Pergamon

Tetrahedron 57 (2001) 607–615

TETRAHEDRON

Palladium catalysed tandem cyclisation–anion capture. Part 7:[1] Synthesis of derivatives of α-amino esters, nitrogen heterocycles and β-aryl/heteroaryl ethylamines via in situ generated vinylstannanes

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Received 25 July 2000; revised 3 October 2000; accepted 26 October 2000

Abstract—Palladium catalysed in situ hydrostannylation of terminal alkynes containing a β-N atom affords mainly α-vinylstannanes which serve as anion capture agents in palladium catalysed cyclisation–anion capture processes leading to derivatives of α-amino esters, nitrogen heterocycles and β-aryl/heteroaryl ethylamines in good yield. © 2001 Elsevier Science Ltd. All rights reserved.

In previous papers in this series we have reported a series of palladium catalysed cascade cyclisation–anion capture processes, which terminate in sp^3–sp^2 Stille coupling reactions.[1–3] The versatility of these cascades was demonstrated by intermolecular capture of a wide variety of preformed organostannes,[2] intramolecular capture of in situ generated organostannes involving a bis-cyclisation process generating bridged- and spiro-cyclic small and macrocyclic heterocycles[3] and intermolecular capture of in situ generated organostannes which accessed a range of derivatives of sugars, nucleosides, purines, a benzodiazepinone and a β-lactam.[1] This paper describes further examples of intermolecular capture of in situ generated organostannes by derivatives of α-amino esters, nitrogen heterocycles and β- aryl/heteroaryl ethylamines. Generation of organostannes in situ was achieved by palladium catalysed hydrostannylation of terminal alkynes bearing a β-heteroatom.[4] The presence of a β-heteroatom ensures high regioselectivity for the α-vinylstannane. General concepts and scope of palladium catalysed cyclisation–anion capture processes have recently been reviewed.[5]

A range of enantiopure propargylic precursors was prepared via sulphonamides of α-amino esters **1a–d→2a–d**. The tryptophan derivative **2e** was prepared from racemic tryptophan **1e.** Similarly **3–5** were prepared from the appropriate *N*-heterocycles and β-aryl/heteroaryl ethylamine sulphonamides **6a–c** afforded **7a–c**. Histidine **2c** and histamine **7a** derivatives were isolated as 10:1 and >95:5 mixtures, respectively of τ:π isomers according to the ^{1}H NMR chemical shifts of the imidazole protons.[6]

With the *N*-propargyl derivatives to hand the next step was to attempt cascade hydrostannylation–cyclisation–anion capture utilising α-vinylstannes **8** generated in situ (Scheme 1) and cyclisation precursors **10a–c** (Scheme 2). The palladium(0) catalysed hydrostannylation of **2a–e**, **3–5** and **7a–c** was performed in toluene at 0°C for 1 h using tributyltin hydride and a catalyst comprised of 5 mol% $Pd_2(dba)_3$ and 20 mol% tris(2-fury)phosphine. When the reaction was judged complete (TLC monitoring) the ratio of vinyltributylstannanes **8**:**9** was determined by ^{1}H NMR. In all cases **8** was the major regioisomer (Scheme 1 and Table 1). Aryl iodide **10** was then added and the temperature increased to 110°C to initiate a 5-*exo*-trig cyclisation followed by sp^3–sp^2 Stille coupling of **11** with the appropriate vinylstannane **8** furnishing **12** (Scheme 2). The selected catalyst gave the best results for the coupling process.[3,7] Other catalysts [$Pd(PPh_3)_4$, $Pd(AcO)_2/PPh_3$, $Pd_2(dba)_3/AsPh_3$)][7], solvents (NMP, acetonitrile, DMF) and additives (CuI,[8] CuCl,[9] CuO[10]) were tested without any noticeable improvement in yield.

The coupling reaction of the corresponding β-vinylstannanes **9** furnished small amounts of **13** that were discarded during purification of the desired major compounds **12**. When the hydrostannylation–cyclisation–anion capture cascade was carried out on **2b–e** the product comprised a 1:1 mixture of diastereoisomers (^{1}H NMR data). A similar ratio was observed in the earlier stages of the reaction, even at lower temperatures. The reaction time (TLC monitoring) rarely exceeded 4 h except in the cases of imidazole **3** and indoline **5**, which required 20–24 h. Precursors **2d**, **2e**, **7b**

Keywords: palladium catalysis; cascade reaction; hydrostannylation; Stille coupling.

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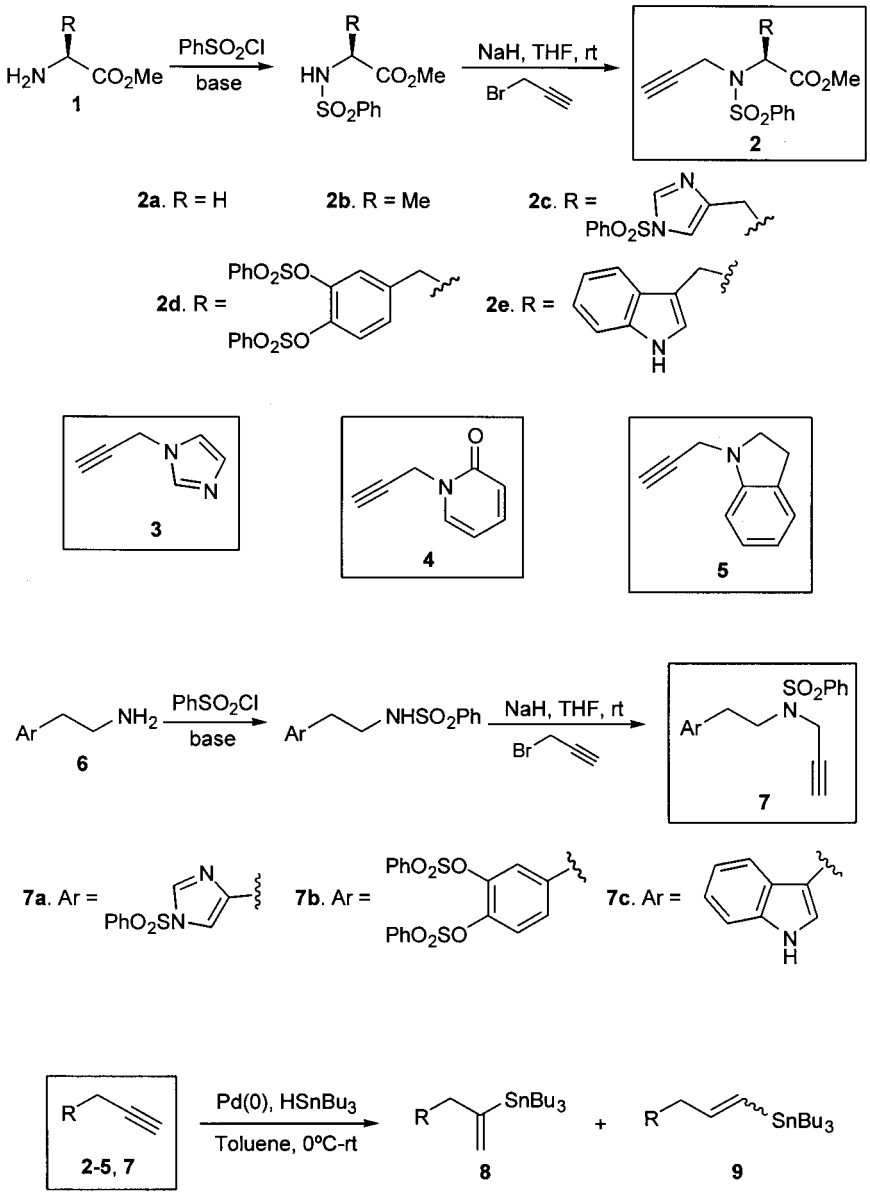
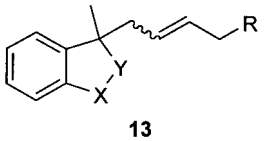
PII: S0040-4020(00)01030-9



Scheme 1.

and **7c** required two equivalents of tributyltin hydride as well as two equivalents of **10** in order to obtain the corresponding cascade product **12** in good yield (Table 1).



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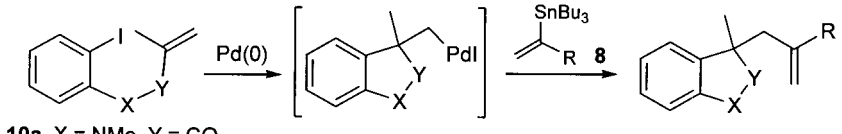
Selective deprotection of the imidazole *N*-sulfonyl group was achieved in products **12e** and **12p** after careful treatment of the reaction mixture with an equimolar amount of NaOH in methanol at room temperature for 2 h. However, these reaction conditions could not be applied to compounds **12f** and **12q** because total decomposition occurred even at low temperatures.

The alternative vinylstannane regioisomer **9** can be



Scheme 2.

Table 1. Cascade synthesis of **12a–u**

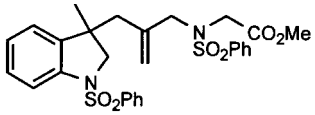
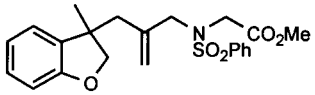
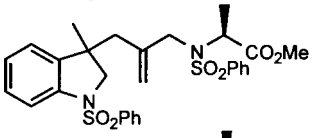
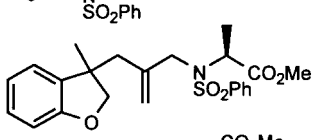
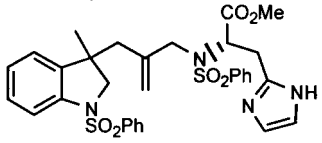
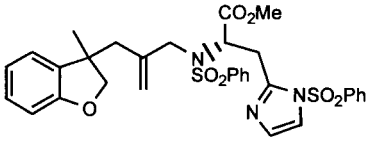
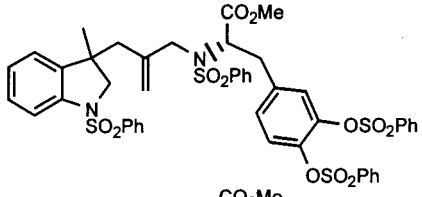
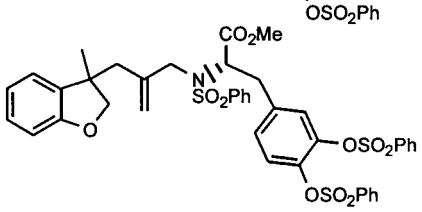
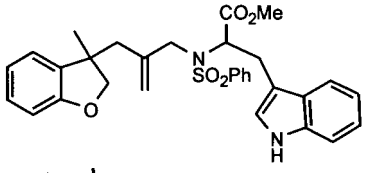
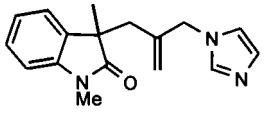
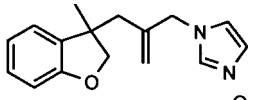
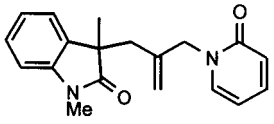
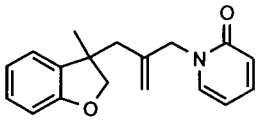
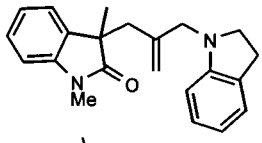
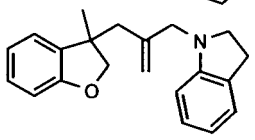
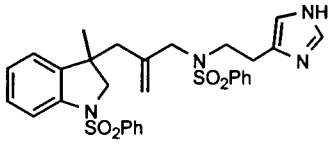
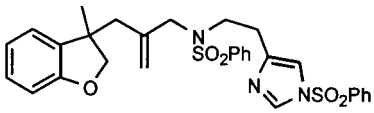
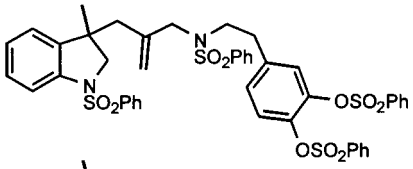
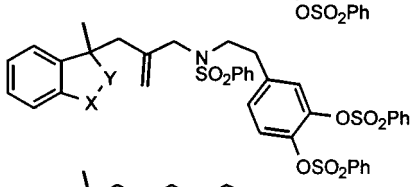
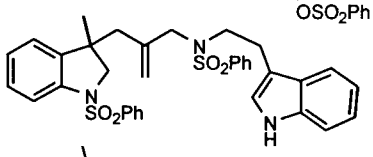
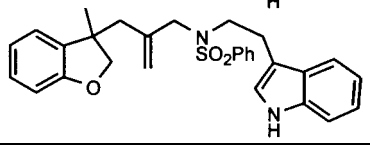
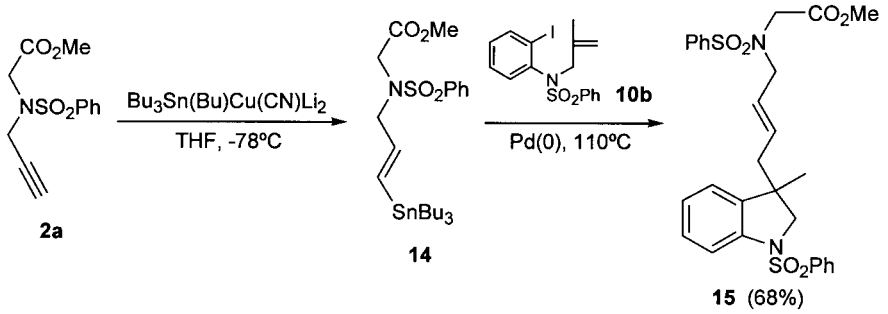
Alkyne	Ary iodide	$HSnBu_3$(eq):**10**(eq)[a]	**8**:**9**[b]	Time (h)[c]	Product	Yield (%)[d]
2a	**10b**	1:1	90:10	3	 **12a**	68
2a	**10c**	1:1	90:10	3	 **12b**	65
2b	**10b**	1:1	90:10	3	 **12c**	68[e]
2b	**10c**	1:1	80:15	3	 **12d**	65[e]
2c	**10b**	1:1	85:15	2	 **12e**	62[e,f]
2c	**10c**	1:1	85:15	2	 **12f**	71[e,g]
2d	**10b**	2:2	85:15	2	 **12g**	63[e]
2d	**10c**	2:2	85:15	2	 **12h**	63[e]
2e	**10c**	2:2	90:10	2	 **12i**	72[e]
3	**10a**	1:1	90:10	24	 **12j**	57
3	**10c**	1:1	90:10	24	 **12k**	55
4	**10a**	1:1	90:10	2	 **12l**	66
4	**10c**	1:1	90:10	2	 **12m**	65

Table 1 (*continued*)

Alkyne	Ary iodide	$HSnBu_3$(eq):**10**(eq)[a]	**8**:**9**[b]	Time (h)[c]	Product	Yield (%)[d]
5	**10a**	1:1	90:10	20	 **12n**	63
5	**10c**	1:1	90:10	20	 **12o**	64
7a	**10b**	1:1	90:10	2	 **12p**	68[f]
7a	**10c**	1:1	90:10	2	 **12q**	69[g]
7b	**10b**	2:2	85:15	2	 **12r**	79
7b	**10c**	2:2	85:15	2	 **12s**	78
7c	**10b**	2:2	85:15	1.5	 **12t**	71
7c	**10c**	2:2	85:15	1.5	 **12u**	80

[a] Based on alkyne (1 equiv).
[b] Calculated by ^1H NMR.
[c] Reaction time for the Stille coupling reaction.
[d] Isolated compounds, based on alkyne, after column chromatography.
[e] Obtained as a 1:1 mixture of diastereomers (^1H NMR).
[f] Isolated compound after treatment with 1 equiv. of NaOH in MeOH at rt, 2 h.
[g] The product decomposes in basic media.



Scheme 3.

generated as the main product from hydrostannylation of alkynes[11] using a lithium cuprate[12] at −78°C (Scheme 3). This methodology was used to generate *E*-vinylstannane **14**. *E*-Vinylstannane **14** could not be generated and used in situ because of decomposition problems. However, **14** could be isolated by quenching the reaction at −78°C with water. The coupling process using isolated **14** was completed in 2 h furnishing **15** in 68% yield.

In conclusion, a wide range of α-amino ester, imidazole, 2-pyridone, indoline and β-aryl/heteroaryl ethylamine derivatives can be accessed through a simple one pot cascade protocol proceeding via palladium(0) catalysed hydrostannylation followed by cyclisation–anion capture. The cascade process results in the formation of two bonds, one ring and one tetrasubstituted carbon centre. The presence of the 1,1-disubstituted alkene moiety in the products offers further opportunities for creative chemistry.

1. Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec mass spectrometer operating at 70 eV. Nuclear magnetic resonance spectra were recorded on Bruker QE300 and AM 400 machines operating at 300 and 400 MHz, respectively. Unless otherwise specified, deuterochloroform was used as solvent for NMR samples with tetramethylsilane as internal standard. Optical rotations were determined at ambient temperature with a AA-100 polarimeter and are the average of at least four measurements. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. The enantiomeric purity was determined by chiral HPLC using a KONTRON-323 system and a Chiralcel-OD column eluting with 4:1 v/v *n*-hexane/isopropyl alcohol. Thin layer chromatography was carried out on Whatman PESIL G/UV polyester plates coated with a 0.2 mm layer of silica-gel 60 (Merck 9385). Column chromatography was performed with silica gel 60 (Merck 9385). Petroleum ether refers to the fraction with bp 40–60°C. Anhydrous DMF was commercially available (Aldrich), THF and toluene were sodium dried under a nitrogen atmosphere and *n*-hexane was distilled prior to use.

1.1. Propargylamides 2a,b

Triethylamine (4.17 mL, 30 mmol), *N*,*N*-dimethylaminopyridine (DMAP) (10 mg) and phenylsulfonyl chloride (1.77 g, 10 mmol) were added at 0°C to a stirred suspension of glycine methyl ester hydrochloride or L-alanine methyl ester hydrochloride (10 mmol) in dichloromethane (25 mL). The resulting suspension was stirred at room temperature for 1 day when 2 M hydrochloric acid (40 mL) was added. The organic layer was separated, dried (Na_2SO_4) and evaporated in vacuo giving a residue which was dissolved in dry DMF (15 mL) and treated with sodium hydride (60% dispersion in mineral oil, 200 mg, 5 mmol) at 0°C. The resulting solution was stirred at room temperature for 30 min, propargyl bromide (669 μL, 6 mmol) added and stirring continued at room temperature for 2 h. The DMF was evaporated in vacuo, the residue partitioned between dichloromethane (30 mL) and water (30 mL), the organic phase separated, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography eluting with mixtures of *n*-hexane/ether furnishing products **2a** and **2b** in 82 and 86% overall yield, respectively.

2a. Colourless solid from *n*-hexane/ether, mp 53–54°C. (Found: C, 53.9; H, 4.9; N, 5.25; S, 12.0. $C_{12}H_{13}NO_4S$ requires: C, 53.9; H, 4.9; N, 5.25; S, 12.0%). δ 2.14 (t, *J*=2.4 Hz, 1H, C≡CH), 3.69 (s, 3H, CH_3), 4.14 (s, 2H, CH_2CO), 4.28 (d, *J*=2.4 Hz, 2H, $CH_2C{\equiv}C$), 7.05–7.86 (m, 5H, ArH). *m*/*z* (%) 267 (M^+, 3), 209 (15), 208 (65), 141 (61), 126 (99), 78 (18), 77 (100), 66 (37), 51 (35) and 39 (35).

2b. Colourless needles mp 78–79°C, $[\alpha]_D$=−44.7 (*c*=1.7, MeOH). (Found: C, 55.6; H, 5.2; N, 4.8; S, 11.5. $C_{13}H_{15}NO_4S$ requires: C, 55.5; H, 5.3; N, 4.95; S, 11.4%). δ 1.49 (d, *J*=7.3 Hz, 3H, CH_3C), 2.23 (t, *J*=2.3 Hz, 1H, C≡CH), 3.57 (s, 3H, CH_3O), 4.13, 4.30 (2×dd, *J*=18.7 and 2.3 Hz, 2H, CH_2), 4.65 (q, *J*=7.3 Hz, 1H, CHN), 7.48–7.61 (m, 5H, ArH). *m*/*z* (%) 281 (M^+, 0.03), 223 (18), 222 (100), 141 (42), 140 (42), 125 (17), 80 (46), 77 (88), 51 (20) and 39 (21).

1.2. Propargylamides 2c and 7a

Sodium bicarbonate (420 mg, 5 mmol) and phenylsulfonyl chloride (354 mg, 2 mmol) were added to a solution of histamine dihydrochloride or L-histidine methyl ester dihydrochloride (1 mmol) in 1:1 v/v THF/H_2O (10 mL) and the mixture was stirred at room temperature for 1 day. Ethyl acetate (20 mL) and 2 M hydrochloric acid (10 mL) were added, the organic layer separated, dried (Na_2SO_4) and the solvent evaporated in vacuo. *N*-Alkylation of the resulting amide was carried out as above furnishing **2c** (67% as a 10.1, τ:π mixture by ^{1}H NMR) and **7a** (66%, τ:π>95.5 by ^{1}H NMR).[6]

2c. Thick colourless oil, $[\alpha]_D$=−28.5 (*c*=1.15, MeOH). (Found: C, 53.9; H, 4.8; N, 8.9; S, 13.0. $C_{22}H_{21}N_3O_6S_2$ requires: C, 54.2; H, 4.35; N, 8.65; S, 13.15%). δ (major regioisomer) 2.10 (t, *J*=2.5 Hz, 1H, C≡CH), 3.04 (dd, *J*=15.3 and 9.3 Hz, 1H, CH_2CN), 3.23 (dd, *J*=15.3 and 5.8 Hz, 1H, CH_2CN), 3.52 (s, 3H, CH_3O), 4.09, 4.26 (2×dd, *J*=18.6 and 2.5 Hz, 2H, CH_2N), 4.89 (dd, *J*=9.3 and 5.8 Hz, 1H, CHN), 7.18 (s, 1H, 5^{im}-H), 7.42–7.99 (m, 11H, ArH). *m*/*z* (%) 487 (M^+, 0.5), 346 (66), 266 (22), 141 (56), 125 (23), 124 (22), 81 (31), 78 (21), 77 (100), 51 (27) and 43 (33).

7a. Colourless prisms from *n*-hexane/ether, mp 98–99°C. (Found: C, 56.05; H, 4.25; N, 9.85; S, 15.0. $C_{20}H_{19}N_3O_4S_2$ requires: C, 55.9; H, 4.45; N, 9.8; S, 14.95%). δ 1.99 (t, *J*=2.1 Hz, 1H, C≡CH), 2.85, 3.48 (2×t, *J*=7.2 Hz, 4H, CH_2CH_2N), 4.05 (d, *J*=2.1 Hz, 2H, $CH_2C{\equiv}C$), 7.17 (s, 1H, 5^{im}-H) and 7.46–7.99 (m, 11H, ArH). *m*/*z* (%) 429 (M^+, 0.4), 428 (1), 288 (68), 208 (55), 141 (67), 81 (17), 77 (100) and 51 (17).

1.3. Propargylamides 2d and 7b

Phenylsulfonyl chloride (531 mg, 3 mmol) and sodium bicarbonate (420 mg, 5 mmol) were added to a suspension

of dopamine hydrobromide or L-dopa methyl ester hydrochloride (1 mmol) in THF (6 mL) and the resulting mixture was stirred at 68°C for 1 day. Ethyl acetate (15 mL) and water (10 mL) were added, the organic layer separated, dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (SiO_2) and the isolated amide alkylated as described above affording **2d** and **7b** in 77 and 72% yield, respectively.

2d. Colourless needles from *n*-hexane/ether, mp 113–114°C. $[\alpha]_D=-27.2$ (c=0.25, $CHCl_3$). (Found: C, 55.6; H, 3.8; N, 2.1; S, 14.4. $C_{31}H_{27}NO_{10}S_3$ requires: C, 55.6; H, 4.05; N, 2.1; S, 14.35%). δ 2.21 (t, J=2.4 Hz, 1H, C≡CH), 3.05 (dd, J=14.3 and 8.3 Hz, 1H, CH_2CN), 3.30 (dd, J=14.3 and 6.9 Hz, 1H, CH_2CN), 3.45 (s, 3H, CH_3), 4.17, 4.24 (2×dd, J=18.8, 2.4 Hz, 2H, CH_2N), 4.71 (dd, J=8.3 and 6.9 Hz, 1H, CHN) and 7.14–7.83 (m, 18H, ArH). *m/z* (%) 669 (M^+, 0.1), 610 (17), 528 (21), 267 (19), 266 (87), 141 (65), 125 (28), 141 (31), 78 (22), 77 (100) and 51 (18).

7b. Colourless oil. (Found: C, 57.2; H, 3.8; N, 2.2; S, 15.6. $C_{29}H_{25}NO_8S_3$ requires: C, 56.95; H, 4.1; N, 2.3; S, 15.7%). δ 2.07 (t, J=2.0 Hz, 1H, C≡CH), 2.87, 3.40 (2×t, J=7.3 Hz, 4H, CH_2CH_2N), 4.06 (d, J=2.0 Hz, 2H, CH_2C≡C), 7.06–7.89 (m, 18H, ArH). *m/z* (%) 611 (M^+, 6), 209 (21), 208 (100), 141 (65), 78 (17), 77 (92) and 51 (26).

1.4. (±)-*N*-Propargyl-*N*-phenylsulphonyl tryptophan 2e

Benzensulphonyl chloride (1.8 g, 10 mmol) was added to a stirred solution of (±)-tryptophan (2.18 g, 10 mmol) and triethylamine (1, 10 mmol) in dry dichloromethane (50 mL) cooled at 0°C and the mixture allowed to warm up and stirred for 16 h at room temperature. Water was added, the organic layer separated, dried ($MgSO_4$), filtered and evaporated in vacuo to yield a pale yellow solid. Sodium hydride (95% powder, 177 mg, 7 mmol) was slowly added to a solution of sulfonylated amino acid (2.5 g, 7 mmol) in dry DMF (10 mL). After 2 h at room temperature propargyl bromide (80% in toluene, 2 g, 14 mmol) was added and stirring continued for further 2 h at the same temperature. The mixture was diluted with Et_2O (30 mL) and water (50 mL) was added. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated in vacuo yielding a thick yellow oil, which was purified by column chromatography eluting with 1:1 v/v *n*-hexane/ethyl acetate affording **2e** (2.1 g, 76%) as a thick yellow oil. (Found: C, 63.35; H, 5.05; N, 6.85; S, 7.9. $C_{21}H_{20}N_2O_4S$ requires: C, 63.7; H, 5.1, N, 7.1; S, 8.1%). δ 2.18 (t, J=2.1 Hz, 1H, C≡CH), 3.25 (dd, J=14.7 and 7.5 Hz, 1H, 8-H_a), 3.51 (s, 3H, COOMe), 3.54 (dd, J=14.7 and 7.5 Hz, 1H, 8-H_b), 3.35, 4.35 (2×d, J=2.1 Hz, 2H, NCH_2C≡C), 4.90 (t, J=7.5 Hz, 1H, 9-H), 7.0–7.80 (m, 9H, ArH), 6.74 (t, 1H, ArH), and 8.20 (s, 1H, NH). *m/z* (%) 396 (M^+, 6), 255 (6), 130 (100).

1.5. *N*-Propargylimidazole 3

A solution of propargyl bromide (80% in toluene, 10.8 g, 73 mmol) was added to a stirred mixture of imidazole (2.5 g, 36.5 mmol), tetrabutylammonium iodide (6.5 g, 1.8 mmol) and sodium hydroxide (50% aqueous solution, 125 mL) in toluene (100 mL). After 15 min at room temperature the mixture was diluted with toluene (50 mL) and water (50 mL) was added. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated in vacuo to yield a yellow oil, which was chromatographed eluting with 97:3 v/v petroleum ether/methanol affording **3** (2.4 g, 68%) as a yellow oil. (Found: C, 67.7; H, 5.9; N, 26.4. $C_6H_6N_2$ requires: C, 67.9; H, 5.7; N, 26.3%). δ 2.56 (t, J=2.44 Hz, 1H, C≡CH), 4.72 (t, J=2.44 Hz, 2H, NCH_2), 7.04 (s, 1H, 4-H), 7.06 (s, 1H, 5-H), and 7.57 (s, 1H, 2-H). *m/z* (%) 106 (M^+, 87), and 79 (100).

1.6. *N*-Propargyl-2-pyridone 4

A solution of propargyl bromide (80% in toluene, 4.4 g, 30 mmol) was added to a solution of 2-pyridone (2.0 g, 20 mmol) and potassium carbonate (5.5 g, 40 mmol) in dry DME (40 mL) and the mixture was stirred at 60°C for 16 h. The mixture was then filtered, the filtrate evaporated in vacuo and the residue dissolved in dichloromethane (250 mL) and washed with water (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated in vacuo to yield a brown oil which was chromatographed eluting with 1:9 v/v *n*-hexane/ethyl acetate affording **4** (2.12 g, 80%) as a brown oil. (HRMS Found: 133.0530. C_8H_7NO requires: 133.0528). δ 2.56 (t, J=2.3 Hz, 1H, C≡CH), 4.75 (d, J=2.3 Hz, 2H, NCH_2), 6.25 (t, J=6.6 Hz, 1H, 5-H), 6.55 (d, J=9.21 Hz, 1H, 3-H), 7.35 (m, 1H, 4-H), and 7.65 (m, 1H, 6-H). *m/z* (%) 133 (M^+, 100), 104 (53), and 79 (44).

1.7. *N*-Propargylindoline 5

Sodium hydride (95% powder, 500 mg, 20 mmol) was slowly added to a stirred solution of indoline (2.4 g, 20 mmol) in dry DMF (40 mL). After 2 h at room temperature the mixture was added to a solution of propargyl bromide (80% in toluene, 5.9 g, 40 mmol) and stirred at the same temperature for further 16 h. The mixture was diluted with Et_2O (80 mL) and washed with water (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated in vacuo to yield a yellow oil, which was chromatographed eluting with 4:1 v/v petroleum ether/diethyl ether affording **5** (2.4 g, 76%) as yellow prisms from pentane/diethyl ether, mp 51°C. (Found: C, 83.85; H, 6.95; N, 8.8. $C_{11}H_{11}N$ requires: C, 84.05; H, 7.05, N, 8.9%). δ 2.14 (t, J=2.1 Hz, 1H, C≡CH), 2.98, 3.39 (2×t, J=8.1 Hz, 2H, $NCCH_2$), 3.42 (dd, J=12.0 and 2.1 Hz, 2H, CH_2C≡C), 3.94 (t, J=2.1 Hz, 2H, NCH_2), 6.59 (d, J=7.3 Hz, 1H, ArH), 6.74 (t, J=6.7 Hz, 1H, ArH), and 7.12 (m, 2H, ArH). *m/z* (%) 157 (M^+, 100), 117 (44), 91 (65).

1.8. *N*-Propargyltryptamine 7c

Prepared from tryptamine by the method previously described for the synthesis of **2a**. The product (81%) formed colourless needles from *n*-hexane/ether, mp 113–114°C. (Found: C, 67.45; H, 5.3; N, 8.15; S, 9.5. $C_{19}H_{18}N_2O_2S$ requires: C, 67.45; H, 5.35; N, 8.25; S, 9.5%). δ 2.03 (t, J=2.4 Hz, 1H, C≡CH), 3.08, 3.54 (2×t, J=7.7 Hz, 4H, CH_2CH_2N), 4.17 (d, J=2.4 Hz, 2H, CH_2C≡C), 7.08–7.85 (m, 10H, ArH) and 8.04 (br. s, 1H, NH). *m/z* (%) 338 (M^+, 19), 208 (13), 197 (21), 141 (17), 131 (19), 130 (100), 103 (11) and 77 (30).

1.9. General procedure for cyclisation–anion capture 12a–u

Tri-*n*-butyltin hydride (0.5 or 1 mmol, see Table 1) was added dropwise to a stirred solution of **2**–**5**, **7** (0.5 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.025 mmol) and tri-(2-furyl)phosphine (11.6 mg, 0.10 mmol) in anhydrous toluene (5 mL) cooled at 0°C. The ice bath was removed and the mixture was stirred at room temperature for 1 h when iodide **10** (0.5 or 1 mmol, see Table 1) and toluene (2 mL) were added. The resulting mixture was heated to reflux for the time indicated in Table 1. Ethyl acetate (10 mL) and 2 M aqueous potassium fluoride (10 mL) were then added and the resulting suspension vigorously stirred for 1 h, filtered, the organic layer separated, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography eluting with mixtures of *n*-hexane/ether or *n*-hexane/ethyl acetate to furnish **12a**–**u**. Yields and reaction times are collected in Table 1.

12a. Colourless needles from *n*-hexane/ether, mp 37–38°C. (Found: C, 60.45; H, 3.35; N, 5.05; S, 11.65. $C_{28}H_{30}N_2O_6S_2$ requires: C, 60.6; H, 5.45; N, 5.05; S, 11.55%). δ 1.18 (s, 3H, CH_3C), 2.18, 2.29 (2×d, J=14.3 Hz, 2H, $CCH_2C{=}C$), 3.45 (d, J=10.3 Hz, 1H, CH_2NAr), 3.46 (d, J=9.5 Hz, 1H, $NCH_2C{=}C$), 3.52 (s, 3H, CH_3O), 3.63 (d, J=9.5 Hz, 1H, $NCH_2C{=}C$), 3.87 (s, 2H, CH_2CO_2Me, 4.00 (d, J=10.3 Hz, 1H, CH_2NAr), 4.65, 4.87 (2×s, 2H, $C{=}CH_2$) and 6.98–7.86 (m, 14H, ArH). *m/z* (%) 554 (M^+, 5), 273 (28), 272 (100), 170 (12), 142 (19), 141 (40), 131 (19), 130 (38) and 77 (50).

12b. Sticky oil. (Found: C, 63.35; H, 6.2; N, 3.35; S, 7.75. $C_{22}H_{25}NO_5S$ requires: C, 63.6; H, 6.05; N, 3.35; S, 7.7%). δ 1.34 (s, 3H, CH_3C), 2.30, 2.36 (2×d, J=14.4 Hz, 2H, $CCH_2C{=}C$), 3.52 (s, 3H, CH_3O), 3.57 (s, 2H, $NCH_2C{=}C$), 3.90 (s, 2H, NCH_2CO), 4.13, 4.50 (2×d, J=8.8 Hz, 2H, CH_2O), 4.83, 4.97 (2×s, 2H, $CH_2{=}C$) and 6.74–7.76 (m, 9H, ArH). *m/z* (%) 415 (M^+, 25), 284 (22), 283 (18), 187 (39), 142 (33), 134 (25), 133 (100), 105 (46) and 77 (26).

12c. Colourless prisms from *n*-hexane/ether, mp 45–46°C. (Found: C, 61.05; H, 5.45; N, 4.7; S, 11.3. $C_{29}H_{32}N_2O_6S_2$ requires: C, 61.25; H, 5.65; N, 4.9; S, 11.3%). δ (mixture of diastereoisomers) 1.15, 1.18 (2×s, 3H, CH_3CCH_2N), 1.32 (d, J=7.2 Hz, 3H, CH_3CN), 2.15, 2.18, 2.31, 2.33 (4×d, J=14.2 Hz, 2H, $CCH_2C{=}C$), 3.42–3.80 (m with 2×s at 3.44 and 3.47, 5H, CH_2NAr and CH_3O), 3.99, 4.03 (2×d, J=10.6 Hz, 2H, $NCH_2C{=}C$), 4.44 (q, J=7.2 Hz, 1H, $CHCH_3$), 4.59, 4.68, 5.03, 5.04 (4×s, 2H, $C{=}CH_2$) and 6.97–7.93 (m, 14H, ArH). *m/z* (%) 568 (M^+, 6), 273 (31), 272 (100), 271 (16), 156 (18), 141 (33), 131 (38) and 77 (55).

12d. Colourless oil. (Found: C, 64.1; H, 6.6; N, 3.15; S, 7.5. $C_{23}H_{27}NO_5S$ requires: C, 64.3; H, 6.3; N, 3.25; S, 7.5%). δ (mixture of diastereoisomers) 1.23, 1.33 (2×d, J=7.2 Hz, 3H, CH_3CN), 1.37, 1.38 (2×s, 3H, CH_3CCO), 2.32, 2.42 (2×d, J=14.1 Hz, 2H, $CCH_2C{=}C$), 3.26–3.68 (m with 2×s at 3.42 and 3.46, 6H, $NCH_2C{=}C$, 1H of CH_2O and CH_3O), 4.15 (d, J=8.8 Hz, 1H, CH_2O), 4.44 (q, J=7.2 Hz, 1H, $CHCH_3$), 4.82, 4.91, 5.15, 5.19 (4×s, 2H, $C{=}CH_2$) and 6.72–7.75 (m, 9H, ArH). *m/z* (%) 429 (M^+, 5), 297 (13), 238 (14), 187 (15), 156 (29), 134 (25), 133 (100), 132 (22), 131 (15), 105 (54), 77 (37) and 55 (13).

12e. Colourless prisms from *n*-hexane/ether, mp 74–75°C. (Found: C, 60.2; H, 5.5; N, 8.5; S, 10.0. $C_{32}H_{34}N_4O_6S_2$ requires: C, 60.55; H, 5.4; N, 8.8; S, 10.1%). δ (mixture of diastereoisomers) 1.08, 1.13 (2×s, 3H, CH_3C), 2.03, 2.22 (2×d, J=14.4 Hz, 2H, $CCH_2C{=}C$), 2.88–4.95 (m with 2×s at 3.44 and 3.49, 9H, CH_3O, CH_2CCO, $NCH_2C{=}C$ and CH_2NAr), 4.51 (m, 1H, CHCO), 4.53, 4.90 (2×s, 2H, $CH_2C{=}C$) and 6.73–7.85 (m, 17H, NH and ArH). *m/z* (%) 634 (M^+, 0.1), 507 (22), 272 (77), 184 (42), 182 (26), 144 (45), 141 (45), 132 (29), 131 (32), 130 (68), 96 (24), 95 (24), 78 (51), 77 (100), 51 (37) and 44 (21).

12f. Colourless prisms from *n*-hexane/ether, mp 45–46°C. (Found: C, 60.5; H, 5.05; N, 6.2; S, 10.1. $C_{32}H_{33}N_3O_7S_2$ requires: C, 60.5; H, 5.2; N, 6.6; S, 10.1%). δ (mixture of diastereoisomers) 1.31, 1.33 (2×s, 3H, CH_3C), 2.15, 2.31 (m, 2H, $CCH_2C{=}C$), 2.67–3.61 (m with 2×s at 3.41 and 3.43, 7H, CH_3O, CH_2CCO and $NCH_2C{=}C$), 4.08 (2×d, J=9.5 Hz, 1H, CH_2OAr), 4.39 (2×d, J=8.9 Hz, 1H, CH_2OAr), 4.65, 4.70, 4.87, 4.90 (4×s, 2H, $CH_2C{=}C$) 4.68 (m, 1H, CHCO) and 6.73–7.92 (m, 16H, ArH). *m/z* (%) 635 (M^+, 0.1), 507 (22), 272 (77), 184 (42), 182 (26), 144 (45), 141 (45), 132 (29), 131 (32), 130 (68), 96 (24), 95 (24), 78 (51), 77 (100), 51 (37) and 44 (21).

12g. Colourless prisms from *n*-hexane/ether, mp 57–58°C. (Found: C, 58.9; H, 4.45; N, 2.75; S, 13.4. $C_{47}H_{44}N_2O_{12}S_4$ requires: C, 59.0; H, 4.6; N, 2.9; S, 13.4%). δ (mixture of diastereoisomers) 1.14, 1.17 (2×s, 3H, CH_3C), 2.06, 2.09, 2.24, 2.29 (4×d, J=15.8 Hz, 2H, $CCH_2C{=}C$), 2.80, 2.87 (2×dd, J=13.8 and 6.2 Hz, 1H, CH_2CN), 3.05, 3.22 (2×dd, J=13.8 and 8.1 Hz, 1H, CH_2CN), 3.45–3.66 (m with 2×s at 3.37 and 3.43, 6H, CH_3O, $NCH_2C{=}C$ and 1H of CH_2NAr), 4.00, 4.02 (2×d, J=10.2 Hz, 1H, CH_2NAr), 4.37 (dd, J=8.2 and 6.2 Hz, 1H, CHN), 4.45 (dd, J=8.2 and 8.2 Hz, 1H, CHN), 4.55, 4.64, 4.86, 4.90 (4×s, 2H, $CH_2{=}C$) and 7.03–7.77 (m, 27H, ArH). *m/z* (%) 956 (M^+, 0.01), 305 (38), 269 (36), 267 (28), 205 (67), 177 (29), 149 (63), 141 (24), 78 (36), 77 (84), 71 (45), 57 (100), 55 (40), 51 (34), 43 (57) and 41 (58).

12h. Colourless prisms from *n*-hexane/ether, mp 44–45°C. (Found: C, 60.05; H, 4.85; N, 1.6; S, 11.7. $C_{41}H_{39}NO_{11}S_3$ requires: C, 60.2; H, 4.8; N, 1.7; S, 11.75%). δ (mixture of diastereoisomers) 1.35, 1.37 (2×s, 3H, CH_3C), 2.25, 2.27, 2.34 (3×d, J=14.1 Hz, 2H, $CCH_2C{=}C$), 2.74, 2.87 (2×dd, J=14.2 and 6.5 Hz, 1H, CH_2CN), 3.05, 3.17 (2×dd, J=14.2 and 8.0 Hz, 1H, CH_2CN), 3.31–3.61 (m with 2×s at 3.36 and 3.41, 5H, CH_3O and $NCH_2C{=}C$), 4.12, 4.15 (2×d, J=9.1 Hz, 1H, CH_2O), 4.38–4.51 (m, 2H, CHN and 1H of CH_2O), 4.78, 4.89, 4.95, 4.96 (4×s, 2H, $CH_2{=}C$) and 6.75–7.76 (m, 22H, ArH). *m/z* (%) 817 (M^+, 0.01), 282 (21), 268 (24), 205 (24), 149 (42), 141 (36), 133 (100), 105 (33), 78 (28), 77 (75), 71 (26), 69 (21), 57 (55), 55 (29), 52 (21), 43 (34) and 41 (36).

12i. Colourless prisms from pentane/diethyl ether, mp 59°C. (Found: C, 68.1; H, 5.7; N, 4.9; S, 6.05. $C_{31}H_{32}N_2O_5S$ requires: C, 68.35; H, 5.9; N, 5.15; S, 5.9%). δ (mixture of diastereoisomers) 1.30 and 1.31 (2×s, 3H, 3-CH_3), 2.25 (m, 2H, 8-CH_2), 3.00–3.45 (m, 2H, 13-H), 3.36 and 3.37 (2×s, 3H, $COOCH_3$), 3.45–3.75 (m, 2H, 10-H), 4.08, 4.10, 4.39, 4.42 (4×s, 2H, 9-CH_2), 4.39, 4.72 (2×s, 2H, 9-CH_2),

4.66 (t, 1H, 12-H), 6.80–7.80 (m, 15H, ArH), and 8.0 (s, 1H, 15-H). *m/z* (%) 544 (M^+, 5), 403 (7), 274 (42), and 130 (100).

12j. Pale yellow oil. (HRMS found: 281.1521. $C_{17}H_{19}N_3O$ requires: 281.1528). δ 1.37 (s, 3H, 3-CH_3), 2.31 (2×d, J=13.7 Hz, 2H, 8-H), 3.18 (s, 3H, 1-NCH_3), 3.98, 3.99 (2×d, J=15.9 Hz, 2H, 10-H), 4.51, 4.74 (2×s, 2H, 9-CH_2), and 6.60–7.40 (m, 7H, ArH). *m/z* (%) 281 (M^+, 59.51), 160 (100), and 121 (62.69).

12k. Pale yellow oil. (HRMS found: 254.1427. $C_{16}H_{18}N_2O$ requires: 254.1419). δ 1.41 (s, 3H, 3-CH_3), 2.25 (s, 2H, 2-CH_2), 3.79, 3.93 (d, J=15.8 Hz, 2H, 10-H), 4.17, 4.49 (d, J=8.8 Hz, 2H, 2-H), 4.82, 5.00 (2×s, 2H, 9-CH_2), and 6.60–7.20 (m, 7H, ArH). *m/z* (%) 254 (M^+, 10), 133 (100), 105 (72).

12l. Colourless prisms from petroleum ether/diethyl ether, mp 86°C. (HRMS found: 308.1524. $C_{19}H_{20}N_2O_2$ requires: 308.1525). δ 1.43 (s, 3H, 3-CH_3), 2.49, 2.74 (2×d, J= 13.7 Hz, 2H, 8-H), 3.22 (s, 3H, NCH_3), 3.76, 4.44 (2×d, J=15.8 Hz, 2H, 10-H), 4.39, 4.72 (2×s, 2H, 9-CH_2), 6.07 (t, 1H, 15-H), 6.50 (d, 1H, 13-H), 6.72 (d, 1H, ArH), 6.82 (d, 1H, ArH), 7.12 (t, 1H, ArH), and 7.20–7.40 (m, 3H, ArH). *m/z* (%) 308 (M^+, 21), 160 (71), and 148 (100).

12m. Pale yellow oil. (HRMS found: 281.1425. $C_{18}H_{19}NO_2$ requires: 281.1416). δ 1.40 (s, 3H, 3-CH_3), 2.36 (s, 2H, C=CCH_2), 3.84 (d, J=15.9 Hz, 1H, 2_a-H), 4.44 (d, J= 8.8 Hz, 1H, 10_a-H), 4.26 (d, J=15.9 Hz, 1H, 2_b-H), 4.52 (d, J=8.8 Hz, 1H, 10_b-H), 4.57, 4.82 (2×s, 2H, C=CH_2), 6.06 (t, 1H, 15-H), 6.51 (d, 1H, 13-H), 6.74 (d, 1H, ArH), and 6.80–7.25 (m, 5H, ArH). *m/z* (%) 281 (M^+, 7), 148 (83), 133 (90), and 105 (100).

12n. Pale yellow oil. (HRMS found: 332.1890. $C_{22}H_{24}N_2O$ requires: 332.1889). δ 1.40 (s, 3H, 3-CH_3), 2.58, 2.77 (2×d, J=13.5 Hz, 2H, 8-H), 2.82–3.10 (m, 4H, 12-CH_2, 13-CH_2), 3.13, 3.18 (2×d, J=13.8 Hz, 2H, 10-H), 3.16 (s, 1H, NCH_3), 4.74, 4.83 (2×s, 2×1H, 9-CH_2), 6.00 (d, 1H, 17-H, ArH), 6.83 (t, 1H, 16-H, ArH), 6.83 (d, 1H, ArH), and 6.90–7.40 (m, 5H, ArH). *m/z* (%) 332 (M^+, 9), 172 (100), and 132 (20).

12o. Pale yellow oil. (HRMS found: 305.1788. $C_{21}H_{23}NO$ requires: 305.1780). δ 1.41 (s, 3H, CCH_3), 2.44, 2.53 (2×d, J=13.4 Hz, 2H, 8-H), 2.92 (t, J=8.1 Hz, 2H 13-CH_2), 3.05–3.22 (t, 2H, 12-CH_2), 3.24 (s, 2H, 10-CH_2, 4.20, 4.58 (2×d, J=8.5 Hz, 2H, 2-H), 4.89, 5.13 (2×s, 2H, C=CH_2), 6.25 (d, 1H, 17-H, ArH), 6.80 (t, 1H, 16-H, ArH), and 6.80–7.20 (m, 6H, ArH). *m/z* (%) 305 (M^+, 44), 232 (100), 132 (76).

12p. Colourless prisms from *n*-hexane/ether, mp 65–67°C. (Found: C, 62.2; H, 5.8; N, 9.4; S, 10.9. $C_{30}H_{32}N_4O_4S_2$ requires: C, 62.45; H, 5.6; N, 9.7; S, 11.1%). δ 1.16 (s, 3H, CH_3C), 2.13, 2.25 (2×d, J=14.2 Hz, 2H, CCH_2C=C), 2.72, 3.27 (2×t, J=8.0 Hz, 4H, CH_2CH_2N), 3.38, 3.47 (2×d, J=15.8 Hz, 2H, NCH_2C=C), 3.68, 3.99 (2×d, J=10.2 Hz, 2H, CH_2NAr), 4.60, 4.88 (2×s, 2H, CH_2=C) and 6.72–7.93 (m, 17H, ArH and NH). *m/z* (%) 576 (M^+, 13), 436 (27), 435 (79), 354 (47), 304 (29), 272 (74), 185 (26), 184 (96), 164 (53), 144 (21), 141 (49), 132 (49), 131 (35), 130 (81), 95 (29), 94 (40), 82 (58), 81 (34), 78 (25) and 77 (100).

12q. Colourless oil. (Found: C, 62.05; H, 5.5; N, 7.0; S, 11.0. $C_{30}H_{31}N_3O_5S_2$ requires: C, 62.35; H, 5.4; N, 7.25; S, 11.1%). δ 1.36 (s, 3H, CH_3), 2.28, 2.35 (2×d, J=14.0 Hz, 2H, CCH_2C=C), 2.63, 3.27 (2×t, J=7.9 Hz, 4H, CH_2CH_2N), 3.35, 3.43 (2×d, J=15.8 Hz, 2H, NCH_2C=C), 4.12, 4.49 (2×d, J=8.8 Hz, 2H, CH_2O), 4.76, 4.95 (2×s, 2H, CH_2=C) and 6.72–7.93 (m, 16H, ArH). *m/z* (%) 577 (M^+, 31), 444 (22), 436 (29), 304 (50), 187 (21), 141 (36), 133 (100), 105 (91), 82 (22), 81 (31), 77 (90) and 51 (25).

12r. Colourless prisms from *n*-hexane/ether, mp 46–47°C. (Found: C, 60.0; H, 4.75; N, 2.9; S, 14.1. $C_{45}H_{42}N_2O_{10}S_4$ requires: C, 60.1; H, 4.7; N, 3.1; S, 14.3%). δ 1.20 (s, 3H, CH_3), 2.13, 2.27 (2×d, J=14.0 Hz, 2H, CCH_2C=C), 2.64 (t, J=7.6 Hz, 2H, CH_2CH_2N), 3.11 (m, 2H, CH_2CH_2N), 3.33 (d, J=15.0 Hz, 1H, NCH_2C=C), 3.45 (d, J=10.2 Hz, 1H, CH_2NAr), 3.55 (d, J=15.0 Hz, 1H, NCH_2C=C), 4.04 (d, J=10.2 Hz, 1H, CH_2NAr), 4.64, 4.87 (2×s, 2H, CH_2=C) and 6.95–7.89 (m, 27H, ArH). *m/z* (%) 898 (M^+, 15), 272 (59), 184 (22), 179 (39), 144 (79), 141 (20), 133 (100), 132 (75) and 130 (48).

12s. Sticky colourless oil. (Found: C, 61.35; H, 4.75; N, 1.6; S, 12.5. $C_{39}H_{37}NO_9S_3$ requires: C, 61.6; H, 4.9; N, 1.85; S, 12.65%). δ 1.39 (s, 3H, CH_3), 2.29, 2.37 (2×d, J=14.0 Hz, 2H, CCH_2C=C), 2.64, 3.13 (2×t, J=8.2 Hz, 4H, CH_2CH_2N), 3.49 (s, 2H, NCH_2C=C), 4.15, 4.53 (2×d, J=8.9 Hz, 2H, CH_2O), 4.82, 4.95 (2×s, 2H, CH_2=C) and 6.75–7.86 (m, 22H, ArH). *m/z* (%) 759 (M^+, 0.2), 224 (31), 141 (23), 133 (100), 105 (55), 78 (17), 77 (67) and 51 (18).

12t. Colourless needles from *n*-hexane/ether, mp 48–49°C. (Found: C, 67.1; H, 5.7; N, 7.05; S, 10.0. $C_{35}H_{35}N_3O_4S_2$ requires: C, 67.15; H, 5.65; N, 6.7; S, 10.25%). δ 1.14 (s, 3H, CH_3), 2.12, 2.26 (2×d, J=14.2 Hz, 2H, CCH_2C=C), 2.84, 3.34 (2×m, 4H, CH_2CH_2N), 3.41 (d, J=15.0 Hz, 1H, NCH_2C=C), 3.45 (d, J=10.2 Hz, 1H, CH_2NAr), 3.61 (d, J=15.0 Hz, 1H, NCH_2C=C), 3.99 (d, J=10.2 Hz, 1H, CH_2NAr), 4.61, 4.92 (2×s, 2H, CH_2=C), 6.86–7.84 (m, 19H, ArH) and 8.20 (br. s, 1H, NH). *m/z* (%) 625 (M^+, 7), 484 (19), 356 (17), 355 (38), 354 (31), 272 (39), 213 (15), 184 (21), 149 (20), 144 (27), 141 (20), 132 (26), 131 (27), 130 (100), 83 (16), 77 (41), 69 (16), 57 (35), 55 (22), 43 (19) and 41 (19).

12u. Pale yellow oil. (Found: C, 71.6; H, 6.0; N, 5.9; S, 6.5. $C_{29}H_{30}N_2O_3S$ requires: C, 71.6; H, 6.2; N, 5.75; S, 6.6%). δ 1.21 (s, 3H, CH_3), 2.32, 2.36 (2×d, J=14.1 Hz, 2H, CCH_2C=C), 2.87, 3.30 (2×m, 4H, CH_2CH_2N), 3.45, 3.54 (2×d, J=15.5 Hz, 2H, NCH_2C=C), 4.12, 4.51 (2×d, J= 8.8 Hz, 2H, CH_2O), 4.81, 5.03 (2×s, 2H, CH_2=C), 6.75–7.79 (m, 14H, ArH) and 8.10 (br. s, 1H, NH). *m/z* (%) 486 (M^+, 11), 210 (18), 187 (18), 141 (16), 133 (30), 131 (26), 130 (100), 105 (17), 103 (11), 77 (31), 71 (14), 57 (14), 55 (13), 43 (13) and 41 (13).

1.10. Cyclisation-anion capture product 15

A solution of **2a** (0.5 mmol) in THF (5 mL) at −78°C was treated with freshly prepared organocuprate[12] (0.5 mmol) and the mixture stirred at the same temperature for 1 h. Water was added and the organic phase separated, dried (Na_2SO_4) and evaporated in vacuo. The residue was

dissolved in toluene (7 mL) containing $Pd_2(dba)_3$ (11.2 mg, 0.025 mmol), tri-(2-furylphosphine (11.6 mg, 0.10 mmol) and sulfonamide **10b** (207 mg, 0.5 mmol) and the resulting mixture boiled under relfux for 2 h. After the usual work-up and purification (above), **15** (186 mg, 68%) was isolated as a colourless oil. (Found: C, 60.25; H, 5.2; N, 4.9; S, 11.4. $C_{28}H_{30}N_2O_6S_2$ requires: C, 60.6; H, 5.45; N, 5.05; S, 11.55%). δ 1.08 (s, 3H, CH_3C), 2.14 (m, 2H, $CCH_2C{=}C$), 3.46 (d, J=10.4 Hz, 1H, CH_2NAr), 3.52 (m, 1H, $NCH_2C{=}C$), 3.65 (s, 3H, CH_3O), 3.70–3.99 (m, 2H, CH_2CO, 1H of $NCH_2C{=}C$ and 1H of CH_2NAr), 5.31 (m, 2H, CH=CH) and 6.93–7.84 (m, 14H, ArH). *m/z* (%) 554 (M^+, 3), 273 (26), 272 (100), 141 (33), 132 (31), 131 (17), 130 (27) and 77 (46).

Acknowledgements

We thank the EPSRC, the Spanish Government (MEC), the E. U. Human Capital and Mobility Scheme and Leeds University for support.

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