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X=Y-ZH Compounds as Potential 1,3-Dipoles. Part 64.[3b] Synthesis of Highly Substituted Conformationally Restricted and Spiro Nitro-pyrrolidines *via* Ag (I) Catalysed Azomethine Ylide Cycloadditions

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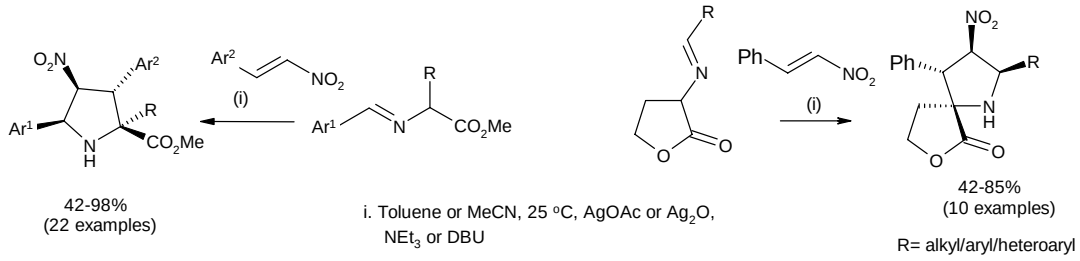

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X=Y-ZH Compounds as Potential 1,3-Dipoles. Part 64.[3b] Synthesis of Highly Substituted Conformationally Restricted and Spiro Nitro-pyrrolidines *via* Ag (I) Catalysed Azomethine Ylide Cycloadditions

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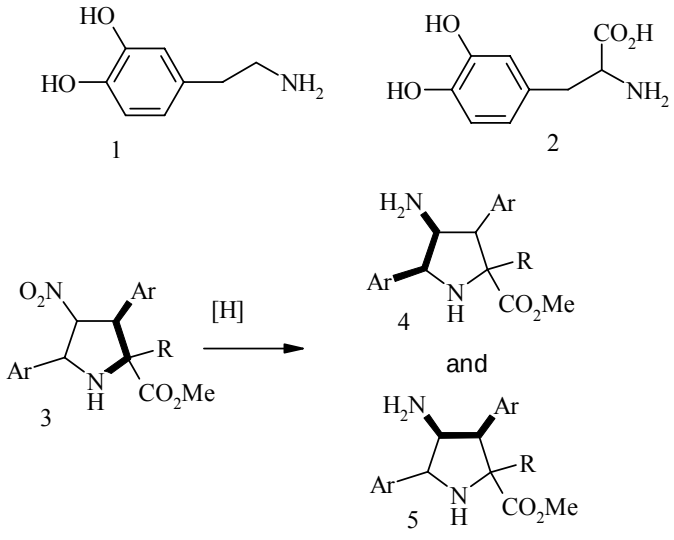
Abstract—1,3-Dipolar reactions of imines of both acyclic and cyclic α-amino esters with a range of nitroolefins using a combination of AgOAc or Ag_2O with NEt_3 are described. In most cases the reactions were highly regio- and stereo-specific and endo-cycloadducts were obtained in good yield. However, in a few cases the initially formed cycloadducts underwent base catalysed epimerisation. The stereochemistry of the cycloadducts was assigned from n.O.e data and established unequivocally in several cases by X-ray crystallography.

***Keywords*:** Metallo-azomethine ylides, cycloaddition, silver oxide, nitroolefins, pyrrolidines, spirocycles.



We introduced facile and wide ranging metal salt-tertiary amine catalysed cycloaddition reactions of imines, activated by an appropriately located carbanion stabilising substituent, with electron deficient alkenes.[1] Subsequently, we have utilized this methodology for the synthesis of a wide variety of heterocycles including pyrrolizidines, indolizidines[2] and spiro nitrogen heterocycles[3] as well as the synthesis of pyrrolidine based β-lactams[4], epibatidine analogues[5a] and uracil polyoxin C analogues.[5b]

Dopamine **1** is one of the most important neurotransmitters, the body's natural stimulants, and plays a key role in schizophrenia and Parkinson's disease. Several reports appear in the literature for the synthesis of both simple and conformationally restricted dopamine analogues[6] and evaluation of their biological properties. Nitropyrrolidines are potentially useful as sources of conformationally restricted analogues of dopamine **1** and DOPA **2**[7] (vide infra). This type of compound e.g **3**-**5** is accessible *via* 1,3-dipolar cycloaddition of appropriate azomethine ylides and nitrostyrenes. Nyerges et al.[8] applied this cycloaddition methodology to the stereoselective synthesis of aza-cephalotaxine[8a,b] and indolic aza-analogues[8c] of cephalotaxine. They have also reported a new method for the synthesis of substituted pyrroles[8d] from nitropyrrolidines. Several authors explored the 1,3-dipolar cycloaddition of both non-stablized[9] and stablized[10] azomethine ylides with nitroolefins for the synthesis of substituted nitropyrrolidines. For stabilized azomethine ylides it was concluded that lithio-azomethine ylides[10] undergo preferential formation of endo-cycloadducts whilst silver salts favour the formation of exo-cycloadducts. Further work showed that incorporating certain groups in the aromatic moiety of aryl azomethine ylides modifies the

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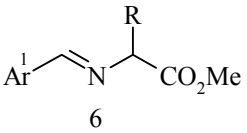
stereoselectivity[10b]. These latter results confirmed prior work by our group on proton-sponge effects in azomethine ylide formation.[11] An asymmetric catalytic version of 1,3-dipolar cycloaddition of nitroalkenes to an imino ester derived from glycine has been reported[12] as has microwave assisted synthesis of highly substituted nitroproline esters via 1,3-dipolar cycloaddition.[13]

This paper describes our studies of the silver catalysed synthesis of nitropyrrolidines **3** and their derivatives **4,5** all of which proceed *via endo*-transition states. The latter provide interesting dopamine mimetics because of the conformational rigidity conferred by the 5-membered ring and the differing dihedral angle between the aryl and amine moieties. We further report a series of spirocyclic nitropyrrolidines arising from homoserine lactone **11**.

Cycloadditions of non-cyclic imines 6a-f

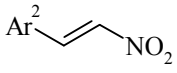
A number of nitro-olefins **7a-f** were examined to explore the diversification of the metallo-azomethine ylide cycloaddition. These were prepared from the corresponding aryl aldehydes by the Henry reaction[14] and were reacted with a series of aryl or aliphatic imines of cyclic or acyclic α-amino esters.

The aryl imines **6a-f** underwent cycloaddition reactions with nitroolefins in toluene in the presence of NEt_3 and Ag_2O (10 mol%) or AgOAc (1.5 mol equiv.) (Scheme 1). The results of the reactions are presented in Table 1. The cycloaddition of the less hindered imines **6a,d** with anthracene nitrostyrene **7a** afforded single cycloadducts endo-**9a,b** in good yield (72-80%)(Table 1, entries 1 and 2), whereas imines **6b,c** from alanine and phenylalanine failed to react under the same conditions due to the steric hindrance between the Me and Bn groups of the imines and the anthracenyl group of the dipolarophile.



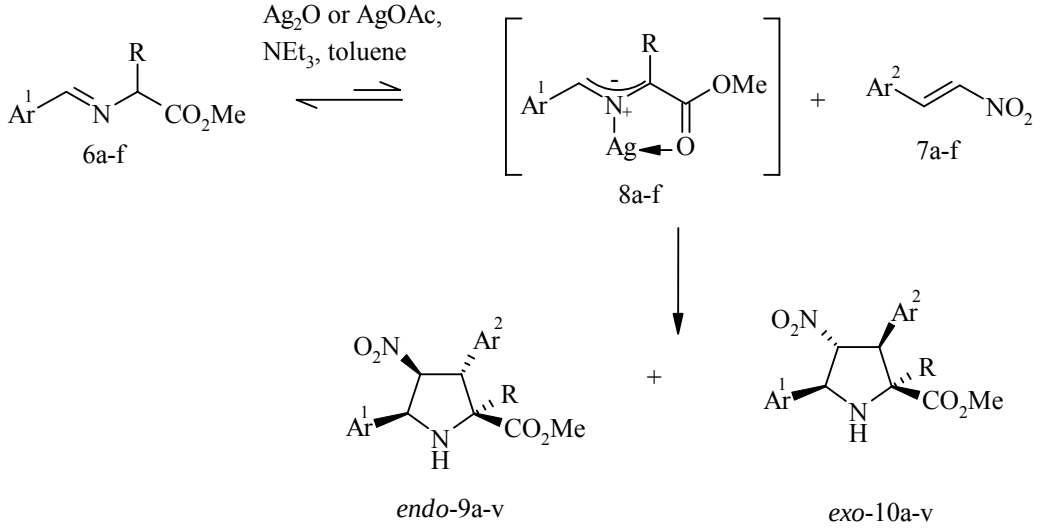
6

a. Ar^1 = naphthyl, R = H
b. Ar^1 = naphthyl, R = CH_3
c. Ar^1 = naphthyl, R = CH_2Ph
d. Ar^1 = biphenyl, R = H
e. Ar^1 = biphenyl, R = CH_3
f. Ar^1 = biphenyl, R = CH_2Ph



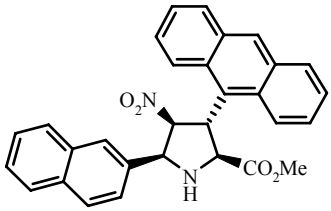
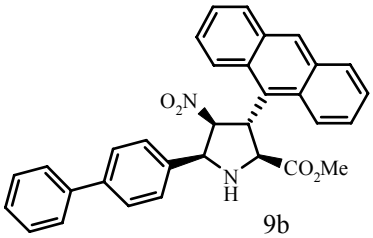
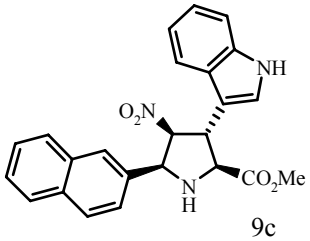
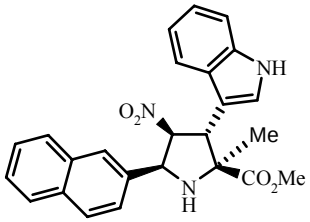
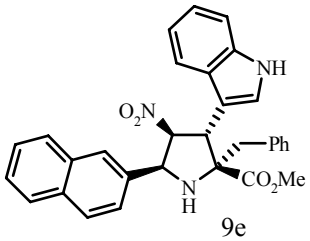
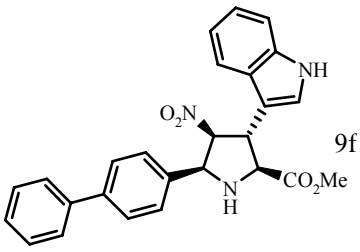
7

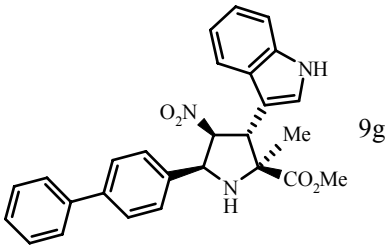
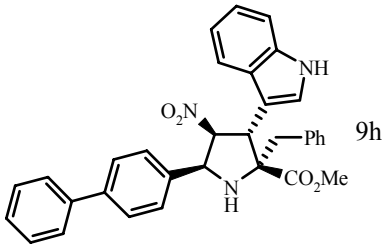
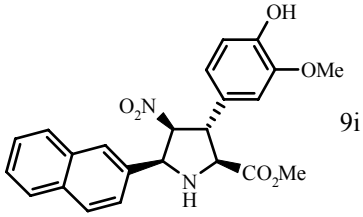
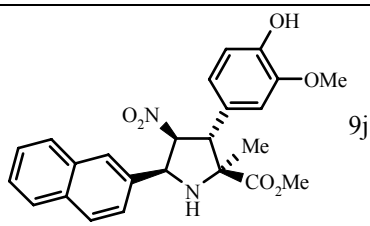
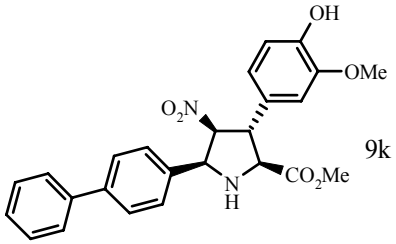
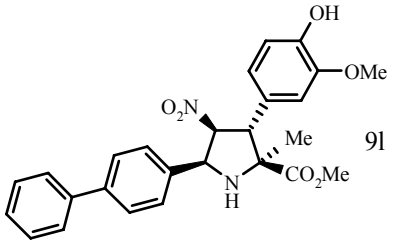
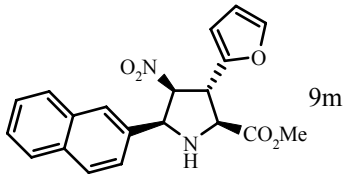
a. Ar^2 = 9-anthracenyl
b. Ar^2 = 3-indolyl
c. Ar^2 = 4-hydroxy-3-methoxyphenyl
d. Ar^2 = 2-furyl
e. Ar^2 = 2-thienyl
f. Ar^2 = 3-pyridyl

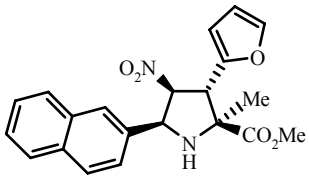
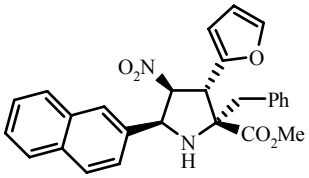
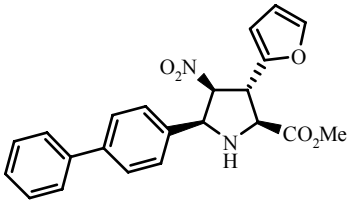
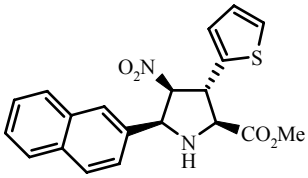
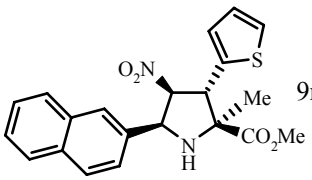
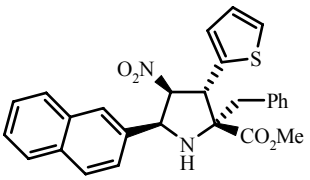
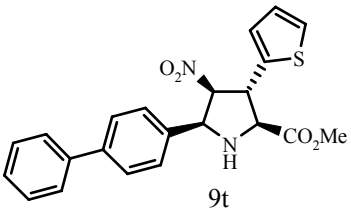
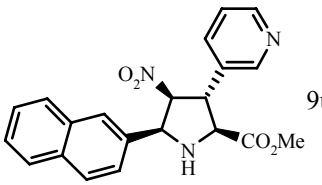


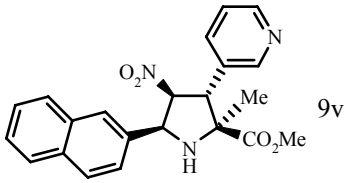
Scheme 1

Table 1: Silver salt/NEt_3 catalysed cycloaddition of **6a-f** with *E* - nitroolefins **7a-f**.[a]

Entry	Imine	Dipolarophile	Cycloadduct	Ag salt	Time (h)	Yield (%)[b]
1	6a	7a	 9a	AgOAc	18	80
2	6d	7a	 9b	AgOAc	18	72
3	6a	7b	 9c	AgOAc	18	95[c]
4	6b	7b	 9d	Ag_2O	18	60
5	6c	7b	 9e	Ag_2O	18	60
6	6d	7b	 9f	Ag_2O	18	95[d]

7	6e	7b	 9g	Ag_2O	18	72
8	6f	7b	 9h	Ag_2O	18	62
9	6a	7c	 9i	Ag_2O	16	42[e]
10	6b	7c	 9j	Ag_2O	17	91
11	6d	7c	 9k	AgOAc	16	82
12	6e	7c	 9l	Ag_2O	18	65
13	6a	7d	 9m	AgOAc	15	87

14	6b	7d	 9n	AgOAc	18	80
15	6e	7d	 9o	AgOAc	16	78
16	6d	7d	 9p	AgOAc	22	98
17	6a	7e	 9q	AgOAc	16	90[c]
18	6b	7e	 9r	Ag_2O	16	91
19	6c	7e	 9s	Ag_2O	17	70
20	6d	7e	 9t	AgOAc	16	70
21	6a	7f	 9u	Ag_2O	16	73

22	6b	7f	 9v	AgOAc	18	78[c]

a. Toluene, NEt_3(1.5 eq.), Ag_2O (10 mol%) or AgOAc (1.5 eq.), 25 °C.
b. Isolated yield. c. 3:1 endo/exo mixture. d. 5:1 endo/exo mixture.
e. 2:1 endo-exo mixture.

Similar cycloaddition of imines **6b,c,e,f** with indolyl nitrostyrene **7b** afforded single cycloadducts **9d,e,g,h** (Table 1, entries 4, 5, 7 and 8), whereas glycine imines **6a,d** afforded a 3-5:1 mixture of *endo*-**9c,f** and *exo*-**10c,f** cycloadducts (Table 1, entries 3 and 6) respectively. Toke et al.[10] have observed similar results in the 1,3-dipolar cycloaddition of glycine imine with different nitroolefins and they have reported that silver salts favour the formation of *exo*-cycloadduct in the case of nitroolefins with bicyclic aryl groups. They have suggested that secondary orbital interactions of the aryl groups play a major role in this change of stereoselectivity. This type of interaction is not possible in the case of imines **6** (R = Me or Bn) because of the steric hindrance between the bulkier groups (Me and Bn) of the imines and the aryl group of the nitroolefins. Therefore, in all cases the cycloaddition reactions were overwhelmingly *endo*-specific.

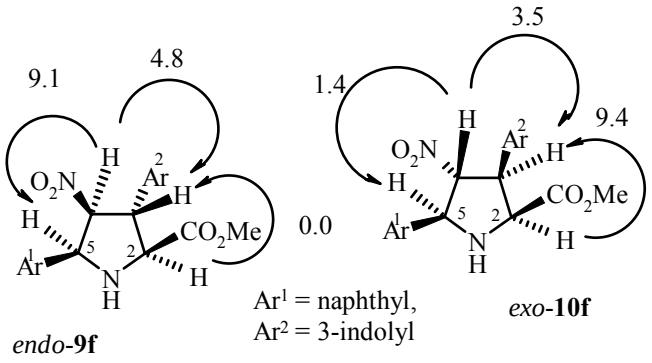


Figure 1

Similarly, cycloaddition of imines **6b-e** with nitroolefins **7c-f** afforded endo cycloadducts **9j-p,r-u** (Table 1, entries 10-16 and 18-21) whereas glycine imine **6a** with nitroolefins **7c,e** afforded a 2-3:1 mixture of *endo*-**9i,q** and *exo*-**10i,q** cycloadducts (Table 1, entries 9 and 17) respectively. Nitroolefin **7f** reacted with alanine imine **6b** to give a 3:1 mixture of *endo*-**9v** and *exo*-**10v** cycloadducts (Table 1, entry 22).

Product structures indicate that in all cases the imines generate the expected metallo-1,3-dipoles **8a-f** stereoselectively under kinetic control and the coordination of the metal ion depicted in **8** is believed to be responsible for this kinetic preference.[15] The potential cycloadducts **9** and **10** arise from the dipoles **8** *via endo*- and *exo*-transition states respectively. Structural assignments are based on ^{1}H COSY and n.O.e data. For example, the methoxy signal at 3.86 ppm in **9f** indicated a *trans* disposition of the ester and the indolyl groups, whilst in **10f** the methoxy signal occurs at 3.06 ppm suggesting shielding of the OMe by a *cis*-indolyl group. This observation was confirmed (Fig. 1) by n.O.e experiments. Thus the irradiation of H-4 in **9f** effects a 9.1% enhancement of the signal for H-5 suggesting *cis* relationship between H-4 and H-5, whereas a smaller enhancement (4.8%) of the H-3 signal indicates H-3 and H-4 are *trans* related. Irradiation of H-2 in **9f** shows no enhancement of the H-3 proton indicating a *trans* relationship between H-2 and H-3. Similarly irradiation of H-4 in **10f** gave a small enhancement (1.4%) of H-5 and H-3 (3.5 %) suggesting *trans* relationship of both H-5 and H-3 with H-4 whilst irradiation of H-2 effected a 9.4% enhancement of H-3. These data suggest that H-4 and H-5 are *trans*-related and H-2 and H-3 are *cis*-related in **10f**.

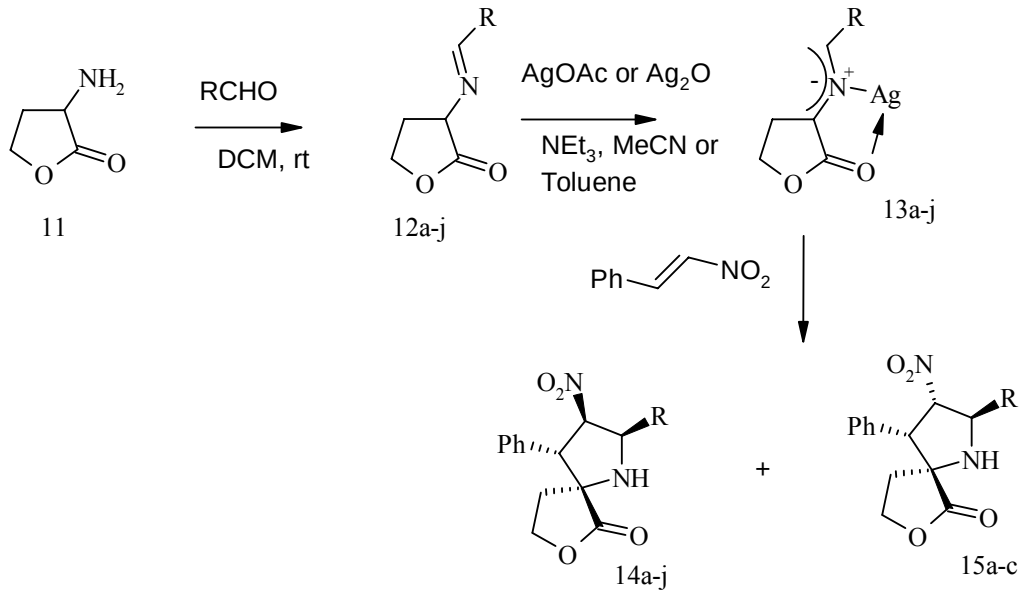
The 5 examples of *endo*/*exo* cycloadduct mixtures comprise of 4 cases involving glycine imines (Table 1, entries 3, 6, 9, 17) and one involving an alanine imine (entry 22). In the former case we hypothesise that π-stacking of the electron rich C(3)-Ar substituent and the C(2)-ester carbonyl group lowers the *exo*-transition state energy sufficiently to make it competitive. Factors favouring the *exo* isomer in the latter case (entry 22) are unclear.

Cycloaddition of imines 12a-f [3b] of homoserine lactone 11

We extended our studies to spiro nitropyrrolidines employing metallo-azomethine ylide formation from aldimines of cyclic α-amino ester **11** using a combination of AgOAc in MeCN or Ag_2O in toluene with NEt_3. Imines of a range of aldehydes (aryl, heteroaryl, aliphatic) were examined to explore the diversification of the metallo-azomethine ylide cycloaddition. In some cases imines of long chain aliphatic aldehydes were used to increase the lipophilicity of the cycloadducts. The aryl **12a-c** and aliphatic **12d-j** imines were employed in cycloadditions with a range of nitrostyrenes (Table 2).

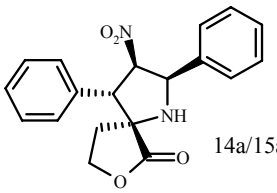
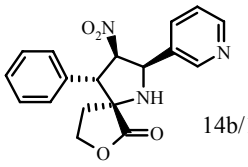
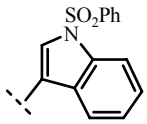
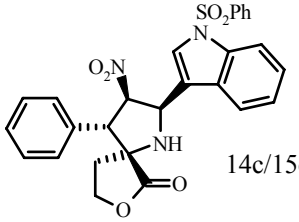
Imines **12a-c** reacted with various nitrostyrenes in acetonitrile in the presence of triethylamine and AgOAc to give mixtures of **14a-c** (major) and **15a-c** (minor) cycloadducts in 59-83% yield (Scheme 2)(Table 2, entries 1-3). The isomer ratio varied from 4.5:1 to 2:1 depending

on the aryl group present in the imines **12a-c**. Endo cycloadducts **14** are formed from metallo-dipole **13** *via endo*-transition states. Cycloadducts **15** arise by the base catalysed epimerisation of **14**. Fejes et al[16] reported similar epimerised cycloadducts due to the strongly activated nature of the proton (low pK_a) adjacent to the nitro-group. Cossio et al[10b] carried out similar cycloadditions with *trans* nitrostyrene using $LiClO_4$ as catalyst and proposed a stepwise mechanism for the formation of this type of cycloadduct.



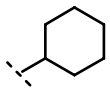
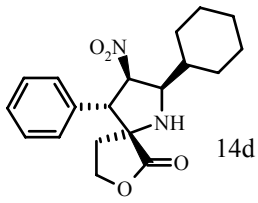
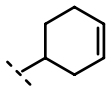
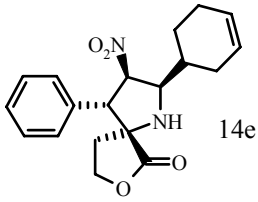
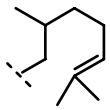
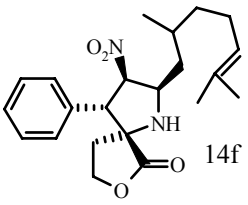
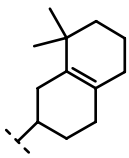
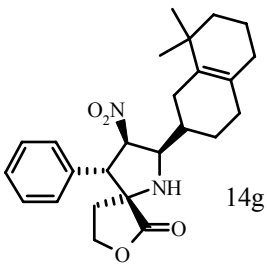
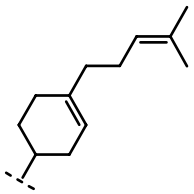
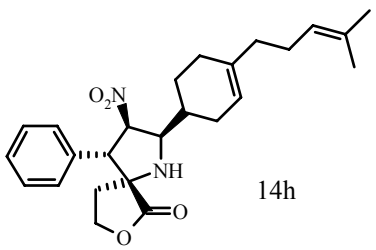
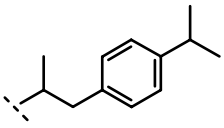
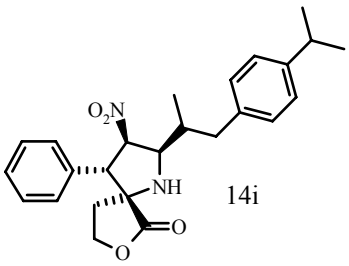
Scheme 2

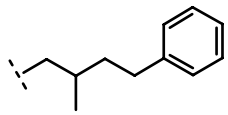
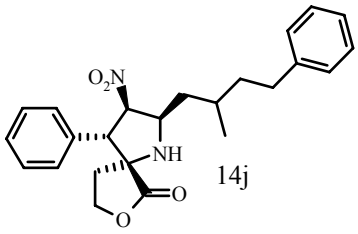
Table 2: Catalysed cycloaddition of imines **12a-c** with *E*-nitrostyrene using AgOAc in MeCN[a].

Entry	Imine	R	Time (h)	Cycloadduct	Epimer ratio	Yield (%)[b]
1[a]	12a		4	 14a/15a	3:1	73
2[a]	12b		4	 14b/15b	2:1	59
3[a]	12c		24	 14c/15c	4.5:1	83

a. Acetonitrile, NEt_3 (1.1 mol equiv.), AgOAc (1.5 mol equiv.), 25 °C, 4-24 h. b. Isolated yield.

Table 3: Catalysed cycloaddition of imines **12d-j** with *E*-nitrostyrenes using Ag_2O/NEt_3 in toluene[a].

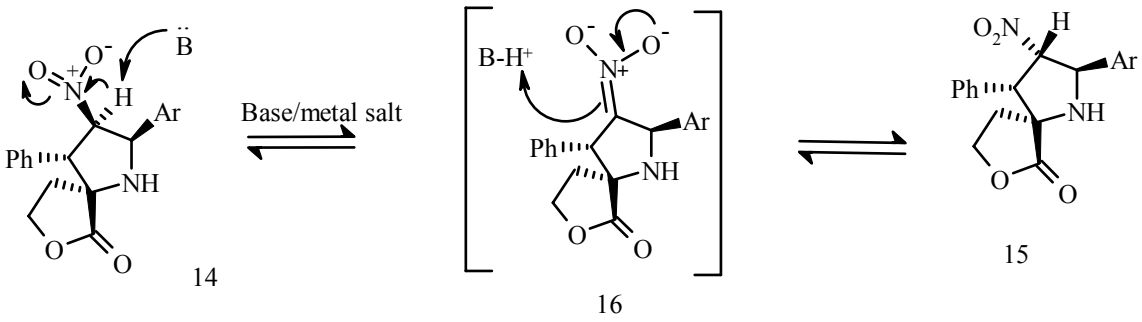
Entry	Imine	R	Time (h)	Cycloadduct	dr.	Yield (%)[b]
1	12d		1h	 14d	-	74
2	12e		1h	 14e	1:1	51
3	12f		4h	 14f	1:1	42
4	12g		3h	 14g	1: 1	58
5	12h		4h	 14h	1:1	85
6	12i		5h	 14i	1:3	72

7	12j		4h	 14j	1:1	59

a. Toluene, NEt_3(1.1 mol equiv.), Ag_2O (10 mol%), 25 °C, 1-5 h. b. Isolated yield.

In order to rule out formation of **15** by a non-concerted cycloaddition, the major isomer **14a** was subjected to base catalysed isomerisation, to probe epimerization, with the following results. Et_3N, AgOAc, acetonitrile, 25 °C, 48 h gave a 3:1 mixture of **14a** and **15a**. The same ratio of isomers was obtained by changing the base to i-Pr_2NEt. In the original reaction, carried out in acetonitrile in the presence of AgOAc and NEt_3, the ratio of the isomers was 3:1 after 4 h and 16 h. The observation of the same isomer ratio in both the original reaction and base catalysed isomerisation of major isomer **14a** is compelling evidence that the formation of **15a** occurs by equilibration of **14a** *via* **16**. The pK_a of the C-3 proton is expected to be ca. 10 while the pK_a's of the protonated amines are also approximately 10. Equilibrium is reached between the two stereoisomers with steric factors favouring **14a** as the major isomer (Scheme 3). The structure and relative stereochemistry of the cycloadducts **14a** and **15a** was partly established by ^{1}H NMR, 2D-$COSY_{H-H}$ and n.O.e. studies (see experimental section). Subsequently X-ray crystallographic studies firmly established the stereochemical relationships (Figs. 2 and 3).

Aliphatic aldimines **12d-j** underwent Ag_2O catalysed cycloaddition with *trans*-nitrostyrene in toluene in the presence of NEt_3 to afford the corresponding endo-cycloadducts **14d-j** in 42-85% yield (Table 3, entries 1-7). Cycloadducts **14e,g-j** comprised 1:1 mixtures of racemic diastereomers (due to the chiral centre present in the side chain) and it was possible to separate both isomers in the case of **14i** using silica gel chromatography. Cycloadducts **14f** comprised an inseparable 1:1 mixture of chiral diastereomers. In all cases the cycloaddition was regio-and stereo-selective and involved only the *E,E*-dipole **13** (Scheme 2). The stereochemistry of the cycloadducts **14d-j** was established by comparison of their 1H NMR spectra with those of the previously described analogues.[3b]



14

Scheme 3

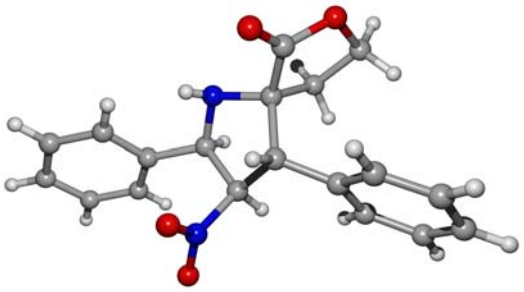


Figure 2: X-ray crystal structure of **14a**

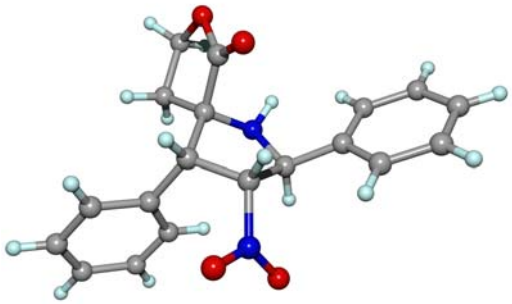


Figure 3: X-ray crystal structure of **15a**

Reduction of nitro compounds to amines

Several attempts at reducing the nitro moiety to the amine based on literature methods (ammonium formate, 10 % Pd/C in dry methanol,[17] metal acid combinations eg, $SnCl_2$/AcOH in methanol,[18] In/HCl in aq. THF,[19] Zn/conc. HCl, Fe/AcOH[20]) failed. However the reduction of the nitro group to amine was successful using Zn/ethanol/conc. HCl after protecting the NH of the pyrrolidine ring as the N-acetyl derivative[8b] (Scheme 4).

The reaction of the 3:1 mixture of thienyl cycloadducts **9q** and **10q** with acetic anhydride (11 mol eq) in pyridine at 0 ºC to rt gave a 1.5:1 mixture of N-acetyl derivatives **16a** and **16b** in 66% yield. The two *N*-acylated isomers were separated by column chromatography. Close examination of the *major* product **16a** showed it had undergone epimerisation at C-4. Thus the ^{1}H- and ^{13}C-NMR spectra were consistent with the general structure of both *N*-acetyl derivatives, but n.O.e experiments (Figure 4) were necessary to assign the relative disposition of the substituents.

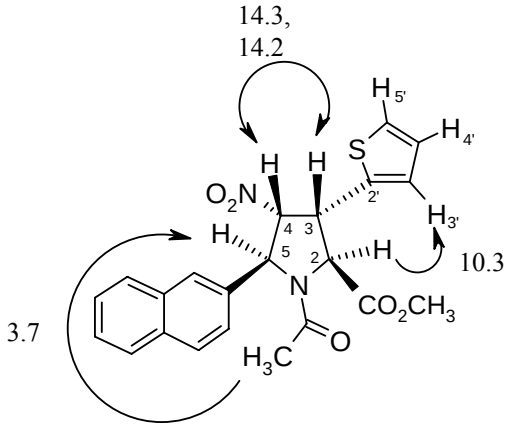


Figure 4**.** N.O.e. data of compound **16a**

Irradiation of 3-H and 4-H in compound **16a** effects a 14.3% and 14.2% enhancement of 4-H and 3-H respectively, suggesting a *cis* relationship between them. Irradiation of 2-H produced a 10.3 % enhancement of the thienyl 3'-H. Finally, irradiation of the methyl group of the *N*-acetyl group produced a 3.7 % enhancement of 5-H but no enhancement of 2-H establishing that the *major* solution phase conformer of the amide group is as shown in Figure 4, supporting the relative disposition shown.

Acid / base catalysed epimerisation occurred at C-4 of the *major* isomer ***endo*-9q,** facilitated by the low pKa of the 4 – H, to provide **16a**. The C-4 epimerisation was confirmed by the X-ray crystal structure of **16a** (Figure 5) which shows the naphthyl ring and the ester group on one face of the pyrrolidine ring and the nitro group and the thienyl ring on the opposite side. Additionally, distances and dihedral angles were calculated from the X-ray structure (Figure 5) to add further proof of the relative disposition of the substituents on the pyrrolidine ring: 2-H – 3'-H = 2.4205 Å and 12.18 deg , establishing that the 3-(2'-thienyl) group is orthogonal to the plane on the pyrrolidine ring. It was also found that in this crystal structure there is a disorder in the thiophene ring and in about half the molecules in the crystal the thiophene ring is rotated 180º, so that the sulphur occupies the position of C-3' as shown in Figure 5.

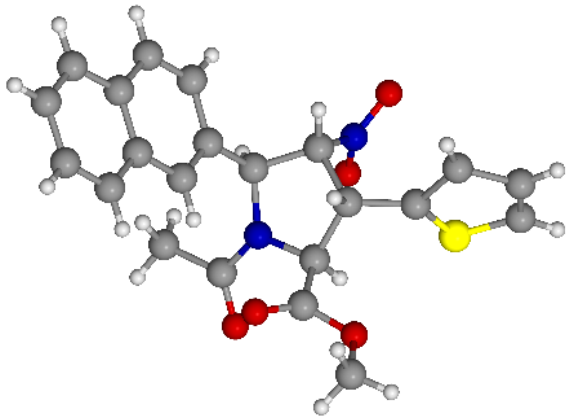


Figure 5: X-ray crystal structure of **16a**

The X-ray crystal structure shows that the pyrrolidine ring of compound **16a** is in the shape of an envelope where C-4, bearing the nitro group, is now the atom out of the plane (pointing downwards on the left side of the "stick" model below) formed by N, C-2, C-3 and C-5 of the pyrrolidine ring. Calculated values for the dihedral angles from the X-ray crystal structure of **16a** are : 2-H – C-2 – C-5 – 5-H = 150.65 deg, 5-H – C-5 – C-4 – 4-H = -36.69 deg and 4-H – C-4 – C-3 – 3-H = -98.55 deg. The *N*-acetyl group remains in the same plane of those four atoms, the methyl group oriented towards C-5. Thus the solid state orientation of the amide matches that established for the solution phase from the n.O.e. data. The 4-nitro group has a pseudo axial disposition while the 3-(2'-thienyl), 5-(2'-naphthyl) rings and 2-methyl ester group are pseudo equatorial. The 3-(2'-thienyl) and 5-(2'-naphthyl) rings are orthogonal to the plane formed by N, C-2, C-3 and C-5 (Figure 6).

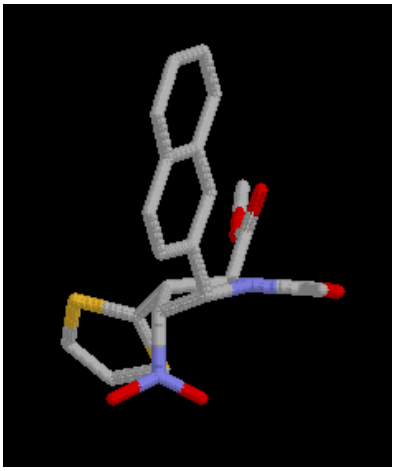


Figure 6**.** Stick model of **16a**

The relative stereochemistry of the substituents *minor* isomer **16b** was assigned in the same way from n.O.e. experiments. Irradiation of 3-H effected a 13.0% enhancement of 2-H, suggesting a *cis* relationship between them, and a 6.3% enhancement of 5-H. Irradiation of 4-H produced a 9.6% enhancement of the thienyl 4'-H. Finally, irradiation of 5-H led to a 4.5% enhancement of the methyl group of the *N*-acetyl group, suggesting the relative disposition shown on Figure 7 and establishing the same preferred amide orientation in both *major* and *minor* isomers.

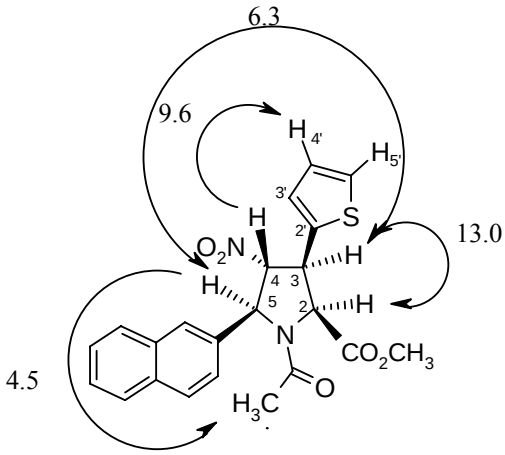


Figure 7. N.O.e. data of compound **16b**

The relative disposition of the substituents in compound **16b** was confirmed by an X-ray crystal structure (Figure 8), which showed the 5-(2'-naphthyl) ring, 3-(2'-thienyl) ring and ester group are on the same face of the pyrrolidine ring. Calculated values for the dihedral angles from the X-ray crystal structure of **16b** also provide further data on the relative orientation of the substituents: 5-H – C-5 – C-2 – 2-H = 34.13 deg, 4-H – C-4 – C-5 – 5-H = -168.69 deg and 3-H – C-3 – C-4 – 4-H = 158.78 deg.

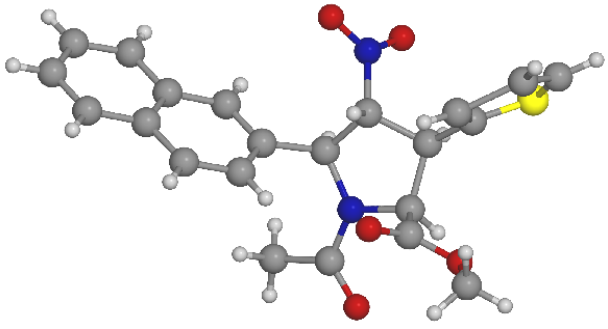


Figure 8: X-ray crystal structure of **16b**

As in compound **16a** the 3-(2'-thienyl) and the 5-(2'-naphthyl) rings in compound **16b** are orthogonal to the pyrrolidine ring, and the methyl group of the acetyl group is oriented towards C-5 as shown in Figure 9a.

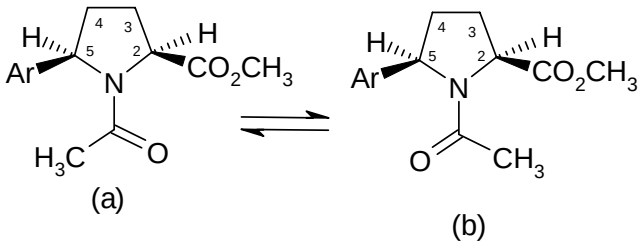


Figure 9**.** Two possible orientations of the *N*-acetyl

The preference for orientation (a) (Figure 9) might be dipole-dipole interaction of the amide and ester carbonyl groups (Figure 10). Calculated distances, from the X-ray structures, confirm the proximity between the pairs of carbonyl carbon atoms and the corresponding oxygen atoms. Thus for **16a** the O (carbonyl ester) – C (carbonyl amide) distance is 3.1914 Å, whilst the O (carbonyl amide) – C (carbonyl ester) distance is 3.0204 Å. In **16b** the O (carbonyl ester) – C (carbonyl amide) distance is 3.4971 Å and the O (carbonyl amide) – C (carbonyl ester) distance is 3.0731 Å. These data show the mutual orientation of the *N*-acetyl groups and ester groups are consistent with π–stacking in a manner that is dictated by dipole-dipole interaction (Figure 10).

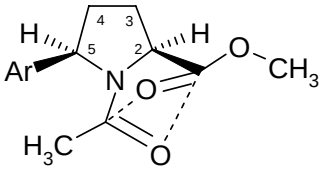


Figure 10. Possible dipole-dipole interaction

In **16b** C-4, bearing the nitro group, is the atom out of the plane pointing upwards on the right side of the "stick" model (Fig.11) formed by N, C-2, C-3 and C-5 of the pyrrolidine ring, whilst the *N*-acetyl group is in the same plane as these four atoms. The 4-nitro group has a pseudo equatorial disposition *trans* to the 3-(2'-thienyl), 5-(2'-naphthyl) rings and the 2 - ester group. These last three substituents are in pseudo equatorial disposition minimising the axial interactions. The 3-(2'-thienyl) and 5-(2'-naphthyl) rings are orthogonal to the plane formed by N, C-2, C-3 and C-5 of the pyrrolidine ring (Figure 11).

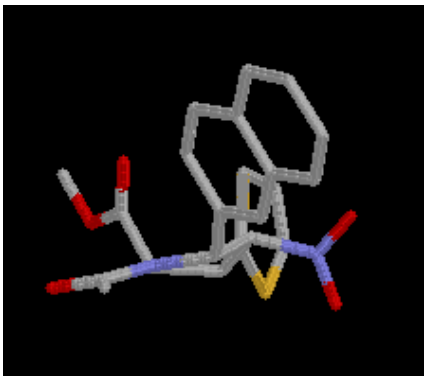
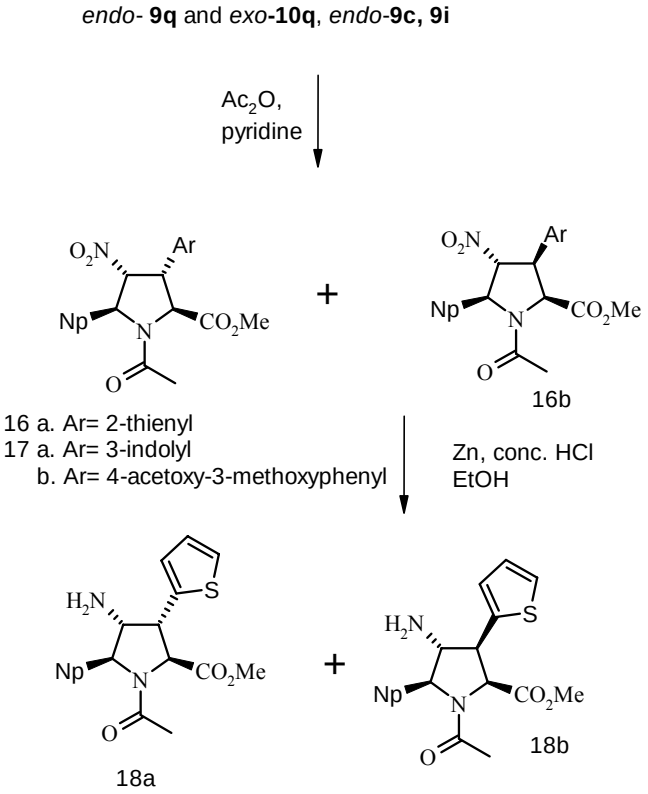


Figure 11. Model of **16b**

Note that because of C-4 epimerisation compounds **16a** and **16b** no longer have an *endo* / *exo* relationship.

To probe the generality of C-4 epimerisation two further examples were studied using the same reaction conditions but this time starting from the single *endo* cycloadducts ***exo*-9c** and ***endo*-9i** (Scheme 4). These gave exclusively the *N*-acylated epimerised products **17a,b** in 90-93 % yield.



Scheme 4

In both cases the relative disposition of the substituents in the *N*-acetylated derivatives **17a** and **17b** were determined by n.O.e. experiments. It was concluded that the nitro

group and the C-3 aryl ring are *cis*-related in both compounds, and that there is a *trans*-relationship between the biphenyl / naphthyl rings and the nitro groups. Thus epimerisation at C-4 in the course of the *N*-acetylation reaction appears to be general. In the case of ***endo*-9i** the acetylation not only occurred at the pyrrolidine NH, but also at the phenolic OH.

N.O.e. studies on **17b** are summarised in Figure 12. Thus irradiation of 4-H produced a 9.15 % enhancement of 3-H, but only a 3.6 % enhancement of 5-H. Likewise irradiation of 3-H caused an 9.0 % enhancement of 4-H, whilst irradiation of 5-H gave a 3.7 % enhancement of 4-H, establishing a *cis*-relationship between 3-H and 4-H, and a *trans*-relationship between 4-H and 5-H. Finally irradiation of 5-H also produced a 7.7 % enhancement of the methyl of the *N*-acetyl group and no enhancement of 2-H establishing the same orientation of the amide as observed previously.

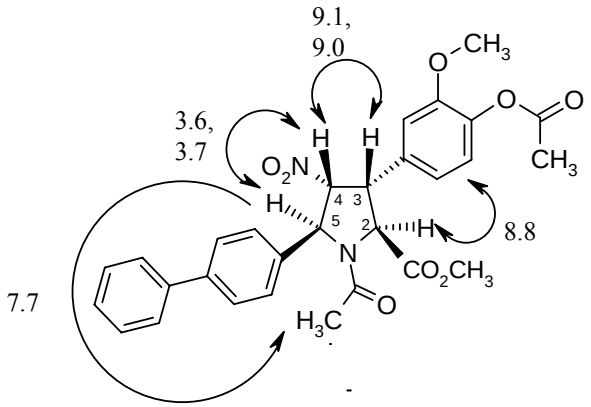


Figure 12. N.O.e data of compound **17b**

Reduction of **16a** and **16b** was carried out with zinc dust (17 mol eq) in 50:1 ethanol/conc.hydrochloric acid at 40-50°C, then for 12 h at reflux giving the corresponding amino derivatives **18a** and **18b** in 88-95% yield.

The relative stereochemistry of the pyrrolidine ring substituents in the amino derivative **18a** was assigned from n.O.e. data. (Figure 13) Irradiation of 3-H effects an 8.6 % enhancement of 4-H, suggesting a *cis* relationship between them, whilst an 8.8% enhancement of the thienyl 3'-H occurred on irradiating 2-H. Finally, irradiation of the methyl of the *N*-acetyl group gave a 2.3% enhancement of 5-H and no enhancement of 2-H suggesting the relative stereochemistry and conformation of the *N*-acetyl group shown in Figure 13.

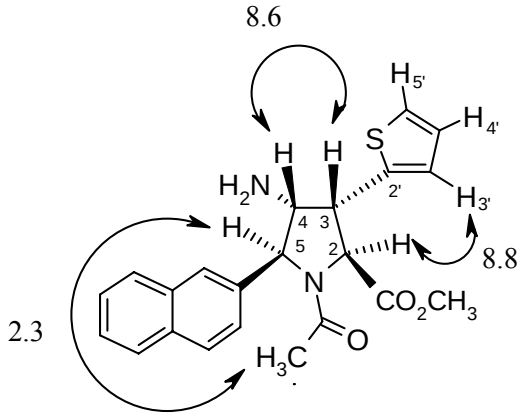


Figure 13. N.O.e of compound **18a**

In conclusion we have shown that (i) *in situ* generated argento azomethine ylides undergo concerted cycloaddition to *E* – nitrostyrenes via *endo* – transition states in good yield (ii) the pyrrolidine ring has an envelope conformation with the C-4 nitro bearing carbon the out-of-plane atom (iii) *N*-acetylation with Ac_2O is accompanied by C-4 epimerisation (iv) a combination of nOe solution studies and X-ray crystallography show a dipole-dipole stacking interaction involving the C-2 ester and *N*-acetyl carbonyl groups with the methyl group of the latter oriented towards the C-5 aryl substituent. (v) reduction of the C-4 nitro group with Zn/HCl/EtOH affords the corresponding amines.

Acknowledgements

We thank Leeds University for support and the Commonwealth Scholarship Commision for a studentship (to M.A.B. Sarker).

Experimental

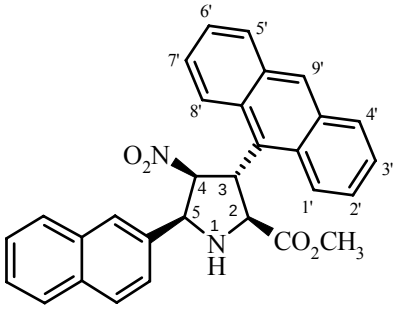
Melting points were determined on a Reichert hot-stage or Buchi B-545 apparatus and are uncorrected. Microanalysis was performed using a Carlo Erba MOD 1108 or 11016 instrument. Mass spectral data were recorded on a V.G.-AutoSpec instrument operating at 70 eV. Accurate molecular weights were recorded on a Micromass LCT KAIII electrospray (ES) machine. Infra-red spectra were recorded either on KBr discs or on films, prepared by evaporation of a dichloromethane solution, on a Nicolet Magna FT-IR or Nicolet 460ESP FT-IR Spectrometer. Nuclear magnetic resonance spectra were recorded at 250 MHz on a Bruker AC250 instrument or at 300 MHz on a Bruker DPX300 or at 500 MHz on a Bruker DRX500 instrument. Chemical shifts (δ) are given in parts per million (ppm). Deuterochloroform was used as the solvent unless otherwise stated. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, ddd = double double doublet, m = multiplet, b = broad, app = apparent. Flash

chromatography was performed either with silica gel 60 (230-400 mesh) or with 10 g/20 g SPE-Anachem SI Mega Bond-Elut. All solvents were purified according to standard procedures. The term ether refers to diethyl ether. Analytical grade anhydrous silver salts were used as purchased. In all reactions involving silver (I) salts the reaction flask was covered with aluminium foil.

General Procedure for Silver(I) Catalysed Cycloaddition Reactions

The appropriate aldimine (1 mol equiv.), triethylamine, dipolarophile (1 mol equiv.) and silver acetate (1.5 mol equiv.) were mixed in freshly distilled acetonitrile. Silver oxide (10 mol%) as metal catalyst and toluene (dried over sodium wire) as solvent were used in the case of aliphatic aldimines. The resulting suspension was stirred for an appropriate period at room temperature (monitored by TLC and ^{1}H NMR). After completion of the reaction the mixture was quenched with saturated aqueous ammonium chloride and extracted with ether or dichloromethane (2 x). The dried (magnesium sulphate) organic layer was concentrated under reduced pressure. The ratio of any isomers present in the residue was calculated from the integrals of appropriate peaks in the ^{1}H NMR spectrum. Flash chromatography afforded the individual stereoisomers when present.

Methyl 3-(9-anthryl)-5-(2-naphthyl)-4-nitro-prolinate (9a) Obtained from imine **6a** (227 mg, 1 mmol), *E*-nitrostyrene **7a** (249 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 18 h. Purification was achieved by triturating with ether and filtering to afford the product (380 mg, 80%) as a pale yellow amorphous solid, m.p. 130-132 °C. Found: C, 75.35; H, 5.15; N, 5.75. $C_{30}H_{24}N_2O_4$ requires C, 75.60; H, 5.10; N, 5.90 %; δ (^{1}H, 250 MHz): 8.51 (s, 1H, ArH), 8.00-7.50 (m, 15H, ArH), 6.17 (dd, 1H, J 6.2 and 7.5 Hz, 4-H), 6.01 (dd, 1H, J 6.2 and 9.7 Hz, 3-H), 5.76 (d, 1H, J 7.5 Hz, 5-H), 4.81 (d, 1H, J 9.7 Hz, 2-H), 3.60 (bt, 1H, J 9.7 Hz, NH) and 3.48 (s, 3H, OMe); δ (^{13}C): 172.4 (CO), 133.8, 133.5, 132.6, 129.8 (C_q), 129.7, 128.9, 128.6, 128.2 (2 x ArCH), 127.6, 127.0 (C_q), 126.9, 126.4, 124.7, 123.5 (2 x ArCH), 97.7 (C_4), 68.2 (C_2), 66.1 (C_3), 52.9 (C_5) and 50.8 (OCH_3); ν_{max} (KBr): 3057, 1737, 1557, 1266, 1214 and 756 cm^{-1}; m/z(%): 476 ($M^{+\cdot}$, 20), 427 (20), 370 (50) and 202 (100); m/z (ES^+): 500 ($M^{+\cdot}$+1+Na), 499 ($M^{+\cdot}$+Na), 477 ($M^{+\cdot}$+1, 100).



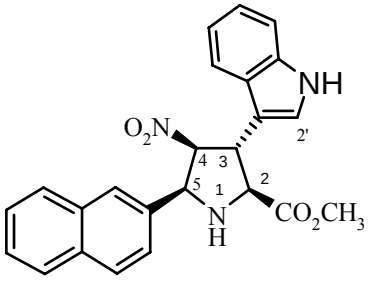
	% Enhancement				
Irradiated proton	H-1	H-2	H-3	H-4	H-5
H-2	2.5		-	-	3.2
H-3	0.8	-		-	-
H-4	-	-	-		6.0
H-5	-	4.2	-	8.8	

Methyl 3-(9-anthryl)-5-(1,1′-biphenyl-4-yl)-4-nitro-prolinate (9b) Obtained from imine **6d** (253 mg, 1 mmol), *E*-nitrostyrene **7a** (249 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 18 h. Purification by flash chromatography eluting with DCM/ hexane (20%) afforded the product (361 mg, 72%) as a pale yellow powder, m.p. 270-272 °C. Found: C, 76.55; H, 5.25; N, 5.45. $C_{32}H_{26}N_2O_4$ requires C, 76.50; H, 5.20; N, 5.55 %; δ (^{1}H, 250 MHz): 8.50 (s, 1H, ArH), 8.34-7.97 (m, 5H, ArH), 7.95-7.80 (m, 3H, ArH), 7.75-7.39 (m, 7H, ArH), 7.30-7.05 (m, 2H, ArH), 6.17 (dd, 1H, J 6.3 and 7.5Hz, 4-H), 6.00 (dd, 1H, J 6.3 and 9.8Hz, 3-H), 5.74 (d, 1H, J 7.5Hz, 5-H), 4.81 (d, 1H, J 9.8Hz, 2-H), 3.48 (s, 3H, OMe) and 2.35 (s, 1H, NH); δ (^{13}C): 172.4 (CO), 133.8, 133.5, 132.6 (C_q), 129.7 (2 x ArCH), 129.5 (2 x C_q), 128.9 (2 x ArCH), 128.6 (4 x ArCH), 128.2 (2 x ArCH), 127.6 (C_q), 127.0 (2 x ArCH), 126.9 (C_q), 126.4 (2 x ArCH), 125.7 (C_q), 124.7, 123.5 (2 x ArCH), 97.7 (C_4), 68.2 (C_2), 66.1 (C_3), 52.9 (C_5) and 50.8 (OCH_3); ν_{max} (KBr): 3353, 3053, 3031, 2953, 2849, 1737, 1557, 1438, 1231, 891, 765, 730, and 700 cm^{-1}; m/z (ES^+): 502 ($M^{+\cdot}$, 100).

Methyl 3-(1H-indol-3-yl)-5-(2-naphthyl)-4-nitro-prolinate (9c and 10c) Obtained from imine **6a** (227 mg, 1 mmol), *E*-nitrostyrene **7b** (188 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 18 h. Purification by cartridge column SPE-Anachem 20g SI Mega Bond-Elut eluting with 100% hexane to 100% ethyl acetate gradient elution afforded first *endo*-**9c** (291 mg, 70%), followed by *exo*-**10c** (104 mg, 25%).

endo-**9c**: Obtained as colourless plates, m.p. 163-165 °C. Found: C, 69.25; H, 5.15; N, 9.85. $C_{24}H_{21}N_3O_4$ requires C, 69.40; H, 5.10; N, 10.10 %; δ (^{1}H, 300 MHz): 10.50 (bs, 1H, indole NH), 7.88-7.11 (m, 12H, ArH), 5.49 (dd, 1H, J 2.8 and 5.9 Hz, 4-H), 5.11 (dd, 1H, J 5.9 and 10.9 Hz, 5-H), 4.57 (dd, 1H, J 3.0 and 7.2 Hz, 3-H), 4.44 (2 x overlapping d, 1H, J 9.0, 7.0 Hz, 2-H), 3.82 (s, 3H, OMe) and 3.62 (t, 1H, J 10.9 Hz, NH); δ (^{13}C): 172.6 (CO), 137.1, 133.6, 133.5, 132.0 (C_q), 128.9, 128.5, 128.0 (ArCH), 126.8 (2 x

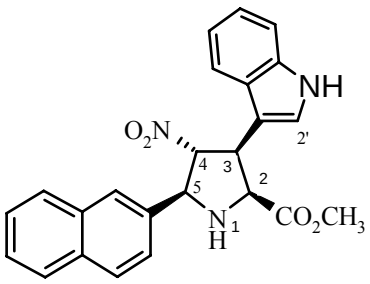
ArCH), 126.3 (C_q), 125.9 124.4, 123.5, 122.3, 120.8, 119.0 (ArCH), 114.0 (C_q), 112.1 (ArCH), 96.4 (C_4), 67.8 (C_2), 65.9 (C_3), 53.1 (C_5) and 48.7 (OCH_3); ν_{max} (KBr): 3328, 3057, 1733, 1552, 1384, 1215,1112 and 747 cm^{-1}; m/z (ES): 416 ($M^{+\cdot}$+1), 414 ($M^{+\cdot}$-1).



nOe data for **9c**:

	% Enhancement				
Irradiated proton	H-3	H-4	H-5	H-2′	Aryl
H-1	6.4	2.1	-	-	-
H-2	-	-	4.1	7.7	3.1
H-3		3.9	-	2.7	3.5
H-4	4.8		9.1	-	2.7, 4.0
H-5	4.6	12.8		-	5.7, 2.8

exo-**10c**: Obtained as pale orange plates, m.p. 207-209 °C. Found: C, 69.45; H, 5.15; N, 10.00. $C_{24}H_{21}N_3O_4$ requires C, 69.40; H, 5.10; N, 10.10 %; δ (^{1}H, 300 MHz, $CDCl_3$+2 drops DMSO): 9.87 (bs, 1H, indole NH), 7.85-6.93 (m, 12H, ArH), 5.27 (t, 1H, J 8.1 Hz, 4-H), 4.86 (t, 1H, J 8.1 Hz, 5-H), 4.65 (t, 1H, J 8.1 Hz, 3-H), 4.51 (dd, 1H, J 6.7 and 8.1 Hz, 2-H), 3.06 (s, 3H, OMe) and 2.92 (dd, 1H, J 6.7 and 8.1 Hz, NH); δ (^{13}C, $CDCl_3$+2 drops d_6-DMSO): 172.9 (CO), 136.6 (C_q), 136.2 (2 x C_q), 133.7, 133.5, (C_q), 129.3, 128.4, 128.0, 126.8, 126.7, 126.5, 124.6, 122.7, 122.3, 119.7, 118.7, 111.9 (ArCH), 109.7 (C_q), 95.6 (C_4), 67.8 (C_2), 63.9 (C_3), 51.9 (C_5) and 46.3 (OCH_3); ν_{max} (KBr) 3418, 3356, 2948, 1742, 1543, 1361, 1204 and 739 cm^{-1}; m/z (ES): 417 ($M^{+\cdot}$), 416 ($M^{+\cdot}$+1, 100).



nOe data for *exo*-**10c**:

	% Enhancement					
Irradiated proton	H-2	H-3	H-4	H-5	H-2′	Aryl
H-1	5.4	-	-	-	5.8	4.8,4.0
H-2		9.4	-	3.5	-	-
H-3	11.8		3.6	5.2	2.5	9.3
H-4	-	3.5		1.5	9.2	4.1, 4.9
H-5	3.6	4.3	-		-	10.3,3.5

Methyl 3-(1H-indol-3-yl)-2-methyl-5-(2-naphthyl)-4-nitro-prolinate (9d) Obtained from imine **6b** (241 mg, 1 mmol), *E*-nitrostyrene **7b** (188 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 18 h. Purification by triturating with ether and filtering afforded the product (258 mg, 60%) as a pale orange amorphous solid, m.p. 190-193 °C. Found: C, 70.05; H, 5.25; N, 9.80. $C_{25}H_{23}N_3O_4$ requires C, 69.90; H, 5.40; N, 9.80 %; δ (^{1}H, 250 MHz, $CDCl_3$+2 drops d_6-DMSO): 10.33 (bs, 1H, indole NH), 7.42 (s, 1H, ArH), 7.33-6.50 (m, 11H, ArH), 5.43 (bt, 1H, J 7.7 Hz, 4-H), 4.80 (bt, 1H, J 9.1 Hz, 5-H), 4.35 (bd, 1H, J 7.7 Hz, 3-H), 3.26 (s, 3H, OMe), 3.09 (bd, 1H, J 9.1 Hz, NH), 0.75 (s, 3H, CH_3); δ (^{13}C, $CDCl_3$+2 drops DMSO): 175.5 (CO), 136.6, 133.9, 133.4, 133.2 (C_q), 128.4, 127.9 (ArCH), 127.3 (C_q), 126.6 (2 x ArCH), 126.3, 125.1, 123.4, 122.1 119,6, 118.9, 112.1 (ArCH), 109.9 (C_q), 96.6 (C_4), 68.6 (C_2), 64.4 (C_3), 53.1 (C_5), 50.2 (OCH_3) and 21.9 (CH_3); ν_{max} (KBr): 3070, 3425, 1722, 1544, 1456, 1395, 1139, 855, 819 and 747 cm^{-1}; m/z (ES): 430 ($M^{+\cdot}$+1, 100), 428 ($M^{+\cdot}$-1, 100).

Methyl 2-benzyl-3-(1H-indol-3-yl)-5-(2-naphthyl)-4-nitro-prolinate (9e) Obtained from imine **6c** (377 mg, 1 mmol), *E*-nitrostyrene **7b** (188 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 18 h. Purification by flash chromatography eluting with 19:1 v/v dichloromethane /hexane afforded the product (303 mg, 60%) as pale yellow needles, m.p. 143-146 °C. Found (HRMS, M^+ +Na): 528.1899. $C_{31}H_{27}N_3O_4Na$ requires: 528.1899; δ (^{1}H, 250 MHz): 8.30 (s, 1H, indole NH), 7.98 (s, 1H, ArH), 7.85-7.77 (m, 4H, ArH), 7.49-7.42 (m, 4H, ArH), 7.26-7.10 (m, 8H, ArH), 5.81 (dd, 1H, J 5.0 and 7.1 Hz, 4-H), 5.46 (dd, 1H, J 7.1 and 9.3 Hz, 5-H), 4.90 (d, 1H, J 5.0 Hz, 3-H), 3.75 (s, 3H, OMe), 3.53 (d, 1H, J 9.3 Hz, NH) and 2.86 (S_{AB}, 2H, CH_2); δ (^{13}C): 174.2 (CO), 136.7, 136.1, 133.4, 133.2, 133 (C_q), 130.0, 128.9, 128.4, 128.2, 128.0, 127.7 (ArCH), 127.3 (C_q), 126.8, 126.4, 126.2, 124.6, 122.8, 120.4, 119.2, 111.6 (ArCH), 111.0 (C_q), 96.8 (C_4), 73.1

(C_2) 65.2 (C_3), 52.4 (C_5), 50.6 (OCH_3) and 40.6 (CH_2); ν_{max} (KBr) 3377, 3057, 1727, 1555, 1457, 1430, 1370, 1200, 819, 749 and 707 cm^{-1}; m/z (ES^+): 530 ($M^{+\cdot}$+2+Na), 529 ($M^{+\cdot}$+1+Na), 506 ($M^{+\cdot}$+1, 100), (ES^-) 505 ($M^{+\cdot}$), 504 ($M^{+\cdot}$-1, 100).

Methyl 5-(1,1'-biphenyl-4-yl)-3-(1H-indol-3-yl)-4-nitro-prolinate (9f and 10f) Obtained from imine **6d** (253 mg, 1 mmol), *E*-nitrostyrene **7b** (188 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 18 h. Purification by SPE-Anachem 20 g SI Mega Bond-Elut cartridge using 100% hexane to 100% ethyl acetate gradient elution afforded first *endo*-**9f** (304 mg, 69%), followed by *exo*-**10f** (114 mg, 26%).

endo-**9f**: Obtained as colourless plates, m.p. 152-154 °C. Found: C, 70.80; H, 5.30; N, 9.25. $C_{26}H_{23}N_3O_4$ requires C, 70.75; H, 5.25; N, 9.50 %; δ (^{1}H, 300 MHz): 8.30 (bs, 1H, indole NH), 7.66-7.19 (m, 14H, ArH), 5.43 (dd, 1H, J 2.6 and 6.0 Hz, 4-H), 4.97 (d, 1H, J 6.0 Hz, 5-H), 4.58 (dd, 1H, J 2.6 and 6.8 Hz, 3-H), 4.43 (d, 1H, J 6.8 Hz, 2-H), 3.85 (s, 3H, OMe) and 3.56 (m, 1H, NH); δ (^{13}C): 172.6 (CO), 141.8, 140.7, 137.1, 133.7 (C_q), 129.2 (2 x ArCH), 127.9 (ArCH), 127.8 (2 x ArCH), 127.5 (2 x ArCH), 127.2 (2 x ArCH), 126.3 (C_q), 123.5 (indole $C_{2'}$), 122.3 (indole $C_{5'}$), 120.8 (indole $C_{4'}$), 118.9 (indole $C_{6'}$), 113.9 (indole $C_{3'}$), 112.1 (indole $C_{7'}$), 96.5 (C_4), 67.5 (C_2), 65.9 (C_3), 53.1 (C_5) and 48.6 (OCH_3); ν_{max} (KBr) 3294, 3038, 2953, 2903, 1735, 1542, 1372, 1212, 1095, 835, 765, 745 and 701 cm^{-1}; m/z (ES^+): 464 ($M^{+\cdot}$+Na), 443 ($M^{+\cdot}$+2), 442 ($M^{+\cdot}$+1, 100); (ES^-): 441 ($M^{+\cdot}$), 440 ($M^{+\cdot}$-1, 100).

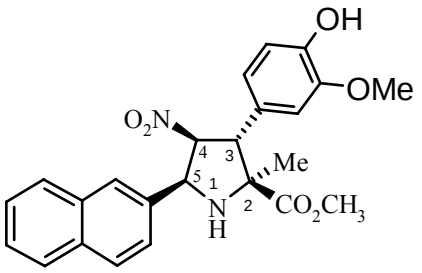
exo-**10f**: Obtained as pale orange plates, m.p. 171-173 °C. Found: C, 70.50; H, 5.10; N, 9.25. $C_{26}H_{23}N_3O_4$ requires C, 70.75; H, 5.25; N, 9.50 %; δ (^{1}H, 300 MHz): 8.21 (bs, 1H, indole NH), 7.67-7.06 (m, 14H, ArH), 5.31 (t, 1H, J 7.9 Hz, 4-H), 4.88 (d, 1H, J 7.9 Hz, 5-H), 4.76 (t, 1H, J 7.9 Hz, 3-H), 4.63 (d, 1H, J 7.9 Hz, 2-H), 3.18 (s, 3H, OMe) and 2.92 (bs, 1H, NH); δ (^{13}C): 172.8 (CO), 142.1, 140.9, 137.6, 136.4, 130 (C_q), 129.2 (2 x ArCH), 128.1 (2 x ArCH), 127.9 (C_q), 127.6 (2 x ArCH), 127.5 (2 x ArCH), 123.1, 122.2, 120.4, 119.2 (indole $C_{2'-6'}$), 111.6 (indole $C_{7'}$), 111.3 ($C_{3'}$), 95.8 (C_4), 67.6 (C_2), 64.1 (C_3), 52.1 (C_5) and 46.2 (OCH_3); ν_{max} (KBr): 3382, 3059, 2954, 2873, 1743, 1547, 1362, 1200, 909, 853, 768, 734 and 702 cm^{-1}; m/z (ES^+): 443 ($M^{+\cdot}$+2), 442 ($M^{+\cdot}$+1, 100); (ES^-): 441 ($M^{+\cdot}$), 440 ($M^{+\cdot}$-1, 100).

Methyl 5-(1,1'-biphenyl-4-yl)-3-(1H-indol-3-yl)-2-methyl-4-nitro-prolinate (9g) Obtained from imine **6e** (267 mg, 1 mmol), *E*-nitrostyrene **7b** (188 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 18 h. Purification by flash chromatography eluting with 9:1 v/v dichloromethane/hexane afforded the product (327 mg, 72%) as pale orange plates m.p. 132-136 °C. Found: C, 71.15; H, 5.30; N, 9.15. $C_{27}H_{25}N_3O_4$ requires C, 71.20; H, 5.55; N, 9.20 %; δ (^{1}H, 250 MHz): 8.31 (bs, 1H, indole NH), 7.69-7.14 (m, 14H, ArH), 5.75 (dd, 1H, J 6.5 and 7.5 Hz, 4-H), 5.21 (d, 1H, J 7.5 Hz, 5-H), 4.90 (d, 1H, J 6.5 Hz, 3-H), 3.86 (s, 3H, OMe) and 1.32 (s, 3H, CH_3); δ (^{13}C): 175.7 (CO), 142.0, 140.8, 136.5, 134.9 (C_q), 129.2 (2 x ArCH), 127.9 (ArCH), 127.8, 127.5 (3 x ArCH), 127.4 (C_q), 123.1, 122.8, 120.6, 119.5 (indole $C_{2'-6'}$), 111.9 (indole $C_{7'}$), 111.5 ($C_{3'}$), 96.8 (C_4), 69.0 (C_2), 64.9 (C_3), 53.4 (C_5), 50.4 (OCH_3) and 22.3 (CH_3); ν_{max} (KBr): 3406, 3298, 3039, 1735, 1543, 1435, 1251, 1138, 1115, 846, 764, 745 and 700 cm^{-1}; m/z (%, FAB): 456 ($M^{+\cdot}$+1, 80), 308 (100), 268(85); m/z (ES^+): 479 ($M^{+\cdot}$+1+Na), 478 ($M^{+\cdot}$+Na), 456 ($M^{+\cdot}$+1, 100); (ES^-): 455 ($M^{+\cdot}$), 454 ($M^{+\cdot}$-1).

Methyl 2-benzyl-5-(1,1'-biphenyl-4-yl)-3-(1H-indol-3-yl)-4-nitro-prolinate (9h) Obtained from imine **6f** (343 mg, 1 mmol), *E*-nitrostyrene **7b** (188 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 18 h. Purification by flash chromatography eluting with 9:1 v/v dichloromethane/hexane afforded the product (330 mg, 62%) as pale yellow plates, m.p. 174-178 °C. Found: C, 74.55; H, 5.50; N, 7.90. $C_{33}H_{29}N_3O_4$ requires C, 74.55; H, 5.50; N, 7.90 %; δ (^{1}H, 250 MHz): 8.30 (bs, 1H, indole NH), 7.90-6.90 (m, 19H, ArH), 5.75 (dd, 1H, J 6.6 and 5.2 Hz, 4-H), 5.34 (d, 1H, J 6.6 Hz, 5-H), 4.87 (d, 1H, J 5.2 Hz, 3-H), 3.73 (s, 3H, OMe), 3.42 (bs, 1H, NH) and 2.84 (s, 2H, CH_2); δ (^{13}C) 174.6 (CO), 142.1, 140.9, 137.1, 136.5, 135.1 (C_q), 130.4, 129.2, 128.5 (2 x ArCH), 127.9, 127.8 (3 x ArCH), 127.7 (C_q), 127.5 (2 x ArCH), 127.2, 123.2, 120.8, 119.6, 111.9 (ArCH), 111.4 ($C_{3'}$), 97.2 (C_4), 73.4 (C_2), 65.2 (C_3), 52.9 (C_5) 50.8 (OCH_3) and 41.0 (CH_2); ν_{max} (KBr): 3381, 3055, 2963, 1728, 1553, 1457, 1428, 1370, 1200, 819, 748 and 706 cm^{-1}; m/z (%, FAB^+): 532 ($M^{+\cdot}$+1, 80), 308 (100).

Methyl 3-(4-hydroxy-3-methoxyphenyl)-5-(2-naphthyl)-4-nitro-prolinate (9i) Obtained from imine **6a** (227 mg, 1 mmol), *E*-nitrostyrene **7c** (195 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 16 h. Trituration with 9:1 v/v dichloromethane/methanol and filtration afforded the product (177 mg, 42%) as colourless plates, m.p. 208-210 °C. Found: C, 65.40; H, 5.25; N, 6.50. $C_{23}H_{22}N_2O_6$ requires C, 65.40; H, 5.25; N, 6.65 %; δ (^{1}H, 300 MHz): 8.0 (bs, 1H, OH), 7.93 (d, 1H, J 8.7 Hz, ArH), 7.86 (dd, 2H, J 6.0 and 3.4 Hz, ArH), 7.72 (dd, 1H, ArH), 7.52 (dd, 2H, J 6.0 and 3.4 Hz ArH), 6.85 (d, 1H, J 8.7 Hz, ArH), 6.78 (m, 2H, ArH), 5.70 (m, 1H, NH), 5.26 (t, 1H, J 7.7 Hz, 4-H), 4.93 (d, 1H, J 7.7 Hz, 5-H), 4.55 (d, 1H, J 8.7 Hz, 2-H), 4.35 (dd, 1H, J 8.7 and 7.7 Hz, 3-H), 3.84 (s, 3H, CO_2Me) and 3.42 (s, 3H, OMe); δ (^{1}H, 250 MHz, D_6 DMSO): 9.06 (s, 1H, OH), 7.92 (m, 4H, ArH), 7.61 (dd, 1H, J 1.5 and 8.5 Hz, ArH), 7.53 (m, 2H, ArH), 7.02 (d, 1H, J 1.8 Hz, ArH), 6.82 (dd, 1H, J 1.8 and 8.1 Hz, ArH), 6.75 (d, 1H, J 8.1 Hz, ArH), 5.71 (dd, 1H, J 5.0 and 7.9 Hz, NO_2CH), 5.22 (t, 1H, J 7.9 Hz, naphthyl-CH), 4.08 (m, 2H, $H+H_2$), 3.93 (t, 1H, J 7.9 Hz, phenyl-CH), 3.81 (s, 3H, CO_2Me) and 3.71 (s, 3H, OMe); δ (^{13}C, D_6 DMSO): 172.3 (CO), 148.1, 146.4, 135.1, 133.0, 132.9, 129.2 (C_q), 128.3, 127.9, 127.8, 126.6, 126.5, 126.0, 125.7, 120.9, 115.8, 112.3 (ArCH), 96.5 (C_4), 66.5 (C_2), 65.6 (C_3), 56.1 ($ArOCH_3$), 54.0 ($CO_2\underline{C}H_3$) and 52.5 (C_5); ν_{max} (KBr): cm^{-1}; m/z (ES^+): 423 ($M^{+\cdot}$+1, 100).

Methyl 3-(4-hydroxy-3-methoxyphenyl)-2-methyl-5-(2-naphthyl)-4-nitro-prolinate (9j) Obtained from imine **6b** (241 mg, 1 mmol), *E*-nitrostyrene **7c** (195 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 17 h. Purification by triturating with dichloromethane and filtering afforded the product (396 mg, 91%) as a pale yellow solid, m.p. 164-166 °C. Found: C, 65.90; H, 5.55; N, 6.40. $C_{24}H_{24}N_2O_6$ requires C, 66.05; H, 5.55; N, 6.40 %; δ (^{1}H, 250 MHz, d_6-DMSO): 9.07 (s, 1H, OH), 7.96-7.87 (m, 4H, ArH), 7.64-7.49 (m, 3H, ArH), 6.95 (d, 1H, J 1.9 Hz, ArH), 6.83 (dd, 1H, J 1.9 and 8.2 Hz, ArH), 6.74 (d, 1H, J 8.2 Hz, ArH), 6.27 (t, 1H, J 8.6 Hz, 4-H), 5.29 (t, 1H, J 8.6 Hz, 5-H), 4.53 (d, 1H, J 8.6 Hz, 3-H), 3.93 (d, 1H, J 8.6 Hz, NH), 3.81 (s, 3H, CO_2Me), 3.79 (s, 3H, OMe) and 1.21 (CH_3); δ (^{13}C, $CDCl_3$ +2 drops DMSO): 174.7 (CO), 147.5, 146.3, 134.0, 133.1, 132.9 (C_q), 128.0, 127.9, 127.6 (ArCH), 126.3 (C_q), 126.1, 125.0, 120.8, 115.4, 112.7 (ArCH), 95.0 (C_4), 68.3 (C_2), 63.8 (C_3), 56.1 (ArO<u>C</u>H$_3$), 56.0 (CO_2<u>C</u>H$_3$), 52.7 (C_5) and 21.4 (CH_3); ν_{max} (KBr): 3294, 2952, 1740, 1547, 1436, 1264, 1128, 863, 832 and 746 cm^{-1}; m/z (ES$^+$): 460 ($M^{+\cdot}$+1+Na), 437 ($M^{+\cdot}$+1, 100); (ES$^-$): 436 ($M^{+\cdot}$), 435 ($M^{+\cdot}$-1, 100).



nOe data for **9j**:

	% Enhancement					
Irradiated proton	H-3	H-4	H-5	Phenyl	Naph-	CH_3
H-3		4.2	-	10.7	1.3, 1.4	11.8
H-4	1.9		4.8	7.9	2.8, 2.4	-
H-5	-	8.2		3.0	5.3, 4.8	3.3
CH_3	0.4	0.8	2.0	1.8	-	-

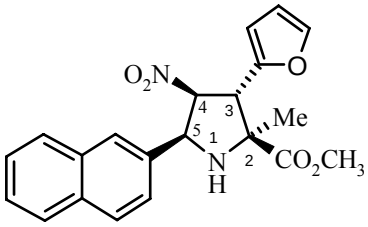
Methyl 5-(1,1'-biphenyl-4-yl)-3-(4-hydroxy-3-methoxyphenyl)-4-nitro-prolinate (9k) Obtained from imine **6d** (401 mg, 1.6 mmol), *E*-nitrostyrene **7c** (309 mg, 1.6 mmol), triethylamine (0.33 mL, 2.4 mmol) and silver acetate (395 mg, 2.4 mmol) in toluene (30 mL) over 16 h. Purification by triturating with 9:1 v/v ethyl acetate/hexane afforded the product (367 mg, 82%) as a colourless solid, m.p. 187-190 °C. HRMS (M^+ + H): 449.1710. $C_{25}H_{24}N_2O_6$ requires 449.1712. δ (^{1}H, 300 MHz, $CDCl_3$ + 2 drops d_6-DMSO): 7.56-7.52 (m, 4H, ArH), 7.42-7.28 (m, 5H, ArH), 6.95 (s, 1H, OH), 6.90 (d, 1H, J 7.5 Hz, ArH), 6.75 (dd, 1H, J 2.3 and 7.5 Hz, ArH), 6.74 (s, 1H, ArH), 5.70 (m, 1H, NH), 5.24 (dd, 1H, J 3.4 and 6.4 Hz, 4-H), 4.90 (dd, 1H, J 6.4 and 10.9 Hz, 5-H), 4.12 (m, 2H, 2-H + 3-H), 3.87 (s, 3H, CO_2Me), 3.78 (s, 3H, OMe) and 3.32 (m, 1H, OH); δ (^{13}C, $CDCl_3$ + 2 drops DMSO): 172.3 (CO), 147.8, 146.3, 130.2 (C_q), 129.1 (2 x ArCH), 127.9 (ArCH), 127.7 (2 x ArCH), 127.4 (2 x ArCH), 127.3 (2 x ArCH), 120.1, 115.9, 111.2 (ArCH), 104.4 (C_q), 97.5 (C_4), 73.1 (C_2), 67.6 (C_3), 55.5 ($ArOCH_3$), 53.0 (C_5) and 40.7 (OCH_3); ν_{max} (KBr): 3459, 3254, 3008, 2956, 1739, 1601, 1555, 1457, 1438, 1367, 1204, 1008 816, 759 and 697 cm^{-1}; m/z (ES$^+$): 473 ($M^{+\cdot}$+Na+2), 472 ($M^{+\cdot}$+Na+1), 471 ($M^{+\cdot}$+Na), 449 ($M^{+\cdot}$+1, 100); (ES$^-$): 448 ($M^{+\cdot}$), 447 ($M^{+\cdot}$-1, 100); m/z (%, FAB$^+$): 449 ($M^{+\cdot}$+1, 100), 315 (50).

Methyl 5-(1,1'-biphenyl-4-yl)-3-(4-hydroxy-3-methoxyphenyl)-2-methyl-4-nitro-prolinate (9l) Obtained from imine **6e** (267 mg, 1 mmol), *E*-nitrostyrene **7c** (195 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 18 h. Purification by flash chromatography eluting with dichloromethane afforded the product (300 mg, 65%) as a pale yellow amorphous solid, m.p. 172-175 °C. Found: C, 67.70; H, 5.70; N, 6.35. $C_{26}H_{26}N_2O_6$ requires C, 67.50; H, 5.70; N, 6.05 %; δ (^{1}H, 300 MHz): 7.62-7.59 (m, 5H, ArH), 7.55 (m, 4H, ArH), 6.92 (m, 1H, ArH), 6.78 (m, 2H, ArH), 5.69 (t, 1H, J 7.3 Hz, 4-H), 5.12 (d, 1H, J 7.3 Hz, 5-H), 4.53 (d, 1H, J 7.3 Hz, 3-H), 3.88 (s, 6H, CO_2Me and OMe), 3.30 (m, 1H, NH) and 1.24 (s, 3H, CH_3); δ (^{13}C, $CDCl_3$ + 2 drops d_6-DMSO): 175.1 (CO), 147.6, 146.5, 141.5, 140.6, 135.4 (C_q), 129.1 (2 x ArCH), 127.8 (3 x ArCH), 127.4 (2 x ArCH), 127.3 (2 x ArCH), 126.8 (C_q), 120.9, 115.5, 112.8 (ArCH), 104.4 (C_q), 95.6 (C_4), 68.8 (C_2), 64.3 (C_3), 56.7 ($ArOCH_3$), 56.3 (C_5), 53.2 (OCH_3) and 21.9 (CH_3); ν_{max} (KBr): 3258, 1736, 1600, 1558, 1437, 1258, 1137, 853, 760 and 717 cm^{-1}; m/z (%, FAB): 463 ($M^{+\cdot}$+1, 100), 315 (95); m/z (ES$^+$): 485 ($M^{+\cdot}$+Na), 463 ($M^{+\cdot}$+1, 100); (ES$^-$): 462 ($M^{+\cdot}$), 461 ($M^{+\cdot}$-1, 100).

Methyl 3-(2-furyl)-5-(2-naphthyl)-4-nitro-prolinate (9m) Obtained from imine **6a** (227 mg, 1 mmol), *E*-nitrostyrene **7d** (139 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 15 h. Trituration with ether and filtration afforded the product (318 mg, 87%) as pale yellow needles, m.p. 131-133 °C. Found: C, 65.30; H, 4.90; N, 7.80. $C_{20}H_{18}N_2O_5$ requires C, 65.55; H, 4.95; N, 7.65 %; δ (^{1}H, 300 MHz): 7.87-7.83 (m, 4H, ArH), 7.54-7.47 (m, 3H, ArH), 7.43 (d, 1H, J 1.9 Hz, furyl-H$_{5'}$), 6.42 (dd, 1H, J 1.9 and 3.4 Hz, furyl-H$_{4'}$), 6.34 (d, 1H, J 3.4 Hz, furyl-H$_{3'}$), 5.46 (dd, 1H, J 6.0 and 2.6 Hz, 4-H), 5.05 (bs, 1H, 5-H), 4.38 (dd, 1H, J 6.8 and 2.6 Hz, 3-H), 4.29 (bd, 1H, J 6.0 Hz, 2-H), 3.90 (s, 3H, OMe) and 3.48 (bs, 1H, NH); δ (^{13}C, $CDCl_3$ + 2 drops d_6-DMSO): 171.4 (CO), 150.7 (furan $C_{2'}$), 143.0 (furan $C_{5'}$) 133.1, 133.0 (C_q), 128.2, 128.1, 127.6 (ArCH), 126.5 (2 x ArCH), 125.6, 124.5 (ArCH), 110.8, 107.9 (furan $C_{3'}$, $C_{4'}$), 93.9 (C_4), 67.1 (C_2), 64.3 (C_3), 52.7 (C_5) and 48.2 (OCH_3); ν_{max} (KBr) 3302, 1743, 1541, 1436, 1127, 863, 812 and 747

cm^{-1}; m/z (ES^+) 390 ($M^{+\cdot}$+1+Na), 389 ($M^{+\cdot}$+ Na, 100), 367 ($M^{+\cdot}$+1); m/z (%, FAB): 367 ($M^{+\cdot}$+1, 100), 233 (55).

Methyl 3-(2-furyl)-2-methyl-5-(2-naphthyl)-4-nitro-prolinate (9n) Obtained from imine **6b** (241 mg, 1 mmol), *E*-nitrostyrene **7d** (139 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 18 h. Trituration with ether and filtration afforded the product (304 mg, 80%) as a colourless solid, m.p. 110-112 °C. Found: C, 66.20; H, 5.25; N, 7.35. $C_{21}H_{20}N_2O_5$ requires C, 66.30; H, 5.30; N, 7.35 %; δ (^{1}H, 250 MHz): 7.87-7.80 (m, 4H, ArH), 7.52-7.41 (m, 4H, ArH), 6.39 (dd, 1H, J 2.0 and 3.2 Hz, furyl-H), 6.31 (d, 1H, J 3.2 Hz, furyl-H), 5.69 (dd, 1H, J 4.5 and 6.8 Hz, 4-H), 5.28 (dd, 1H, J 6.8 and 10.1 Hz, 5-H), 4.64 (d, 1H, J 4.5 Hz, 3-H), 3.92 (s, 3H, OMe), 3.54 (d, 1H, J 10.1 Hz, NH) and 1.29 (s, 3H, CH_3); δ (^{13}C): 175.0 (CO), 150.1 (furan $C_{2'}$), 143.1 (furan $C_{5'}$) 133.8, 133.5 (C_q), 128.9, 128.6, 128.1, 126.9, 126.8, 126.4, 124.8 (ArCH), 111.2, 109.7 (furan $C_{3'}$, $C_{4'}$), 94.2 (C_4), 69.9 (C_2), 65.8 (C_3), 53.5 (C_5), 51.5 (OCH_3) and 22.5 (CH_3); ν_{max} (KBr): 3361, 2998, 2949, 1734, 1552, 1436, 1148, 1014, 863, 772 and 752 cm^{-1}; m/z (%): 379 ($M^{+\cdot}$-1, 10), 363 (25), 333 (40); m/z (ES): 404 ($M^{+\cdot}$+1+Na), 403 ($M^{+\cdot}$+Na), 381 ($M^{+\cdot}$+1, 100).



nOe data for **9n**:

	% Enhancement				
Irradiated proton	H-3	H-4	H-5	Furyl	Naph-
H-3		2.9	-	5.5	-
H-4	4.5		7.4	2.0	-
H-5		13.5		6.2	6.7
CH_3	1.5	0.8	2.1	-	-

Methyl 2-benzyl-3-(2-furyl)-5-(2-naphthyl)-4-nitro-prolinate (9o) Obtained from imine **6c** (377 mg, 1 mmol), *E*-nitrostyrene **7d** (139 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 16 h. Trituration with ether and filtration afforded the product (355 mg, 78%) as a pale orange amorphous solid, m.p. 151-154°C. Found: C, 70.80; H, 5.30; N, 6.05. $C_{27}H_{24}N_2O_5$ requires C, 71.05; H, 5.30; N, 6.15 %; δ (^{1}H, 300 MHz): 7.92 (bs, 1H, ArH), 7.87-7.79 (m, 4H, ArH), 7.53-7.47 (m, 4H, ArH), 7.25-7.14 (m, 5H, ArH), 6.48-6.44 (m, 2H, furyl-H), 5.63 (dd, 1H, J 3.8 and 6.4 Hz, 4-H), 5.34 (bt, 1H, J 7.7 Hz, 5-H), 4.55 (d, 1H, J 3.8 Hz, 3-H), 3.79 (s, 3H, OMe), 3.48 (bd, 1H, J 9.4 Hz, NH), 2.78 (AB, d, J 13.6 Hz, 1H, CH**H**) and 2.63 (AB, d, J 13.6 Hz, 1H, C**H**H) ; δ (^{13}C): 173.9 (CO), 149.9 (furan $C_{2'}$), 136.8, 133.8, 133.6, 132.7 (C_q), 130.4 (2 x ArCH), 128.6 (ArCH), 128.5 (2 x ArCH), 128.1, 127.4, 126.9, 126.8, 126.4, 124.9 (ArCH), 111.3, 110.5 (furan $C_{3'}$, $C_{4'}$), 94.4 (C_4), 74.4 (C_2), 66.1 (C_3), 53.0 (C_5), 52.3 (OCH_3) and 40.8 (CH_2); ν_{max} (film): 3328, 3122, 3056, 2951, 1740, 1602, 1542, 1455, 1429, 1195, 900, 868, 750 and 701 cm^{-1}; m/z (ES^+): 457 ($M^{+\cdot}$+1, 100).

Methyl 5-(1,1'-biphenyl-4-yl)-3-(2-furyl)-4-nitro-prolinate (9p) Obtained from imine **6d** (253 mg, 1 mmol), *E*-nitrostyrene **7d** (139 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 22 h. Purification by flash chromatography eluting with 19:1 v/v dichloromethane/ hexane afforded the product (384 mg, 98%) as a colourless powder, m.p. 144-148 °C. Found: C, 67.30; H, 5.15; N, 7.20. $C_{22}H_{20}N_2O_5$ requires C, 67.35; H, 5.15; N, 7.15 %. δ (^{1}H, 250 MHz): 7.61-7.51 (m, 4H, ArH), 7.48-7.30 (m, 6H, ArCH), 6.39 (dd, 1H, J 1.9 and 3.6 Hz, furyl-H), 6.31 (dd, 1H, J 0.5 and 3.6 Hz, furyl-H), 5.38 (dd, 1H, J 2.6 and 6.2 Hz, 4-H), 4.91 (dd, 1H, J 6.4 and 11.4 Hz, 5-H), 4.33 (dd, 1H, J 2.6 and 7.0 Hz, 3-H), 4.25 (dd, 1H, J 7.0 and 9.3 Hz, 2-H), 3.86 (s, 3H, OMe) and 3.37 (dd, 1H, J 9.3 and 11.4 Hz, NH); δ (^{13}C, 250 MHz): 171.8 (CO), 151.2 (furyl $C_{2'}$), 143.4 (furyl $C_{5'}$), 142.0, 140.7, 133.3 (C_q), 129.2 (2 x ArCH), 128.0 (ArCH), 127.9, 127.5, 127.3 (2 x ArCH), 111.2, 108.4 (furyl $C_{3'}$+$C_{4'}$), 94.4 (C_4), 67.9 (C_2), 65.2 (C_3), 53.3 (C_5) and 49.3 (OCH_3); ν_{max} (NaCl): 3375, 3030, 2952, 1742, 1551, 1437, 1214, 1008, 840, 766 and 699 cm^{-1}; m/z (%): 393 ($M^{+\cdot}$+1, 100).

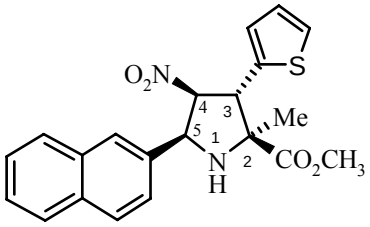
Methyl 5-(2-naphthyl)-4-nitro-3-thien-2-yl-prolinate (*endo*-9q and *exo*-10q) Obtained from imine **6a** (227 mg, 1 mmol), *E*-nitrostyrene **7e** (155 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 16 h. Trituration with ether and filtration afforded the product (343 mg, 90%)(3:1 mixture of *endo*-**9q** and *exo*-**10q**) as colourless plates, m.p. 124-130 °C. Found: C, 62.70; H, 4.80; N, 7.30; S, 8.40. $C_{20}H_{18}N_2O_4S$ requires C, 62.80; H, 4.75; N, 7.30; S, 8.40 %; NMR for both isomers were assigned from the 3:1 mixture.

δ_A (^{1}H, 300 MHz) for *endo*-**9q**: 7.85-7.80 (m, 4H, ArH), 7.60-7.55 (m, 4H, ArH), 7.03 (m, 2H, thienyl-H), 5.38 (dd, 1H, J 3.1 and 6.2 Hz, 4-H), 5.06 (d, 1H, J 6.2 Hz, 5-H), 4.59 (dd, 1H, J 3.1 and 7.1 Hz, 3-H), 4.26 (d, 1H, J 7.1 Hz, 2-H) and 3.88 (s, 3H, OMe); δ_A (^{13}C): 171.7 (CO), 141.6, 133.7, 133.5, 131.7 (C_q), 129.0, 128.6, 128.1, 128.0, 127.0, 126.9, 126.3, 126.1, 125.8, 124.5, (ArCH), 97.2 (C_4), 68.5 (C_2), 67.8 (C_3), 53.3 (C_5) and 50.9 (OCH_3);

δ_B (^{1}H, 300 MHz) for *exo*-**10q**: 8.06-7.84 (m, 4H, ArH), 7.69-7.48 (m, 3H, ArH), 7.23 (dd, 1H, J 1.6, 4.9Hz, thienyl-H), 6.97 (m, 2H, thienyl-H), 5.24 (dd, 1H, J 6.5 and 7.6 Hz, 4-H), 4.87 (d, 1H, J 7.6 Hz, 5-H), 4.69 (dd, 1H, J 6.5 and 8.1 Hz, 3-H), 4.55 (d, 1H, J 8.1 Hz, 2-H) and 3.50 (s, 3H, OMe); δ_B (^{13}C): 171.6 (CO), 138.3, 135.3, 133.8 (C_q), 129.6, 128.2, 127.4, 126.8, 124.5, (ArCH), 96.7 (C_4), 68.2

(C_2), 64.9 (C_3), 52.6 (C_5) and 49.4 (OCH_3); ν_{max} (KBr): 3365, 3322, 2950, 1740, 1546, 1436, 1203, 832, 751 and 709 cm^{-1}; m/z (%, FAB) 383 ($M^{+\cdot}$, 100); m/z (ES^+): 406 (M^+ +1+Na, 22), 405 ($M^{+\cdot}$+Na, 100), 383 ($M^{+\cdot}$+1, 48).

Methyl 2-methyl-5-(2-naphthyl)-4-nitro-3-thien-2-yl-prolinate (9r) Obtained from imine **6b** (241 mg, 1 mmol), *E*-nitrostyrene **7e** (155 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 16 h. The crude material was washed with ether and filtered to afford the product (360 mg, 91%) as pale brown prisms, m.p. 156-158 °C. Found: C, 63.50; H, 5.00; N, 7.10; S, 8.20. $C_{21}H_{20}N_2O_4S$ requires C, 63.60; H, 5.10; N, 7.05; S, 8.10 %; δ (^{1}H, 250 MHz): 7.88-7.80 (m, 4H, ArH), 7.53-7.45 (m, 3H, ArH), 7.29-7.27 (m, 1H, thienyl-H), 7.02 (m, 2H, thienyl-H), 5.68 (t, 1H, J 7.0 Hz, 4-H), 5.24 (t, 1H, J 9.0 Hz, 5-H), 4.93 (d, 1H, J 6.8 Hz, 3-H), 3.95 (s, 3H, OMe), 3.35 (d, 1H, J 9.4 Hz NH) and 1.34 (s, 3H, CH_3); δ(^{13}C): 174.7 (CO), 138.2, 133.8, 133.5, 133.2 (C_q), 128.8, 128.6, 128.1, 127.5, 127.1, 126.9, 126.8, 126.7 125.7, 124.9, (ArCH), 96.3 (C_4), 68.8 (C_2), 64.4 (C_3), 53.4 (C_5), 52.3 (OCH_3) and 22.2 (CH_3); ν_{max} (KBr): 3355, 2997, 2947, 1747, 1553, 1435, 1147, 822, 752 and 713 cm^{-1}; m/z (%, FAB): 397 ($M^{+\cdot}$+1, 85); m/z (ES^+): 420 (M^+ +1+Na), 419 ($M^{+\cdot}$+Na), 397 ($M^{+\cdot}$+1, 71).



nOe data for **9r**:

	% Enhancement				
Irradiated proton	H-3	H-4	H-5	Thiophe-	Naph-
H-3		1.9	-	3.0	1.5, 1.3
H-4	2.5		7.8	4.5	-
H-5	-	9.8		0.8	4.6, 4.7

Methyl 2-benzyl-5-(2-naphthyl)-4-nitro-3-thien-2-yl-prolinate (9s) Obtained from imine **6c** (317 mg, 1 mmol), *E*-nitrostyrene **7e** (155 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 17 h. Purification was achieved by triturating the residue with ether and filtration to afford the product (330 mg, 70%) as a pale brown amorphous solid, m.p. 158-161 °C. Found: C, 68.35; H, 5.15; N, 6.10; S, 7.00. $C_{27}H_{24}N_2O_4S$ requires C, 68.65; H, 5.10; N, 5.95; S, 6.80 %; δ (^{1}H, 250 MHz): 7.93 (bs, 1H, ArH), 7.87-7.00 (m, 14H, ArH), 5.72 (dd, 1H, J 5.5 and 7.3 Hz, 4-H), 5.38 (bs, 1H, 5-H), 4.87 (d, 1H, J 5.5 Hz, 3-H), 3.81 (s, 3H, OMe), 3.39 (bs, 1H, NH) and 2.83 (s, 2H, CH_2); δ (^{13}C): 173.9 (CO), 137.9, 136.6, 133.8, 133.5, 133.1 (C_q), 130.4 (2 x ArCH), 128.9 (ArCH), 128.6 (3 x ArCH), 128.1, 128.0, 127.6, 127.5, 127.0, 126.9, 126.7, 126.0, 124.9 (ArCH), 97.1 (C_4), 73.1 (C_2), 64.9 (C_3), 53.4 (C_5), 53.0 (OCH_3) and 40.9 (CH_2); ν_{max} (KBr) 3330, 3118, 3094, 3055, 2948, 1743, 1543, 1453, 1428, 1194, 954, 902, 867, 749 and 702 cm^{-1}; m/z (ES^+): 496 (M^+ +1+Na), 495 ($M^{+\cdot}$+Na), 473 ($M^{+\cdot}$+1, 100); (ES^-): 471 ($M^{+\cdot}$-1, 100).m/z (FAB^+): 495 ($M^{+\cdot}$+Na, 10), 473 ($M^{+\cdot}$+ 1, 100).

Methyl 5-(1,1'-biphenyl-4-yl)-4-nitro-3-thien-2-yl-prolinate (9t) Obtained from imine **6d** (253 mg, 1 mmol), *E*-nitrostyrene **7e** (155 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 16 h. Purification was achieved by dissolving the residue in toluene and adding ether dropwise which afforded the product (285 mg, 70%) as colourless needles, m.p. 162-164 °C. Found: C, 64.65; H, 5.05; N, 6.85; S, 7.85. $C_{22}H_{20}N_2O_4S$ requires C, 64.70; H, 4.95; N, 6.85; S, 7.85 %; δ (^{1}H, 300 MHz): 7.60-7.48 (m, 5H, ArH), 7.43-7.24 (m, 5H, ArH and thienyl-H), 6.31 (dd, 1H, J 2.3 and 3.0 Hz, thienyl-H), 6.23 (d, 1H, J 3.0 Hz, thienyl-H), 5.30 (dd, 1H, J 3.0 and 6.0 Hz, 4-H), 4.83 (bd, 1H, J 6.0 Hz, 5-H), 4.25 (dd, 1H, J 3.0 and 6.8 Hz, 3-H), 4.15 (d, 1H, J 6.8 Hz, 2-H), and 3.79 (s, 3H, OMe); δ (^{13}C): 171.5 (CO), 151.0 ($C_{2'}$), 143.2 (ArCH), 141.8, 140.5, 133.0 (C_q), 129.0 (2 x ArCH), 127.7 (ArCH), 127.6 (2 x ArCH), 127.3 (2 x ArCH), 127.0 (2 x ArCH), 111.0, 108.1 (thienyl CH), 94.2 (C_4), 67.6 (C_3) 65.0 (C_5), 53.0 (C_2) and 49.1 (OCH_3); ν_{max} (KBr): 3303, 3031, 2998, 2958, 1744, 1547, 1435, 1211, 1012, 830, 761 and 696 cm^{-1}; m/z (ES^+): 431 ($M^{+\cdot}$+Na), 393 ($M^{+\cdot}$-15, 100), 375 ($M^{+\cdot}$-33).

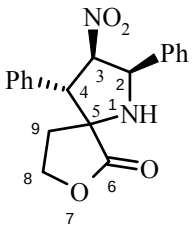
Methyl 5-(2-naphthyl)-4-nitro-3-pyridin-3-yl-prolinate (9u) Obtained from imine **6a** (227 mg, 1 mmol), *E*-nitrostyrene **7f** (150 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver oxide (30 mg, 0.13 mmol) in toluene (20 mL) over 16 h. Purification was achieved by washing with ether and filtering off the product (150 mg, 40%) as pale yellow plates, m.p. 159-162 °C. Found: C, 66.95; H, 5.20; N, 11.30. $C_{21}H_{19}N_3O_4$ requires C, 66.85; H, 5.05; N, 11.15 %; δ (^{1}H, 300 MHz, $CDCl_3$ + 2 drops d_6-DMSO): 8.39 (bd, 1H, J 1.9 Hz, pyridyl-H), 8.34 (dd, 1H, J 1.9 and 4.7 Hz, pyridyl-H), 7.66 (bs, 1H, ArH), 7.62-7.56 (m, 3H, ArH), 7.52 (dt, 1H, J 1.9 and 7.9 Hz, pyridyl-H), 7.27-7.23 (m, 3H, ArH), 7.13 (dd, 1H, J 4.7 and 7.9 Hz, pyridyl-H), 5.28 (dd, 1H, J 4.7 and 7.3 Hz, 4-H), 4.94 (dd, 1H, J 7.3 and 9.4 Hz, 5-H), 4.06 (dd, 2H, J 4.7 and 8.3 Hz, 3-H), 3.93 (t, 1H, J 8.3 Hz, 2-H), 3.57 (s, 3H, OMe) and 3.29 (bt, 1H, J 9.4 Hz, NH); δ (^{13}C, $CDCl_3$ +2 drops d_6-DMSO): 171.6 (CO), 149.8, 149.6 (pyridyl $C_{2'}$, $C_{6'}$), 135.5 (pyridyl CH), 134.3, 133.5, 133.3 (C_q), 128.7, 128.4, 128.0 (ArCH), 126.8 (2 x ArCH), 126.2, 124.7, 124.3, (ArCH), 96.4 (C_4), 67.6 (C_2), 67.2 (C_3), 53.1, (C_5) and 52.4 (OCH_3); ν_{max} (KBr): 3276, 3024, 2959, 1746, 1544, 1432, 1213, 832, 750 and 719 cm^{-1}; m/z (%, FAB): 378 ($M^{+\cdot}$+1, 80); m/z (ES^+): 401 (M^+ +1+Na), 400 ($M^{+\cdot}$+Na), 378 ($M^{+\cdot}$+1, 100); (ES^-): 377 ($M^{+\cdot}$) 376 ($M^{+\cdot}$-1, 100).

Methyl 2-methyl-5-(2-naphthyl)-4-nitro-3-pyridin-3-yl-prolinate (9v) Obtained from imine **6b** (241 mg, 1 mmol),

E-nitrostyrene **7f** (150 mg, 1 mmol), triethylamine (0.21 mL, 1.5 mmol) and silver acetate (250 mg, 1.5 mmol) in toluene (20 mL) over 18 h. Purification was achieved using a SPE-Anachem SI Mega Bond-Elut (20 g). Eluting with 100% hexane to 100% ethyl acetate gradient elution afforded the product (305 mg, 78 %) as a colourless powder, m.p. 127-129 °C. Found: C, 67.50; H, 5.35; N, 10.55. $C_{22}H_{21}N_3O_4$ requires C, 67.50; H, 5.40; N, 10.75 %; δ (^{1}H, 300 MHz): 8.63 (bs, 1H, pyridyl-H), 8.61 (dd, 1H, J 1.7 and 4.5 Hz, pyridyl-H), 7.92 (bs, 1H, ArH), 7.86 (m, 3H, ArH), 7.68 (dt, 1H, J 1.7 and 7.9 Hz, pyridyl-H), 7.51 (m, 3H, ArH), 7.38 (dd, 1H, J 4.5 and 7.9 Hz, ArH), 5.75 (dd, 1H, J 6.6 and 7.3 Hz, 4-H), 5.28 (d, 1H, J 7.3 Hz, 5-H), 4.64 (d, 1H, J 6.6 Hz, 3-H), 3.93 (s, 3H, OMe), 3.50 (bs, 1H, NH) and 1.29 (s, 3H, CH_3); δ (^{13}C): 174.6 (CO), 150.4, 149.9 (pyridyl $C_{2'}$, $C_{6'}$), 136.4 (ArCH), 133.8, 133.5, 132.9, 131.8 (C_q), 128.9, 128.6, 128.1, 126.93, 126.86, 126.7, 124.8, 123.9 (ArCH), 95.2 (C_4), 68.8 (C_2), 65.1 (C_3), 54.6 (C_5), 53.5 (OCH_3) and 22.8 (CH_3); ν_{max} (KBr) 3367, 3322, 3024, 2947, 1757, 1741, 1547, 1430, 1136, 819, 757 and 715 cm^{-1}; m/z (ES): 414 ($M^{+\cdot}$+Na), 393 ($M^{+\cdot}$+2), 392 ($M^{+\cdot}$+1, 100); (ES^-): 392, 391 ($M^{+\cdot}$), 390($M^{+\cdot}$-1, 100).

3-Nitro-2,4-diphenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14a and 15a) Obtained from imine **12a** (200 mg, 1.05 mmol), *E*-nitrostyrene (0.16 g, 1.05 mmol), triethylamine (0.16 mL, 1.55 mmol) and silver acetate (0.26 g, 1.6 mmol) in acetonitrile (10 mL) over 4 h. Purification by flash chromatography eluting with 4:1 v/v ether:hexane afforded first **15a** (70 mg, 20%), followed by **14a** (0.19 g, 54%) as colourless solids.

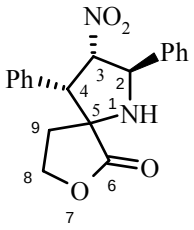
Cycloadduct 14a. Crystallised from dichloromethane /hexane as colourless plates, m.p. 144 -146 °C. Found: C, 67.20; H, 5.40; N, 8.10. $C_{19}H_{18}O_4N_2$ requires: C, 67.40; H, 5.40; N, 8.30 %; δ (^{1}H, 500 MHz): 7.42-7.26 (m, 10H, Ar-H), 5.79 (t, 1H, J 8.0 Hz, 3-H), 4.92 (dd, 1H, J 8.0 and 10.9 Hz, 2-H), 4.65 (d, 1H, J 8.0 Hz, 4-H), 4.18 (ddd, 1H, J 5.3, 8.0 and 8.9 Hz, 8-CH_2), 3.32 (dd, 1H, J 7.3 and 8.9 Hz, 8-CH_2), 3.19 (d, 1H, J 10.9 Hz, NH) and 2.28-2.18 (m, 2H, 9-CH_2); ν_{max} (film): 1768, 1552, 1497, 1456, 1370, 1219, 1181, 1146, 1125 and 1053 cm^{-1}; m/z (%): 339(M^++1, 0.4), 328(2.2), 248(54), 247(53), 232(86), 189(43), 149(60), 77(92) and 57(100).



nOe data for **14a**:

	% Enhancement					
Irradiated proton	H-4	H-3	H-2	NH	8-CH_2	ArH
H-4		-	-	2.0	-	7.3
H-3	1.0		6.8	-	-	8.5
H-2	-	6.7		1.0	3.8	5.6

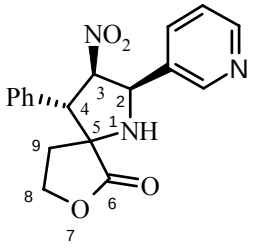
Cycloadduct 15a. Crystallised from dichloromethane/hexane as colourless plates, m.p. 174-176 °C. Found: C, 67.35; H, 5.50; N, 8.30. $C_{19}H_{18}O_4N_2$ requires: C, 67.40; H, 5.40; N, 8.30 %; δ (^{1}H, 500MHz), 7.65 (d, 2H, J 7.4 Hz, Ar-H), 7.41-7.26 (m, 8H, Ar-H), 5.76 (t, 1H, J 8.3 Hz, 3-H), 5.28 (d, 1H, J 8.3 Hz, 2-H), 4.28 (ddd, 1H, J 4.2, 6.8 and 9.3 Hz, 8-CH_2), 4.12-4.08 (m, 2H, 8-CH_2 and 4-H), 2.44 (b, 1H, NH), 2.36 (dt, 1H, J 6.8 and 13.6 Hz, 9-CH_2) and 2.27 (dt, 1H, J 6.8 and 10.3 Hz, 9-CH_2); ν_{max} (film): 1762, 1547, 1496, 1456, 1372, 1219, 1182 and 1022 cm^{-1}; m/z (%): 339(M^+ +1, 0.3), 292 (26), 248(66), 232(88), 193(100) and 115(89).



nOe data for **15a**:

	% Enhancement			
Irradiated proton	H-4	H-3	H-2	ArH
H-4		4.7	-	4.2
H-3	8.5		-	4.8
H-2	-	1.6		15.0

3-Nitro-4-phenyl-2-pyridin-3-yl-7-oxa-1-azaspiro[4.4]nonan-6-one (14b) Obtained from imine **12b** (200 mg, 1.05 mmol), *E*-nitrostyrene (0.16 g, 1.05 mmol), triethylamine (0.16 mL, 1.55 mmol) and silver acetate (0.26 g, 1.6 mmol) in acetonitrile (10 mL) over 4 h. Purification by flash chromatography eluting with ethyl acetate afforded the cycloadduct **14b** (144 mg, 40%) as a colourless solid together with small amount of epimerised cycloadduct. Product **14b** crystallised from dichloromethane/hexane as colourless needles, m.p. 170-172 °C. Found: C, 63.45; H, 5.00; N, 12.55. $C_{18}H_{17}O_4N_3$ requires: C, 63.71; H, 5.05; N, 12.38 %; δ (^{1}H, 250 MHz): 8.63 (m, 2H, pyridyl-H), 7.9 (m, 1H, pyridyl-H), 7.45-7.26 (m, 6H, pyridyl-H and Ar-H), 5.82 (t, 1H, J 8.3 Hz, 3-H), 4.96 (dd, 1H, J 8.3 and 10.2 Hz, 2-H), 4.65 (d, 1H, J 8.3 Hz, 4-H), 4.17 (dd, 1H, J 5.0 and 8.6 Hz, 8-CH_2), 3.28 (dd, 1H, J 7.4 and 8.6 Hz, 8-CH_2), 3.08 (d, 1H, J 10.2 Hz, NH) and 2.36-2.15 (m, 2H, 9-CH_2); ν_{max} (film): 1769, 1552, 1372, 1218, 1183 and 1024 cm^{-1}; m/z (%): 340 (M^+ +1, 7), 293(12), 249(59), 233(91), 194(100) and 115(21).



nOe data for **14b**:

	% Enhancement				
Irradiated proton	H-4	H-3	H-2	NH	ArH
H-4		-	-	1.8	12.0
H-3	-		7.7	-	13.4
H-2	-	8.4		1.7	7.9

3-Nitro-4-phenyl-2-N-sulphonylindol-3-yl-7-oxa-1-azaspiro[4.4]nonan-6-one (14c and 15c) Obtained from imine **12c** (200 mg, 0.54 mmol), *E*-nitrostyrene (0.08 mg, 0.54 mmol), triethylamine (0.08 mL, 0.6 mmol) and silver acetate (0.14 g, 0.59 mmol) in acetonitrile (20 mL) over 24 h. Purification by flash chromatography eluting with 9:1 v/v ether:hexane afforded first **15c** (191 mg, 68%) followed by **14c** (42 mg, 15%).

Cycloadduct 14c Crystallised from dichloromethane/hexane as colourless needles, m.p. 138-140 °C. Found (HRMS, M^++H): 518.1388. $C_{27}H_{23}O_6N_3S$ requires: 518.1386; δ (^{1}H, 250 MHz): 7.97-7.24 (m, 10H, ArH), 5.83 (t, 1H, J 7.5 Hz, 3-H), 5.12 (dd, 1H, J 7.5 and 11.0 Hz, 2-H), 4.68 (d, 1H, J 7.5 Hz, 4-H), 4.19 (ddd, 1H, J 5.9, 7.6 and 11.3 Hz, 8-CH_2), 3.36 (dd, 1H, J 7.2 and 11.3 Hz, 8-CH_2), 3.21 (d, 1H, J 11.0 Hz, NH) and 2.28-2.21(m, 2H, 9-CH_2); ν_{max} (film): 1769, 1552, 1448, 1368, 1216 and 1175 cm^{-1}; m/z (%): 517(1.3), 471(6), 427(9), 368(54), 285(11), 271(8), 227(28) and 77(100).

Cycloadduct 15c Crystallised from dichloromethane/hexanae as colourless plates, m.p. 157-159 °C. Found (HRMS, M^++H): 518.1390. $C_{27}H_{23}O_6N_3S$ requires: 518.1386; δ (^{1}H, 250 MHz): 7.98-7.23 (m, 10H, ArH), 5.73 (t, 1H, J 6.4 Hz, 3-H), 5.47 (d, 1H, J 6.4 Hz, 2-H), 4.34 (m, 1H, 8-CH_2), 4.16-4.07 (m, 2H, 8-CH_2 and 4-H), 2.66 (b, 1H, NH) and 2.48-2.32 (m, 2H, 9-CH_2); ν_{max} (film): 1766, 1549, 1448, 1371, 1175 and 1125 cm^{-1}; m/z (%): 517(M^+, 1.5), 427(28), 368(24), 329(6), 285(38), 230(41) and 77(100).

2-Cyclohexyl-3-nitro-4-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14d) Obtained from imine **12d** (1 g, 5.11 mmol), *E*-nitrostyrene (0.76 g, 5.11 mmol), triethylamine (0.8 mL, 5.62 mmol) and silver oxide (0.12 g, 0.5 mmol) in toluene (50 mL) over 1 h. Purification by flash chromatography eluting with 1:1 v/v ether:hexane afforded the product (1.32 g, 74%) which crystallised from dichloromethane/hexane as colourless plates, m.p. 159-161 °C. Found: C, 66.25; H, 7.15; N, 8.40. $C_{19}H_{24}O_4N_2$ requires: C, 66.25; H, 7.00; N, 8.15%; δ (^{1}H, 250 MHz): 7.57-7.12 (m, 5H, Ar-H), 5.51 (dd, 1H, J 4.7 and 5.9 Hz, 3-H), 4.40 (d, 1H, J 4.7 Hz, 4-H), 4.16 (dt, 1H, J 6.8 and 8.7 Hz, 8-CH_2), 3.45 (m, 1H, 8-CH_2), 3.19 (m, 1H, 2-H), 2.79 (d, 1H, J 14.1 Hz, NH), 2.05-1.99 (m, 3H, 9-CH_2 and cyclohexyl-H) and 1.89-1.21 (m, 10H, cyclohexyl-H); ν_{max} (film): 2925, 2853, 1769, 1546, 1452, 1369, 1218 and 1175 cm^{-1}; m/z (%): 345 (M^+ +1, 0.7), 298(16), 254(76), 199(91), 170(73), 156(77), 143(40) and 117(100).

2-Cyclohex-3-en-1-yl-3-nitro-4-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14e) Obtained from imine **12e** (400 mg, 2.06 mmol), *E*-nitrostyrene (0.31 g, 2.06 mmol), triethylamine (0.3 mL, 2.26 mmol) and silver oxide (47 mg, 0.2 mmol) in toluene (30 mL) over 1 h. Purification by flash chromatography eluting with ether afforded the product (0.36 g, 51%) as a 1:1 mixture of diastereomers which crystallised from dichloromethane/hexane as colourless plates, m.p. 134-142 °C. Found: C, 66.45; H, 6.50; N, 8.00. $C_{19}H_{22}O_4N_2$ requires: C, 66.65; H, 6.50; N, 8.20 %; δ (^{1}H, 250 MHz): 7.38-7.14 (m, 5H, Ar-H), 5.68-5.48 (m, 3H, olefinic-H and 3-H), 4.44 and 4.43 (d, 1H, J 4.5 Hz, 4-H), 4.16 (m, 1H, 8-CH_2), 3.49-3.30 (m, 2H, 8-CH_2 and 2-H), 2.86 and 2.80 (d, 1H, J 6.4 Hz, NH) and 2.27-1.59 (m, 9H, 9-CH_2 and cyclohexenyl-H); ν_{max} (film): 2918, 1769, 1733, 1653, 1546, 1506, 1496, 1437, 1317 and 1271 cm^{-1}; m/z (%): 342(M^+, 0.4), 325(0.6), 252(90), 215(23), 197(64), 170(71), 156(93), 143(73) and 117(100).

2-(2,6-Dimethyl-5-heptenyl)-3-nitro-4-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14f) Obtained from imine **12f**

(700 mg, 2.95 mmol), *E*-nitrostyrene (0.44 g, 2.95 mmol), triethylamine (0.5 mL, 3.24 mmol) and silver oxide (68 mg, 0.3 mmol) in toluene (30 mL) over 4 h. Purification by flash chromatography eluting with 1:1 v/v ether:hexane afforded the product (0.44 g, 42%) as a pale yellow oil which comprised a 1:1 mixture of diastereomers. Found: C, 68.50; H, 7.90; N, 7.10. $C_{19}H_{22}O_4N_2$ requires: C, 68.40; H, 7.80; N, 7.25 %; δ (^{1}H, 250 MHz): 7.41-7.16 (m, 5H, Ar-H), 5.48 (m, 1H, 3-H), 5.06 (m, 1H, olefinic-H), 4.49 (m, 1H, 4-H), 4.16 (m, 1H, 8-CH_2), 3.65 (m, 1H, 2-H), 3.35 (m, 1H, 8-CH_2), 2.50 (b, 1H, NH), 2.12-1.91 (m, 4H, 9-CH_2 and citronellyl-H), 1.69 and 1.60 (2 x s, 2 x 3H, Me_2C=C) and 1.58-1.14 (m, 3H, citronellyl-CH_3); ν_{max} (film): 2954, 2916, 1770, 1549, 1373, 1219, 1180 and 1023 cm^{-1}; m/z (%): 386(M^+, 1.2), 340(16), 312(21), 296(100), 282(20), 256(6), 241(9), 210(12), 184(41), 170(83) and 156(96).

2-(8,8-Dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenyl)-3-nitro-4-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14g) Obtained from imine **12g** (1.0 g, 3.6 mmol), *E*-nitrostyrene (0.53 g, 3.6 mmol), triethylamine (0.55 mL, 3.9 mmol) and silver oxide (0.08 g, 0.36 mmol) in toluene (40 mL) over 3 h. Purification by flash chromatography eluting with 1:1 v/v ether:hexane afforded the product (0.89 g, 58%) as a 1:1 mixture of diastereomers which crystallised from dichloromethane/ hexane as colourless plates, m.p. 165-172 °C. Found: C, 71.00; H, 7.65; N, 6.35. $C_{25}H_{32}O_4N_2$ requires: C, 70.75; H, 7.60; N, 6.60 %; δ (^{1}H, 250 MHz): 7.38-7.35 (m, 3H, Ar-H), 7.16-7.14 (m, 2H, Ar-H), 5.53 (m, 1H, 3-H), 4.45 (m, 1H, 4-H), 4.18 and 3.46 (2 x m, 2 x 1H, 8-CH_2), 3.43 (m, 1H, 2-H), 2.84 (b, 1H, NH), 2.06-1.43 (m, 15H, 9-CH_2 and aliphatic-H), 1.02 and 0.95 (2 x s, 2 x 3H, CH_3); ν_{max} (film): 2924, 1771, 1547, 1369, 1219, 1176 and 1023 cm^{-1}; m/z (%): 424(M^+, 1.5), 407(5), 378(10), 334(25), 216(62), 143(80), 117(80) and 91(100).

2-[3-(4-Methyl-3-pentenyl)-3-cyclohexen-1-yl]-3-nitro-4-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14h) Obtained from imine **12h** (1.5 g, 5.4 mmol), *E*-nitrostyrene (0.81 g, 5.4 mmol), triethylamine (0.83 mL, 5.9 mmol) and silver oxide (0.12 g, 0.54 mmol) in toluene (40 mL) over 4 h. Purification by flash chromatography eluting with 1:1 v/v ether:hexane afforded the product (1.96g, 85%) as a 1:1 mixture of diastereomers which crystallised from dichloromethane/hexane as colourless plates, m.p. 94-102 °C. Found: C, 70.75; H, 7.60; N, 6.60. $C_{25}H_{32}O_4N_2$ requires: C, 70.75; H, 7.60; N, 6.60 %; δ (^{1}H, 250 MHz): 7.38-7.33 (m, 3H, Ar-H), 7.17-7.14 (m, 2H, Ar-H), 5.58 and 5.51 (dd, 1H, J 4.5 and 5.9 Hz, 3-H), 5.36 (b, 1H, olefinic-H), 4.45 and 4.42 (d, 1H, J 4.5 Hz, 4-H), 4.17 (ddd, 1H, J 1.9, 6.7 and 8.7 Hz, 8-CH_2), 3.44 (m, 1H, 8-CH_2), 3.34 (m, 1H, 2-H), 2.84 (b, 1H, NH), 2.25 (m, 1H, aliphatic-H), 2.06-1.98 (m, 11H, 9-CH_2 and aliphatic-H), 1.69 and 1.61 (2 x s, 2 x 3H, 2 x CH_3) and 1.43 (m, 1H, aliphatic-H); ν_{max} (film): 2917, 1771, 1547, 1369, 1219, 1176, 1119 and 1023 cm^{-1}; m/z (%): 424(M^+, <1), 407(3), 378(5), 333(3), 91(34), 77(16) and 69(100).

2-[2-(4-Isopropylphenyl)-1-methylethyl)-3-nitro-4-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14i) A mixture of imine **12i** (1.0 g, 3.6 mmol), *E*-nitrostyrene (0.54 g, 3.6 mmol), triethylamine (0.56 mL, 4.0 mmol) and silver oxide (0.08 g, 0.36 mmol) in toluene (40 mL, was stirred for 5 h. Flash chromatography eluting with 1:1 v/v ether:hexane separated the 1:1 mixture of diastereomers (combined yield 1.11 g, 72%).

First eluting isomer: Crystallised from dichloromethane/hexane as colourless rods, m.p. 143-145 °C. Found: C, 71.15; H, 7.25; N, 6.45. $C_{25}H_{30}O_4N_2$ requires: C, 71.10; H, 7.15; N, 6.65 %; δ (^{1}H, 250 MHz): 7.39-7.34 (m, 3H, Ar-H), 7.15-7.10 (m, 6H, Ar-H), 5.46 (dd, 1H, J 4.6 and 5.7 Hz, 3-H), 4.43 (d, 1H, J 4.6 Hz, 4-H), 4.25 (ddd, 1H, J 6.5, 7.5 and 8.7 Hz, 8-CH_2), 3.54 (ddd, 1H, J 5.8, 7.5 and 8.7 Hz, 8-CH_2), 3.14 (m, 1H, 2-H), 3.03-2.83 (m, 3H, NH and aliphatic-H), 2.59 (dd, 1H, J 8.1 and 14.5 Hz, aliphatic-CH_2), 2.09-1.92 (m, 3H, 9-CH_2 and aliphatic-H), 1.24 (d, 2 x 3H, J 6.9 Hz, 2 x CH_3) and 0.97 (d, 3H, J 6.6 Hz, CH_3); ν_{max} (film): 2969, 1772, 1548, 1457, 1370, 1220 and 1022 cm^{-1}; m/z (%): 422(M^+, <1), 407(<1), 378(13), 332(47), 277(9), 244(10), 170(57), 133(100), 117(51) and 91(38).

Second eluting isomer: Crystallised from dichloromethane/hexane as colourless rods, m.p. 120-122 °C. Found: C, 70.95; H, 7.00; N, 6.70. $C_{25}H_{30}O_4N_2$ requires: C, 71.10; H, 7.15; N, 6.65 %; δ (^{1}H, 250 MHz): 7.42-7.33 (m, 3H, Ar-H), 7.17-7.05 (m, 6H, Ar-H), 5.61 (dd, 1H, J 5.2 and 6.3 Hz, 3-H), 4.50 (d, 1H, J 5.2 Hz, 4-H), 4.18 (dt, 1H, J 6.8 and 8.8 Hz, 8-CH_2), 3.44 (dt, 1H, J 6.8 and 8.8 Hz, 8-CH_2), 3.31 (m, 1H, 2-H), 2.99-2.77 (m, 3H, NH and aliphatic-H), 2.34 (dd, 1H, J 9.8 and 13.2 Hz, aliphatic-CH_2), 2.06-2.01 (t, 2H, J 6.8 Hz, 9-CH_2), 1.90 (m, 1H, aliphatic-H), 1.24 (d, 2 x 3H, J 7.0 Hz, 2 x CH_3) and 1.01 (d, 3H, J 6.6 Hz, CH_3); ν_{max} (film): 2961, 1771, 1652, 1547, 1507, 1497, 1369 and 1219 cm^{-1}; m/z (%): 422(M^+, <1), 407(1), 376(9), 332(61), 277(12), 244(15), 170(56) and 133(100).

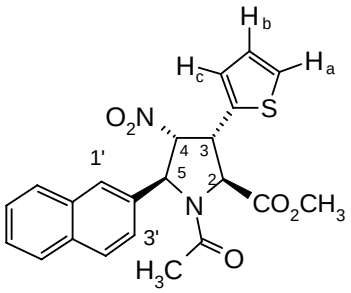
2-(2-Methyl-4-phenylbutyl)-3-nitro-4-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (14j) Obtained from imine **12j** (1.0 g, 3.85 mmol), *E*-nitrostyrene (0.57 g, 3.85 mmol), triethylamine (0.6 ml, 4.23 mmol) and silver oxide (0.089 g, 0.38 mmol) in toluene (40 mL) over 4 h. Purification by flash chromatography eluting with 1:1 v/v ether:hexane afforded the product (0.93 g, 59%) as a 1:1 mixture of diastereomers which crystallised from dichloromethane/ hexane as colourless plates, m.p. 75-83 °C. Found: C, 70.80; H, 6.70; N, 6.60. $C_{24}H_{28}O_4N_2$ requires: C, 70.60; H, 6.90; N, 6.85 %; δ (^{1}H, 250 MHz): 7.38-7.14 (m, 10H, Ar-H), 5.44 (m, 1H, 3-H), 4.50 (m, 1H, 4-H), 4.13 (m, 1H, 8-CH_2), 3.63 (m, 1H, 2-H), 3.34 (m, 1H, 8-CH_2), 2.70-2.47 (m, 3H, NH and aliphatic-H), 2.09-1.98 (m, 2H, 9-CH_2), 1.73-1.39(m, 5H, aliphatic-H) and 1.04 and 1.0 (d, 3H, J 6.4 Hz, CH_3); ν_{max} (film): 2922, 1770, 1548, 1496, 1455, 1370, 1270 and 1177 cm^{-1}; m/z (%): 408 (M^+, <1), 362(6), 334(7), 318(70), 304(10), 263(8), 185(14) and 91(100).

***N*-Acetylation of Cycloadducts[8b]**

Acetic anhydride (11mol equiv., 0.46 mL, 0.5 g, 4.86 mmol) was added at 0 °C to a solution of cycloadducts *endo*-**9q** and *exo*-**10q** (170 mg, 0.44 mmol) in pyridine (3 mL). The mixture was stirred at room temperature for 3 h., and then poured into ice water. The products were extracted with dichloromethane and the organic layer washed sequentially with 5 % aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. The isomers were separated by column chromatography eluting with 3:2 v/v hexane / ethyl acetate.

Methyl *N*-acetyl-5-naphthalen-2-yl-4-nitro-3-thiophen-2-yl-pyrrolidine-2-carboxylate (16a*)*

The *major isomer* (255 mg, 40 %) crystallised as colourless prisms from hexane-EtOAc, R_f 0.3, m.p. 203-205 °C.Found: C, 62.25; H, 4.90; N, 6.65; S, 7.70. $C_{22}H_{20}N_2O_5S$ requires C, 62.25; H, 4.75; N, 6.60; S, 7.55 %. δ (^{1}H, 500 MHz, C_6D_6) 8.61 (s, 1H, 1′-H), 8.00 (dd, 1H, *J* 1.1, 8.5 Hz, 3′-H), 7.98 (m, 1H, ArH), 7.83 (d, 1H, *J* 8.5 Hz, ArH), 7.74 (m, 1H, ArH), 7.35 (m, 2H, ArH), 7.06 (dd, 1H, *J* 1.1, 5.1 Hz, Ha), 6.99 (d, 1H, *J* 3.6 Hz, Hc), 6.72 (dd, 1H, *J* 3.6, 5.1 Hz, Hb), 6.12 (s, 1H, 5-H), 5.45 (d, 1H, *J* 6.0 Hz, 4-H), 5.28 (d, 1H, *J* 10.9 Hz, 2-H), 4.52 (dd, 1H, *J* 6.0, 10.9 Hz, 3-H), 3.44 (s, 3H, CO_2CH_3), and 1.78 (s, 3H, $COCH_3$). δ (^{13}C) 171.9 (ester CO), 171.1 (amide CO), 134.9 (C_q), 133.8 (2 x C_q), 132.8 (C_q), 130.3, 128.9, 128.2, 127.9, 127.6 (ArCH), 127.5, 126.8 (2 x ArCH), 123.9 (ArCH), 96.3 (C_4), 66.8 (C_5), 64.2 (C_2), 53.4 (OCH_3), 45.1 (C_3), and 22.4 (CH_3). IR (DCM) 2952, 1746, 1663, 1556, 1437, 1367, 1207, 1178, 860, and 737 cm^{-1}. m/z (ES$^+$) 425 (M^+ + 1, 100).

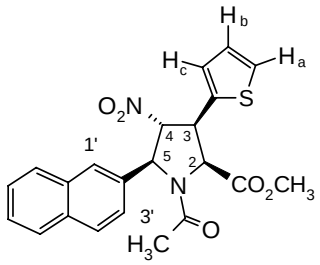


n.O.e data for **16a**:

	% Enhancement						
Irradiated proton	H-4	$COCH_3$	H-1′	H-3′	H-5	H-3	H_c
H-5	7.9	9.0	6.1	7.2	-	-	-
H-4	-	-	1.5	3.2	4.4	13.4	-
H-3	18.6	-	4.5	2.2	-	-	3.2
H-2	-	-	2.6	-	1.1	3.0	10.3

Methyl *N*-acetyl-5-naphthalen-2-yl-4-nitro-3-thiophen-2-yl-pyrrolidine-2-carboxylate (16b)

The *minor* isomer (166 mg, 26 %) crystalised from hexane-EtOAc as colourless prisms, R_f 0.2, m.p. 212-214 °C. Found: C, 61.95; H, 4.90; N, 6.55; S, 7.60. $C_{22}H_{20}N_2O_5S$ requires C, 62.25; H, 4.75; N, 6.60; S, 7.55 %. δ (^{1}H, 500 MHz) 7.97 (m, 3H, ArH), 7.87 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.29 (dd, 1H, *J* 1.0, 5.0 Hz, Ha), 7.00 (d, 1H, *J* 3.5 Hz, Hc), 6.97 (dd, 1H, *J* 3.5, 5.0 Hz, Hb), 5.67 (dd, 1H, *J* 8.5, 11.6 Hz, 4-H), 5.49 (d, 1H, *J* 8.5 Hz, 5-H), 5.19 (d, 1H, J 9.4 Hz, 2-H), 4.67 (dd, 1H, *J* 9.4, 11.6 Hz, 3-H), 3.54 (s, 3H, CO_2CH_3), and 1.68 (s, 3H, $COCH_3$). δ (^{13}C) 171.3, 171.2 (CO), 135.2, 134.1, 133.6, 133.4 (C_q), 130.6, 128.6, 128.3, 127.7, 127.4 (ArCH), , 127.3 (2 x ArCH), 127.2, 126.9, 123.8 (ArCH), 95.2 (C_4), 67.5 (C_2), 64.3 (C_3), 52.9 (C_5), 45.6 (OCH_3), and 23.2 (CH_3). IR (DCM) 2951, 1742, 1663, 1558, 1437, 1369, 1215, 862, and 752 cm^{-1}. m/z (ES$^+$) 448 (M^+ + 1 + Na, 30), 446 (M^+ + Na, 100).



n.O.e data for **16b**:

	% Enhancement					
Irradiated proton	H-5	H-4	H-1′	H-2	H-3	
H-1′	11.3	4.46	1.03	-	-	-
H-5	5.6	-	5.28	5.54	2.02	-
H-4	-	6.47	-	-	-	14.2
H-3	-	-	14.3	-	-	-
H-2	-	3.66	-	-	-	-

Methyl N-acetyl-3(1-H-indol-3-yl)-5-naphthalen-2-yl-4-nitro-pyrrolidine-2-carboxylate (17a)

Prepared by the general method from *endo*-**9c**. Trituration with ether afforded the *product* as pale yellow needles (618

mg, 90 %), mp 190-192 °C. Found: C, 68.25; H, 5.25; N, 9.30. $C_{26}H_{23}N_3O_5$ requires C, 68.26; H, 5.07; N, 9.18%. δ (^{1}H, 250 MHz) 8.41 (s, 1H, indole NH), 8.27 (s, 1H, ArH), 7.90-7.65 (m, 4H, ArH), 7.60-7.40 (m, 3H, ArH), 7.30 (d, 1H, *J* 8.0 Hz, ArH), 7.20-7.05 (m, 3H, ArH), 5.72 (m, 2H, 5-H + 4-H), 4.83 (d, 1H, *J* 10.0 Hz, 2-H), 3.78 (t, 1H, *J* 10.0 Hz, 3-H), 3.65 (s, 3H, CO_2CH_3), and 1.83 (s, 3H, CH_3). δ (^{13}C) 171.9 (ester CO), 171.2 (amide CO), 137.0, 134.0, 133.6, 132.6 (C_q), 129.6, 128.9, 128.2, 127.8, 127.3, 127.1 (ArCH), 125.9 (C_q), 124.7, 123.4, 123.2, 120.7, 118.9, 112.3 (ArCH), 108.5 (C_q), 90.8 (C_4), 64.3 (C_5), 63.3 (C_2), 53.2 (OCH_3), 41.5 (C_3), and 22.6 (CH_3). IR (DCM) 3420, 3058, 2951, 1745, 1653, 1558, 1436, 1349, 1214, 1014, 867, and 744 cm^{-1}. m/z (ES$^+$) 458 (M^+ + 1, 100).

Methyl *N*-acetyl-3-[4-(acetyloxy)-3-methoxyphenyl]-5-biphenyl-4-yl-4-nitro-pyrrolidine-2-carboxylate (17b)

Prepared by the general method from *endo*-**9i**. Trituration with ether afforded the *product* as a colourless amorphous powder (707 mg, 93%), m.p. 206-208 °C. HRMS found 533.1918 $C_{29}H_{29}N_2O_8$ requires 533.1924. Found: C, 65.70; H, 5.35; N, 5.05. $C_{29}H_{28}N_2O_8$ requires C, 65.40; H, 5.30; N, 5.26%. δ (^{1}H, 500 MHz, $CDCl_3$ + C_6D_6) 7.80 (d, 2H, *J* 8.3 Hz, ArH), 7.68 (dd, 2H, *J* 1.9, 8.3 Hz, ArH), 7.57 (dd, 2H, *J* 1.2, 8.4 Hz, ArH), 7.42 (dd, 2H, *J* 7.0, 8.4 Hz, ArH), 7.33 (m, 1H, ArH), 6.94 (d, 1H, *J* 8.2 Hz, Hc), 6.79 (d, 1 H, *J* 1.9 Hz, Ha), 6.72 (dd, 1H, *J* 1.9, 8.2 Hz, Hb), 5.43 (s, 1H, 5-H), 5.22 (d, 1H, *J* 10.8 Hz, 2-H), 5.10 (dd, 1H, *J* 0.7, 6.2 Hz, 4-H), 4.02 (dd, 1H, *J* 10.8, 6.2 Hz, 3-H), 3.71 (s, 3H, CO_2CH_3), 3.70 (s, 3H, $ArOCH_3$), 2.20 (s, 3H, ester CH_3), and 1.89 (s, 3H, $NCOCH_3$). δ (^{13}C, 125 MHz, $CDCl_3$ + C_6D_6) 171.9 (-CO), 170.6 (amide CO), 168.5 (ester -OCO), 151.6, 142.2, 140.3, 140.0, 136.5, 129.9 (C_q), 129.0, 128.4 (2 x ArCH), 127.9 (ArCH), 127.1, 127.0 (2 x ArCH), 123.5, 120.1, 111.8 (Vanillin ArCH), 96.3 (C_4), 66.4 (C_5), 62.2 (C_2), 55.9 ($ArOCH_3$), 52.9 (OCH_3), 48.7 (C_3), 21.9 (N-acetyl CH_3), and 20.5 (O-acetyl CH_3). IR (DCM) cm^{-1} 3248, 3062, 3029, 2953, 1748, 1663, 1554, 1516, 1402, 1368, 1351, 1264, 1204, 1033, 1009, and 856. m/z (ES$^+$) 556 (M^+ + 1+ Na, 36), 555 (M^+ + Na, 100).

General Procedure for Reduction of the NO_2 group

Zinc dust (135 mg, 2.06 mmol) was added to a stirred solution of nitro compound (52 mg, 0.12 mmol) in ethanol (10 ml). The mixture was then heated to 40-45 °C and conc. HCl (0.2 ml) was added keeping the temperature in between 45-50 °C. The reaction mixture was then refluxed for 12 h, filtered, and the filtrate evaporated *in vacuo* nearly to dryness. The residue was extracted with DCM and saturated $NaHCO_3$ solution was added until the pH was slightly basic and then extracted with more DCM. The combined DCM extracts were dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure.

Methyl *N*-acetyl-4-amino-5-naphthalene-2-yl-3-thiophen-2-yl-pyrrolidine-2-carboxylate (18a)

Flash column chromatography eluting with ethyl acetate followed by 3:1 v/v methanol/ hexane afforded the *product* as colourless plates (347 mg, 88 %), R_f 0.33, m.p. 81-83 °C. Found: C, 66.70; H, 5.70; N, 6.85; S, 8.00. $C_{22}H_{22}N_2O_3S$ requires C, 66.98; H, 5.62; N, 7.10; S, 8.13 %. δ (^{1}H, 250 MHz) 8.07 (s, 1H, ArH), 7.75-7.51 (m, 3H, ArH), 7.35-7.30 (m, 2H, ArH), 7.10-7.05 (m, 1H, ArH), 6.85-6.80 (m, 2H, ArH), 4.79 (d, 1H, *J* 7.4 Hz, 5-H), 4.66 (d, 1H, *J* 4.6 Hz, 2-H), 3.78 (dd, 1H, *J* 4.6, 7.4 Hz, 4-H), 3.63 (s, 3H, CO_2CH_3), 3.47 (t, 1H, *J* 4.6 Hz, 3-H), and 1.69 (s, 3H, CH_3). δ (^{13}C) 172.5, 171.8 (CO), 138.0, 137.6, 133.8, 133.4 (C_q), 129.5, 128.6, 128.1, 127.6, 127.1, 126.9, 126.8, 126.3, 125.6, 124.7 (ArCH), 70.7 (C_4), 64.3 (C_2), 63.8 (C_3), 53.0 (C_5), 46.4 (OCH_3), and 22.7 (CH_3). IR (DCM) 2950, 1743, 1653, 1559, 1436, 1406, 1351, 1201, 861, and 755 cm^{-1}. m/z (ES$^+$) 396 (M^+ + 2), 395 (M^+ + 1, 100).

Methyl *N*-acetyl-4-amino-5-naphthalene-2-yl-3-thiophen-2-yl-pyrrolidine-2-carboxylate (18b)

Trituration with ether afforded the *product* as a colourless amorphous powder (375 mg, 95 %), m.p. 209-211 °C. HRMS found 395.1429 $C_{22}H_{22}N_2O_3S$ requires 395.1424. Found: C, 66.40; H, 5.75; N, 6.90. $C_{22}H_{22}N_2O_3S$ requires C, 66.98; H, 5.62; N, 7.10 %. δ (^{1}H, 250 MHz) 8.07 (s, 1H, ArH), 7.75-7.51 (m, 3H, ArH), 7.35-7.30 (m, 2H, ArH), 7.10-7.05 (m, 1H, ArH), 6.85-6.80 (m, 2H, ArH), 4.79 (d, 1H, *J* 7.4 Hz, 5-H), 4.66 (d, 1H, *J* 4.6 Hz, 2-H), 3.78 (dd, 1H, *J* 4.6, 7.4 Hz, 4-H), 3.63 (s, 3H, CO_2CH_3), 3.47 (t, 1H, *J* 4.6 Hz, 3-H), and 1.69 (s, 3H, CH_3). δ (^{13}C) 172.5, 171.8 (CO), 138.0, 137.6, 133.8, 133.4 (C_q), 129.5, 128.6, 128.1, 127.6, 127.1, 126.9, 126.8, 126.3, 125.6, 124.7 (ArCH), 70.7 (C_4), 64.3 (C_2), 63.8 (C_3), 53.0 (C_5), 46.4 (OCH_3), and 22.7 (CH_3). IR (DCM) 3058, 2949, 1740, 1652, 1559, 1436, 1403, 1351, 1201, 861, and 754 cm^{-1}. m/z (ES$^+$) 396 (M^+ + 2), 395 (M^+ + 1, 100).

Supplementary information

Crystallographic data (excluding structural factors) for the structures in this paper have been deposited at the CambridgeCrystallographic Data Centre as supplementary publication nos. CCDC 682218 (compound **14a**), CCDC 682219 (**15a**), CCDC 682220 (**16a**), and CCDC 682221 (**16b**).
Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or via the web at: http://www.ccdc.cam.ac.uk/products/csd/request/).

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