.75 mmol) and DBU (91 mg, 0.6 mmol) in toluene (10 ml) for 15 h. Flash chromatography (1:1 v/v EtOAc-petroleum ether) afforded the separated stereoisomers **18b** and **18a** (145 mg, 57% combined yield) in a 3:1 ratio.

Major isomer **18b**: obtained as colourless needles from EtOAc/cyclohexane, m.p. 155 - 156°C. (**Found**: C, 63.95, H, 5.95, N, 8.15. **$C_{27}H_{29}O_7N_3$ requires**: C, 63.9, H, 5.8, N, 8.3%); δ 1.42 (s, 3H, Me), 2.0 (br, 1H, NH), 3.01(s, 3H, NMe), 3.10 (d, *J* 7.7 Hz, 1H, CH^E), 3.66 (t, *J* 7.7 Hz, 1H, CH^D), 3.77 (m, 7H, NCH^C and 2 × OMe), 4.37 (dd, *J* 5.3 and 9.5 Hz, 1H, β-lactam ring NCH^B), 4.92 (d, *J* 11.2 Hz, 1H, PhC<u>H</u>H), 5.05 (m, 2H, β-lactam ring CH^A and PhCH<u>H</u>), 6.84 (d, *J* 8.8 Hz, 2H, ArH) and 7.30 – 7.46 (m, 7H, ArH); **m/z (%)**: 507 (M$^+$, 25), 398 (7), 300 (13), 283 (34), 225 (41), 189 (9), 175 (19), 165 (57), 149 (51), 132 (42), 108 (34), 91 (100), 89 (31) and 44 (26).

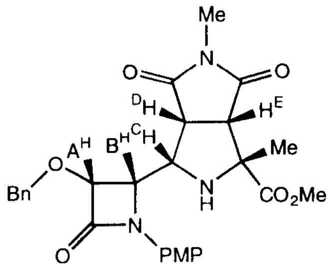


NOE ($CDCl_3$, 400 MHz)

proton irradiated	Enhancement (%)			
	H^C & OMe	H^D	H^E	Me
H^D			8.4	
H^E		9.6		4.7
Me	6.0		6.2	

Minor isomer **18a**: obtained as colourless prisms from CH_2Cl_2, m.p. 211 - 212°C. (**Found**: C, 64.0, H, 5.75, N, 8.1. **$C_{27}H_{29}O_7N_3$ requires**: C, 63.9, H, 5.8, N, 8.3%; δ 1.37 (s, 3H, Me), 2.51 (s, 1H, NMe), 3.16 (d, *J* 7.7 Hz, 1H, CH^E), 3.33 (t, *J* 7.7 Hz, 1H, CH^D), 3.67 and 3.79 (2 × s, 2 × 3H, 2 × OMe), 3.98 (d, *J* 11.8 Hz, 1H, NH), 4.1

(m, 1H, NCH^C), 4.63 (d, *J* 11.3 Hz, 1H, PhC$\underline{H}$H), 4.94 (d, *J* 5.3 Hz, 1H, β-lactam ring CH^A), 4.98 (dd, *J* 5.3 and 8.4 Hz, 1H, β-lactam ring CH^B), 5.11 (d, *J* 11.3 Hz, 1H, PhCH$\underline{H}$), 6.89 (d, *J* 9.0 Hz, 2H, ArH) and 7.40 (m, 7H, ArH); **m/z (%)**: 507 (M$^+$, 38), 448 (6), 398 (7), 300 (15), 283 (46), 267 (8), 247 (8), 225 (57), 165 (60), 156 (33), 149 (53), 134 (17), 122 (13), 108 (33), 91 (100), 80 (12), 77 (8), 65 (10) and 43 (24).



NOE (CDCl$_3$, 400 MHz)

proton irradiated	Enhancement (%)			
	H^C	H^D	H^E	Me
H^D	9.8		8.9	
H^E		10.8		4.8
Me	4.1		6.7	

***endo*-Methyl 3-(*R*,*S*)-[*cis*-1-(4-methoxyphenyl)-3-phthalimidyl-4-oxo-azetidin-2-(*R*,*S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 19a** and ***endo*-Methyl 3-(*R*,*S*)-[*cis*-1-(4-methoxyphenyl)-3-phthalimidyl-4-oxo-azetidin-2-(*S*,*R*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 19b.**

a). Toluene as solvent: Prepared by the general procedure from imine **11** (87 mg, 0.2 mmol), AgOAc (40 mg, 0.24 mmol), *N*-methylmaleimide (33 mg, 0.3 mmol) and DBU (35 mg, 0.24 mmol) in toluene (10 ml) for 12 h. Flash chromatography (1:6 to 1:4 v/v EtOAc-CH$_2$Cl$_2$) afforded the **product 19a** (96 mg, 88%) as colourless needles from CH$_2$Cl$_2$, m.p. 224 - 225°C. (**Found**: C, 61.25, H, 4.5, N, 10.05. **$C_{28}H_{26}O_8N_4$ requires**: C, 61.55, H, 4.8, N, 10.25%); δ 0.98 (s, 3H, Me), 2.36 (d, *J* 14.5 Hz, 1H, NH), 2.89 (s, 3H, NMe), 2.90 (d, *J* 6.3 Hz, 1H, COCH), 3.16 (t, *J* 6.3 Hz, 1H, COCH), 3.59 (s, 3H, OMe), 3.70 (ddd, *J* 5.2, 9.5, 14.5 Hz, 1H, NCH), 3.81 (s, 3H, OMe), 5.30 (dd, *J* 5.2 and 9.5 Hz, 1H, β-lactam ring CH), 5.65 (d, *J* 5.2 Hz, 1H, β-lactam ring, CH^A), 6.92 (d, *J* 8.9 Hz, 2H, ArH) and 7.77 (m, 6H, ArH); **m/z (%)**: 546 (M$^+$, 19), 396 (12), 338 (22), 322 (67), 294 (32), 279 (7), 225 (63), 189 (10), 165 (67), 160 (20), 149 (100), 134 (33), 123 (12), 108 (43), 104 (31), 92 (7), 80 (19), 77 (18) and 53 (6).

b). DMSO as solvent: Prepared by the general procedure from imine **11** (217 mg, 0.5 mmol), AgOAc (100 mg, 0.6 mmol), *N*-methylmaleimide (83 mg, 0.75 mmol) and Et$_3$N (83 μl, 0.6 mmol) in DMSO (15 ml) for 15 h. Flash chromatography (1:8 to 1:4 v/v EtOAc-CH$_2$Cl$_2$) afforded the separated stereoisomers **19b** and **19a** (246 mg, 90% combined yield) in a 1.2:1 ratio.

Major isomer **19b**: obtained as colourless prisms from EtOAc, m.p. 243 - 244°C. **HRMS** (**Found**: 546.1739. **$C_{28}H_{26}O_8N_4$ requires**: 546.1750); δ 1.41 (s, 3H, Me), 2.01 (d, *J* 7.1 Hz, 1H, NH), 2.95 (s, 3H, NMe), 3.01 (m, 2H, 2 × COCH), 3.77 and 3.88 (2 × s, 2 × 3H, 2 × OMe), 4.21 (m, 1H, CH), 4.64 (dd, *J* 5.5 and 9.5 Hz, 1H, β-lactam ring CH), 5.92 (d, *J* 5.5 Hz, 1H, β-lactam ring, CH), 6.90 and 7.54 (2 × d, *J* 9.0 Hz, 2 × 2H, ArH) and

7.80 and 7.94 (2 × m, 2 × 2H, ArH); **m/z (%):** 546 (M^+, 39), 396 (23), 338 (17), 322 (51), 294 (36), 279 (11), 225 (63), 189 (12), 175 (10), 165 (79), 160 (22), 149 (100), 134 (32), 123 (11), 108 (45), 104 (27), 80 (20) and 77 (19).

Minor isomer **19a**: was identical to that described above.

***endo*-Methyl 3-(*R,S*)-[*cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*S,R*)-yl]-5-methyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 20b** and ***endo*-Methyl 3-(*R,S*)-[*cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*R,S*)-yl]-5-methyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 20a.** Prepared by the general procedure from imine **12** (288 mg, 0.75 mmol), AgOAc (150 mg, 0.9 mmol), *N*-methylmaleimide (124 mg, 1.125 mmol) and DBU (136 mg, 0.9 mmol) in toluene (8 ml) for 15 h. Flash chromatography (2:1 to 1:1 v/v EtOAc-petroleum ether) afforded the separated stereoisomers **20b** and **20a** (294 mg, 80% combined yield) in a 7:1 ratio.

Major isomer **20b**: obtained as colourless prisms from EtOAc/CH_2Cl_2, m.p. 182 - 184°C. (**Found**: C, 63.2, H, 5.35, N, 8.4. **$C_{26}H_{27}O_7N_3$ requires**: C, 63.3, H, 5.5, N, 8.5%); δ 2.08 (t, *J* 5.1 Hz, 1H, NH), 3.02 (s, 3H, NMe), 3.39 (t, *J* 7.7 Hz, 1H, COCH), 3.50 (m, 1H, NCH), 3.60 (t, *J* 7.7 Hz, 1H, COCH), 3.77 (m, 7H, CHO_2Me and 2 × OMe), 4.44 (dd, *J* 5.3 and 9.4 Hz, 1H, β-lactam ring NCH), 4.90 and 5.03 (2 × d, *J* 11.1 Hz, 2 × 1H, $PhCH_2$), 5.06 (d, 5.3 Hz, 1H, β-lactam ring CH), 6.84 (d, *J* 8.9 Hz, 2H, ArH) and 7.30 – 7.40 (m, 7H, ArH); **m/z (%):** 493 (M^+, 29), 402 (20), 384 (8), 286 (8), 283 (20), 253 (9), 233 (14), 226 (28), 211 (26), 179 (14), 175 (35), 164 (58), 151 (22), 149 (50), 142 (36), 134 (20), 123 (14), 108 (9), 94 (31), 91 (100), 77 (8) and 65 (11).

Minor isomer **20a**: obtained as colourless needles from CH_2Cl_2/ petroleum ether, m.p. 206 - 208°C. (**Found**: C, 63.05, H, 5.4, N, 8.25. **$C_{26}H_{27}O_7N_3$ requires**: C, 63.3, H, 5.5, N, 8.5%); δ 2.40 (s, 3H, NMe), 3.28 and 3.49 (2 × t, *J* 7.9 Hz, 2 × 1H, 2 × COCH), 3.61(t, *J* 11.2 Hz, 1H, NH), 3.78 and 3.79 (2 × s, 2 × 3H, 2 × OMe), 3.85 (m, 2H, CHNHCH), 4.61 (d, *J* 11.3 Hz, 1H, PhCHH), 4.97 (m, 2H, 2 × β-lactam ring CH), 5.17 (d, *J* 11.3 Hz, 1H, PhCHH), 6.89 (d, *J* 8.9 Hz, 2H, ArH) and 7.33 – 7.44 (m, 7H, ArH); **m/z (%):** 493 (M^+, 46), 402 (16), 384 (6), 286 (7), 283 (17), 253 (11), 233 (15), 226 (25), 211 (27), 179 (10), 175 (38), 164 (44), 151 (19), 149 (48), 142 (34), 134 (20), 123 (12), 108 (11), 94 (28), 91 (100), 77 (8) and 65 (12).

***endo*-Methyl 3-(*R,S*)-[*cis*-1-(4-methoxyphenyl)-3-phthalimidyl-4-oxo-azetidin-2-(*R,S*)-yl]-5-methyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 21a.** Prepared by the general procedure from imine **13** (168 mg, 0.4 mmol), AgOAc (80 mg, 0.48 mmol), *N*-methylmaleimide (67 mg, 0.6 mmol) and DBU (73 mg, 0.45 mmol) in toluene (15 ml) for 3 d. Flash chromatography (1:10 to 1:3 v/v EtOAc-CH_2Cl_2) afforded the separated stereoisomers **21a** and **21b** (184 mg, 86% combined yield) in a 24:1 ratio. The major isomer crystallised from CH_2Cl_2 as colourless prisms, m.p. 210°C (decomp.). (**Found**: C, 60.9, H, 4.6, N, 10.5. **$C_{27}H_{24}O_8N_4$ requires**: C, 60.9, H, 4.5, N, 10.55%); δ 1.84 (t, *J* 12 Hz, 1H, NH), 2.91 (s, 3H, NMe), 3.13 and 3.30 (2 × t, *J* 7.5 Hz, 2 × 1H, 2 × COCH), 3.60 - 3.81 (m, 8H, 2 × NCH and 2 × OMe), 5.24 (dd, *J* 5.2 and 9.1

Hz, 1H, β-lactam ring NCH), 5.66 (d, *J* 5.2 Hz, 1H, β-lactam ring, CH), 6.92 (d, *J* 8.9 Hz, 2H, ArH) and 7.73 – 7.87 (m, 6H, ArH); **m/z (%):** 532 (M^+, 37), 382 (14), 345 (6), 322 (46), 294 (31), 286 (9), 211 (34), 179 (11), 175 (16), 160 (11), 149 (100), 134 (30), 104 (23), 94 (30), 77 (13) and 43 (8).

***endo*-Methyl 3-(*R*,*S*)-[*cis*-3-*t*-butyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*S*,*R*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 22a.** Prepared by the general procedure from imine **14** (220 mg, 0.635 mmol), AgOAc (130 mg, 0.78 mmol), *N*-methylmaleimide (108 mg, 0.975 mmol) and DBU (119 mg, 0.78 mmol) in cyclohexane (10 ml) for 15 h. Flash chromatography (1:4 v/v EtOAc-petroleum ether) afforded the **product 22a** (166 mg, 57%) as colourless needles from CH_2Cl_2/hexane, m.p. 186 - 188°C. (**Found**: C, 62.85, H, 7.05, N, 9.1. $C_{24}H_{31}O_6N_3$ **requires**: C, 63.0, H, 6.85, N, 9.2%); δ 1.17 (s, 9H, 3 × Me), 1.52 (s, 3H, Me), 2.63 (br d, 1H, NH), 2.85 (s, 3H, NMe), 3.00 (m, 2H, 2 × COCH), 3.38 (d, *J* 5.3 Hz, 1H, β-lactam ring CH), 3.54 (m, 1H, NCH), 3.75 and 3.76 (2 × s, 2 × 3H, 2 × OMe), 5.01 (dd, *J* 5.3 and 9.9 Hz, 1H, β-lactam ring NCH) and 6.85 and 7.48 (2 × d, *J* 8.9 Hz, 2 × 2H, ArH); **m/z (%):** 457 (M^+, 63), 300 (18), 233 (76), 225 (100), 204 (39), 189 (34), 165 (93), 149 (35), 134 (63) and 108 (35).

***endo*-Methyl 3-(*S*)-[*cis*-1-allyl-3-benzyloxy-4-oxo-azetidin-2-(*S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 23a and *endo*-Methyl 3-(*R*)-[*cis*-1-allyl-3-benzyloxy-4-oxo-azetidin-2-(*S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 23b.** AgOAc (150 mg, 0.9 mmol) was added at room temperature in the dark with stirring, to a solution of imine **15** (248 mg, 0.75 mmol) in toluene, followed *N*-methylmaleimide (125 mg, 1.125 mmol). Finally the triethylamine (128 μl, 0.9 mmol) was added and the resulting mixture was stirred for 15 h, then diluted with EtOAc, washed with a saturated solution of NH_4Cl and water. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to give the residue which was purified by column chromatography (Et_2O then 1:1 v/v Et_2O/EtOAc) to afford the separated stereoisomers **23a** and **23b** (175 mg, 83% combined yield) in a 1.5:1 ratio.

Major isomer **23a**: obtained as colourless needles from EtOAc/petroleum ether, m.p. 97 - 99°C, $[\alpha]_D$ + 153.2 (1.0, $CHCl_3$); (**Found**: C, 62.65, H, 6.35, N, 9.55. $C_{23}H_{27}O_6N_3$ **requires**: C, 62.55, H, 6.15, N, 9.5%); δ 1.43 (s, 3H, Me), 2.74 (s, 3H, NMe), 3.14 (d, *J* 7.8 Hz, 2H, COCH and NH), 3.33 (t, *J* 7.8 Hz, 1H, COCH), 3.73 (m, 4H, OMe and NCH), 4.03 (dd, *J* 5.1 and 16.0 Hz, 1H, NC$\underline{H}$H), 4.13 (dd, *J* 6.4 and 16.0 Hz, 1H, NCH$\underline{H}$), 4.20 (dd, *J* 5.1 and 6.7 Hz, 1H, β-lactam ring NCH), 4.62 (d, *J* 11.2 Hz, 1H, PhC$\underline{H}$H), 4.78 (d, *J* 5.1 Hz, 1H, β-lactam ring CH), 5.03 (d, *J* 11.2 Hz, 1H, PhCH$\underline{H}$), 5.21 (d, *J* 10.1 Hz, 1H, C=C$\underline{H}$H), 5.29 (d, *J* 17.2 Hz, 1H, C=CH$\underline{H}$), 5.90 (m, 1H, C$\underline{H}$=CH$_2$) and 7.31 (m, 5H, ArH); **m/z (%):** 441 (M^+, <1), 382 (20), 299 (18), 267 (16), 247 (14), 225 (78), 193 (6), 179 (14), 165 (55), 156 (51), 122 (6), 108 (22), 91 (100), 80 (11) and 65 (10).

Minor isomer **23b**: obtained as colourless prisms from EtOAc/petroleum ether, m.p. 64 - 66°C, $[\alpha]_D$ + 74.8 (1.0, $CHCl_3$); (**Found**: C, 62.5, H, 6.25, N, 9.45. $C_{23}H_{27}O_6N_3$ **requires**: C, 62.55, H, 6.15, N, 9.5%); δ 1.46 (s, 3H, Me), 2.48 (d, *J* 11.8 Hz, 1H, NH), 2.94 (s, 3H, NMe), 3.14 (d, *J* 7.2 Hz, 1H, COCH), 3.56 (m, 2H, COCH and NCH), 3.81 (m, 5H, OMe, β-lactam ring NCH and NC$\underline{H}$H), 4.10 (d, *J* 4.5 and 17.1 Hz, 1H, NCH$\underline{H}$), 4.84

(d, *J* 11.4 Hz, 1H, PhCHH), 4.96 (d, *J* 5.3 Hz, 1H, β-lactam ring CH), 4.99 (d, *J* 11.4 Hz, 1H, PhCHH), 5.20 (d, *J* 9.0 Hz, 1H, C=CHH), 5.23 (d, *J* 18.5 Hz, 1H, C=CHH), 5.72 (m, 1H, $CH=CH_2$) and 7.37 (m, 5H, ArH); **m/z (%):** 441 (M^+, <1), 382 (8), 299 (23), 267 (19), 247 (26), 225 (43), 179 (12), 165 (35), 156 (65), 108 (18), 91 (100), 80 (10), 65 (10) and 41 (18).

***endo*-Methyl 3-(*S*)-[*cis*-3-benzyloxy-1-(2,2-dimethyloxyethyl)-4-oxo-azetidin-2-(*S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 24a** and ***endo*-Methyl 3-(*R*)-[*cis*-3-benzyloxy-1-(2,2-dimethyloxyethyl)-4-oxo-azetidin-2-(*S*)-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 24b.** The same procedure was followed as for the preparation of **8c** starting from imine **16** (303 mg, 0.8 mmol), AgOAc (160 mg, 0.96 mmol), *N*-methylmaleimide (133 mg, 1.2 mmol) and triethylamine (133 μl, 0.96 mmol) in toluene for 7 h. Column chromatography (Et_2O then 1:1 v/v Et_2O/EtOAc) afforded the separated stereoisomers **24a** and **24b** (277 mg, 71% combined yield) in a 2:1 ratio.

Major isomer **24a**: obtained as colourless prisms from Et_2O/petroleum ether, m.p. 93 - 95°C, $[\alpha]_D$ + 119.6 (1.0, $CHCl_3$); (**Found**: C, 58.9, H, 6.6, N, 8.5. **$C_{24}H_{31}O_8N_3$ requires**: C, 58.9, H, 6.4, N, 8.6%); δ 1.45 (s, 3H, Me), 2.68 (s, 3H, NMe), 3.16 (d, *J* 7.8, Hz, 1H, COCH), 3.25 (br s, 1H, NH), 3.31 (dd, *J* 5.1 and 14.6 Hz, 1H, NCHH), 3.43 (m, 7H, MeOCOMe and COCH), 3.72 (s, 3H, OMe), 3.79 (m, 2H, NCH and NCHH), 4.27 (dd, *J* 5.0 and 6.1 Hz, 1H, β-lactam ring NCH), 4.60 (d, *J* 11.3 Hz, 1H, PhCHH), 4.64 (t, *J* 5.1 Hz, 1H, MeOCHOMe), 4.77 (d, *J* 5.0 Hz, 1H, β-lactam ring CH), 5.02 (d, *J* 11.3 Hz, 1H, PhCHH) and 7.32 (m, 5H, ArH); **m/z (%):** (Fab) 490 (M^++1, 75), 458 (19), 430 (6), 426 (14), 267 (5), 225 (17), 206 (11), 165 (14), 154 (9), 136 (10), 108 (9), 91 (100) and 75 (36).

Minor isomer **24b**: obtained as colourless syrup, $[\alpha]_D$ + 82.1 (1.0, $CHCl_3$); (**Found**: C, 58.85, H, 6.5, N, 8.75. **$C_{24}H_{31}O_8N_3$ requires**: C, 58.9, H, 6.35, N, 8.6%); δ 1.47 (s, 3H, Me), 2.96 (s, 3H, NMe), 3.14 (br d, 1H, NH), 3.36 - 3.61(m, 11H, MeOCOMe, NCH_2, NCH and COCHCHCO), 3.81 (s, 3H, OMe), 3.88 (dd, *J* 4.9 and 9.4 Hz, 1H β-lactam ring NCH), 4.48 (t, *J* 4.9 Hz, 1H, MeOCHOMe), 4.84 (d, *J* 11.3 Hz, 1H, PhCHH), 4.96 (d, *J* 4.9 Hz, 1H, β-lactam ring CH), 5.98 (d, *J* 11.3 Hz, 1H, PhCHH) and 7.30 - 7.42 (m, 5H, ArH); **m/z (%):** (Fab) 490 (M^++1, 55), 458 (61), 426 (50), 398 (9), 357 (6), 307 (7), 267 (7), 225 (26), 206 (21), 176 (15), 165 (20), 154 (34), 136 (28), 91 (100) and 75 (42).

***endo*-Dimethyl 5-(*R,S*)-[*cis*-3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*R,S*)-yl]-2-methyl-pyrrolidine-2,4-carboxylate 26b** and ***endo*-Dimethyl 5-(*S,R*)-[3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*R,S*)-yl]-2-methyl-pyrrolidine-2,4-carboxylate 26a.** Prepared by the general procedure from imine **9** (154 mg, 0.48 mmol), AgOAc (100 mg, 0.6 mmol), methyl acrylate (65 mg, 0.75 mmol) and DBU (91 mg, 0.6 mmol) in toluene (10 ml) for 15 h. Flash chromatography (1:1 v/v EtOAc- petroleum ether) afforded the separated stereoisomers **26b** and **26a** (149 mg, 76% combined yield) in a 2:1 ratio.

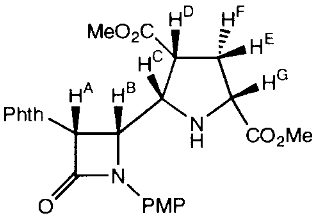
Major isomer **26b**: obtained as colourless cubes from CH_2Cl_2/ hexane, m.p. 132 - 135°C. (**Found**: C, 62.15, H, 7.0, N, 6.85. **$C_{21}H_{28}O_6N_2$ requires**: C, 62.35, H, 6.95, N, 6.95%); δ 1.23 (t, *J* 7.4 Hz, 3H, Me), 1.32 (s, 3H, Me), 1.90 (m, 3H, MeC$\underline{H}_2$ and CH^E), 2.10 (br s, 1H, NH), 2.78 (dd, *J* 2.8 and 13.7 Hz, 1H, CH^F), 3.16 - 3.22 (m, 2H, CH^D and β-lactam ring CH^A), 3.71 - 3.79 (m, 10H, 3 × OMe and NCH^C), 4.13 (dd, *J* 5.7 and 9.9 Hz, 1H, β-lactam ring NCH^B) and 6.87 and 7.51 (2 × d, *J* 8.9 Hz, 2 × 2H, ArH); **δ (^{13}C):** 176.1 (CO), 173.0 (CO), 168.6 (CO), 156.5 (ArC), 130.9 (ArC), 121.2 (2 × ArC), 114.0 (2 × ArC), 65.2 ($\underline{C}CO_2Me$), 62.2, 58.0, 55.4, 53.2, 52.3, 51.8, 45.8, 40.1 (CH$_2$), 27.1, 19.2 (CH$_2$) and 12.6; **m/z (%):** 404 (M$^+$, 20), 345 (7), 275 (12), 205 (33), 200 (100), 140 (72), 108 (28) and 82 (21).

Minor isomer 26a: obtained as colourless syrup. (**Found**: C, 62.45, H, 7.1, N, 6.75. **$C_{21}H_{28}O_6N_2$ requires**: C, 62.35, H, 6.95, N, 6.95%); δ 1.20 (t, *J* 7.4 Hz, 3H, Me), 1.39 (s, 3H, Me), 1.96 (m, 3H, MeC$\underline{H}_2$ and CH^E), 2.52 (dd, *J* 1.4 and 14.0 Hz, 1H, CH^F), 2.66 - 2.70 (m, 1H, CH^D), 2.90 (br s, 1H, NH), 3.27 - 3.36 (m, 2H, CH^C and β-lactam ring CH^A), 3.52, 3.72 and 3.78 (3 × s, 3 × 3H, 3 × OMe), 4.56 (dd, *J* 5.7 and 8.8 Hz, 1H, β-lactam ring NCH^B) and 6.85 and 7.15 (2 × d, *J* 8.8 Hz, 2 × 2H, ArH); **m/z (%):** 404 (M$^+$, 69), 345 (10), 275 (10), 222 (15), 205 (26), 200 (100), 149 (54), 140 (50), 108 (50) and 43 (55).

***endo*-Dimethyl 5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phthalimidyl-4-oxo-azetidin-2-(*S*,*R*)-yl]-2-methyl-pyrrolidine-2,4-carboxylate 27a.** Prepared by the general procedure from imine **11** (176 mg, 0.4 mmol), AgOAc (80 mg, 0.48 mmol), methyl acrylate (52 mg, 0.6 mmol) and Et$_3$N (50 mg, 0.48 mmol) in toluene (15 ml) at rt for 24 h. Flash chromatography (1:1 v/v EtOAc-petroleum ether) afforded a mixture of the stereoisomers **27a** and **27b** (182 mg, 87% combined yield) in a 9:1 ratio. The major isomer **27a** crystallised from CH$_2$Cl$_2$/ petroleum ether as colourless rhombs, m.p. 186 - 188°C. (**Found**: C, 62.2, H, 5.0, N, 7.9. **$C_{27}H_{27}O_8N_3$ requires**: C, 62.2, H, 5.2, N, 8.1%); δ 0.75 (s, 3H, Me), 1.74 (dd, *J* 7.4 and 14.1 Hz, 1H, C$\underline{H}$H), 2.35 (d, *J* 14.1 Hz, 1H, CH$\underline{H}$), 2.65 (d, *J* 4.5 and 7.4 Hz, 1H, COCH), 2.74 (br s, 1H, NH), 3.39 (dd, *J* 4.5 and 9.9 Hz, 1H, NCH), 3.61, 3.63 and 3.81 (3 × s, 3 × 3H, 3 × OMe), 4.81 (dd, *J* 5.2 and 9.9 Hz, 1H, β-lactam ring NCH), 5.64 (d, *J* 5.2 Hz, 1H, β-lactam ring CH), 6.89 and 7.35 (2 × d, *J* 8.7 Hz, 2 × 2H, ArH) and 7.43 and 7.86 (2 × m, 2 × 2H, ArH); **m/z (%)**: 521 (M$^+$, 8), 462 (8), 371 (7), 322 (47), 294 (13), 275 (8), 200 (100), 189 (7), 160 (8), 149 (29), 140 (42), 134 (18), 108 (14), 104 (15) and 82 (13).

***endo*-Dimethyl 5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phthalimidyl-4-oxo-azetidin-2-(*S*,*R*)-yl]-pyrrolidine-2,4-carboxylate 28a** and ***endo*-Dimethyl 5-(*R*,*S*)-[*cis*-1-(4-methoxyphenyl)-3-phthalimidyl-4-oxo-azetidin-2-(*S*,*R*)-yl]-pyrrolidine-2,4-carboxylate 28.** Prepared by the general procedure from imine **13** (168 mg, 0.4 mmol), AgOAc (80 mg, 0.48 mmol), methyl acrylate (52 mg, 0.6 mmol) and DBU (73 mg, 0.48 mmol) in toluene (15 ml) for 15 h. Flash chromatography (1:1 to 2:1 v/v EtOAc- petroleum ether) afforded the separated stereoisomers **28a** and **28b** (148 mg, 73% combined yield) in a 1:1 ratio.

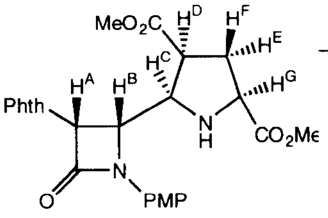
Isomer 28a: obtained as colourless prisms from CH$_2$Cl$_2$/petroleum ether, m.p. 186 - 187°C. (**Found**: C, 61.35, H, 5.05, N, 8.05. **$C_{26}H_{25}O_8N_3$ requires**: C, 61.55, H, 4.95, N, 8.3%); δ 2.03 (ddd, *J* 1.5, 4.5 and 13.9 Hz, 1H, CH^F), 2.25 (ddd, *J* 8.2, 10.4 and 13.9 Hz, 1H, CH^E), 2.35 (br, 1H, NH), 2.62 (ddd, *J* 1.5, 4.8 and 8.2 Hz, 1H, CH^D), 3.36 (dd, *J* 4.8 and 9.8 Hz, 1H, CH^C), 3.41 (dd, *J* 4.5 and 10.4 Hz, 1H, CH^G), 3.61, 3.63 and 3.82 (3 × s, 3 × 3H, 3 × OMe), 4.82 (dd, *J* 5.2 and 9.8 Hz, 1H, β-lactam ring NCH^B), 5.65 (d, *J* 5.2 Hz, 1H, β-lactam ring CH^A), 6.90 and 7.31 (2 × d, *J* 9.0 Hz, 2 × 2H, ArH) and 7.34 - 7.79 and 7.86 - 7.89 (2 × m, 2 × 2H, ArH); **m/z (%)**: 507 (M^+, 19), 448 (7), 357 (8), 322 (52), 294 (24), 186 (100), 175 (17), 160 (18), 149 (62), 134 (28), 126 (44), 104 (31), 92 (11), 82 (8), 76 (19), 68 (22) and 59 (17).



NOE ($CDCl_3$, 500 MHz)

proton irradiated	Enhancement (%) H^C	H^D	H^E	H^F	H^G
H^C		7.3	1.8		
H^D	5.9		1.8	1.2	
H^E		7.7		27.0	4.5
H^F		1.8	14.0		
H^G		1.7	2.5		

Isomer **28b**: obtained as colourless prisms from CH_2Cl_2/petroleum ether, m.p. 213 - 215°C. (**Found**: C, 61.65, H, 5.1, N, 8.15. $C_{26}H_{25}O_8N_3$ **requires**: C, 61.55, H, 4.95, N, 8.3%); δ (C_6D_6) 1.61 (dt, *J* 9.5 and 13.2 Hz, 1H, CH^E), 2.18 (ddd, *J* 3.7, 6.7 and 13.2 Hz, 1H, CH^F), 2.48 (ddd, *J* 3.7, 7.2 and 9.5 Hz, 1H, CH^D), 3.15 (dd, *J* 6.7 and 9.5 Hz, 1H, CH^G), 3.36, 3.38 and 3.55 (3 × s, 3 × 3H, 3× OMe), 4.02 (dd, *J* 7.2 and 9.5 Hz, 1H, CH^C), 4.42 (dd, *J* 5.7 and 9.5 Hz, 1H, β-lactam ring NCH^B), 5.30 (d, *J* 5.7 Hz, 1H, β-lactam ring CH^A), 6.90 - 6.96 (m, 4H, ArH), 7.48 - 7.50 (m, 2H, ArH) and 8.11 (d, *J* 9.1 Hz, 2H, ArH); **m/z (%)**: 507 (M^+, 43), 448 (10), 357 (5), 322 (35), 294 (28), 186 (100), 175 (16), 160 (18), 149 (54), 134 (25), 126 (45), 104 (25), 94 (9), 77 (15), 68 (20) and 59 (14).



NOE (C_6D_6, 500 MHz)

proton irradiated	Enhancement (%) H^C	H^D	H^E	H^F	H^G
H^C		7.4			2.7
H^D	9.5		2.3		
H^E		2.5		9.3	3.6
H^F			12.9		
H^G	3.6		4.6		

Single crystal X-ray diffraction analysis of ***17b, 19a, 19b, 20a, 20b*** *and* ***26b*** - Crystallographic data for **17b**, **19a**, **19b**, **20a** and **20b** were measured on a Stoe STADI4 4-circle diffractometer using ω-θ scans whilst data for

26b were collected on a Nonius KappaCCD area-detector diffractometer with the using 1° ϕ- and omega-slices. All structures were solved by direct methods using SHELXS-86[12] and were refined by full-matrix least-squares (based on F^2) using SHELXL-97.[13] The weighting scheme used in all refinements was $w = [\sigma^2(F_o^2) + (xP)^2 + yP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. In all cases all non-hydrogen atoms were refined with anisotropic displacement parameters (apart from those of solvent atoms in **17b** and **19a** which in both cases were disordered and refined with isotropic displacement parameters) whilst hydrogen atoms were constrained to predicted positions. All refinements included an isotropic extinction parameter, x, so that $F_c' = kF_c[1+0.001*x*F_c^2*\lambda^3]^{-1/4}$ where k is the overall scale factor. The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\Sigma[w(F_o-F_c^2)^2] / \Sigma[wF_o^4])^{1/2}$ and $R_1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$.

Crystal data for 17b - $C_{22}H_{27}N_3O_6$, 0.58 x 0.33 x 0.28 mm, M = 429.52, orthorhombic, space group *Pcca*, a = 39.460(2), b = 25.9229(15), c = 17.4205(10) Å, U = 17820(2) Å^3, Z = 32, D_c = 1.30 Mg m^{-3}, μ = 0.79 mm^{-1}, $F(000)$ = 7392, T = 160K.

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 < 2θ < 130.0°, 15353 Data collected 13828 of which were unique, R_{int} = 0.0263, R_{sig} = 0.0358. There were 10705 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 1154, isotropic extinction parameter, x = 0.000192(16), goodness of fit, s = 1.079; weighting parameters x, y = 0.0896, 29.4867; wR_2 = 0.1944, R_1 = 0.0649.

Crystal data for 19a - $C_{29}H_{28}Cl_2N_4O_8$, 0.55 x 0.49 x 0.44 mm, M = 631.45, Triclinic, space group $P\bar{1}$, a = 9.9314(4), b = 10.2446(6), c = 15.3337(9) Å, α = 99.452(2)°, β = 106.791(4)°, γ = 94.059(4)°, U = 1461.72(13) Å^3, Z = 2, D_C = 1.44 Mg m^{-3}, μ = 0.28 mm^{-1}, $F(000)$ = 656, T = 190 K.

Data collection - Graphite monochromated Mo-$K\alpha$ radiation, λ = 0.71074 Å. The detector was positioned with at 2θ = 0° and a 180° rotation of 1.0° ϕ-slices were measured at χ=0°. 'Cusp' data was measured at χ = 90° and comprised 1° omega-slices over 55°; 5.12 < 2θ < 60.88°. 13558 Data measured, 6568 unique, R_{int} = 0.0469, R_{sig} = 0.0827, 3684 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 423, isotropic extinction parameter, x = 0.070(7), goodness of fit, s = 0.922; weighting parameters x, y = 0.1032, 0.0000; wR_2 = 0.1720, R_1 = 0.0576.

Crystal data for 19b - $C_{28}H_{26}N_4O_8$, 0.48 x 0.46 x 0.19 mm, M = 546.53, Monoclinic, space group *C2/c*, a = 20.3146(5), b = 19.6961(9), c = 12.9613(2) Å, β = 98.144(2)°, U = 5133.8(3) Å^3, Z = 8, D_C = 1.41 Mg m^{-3}, μ = 0.88 mm^{-1}, $F(000)$ = 2288, T = 298 K.

Data collection - as for **17b** above with, 4532 Data collected 3963 of which were unique, R_{int} =0.0078, R_{sig} = 0.0107. There were 3516 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 366, isotropic extinction parameter, x = 0.00050(5), goodness of fit, s = 1.053; weighting parameters x, y = 0.0601, 4.6669; wR_2 = 0.1243, R_1 = 0.0450.

Crystal data for ***20a*** - $C_{26}H_{27}N_3O_7$, 0.65 x 0.50 x 0.40 mm, M = 493.51, triclinic, space group $P\bar{1}$, a = 6.8429(9), b = 13.8592(13), c = 14.2590(18) Å, α = 70.330(8)°, β = 79.960(16)°, γ = 75.041(10)°, U = 1224.5(2) $Å^3$, Z = 2, D_C = 1.34 Mg m^{-3}, μ = 0.82 mm^{-1}, $F(000)$ = 520, T = 293 K.

Data collection - as for **17b** above with, 3884 Data collected 3884 of which were unique, R_{sig} = 0.0130. There were 3465 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 329, isotropic extinction parameter, x = 0.0002(4), goodness of fit, s = 1.114; weighting parameters x, y = 0.0802, 0.5472; wR_2 = 0.1636, R_1 = 0.0554.

Crystal data for ***20b*** - $C_{26}H_{27}N_3O_7$, 0.65 x 0.50 x 0.40 mm, M = 493.51, orthorhombic, space group $P2_12_12_1$, a = 6.9761(3), b = 10.8708(4), c = 31.9441(9) Å, U = 2422.51(14) $Å^3$, Z = 4, D_C = 1.35 Mg m^{-3}, μ = 0.83 mm^{-1}, $F(000)$ = 1040, T = 293 K.

Data collection - as for **17b** above with, 3786 Data collected 3786 of which were unique, R_{sig} = 0.0082. There were 3734 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 329, isotropic extinction parameter, x = 0.0157(11), goodness of fit, s = 1.039; weighting parameters x, y = 0.1147, 0.6671; wR_2 = 0.1498, R_1 = 0.0528.

Crystal data for ***26b*** - $C_{21}H_{28}N_2O_6$, 0.45 x 0.35 x 0.25 mm, M = 404.45, Monoclinic, space group $P2_1/c$, a = 9.0597(6), b = 14.8441(9), c = 15.3440(7) Å, β = 97.583(5)°, U = 2045.5(2) $Å^3$, Z = 4, D_C = 1.31 Mg m^{-3}, μ = 0.80 mm^{-1}, $F(000)$ = 864, T = 160 K.

Data collection - as for **17b** above with, 7426 Data collected 3303 of which were unique, R_{int} = 0.0209, R_{sig} = 0.0198. There were 3182 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 366, isotropic extinction parameter, x = 0.0247(8), goodness of fit, s = 1.124; weighting parameters x, y = 0.0470, 0.7004; wR_2 = 0.0990, R_1 = 0.0389.

Supplementary data-sets for all structures, which include 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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