Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 335–340

TETRAHEDRON

Stereoselective synthesis of 5-(4¹-azetidinyl)-proline esters via 1,3-dipolar cycloaddition reaction of *N*-metalated azomethine ylides

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Received 19 September 2002; revised 28 October 2002; accepted 21 November 2002

Abstract—The conformationally locked *s-trans* enone functionality present in the (*E*)-3-arylidene-4-chromanones undergo regioselective 1,3-dipolar cycloaddition reaction with *N*-metalated azomethine ylides derived from β-lactam imines of glycine methyl ester in the presence of silver acetate to give spiropyrrolidines in moderate to good yield. The regio and stereochemistry of the cycloadducts have been established by single crystal X-ray structure and spectroscopic techniques.

1. Introduction

The 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins offers a convenient one-step route for the construction of a variety of complex pyrrolidine derivatives with stereogenic centers, because the reaction is usually concerted.[1–3] The ease of generation of 1,3-dipoles, the rapid accumulation of polyfunctionality in a relatively small molecular framework, the high stereo control of the cycloaddition and the predictability of its regiochemistry have contributed to the popularity of the reaction in organic synthesis.[4] This method is widely used in the synthesis of natural products such as alkaloids and pharmacologically active compounds.[5] Among the different versions of this reaction, the interaction between *N*-metalated azomethine ylides and π-deficient alkenes is especially interesting. Since in general, it allows the synthesis of pyrrolidines with good chemical yield.[6] It represents one of the most efficient and mild routes for the synthesis of polyfunctional pyrrolidine ring systems.[7] 4-Formyl-β-lactams are versatile building blocks that can serve not only for the synthesis of β-lactam antibiotics, including monobactams, carbapenems, carbacephems and isooxocephems[8] but also for the preparation of other useful non-β-lactam synthetic targets such as β-substituted aspartic acid derivatives, hydroxybutanoic acids and isoserines.[9] 4-Chromanones are versatile intermediates for the synthesis of many natural products such as brazilin, hematoxylin, ripariochromene, clausenin, calonilide (A) and nophyllum (B).[10,11] Chromanone heterocycles have also drawn much attention due to their important pharmacological properties.[10] Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.[12–14] As a part of our ongoing research program in the area of cycloaddition reactions[15] and with a view to synthesizing a rare class of spiroheterocyclic derivatives,[16–18] we herein report the facile synthesis of 4-(5¹-pyrrolidinyl)-β-lactams through regioselective cycloaddition reaction of azomethine ylides derived from β-lactam imines with conformationally locked *s-trans* enone functionality present in the (*E*)-3-arylidene-4-chromanones as dipolarophiles.

2. Results and discussion

Azomethine ylides can be generated by a number of methods of which the thermal tautomerization route offers a convenient method for the synthesis of substituted pyrrolidines.[19] In this method, an aldehyde and a primary amino acid ester are condensed to form imines which undergo thermal 1,2-prototropic shift to generate azomethine ylides. This type of reaction has been intensively investigated by the groups of Grigg,[20] Kanemasa[21] and recently by others.[22] The dipoles thermally generated from the imines of glycine ester undergo stereoselective cycloaddition to highly activated cyclic dipolarophiles such as maleimides and maleic anhydride to give *endo* cycloadducts of the *E*,*E*-ylides.[23] However, their cycloadditions to acyclic olefin dipolarophiles such as maleates and fumarates are no longer stereoselective.[24] Although the cycloaddition to acrylates proceed in a regioselective manner, the *endo*

Keywords: β-lactams; azomethine ylides; cycloadditions; spirocompounds.
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0040–4020/03/$ - see front matter
PII: S0040-4020(02)01521-1

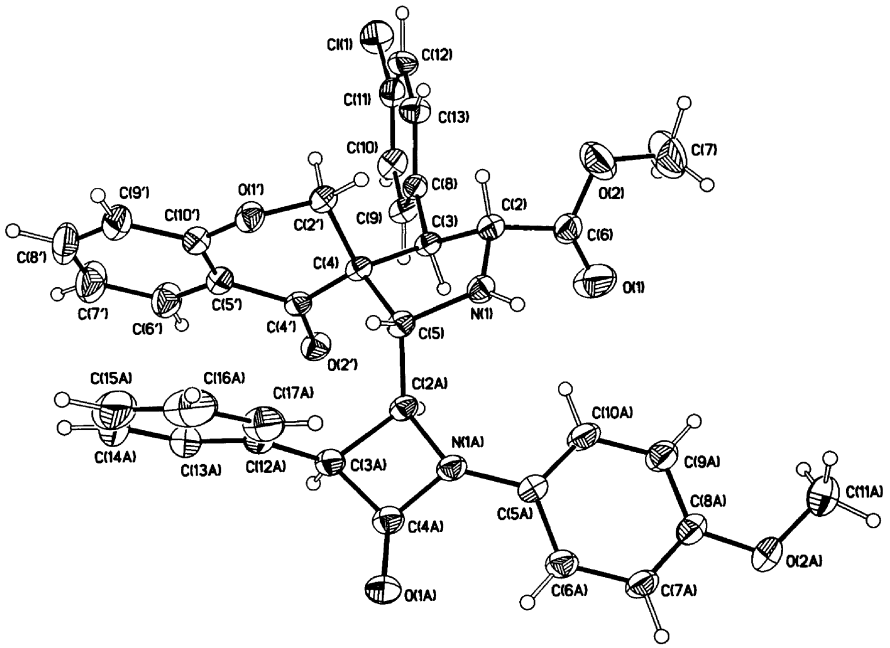


Figure 1. ORTEP diagram of **3b**.

selectivity and/or the *E*,*E*-specificity with respect to dipoles are poor. Now this problem is overcome by the application of a wide range of metal salt/tertiary amine combinations which proved to be effective for increasing the rate of the cycloaddition of aryl imines to less reactive dipolarophiles at room temperature with excellent regio and stereocontrol. We have chosen (*E*)-3-arylidene-4-chromanones as dipolarophiles and *N*-metalated azomethine ylides derived from β-lactam imines[25] as 1,3-dipole for cycloaddition reactions and herein we report the results of our investigation. The required dipolarophile (*E*)-3-arylidene-4-chromanones (**1a**–**e**) were prepared by the acid-catalyzed reaction of 4-chromanone with various benzaldehydes and the products were assigned *E*-configuration on the basis of their NMR spectra, in accordance with the literature.[26] *cis*-4-Formyl-β-lactam were synthesized by the Staudinger reaction as reported in the literature.[27]

Treatment of β-lactam aldehydes with glycine methyl ester in the presence of anhyd. $MgSO_4$ in dry dichloromethane at room temperature afforded the imines (**2a**,**b**) almost in quantitative yield as evidenced by one proton doublet at 7.78 ppm (J=7.8 Hz) (CH=N) and a two proton singlet at 4.22 ppm (N–CH_2) in the ^{1}H NMR spectra. Treating these crude β-lactam imines with (*E*)-3-arylidene-4-chromanones in the presence of silver acetate and triethylamine at room temperature in toluene afforded a series of novel spiropyrrolidine derivatives (**3a**–**j**) in moderate to good yield. It

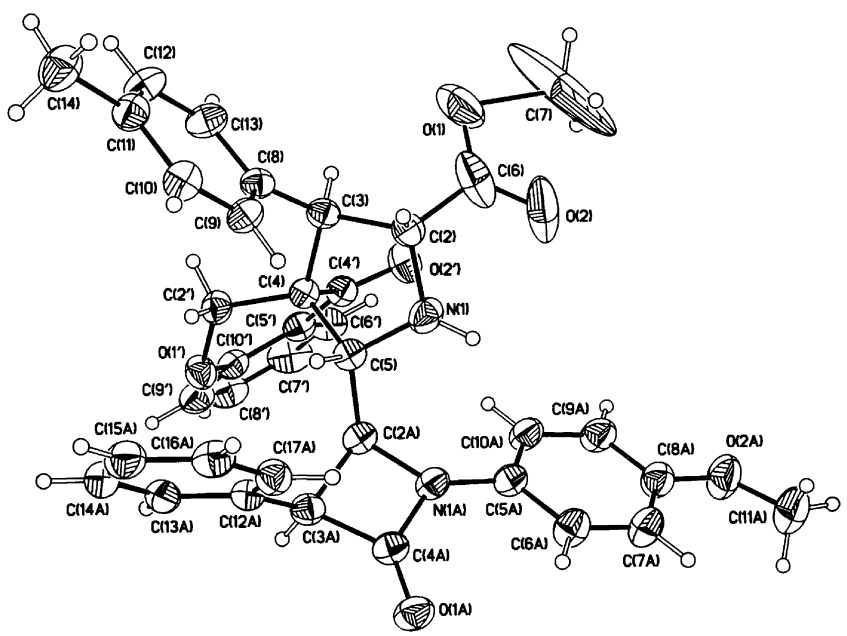
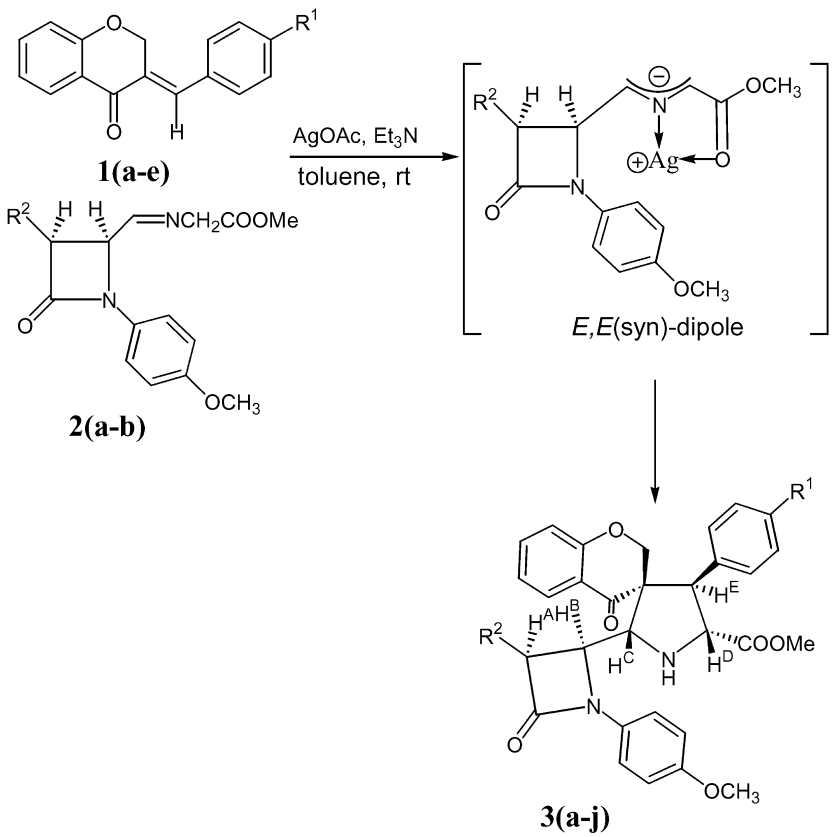


Figure 2. ORTEP diagram of **3c**.



Scheme 1.

was found that, to the limit of ^{1}H NMR detection of the crude reaction mixture, each cycloadduct was obtained as a single diastereomer. Importantly, the β-lactam ring was unaffected by this process. When the reaction was carried out in DBU as base instead of Et_3N, only low yield of cycloadduct was obtained, whereas in the presence of pyridine no characteristic product was obtained. When the same reaction was carried out in acetonitrile as solvent, it afforded the cycloadduct in poor yield.

The cycloaddition proceeds in a regio and stereocontrolled fashion. The regio and stereochemical outcome of the cycloadduct was determined by single crystal X-ray structure of the cycloadducts (**3b**) and (**3c**).[28] The X-ray structure of the cycloadducts (**3b**) (Fig. 1) and (**3c**) (Fig. 2) shows that, the cycloaddition proceeded regio and stereospecifically in toluene at room temperature to afford *syn*-*endo* cycloadduct via *E*,*E*(*syn*-dipole)[3] (Scheme 1, Table 1). The stereochemistry of the products (**3a**–**j**) is based on the usual selectivity and *endo* transition state observed for metallo azomethine ylide cycloadditions. The structure and regiochemistry of the cycloadduct have also been confirmed by spectroscopic data. Thus the keto carbonyl of (**3a**) exhibited a peak at 1672 cm^{-1} in the IR spectrum showing an increase of 8 cm^{-1} from the normal value observed for benzylidine chromanone indicating loss of conjugation. It also exhibited a peak at 1738 cm^{-1} due to the ester carbonyl and at 3399 cm^{-1} due to –NH of the pyrrolidine ring. ^{13}C NMR of the products showed peaks for the nine sp^3 carbons, three carbonyl carbons and aromatic carbons that confirmed the proposed structure. ^{1}H NMR spectra of the cycloadducts add conclusive support for the proposed structure. Moreover, the presence of molecular ion peak at 588 (M^+) in the mass spectrum of (**3a**) confirms the formation of cycloadducts. Identical results were obtained with other derivatives of benzylidene chromanones.

Table 1. 1,3-Dipolar cycloaddition reaction between benzylidenechromanone (**1a**–**e**) and *N*-metalated azomethine ylides derived from β-lactam imines (**2a**–**b**) in the presence of AgOAc

Entry	Product	R^1	R^2	Time (h)	Yield (%)
1	**3a**	H	Ph	40	69
2	**3b**	Cl	Ph	48	75
3	**3c**	CH_3	Ph	54	71
4	**3d**	OCH_3	Ph	72	85
5	**3e**	NO_2	Ph	56	60
6	**3f**	H	PhO	70	62
7	**3g**	Cl	PhO	54	75
8	**3h**	CH_3	PhO	64	78
9	**3i**	OCH_3	PhO	48	80
10	**3j**	NO_2	PhO	50	65

In conclusion, an efficient synthesis of a series of novel spiropyrrolidine derivatives containing a β-lactam ring has been achieved via the [3+2] cycloaddition reaction between the (*E*)-3-arylidene-4-chromanones with *N*-metalated azomethine ylides derived from β-lactam imines.

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded

on SHIMADZU FT-IR 8300 instrument. Mass spectra were recorded on JEOL DX 303 HF spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on JEOL 400 and 100 MHz, respectively. Elemental analyses were carried out on Perkin–Elmer 240 B instrument. The starting materials β-lactam imines were prepared according to literature procedures and it was used without further purification.[25]

3.2. General procedure for the cycloaddition reaction between 3-arylidene-4-chromanones (1a–e) and the β-lactam imines (2a,b) in the presence of silveracetate as catalyst

To a solution of β-lactam imines (0.5 mmol) in toluene (6 mL) were sequentially added silver acetate (0.1 g, 0.6 mmol), the dipolarophile (0.6 mmol) and triethylamine (0.08 mL, 0.6 mmol) and the reaction mixture was stirred at ambient temperature in the dark for the time as shown in the Table 1. After completion of the reaction, the reaction mixture was diluted with chloroform (10 mL) and filtered through a celite pad, washed with saturated aq. solution of NH_4Cl (10 mL) and then extracted with chloroform (2×10 mL). The combined organic layers were washed with brine (20 mL), dried (anhyd. $MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (100–200 mesh) with petroleum ether/ethyl acetate (4:1) to afford the cycloadducts.

3.2.1. Spiro[2-carbomethoxy-3-phenyl-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenyl-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3a). Yield 0.2 g (69%), colorless solid, mp 181–182°C (found: C, 73.59; H, 5.25; N, 4.55. $C_{36}H_{32}N_2O_6$ requires C, 73.45; H, 5.48, N, 4.76%); IR (KBr): 1672, 1738, 3399 cm^{-1}; ^{1}H NMR: 2.73 (bs, 1H), 3.08 (d, *J*=12.2 Hz, 1H, H^D), 3.58–3.63 (m, 5H, OCH_3, OC*H*H, CH^C), 3.80 (s, 3H), 3.97–4.04 (m, 2H, OCH*H*, H^E), 4.44 (d, *J*=5.6 Hz, 1H, β-lactam ring CH^A), 4.72 (dd, *J*=7.9, 5.6 Hz, 1H, β-lactam ring, CH^B), 6.69–7.95 (m, Ar-H, 18H); ^{13}C NMR: 52.15, 54.82, 55.38, 56.37, 57.99, 58.31, 64.19, 64.52, 70.50, 114.06, 117.69, 121.18, 121.88, 121.94, 127.26, 127.56, 128.03, 128.27, 128.39, 128.43, 130.44, 131.02, 131.90, 135.94, 136.35, 156.75, 160.89, 166.46, 171.94, 194.24. CIMS *m*/*z*: 588 (M$^+$).

3.2.2. Spiro[2-carbomethoxy-3-(4-chlorophenyl)-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenyl-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3b). Yield 0.23 g (75%), colorless solid, mp 252–253°C (found: C, 69.56; H, 4.88; N, 4.35. $C_{36}H_{31}ClN_2O_6$ requires C, 69.39; H, 5.01, N, 4.50%); IR (KBr): 1679, 1743, 3363 cm^{-1}; ^{1}H NMR: 2.73 (bs, 1H), 3.14 (d, *J*=12.2 Hz, 1H, H^D), 3.64–3.70 (m, 5H, OCH_3, OC*H*H, CH^C), 3.87 (s, 3H), 4.01–4.11 (m, 2H, OCH*H*, H^E), 4.51 (d, *J*=5.8 Hz, 1H, β-lactam ring CH^A), 4.86 (dd, *J*=8.3, 5.8 Hz, 1H, β-lactam ring, CH^B), 6.72–7.99 (m, Ar-H, 17H); ^{13}C NMR: 52.21, 54.17, 55.40, 56.79, 57.92, 58.14, 63.70, 64.28, 70.17, 114.02, 117.71, 121.37, 121.79, 122.00, 127.24, 128.06, 128.39, 128.45, 129.71, 130.47, 130.96, 131.79, 133.46, 134.17, 136.44, 156.78, 160.71, 166.68, 171.68, 193.89. CIMS *m*/*z*: 622 (M$^+$).

3.2.3. Spiro[2-carbomethoxy-3-(4-methylphenyl)-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenyl-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3c). Yield 0.21 g (71%), colorless solid, mp 228–229°C (found: C, 73.54; H, 5.84; N, 4.48. $C_{37}H_{34}N_2O_6$ requires C, 73.74; H, 5.69, N, 4.65%); IR (KBr): 1672, 1739, 3396 cm^{-1}; ^{1}H NMR: 2.23 (s, 3H), 2.74 (bs, 1H), 3.15 (d, *J*=12.7 Hz, 1H, H^D), 3.58–3.66 (m, 5H, OCH_3, OC*H*H, CH^C), 3.80 (s, 3H), 3.94–3.98 (m, 2H, OCH*H*, H^E), 4.43 (d, *J*=5.6 Hz, 1H, β-lactam ring CH^A), 4.68 (dd, *J*=8.1, 5.6 Hz, 1H, β-lactam ring, CH^B), 6.71–7.94 (m, Ar-H, 17H); ^{13}C NMR: 20.89, 52.13, 54.39, 55.40, 56.29, 58.07, 58.36, 64.40, 64.49, 70.68, 114.08, 117.74, 121.21, 121.94, 127.28, 128.00, 128.29, 128.44, 128.62, 129.01, 130.44, 131.05, 131.92, 132.92, 136.32, 137.29, 156.76, 161.00, 166.49, 172.00, 194.33. CIMS *m*/*z*: 602 (M$^+$).

3.2.4. Spiro[2-carbomethoxy-3-(4-methoxyphenyl)-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenyl-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3d). Yield 0.26 g (85%), colorless solid, mp 238–239°C (found: C, 71.99; H, 5.35; N, 4.64. $C_{37}H_{34}N_2O_7$ requires C, 71.83; H, 5.54, N, 4.53%); IR (KBr): 1681, 1741, 3399 cm^{-1}; ^{1}H NMR: 2.65 (bs, 1H), 3.14 (d, *J*=13.2 Hz, 1H, H^D), 3.59–3.64 (m, 5H, OCH_3, OC*H*H, CH^C), 3.74 (s, 3H), 3.79 (s, 3H) 3.95–4.10 (m, 2H, OCH*H*, H^E), 4.41 (d, *J*=5.3 Hz, 1H, β-lactam ring CH^A), 4.71 (dd, *J*=9.1, 5.3 Hz, 1H, β-lactam ring CH^B), 6.71–7.94 (m, Ar-H, 17H); ^{13}C NMR: 52.12, 52.34, 54.43, 55.39, 56.35, 57.92, 58.22, 63.92, 64.58, 70.68, 113.29, 114.06, 117.78, 121.28, 121.98, 122.21, 127.24, 128.08, 128.29, 128.46, 129.08, 130.44, 131.88, 132.89, 135.88, 136.48, 156.76, 160.94, 166.68, 172.07, 194.22. CIMS *m*/*z*: 618 (M$^+$).

3.2.5. Spiro[2-carbomethoxy-3-(4-nitrophenyl-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenyl-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3e). Yield 0.19 g (60%), colorless solid, mp 185–186°C (found: C, 68.45; H, 4.71; N, 6.47. $C_{36}H_{31}N_3O_8$ requires C, 68.24; H, 4.93, N, 6.63%); IR (KBr): 1674, 1745, 3363 cm^{-1}; ^{1}H NMR: 2.72 (bs, 1H), 3.12 (d, *J*=11.2 Hz, 1H, H^D), 3.59 (s, 3H), 3.59–3.67 (m, 5H, OCH_3, OC*H*H, CH^C), 3.94–4.15 (m, 2H, OCH*H*, H^E), 4.42 (d, *J*=5.7 Hz, 1H, β-lactam ring CH^A), 4.70 (dd, *J*=9.3, 5.7 Hz, 1H, β-lactam ring CH^B), 6.65–8.12 (m, Ar-H, 17H); ^{13}C NMR: 52.18, 54.62, 55.45, 56.42, 57.92, 58.22, 64.27, 64.39, 70.56, 114.48, 117.85, 121.21, 121.98, 127.45, 128.03, 128.29, 128.64, 129.04, 129.72, 130.62, 131.33, 135.96, 136.88, 143.85, 147.38, 156.42, 160.95, 166.25, 172.34, 194.28. CIMS *m*/*z*: 633 (M$^+$).

3.2.6. Spiro[2-carbomethoxy-3-phenyl-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenoxy-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3f). Yield 0.19 g (62%), colorless solid, mp 231–232°C (found: C, 71.42; H, 5.45; N, 4.74. $C_{36}H_{32}N_2O_7$ requires C, 71.51; H, 5.33, N, 4.63%); IR (KBr): 1684, 1745, 3345 cm^{-1}; ^{1}H NMR: 2.61 (bs, 1H), 3.63 (s, 3H), 3.79 (s, 3H), 4.19 (d, *J*=10.7 Hz, 1H, H^D), 4.26 (d, *J*=9.4 Hz, 1H, H^C), 4.32 (d, *J*=9.7 Hz, 1H, OC*H*H), 4.39–4.43 (m, 2H, OCH*H*, H^E), 5.0 (dd, *J*=9.4, 5.4 Hz, 1H, β-lactam ring CH^B), 5.13 (d, *J*=5.4 Hz, 1H, β-lactam ring CH^A), 6.62–7.71 (m, Ar-H, 18H); ^{13}C NMR: 52.25, 53.61, 55.43, 58.82, 59.42, 62.35, 63.55, 70.79,

79.03, 113.79, 115.36, 117.60, 121.67, 121.79, 122.06, 122.18, 127.39, 127.80, 128.35, 128.45, 128.70, 129.09, 130.44, 134.75, 135.89, 156.50, 156.87, 161.19, 164.28, 172.49, 194.23. CIMS *m/z*: 604 (M^+).

3.2.7. Spiro[2-carbomethoxy-3-(4-chlorophenyl)-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenoxy-4-oxo- azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3g). Yield 0.24 g (75%), colorless solid, mp 194–195°C (found: C, 67.80; H, 4.68; N, 4.22. $C_{36}H_{31}ClN_2O_7$ requires C, 67.66; H, 4.89, N, 4.38%); IR (KBr): 1675, 1737, 3344 cm^{-1}; ^{1}H NMR: 1.65 (bs, 1H), 3.59 (s, 3H), 3.78 (s, 3H), 4.12 (d, *J*=10.7 Hz, 1H, H^D), 4.24–4.29 (m, 2H, OC*H*H, H^C), 4.32–4.43 (m, 2H, OCH*H*, H^E), 5.05 (dd, *J*=9.2, 5.4 Hz, 1H, β-lactam ring CH^B), 5.11 (d, *J*=5.4 Hz, 1H, β-lactam ring CH^A), 6.62–7.59 (m, Ar-H, 17H); ^{13}C NMR: 52.21, 53.62, 55.38, 58.86, 59.78, 62.44, 63.43, 70.12, 79.22, 113.82, 114.99, 117.48, 121.62, 121.84, 122.00, 122.25, 127.44, 127.80, 128.34, 128.74, 129.22, 130.48, 134.78, 135.89, 156.52, 156.88, 161.28, 164.38, 172.82, 194.04. CIMS *m/z*: 638 (M^+).

3.2.8. Spiro[2-carbomethoxy-3-(4-methylphenyl)-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenoxy-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3h). Yield 0.24 g (78%), colorless solid, mp 226–227°C (found: C, 71.64. 5.74; H, 4.38; N, 4.22. $C_{37}H_{34}N_2O_7$ requires C, 71.83; H, 5.54, N, 4.53%); IR (KBr): 1689, 1741, 3399 cm^{-1}; ^{1}H NMR: 1.65 (bs, 1H), 2.27 (s, 3H), 3.64 (s, 3H), 3.80 (s, 3H), 4.17 (d, *J*=12.2 Hz, 1H, H^D), 4.21–4.30 (m, 2H, OC*H*H, H^C), 4.37–4.42 (m, 2H, OCH*H*, H^E), 5.08 (dd, *J*=8.7, 5.3 Hz, 1H, β-lactam ring CH^B), 5.13 (d, *J*=5.3 Hz, 1H, β-lactam ring CH^A), 6.58–7.72 (m, Ar-H, 17H); ^{13}C NMR: 21.00, 52.15, 55.38, 56.11, 58.79, 59.33, 62.82, 63.79, 70.84, 79.22, 114.76, 116.14, 117.72, 118.46, 122.44, 122.79, 123.08, 127.38, 128.15, 128.71, 129.50, 129.92, 130.73, 132.86, 135.85, 157.00, 157.86, 162.23, 164.38, 172.45, 194.23. CIMS *m/z*: 618 (M^+).

3.2.9. Spiro[2-carbomethoxy-3-(4-methoxyphenyl)-5-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenoxy-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3i). Yield 0.25 g (80%), colorless solid, mp 232–233°C (found: C, 69.95; H, 5.65; N, 4.22. $C_{37}H_{34}N_2O_8$ requires C, 70.02; H, 5.40, N, 4.41%); IR (KBr): 1672, 1743, 3350 cm^{-1}; ^{1}H NMR: 1.69 (bs, 1H), 3.65 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 4.12 (d, *J*=12.7 Hz, 1H, H^D), 4.23–4.29 (m, 2H, OC*H*H, H^C), 4.31–4.43 (m, 2H, OCH*H*, H^E), 5.03 (dd, *J*=9.4, 4.8 Hz, 1H, β-lactam ring CH^B), 5.14 (d, *J*=4.8 Hz, 1H, β-lactam ring CH^A), 6.78–7.73 (m, Ar-H, 17H); ^{13}C NMR: 52.13, 53.48, 55.18, 55.34, 58.60, 59.74, 62.52, 63.48, 70.74, 79.14, 113.85, 113.96, 115.44, 115.99, 117.74, 119.25, 121.73, 121.91, 122.22, 122.93, 127.44, 129.17, 129.76, 129.83, 134.78, 135.88, 156.46, 161.29, 164.48, 172.83, 194.04. CIMS *m/z*: 634 (M^+).

3.2.10. Spiro[2-carbomethoxy-3-(4-nitrophenyl)-(*S*,*R*)-[*cis*-1-(4-methoxyphenyl)-3-phenoxy-4-oxo-azetidin-2-(*S*,*R*)-yl]pyrrolidine-4,3^1-chroman-4^1-one] (3j). Yield 0.21 g (65%), colorless solid, mp 210–211°C (found: C, 66.42; H, 5.05; N, 6.23. $C_{36}H_{31}N_3O_9$ requires C, 66.56; H, 4.81, N, 6.47%); IR (KBr): 1679, 1738, 3363 cm^{-1}; ^{1}H NMR: 2.68 (bs, 1H), 3.64 (s, 3H), 3.80 (s, 3H), 4.19 (d, *J*=10.5 Hz, 1H, H^D), 4.21 (d, *J*=9.1 Hz, 1H, H^C), 4.32 (d, *J*=11.7 Hz, OC*H*H), 4.39–4.45 (m, 2H, OCH*H*, H^E), 5.0 (dd, *J*=9.1, 5.3 Hz, 1H, β-lactam ring CH^B), 5.13 (d, *J*=5.3 Hz, 1H, β-lactam ring CH^A), 6.68–8.19 (m, Ar-H, 17H); ^{13}C NMR: 52.08, 53.55, 55.64, 58.72, 59.22, 62.48, 63.34, 70.82, 79.13, 114.52, 115.78, 117.45, 121.55, 122.04, 122.22, 127.52, 127.94, 128.45, 128.62, 129.00, 130.74, 134.48, 135.75, 143.54, 147.22, 156.84, 160.89, 164.44, 172.58, 194.03. CIMS *m/z*: 649 (M^+).

Acknowledgements

G. S. thanks Council of Scientific and Industrial Research (CSIR), New Delhi for the award of Senior Research Fellowship. Financial support from CSIR and UGC is gratefully acknowledged. One of us (A. M. M. C.) thanks CAICYT (Grant BQU2000-0246) for financial support.

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28. Crystallographic data for the structural analysis have been deposited at the Cambridge Crystallographic data Centre, CCDC Nos. 190810 and 190811 for the compounds **3b** and **3c**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1FZ. UK (fax: +044-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).