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N-Prop-2-ynylmaleimide. Application to Sequential One-pot Rh(I) Catalysed [2+2+2]-Alkyne Cyclotrimerisation–Imine Cycloaddition

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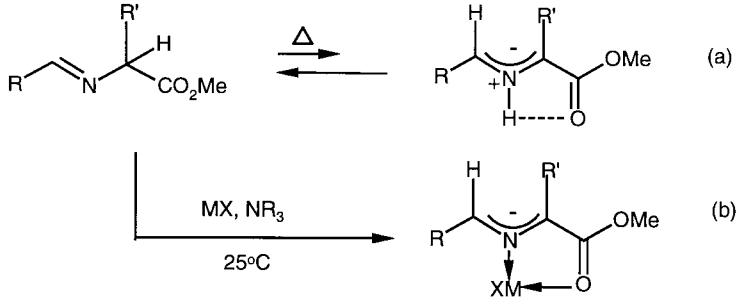
Abstract—Rh(I) catalysed [2+2+2]-cyclotrimerisation of 1,6-diynes with monoynes in combination with stereospecific thermal or Ag(I) catalysed aldimine→(metallo) azomethine ylide→cycloaddition cascades affords rapid access to complex heterocyclic benzene derivatives in one-pot processes with the generation 5 new bonds, 4 stereocentres and 3 rings. © 2000 Elsevier Science Ltd. All rights reserved.

Some time ago we developed a [2+2+2]-cyclotrimerisation of alkynes catalysed by Wilkinson's catalyst $[(PPh_3)_3RhCl]$.[1] We showed that a wide variety of 1,6-diynes could be combined with a range of monoynes to generate polysubstituted benzene derivatives.[2] This process has been used in the synthesis of natural products,[3] unusual α-amino acid derivatives and indoline derivatives.[4a–c] More recently we have successfully combined this chemistry with our Pd(0) catalysed cyclisation- anion capture methodology to assemble a variety of polyfunctional heterocycles[5] and, in related work, to assemble phenanthrene type heterocycles by combination with Pd(0) catalysed arylation.[6]

We have previously developed sequential and cascade imine cycloaddition-Pd(0) catalysed carbonylation—cyclisation reactions[7] and now reported related studies involving the combination of Rh(I) catalysed cyclotrimerisation with imine cycloaddition reactions. These latter reactions, which involve azomethine ylides, can be carried out under thermal activation (Scheme 1a), when a formal 1,2-prototropy is involved, or at room temperature under the influence of a metal salt and a tertiary amine (Scheme 1b).[8]

The imine→azomethine ylide→cycloaddition cascade is both powerful and versatile. The (metallo) azomethine ylides are generated stereospecifically and the cycloaddition reactions occur regio- and stereo-specifically. Variation of the metal salt engenders reversal of the regioselectivity of the cycloaddition [e.g. Ag(I) versus Ti(IV)].[8] Use of appropriate chiral auxiliaries results in >95% ee in the product pyrrolidines[9] whilst use of chiral catalysts gives up to 70% ee[10a] with Ag(I) salts and 96% ee with Co(II) complexes.[10b]

N-Prop-2-ynylmaleimide **2**[11] (Scheme 2) was selected as a bifunctional substrate that would participate in both the Rh(I) catalysed cyclotrimerisation and the imine



Scheme 1.

Keywords: azomethine ylide; cycloaddition; heterocycles; β-lactam.

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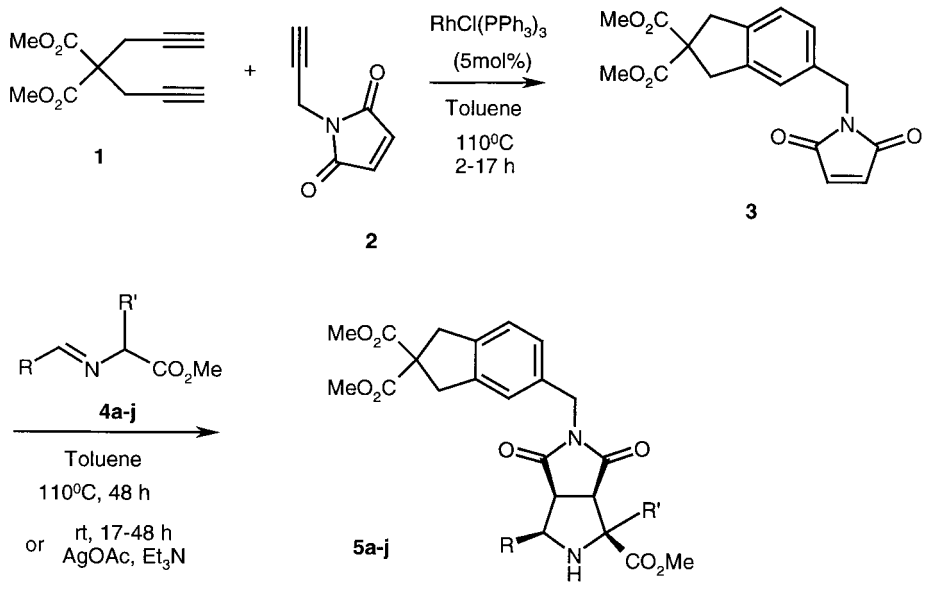


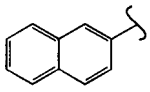
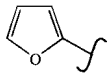
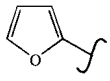
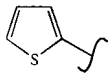
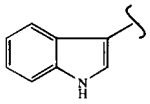
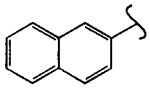
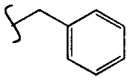
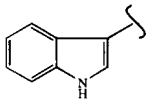
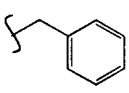
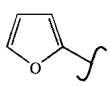
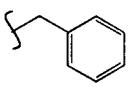
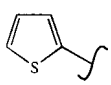
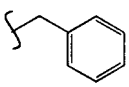
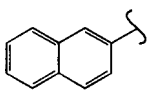
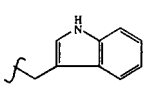
Scheme 2.

cycloaddition reactions. Initially, the diyne **1**[12] and **2** were reacted (toluene, 110°C, 2 h) in the presence of 5 mol% Wilkinson's catalyst monitoring the reaction by tlc. After the [2+2+2]-cycloaddition generating **3** was complete, the imine **4a** was added, and the cycloaddition reaction was allowed to proceed under the same conditions for a further 48 h. Work up afforded the *endo*-cycloadduct **5a** in 68% yield as the sole product (Scheme 2). A series of sequential one-pot processes employing metalloazomethine ylide cycloadditions was then developed. In these cases the cyclotrimerisation mixture was cooled, after the [2+2+2]-cycloaddition was complete, and the imine **4b**–**4j**, silver acetate (1.3 mol equiv.) and triethylamine (1.3 mol equiv.) added. The 1,3-dipolar cycloaddition reaction was allowed to proceed for 17–48 h at rt to afford the products **5b**–**j** (Table 1) in *endo*-specific processes.

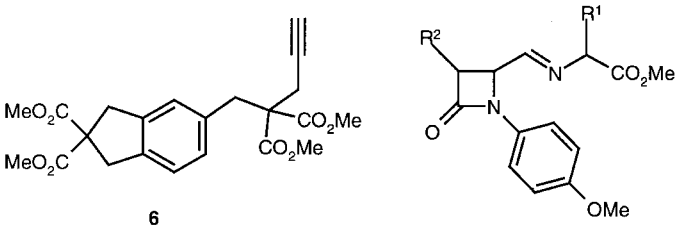
The stereochemistry of **5a**–**j** was determined by ^{1}H NMR together with analysis of H–H coupling constants and NOE experiments. The *cis*- vicinal H–H coupling constants in the pyrrolidine ring were 5–8 Hz compared to 2–4 Hz for the *trans*-isomers.

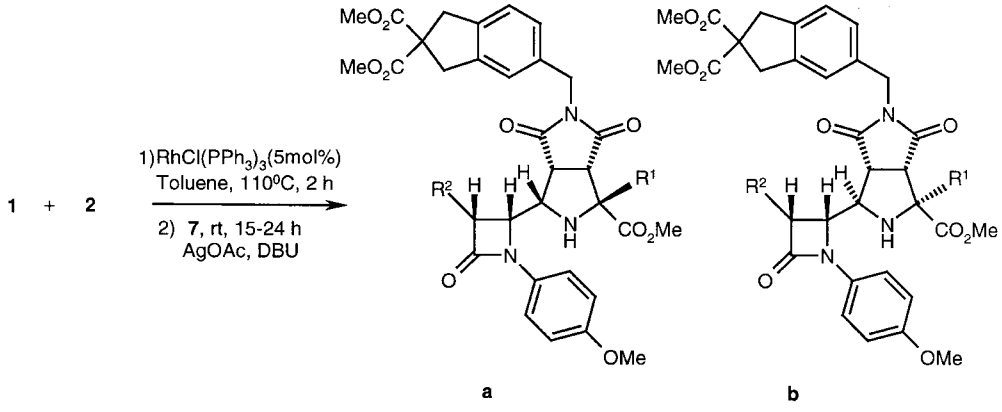
Optimisation studies demonstrated that both solvent and temperature are key factors for this reaction. There is competition between the formation of the desired cyclotrimerisation products and the diyne dimer **6**. THF allows the [2+2+2]-cycloaddition reactions to be carried out under mild conditions (room temperature), but dimer formation occurs to a greater extent in this solvent than in the nonpolar solvent, toluene, which allows an excess of monoyne to be avoided. The cyclotrimerisation reaction cannot be achieved at room temperature in toluene, although good yields are obtained when the reactions are performed at 110°C. Table 1 shows that the sequential one-pot process employing aryl aldimines proceeds in moderate to high yield. These sequential processes involve the formation of 3 rings, 5-bonds and 4-stereocentres and furnish single stereoisomers.

Table 1. Sequential one-pot Rh(I) catalysed [2+2+2]-cyclotrimerisation–imine cycloaddition processes

Product	R	R′	Yield (%)[a]
5a		Me	68
5b		Me	51
5c		$(CH_2)_2SMe$	59
5d		$(CH_2)_2SMe$	51
5e		$(CH_2)_2SMe$	38
5f			71
5g			55
5h			66
5i			60
5j			83

[a] Overall yield for the one-pot sequential process.





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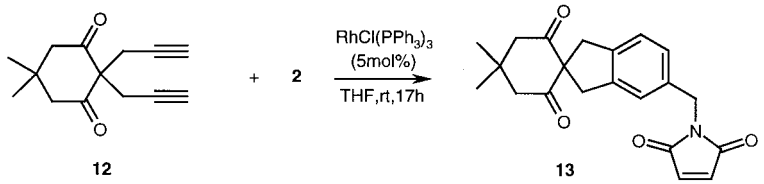
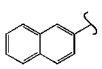
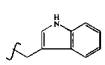
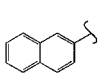
	R^2	R^1	Yield(%)[a]	a:b
8	BnO	Me	69	1:1
9	Phth	Me	70	>30:1
10	Phth	H	73	4:1
11	Phth	$PhCH_2$	55	>30:1

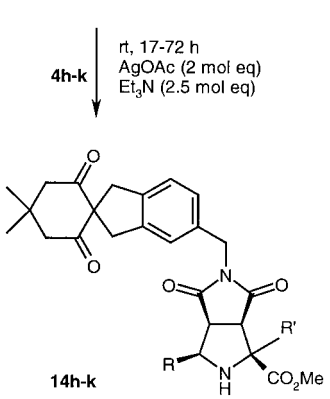
a. Isolated yield

Scheme 3.

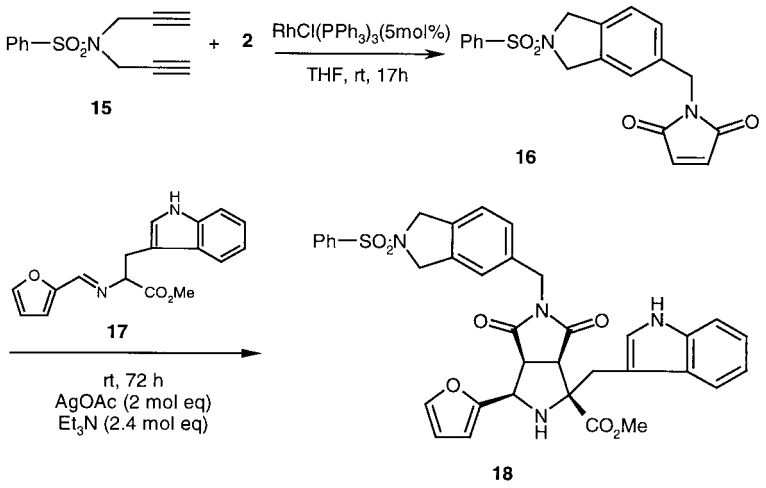


	R	R'	Yield (%)[a]
h			44
i			34
j			59
k		$(CH_2)_2SMe$	54

a. isolated yield



Scheme 4.



Scheme 5.

A series of sequential one-pot processes employing aliphatic aldimines was studied next (Scheme 3). The β-lactam imines **7a**–**c** were prepared as previously described.[13] The two step protocol employed a AgOAc (1.2 mol equiv.)/DBU (1.2 mol equiv.) combination for the room temperature cycloaddition step. The final products **8a**,**b**–**11a**,**b**, in these cases, comprised mixture of *endo* diastereoisomers whose ratio depended on the stereochemical demands imposed by the β-lactam ring.[13] Imine cycloaddition facial selectivity was high when a bulky substituent was present on the β-lactam (R^2=Phth) in combination with the imine substituent $R^1 \neq H$ (Scheme 3).

Two further series of one-pot sequential processes were evaluated the first of which employed the diyne **12**,[2] a precursor of spirocyclic products **13** and **14**. In the reaction of diyne **12** both the Rh(I) catalysed cyclotrimerisation and the imine cycloaddition could be achieved in THF at room temperature (Scheme 4). Contrary to experience with the diyne **1**, no improvement in yield was obtained on changing the solvent from THF to toluene.

Finally, one example of a *N*-substituted diyne **15**[14] was studied (Scheme 5). The one-pot reaction with **2** and **17** was carried out in THF at room temperature and employed a AgOAc (2 mol equiv.)/Et_3N (2.5 mol equiv.) catalyst. The desired product **18** was obtained in 28% overall yield. The low yield of **18** in this case is accompanied by substantial amounts of dimer formation.

The mechanism for [2+2+2] reaction has not been unequivocally proven. However, several investigations into transition metal mediated formation of benzenes from acetylenes[2,15] indicated the process involves metalla-cyclopentadienes and -heptatrienes as pivotal intermediates.[16]

In summary, [2+2+2]-cycloadditions catalysed by Wilkinson's catalyst in combination with imine cycloaddition allows the rapid synthesis of novel complex heterocyclic benzene derivatives in satisfactory yields with the creaction of five new bonds, four stereocentres and three rings (Scheme 5).

Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. ^1H Nuclear magnetic resonance spectra were recorded at 300 MHz on a Bruker DPX 300 instrument, at 250 MHz on a Bruker AC 250 instrument, at 400 MHz on a Bruker WP 400 instrument or at 500 MHz on a Bruker DRX 500 instrument. Deuterochloroform was used as solvent unless stated otherwise, and chemical shifts are given in parts per million (δ) downfield from tetramethylsilane. ^1H spectra are referenced to tetramethylsilane or residual protonated. Assignments of ^1H signals were made with the aid of 2D COSY spectra where necessary. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument. Infrared spectra were recorded as nujol mulls on a Nicolet FTIR spectrophotometer. Mass spectra were recorded on a V.G.-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 the literature procedures.[17] Imines **4** and **17** were prepared by the general method noted below and most of them were known compounds.[18]

General method for the preparation of imines

Aldehyde (1 mol equiv.) was added to a stirred mixture of α-amino methyl ester hydrochloride (1.05 mol equiv.), Et_3N (1.5 mol equiv.) and $MgSO_4$ (excess) in dry CH_2Cl_2 under N_2 at room temperature and stirring continued for 16 h. The mixture was then filtered and the filtrate washed with water. The organic layer was separated, dried ($MgSO_4$), and the solvent evaporated. The residue was purified by column chromatography on silica pretreated with Et_3N to afford the imines.

Imine 4c. The general method was applied to 2-furaldehyde (480 mg, 5 mmol), methionine methyl ester hydrochloride (1.05 g, 5.25 mmol), Et_3N (1.05 ml, 7.5 mmol) and $MgSO_4$ (ca. 2 g) in dry CH_2Cl_2 (20 ml). Flash chromatography (1:1,

v/v, petroleum ether–Et_2O) afforded the *product* (908 mg, 75%) as a pale yellow oil. (Found: C, 54.55, H, 6.45, N, 5.6, S, 13.2. $C_{11}H_{15}NO_3S$ requires: C, 54.75, H, 6.25, N, 5.8, S, 13.3%); δ 2.09 (s, 3H, SMe), 2.11–2.31 (m, 2H, CH_2), 2.43 and 2.60 (2×m, 2×1H, CH_2), 3.75 (s, 3H, OMe), 4.17 (dd, *J*=5.1, 8.3 Hz, 1H, CH), 6.51, 6.86 and 7.56 (3×m, 3×1H, ArH) and 8.13 (s, 1H, CH=N); *m/z* (%) (FAB): 242 (M^++1, 100), 182 (9), 167 (16) and 61 (12).

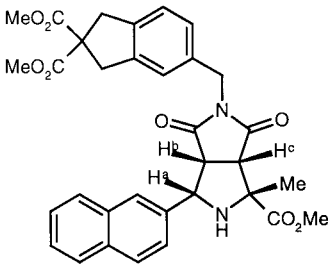
Imine 4e. The general method was applied to indole-3-carboxaldehyde (726 mg, 5 mmol), methionine methyl ester hydrochloride (1.05 mg, 5.25 mmol), Et_3N (1.05 ml, 7.5 mmol) and $MgSO_4$ (ca. 2 g) in dry CH_2Cl_2 (20 ml). Flash chromatography (1:3, v/v, petroleum ether–Et_2O) afforded the *product* (1.19 g, 82%) as a colourless gum. (Found: C, 62.5, H, 6.5, N, 9.55. $C_{15}H_{18}N_2O_2S$ requires: C, 62.05, H, 6.25, N, 9.65%); δ 2.09 (s, 3H, SMe), 2.27 and 2.56 (2×m, 2×2H, CH_2CH_2), 3.74 (s, 3H, OMe), 4.14 (dd, *J*=5.9, 8.4 Hz, 1H, CH), 7.13–7.24 (m, 2H, ArH), 7.36, 7.48 and 8.29 (3×m, 3×1H, ArH), 8.49 (s, 1H, CH=N) and 9.00 (bs, 1H, NH); *m/z* (%) (FAB): 291 (M^++1, 100), 216 (7), 146 (5) and 61 (6).

Imine 4g. The general method was applied to indole-3-carboxaldehyde (726 mg, 5 mmol), phenylalanine methyl ester hydrochloride (1.16 g, 5.25 mmol), Et_3N (1.05 ml, 7.5 mmol) and $MgSO_4$ (ca. 2 g) in dry CH_2Cl_2 (20 ml). Flash chromatography (1:2, v/v, petroleum ether–Et_2O) afforded the *product* (980 mg, 64%) as a pale yellow gum. (Found: C, 74.5, H, 6.2, N, 9.25. $C_{19}H_{18}N_2O_2$ requires: C, 74.5, H, 5.9, N, 9.15%); δ 3.18 (dd, *J*=8.5, 13.5 Hz, 1H, C*H*H), 3.38 (dd, *J*=5.3, 13.5 Hz, 1H, CH*H*), 3.72 (s, 3H, OMe), 4.13 (dd, *J*=5.3, 8.5 Hz, 1H, CH), 7.13–7.32 (m, 9H, ArH), 8.12 (s, 1H, CH=N) and 8.82 (bs, 1H, NH); *m/z* (%) (FAB): 307 (M^++1, 100) and 247 (6).

Imine 4i. The general method was applied to thiophene-2-carboxaldehyde (560 mg, 5 mmol), phenylalanine methyl ester hydrochloride (1.16 mg, 5.25 mmol), Et_3N (1.05 ml, 7.5 mmol) and $MgSO_4$ (ca. 2 g) in dry CH_2Cl_2 (20 ml). Flash chromatography (1:2, v/v, petroleum ether–Et_2O) afforded the *product* (1.05 g, 77%) as a pale yellow gum. (Found: C, 65.75, H, 5.7, N, 4.95, S, 11.55. $C_{15}H_{15}NO_2S$ requires: C, 65.9, H, 5.55, N, 5.15, S, 11.75%); δ 3.14 (dd, *J*=9.0, 13.5 Hz, 1H, C*H*H), 3.35 (dd, *J*=5.1, 13.5 Hz, 1H, CH*H*), 3.74 (s, 3H, OMe), 4.13 (dd, *J*=5.1, 9.0 Hz, 1H, CH), 7.03 (dd, *J*=3.7, 5.0 Hz, 1H, ArH), 7.15–7.27 (m, 6H, ArH), 7.32 (m, 1H, ArH), 7.42 (d, *J*=5.0 Hz, 1H, ArH) and 8.00 (m, 1H, CH=N); *m/z* (%) (FAB): 274 (M^++1, 100), 214 (14), and 182 (12).

Imine 17. The general method was applied to 2-furaldehyde (480 mg, 5 mmol), tryptophan methyl ester hydrochloride (1.29 mg, 5.25 mmol), Et_3N (1.05 ml, 7.5 mmol) and $MgSO_4$ (ca. 2 g) in dry CH_2Cl_2 (20 ml). Flash chromatography (1:2–3:1, v/v, petroleum ether–Et_2O) afforded the *product* (1.29 g, 87%) as a pale yellow gum. (Found: C, 69.0, H, 5.65, N, 9.6. $C_{17}H_{16}N_2O_3$ requires: C, 68.9, H, 5.45, N, 9.45%); δ 3.23 (dd, *J*=8.8, 14.4 Hz, 1H, C*H*H), 3.57 (dd, *J*=4.9, 14.4 Hz, 1H, CH*H*), 3.73 (s, 3H, OMe), 4.21 (dd, *J*=4.9, 8.8 Hz, 1H, CH), 6.42, 6.65, 6.94 (3×m, 3×1H, ArH), 7.08–7.20 (m, 2H, ArH), 7.32 (m, 1H, ArH), 7.48 (s, 1H, ArH), 7.64 (m, 2H, CH=N and ArH) and 8.21 (bs, 1H, NH); *m/z* (%) (FAB): 297 (M^++1, 100), 202 (7), 167 (7) and 130 (48).

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-4-methyl-6-(2-naphthyl)-1,3-dioxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5a. A mixture of dimethyl 2,2-diprop-2-ynylmalonate **1** (0.36 mmol, 75 mg), *N*-prop-2-ynylmaleimide **2** (0.3 mmol, 40.5 mg) and tris(triphenylphosphine)rhodium(I) chloride (0.015 mmol, 14 mg) in toluene (5 ml) was heated to reflux for 2 h. Imine *4a* (0.3 mmol, 73 mg) was added to the resulting mixture and the stirring continued for 48 h at 110°C. The solvent was evaporated and the residue purified by flash chromatography (4:1–0:1 v/v petroleum ether–Et_2O) to afford the *product* (111 mg, 68%) as colourless plates from Et_2O/petroleum ether, mp 83–85°C. (Found: C, 67.8, H, 5.5, N, 4.7. $C_{33}H_{32}N_2O_8$ requires: C, 67.8, H, 5.5, N, 4.8%); δ 1.64 (s, 3H, Me), 2.64 (d, *J*=8.3 Hz, 1H, NH), 3.31 (d, *J*=7.6 Hz, 1H, $COCH^c$), 3.54 (m, 5H, $COCH^b$ and CH_2ArCH_2), 3.71, 3.75, 3.88 (3×s, 3×3H, 3×OMe), 4.44 (s, 2H, NCH_2), 4.90 (t, *J*=8.3 Hz, 1H, NCH^a), 7.08 (m, 3H, ArH), 7.21 (d, *J*=8.3 Hz, 1H, ArH), 7.45 (m, 2H, ArH), 7.67 (m, 3H, ArH) and 7.81 (m, 1H, ArH). δ (500 MHz, C_6D_6) 1.23 (s, 3H, Me), 2.36 (d, *J*=7.9 Hz, 1H, NH), 2.51 (d, *J*=7.6 Hz, 1H, $COCH^c$), 2.75 (dd, *J*=7.6, 9.1 Hz, 1H, $COCH^b$), 3.23 and 3.28 (2×s, 2×3H, 2×OMe), 3.62–3.65 (m, 4H, CH_2ArCH_2), 3.69 (s, 3H, OMe), 4.25 and 4.32 (2×d, *J*=14.1 Hz, 2×1H, NCH_2), 4.34–4.37 (m, 1H, NCH^a), 6.88 (d, *J*=7.8 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.18–7.22 (m, 2H, ArH), 7.28–7.31 and 7.33–7.36 (2×m, 2×1H, ArH), 7.55 (d, *J*=7.7 Hz, 1H, ArH), 7.62–7.66 (m, 1H, ArH) and 7.74 (d, *J*=7.9 Hz, 1H, ArH); *m/z* (%): 584 (M^+, 27), 525, (100), 465 (51), 283 (16), 266 (11), 241 (51), 206 (20), 187 (85), 181 (48), 166 (12), 155 (34), 140 (19), 128 (57), 115 (14), 77 (14) and 59 (13); ν_{max}: 2924, 2854, 1732, 1703, 1462 and 1456 cm^{-1}.



NOE (500 MHz, C_6D_6)

Proton irradiated	Enhancement (%)			
	H^a	H^b	H^c	Me
H^a		3.6	0.85	1.4
H^b	2.5		2.6	
H^c		1.9		1.2
Me	3.0		3.5	

General procedure for sequential one-pot [2+2+2]- and 1,3-dipolar cycloaddition generating 5b–j and 8–11

A mixture of diyne **1** (0.5–1.5 mol equiv.), monoyne **2** (1.0 mol equiv.) and Wilkinson's catalyst (0.05 mol equiv.) in toluene (3–8 ml) was boiled under reflux for 2–17 h. The stirred mixture was then cooled to room temperature and imine (1.0–1.3 mol equiv.), AgOAc (1.0–1.3 mol equiv.) and Et_3N or DBU (1.0–1.3 mol equiv.) added. The flask was protected by foil (for AgOAc) and the resulting mixture stirred for 15 h – 48 h at room temperature. The solvent was then evaporated and the residue purified by column chromatography to afford the cycloadducts.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-6-(2-furyl)-4-methyl-1,3-dioxohexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl]-methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5b. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.36 mmol, 75 mg), *N*-prop-2-ynylmaleimide **2** (0.3 mmol, 41 mg), $RhCl(PPh_3)_3$ (0.015 mmol, 14 mg), imine **4b** (0.39 mmol, 71 mg), AgOAc (0.39 mmol, 65 mg) and Et_3N (0.39 mmol, 54 μl) in toluene (5 ml) at 110°C for 17 h and rt for 48 h. Flash chromatography (1:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (80 mg, 51%) as colourless needles from petroleum ether–dichloromethane, mp 111–113°C. (Found: C, 62.05, H, 5.6, N, 5.2. $C_{27}H_{28}N_2O_9$ requires: C, 61.85, H, 5.4, N, 5.35%); δ 1.53 (s, 3H, Me), 3.42 (m, 7H, CH_2ArCH_2, 2×COCH and NH), 3.72, 3.74 and 3.83 (3×s, 3×3H, 3×OMe), 4.46 and 4.54 (2×d, *J*=14.0 Hz, 2×1H, NCH_2), 4.74 (d, *J*=9.0 Hz, 1H, NCH), 6.25 (m, 2H, ArH) and 7.12 (m, 4H, ArH); *m/z* (%) (FAB): 525 (M^+ +1, 36), 465 (12), 323 (10), 187 (22), 181 (19), 159 (9), 145 (13), 133 (14), 129 (15), 121 (27), 109 (35), 95 (60), 81 (73) and 69 (100); ν_{max}: 2924, 2853, 1759, 1727, 1708 and 1455 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-6-(2-furyl)-4-[2-(methylthio)ethyl]-1,3-dioxohexahydropyrrolo[3,4-c]-pyrrol-2(1H)-yl]methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5c. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.6 mmol, 125 mg), *N*-prop-2-ynylmaleimide **2** (0.5 mmol, 68 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **4c** (0.65 mmol, 157 mg), AgOAc (0.65 mmol, 109 mg) and Et_3N (0.65 mmol, 90 μl) in toluene (5 ml) at 110°C for 17 h and rt for 48 h. Flash chromatography (1:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (173 mg, 59%) as colourless plates from petroleum ether–dichloromethane, mp 99–100°C. (Found: C, 59.6, H, 5.5, N, 4.5, S, 5.6. $C_{29}H_{32}N_2O_9S$ requires: C, 59.6, H, 5.5, N, 4.8, S, 5.5%); δ 2.10 (s, 3H, SMe), 2.42 (m, 4H, SCH_2CH_2), 3.12 (m, 1H, NH), 3.28 (d, *J*=8.0 Hz, 1H, COCH), 3.42 (m, 1H, COCH), 3.55 (s, 4H, CH_2ArCH_2), 3.72, 3.74 and 3.85 (3×s, 3×3H, 3×OMe), 4.43 and 4.54 (2×d, *J*=14.0 Hz, 2H, NCH_2), 4.63 (brt, 1H, NCH), 6.25 (m, 2H, ArH) and 7.10 (m, 4H, ArH); *m/z* (%) (FAB): 585 (M^++1, 66), 525 (10), 477 (5), 323 (7), 247 (5), 187 (54), 160 (9), 143 (10), 129 (19), 109 (32), 95 (56), 81 (65) and 69 (100); ν_{max}: 2953, 2923, 2853, 1735, 1695 and 1428 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-4-[2-(methylthio)-ethyl]-1,3-dioxo-6-(2-thienyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5d. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.6 mmol, 125 mg), *N*-prop-2-ynylmaleimide **2** (0.5 mmol, 68 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine $_{4d}$ (0.65 mmol, 167 mg), AgOAc (0.65 mmol, 109 mg) and Et_3N (0.65 mmol, 90 μl) in toluene (5 ml) at 110°C for 17 h and rt for 48 h. Flash chromatography (2:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (154 mg, 51%) as colourless rods from petroleum ether–dichloromethane, mp 127–129°C. (Found: C, 58.0, H, 5.4, N, 4.6, S, 10.6. $C_{29}H_{32}N_2O_8S_2$ requires: C, 58.0, H, 5.35, N, 4.65, S, 10.7%); δ 2.10 (s, 3H, SMe), 2.46 (m, 4H, SCH_2CH_2), 2.86 (brd, 1H, NH), 3.39 (m, 6H, CH_2ArCH_2 and 2×COCH), 3.72, 3.74 and 3.86 (3×s, 3×3H, 3×OMe), 4.44 (s, 2H, NCH_2), 4.90 (brt, 1H, NCH) and 7.04 (m, 6H, ArH); *m/z* (%): 600 (M^+, 94), 569 (7), 539 (51), 526 (14), 493 (12), 479 (18), 466 (9), 433 (11), 353 (7), 283 (7), 257 (8), 247 (8), 209 (14), 196 (75), 187 (100), 176 (16), 162 (8), 155 (15), 149 (13), 143 (12), 136 (25), 128 (66), 115 (13), 109 (20), 96 (11), 75 (16), 61 (47) and 45 (9); ν_{max}: 2923, 2853, 1739, 1694 and 1279 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-6-(1H-indol-3-yl)-4-[2-(methylthio)ethyl]-1,3-dioxohe xahydropyrrolo [3,4-c]pyrrol-2(1H)-yl]methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5e. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.6 mmol, 125 mg), *N*-prop-2-ynylmaleimide **2** (0.5 mmol, 68 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **4e** (0.65 mmol, 189 mg), AgOAc (0.65 mmol, 109 mg) and Et_3N (0.65 mmol, 90 μl) in toluene (5 ml) at 110°C for 17 h and rt for 48 h. Flash chromatography (1:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (110 mg, 38%) as colourless prisms from petroleum ether–dichloromethane, mp 101–103°C. (Found: C, 62.5, H, 5.75, N, 6.4, S, 4.95. $C_{33}H_{35}N_3O_8S$ requires: C, 62.55, H, 5.55, N, 6.65, S, 5.05%); δ 2.10 (s, 3H, SMe), 2.32–2.62 (m, 4H, SCH_2CH_2), 2.74 (brs, 1H, NH), 3.31–3.73 (m, 6H, CH_2ArCH_2 and 2×COCH), 3.78, 3.81 and 3.93 (3×s, 3×3H, 3×OMe), 4.32 and 4.44 (2×d, *J*=14.0 Hz, 2H, NCH_2), 4.96 (brd, 1H, NCH), 6.12 (brd, 1H, ArH), 7.05–7.35 (m, 6H, ArH), 7.53 (brd, 1H, ArH) and 8.71 (brs, 1H, NH); *m/z* (%): 633 (M^+, 13), 572 (17), 559 (23), 526 (6), 499 (14), 441 (5), 350 (6), 290 (39), 283 (11), 229 (100), 209 (6), 187 (43), 169 (14), 155 (17), 142 (15), 129 (32), 117 (12), 71 (13), 61 (22) and 43 (30); ν_{max}: 3379, 2923, 2853, 1732, 1699, 1456 and 1254 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-4-benzyl-6-(2-naphthyl)-1,3-dioxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5f. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.3 mmol, 62 mg), *N*-prop-2-ynylmaleimide **2** (0.6 mmol, 81 mg), $RhCl(PPh_3)_3$ (0.015 mmol, 14 mg), imine **4f** (0.6 mmol, 190 mg), AgOAc (0.6 mmol, 100 mg) and Et_3N (0.6 mmol, 83 μl) in toluene (5 ml) at 110°C for 5 h and rt for 17 h. Flash chromatography (2:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (141 mg, 71%)%) as colourless rods from petroleum ether–dichloromethane, mp 150–152°C. (Found: C, 71.05, H, 5.65, N, 4.25. $C_{39}H_{36}N_2O_8$ requires: C, 70.9, H, 5.5, N, 4.25%); δ 2.45 (brs, 1H,

NH), 3.11 (d, J=13.5 Hz, 1H, ArC*H*H), 3.44 (d, J=7.6 Hz, 1H, COCH), 3.49–3.55 (m, 5H, ArCH*H* and CH_2ArCH_2), 3.60 (dd, J=7.6, 9.0 Hz, 1H, COCH), 3.71, 3.74 and 3.89 (3×s, 3×3H, 3×OMe), 4.33 and 4.42 (2×d, J=14.0 Hz, 2×1H, NCH_2), 4.98 (d, J=9.0 Hz, 1H, NCH), 7.04–7.14 (m, 5H, ArH), 7.19–7.33 (m, 4H, ArH), 7.40–7.46 (m, 2H, ArH) and 7.62–7.82 (m, 4H, ArH); *m/z* (%) (FAB): 661 (M^++1, <1), 187 (6), 149 (9), 133 (14), 109 (16), 97 (21), 83 (34), 69 (72) and 55 (100); ν_{max}: 2924, 2854, 1751, 1728, 1698 and 1181 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-4-benzyl-6-(1H-indol-3-yl)-1,3-dioxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5g. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.6 mmol, 125 mg), *N*-prop-2-ynylmaleimide **2** (0.5 mmol, 68 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **4g** (0.65 mmol, 199 mg), AgOAc (0.65 mmol, 109 mg) and Et_3N (0.65 mmol, 90 μl) in toluene (5 ml) at 110°C for 17 h and rt for 48 h. Flash chromatography (1.5:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (180 mg, 55%) as colourless prisms from petroleum ether–dichloromethane, mp 183–185°C. (Found: C, 68.3, H, 5.4, N, 6.25. $C_{37}H_{35}N_3O_8$ requires: C, 68.4, H, 5.45, N, 6.45%); δ 2.37 (brs, 1H, NH), 3.13 (d, J=13.5 Hz, 1H, ArC*H*H), 3.57 (m, 7H, CH_2ArCH_2, ArCH*H* and 2×COCH), 3.76, 3.78 and 3.9 (3×s, 3×3H, 3×OMe), 4.37 and 4.49 (2×d, J=14.0 Hz, 2×1H, NCH_2), 5.17 (d, J=9.0 Hz, 1H, NCH), 6.25 (d, J=3.0 Hz, 1H, ArH), 7.18 (m, 11H, ArH), 7.62 (m, 1H, ArH) and 8.64 (brs, 1H, NH); *m/z* (%) (FAB): 650 (M^++1, 38), 591 (9), 559 (30), 534 (29), 473 (5), 413 (7), 306 (100), 246 (16), 187 (47), 143 (6), 129 (22), 91 (15), 81 (6), 69 (9) and 55 (10); ν_{max}: 3379, 2924, 2853, 1751, 1720, 1703, 1456 and 1288 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-4-benzyl-6-(2-furyl)-1,3-dioxohexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl]methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5h. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.6 mmol, 125 mg), *N*-prop-2-ynylmaleimide **2** (0.5 mmol, 68 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **4h** (0.65 mmol, 167 mg), AgOAc (0.65 mmol, 109 mg) and Et_3N (0.65 mmol, 90 μl) in toluene (5 ml) at 110°C for 17 h and rt for 48 h. Flash chromatography (1.5:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (197 mg, 66%) as colourless needles from petroleum ether–dichloromethane mp 157–159°C. (Found: C, 65.8, H, 5.45, N, 4.4. $C_{33}H_{32}N_2O_9$ requires: C, 66.0, H, 5.35, N, 4.65%); δ 1.43 (brs, 1H, NH), 2.96 (d, J=14.0 Hz, 1H, ArC*H*H), 3.42 (m, 3H, ArCH*H* and 2×COCH), 3.54 (s, 4H, CH_2ArCH_2), 3.71, 3.72 and 3.82 (3×s, 3×3H, 3×OMe), 4.48 (s, 2H, NCH_2), 4.77 (d, J=8.0 Hz, 1H, NCH), 6.19 (m, 2H, ArH) and 7.18 (m, 9H, ArH); *m/z* (%): 600 (M^+, <1), 541 (10), 509 (100), 449 (21), 417 (19), 257 (13), 225 (9), 197 (14), 187 (53), 155 (5), 143 (7), 129 (24), 91 (23) and 59 (10); ν_{max}: 2924, 2853, 1759, 1727, 1708 and 1455 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-4-benzyl-1,3-dioxo-6-(2-thienyl)hexahydropyrrolo[3,4-c]pyrrol- 2(1H)-yl]-methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5i. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.6 mmol, 125 mg), *N*-prop-2-ynylmaleimide **2** (0.5 mmol, 68 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **4i** (0.65 mmol, 178 mg), AgOAc (0.65 mmol, 109 mg) and Et_3N (0.65 mmol, 90 μl) in toluene (5 ml) at 110°C for 17 h and rt for 48 h. Flash chromatography (2:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (184 mg, 60%) as colourless rods from petroleum ether–dichloromethane, mp 169–171°C. (Found: C, 64.1, H, 5.35, N, 4.45, S, 5.35. $C_{33}H_{32}N_2O_8S$ requires: C, 64.25, H, 5.2, N, 4.55, S, 5.2%); δ 2.57 (d, J=4.0 Hz, 1H, NH), 2.97 (d, J=14.0 Hz, 1H, ArC*H*H), 3.45 (m, 7H, ArCH*H*, CH_2ArCH_2 and 2×COCH), 3.72, 3.73 and 3.84 (3×s, 3×3H, OMe), 4.4 and 4.5 (2×d, J=14.0 Hz, 2×1H, NCH_2), 5.12 (m, 1H, NCH) and 7.10 (m, 11H, ArH); *m/z* (%): 616 (M^+,<1), 557 (13), 525 (100), 465 (24), 433 (24), 283 (7), 273 (9), 247 (7), 233 (5), 213 (16), 187 (85), 143 (10), 128 (34), 96 (9), 91 (31) and 59 (13); ν_{max}: 2953, 2922, 2853, 1735, 1695 and 1428 cm^{-1}.

(±)-*endo*-Dimethyl 5-{[4-(acetyloxy)-4-(1H-indol-2-yl-methyl)-6-(2-naphthyl)-1,3-dioxohexah ydropyrrolo [3,4-c]pyrrol-2(1H)-yl]methyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate 5j. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (0.3 mmol, 62 mg), *N*-prop-2-ynylmaleimide **2** (0.6 mmol, 81 mg), $RhCl(PPh_3)_3$ (0.015 mmol, 14 mg), imine **4j** (0.6 mmol, 214 mg), AgOAc (0.6 mmol, 100 mg) and Et_3N (0.6 mmol, 83 μl) in toluene (5 ml) at 110°C for 5 h and rt for 17 h. Flash chromatography (1:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (175 mg, 83%) as a colourless amorphous solid from petroleum ether–dichloromethane, mp 134–136°C. (Found: C, 70.25, H, 5.65, N, 5.7. $C_{41}H_{37}N_3O_8$ requires: C, 70.4, H, 5.35, N, 6.0%); δ 2.62 (brs, 1H, NH), 3.31 (d, J=14.6 Hz, 1H, ArC*H*H), 3.48 (m, 3H, $ArCH_2$ and COCH), 3.55 (s, 2H, $ArCH_2$), 3.64 (m, 2H, COCH and ArCH*H*), 3.70, 3.74 and 3.81 (3×s, 3×3H, 3×OMe), 4.33 and 4.43 (2×d, J=14.0 Hz, 2×1H, NCH_2), 5.04 (d, J=9.1 Hz, 1H, NCH), 7.01–7.16 (m, 6H, ArH), 7.28 and 7.42 (2×m, 2×2H, ArH), 7.57–7.80 (m, 5H, ArH) and 8.13 (brs, 1H, NH); *m/z* (%): 699 (M^+, <1), 569 (30), 509 (19), 477 (11), 283 (22), 252 (9), 227 (11), 187 (44), 167 (12), 130 (100), 91 (13), 77 (6), 57 (7) and 43 (7); ν_{max}: 3380, 2953, 2924, 2853, 1733, 1703 and 1457 cm^{-1}.

(±)-5-{*endo*-6-[*cis*-3-Benzyloxy-1-(4-methoxy-phenyl)-4-oxo-azetidin-2-yl]-4-methoxycarbonyl-4-methyl-1,3-dioxo-hexahydro-pyrrolo[3,4-c]pyrrol-2-ylmethyl}-indan-2,2-dicarboxylic acid dimethyl ester 8a and 8b. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (42 mg, 0.2 mmol), *N*-prop-2-ynylmaleimide **2** (20.3 mg, 0.15 mmol), $RhCl(PPh_3)_3$ (7 mg, 0.0075 mmol), β-lactam imine **7a** (71 mg, 0.18 mmol), AgOAc (30 mg, 0.18 mmol) and DBU (27 μl, 0.18 mmol) in toluene (3 ml) at 110°C for 2 h and rt for 15 h. Flash chromatography (3:1–1:0 v/v Et_2O-petroleum ether) afforded the two separated stereoisomers **8b** and **8a** (77 mg, 69% combined yield) in a 1:1 ratio.

8a. Obtained as colourless needles from Et_2O/petroleum ether, mp 142–143°C. (Found: C, 64.85, H, 5.4, N, 5.45. $C_{40}H_{41}N_3O_{11}$ requires: C, 64.95, H, 5.6, N, 5.7%); δ 1.41 (s,

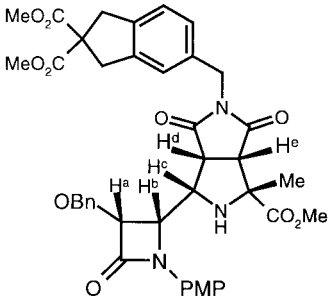
3H, Me), 1.81 (d, J=6.9 Hz, 1H, NH), 3.11 (d, J=7.8 Hz, 1H, COCH), 3.55 (s, 2H, $ArCH_2$), 3.59 (m, 3H, $ArCH_2$ and COCH), 3.70, 3.72 and 3.74 (3×s, 3×3H, 3×OMe), 3.79 (m, 4H, OMe and NCH), 4.16 (dd, J=5.2, 9.6 Hz, 1H, β-lactam NCH), 4.57 and 4.69 (2×d, J=14.3 Hz, 2×1H, $ArCH_2$), 4.90 (d, J=11.2 Hz, 1H, ArC*H*HO), 5.00 (d, J=5.2 Hz, 1H, β-lactam CH), 5.03 (d, J=11.2 Hz, 1H, ArCH*H*O), 6.86 (d, J=9.0 Hz, 2H, ArH), 7.20 (m, 3H, ArH) and 7.37 (m, 7H, ArH); *m/z* (%): 739 (M^+, 7), 457 (14), 397 (6), 337 (5), 283 (9), 247 (6), 226 (10), 187 (36), 164 (25), 156 (21), 149 (24), 128 (12), 108 (8), 91 (100), 77 (9) and 59 (11); ν_{max}: 2954, 2924, 2854, 1737, 1703 and 1461 cm^{-1}.

8b. Obtained as colourless needles from Et_2O/petroleum ether, mp 110–112°C. (Found: C, 64.65, H, 5.55, N, 5.55. $C_{40}H_{41}N_3O_{11}$ requires: C, 64.95, H, 5.6, N, 5.7%); δ 1.35 (s, 3H, Me), 3.15 (d, J=7.9 Hz, 1H, COCH), 3.30 (t, J=7.9 Hz, 1H, COCH), 3.51 (s, 4H, CH_2ArCH_2), 3.71 (s, 3H, OMe), 3.72 (d, J=14.0 Hz, 1H, ArC*H*HN), 3.73 (s, 2×3H, 2×OMe), 3.97 (s, 3H, OMe), 4.01 (d, J=12.1 Hz, 1H, NH), 4.03 (d, J=14.0 Hz, 1H, ArCH*H*N), 4.13 (m, 1H, NCH), 4.63 (d, J=11.2 Hz, 1H, ArC*H*HO), 4.97 (s, 2H, 2×β-lactam CH), 5.16 (d, J=11.2 Hz, 1H, ArCH*H*O), 6.89 (d, J=9.0 Hz, 2H, ArH), 7.04 (m, 3H, ArH) and 7.39 (m, 7H, ArH); *m/z* (%): 739 (M^+, 9), 591 (6), 532 (5), 471 (6), 457 (36), 397 (25), 365 (6), 337 (16), 283 (44), 246 (14), 226 (25), 187 (74), 175 (18), 164 (25), 156 (36), 149 (42), 128 (33), 108 (16), 91 (100), 77 (9) and 59 (12); ν_{max}: 2955, 2924, 2854, 1737, 1704 and 1462 cm^{-1}.

(±)-5-{*endo*-6(*S*,*R*)-[*cis*-3-Phthalimidyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-(*S*,*R*)-yl]-4-methoxycarbonyl-4-methyl-1,3-dioxo-hexahydro-pyrrolo[3,4-c]pyrrol-2-ylmethyl}-indan-2,2-dicarboxylic acid dimethyl ester 9a. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (47 mg, 0.225 mmol), *N*-prop-2-ynylmaleimide **2** (20.3 mg, 0.15 mmol), $RhCl(PPh_3)_3$ (7 mg, 0.0075 mmol), β-lactam imine **7b** (75 mg, 0.17 mmol), AgOAc (30 mg, 0.18 mmol) and DBU (27 μl, 0.18 mmol) in toluene (8 ml) at 110°C for 2 h and rt for 15 h. Flash chromatography (9:1–5:1 v/v CH_2Cl_2–EtOAc) afforded the *product* (82 mg, 70%) as colourless fine needles from CH_2Cl_2/petroleum ether, mp 269–271°C. (Found: C, 63.15, H, 5.0, N, 7.05. $C_{41}H_{38}N_4O_{12}$ requires: C, 63.25, H, 4.9, N, 7.2%); δ 0.97 (s, 3H, Me), 2.31 (d, J=14.5 Hz, 1H, NH), 2.88 (d, J=6.9 Hz, 1H, $COCH^e$), 3.13 (t, J=6.9 Hz, 1H, $COCH^d$), 3.41 (s, 3H, OMe), 3.57 (s, 4H, CH_2ArCH_2), 3.67 (m, 1H, NCH^c), 3.74, 3.74 and 3.80 (3×s, 3×3H, 3×OMe), 4.43 and 4.52 (2×d, J=14.0 Hz, 2×1H, $ArCH_2N$), 5.27 (dd, J=5.2, 9.6 Hz, 1H, β-lactam NCH^b), 5.65 (d, J=5.2 Hz, 1H, β-lactam CH^a), 6.91 (d, J=9.0 Hz, 2H, ArH), 7.22 (m, 3H, ArH) and 7.77 (m, 6H, ArH); *m/z* (%): 778 (M^+, <1), 187 (7), 167 (8), 149 (67), 137 (8), 125 (13), 111 (24), 97 (39), 85 (40), 71 (64) and 57 (100); ν_{max}: 2953, 2923, 2853, 1738, 1704, 1515 and 1456 cm^{-1}.

(±)-5-{*endo*-6-Methoxycarbonyl-4-[*cis*-1-(4-methoxyphenyl)-3-phthalimidyl-4-oxo-azetidin-2-yl]-1,3-dioxo-hexahydro-pyrrolo[3,4-c]pyrrol-2-ylmethyl}-indan-2,2-dicarboxylic acid dimethyl ester 10a. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate **1** (42 mg, 0.2 mmol), *N*-prop-2-ynylmaleimide **2** (20.3 mg, 0.15 mmol), $RhCl(PPh_3)_3$ (7 mg, 0.0075 mmol), β-lactam imine **7c** (76 mg, 0.18 mmol), AgOAc (30 mg, 0.18 mmol) and DBU (27 μl, 0.18 mmol) in toluene (8 ml) at 110°C and rt for 15 h. Flash chromatography (9:1–5:1 v/v CH_2Cl_2–EtOAc) afforded the two separated stereoisomers **10a** and **10b** (84 mg, 73% combined yield) in a 4:1 ratio. The major isomer **10a** crystallised from CH_2Cl_2/petroleum ether as a colourless amorphous solid, mp 239–241°C. (Found: C, 62.55, H, 4.65, N, 7.1. $C_{40}H_{36}N_4O_{12}$ requires: C, 62.8, H, 4.75, N, 7.35%); δ 2.76 (t, J=12.3 Hz, 1H, NH), 3.10 and 3.28 (2×t, J=7.5 Hz, 2×1H, 2×COCH), 3.55 (m, 9H, CH_2ArCH_2, pyrrolidine *H*CNHC*H* and OMe), 3.74 (s, 6H, 2×OMe), 3.80 (s, 3H, OMe), 4.42 and 4.59 (2×d, J=13.9 Hz, 2×1H, $ArCH_2N$), 5.20 (dd, J=5.2, 9.2 Hz, 1H, β-lactam NCH), 5.65 (d, J=5.2 Hz, 1H, β-lactam CH), 6.91 (d, J=9.0 Hz, 2H, ArH), 7.15 (m, 3H, ArH), 7.72–7.76 (m, 4H, ArH) and 7.85 (m, 2H, ArH); *m/z* (%): 764 (M^+, 29), 614 (8), 577 (17), 556 (6), 518 (11), 464 (7), 443 (23), 383 (20), 351 (12), 322 (74), 294 (29), 279 (7), 247 (9), 221 (6), 187 (92), 149 (100), 134 (28), 128 (37), 104 (25), 91 (24), 76 (16), and 59 (15); ν_{max}: 2953, 2924, 2853, 1750, 1742, 1712, 1700 and 1513 cm^{-1}.

(±)-5-{*endo*-4-Benzyl-4-methoxycarbonyl-6(*S*,*R*)-[*cis*-1-(4-methoxy-phenyl)-3-phthalimidyl-4-oxo-azetidin-2-(*S*,*R*)-yl]-1,3-dioxo-hexahydro-pyrrolo[3,4-c]pyrrol-2-ylmethyl}-indan-2,2-dicarboxylic acid dimethyl ester 11a. Prepared by the general procedure from dimethyl 2,2-diprop-2-ynylmalonate (42 mg, 0.2 mmol), *N*-prop-2-ynylmaleimide (20.3 mg, 0.15 mmol), $RhCl(PPh_3)_3$ (7 mg,



NOE (400 MHz)

Proton irradiated	Enhancement (%)					
	H^a	H^b	H^c	H^d	H^e	Me
H^a		6.8				
H^b	15.9					
H^c				5.3		3.4
H^d			7.0		7.0	
H^e				11.5		4.2
Me			3.8		5.9	

0.0075 mmol), β-lactam imine **7d** (77 mg, 0.15 mmol), AgOAc (30 mg, 0.18 mmol) and DBU (27 μl, 0.18 mmol) in toluene (3 ml) at 110°C and rt for 15 h. Flash chromatography (9:1–6:1 v/v CH_2Cl_2–EtOAc) afforded the *product* (70 mg, 55%) as colourless prisms from CH_2Cl_2/petroleum ether, mp 147–149°C. (Found: C, 65.8, H, 5.1, N, 6.55. $C_{47}H_{42}N_4O_{12}$ requires: C, 66.05, H, 4.95, N, 6.55%); δ 2.09 (brd, 1H, NH), 2.77 (d, *J*=13.6 Hz, 1H, ArC*H*H), 2.99 (t, *J*=7.6 Hz, 1H, COCH), 3.15 (d, *J*=7.6 Hz, 1H, COCH), 3.34 (d, *J*=13.6 Hz, 1H, ArCH*H*), 3.52 and 3.54 (2×s, 2×2H, CH_2ArCH_2), 3.69, 3.71, 3.72 and 3.75 (4×s, 4×3H, 4×OMe), 4.40 (m, 1H, NCH), 4.52 (dd, *J*=5.3, 9.7 Hz, 1H, β-lactam NCH), 4.57 and 4.66 (2×d, *J*=14.3 Hz, 2×1H, NCH_2), 5.88 (d, *J*=5.3 Hz, 1H, β-lactam CH), 6.80 (d, *J*=9.0 Hz, 2H, ArH), 6.89 (m, 2H, ArH), 6.98–7.17 (m, 6H, ArH), 7.38 (d, *J*=9.0 Hz, 2H, ArH), 7.80 (m, 2H, ArH) and 7.94 (m, 2H, ArH); *m/z* (%): 854 (M^+, 2), 763 (16), 667 (17), 576 (100), 544 (17), 533 (30), 516 (7), 473 (7), 413 (8), 322 (20), 293 (11), 233 (13), 187 (84), 149 (24), 129 (32), 91 (38) and 49 (38); ν_{max}: 2922, 2853, 1757, 1723 and 1515 cm^{-1}.

General procedure for the one-pot synthesis of 14h–k and 18

A solution of diyne **12** (0.5 mmol) in dry THF (6 ml) was added dropwise over 2 h to a stirred mixture of *N*-prop-2-ynylmaleimide **2** (1 mmol) and $RhCl(PPh_3)_3$ (0.025 mmol) in dry THF (2 ml) under N_2 at room temperature and stirring continued for 15 h. Then imine **4** (1 mmol), AgOAc (1 mmol) and Et_3N (1.25 mmol) were added and stirring continued for a further 17–72 h. The solvent was evaporated and the residue purified by column chromatography to give the cycloadducts.

Cycloadduct 14h. Prepared according to the general procedure from diyne **12** (0.5 mmol, 108 mg), *N*-prop-2-ynylmaleimide **2** (1 mmol, 135 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **4h** (1.05 mmol, 270 mg), AgOAc (1.05 mmol, 175 mg) and Et_3N (1.2 mmol, 167 μl) for a further 72 h. Flash chromatography (3:2:2, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (135 mg, 44%) as colourless needles from petroleum ether–dichloromethane mp 119–121°C. (Found: C, 71.05, H, 6.2, N, 4.4. $C_{36}H_{36}N_2O_7$ requires: C, 71.05, H, 5.95, N, 4.6%); δ 1.00 and 1.03 (2×s, 2×3H, 2×Me), 2.67 (m, 4H, 2×$COCH_2$), 2.82 (br, 1H, NH), 2.96 (d, *J*=14.0 Hz, 1H, ArC*H*H), 3.34–3.49 (m, 7H, CH_2ArCH_2, ArCH*H* and 2×COCH), 3.83 (s, 3H, OMe), 4.43 and 4.45 (2×d, *J*14.0 Hz, 2×1H, NCH_2), 4.75 (brt, 1H, NCH), 6.14 and 6.24 (2×m, 2H, ArH), and 7.05–7.27 (m, 9H, ArH); *m/z* (%) (FAB): 609 (M^+ +1, 100), 549 (13), 517 (57), 257 (7), 237 (6), 195 (7), 171 (6), 153 (7), 129 (10), 91 (17) and 83 (15); ν_{max}: 2923, 2853, 1699 and 1455 cm^{-1}.

Cycloadduct 14i. Prepared according to the general procedure from diyne **12** (0.5 mmol, 108 mg), *N*-prop-2-ynylmaleimide **2** (1 mmol, 135 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg) imine **4i** (1.05 mmol, 287 mg), AgOAc (1.05 mmol, 175 mg) and Et_3N (1.2 mmol, 167 μl) for a further 72 h. Flash chromatography (1:1:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (105 mg, 34%) as colourless prisms from petroleum ether–dichloromethane mp130–132°C. (Found: C, 69.4, H, 6.1, N, 4.25, S, 5.2. $C_{36}H_{36}N_2O_6S$ requires: C, 69.2H, 5.8, N, 4.5, S, 5.15%); δ 1.00 and 1.03 (2×s, 2×3H, 2×Me), 2.60 (m, 1H, NH), 2.70 (m, 4H, 2×$COCH_2$), 2.96 (d, *J*=14.0 Hz, 1H, ArC*H*H), 3.36–3.51 (m, 7H, CH_2ArCH_2, ArCH*H* and 2×COCH), 3.84 (s, 3H, OMe), 4.38 and 4.42 (2×d, *J*14.0 Hz, 2×1H, NCH_2), 5.11 (d, *J*=9.0 Hz, 1H, NCH) and 6.91–7.28 (m, 11H, ArH). *m/z* (%): 624 (M^+, <1), 565 (7), 533 (100), 273 (11), 255 (9), 237 (18), 213 (15), 195 (10), 171 (9), 153 (13), 129 (23), 91 (25), 83 (11) and 55 (6); ν_{max}: 2923, 2853, 1727, 1703 and 1464 cm^{-1}.

Cycloadduct 14j. Prepared according to the general procedure from diyne **12** (0.4 mmol, 87 mg), *N*-prop-2-ynylmaleimide **2** (0.8 mmol, 109 mg), $RhCl(PPh_3)_3$ (0.02 mmol, 19 mg), imine **4j** (0.84 mmol, 299 mg), AgOAc (0.84 mmol, 140 mg) and Et_3N (0.96 mmol, 133 μl) for a further 17 h. Flash chromatography (1:2:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (167 mg, 59%) as a colourless amorphous solid from petroleum ether–dichloromethane mp 156–159°C. (Found: C, 74.55, H, 5.9, N, 5.7. $C_{44}H_{41}N_3O_6$ requires: C, 74.65, H, 5.85, N, 5.95%); δ 0.98 and 1.01 (2×s, 2×3H, 2×Me), 2.65 (m, 5H, 2×$COCH_2$, NH), 3.26 (d, *J*=14.6 Hz, 1H, ArC*H*H), 3.31 (s, 2H, $ArCH_2$), 3.41–3.57 (m, 4H, $ArCH_2$ and 2×COCH), 3.63 (d, *J*=14.6 Hz, 1H, ArCH*H*), 3.79 (s, 3H, OMe), 4.33 and 4.38 (2×d, *J*14.0 Hz, 2×1H, NCH_2), 4.98 (brd, 1H, NCH), 7.02 (m, 6H, ArH), 7.25 and 7.43 (2×m, 2×2H, ArH), 7.56–7.79 (m, 5H, ArH) and 8.17 (brs, 1H, NH); *m/z* (%): 707 (M^+, <1), 577 (27), 356 (6), 333 (8), 267 (45), 252 (7), 227 (17), 213 (12), 170 (21), 167 (16), 153 (8), 141 (8), 130 (100), 115 (9), 83 (10) and 55 (8); ν_{max}: 2923, 2853, 1699 and 1456 cm^{-1}.

Cycloadduct 14k. Prepared according to the general procedure from diyne **12** (0.5 mmol, 108 mg), *N*-prop-2-ynylmaleimide **2** (1 mmol, 135 mg), $RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **4k** (1 mmol, 301 mg), AgOAc (1 mmol, 167 mg) and Et_3N (1.25 mmol, 174 μl) for a further 70 h. Flash chromatography (2:2:1, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (178 mg, 54%) as a colourless amorphous solid from petroleum ether–dichloromethane mp 203–205°C. (Found: C, 69.75, H, 6.25, N, 4.2, S, 4.95. $C_{38}H_{40}N_2O_6S$ requires: C, 69.9, H, 6.2, N, 4.2, S, 4.9%); δ 1.01, 1.05 and 2.12 (3×s, 3×3H, 2×Me and SMe), 2.38–2.74 (m, 8H, 2×$COCH_2$, SCH_2CH_2), 2.90 (brd, 1H, NH), 3.30 (d, *J*=7.6 Hz, 1H, COCH), 3.36 and 3.45 (2×s, 2×2H, CH_2ArCH_2), 3.55 (dd, *J*=7.6, 9.0 Hz, 1H, COCH), 3.91 (s, 3H, OMe), 4.34 (s, 2H, NCH_2), 4.78 (brd, 1H, NCH), 7.05–7.15 (m, 4H, ArH), 7.44–7.48 (m, 2H, ArH), 7.63–7.67 (m, 3H, ArH) and 7.81–7.84 (m, 1H, ArH); *m/z* (%): 652 (M^+, <1), 637 (5), 605 (6), 591 (89), 545 (40), 518 (8), 397 (7), 323 (5), 301 (8), 267 (29), 253 (22), 240 (100), 225 (26), 195 (22), 180 (27), 171 (32), 153 (59), 141 (21), 129 (46), 115 (10), 83 (27), 61 (33) and 41 (10); ν_{max}: 2924, 2853, 1751, 1703, 1691 and 1172 cm^{-1}.

3-(2-Furyl)-1-(1H-indol-2-ylmethyl)-4,6-dioxo-5-{[2-(phenylsulfonyl)-2,3-dihydro-1H-isoindol-5-yl]methyl}-octahydrocyclopenta[c]pyrrol-1-yl acetate 18. Prepared according to the general procedure from **15** (0.5 mmol, 117 mg), *N*-prop-2-ynylmaleimide **2** (1 mmol, 135 mg),

$RhCl(PPh_3)_3$ (0.025 mmol, 23 mg), imine **17** (1.05 mmol, 311 mg), AgOAc (1.05 mmol, 175 mg) and Et_3N (1.2 mmol, 167 μl). Flash chromatography (2:3:3, v/v/v, petroleum ether–dichloromethane–Et_2O) afforded the *product* (93 mg, 28%) as a colourless amorphous solid from petroleum ether–dichloromethane mp 128–130°C. (Found: C, 64.9, H, 5.1, N, 8.2, S, 4.7. $C_{36}H_{32}N_4O_2S$ requires: C, 65.05H, 4.85, N, 8.45, S, 4.8%) δ 2.87–2.90 (brd, 1H, NH), 3.17 (d, *J*=14.7 Hz, 1H, C*H*H-indole), 3.45–3.55 (m, 3H, CH*H*-indole and 2×COCH), 3.73 (s, 3H, OMe), 4.48 (s, 2H, NCH_2), 4.57 and 4.58 (2×s, 2×2H, CH_2ArCH_2), 4.83 (brm, 1H, NCH), 6.08–6.16 (m, 2H, ArH), 7.06–7.33 (m, 8H, ArH), 7.47–7.58 (m, 4H, ArH), 7.85–7.88 (m, 2H, ArH) and 8.19 (s, 1H, NH); *m*/*z* (%): 664 (M^+, <1), 534 (12), 227 (23), 130 (100), 103 (6), 77 (24) and 51 (6); ν_{max}: 2924, 2853, 1759, 1703, 1457 and 1146 cm^{-1}.

Acknowledgements

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