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Kinetic acidity of iminium ions. 2-Alkynyl- and 2,5-dialkynyl-pyrrolidines via the iminium ion route to azomethine ylides

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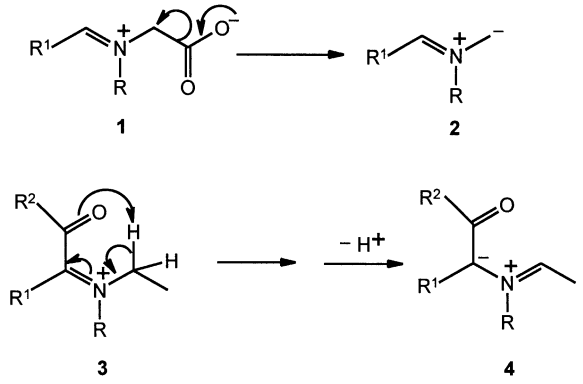
Abstract—Condensation of carboxaldehydes with appropriate secondary propargylamines furnishes iminium ions which undergo regioselective deprotonation at the propargylic methylene group to generate azomethine ylides. Interception of the latter by *N*-methyl or *N*-phenyl maleimide furnishes 2- and 2,5-dialkynyl-pyrrolidines.

We have developed several variants of the iminium ion route to azomethine ylides involving either condensation of aldehydes and ketones with acyclic or cyclic α-amino acids[1] or condensation of α-dicarbonyl compounds (or carbonylimines) with secondary amines.[2] In the former case the iminium ion intermediate generates the azomethine ylide by decarboxylation **1→2** whilst in the later case deprotonation occurs either via a 1,5-H shift **3→4** or by interaction of an external base (Scheme 1).



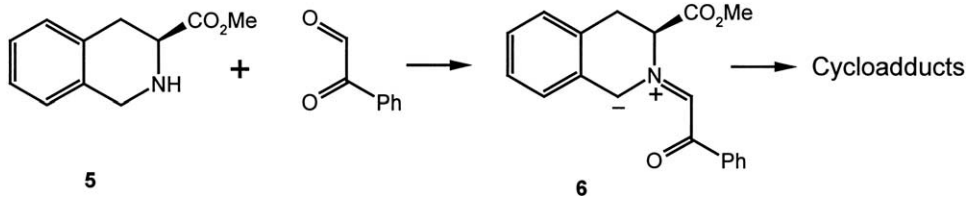
Scheme 1.

Whilst exploring aspects of **3→4** in which the R substituent contained benzylic α-protons we observed synthetically useful regiospecific azomethine ylide formation involving deprotonation at the site bearing the less acidic protons, e.g. **5→6**, i.e. the regioselectivity of azomethine ylide formation was controlled by kinetic acidity and, moreover, the chiral centre in **5** was not racemised (Scheme 2).[3]

We now report further synthetically useful examples where kinetic acidity controls the regioselectivity of azomethine ylide formation involving imines of secondary propargylamines.

1. Secondary propargylamines as azomethine ylide precursorss

Several related series of azomethine ylides have been generated in situ by condensation of secondary propargylamines with carboxaldehydes. In the first series the chiral propargylamines **7a**, **b** derived from *S*-amino esters and **7c** derived from the *R*-amino ester were reacted (toluene, 100°C, 24 h) with (trimethylsilyl) propynal **8** and *N*-methyl- or *N*-phenyl-maleimide **12a**, **b** (Scheme 3). The initial mixture of four diastereomers simplified to two, **13**



Scheme 2.

Keywords: iminium ions; azomethine ylide; 1,3-dipolar cycloaddition; regioselective deprotonation.
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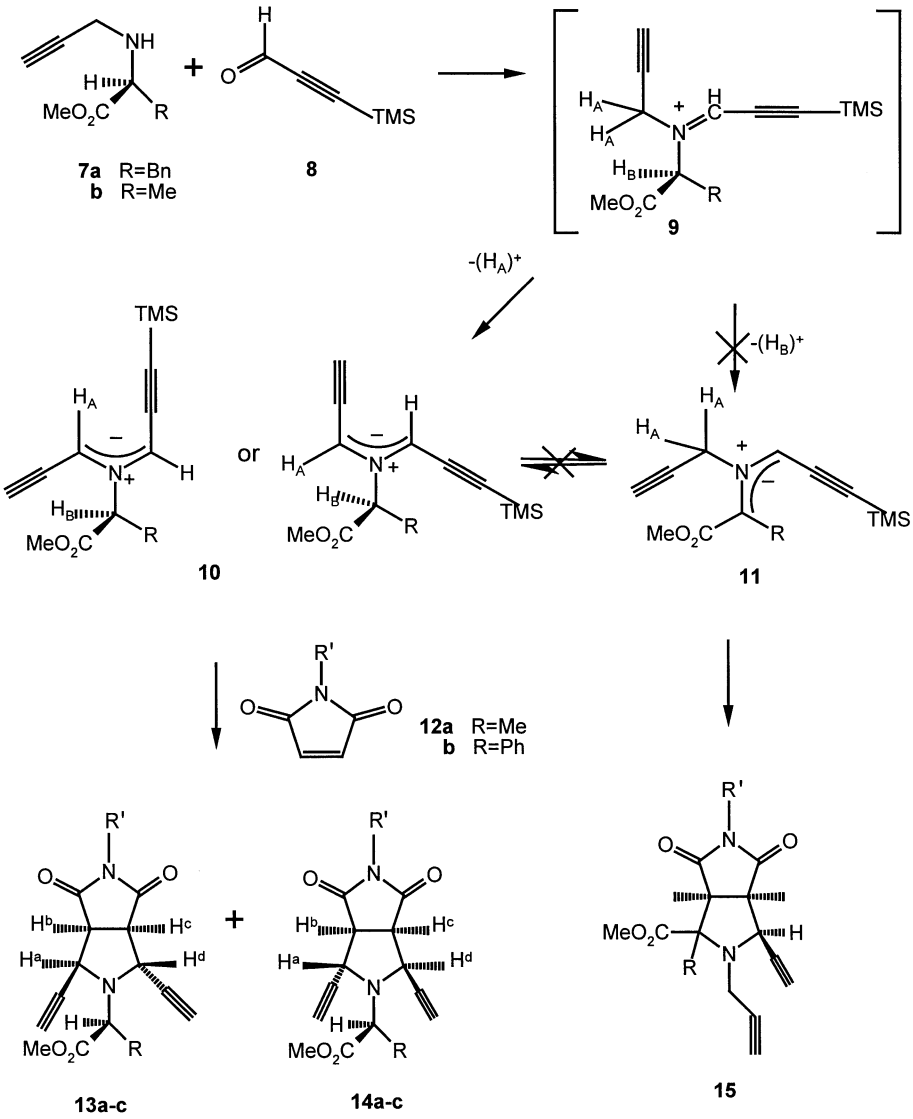


Scheme 3.

and **14**, on removal (TBAF, rt, 1 h) of the TMS group and then were separated by flash column chromatography on silica (Table 1).

The stereochemistry of the cycloadducts was established from n.O.e. data and confirmed in some cases by X-ray crystal structures. Typical n.O.e. enhancements for vicinal *cis*-protons were 10.3–12.0% whilst for vicinal *trans*-protons enhancements were 4.3–7.4% (see Section 2).

The X-ray crystal structure of **13b** is shown in Fig. 1. Based on the known absolute configuration of **7b**, this established the configuration of the new chiral centres in **13b** as $C_1(R)$,

Table 1.

	R	R′	Ratio (**13/14**)	Yield (%)
a	Bn	Me	64:36	66
b	Bn	Ph	60:40	50
c	Me	Me	75:25	54
d	Ph	Me	67:33	42[a]

[a] Product comprises a 47:23:30 mixture of **13d**, **14d** and **15d**.

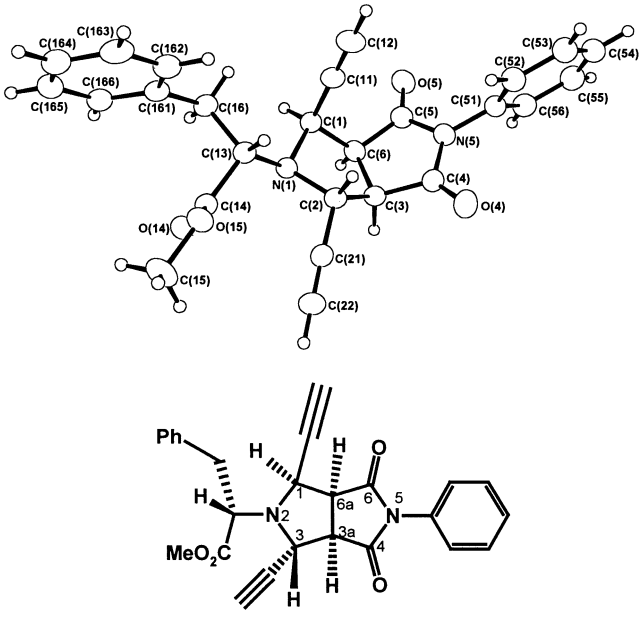
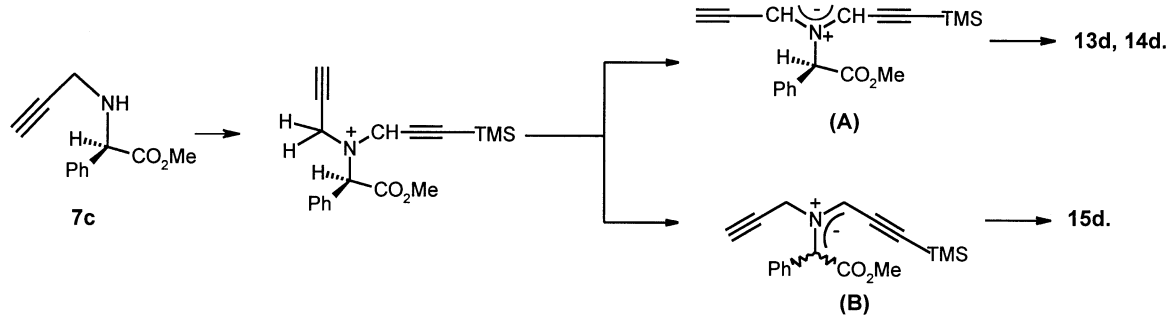
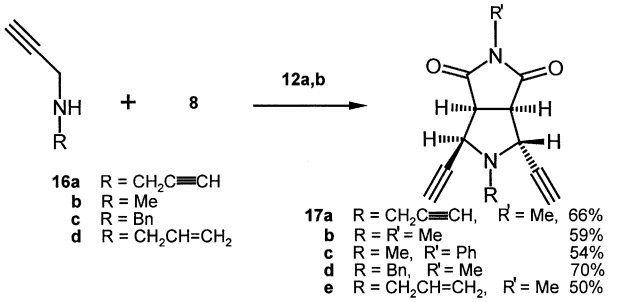


Figure 1. The X-ray crystal structure of **13b**.



Scheme 4.



Scheme 5.

$C_3(R)$, $C_{3a}(R)$, $C_{6a}(S)$ (see numbering on formula in Fig. 1). The absolute configurations of **13a–d** and **14a–d** are assigned by analogy with **13b**.

It is clear from the cycloadduct structures that the products arise from removal of one of the H_A protons of the intermediate iminium ion **9**. Moreover since the cycloadducts **13a–d** and **14a–d** are optically active we can rule out equilibria involving azomethine ylide **11** which would arise from removal of the H_B proton in **9**. Additionally we have previously shown that the highly reactive maleimide dipolarophiles trap the azomethine ylide(s) formed under kinetic control.[4] However, in the case of the *N*-propargyl phenylglycine ester **7c** the reaction affords a 47:23:30 mixture of **13d**, **14d** and **15d** (Scheme 4). Thus in this case there is competitive formation of the corresponding azomethine ylides **10** and **11**. However, since both **13d** $[(\alpha)_D=+16]$ and **14d** $[(\alpha)_D=+6]$ are optically active, equilibration of azomethine ylides A and B (Scheme 4) is ruled out. The stereochemistry of the cycloadducts implicates the *anti*-dipole **10a** and/or **10b** and an *endo*-transition state for the cycloaddition.

When achiral secondary propargylamines **16a–c** were reacted (toluene, 100°C, 24 h) with **8** and **12a**, **b** followed by removal of the TMS group (TBAF, rt, 1 h) single cycloadducts **17a–d** were obtained in 50–70% yield (Scheme 5).

Cycloadducts **17a–d** again arise from *anti*-dipole **10a** and/or **10b** via an *endo*-transition state. In the case of the iminium ion **18** derived from **16d** none of the alternative cycloadduct derived from azomethine ylide **19**, requiring deprotonation at the allylic methylene group, was observed (Scheme 6).

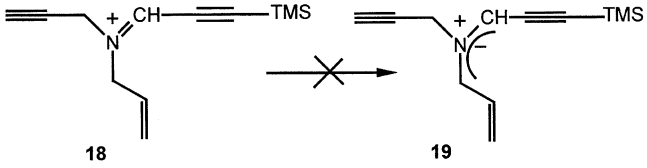
An analogous series of reactions was carried out between **16a–d**, aryl/heteroaryl aldehydes **20** and dipolarophiles **12a**, **b**. In all cases the products (Table 2) comprised 1:1 mixtures of diastereomers **21** and **22**.

The 1:1 mixtures of **21** and **22** were separated by flash chromatography on silica and the stereochemistry of **21a–q** and **22a–q** was assigned from n.O.e. data and coupling constants and confirmed in the case of one pair of isomers, **21n** and **22n** by X-ray crystal structures (Fig. 2).

Typical n.O.e. enhancements for the *cis*-vicinal protons in **21a–q** and **22a–q** were 6.6–12.0% whilst for *trans*-vicinal protons the enhancements were 1.7–5.6%. Isomers **21** and **22** can be distinguished by the coupling constants J_{HaHb} and J_{HcHd} (Scheme 7). Thus J_{HaHb} is 8.7–9.2 Hz and J_{HcHd} is 0 Hz for **21a–q** whilst J_{HaHb} is 3.5–6.5 Hz and J_{HcHd} is 7.9–8.4 Hz for **22a–q**.

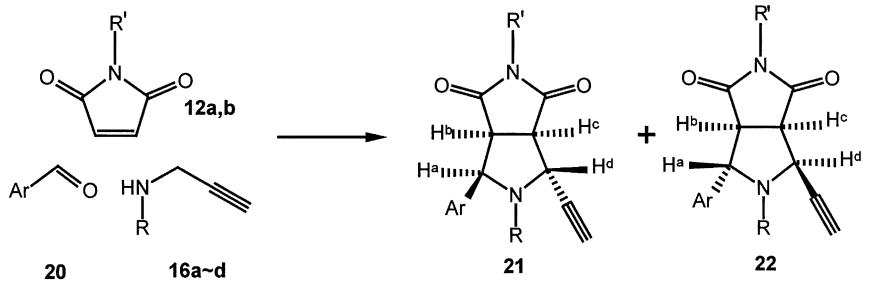
2. Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance spectra were recorded at 300 MHz on a Bruker DPX 300 instrument, at 250 MHz on a Bruker AC 250 instrument or at 500 MHz on a Bruker DRX 500 instrument. Deuterochloroform was used as solvent unless otherwise stated, and chemical shifts are given in parts per million (δ) downfield from tetramethylsilane. ^{1}H spectra are referenced to tetramethylsilane or residual protonated solvent. Assignments of ^{1}H signals were made with the aid of 2D COSY spectra where necessary. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument.



Scheme 6.

Table 2. Reaction of **16a–d**, **20** and **12a**, **b** to give cycloadducts **21a–q** and **22a–q**



	R	Ar	R′	Yield (%)[a,b]
a	$CH_2C{\equiv}CH$	2-Thienyl	Me	59
b	$CH_2C{\equiv}CH$	2-Thiazolyl	Me	88
c	$CH_2C{\equiv}CH$	Ph	Me	67
d	$CH_2CH{=}CH_2$	2-Thienyl	Me	61
e	$CH_2CH{=}CH_2$	Ph	Me	50
f	Me	2-Furyl	Me	85
g	Me	2-Thienyl	Me	58
h	Me	2-Thiazolyl	Me	80
i	Me	Ph	Me	62
j	Me	2-Pyridyl	Me	53
k	Me	6-Me-2-pyridyl	Me	56
l	Me	4-$MeOC_6H_4$	Me	46
m	Me	2-Furyl	Ph	44
n	Me	2-Thienyl	Ph	43
o	Me	2-Thiazolyl	Ph	76
p	Me	Ph	Ph	55
q	Me	6-Me-2-pyridyl	Ph	52

All reaction carried out in toluene at 100°C (bath temperature) for 24 h.
[a] Isolated yields.
[b] All reaction afforded 1:1 mixtures of diastereomers **21** and **22**.

Infrared spectra were recorded as nujol mulls on a Nicolet FTIR spectrophotometer. Mass spectra were recorded on a VG-AutoSpec using electron impact (EI) at 70 eV or fast atom bombardment (FAB), as specified. Flash column chromatography was performed on silica gel 60 (Merk 230–400 mesh). Ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40–60°C. All reagents and solvents were purified according to literature procedures.[5]

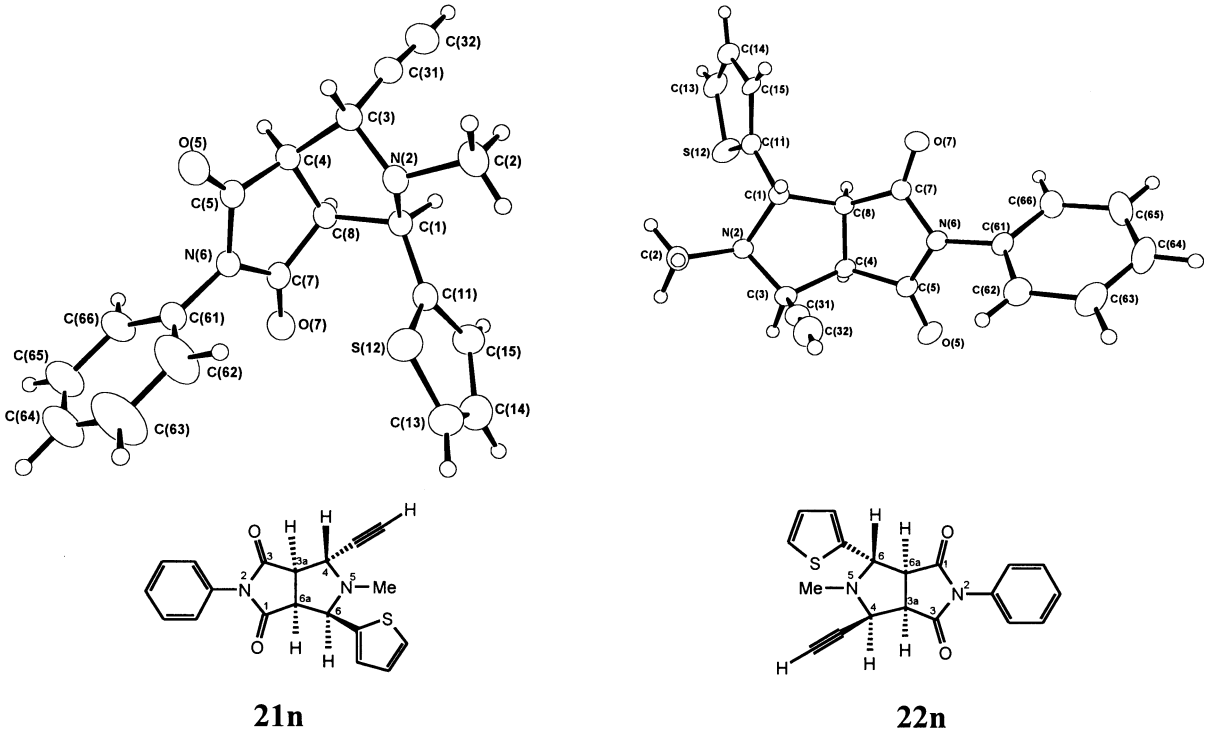


Figure 2. The X-ray crystal structures of **21n** and **22n**.

2.1. General method for the preparation of chiral secondary amines 7a–c

Propargyl bromide (10.5 mmol) was added to a solution of the α-amino acid ester hydrochloride (10 mmol) and potassium carbonate (21 mmol) in dry DMF (or acetone) at room temperature under N_2. The mixture was stirred for 1–3 d, the solvent evaporated under reduced pressure and the residue partitioned between water (50 ml) and DCM (30 ml). The organic phase was separated and the aqueous phase was extracted with DCM (2×30 ml). The organic phases were combined, dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by column chromatography to give secondary amines **7a**–**c**.

2.1.1. Methyl *N*-(2-propynyl)-*S*-phenylalaninate 7a

This compound is prepared by the general procedure from *S*-phenylalaninate methyl ester hydrochloride (2.16 g, 10 mmol), propargyl bromide (1.56 g, 80% in toluene solution, 10.5 mmol) and potassium carbonate (2.9 g, 21 mmol) in dry DMF (100 ml) for 3 d. Flash column chromatography eluting with 3:1 v/v petroleum ether–ether afforded **7a** (1.79 g, 82%) as a pale yellow liquid. Bp 206°C/0.3 mm (Kugelrohr distillation). $[\alpha]_D^{25}=+16.0$ (1.0, $CHCl_3$). (Found: C, 71.9, H, 6.9, N, 6.6, $C_{13}H_{15}NO_2$ requires: C, 71.85, H, 6.95, N, 6.45%); δ 1.68 (br, 1H, NH), 2.18 (t, 1H, *J*=2.4 Hz, C≡CH), 2.95 (dd, 1H, *J*=6.2 and 13.6 Hz, ArC*H*H), 3.03 (dd, 1H, *J*=7.3 and 13.6 Hz, ArCH*H*), 3.36 and 3.44 (2×dd, 2×1H, *J*=2.4 and 17.0 Hz, NCH_2), 3.68 (s, 3H, OCH_3), 3.76 (dd, 1H, *J*=6.3 and 7.2 Hz, NC*H*CO_2Me) and 7.18–7.33 (m, 5H, ArH); δ (^{13}C): 37.2, 39.8, 52.2, 61.5, 72.2, 81.6, 127.3, 128.9, 129.6, 137.3 and 174.7; *m*/*z* (%): 217 (M^+, 2), 162 (100), 158 (8), 91 (82) and 77 (10); ν_{max}: 3284, 2948, 1734 and 1446 cm^{-1}.

2.1.2. Methyl *N*-(2-propynyl)-*S*-alaninate 7b

This compound is prepared by the general procedure from *S*-alanine methyl ester hydrochloride (1.396 g, 10 mmol), propargyl bromide (1.56 g, 10.5 mmol) and potassium carbonate (2.9 g, 21 mmol) in dry DMF for 3 d. Flash column chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product **7b** (324 mg, 23%) as a pale yellow gum. $[\alpha]_D^{25}=-62.0$ (1.0, $CHCl_3$). (Found: C, 59.4, H, 7.75, N, 9.6, $C_7H_{11}NO_2$ requires: C, 59.55, H, 7.85, N, 9.9%.); δ 1.33 (d, *J*=7.0 Hz, 3H, NCH*Me*), 2.23 (t, *J*=2.5 Hz, 1H, C≡CH), 3.44 (dd, *J*=2.5 and 6.7 Hz, 2H, NCH_2), 3.56 (q, *J*=7.0 Hz, 1H, NCH) and 3.74 (s, 3H, CO_2Me); *m*/*z* (%): (FAB) 140 (M^+-1, 25), 126 (100), 120 (21), 115 (10) and 109 (10).

2.1.3. Methyl *N*-(2-propynyl)-*R*-phenylglycinate 7c

This compound is prepared by the general procedure from *R*-phenylglycine methyl ester hydrochloride (3.025 g, 15 mmol), propargyl bromide (1.78 g, 15 mmol) and potassium carbonate (4.354 g, 31.5 mmol) in dry DMF (100 ml) for 62 h. Flash column chromatography eluting with 2:1 v/v petroleum ether–ether afforded the product **7c** (2.537 g, 83%) as a pale yellow gum. $[\alpha]_D^{25}=-110.0$ (1.0, $CHCl_3$). (Found: C, 70.75, H, 6.25, N, 6.6, C_{12} $H_{13}NO_2$ requires: C, 70.9, H, 6.45, N, 6.9%.); δ 2.11 (bs, 1H, NH), 2.26 (t, *J*=2.4 Hz, 1H, C≡CH), 3.27 and 3.47 (2×dd, *J*=2.4 and 17.2 Hz, 2×H, NCH_2), 3.70 (s, 3H, Me), 4.64 (s, 1H NCH) and 7.31–7.42 (m, 5H, ArH); *m*/*z* (%): (FAB) 204 (M^++1, 67), 188 (7), 159 (9), 144 (48), 131 (13), 121 (17), 109 (32), 97 (58), 83 (63) and 69 (100).

2.2. General method for the preparation of cycloadducts 13a–d, 14a–d and 17a–e

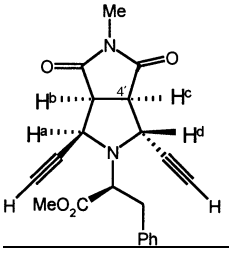
Secondary amine **7a**–**c** (1.5 mmol) or **16a**–**d** (1.5 mmol) were added to a solution of 3-(trimethylsilyl)propynal **8**[6] (1.5 mmol) and dipolarophile **12** (1.8 mmol) in toluene (5 ml). The mixture was stirred and heated at 100°C under N_2 for 24 h. The solvent was then removed under reduced pressure, THF (5 ml) and TBAF (Tetra-*n*-butylammonium fluoride, 1 M soln in THF; 3 ml) added and the mixture stirred at room temperature for 1 h when EtOAc (50 ml) was added. The mixture was washed with water (3×30 ml), the organic phase collected, dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by column chromatography to give the cycloadducts.

2.2.1. Methyl (2*S*)-2-[(1*R*,3*R*,3a*R*,6a*S*)-1,3-diethynyl-5-methyl-4,6-dioxohexahydro-pyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]-3-phenylpropanoate 13a and methyl (2*S*)-2-[(1*S*,3*S*,3a*R*,6a*S*)-1,3-diethynyl-5-methyl-4,6-dioxohexahydro-pyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]-4-phenyl-propanoate 14a.

Chiral amine **7a** (434 mg, 2 mmol), 3-(trimethylsilyl)-propynal **8** (252 mg, 2 mmol) and *N*-methylmaleimide **12a** (222 mg, 2 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography of the 1.8:1 mixture of **13a** and **14a** eluting with 1:3 v/v petroleum ether–ether afforded two distereoisomers **13a** (208 mg, 29%) and **14a** (87 mg, 12%).

Major isomer **13a**. Colourless plates from ether mp 79–81°C. $[\alpha]_D^{25}=+165$ (1.0, $CHCl_3$). (Found: C, 69.3, H, 5.45, N, 7.85, $C_{21}H_{20}N_2O_4$ requires: C, 69.2, H, 5.55, N, 7.7%). δ (500 Hz): 2.52 (d, *J*=2.2 Hz, 1H, C≡CH), 2.61 (d, *J*=2.3 Hz, 1H, C≡CH), 2.99 (s, 3H, NCH_3), 3.07 (dd, *J*=9.9 and 12.9 Hz, 1H, PhC*H*H), 3.28 (dd, *J*=5.9 and 12.9 Hz, 1H, PhCH*H*), 3.31 (dd, *J*=1.8 and 8.2 Hz, 1H, H^c), 3.44 (t, *J*=8.2 Hz, 1H, H^b), 3.50 (s, 3H, OCH_3), 3.75 (dd, *J*=5.9 and 9.9 Hz, 1H, NC*H*CO_2Me), 4.34 (t, *J*=1.8 Hz, 1H, H^d), 4.40 (dd, *J*=2.3 and 8.2 Hz, 1H, H^a), 7.14–7.16 (m, 2H, ArH), 7.20 (m, 1H, ArH) and 7.24–7.27 (m, 2H, ArH). *m*/*z* (%): 364 (M^+, 2), 305 (3), 273 (100), 188 (6) and 91 (19). ν_{max}: 3273, 1707 and 1431 cm^{-1}.

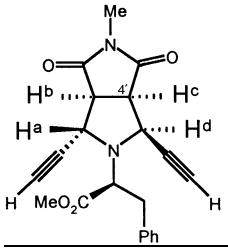
n.O.e. (500 MHz, $CDCl_3$) of **13a**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	11.1	3.3	–
H^b	9.6	–	3.5	
H^c	2.9	2.6	–	6.5
H^d	–	–	8.3	–

Minor isomer **14a**. Colourless prisms from ether, mp 110–120°C. $[\alpha]_D^{25}=-250$ (1.0, $CHCl_3$). (Found: C, 69.05, H, 5.65, N, 7.8. $C_{21}H_{20}N_2O_4$ requires: C, 69.2, H, 5.55, N, 7.7%). δ (500 MHz): 2.39 (d, J=2.1 Hz, 1H, C≡CH), 2.55 (d, J=2.3 Hz, 1H, C≡CH), 2.73 (s, 3H, NCH_3), 2.91 (dd, J=10.5 and 14.9 Hz, 1H, PhC*H*H), 3.18 (dd, J=5.8 and 14.9 Hz, 1H, PhCH*H*), 3.20 (dd, J=1.0 and 7.8 Hz, 1H, H^b), 3.27 (dd, J=7.8 and 8.0 Hz, 1H, H^c), 3.69 (s, 3H, OCH_3), 4.26 (dd, J=5.8 and 10.5 Hz, 1H, NC*H*CO_2Me), 4.47 (dd, J=1.0 and 2.1 Hz, 1H, H^a), 4.49 (dd, J=2.3 and 8.0 Hz, 1H, H^d), 7.08–7.09 (m, 2H, ArH), 7.14 (m, 1H, ArH) and 7.19–7.23 (m, 2H, ArH). *m/z* (%): 364 (M^+, 2), 305 (3), 273 (100), 188 (5) and 91 (23). ν_{max}: 3262, 1700 and 1439 cm^{-1}.

n.O.e. (500 MHz, $CDCl_3$) of **14a**:

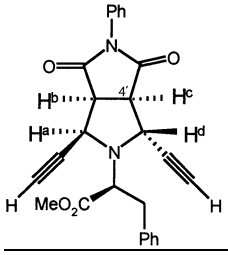


Proton irradiated	Enhancement (%)		
	H^a	H^b	H^c
H^a	–	4.6	8.0
H^b	5.6	–	–
H^c	15.46	–	–

2.2.2. Methyl (2*S*)-2-[(1*R*,3*R*,3a*R*,6a*S*)-1,3-diethynyl-4,6-dioxo-5-phenylhexahydro-pyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]-3-phenylpropanoate 13b and methyl (2*S*)-2-[(1*S*,3*S*,3a*R*,6a*S*)-1,3-diethynyl-4,6-dioxo-5-phenylhexahydro-pyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]-4-phenyl-propanoate 14b. Chiral amine **7a** (434 mg, 2 mmol), 3-(trimethylsilyl)propynal **8** (252 mg, 2 mmol) and *N*-phenylmaleimide **12b** (346 mg, 2 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography of the 1.5:1 mixture of **13b** and **14b** eluting with 1:2 v/v petroleum ether–ether afforded the separated isomers **13b** and **14b** (428 mg, 50%).

Major isomer **13b**. Colourless rods from methanol mp 129–131°C. $[\alpha]_D^{25}=+136$ (1.0, $CHCl_3$). (Found: C, 73.0, H, 5.1, N, 6.5, $C_{26}H_{22}N_2O_4$ requires: C, 73.25, H, 5.2, N, 6.55%). δ (500 MHz): 2.54 (d, J=2.0 Hz, 1H, C≡CH), 2.64 (d, J=2.3 Hz, 1H, C≡CH), 3.11 (dd, J=10 and 13.0 Hz, 1H, PhC*H*H), 3.33 (dd, J=5.7 and 13.0 Hz, 1H, PhCH*H*), 3.50 (dd, J=2.0 and 8.3 Hz, 1H, H^c), 3.51 (s, 3H, OCH_3), 3.61 (t, J=8.3 Hz, 1H, H^b), 3.83 (dd, J=5.7 and 10 Hz, 1H, NC*H*CO_2Me), 4.46 (t, J=2.0 Hz, 1H, H^d), 4.53 (dd, J=2.3 and 8.3 Hz, 1H, H^a), 7.17–7.28 (m, 7H, ArH), 7.40 (m, 1H, ArH) and 7.46–7.49 (m, 2H, ArH). *m/z* (%): 426 (M^+, 2), 367 (18), 335 (99) and 91 (100).

n.O.e. (500 MHz, $CDCl_3$) of **13b**:



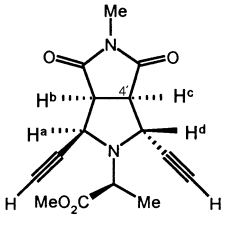
Proton irradiated	Enhancement (%)		
	H^a	H^b	H^c
H^a	–	11.7	–
H^b	11.5		
H^c	–	1.4	4.3

Minor isomer **14b**. Evaporation of the mother liquors and purification of the residue by chromatography over Kieselgel eluting with 1:1 v/v ether–petroleum ether afforded **14b** which crystallised from ether as colourless needles. Mp 156–158°C. $[\alpha]_D^{25}=-156$ (1.0, $CHCl_3$). (Found: C, 73.05, H, 5.15, N, 6.6. $C_{26}H_{22}N_2O_4$ requires: C, 73.25, H, 5.2, N, 6.55%). δ (500 MHz): 2.43 (d, J=2.0 Hz, 1H, C≡CH), 2.54 (d, J=2.2 Hz, 1H, C≡CH), 2.94 (dd, J=10.2 and 14.9 Hz, 1H, PhC*H*H), 3.23 (dd, J=5.7 and 14.9 Hz, 1H, PhCH*H*), 3.42 (dd, J=1.0 and 8.0 Hz, 1H, H^b), 3.47 (dd, J=8.0 and 8.4 Hz, 1H, H^c), 3.70 (s, 3H, OCH_3), 4.31 (dd, J=5.7 and 10.2 Hz, 1H, NC*H*CO_2Me), 4.63 (dd, J=2.2 and 8.4 Hz, 1H, H^d), 4.65 (dd, J=1.0 and 2.0 Hz, 1H, H^a), 6.93–6.95 (m, 2H, ArH), 7.04–7.12 (m, 5H, ArH) and 7.36–7.42 (m, 3H, ArH). *m/z* (%): 426 (M^+, 3), 367 (55), 335 (100) and 91 (63). ν_{max}: 3266, 1715, 1495 and 1382 cm^{-1}.

2.2.3. Methyl (2*S*)-2-[(1*R*,3*R*,3a*R*,6a*S*)-1,3-diethynyl-5-methyl-4,6-dioxohexahydro-pyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]-propanoate 13c and methyl (2*S*)-2-[(1*S*,3*S*,3a*R*,6a*S*)-1,3-diethynyl-5-methyl-4,6-dioxohexahydropyrrolo[3,4-*c*]-pyrrol-2(1*H*)-yl]-propanoate 14c. Chiral amine **7b** (141 mg, 1 mmol), 3-(trimethylsilyl)propynal **8** (126 mg, 1 mmol), and *N*-methylmaleimide **12a** (133 mg, 1.2mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography of the 3:1 mixture of **13c** and **14c** eluting with 1:3 v/v petroleum ether–ether afforded **13c** (102 mg) and a mixture of **13c** and **14c** (55 mg) in 54% combined yield.

Major isomer **13c**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 117–118°C. $[\alpha]_D^{25}=-266$ (1.09, $CHCl_3$). (Found: C, 62.65, H, 5.55, N, 9.65, C_{15} $H_{16}N_2O_4$ requires: C, 62.5, H, 5.6, N, 9.7%). δ (500 Hz) 1.36 (d, J=7.2 Hz, 3H, NCH*Me*), 2.38 (d, J=2.0 Hz, 1H, C≡CH), 2.55 (d, J=2.2 Hz, 1H, C≡CH), 3.00 (s, 3H, NMe), 3.30 (dd, J=2.0 and 7.9 Hz, 1H, H^c), 3.41 (dd, J=7.9 and 8.3 Hz, 1H, H^b), 3.67 (s, 3H, CO_2Me), 3.98 (q, J=7.2 Hz, 1H, C*H*CO_2Me), 4.44 (t, J=2.0 Hz, 1H, H^d) and 4.57 (dd, J=2.2 and 8.3 Hz, 1H, H^a). *m/z* (%): (FAB) 289 (M+1, 69), 263 (15), 229 (100), 144 (7), 118 (9) and 80 (5).

n.O.e. (500 MHz, $CDCl_3$) of **13c**:

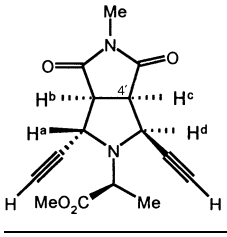


Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	11.59	–	–
H^b	12.95	–	3.87	–
H^c	–	3.53	–	4.85
H^d	–	–	4.57	–

Minor isomer **14c**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 134–136°C. $[\alpha]_D^{25}=+99$ (1.04, $CHCl_3$). (Found: C, 62.45, H, 5.7, N, 9.85, C_{15} $H_{16}N_2O_4$ requires: C, 62.5, H, 5.6, N, 9.7%.). δ (300 Hz) 1.43 (d, J=6.9 Hz, 3H, NCH*Me*), 2.47 (d, J=2.0 Hz, 1H, C≡CH), 2.54 (d, J=2.3 Hz, 1H, C≡CH), 3.02 (s, 3H, NMe), 3.32 (dd, J=2.0 and 8.2 Hz, 1H, H^b), 3.45 (t, J=8.2 Hz, 1H, H^c), 3.55 (q, J=6.9 Hz, 1H, NC*H*Me), 3.67 (s, 3H, CO_2Me), 4.19

(dd, J=2.3 and 8.2 Hz, 1H, H^d) and 4.39 (t, J=2.0 Hz, 1H, H^a). m/z (%): 287 (M−1, <1), 229 (100), 201 (11), 144 (9), 91 (5) and 80 (8).

n.O.e. (500 MHz, $CDCl_3$) of **14c**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	4.37	–	–
H^b	4.32	–	2.94	–
H^c	–	5.43	–	10.83
H^d	–	–	10.77	–

2.2.4. Methyl (2*R*)-[(1*R*,3*R*,3a*R*,6a*S*)-1,3-diethynyl-5-methyl-4,6-dioxohexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl]-(phenyl)ethanoate 13d and methyl (2*R*)-[(1*S*,3*S*, 3a*R*,6a*S*)-1,3-diethynyl-5-methyl-4,6-dioxohexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]-(phenyl)ethanoate 14d. The chiral amine **7c** (203 mg, 1 mmol), 3-(trimethylsilyl)-propynal **8** (120 mg, 1 mmol), and *N*-methylmaleimide **12a** (133 mg, 1.2 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography eluting with 1:1 v/v petroleum ether–ether afforded a 2:1:1.3 mixture of three distereoisomers **13d**, **14d** and **15d** (147 mg, 42%).

Stereoisomer **13d**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 163–165°C $[\alpha]_D^{25}$=+16 (1.0, $CHCl_3$). (Found: C, 68.85, H, 5.2, N, 7.8. $C_{20}H_{18}N_2O_4$ requires: C, 68.55, H, 5.20, N, 8.00%). δ (500 Hz) (C_6D_6) 1.74 (d, J=2.0 Hz, 1H, C≡CH), 2.09 (d, J=2.4 Hz, 1H, C≡CH), 2.48 (dd, J=2.0 and 8.2 Hz, 1H, H^c), 2.61 (s, 3H, NMe), 2.69 (t, J=8.2 Hz, 1H, H^b), 3.22 (s, 3H, CO_2Me), 3.96 (dd, J=2.4 and 8.2 Hz, 1H, H^a), 4.29 (t, J=2.0 Hz, 1H, H^d), 4.51 (s, 1H, PhCH) and 6.99–7.63 (m, 5H, ArH). m/z (%): 351 (M+1, 100), 291 (38), 201 (6), 149 (8) and 121 (11).

Stereoisomer **14d**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 114–116°C $[\alpha]_D^{25}$=+6 (1.0, $CHCl_3$). (Found: C, 68.3, H, 5.3, N, 8.05. $C_{20}H_{18}N_2O_4$ requires: C, 68.55, H, 5.20, N, 8.00%). δ (500 Hz) (C_6D_6) 1.85 (d, J=2.3 Hz, 1H, C≡CH), 1.86 (d, J=2.0 Hz, 1H, C≡CH), 2.60 (s, 3H, NMe), 2.67 (dd, J=2.3 and 8.4 Hz, 1H, H^b), 2.76 (t, J=8.4 Hz, 1H, H^c), 3.19 (s, 3H, CO_2Me), 4.35 (dd, J=2.0 and 8.4 Hz, 1H, H^{sd}), 4.69 (t, J=2.3 Hz, 1H, H^a), 4.73 (s, 1H, PhCH) and 7.00–7.53 (m, 5H, ArH). m/z (%): 351 (M+1, 68), 325 (11), 291 (100), 206 (16) and 167 (6).

Stereoisomer **15d**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 119–121°C. (Found: C, 68.65, H, 5.25, N, 7.85. $C_{20}H_{18}N_2O_4$ requires: C, 68.55, H, 5.20, N, 8.00%). δ 2.25 (t, J=2.4 Hz, 1H, C≡CH), 2.54 (d, J=2.1 Hz, 1H, C≡CH), 3.03 (s, 3H, Me), 3.30 (d, J=10.5 Hz, 1H, COCH), 3.55 (dd, J=7.5 and 10.5 Hz, 1H, COCH), 3.67 (dd, J=2.5 and 18.1 Hz, 1H, NC*H*H), 3.68 (s, 3H, Me), 4.06 (dd, J=2.5 and 18.1 Hz, 1H, NCH*H*), 4.31 (dd, J=2.1 and 7.5 Hz, 1H, NCH), and 7.31–7.53 (m, 5H, ArH). m/z (%): 351 (M+1, 75), 325 (10), 291 (100) and 206 (6).

2.2.5. (±)(3a*R*,4*R*,6*R*,6a*S*)-4,6-Diethynyl-2-methyl-5-(2-propynyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 17a. *N*,*N*-Di(2-propynyl)amine **16a** (186 mg, 2 mmol), 3-(trimethylsilyl) propynal **8** (252 mg, 2 mmol) and *N*-methylmaleimide **12a** (267 mg, 2.4 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography eluting with 1:2 v/v petroleum ether–ether afforded a single stereoisomer **17a** (317 mg, 66%) which crystallised as colourless needles from CH_2Cl_2/ether/petroleum ether, mp 157–158°C. (Found: C, 70.05, H, 5.10, N, 11.70, $C_{14}H_{12}N_2O_2$, requires: C, 70.00, H, 5.05, N, 11.65%). δ (500 Hz) 2.24 (t, J=2.6 Hz, 1H, C≡CH), 2.50 (d, J=2.0 Hz, 1H, C≡CH), 2.57 (d, J=2.2 Hz, 1H, C≡CH), 3.02 (s, 3H, Me), 3.24 (dd, J=2.6 and 16 Hz, 1H, NC*H*H), 3.35 (dd, J=2.0 and 8.1 Hz, 1H, H^c), 3.42 (t, J=8.1 Hz, 1H, H^b), 3.81 (dd, J=2.6 and 16 Hz, 1H, NCH*H*), 3.87 (dd, J=2.2 and 8.1 Hz, 1H, H^a) and 4.52 (t, J=2.0 Hz, 1H, H^d). m/z (%): 239 (M−1, 13), 182 (5), 154 (100), 129 (56), 116 (7), 102 (23), 90 (87), 77 (17), 63 (65), 56 (9), 51 (23) and 39 (55).

2.2.6. (±)(3a*R*,4*R*,6*R*,6a*S*)-4,6-Diethynyl-2,5-dimethyl-tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 17b. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 3-(trimethylsilyl)propynal **8** (189 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography eluting with 1:1 v/v petroleum ether–ether afforded a single stereoisomer **17b** (190 mg, 59%) which crystallised as colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 138–139°C. (Found: C, 66.65, H, 5.7, N, 13.2, $C_{12}H_{12}N_2O_2$, requires: C, 66.65, H, 5.6, N, 12.95%). δ (300 Hz) δ 2.44 (s, 3H, Me), 2.48 (d, J=2.1 Hz, 1H, C≡CH), 2.55 (d, J=2.3 Hz, 1H, C≡CH), 3.02 (s, 3H, Me), 3.32 (dd, J=1.0 and 8.0 Hz, 1H, H^c), 3.40 (t, J=8.0 Hz, 1H, H^b), 3.75 (dd, J=2.3 and 8.0 Hz, 1H, H^a) and 4.20 (dd, J=1.0 and 2.1 Hz, 1H, H^d). m/z (%): 215 (M−1, 16), 130 (34), 105 (100), 90 (19), 77 (21), 66 (63), 56 (14), 51 (31) and 39 (36). ν_{max} (nujol): 2923, 2853, 2953, 1696, 1460, 1377 and 3280.

2.2.7. (±)(3a*R*,4*R*,6*R*,6a*S*)-4,6-Diethynyl-5-methyl-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 17c. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 3-(trimethylsilyl)propynal **8** (189 mg, 1.5 mmol) and *N*-phenylmaleimide **12b** (312 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography eluting with 1:1 v/v petroleum ether–ether afforded a single stereoisomer **17c** (149 mg, 54%) which crystallised as colourless needles from CH_2Cl_2/ether/petroleum ether, mp 118–119°C. (Found: C, 73.3, H, 5.1, N, 10.1, $C_{17}H_{14}N_2O_2$ requires: C, 73.35, H, 5.1, N, 10.05%). δ 2.48 (s, 3H, Me), 2.50 (d, J=2.1 Hz, 1H, C≡CH), 2.56 (d, J=2.2 Hz, 1H, C≡CH), 3.50 (dd, J=1.1 and 7.9 Hz, 1H, H^c), 3.55 (t, J=7.9 Hz, 1H, H^b), 3.86 (dd, J=2.2 and 7.9 Hz, 1H, H^a) 4.29 (d, J=1.1 Hz, 1H, H^d) and 7.26–7.50 (m, 5H, ArH). m/z (%): (FAB) 279 (M+1, 100), 253 (14), 154 (15), 136 (11), 130 (7), 105 (14) and 77 (8). ν_{max} (nujol): 2923, 1710, 2953, 2853, 1204, 1455, 1731, 1393, 3293 and 3207.

2.2.8. (±)(3a*R*,4*R*,6*R*,6a*S*)-5-Benzyl-4,6-diethynyl-2-methyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 17d. *N*-Benzyl-*N*-(2-propynyl)amine **16c** (291 mg, 2 mmol), 3-(trimethylsilyl)propynal **8** (253 mg, 2 mmol) and *N*-methylmaleimide **12a** (267 mg, 2.4 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography eluting with 2:3 v/v petroleum ethyl–ether afforded **17d** (408 mg, 70%) which crystallised as colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 129–131°C. (Found: C, 73.65, H, 5.6, N, 9.9. $C_{18}H_{16}N_2O_2$, requires: C, 73.95, H, 5.50, N, 9.60%). δ (500 Hz) 2.49 (d, J=2.0 Hz, 1H, C≡CH), 2.57 (d, J=2.3 Hz, 1H, C≡CH), 3.03 (s, 3H, Me), 3.30 (dd, J=2.0 and 8.0 Hz 1H, H^c), 3.42 (dd, J=8.0 and 8.3 Hz, 1H, H^b), 3.47 (d, J=13 Hz, 1H, PhC*H*H), 3.95 (dd, J=2.3 and 8.3 Hz, 1H, H^a), 4.00 (t, J=2.0 Hz, 1H, H^d), 4.27 (d, J=13 Hz, 1H, PhCH*H*) and 7.23–7.31 (m, 5H, ArH). *m/z* (%): 293 (M+1, 100), 267 (9), 181 (9) and 91 (34).

2.2.9. (±)(3a*R*,4*R*,6*R*,6a*S*)-4,6-Diethynyl-2-methyl-5-vinyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 17e. *N*-Allyl-*N*-(2-propynyl)amine **16d** (240 mg, 2 mmol), 3-(trimethylsilyl)propynal **8** (253 mg, 2 mmol) and *N*-methylmaleimide **12a** (267 mg, 2.4 mmol) were reacted by the general procedure in toluene (5 ml) for 24 h. Flash column chromatography eluting with 1:1 v/v petroleum ethyl–ether afforded **17e** (239 mg, 50%) which crystallised as colourless needles from CH_2Cl_2/ether/petroleum ether, mp 144–146°C. (Found: C, 69.1, H, 5.85, N, 11.75. $C_{14}H_{14}N_2O_2$, requires: C, 69.4, H, 5.8, N, 11.55%). δ (500 Hz) 2.46 (d, J=2.2 Hz, 1H, C≡CH), 2.54 (d, J=2.3 Hz, 1H, C≡CH), 2.99 (dd, J=7.8 and 13.2 Hz, 1H, NC*H*H), 3.01 (s, 3H, Me), 3.32 (d, J=8.0 Hz, 1H, H^c), 3.39 (dd, J=8.0 and 8.2 Hz, 1H, H^b), 3.69 (dd, J=4.3 and 13.2 Hz, 1H, NCH*H*), 3.85 (dd, J=2.3 and 8.2 Hz, 1H, H^a), 4.25 (d, J=2.2 Hz, 1H, H^d), 5.16 (dtd, J=0.8, 1.8 and 10.1 Hz, 1H, C=C*H*H), 5.27 (dtd, J=0.8, 1.8 and J=17.1 Hz, 1H, C=CH*H*) and 5.73–5.81 (m, 1H, *H*C=CH_2). *m/z* (%): 241 (M−1, 36), 215 (12), 184 (7), 156 (55), 142 (13), 131 (89), 104 (19), 90 (100), 77 (28), 63 (51), 51 (25) and 39 (60).

2.3. General method for the preparation of cycloadducts 21a–q and 22a–q

The achiral secondary amine **16a–d** (1.5 mmol) was added to a solution of aldehyde **20** (1.5 mmol) and dipolarophile **12a**, **b** (1.8 mmol) in toluene (5 ml). The mixture was stirred and heated at 100°C under N_2 for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to give the cycloadducts **21a–q** and **22a–q**.

2.3.1. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2-methyl-5-(2-propynyl)-6-(2-thienyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21a and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2-methyl-5-(2-propynyl)-6-(2-thienyl)tetrahydropyrrolo-[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22a. *N*,*N*-Di(2-propynyl)amine **16a** (140 mg, 1.5 mmol), thiophene-2-carboxyaldehyde **20a** (168 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography of the 1:1 mixture of **21a** and **22a** eluting with 5:2 v/v petroleum ether–ethyl ether afforded the two separated stereoisomers **21a** and **22a** (262 mg, 59% combined yield).

Stereoisomer **21a**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 144–146°C. (Found: C, 64.25, H, 4.6, N, 9.2, S, 10.7. $C_{16}H_{14}N_2O_2S$ requires: C, 64.4, H, 4.75, N, 9.4, S, 10.75%). δ (300 Hz): 2.23 (t, J=2.6 Hz, 1H, C≡CH), 2.52 (d, J=2.0 Hz, 1H, C≡CH), 2.95 (s, 3H, Me), 3.19 (dd, J=2.6 and 16 1 Hz, 1H, NC*H*H), 3.39 (d, J=8.0 Hz, 1H, H^c), 3.42 (dd, J=2.6 and 16.1 Hz, 1H, NCH*H*), 3.53 (dd, J=8.0 and 9.0 Hz, 1H, H^b), 4.42 (d, J=9.0 Hz, 1H, H^a), 4.80 (d, J=2.0 Hz, 1H, H^d) and 6.99–7.30 (m, 3H, ArH). *m/z* (%): 299 (M+1, 100), 273 (13), 215 (51), 187 (11) and 148 (12).

Stereoisomer **22a**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 131–132°C. (Found: C, 64.6, H, 5.0, N, 9.50, S, 10.8. $C_{16}H_{14}N_2O_2S$ requires: C, 64.4, H, 4.75, N, 9.4, S, 10.75%). δ 2.23 (t, J=2.5 Hz, 1H, C≡CH), 2.49 (d, J=2.1 Hz, 1H, C≡CH), 3.02 (s, 3H, Me), 3.15 (dd, J=2.5 and 16 Hz, 1H, NC*H*H), 3.36 (dd, J=5.5 and 9.1 Hz, 1H, H^b), 3.43 (dd, J=2.5 and 16 Hz, 1H, NCH*H*), 3.74 (dd, J=8.1 and 9.1 Hz, 1H, H^c), 4.38 (d, J=5.5 Hz, 1H, H^a), 4.65 (dd, J=2.1 and 8.1 Hz, 1H, H^d), 7.00 (dd, J=3.5 and 5.1 Hz, 1H, ArH), 7.14 (dd, J=0.6 and 3.5 Hz, 1H, ArH) and 7.32 (dd, J=0.6 and 5.1 Hz, 1H, ArH). *m/z* (%): 299 (M+1, 100), 289 (6), 273 (13), 215 (30), 187 (11), 148 (11), 121 (6), 107 (8), 89 (8) and 77 (9).

2.3.2. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2-methyl-5-(2-propynyl)-6-(1,3-thiazol-2-yl)tetrahydropyrrolo[3,4-*c*]-pyrrole-1,3(2*H*,3a*H*)-dione 21b and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2-methyl-5-(2-propynyl)-6-(1,3-thiazol-2-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22b. *N*,*N*-Di(2-propynyl)amine **16a** (140 mg, 1.5 mmol), 2-thiazole carboxaldehyde **20b** (170 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography of the 1:1 mixture of **21b** and **22b** eluting with 1:3 v/v petroleum ether–ethyl ether afforded the two separated stereoisomers **21b** and **22b** (368 mg, 80% combined yield).

Stereoisomer **21b**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 164–165°C. (Found: C, 60.25, H, 4.55, N, 14.3, S, 10.65. $C_{15}H_{13}N_3O_2S$, requires: C, 60.2, H, 4.4, N, 14.05, S, 10.7%). δ 2.26 (t, J=2.5 Hz, 1H, C≡CH), 2.56 (d, J=2.1 Hz, 1H, C≡CH), 2.93 (s, 3H, Me), 3.32 and 3.43 (2×dd, J=2.5 and 16.1 Hz, 2×1H, NCH_2), 3.46 (d, J=8.1, 1H, H^c), 3.73 (dd, J=8.1 and 9.1 Hz, 1H, H^b), 4.64 (d, J=9.1 Hz, 1H, H^a), 4.82 (d, J=2.1 Hz, 1H, H^d) and 7.38 and 7.81 (2×d, J=3.3 Hz, 2×1H, ArH). *m/z* (%): 300 (M^++1, 100), 274 (5), 215 (35) and 130 (6).

Stereoisomer **22b**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 157–159°C. (Found: C, 60.25, H, 4.65, N, 14.1, S, 10.7. $C_{15}H_{13}N_3O_2S$ requires: C, 60.2, H, 4.4, N, 14.05, S, 10.7%). δ 2.20 (t, J=2.5 Hz, 1H, C≡CH), 2.53 (d, J=2.2 Hz, 1H, C≡CH), 3.06 (s, 3H, Me), 3.15 (dd, J=2.5 and 16.5 Hz, 1H, NC*H*H), 3.56 (dd, J=2.6 and 8.4 Hz, 1H, H^b), 3.62 (dd, J=2.5 and 16.5 Hz, 1H, NCH*H*), 3.78 (t, J=8.4, 1H, H^c), 4.49 (dd, J=2.2 and

8.4 Hz, 1H, H^d), 4.88 (d, J=2.6 Hz, 1H, H^a) and 7.37 and 7.81 (2×d, J=3.2 Hz, 2×1H, ArH). m/z (%): 300 (M^++1, 100), 289 (5), 274 (6), 215 (23), 154 (9) and 136 (10).

2.3.3. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2-methyl-6-phenyl-5-(2-propynyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21c and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2-methyl-6-phenyl-5-(2-propynyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22c. *N*,*N*-Di(2-propynyl) amine **16a** (140 mg, 1.5 mmol) benzaldehyde **20c** (159 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography of the 1:1 mixture of **21c** and **22c** eluting with 2:1 v/v petroleum ether–ethyl ether afforded the two separated stereoisomers **21c** and **22c** (296 mg, 67% combined yield).

Stereoisomer **21c**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 129–131°C. (Found: C, 74.05, H, 5.55, N, 9.65. $C_{18}H_{16}N_2O_2$ requires: C, 73.95, H, 5.50, N, 9.60%). δ 2.22 (t, J=2.4 Hz, 1H, C≡CH), 2.52 (d, J=2.0 Hz, 1H, C≡CH), 2.91 (s, 3H, Me), 3.13 and 3.21 (2×d, J=2.4 Hz, 2×1H, NCH_2), 3.40 (d, J=7.8 Hz, 1H, H^c), 3.52 (dd, J=7.8 and 8.9 Hz, 1H, H^b), 4.08 (d, J=8.9 Hz, 1H, H^a), 4.84 (d, J=2.0 Hz, 1H, H^d) and 7.19–7.46 (m, 5H, ArH). m/z (%): 293 (M+1, 100), 267 (17), 215 (10), 206 (7), 181 (9), 142 (13) and 115 (8).

Stereoisomers **22c**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 150–151°C. (Found: C, 73.90, H, 5.60, N, 9.50. $C_{18}H_{16}N_2O_2$ requires: C, 73.95, H, 5.50, N, 9.60%). δ 2.22 (t, J=2.3 Hz, 1H, C≡CH), 2.48 (d, J=2.0 Hz, 1H, C≡CH), 3.01 (s, 3H, Me), 3.19 (dd, J=2.3 and 6.0 Hz, 2H, NCH_2), 3.25 (dd, J=6.5 and 9.1 Hz, 1H, H^b), 3.75 (dd, J=8.0 and 9.1 Hz, 1H, H^c), 3.88 (d, J=6.5 Hz, 1H, H^a), 4.81 (dd, J=2.0 and 8.0 Hz, 1H, H^d) and 7.31–7.46 (m, 5H, ArH). m/z (%): 291 (M−1, 29), 253 (12), 215 (21), 206 (12), 181 (19), 167 (5), 150 (7), 142 (65), 130 (80), 115 (100), 103 (13), 91 (25), 77 (26), 63 (22), 51 (22) and 39 (48).

2.3.4. (±)(3a*R*,4*R*,6*R*,6a*S*)-5-Allyl-4-ethynyl-2-methyl-6-(2-thienyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21d and (3a*R*,4*S*,6*S*,6a*S*)-5-allyl-4-ethynyl-2-methyl-6-(2-thienyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22d. *N*-Allyl-*N*-(2-propynyl)-amine **16d** (240 mg, 2 mmol), thiophene-2-carboxyaldehyde **20a** (224 mg, 2 mmol) and *N*-methylmaleimide **12a** (267 mg, 2.4 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography of the 1:1 mixture of **21d** and **22d** eluting with 2:1 v/v petroleum ether–ethyl ether afforded the two separated stereoisomers **21d** and **22d** (305 mg, 61% combined yield).

Stereoisomer **21d**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 105–107°C. (Found: C, 63.95, H, 5.55, N, 9.40, S, 10.55. $C_{16}H_{16}N_2O_2S$ requires: C, 64.0, H, 5.35, N, 9.35, S, 10.65%). δ (^{1}H) 2.47 (d, J=2.0 Hz, 1H, C≡CH), 2.93 (s, 3H, Me), 3.00 (dd, J=7.1 and 12.4 Hz, 1H, NC*H*H), 3.26 (dd, J=7.1 and 12.4 Hz, 1H, NCH*H*), 3.36 (d, J=7.7 Hz, 1H, H^c), 3.50 (dd, J=7.7 and 9.1 Hz, 1H, H^b), 4.47 (d, J=9.1 Hz, 1H, H^a), 4.50 (d, J=2.0 Hz, 1H, H^d), 5.13 (dd, J=1.6 and 10.1 Hz, 1H, C=C*H*H), 5.23 (dd, J=1.6 and 17.2 Hz, 1H, C=CH*H*), 5.68–5.80 (m, 1H, C*H*=CH_2) and 6.98–7.26 (m, 3H, ArH); δ (^{13}C): 25.58 (Me), 49.74 and 51.05 (2×CO*C*H), 51.61 (N*C*H_2), 53.73 and 63.53 (2×N*C*H), 76.39 (C≡*C*H), 78.29 (*C*≡CH), 118.33 (CH=*C*H_2), 126.29, 126.96 and 127.39 (3×ArC), 134.54 (*C*H=CH_2) and 175.70 and 176.99 (2×C=O); m/z (%): 323 (M+23, 100).

Stereoisomers **22d**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 97–99°C. (Found: C, 63.95, H, 5.5, N, 9.6, S, 10.5. $C_{16}H_{16}N_2O_2S$ requires: C, 64.0, H, 5.35, N, 9.35, S, 10.65%). δ (^{1}H) 2.45 (d, J=2.0 Hz, 1H, C≡CH), 3.00 (s, 3H, Me), 3.01 (d, J=11 Hz, 1H, NC*H*H), 3.25 (m, 1H, NCH*H*), 3.31 (dd, J=5.7 and 8.8 Hz, 1H, H^b), 3.69 (dd, J=8.1 and 8.8 Hz, 1H, H^c), 4.32 (d, J=5.7 Hz, 1H, H^a), 4.42 (dd, J=2.0 and 8.1 Hz, 1H, H^d), 5.13 (d, J=10.0 Hz, 1H, C=C*H*H), 5.27 (d, J=17 Hz, 1H, C=CH*H*), 5.68–5.81 (m, 1H, C*H*=CH_2), 6.98 (m, 1H, ArH), 7.12 (m, 1H, ArH) and 7.28 (m, 1H, ArH); δ (^{13}C): 29.17 (Me), 48.51 and 54.01 (2×CO*C*H), 51.36 (N*C*H_2), 54.04 and 62.95 (2×N*C*H), 76.37 (C≡*C*H), 78.00 (*C*≡CH), 118.75 (CH=*C*H_2), 126.15, 127.02 and 127.37 (3×ArC), 134.44 (*C*H=CH_2), 144.41, 175.0 and 177.0 (2×C=O); m/z (%): 323 (M+23, 100).

2.3.5. (±)(3a*R*,4*R*,6*R*,6a*S*)-5-Allyl-4-ethynyl-2-methyl-6-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21e and (3a*R*,4*S*,6*S*,6a*S*)-5-allyl-4-ethynyl-2-methyl-6-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22e. *N*-Allyl-*N*-(2-propynyl)-amine **16d** (240 mg, 2 mmol), benzaldehyde **20c** (212 mg, 2 mmol) and *N*-methylmaleimide **12a** (267 mg, 2.4 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography of the 1:1 mixture of **21e** and **22e** eluting with 2:1 v/v petroleum ether–ethyl ether afforded the two separated stereoisomers **21e** and **22e** (298 mg, 50% combined yield).

Stereoisomer **21e**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 118–120°C. (Found: C, 73.4, H, 6.25, N, 9.65, $C_{18}H_{18}N_2O_2$ requires: C, 73.45, H, 6.15, N, 9.50%). δ (^{1}H) 2.47 (d, J=2.0 Hz, 1H, C≡CH), 2.90 (s, 3H, Me), 2.93–3.12 (m, 2H, NCH_2), 3.37 (d, J=7.7 Hz, 1H, H^c), 3.50 (dd, J=7.7 and 9.0 Hz, 1H, H^b), 4.15 (d, J=9.0 Hz, 1H, H^a), 4.55 (d, J=2.0 Hz, 1H, H^d), 5.12 (d, J=10.2 Hz, 1H, C=C*H*H), 5.22 (d, J=17.2 Hz, 1H, C=CH*H*), 5.69–5.75 (m, 1H, C*H*=CH_2) and 7.19–7.36 (m, 5H, ArH); m/z (%): 293 (M−1, 57), 253 (8), 217 (28), 208 (15), 183 (35), 142 (100), 115 (52), 104 (16), 91 (21), 77 (17) and 66 (9).

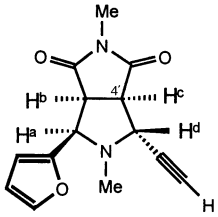
Stereoisomer **22e**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 104–106°C. (Found: C, 73.45, H, 6.05, N, 9.45, $C_{18}H_{18}N_2O_2$ requires: C, 73.45, H, 6.15, N, 9.50%). δ (^{1}H) 2.44 (d, J=2.0 Hz, 1H, C≡CH), 3.00 (s, 3H, Me), 3.02–3.12 (m, 2H, NCH_2), 3.21 (dd, J=6.5 and 9.2 Hz, 1H, H^b), 3.68 (dd, J=8.0 and 9.2 Hz, 1H, H^c), 3.92 (d, J=6.5 Hz, 1H, H^a), 4.50 (dd, J=2.0 and 8.0 Hz, 1H, H^d), 5.12 (dd, J=1.1 and 10.1 Hz, 1H, C=C*H*H), 5.23 (dd, J=1.1 and 17.2 Hz, 1H, C=CH*H*), 5.66–5.80 (m, 1H, C*H*=CH_2) and 7.28–7.47 (m, 5H, ArH); m/z (%): 295 (M+1, 100), 208 (12), 193 (11), 142 (37) and 133 (11).

2.3.6. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-6-(2-furyl)-2,5-dimethyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-

dione 21f and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-6-(2-furyl)-2,5-dimethyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22f*N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 2-furaldehyde **20d** (144 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography of the 1:1 mixture of **21f** and **22f** eluting with 2:3 v/v petroleum ether–ethyl ether afforded the two separated stereoisomers **21f** and **22f** (330 mg, 85% combined yield).

Stereoisomer **21f**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 134–136°C. (Found: C, 65.05, H, 5.45, N, 11.0. $C_{14}H_{14}N_2O_3$ requires: C, 65.10, H, 5.45, N, 10.85%). δ 2.22 (s, 3H, Me), 2.49 (d, J=2.1 Hz, 1H, C≡CH), 2.98 (s, 3H, Me), 3.36 (d, J=7.8 Hz, 1H, H^c), 3.47 (dd, J=7.8 and 8.7 Hz, 1H, H^b), 4.09 (d, J=8.7 Hz, 1H, H^a), 4.41 (d, J=2.1 Hz, 1H, H^d), 6.30 (d, J=2.8 Hz, 1H, ArH), 6.36 (dd, J=1.8 and 3.2 Hz, 1H, ArH) and 7.40 (d, J=1.8 Hz, 1H, ArH). *m/z* (%): 257 (M^+-1, 11), 172 (8), 147 (100), 132 (28), 118 (44), 108 (30), 91 (8), 78 (18), 66 (13), 51 (18) and 42 (28). ν_{max} (nujol): 2923, 2853, 2953, 1698, 1455, and 3231.

n.O.e. (500 MHz, $CDCl_3$) of **21f**:



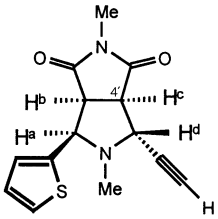
Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	8.12	–	–
H^b	8.20	–	2.97	
H^c	–	1.07	–	3.46
H^d	–	–	3.24	–

Stereoisomer **22f**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 114–116°C. (Found: C, 64.95, H, 5.5, N, 10.80. $C_{14}H_{14}N_2O_3$ requires: C, 65.10, H, 5.45, N, 10.85%). δ 2.23 (s, 3H, Me), 2.48 (d, J=2.2 Hz, 1H, C≡CH), 3.03 (s, 3H, Me), 3.49 (dd, J=3.9 and 8.5 Hz, 1H, H^b), 3.70 (t, J=8.5 Hz, 1H, H^c), 4.15 (dd, J=2.2 and 8.5 Hz, 1H, H^d), 4.21 (d, J=3.9 Hz, 1H, H^a), 6.35 (dd, J=0.8 and 3.2 Hz, 1H, ArH), 6.37 (dd, J=1.8 and 3.2 Hz, 1H, ArH) and 7.42 (d, J=1.0 Hz, 1H, ArH). *m/z* (%): (FAB) 259 (M^++1, 100%). ν_{max} (nujol): 1698, 2923, 1702, 2951, 2853, 1682 and 3281.

2.3.7. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2,5-dimethyl-6-(2-thienyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21g and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2,5-dimethyl-6-(2-thienyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22g. *N*-Methyl-*N*-(2-propynyl) amine **16b** (104 mg, 1.5 mmol), thiophene-2-carboxyaldehyde **20a** (159 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography of the 1:1 mixture of **21g** and **22g** eluting with 1:1 v/v petroleum ether-ethyl ether afforded the two separated stereoisomers **21g** and **22g** (238 mg, 58% combined yield).

Stereoisomer **21g**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 126–128°C. (Found: C, 61.1, H, 5.2, N, 10.5, S, 11.5. $C_{14}H_{14}N_2O_2S$ requires: C, 61.3, H, 5.15, N, 10.2, S, 11.7%). δ 2.29 (s, 3H, Me), 2.48 (d, J=2.1 Hz, 1H, C≡CH), 2.93 (s, 3H, Me), 3.35 (d, J=7.7 Hz, 1H, H^c), 3.49 (dd, J=7.7 and 9.1 Hz, 1H, H^b), 4.34 (d, J=9.1 Hz, 1H, H^a), 4.43 (d, J=2.1 Hz, 1H, H^d) 6.98–7.04 (m, 2H, ArH) and 7.27–7.28 (m, 1H, ArH). *m/z* (%): 275 (M+1, 100). ν_{max} (nujol): 3271, 2923, 2853, 2954, 1696, 1460, 1378 and 716.

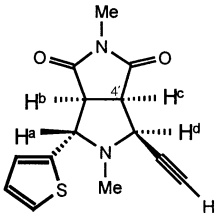
n.O.e. (500 MHz, $CDCl_3$) of **21g**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	ArH
H^a	–	9.21	–	3.29
H^b	7.93	–	3.71	–
H^c	3.56	3.27	–	–
H^d	–	–	3.25	–

Stereoisomer **22g**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 134–136°C. (Found: C, 61.2, H, 5.1, N, 10.05, S, 11.5. $C_{14}H_{14}N_2O_2S$ requires: C, 61.3, H, 5.15, N, 10.2, S, 11.7%). δ 2.27 (s, 3H, Me), 2.46 (d, J=2.1 Hz, 1H, C≡CH), 3.01 (s, 3H, Me), 3.32 (dd, J=5.5 and 9.1 Hz, 1H, H^b), 3.71 (dd, J=8.0 and 9.1 Hz, 1H, H^c), 4.25 (d, J=5.5 Hz, 1H, H^a), 4.32 (dd, J=2.1 and 8.0 Hz, 1H, H^d) 6.99 (dd, J=3.5 and 5.1 Hz, 1H, ArH), 7.10–7.11 (m, 1H, ArH) and 7.27–7.31 (m, 1H, ArH). *m/z* (%): 274 (M^+, 20), 188 (9), 163 (100), 148 (32), 135 (6), 124 (46), 115 (6), 106 (14), 97 (18), 91 (12), 82 (8), 77 (13), 69 (8), 63 (18), 58 (8), 51 (12) and 42 (35). ν_{max} (nujol): 3271, 2923, 2853, 2953, 1696, 1460 and 716.

n.O.e. (500 MHz, $CDCl_3$) of **22g**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	1.71	0.91	–
H^b	1.57	–	6.24	–
H^c	–	7.25	–	6.52
H^d	–	–	6.71	–

2.3.8. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2,5-dimethyl-6-(1,3-thiazol-2-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21h and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2,5-dimethyl-6-(1,3-thiazol-2-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3-(2*H*,3a*H*)-dione 22h. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 2-thiazole carboxaldehyde **20b** (170 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:4 v/v petroleum ether–ether) afforded the two separated stereoisomers **21h** and **22h** (329 mg, 80% combined yield) in a 1:1 ratio.

Stereoisomer **21h**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 139–141°C. (Found: C, 56.7, H, 4.6, N, 15.5, S, 11.75. $C_{13}H_{13}N_3O_2S$ requires: C, 56.7, H, 4.75, N, 15.25, S, 11.65%). δ 2.37 (s, 3H, Me), 2.53 (d, J=1.9 Hz, 1H, C≡CH), 2.92 (s, 3H, Me), 3.42 (d, J=7.8 Hz, 1H, H^c), 3.69 (dd, J=7.8 and 9.2 Hz, 1H, H^b), 4.46 (d, J=1.9 Hz, 1H,

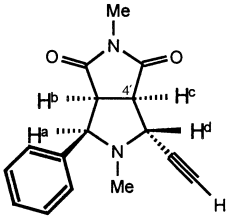
H^d), 4.55 (d, J=9.2 Hz, 1H, H^a) and 7.35 and 7.80 (2×d, J=3.2 Hz, 2×1H, ArH). m/z (%): 276 (M^++1, 100). ν_{max} (nujol): 1688, 1706, 1698, 2934, 2855, 2957, 1121, 1280 and 3264.

Stereoisomer **22h**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 126–128°C. (Found: C, 56.6, H, 4.7, N, 15.15, S, 11.85. $C_{13}H_{13}N_3O_2S$, requires: C, 56.7, H, 4.75, N, 15.25, S, 11.65%). δ 2.31 (s, 3H, Me), 2.50 (d, J=2.2 Hz, 1H, C≡CH), 3.04 (s, 3H, Me), 3.54 (dd, J=3.5 and 8.6 Hz, 1H, H^b), 3.76 (dd, J=8.2 and 8.6 Hz, 1H, H^c), 4.30 (dd, J=2.2 and 8.2 Hz, 1H, H^d), 4.57 (d, J=3.5 Hz, 1H, H^a) and 7.35 and 7.82 (2×d, J=3.3 Hz, 2×1H, ArH). m/z (%): 276 (M^++1, 95) and 191 (100). ν_{max} (nujol): 1694, 1698, 1702, 1781, 3291, 2924, 3112 and 2851.

2.3.9. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2,5-dimethyl-6-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21i and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2,5-dimethyl-6-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22i. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), benzaldehyde **20c** (159 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (3:2 v/v petroleum ether–ether) afforded the two separated stereoisomers **21i** and **22i** (251 mg, 62% combined yield) in a 1:1 ratio.

Stereoisomer **21i**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 137–139°C. (Found: C, 71.65, H, 6.15, N, 10.5. $C_{16}H_{16}N_2O_2$ requires: C, 71.65, H, 6.0, N, 10.45%). δ 2.19 (s, 3H, Me), 2.48 (d, J=2.1 Hz, 1H, C≡CH), 2.90 (s, 3H, Me), 3.36 (d, J=7.7 Hz, 1H, H^c), 3.49 (dd, J=7.7 and 8.9 Hz, 1H, H^b), 4.02 (d, J=8.9 Hz, 1H, H^a), 4.46 (d, J=2.1 Hz, 1H, H^d) and 7.18–7.36 (m, 5H, ArH). m/z (%): 268 (M, 36), 191 (25), 182 (14), 167 (7), 157 (100), 142 (22), 128 (11), 115 (83), 106 (34), 91 (33), 82 (7), 77 (56), 63 (36), 58 (13), 51 (44) and 42 (62). ν_{max} (nujol): 2923, 1694, 2853, 3231, 1441 and 698.

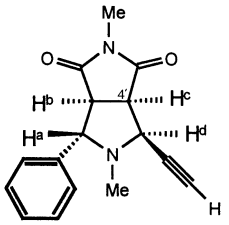
n.O.e. (500 MHz, $CDCl_3$) of **21i**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	8.38	–	–
H^b	7.26	–	3.91	–
H^c	–	3.58	–	3.84
H^d	–	–	3.00	–

Stereoisomer **22i**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 132.5–134.5°C. (Found: C, 71.55, H, 6.1, N, 10.65. $C_{16}H_{16}N_2O_2$ requires: C, 71.65, H, 6.0, N, 10.45%). δ 2.19 (s, 3H, Me), 2.45 (d, J=2.1 Hz, 1H, C≡CH), 3.01 (s, 3H, Me), 3.23 (dd, J=6.4 and 9.3 Hz, 1H, H^b), 3.72 (dd, J=8.0 and 9.3 Hz, 1H, H^c), 3.82 (d, J=6.4 Hz, 1H, H^a), 4.41 (dd, J=2.1 and 8.0 Hz, 1H, H^d) and 7.29–7.45 (m, 5H, ArH). m/z (%): 267 (M−1, 39), 191 (29), 182 (18), 167 (8), 157 (100), 142 (22), 128 (9), 118 (56), 106 (24), 91 (22), 77 (25), 63 (16), 51 (18) and 42 (31).

n.O.e. (500 MHz, $CDCl_3$) of **22i**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	2.59	–	1.04
H^b	1.75	–	7.85	–
H^c	–	9.01	–	8.78
H^d	–	–	8.05	–

2.3.10. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2,5-dimethyl-6-(2-pyridinyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21j and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2,5-dimethyl-6-(2-pyridinyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22j. *N*-Methyl-*N*-(2-propynyl)amine **16b** (107 mg, 1.5 mmol), pyridine-3-carboxaldehyde **20e** (161 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:2 v/v petroleum ether–ether) afforded the two separated stereoisomers **21j** and **22j** (214 mg, 53% combined yield) in a 1:1 ratio.

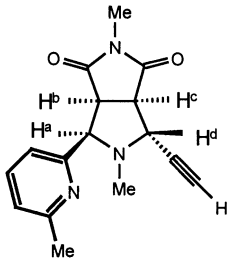
Stereoisomer **21j**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 137–139°C. (Found: C, 66.7, H, 5.65, N, 15.9. $C_{15}H_{15}N_3O_2$ requires: C, 66.90, H, 5.60, N, 15.6%). δ 2.25 (s, 3H, Me), 2.50 (d, J=2.1 Hz, 1H, C≡CH), 2.92 (s, 3H, Me), 3.41 (d, J=7.8 Hz, 1H, H^c), 3.63 (dd, J=7.8 and 8.9 Hz, 1H, H^b), 4.21 (d, J=8.9 Hz, 1H, H^a), 4.48 (d, J=2.1 Hz, 1H, H^d), 7.19–7.27 (m, 2H, ArH), 7.68 (dt, J=1.8 and 7.7 Hz, 1H, ArH) and 8.61–8.63 (m, 1H, ArH). m/z (%): 268 (M^+−1, 56), 254 (30), 240 (26), 211 (8), 191 (45), 183 (45), 169 (39), 157 (79), 143 (63), 131 (32), 117 (62), 106 (100), 92 (40), 78 (82), 63 (40), 56 (15), 51 (61) and 39 (48). ν_{max} (nujol): 2923, 1689, 2853, 2955, 1441, 1285 and 3256.

Stereoisomer **22j**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 132–134°C. (Found: C, 66.7, H, 5.75, N, 15.85. $C_{15}H_{15}N_3O_2$, requires: C, 66.90, H, 5.60, N, 15.6). δ 2.21 (s, 3H, Me), 2.48 (d, J=2.2 Hz, 1H, C≡CH), 3.03 (s, 3H, Me), 3.66 (dd, J=5.1 and 9.0 Hz, 1H, H^b), 3.84 (dd, J=8.1 and 9.0 Hz, 1H, H^c), 4.07 (d, J=5.1 Hz, 1H, H^a), 4.42 (dd, J=2.2 and 8.1 Hz, 1H, H^d), 7.24–7.29 (m, 1H, ArH), 7.35 (d, J=7.7 Hz, 1H, ArH), 7.71 (dt, J=1.8 and 7.7 Hz, 1H, ArH), and 8.66–8.68 (m, 1H, ArH). m/z (%): 270 (M+1, 100), 244 (6), 191 (8) and 157 (5). ν_{max} (nujol): 2923, 2853, 2954, 1696, 1460, 716, 1378 and 3271.

2.3.11. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-2,5-dimethyl-6-(6-methyl-2-pyridinyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21k and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-2,5-dimethyl-6-(6-methyl-2-pyridinyl)tetrahydropyrrolo-[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22k. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 6-methyl-2-pyridine-carboxaldehyde **20f** (182 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:4 v/v petroleum ether–ether) afforded the two separated stereoisomers **21k** and **22k** (330 mg, 56% combined yield) in a 1:1 ratio.

Stereoisomer **21k**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 153–155°C. (Found: C, 67.9, H, 6.0, N, 14.6. $C_{16}H_{17}N_3O_2$, requires: C, 67.85, H, 6.05, N, 14.85). δ 2.24 (s, 3H, Me), 2.47 (d, J=2.0 Hz, 1H, C≡CH), 2.57 and 2.92 (2×s, 2×3H, 2×Me), 3.39 (d, J=7.9 Hz, 1H, H^c), 3.63 (dd, J=7.9 and 8.8 Hz, 1H, H^b), 4.18 (d, J=8.8 Hz, 1H, H^a), 4.46 (d, J=2.0 Hz, 1H, H^d), 6.97 and 7.08 (2×d, J=7.7 Hz, 2×1H, ArH) and 7.54 (t, J=7.7 Hz, 1H, ArH). m/z (%): 284 (M^++1, 100%). ν_{max} (nujol): 1698, 1288, 1439, 1593, 2923 and 3243.

n.O.e. (500 MHz, $CDCl_3$) of **21k**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	8.70	–	–
H^b	9.08	–	6.84	–
H^c	–	5.61	–	3.24
H^d	–	–	3.15	–

Stereoisomer **22k**. Colourless needles from preparative HPLC, mp 134–136°C. (Found: C, 67.8, H, 6.0, N, 15.15. $C_{16}H_{17}N_3O_2$, requires: C, 67.85, H, 6.05, N, 14.85). δ 2.20 (s, 3H, Me), 2.46 (d, J=2.2 Hz, 1H, C≡CH), 2.56 and 3.03 (2×s, 2×3H, 2×Me), 3.72 (dd, J=4.7 and 8.9 Hz, 1H, H^b), 3.83 (dd, J=8.0 and 8.9 Hz, 1H, H^c), 4.07 (d, J=4.7 Hz, 1H, H^a), 4.43 (dd, J=2.2 and 8.0 Hz, 1H, H^d), 7.11 (dd, J=3.6 and 7.7 Hz, 2H, ArH) and 7.58 (t, J=7.7 Hz, 1H, ArH). m/z (%): 283 (M^+, 69), 268 (44), 255 (25), 225 (7), 211 (5), 197 (38), 191 (58), 183 (33), 171 (50), 157 (72), 145 (51), 131 (58), 118 (14), 106 (100), 92 (41), 77 (32), 65 (55), 51 (21) and 39 (50). ν_{max} (nujol): 2923, 1699, 2361, 668, 2343, 2853 and 2954.

2.3.12. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-6-(4-methoxyphenyl)-2,5-dimethyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21l and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-6-(4-methoxyphenyl)-2,5-dimethyltetrahydropyrrolo[3,4-*c*]-pyrrole-1,3(2*H*,3a*H*)-dione 22l. *N*-Methyl-*N*-(2-propynyl)-amine **16b** (104 mg, 1.5 mmol), 4-methoxybenzaldehyde **20g** (204 mg, 1.5 mmol) and *N*-methylmaleimide **12a** (200 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:1 v/v petroleum ether–ether) afforded the two separated stereoisomers **21l** and **22l** (205 mg, 46% combined yield) in a 1:1 ratio.

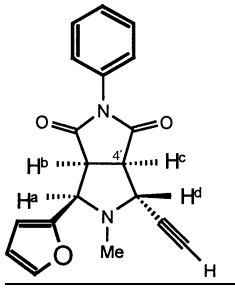
Stereoisomer **21l**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 189–191°C. (Found: C, 68.25, H, 6.2, N, 9.6. $C_{17}H_{18}N_2O_3$ requires: C, 68.45, H, 6.1, N, 9.4%). δ 2.16 (s, 3H, Me), 2.47 (d, J=2.1 Hz, 1H, C≡CH), 2.91 (s, 3H, Me), 3.34 (d, J=7.7 Hz, 1H, H^c), 3.44 (dd, J=7.7 and 8.8 Hz, 1H, H^b), 3.80 (s, 3H, Me), 3.97 (d, J=8.8 Hz, 1H, H^a), 4.44 (d, J=2.1 Hz, 1H, H^d), 6.87 (d, J=8.9 Hz, 2H, ArH) and 7.09 (d, J=8.5 Hz, 2H, ArH). m/z (%): 297 (M−1, 23), 212 (7), 187 (100), 172 (66), 157 (9), 148 (50), 131 (10), 115 (11), 106 (14), 91 (9), 77 (15), 63 (11), 51 (9) and 42 (25).

Stereoisomer **22l**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 177–179°C. (Found: C, 68.55, H, 6.05, N, 9.3. $C_{17}H_{18}N_2O_3$ requires: C, 68.45, H, 6.1, N, 9.4%). δ 2.17 (s, 3H, Me), 2.44 (d, J=2.1 Hz, 1H, C≡CH), 3.00 (s, 3H, Me), 3.20 (dd, J=6.5 and 9.2 Hz, 1H, H^b), 3.70 (dd, J=8.1 and 9.2 Hz, 1H, H^c), 3.76 (d, J=6.5 Hz, 1H, H^a), 3.82 (s, 3H, Me), 4.39 (dd, J=2.1 and 8.1 Hz, 1H, H^d), 6.91 and 7.33 (2×dd, J=2.1 and 6.7 Hz, 2×2H, ArH). m/z (%): 297 (M−1, 13), 212 (5), 187 (100), 172 (76), 157 (8), 148 (41), 133 (6), 121 (8), 115 (11), 105 (9), 91 (8), 77 (13), 63 (10), 51 (8) and 42 (14). ν_{max} (nujol): 1703, 3267, 1694, 1249, 1515, 2847, 2953 and 2903.

2.3.13. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-6-(2-furyl)-5-methyl-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21m and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-6-(2-furyl)-5-methyl-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22m. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 2-furaldehyde **20d** (144 mg, 1.5 mmol) and *N*-phenylmaleimide **12b** (312 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:1 v/v petroleum ether–ether) afforded the two separated stereoisomers **21m** and **22m** (212 mg, 44% combined yield) in a 1:1 ratio.

Stereoisomer **21m**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 136–138°C. (Found: C, 71.05, H, 4.95, N, 8.70. $C_{19}H_{16}N_2O_3$ requires: C, 71.25, H, 5.05, N, 8.75%). δ 2.27 (s, 3H, Me), 2.50 (d, J=2.0 Hz, 1H, C≡CH), 3.52 (d, J=8.0 Hz, 1H, H^c), 3.61 (dd, J=8.0 and 8.8 Hz, 1H, H^b), 4.20 (d, J=8.8 Hz, 1H, H^a), 4.50 (d, J=2.0 Hz, 1H, H^d), 6.36 (d, J=1.2 Hz, 2H, ArH) and 7.27–7.47 (m, 6H, ArH). m/z (%): 320 (M^+, 11), 173 (9), 147 (100), 132 (24), 118 (36), 108 (24), 91 (16), 77 (18), 64 (13), 51 (16) and 42 (24).

n.O.e. (500 MHz, $CDCl_3$) of **21m**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	11.72	–	–
H^b	12.24	–	3.36	–
H^c	–	3.53	–	6.41
H^d	–	–	4.80	–

Stereoisomer **22m**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 139–141°C. (Found: C, 71.25, H, 5.2, N, 8.80. $C_{19}H_{16}N_2O_3$ requires: C, 71.25, H, 5.05, N, 8.75%). δ 2.28 (s, 3H, Me), 2.55 (d, J=2.0 Hz, 1H, C≡CH), 3.69 (dd, J=4.48 and 8.9 Hz, 1H, H^b), 3.86 (dd, J=8.2 and 8.9 Hz, 1H, H^c), 4.26 (d, J=4.48 Hz, 1H, H^a), 4.31 (dd, J=2.0 and 8.2 Hz, 1H, H^d), 6.39 (d, J=2.3 Hz, 2H, ArH) and 7.31–7.50 (m, 6H, ArH). m/z (%): 321 (M^++1, 100), 295 (12), 253 (40), 172 (7), and 147 (42).

2.3.14. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-5-methyl-2-phenyl-6-(2-thienyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21n and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-5-methyl-2-phenyl-6-(2-thienyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3-(2*H*,3a*H*)-dione 22n. *N*-Methyl-*N*-(2-propynyl) amine **16b**

(104 mg, 1.5 mmol), thiophene-2-carboxyaldehyde **20a** (168 mg, 1.5 mmol) and *N*-phenylmaleimide **12b** (312 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:1 v/v petroleum ether–ether) afforded the two separated stereoisomers **21n** and **22n** (218 mg, 43% combined yield) in a 1:1 ratio.

Stereoisomer **21n**. Colourless prism from CH_2Cl_2/ether/petroleum ether, mp 151–152°C. (Found: C, 67.8, H, 4.95, N, 8.25, S, 9.3. $C_{19}H_{16}N_2O_2S$ requires: C, 67.85, H, 4.8, N, 8.35, S, 9.55%). δ 2.36 (s, 3H, Me), 2.51 (d, J=2.1 Hz, 1H, C≡CH), 3.54 (d, J=7.9 Hz, 1H, H^c), 3.64 (dd, J=7.9 and 9.1 Hz, 1H, H^b), 4.45 (d, J=9.1 Hz, 1H, H^a), 4.54 (d, J=2.1 Hz, 1H, H^d) and 6.98–7.43 (m, 8H, ArH). *m/z* (%): 337 (M^++1, 100), 311 (16), 253 (65), 188 (16), 163 (58) and 148 (5).

Stereoisomer **22n**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 156–158°C. (Found: C, 67.7, H, 4.95, N, 8.4, S, 9.5. $C_{19}H_{16}N_2O_2S$ requires: C, 67.85, H, 4.8, N, 8.35, S, 9.55%. δ 2.34 (s, 3H, Me), 2.57 (d, J=2.1 Hz, 1H, C≡CH), 3.50 (dd, J=5.8 and 9.4 Hz, 1H, H^b), 3.86 (dd, J=8.1 and 9.4 Hz, 1H, H^c), 4.35 (d, J=5.8 Hz, 1H, H^a), 4.47 (dd, J=2.1 and 8.1 Hz, 1H, H^d) and 6.98–7.50 (m, 8H, ArH). *m/z* (%): 337 (M+1, 100), 311 (7), 253 (28), 188 (6) and 163 (19).

2.3.15. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-5-methyl-2-phenyl-6-(1,3-thiazol-2-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3-(2*H*,3a*H*)-dione 21o and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-5-methyl-2-phenyl-6-(1,3-thiazol-2-yl)tetrahydropyrrolo-[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22o. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 2-thiazole carboxaldehyde **20b** (170 mg, 1.5 mmol) and *N*-phenylmaleimide **12b** (312 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:1 v/v petroleum ether–ether) afforded the two separated stereoisomers **21o** and **22o** (384 mg, 76% combined yield) in a 1:1 ratio.

Stereoisomer **21o**. Colourless prisms from CH_2Cl_2/ether/petroleum ether, mp 179–182°C. (Found: C, 64.05, H, 4.5, N, 12.75, S, 9.45. $C_{18}H_{15}N_3O_2S$ requires: C, 64.10, H, 4.5, N, 12.45, S, 9.5%). δ 2.43 (s, 3H, Me), 2.55 (d, J=2.0 Hz, 1H, C≡CH), 3.61 (d, J=8.1 Hz, 1H, H^c), 3.85 (dd, J=8.1 and 9.2 Hz, 1H, H^b), 4.57 (d, J=2.0 Hz, 1H, H^d), 4.66 (d, J=9.2 Hz, 1H, H^a), 7.23–7.46 (m, 6H, ArH).and 7.81 (d, J=3.3 Hz, 1H, ArH). *m/z* (%): 338 (M^++1, 19), 253 (7), 181 (15), 91 (100) and 73 (17).

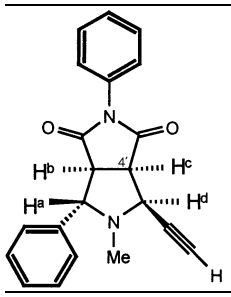
Stereoisomer **22o**. Colourless plates from CH_2Cl_2/ether/petroleum ether, mp 146–149°C. (Found: C, 63.85, H, 4.55, N, 12.7, S, 9.6. C_{18} $H_{15}N_3O_2S$ requires: C, 64.10, H, 4.50, N, 12.45, S, 9.50%). δ 2.38 (s, 3H, Me), 2.57 (d, J=2.1 Hz, 1H, C≡CH), 3.72 (dd, J=4.0 and 8.9 Hz, 1H, H^b), 3.93 (dd, J=8.2 and 8.9 Hz, 1H, H^c), 4.43 (dd, J=2.1 and 8.2 Hz, 1H, H^d), 4.64 (d, J=4.0 Hz, 1H, H^a), 7.32–7.51 (m, 6H, ArH) and 7.84 (d, J=3.2 Hz, 1H, ArH). *m/z* (%): 338 (M^++1, 100), 312 (6), 253 (37), 189 (7), 165 (6), 136 (13), 106 (13) and 77 (7).

2.3.16. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-5-methyl-2,6-diphenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 21p and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-5-methyl-2,6-diphenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22p. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), benzaldehyde **20c** (159 mg, 1.5 mmol) and *N*-phenylmaleimide **12b** (312 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:2 v/v petroleum ether–ether) afforded the two separated stereoisomers **21p** and **22p** (182 mg, 55% combined yield) in a 1:1 ratio.

Stereoisomer **21p**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 155–157°C. (Found: C, 76.1, H, 5.6, N, 8.45. $C_{21}H_{18}N_2O_2$ requires: C, 76.35, H, 5.5, N, 8.5%). δ 2.26 (s, 3H, Me), 2.51 (d, J=2.1 Hz, 1H, C≡CH), 3.54 (d, J=8.0 Hz, 1H, H^c), 3.63 (dd, J=8.0 and 9.0 Hz, 1H, H^b), 4.13 (d, J=9.0 Hz, 1H, H^a), 4.57 (d, J=2.1 Hz, 1H, H^d) and 7.17–7.44 (m, 10H, ArH). *m/z* (%): 330 (M^+, 47), 253 (15), 182 (21), 173 (9), 157 (100), 142 (19), 129 (10), 115 (45), 106 (20), 91 (28), 77 (25), 64 (16), 51 (17) and 42 (23).

Stereoisomer **22p**. Colourless needles from CH_2Cl_2/ether/petroleum ether, mp 148–150°C. (Found: C, 76.1, H, 5.55, N, 8.6. $C_{21}H_{18}N_2O_2$ requires: C, 76.35, H, 5.5, N, 8.5%). δ 2.23 (s, 3H, Me), 2.56 (d, J=2.0 Hz, 1H, C≡CH), 3.36 (dd, J=6.4 and 9.5 Hz, 1H, H^b), 3.80 (dd, J=7.9 and 9.5 Hz, 1H, H^c), 3.93 (d, J=6.4 Hz, 1H, H^a), 4.50 (dd, J=2.0 and 7.9 Hz, 1H, H^d) and 7.16–7.47 (m, 10H, ArH). *m/z* (%): 331 (M+1, 100).

n.O.e. (500 MHz, $CDCl_3$) of **22p**:



Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	H^d
H^a	–	2.17	–	–
H^b	1.81	–	9.06	–
H^c	–	11.15	–	10.64
H^d	–	–	9.64	–

2.3.17. (±)(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-5-methyl-6-(6-methyl-2-pyridinyl)-2-phenyltetrahydropyrrolo[3,4-*c*]-pyrrole-1,3(2*H*,3a*H*)-dione 21q and (3a*R*,4*S*,6*S*,6a*S*)-4-ethynyl-5-methyl-6-(6-methyl-2-pyridinyl)-2-phenyl-tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione 22q. *N*-Methyl-*N*-(2-propynyl)amine **16b** (104 mg, 1.5 mmol), 6-methyl-2-pyridine-carboxaldehyde **20f** (182 mg, 1.5 mmol) and *N*-phenylmaleimide **12b** (312 mg, 1.8 mmol) were reacted by the general procedure in toluene (5 ml) over 24 h. Flash column chromatography (1:2 v/v petroleum ether–ether) afforded the two stereoisomers **21q** and **22q** (271 mg, 52% combined yield) in a 1:1 ratio. But we only got pure stereoisomer **21q**: colourless plates from CH_2Cl_2/ether/petroleum ether, mp 145–147°C. (Found: C, 72.75, H, 5.5, N, 12.45. $C_{21}H_{19}N_3O_2$ requires: C, 73.05, H, 5.55, N, 12.15%). δ 2.30 (s, 3H, Me), 2.50 (d, J=2.0 Hz, 1H, C≡CH), 2.56 (s, 3H, Me), 3.57 (d, J=8.0 Hz, 1H, H^c), 3.80 (dd, J=8.0 and 9.1 Hz, 1H, H^b), 4.31 (d, J=9.1 Hz,

1H, H^a), 4.56 (d, J=2.0 Hz, 1H, H^d) and 7.06–7.58 (m, 8H, ArH). m/z (%): 346 (M^++1, 100), 320 (6), 253 (6), 197 (6), 171 (6), 147 (6) and 106 (6).

2.4. Single-crystal X-ray diffraction analysis of 13b, 21n and 22n

Crystallographic data for all three compounds were collected on a Nonius KappaCCD area-detector diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å) and a mixture of a 1° area-detector ω- and ϕ-scans. All three structures were solved by direct methods using SHELXS-86[7] and were refined by full-matrix least squares (based on F^2) using SHELXL-97.[8] The weighting schemes used in all three refinements was $w=[\sigma^2(F_o^2)+(xP)^2+yP]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. In all cases all non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model with free rotation for methyl groups. The refinements of **13b** and **21n** included an isotropic extinction parameter, x, so that $F_c'=kF_c[1+0.001xF_c^2\lambda^3]^{-1/4}$ where k is the overall scale factor. The residuals wR_2 and R_1, given below, are defined as $wR_2=(\Sigma[w(F_o^2-F_c^2)^2]/\sum[wF_o^2]^2)^{1/2}$ and $R_1=\Sigma\|F_o|-|F_c\|/\sum\|F_o\|$.

Crystal data for **13b**. $C_{26}H_{22}N_2O_4$, 0.57×0.15×0.06 mm^3, M=426.46, monoclinic, space group $P2_1$, a=8.0283(4), b=6.2164(4), c=22.798(2) Å, β=96.810(4)°, U=1129.74(12) $Å^3$, Z=2, D_c=1.254 mg m^{-3}, μ=0.09 mm^{-1}, F(000)=448, T=150 K.

Data collection. 6.8<2θ<52.0°, 9815 data collected 3805 of which were unique [R_{int}=0.084]. There 3503 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=291, isotropic extinction parameter, x=0.09(2), goodness of fit, s=1.089; weighting parameters x, y=0.0327, 0.4211; wR_2=0.1273, R_1=0.0531.

Crystal data for **21n**. $C_{19}H_{16}N_2O_2S$, 0.40×0.17×0.10 mm^3, M=336.40, monoclinic, space group $P2_1/n$, a=13.4799(7), b=5.7298(1), c=21.7238(10) Å, β=92.748(2)°, U=1672.13(12) $Å^3$, Z=4, D_c=1.34 mg m^{-3}, μ=0.21 mm^{-1}, F(000)=704, T=150 K.

Data collection. 6.6<2θ<52.0°, 11484 data collected 3270 of which were unique [R_{int}=0.045]. There 2621 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=219, isotropic extinction parameter, x=0.012(2), goodness of fit, s=1.025; weighting parameters x, y=0.0494, 0.9388; wR_2=0.1274, R_1=0.0481.

Crystal data for **22n**. $C_{19}H_{16}N_2O_2S$, 0.60×0.40×0.27 mm^3, M=336.40, monoclinic, space group $P2_1/c$, a=12.9113(4), b=12.1233(3), c=10.9650(3) Å, β=93.231(2)°, U=1713.60(8) $Å^3$, Z=4, D_c=1.30 mg m^{-3}, μ=0.20 mm^{-1}, F(000)=704, T=150 K.

Data collection. 6.7<2θ<52.0°, 17028 data collected 3335 of which were unique [R_{int}=0.054]. There 2954 reflections with $F_o>4.0\ \sigma(F_o)$.

Structure refinement. Number of parameters=219, goodness of fit, s=1.032; weighting parameters x, y=0.0847, 1.4702; wR_2=0.1567, R_1=0.0532.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 172752 (compound **13b**), CCDC 172753 (compound **21n**) and CCDC 172754 (compound **22n**). 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 e-mail: deposit@ccdc.cam.ac.uk].

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