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Palladium Catalysed Tandem Cyclisation–Anion Capture. Part 5:[1] Cascade Hydrostannylation-bis-cyclisation-intramolecular Anion Capture. Synthesis of Bridged- and Spiro-Cyclic Small and Macrocyclic Heterocycles

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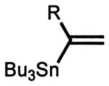
Abstract—A series of *O*- and *N*-α,ω-enyne derivatives of 2-iodoarylethers and 2-iodoarylamides undergo palladium catalysed cascade hydrostannylation of the ω-alkyne moiety at 0–25°C followed by bis-cyclisation at 100–110°C terminating in intramolecular sp^3–sp^2 Stille coupling. These cascades provide a wide range of 5/6 and 5/12–17 membered bicyclic spiro- and bridged-ring heterocycles. © 2000 Elsevier Science Ltd. All rights reserved.

The utility and mildness of Stille coupling reaction are evidenced by their wide application in organic synthesis.[2] Major factors influencing the choice of Stille coupling protocols are: (a) the organotin(IV) coupling partners are air- and moisture-stable and (b) the coupling processes tolerate a wide range of functional groups. Intramolecular versions of this coupling reaction have been utilised to prepare a variety of ring sizes, from four- and five-membered to medium-size rings[2] and macrocyclic natural products.[2] Following the pioneering work of Stille, Hegedus and Hirama in the construction of macrocyclic natural products[3,4] many examples have been reported in the literature employing sp^2–sp^2, sp–sp^2 or allylic sp^3–sp^2 Stille coupling reactions.[2–5] The first macrocycle formation via sp^3–sp^2 Stille coupling reactions, reported by us,[6] were developed as part of an ongoing survey and extension of our cascade cyclisation–anion capture methodology.[7] Our extensive studies have shown that anion capture is invariably slower than cyclisation when 3–7 membered ring are being constructed. These cascade processes are ideal templates to explore the sp^3–sp^2 Stille coupling and its successful implementation via palladium catalysed cascade cyclisation–anion capture is reported herein.

The facile Pd(0) catalysed hydrostannylation of alkynes offered the possibility of a Pd(0) catalysed cascade process in which cyclisation–anion capture occurs intramolecularly. Moreover, it has been established that excellent regioselectivity in the hydrostannylation of terminal alkynes can be achieved by the incorporation of a proximate (β- or γ-) heteroatom.[8] Bis-cyclisation process involving creation of two 5–7 membered rings were explored prior to macrocyclisation studies. In these small ring forming cascade reactions it is essential to generate the α-vinylstannane **1** since it is sterically impossible for the β-vinylstannane **2** to undergo intramolecular anion capture.



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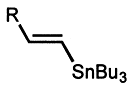

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A series of enynes **4a**–**g**, prepared as outlined in Scheme 1, was allowed to react with tributyltin hydride (1 equiv.) in toluene at 0–25°C over 1 h in the presence of 10 mol% palladium acetate and 20 mol% triphenylphosphine at which time hydrostannylation was judged complete by ^1H NMR or TLC monitoring.

Enynes **4a**, **4b** and **4e** underwent regiospecific hydrostannylation to afford the α-vinylstannanes **6a**, **6b** and **6e**, respectively, as the sole products (Scheme 2), whilst **4c** gave a 3:1 mixture of **6c** and the (*E*)-β-vinylstannane. Enyne **4d** afforded a 1:1 mixture of the α-vinylstannane **6d** and the β-regioisomer. A complex mixture of products was obtained in the case of **4f** and **4g** with only traces of the desired organostannane **6** (Scheme 2).

When the conversion of **4a**–**e** to stannanes **6a**–**e** was judged

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Keywords: cascade reactions; Pd catalysis; hydrostannylation; Stille coupling; cyclisation.

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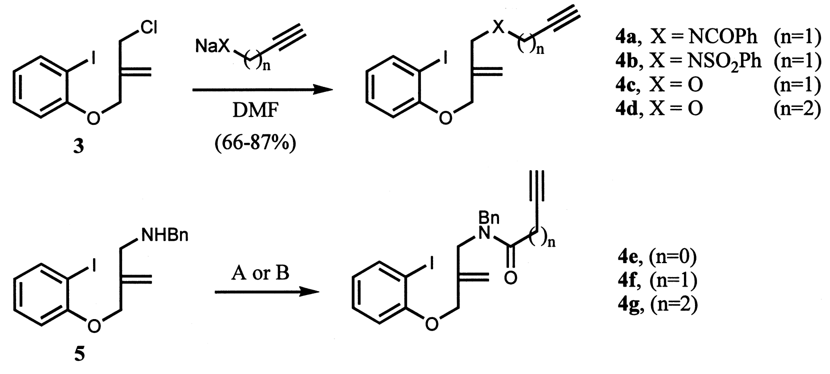
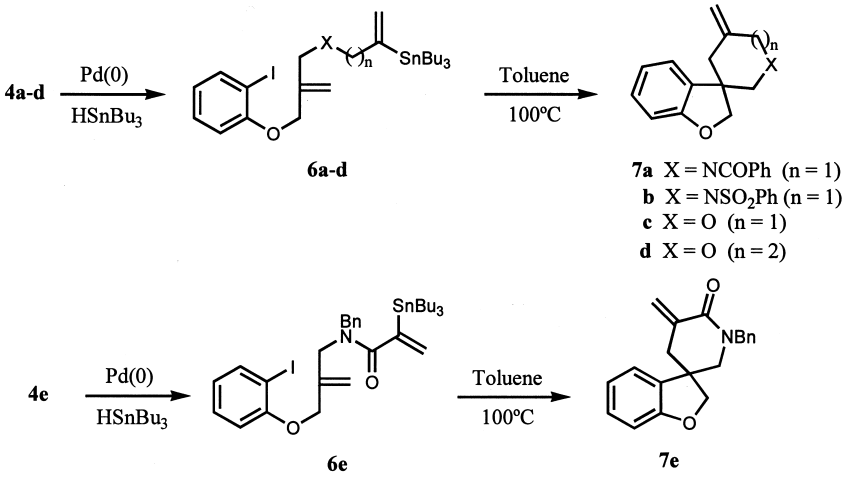


Scheme 1. (A) Propiolic anhydride, EtO_2, rt (n=0, 98%). (B) DCC, THF, $HC\equiv C(CH_2)_nCO_2H$ (n=1 and 2, 45 and 75%).



Scheme 2.

Table 1. Synthesis of spirocycles **7** (reactions were carried out for 0.1 M solutions of **4** in toluene)

Entry	4	Reaction time[a] (h)	Product	Yield (%)[b]
1	**4a**	16	**7a**	67
2	**4b**	16	**7b**	70
3	**4c**	16	**7c**	53
4	**4d**	20	**7d**	0[c]
5	**4e**	16	**7e**	56

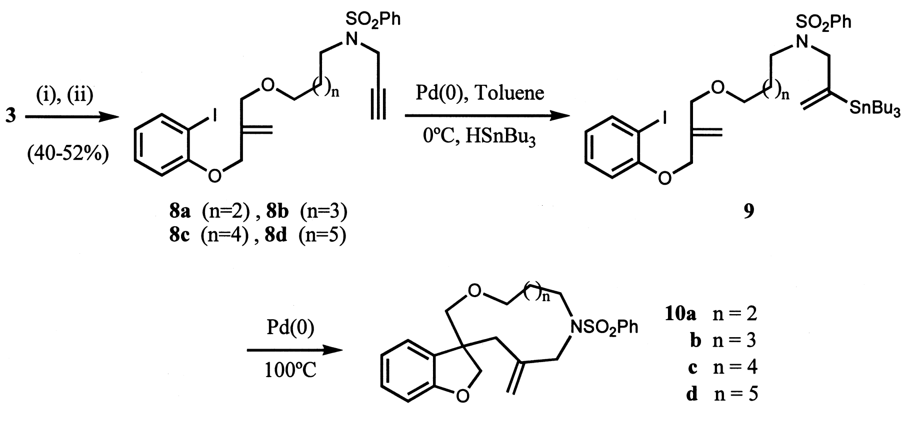
[a] For the conversion of stannanes **6** to spirocycles **7**.

[b] Isolated yields, after purification by column chromatography (SiO_2), based on starting material **4**.

[c] This reaction was also repeated at higher dilution (1.6×10^{-2} M).

complete the temperature of the reaction mixture was raised to 100°C (oil bath) which initiated the bis-cyclisation–anion capture process yielding spirocycles **7** (Scheme 2 and Table 1) via 5-*exo-trig* cyclisation followed by sp^3–sp^2 intramolecular Stille coupling.

Compound **4d**, the precursor of the 5/7-spirocycle, failed to afford the desired product giving only a mixture of decomposition products. It would appear that the failure of this cascade is due to a slow rate of intramolecular anion capture arising from an unfavourable 8-membered palladacycle intermediate. The lower yield of **7c** reflects the 3:1 ratio



Scheme 3. Reagents: (i) $HOCH_2(CH_2)_nCH_2OH$, NaH, DMF, 0°C. (ii) $HC\equiv CCH_2NHSO_2Ph$, ADDP, PBu_3, toluene, 25°C.

Table 2. Synthesis of spiro-macrocycles **10**

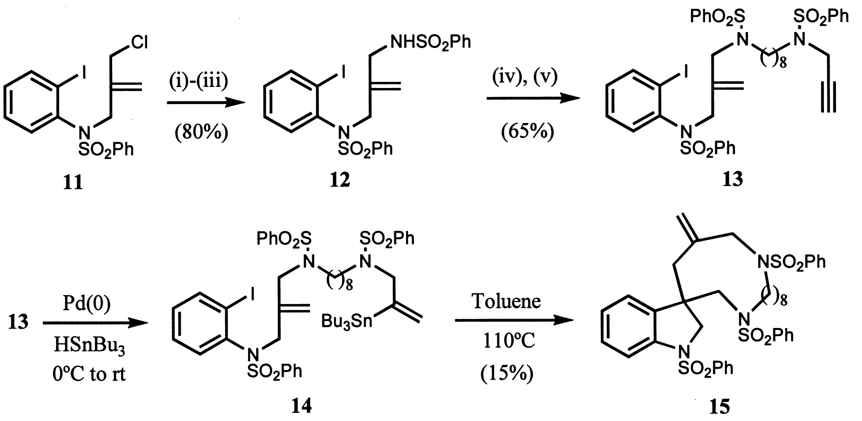
Entry	*n*	Product	Ring size	Yield (%)[a]
1	2	**10a**	5/11	Not observed
2	3	**10b**	5/12	39
3	3	**10b**	5/12	59
4	4	**10c**	5/13	44
5	5	**10d**	5/14	53

[a] Isolated yields, after purification by column chromatography, based on **8**.

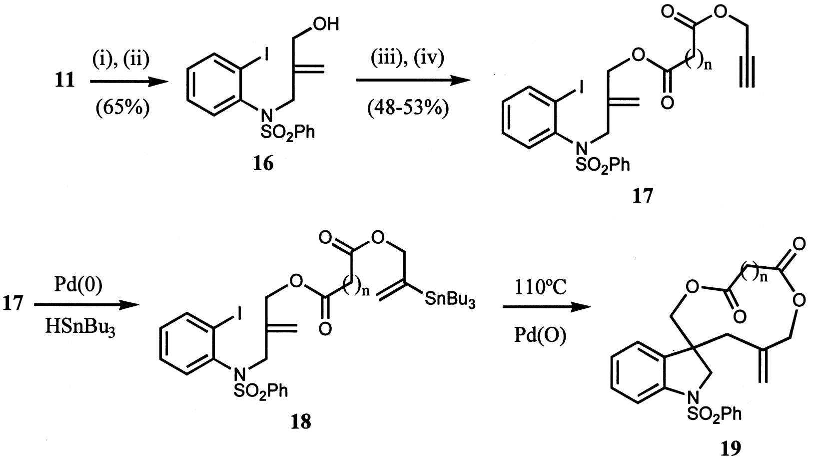
of vinylstannanes and the inability of β-vinylstannanes to participate in intramolecular anion capture, whilst the somewhat lower yield of **7e** probably reflects the sensitivity of acrylamide derivatives to polymerisation (Table 1, entry 5).

The foregoing results encouraged us to explore macrocyclisation cascades which terminate in sp^3–sp^2 Stille coupling. Initially, a series of enynes **8** (Scheme 3) were prepared as precursors for macrocyclisation studies.

Enynes **8a–d** were synthesised using modified Mitsunobu conditions[9] with 1,1′-(azodicarbonyl)-dipiperidine (ADDP) as the coupling reagent. 0.05 M solutions of **8a–d** in toluene were submitted to the Pd(0) catalysed hydrostannylation conditions (0–25°C, 1 h) giving exclusively the corresponding α-vinylstannanes **9a–d** as demonstrated by ^{1}H NMR and TLC monitoring. The vinylstannane solutions were diluted to provide 5×10^{-3} M solutions in toluene and then heated at 100°C (bath temperature) for 24 h to give the macrocyclic spirocycles **10** in moderate yield (Table 2). The 11-membered spirocycle was not formed using this methodology (Table 2, entry 1). The yield of **10b** was raised from 39 to 59% (Table 2, entries 2 and 3) by syringe pump



Scheme 4. Reagents: (i) Potassium phthalimide, DMF. (ii) Hydrazine, MeOH. (iii) $PhSO_2Cl$, Et_3N. (iv) NaH, DMF, $Br(CH_2)_8Br$. (v) $HC{\equiv}CCH_2NNaSO_2Ph$, DMF.

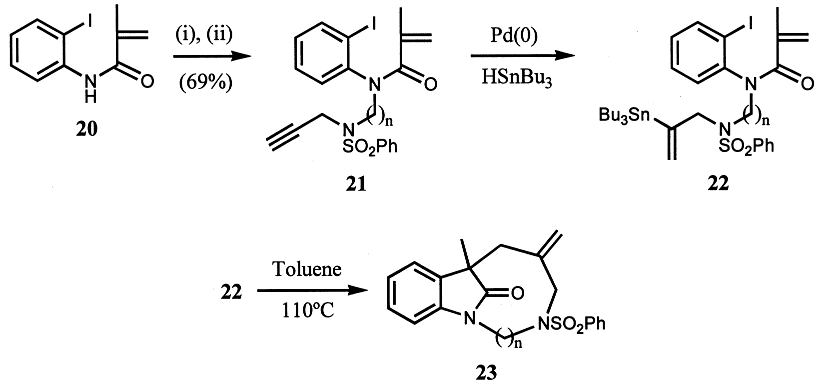


Scheme 5. Reagents: (i) NaOAc, DMF. (ii) MeOH, 3 N HCl. (iii) $HO_2C(CH_2)_nCO_2H$, DCC, DMAP, DMF. (iv) PPh_3, ADDP, $HC{\equiv}CCH_2OH$.

Table 3. Synthesis of spiro-macrocycles **19**

Entry	*n*	Product	Macrocyclic ring size *N*	Yield (%)[a]	%[b]
1	2	**19a**	11	38	51
2	3	**19b**	12	53	71
3	4	**19c**	13	52	70
4	5	**19d**	14	52	70
5	6	**19e**	15	53	71
6	7	**19f**	16	50	67
7	8	**19g**	17	53	71

[a] Based on compound **17**.
[b] Yields in brackets are corrected for the α-/β-vinylstannane ratio.



Scheme 6. Reagents: (i) NaH, DMF, $Br(CH_2)_nBr$. (ii) DMF, $HC{\equiv}CCH_2NNaSO_2Ph$.

Table 4. Synthesis of bridged-ring macrocycles **23**

Entry	*n*	Ring size	Additive (mol equiv.)	Reaction time[a] (h)	Product	Yield (%)[b]
1	6	13	LiCl (1.0)	2	**23a**	51
2	6	13	CuI (0.2)	2	**23a**	34
3	6	13	Et_4NCl (1.0)	16	**23a**	29
4	6	13	Ag_2CO_3 (0.5)	2	**23a**	45
5	7	14	LiCl (1.0)	4	**23b**	30
6	7	14	Ag_2CO_3 (0.5)	4	**23b**	30
7	8	15	LiCl (1.0)	2	**23c**	39
8	8	15	Ag_2CO_3 (0.5)	2	**23c**	37
9	10	17	Ag_2CO_3 (0.5)	4	**23d**	37

[a] For conversion of stannanes **22** to bridges-ring macrocycles **23**.

[b] Based on compound **21**, isolated after purification by column chromatography (SiO_2).

addition of a solution of **9b** (0.05 M solution in toluene) to a mixture containing an additional charge of catalyst (10 mol% palladium acetate, 20 mol% PPh_3) in toluene at 100°C over 20 h.

A second type of spirocycle precursor **13** was prepared based on 2-iodoaniline (Scheme 4). Hydrostannylation (0–25°C, 1 h) afforded the α-vinylstannane **14** which, by cyclisation–anion capture, gave 5/15-spiromacrocycle **15** in only 15% yield. This latter yield was achieved using 5 mol% of Pd_2dba_3 and 20 mol% of tri(2-furyl)phosphine as catalyst[10] in a 5×10^{-3} M solution of **14** in toluene at 110°C (Scheme 4).

Several additives (LiI, Et_4NCl, Ag_2CO_3 and Tl_2CO_3) and catalysts [$Pd(OAc)_2/PPh_3$ and $(Ph_3P)_4Pd$] were evaluated but failed to improve on the 15% yield. It was observed that increasing the amount of palladium catalyst increased the yield [for example, a 23% yield was obtained employing 10 mol% of Pd_2dba_3 and 40 mol% of tri(2-furyl)phosphine], suggesting the product macrocycle **15** may be sequestering the palladium.[11]

A third series of macrocyclic spirocycles **19** has been obtained in better yield (Scheme 5 and Table 3). The starting materials **17**, prepared as outlined in Scheme 5, were submitted to the catalysed hydrostannylation reaction (toluene, 0–25°C, 1 h) in the presence of 5 mol% Pd_2dba_3 and 20 mol% tri(2-furyl)phosphine to afford 2:1 mixtures of α- and β-vinylstannanes **18**. Bis-cyclisation proceeded smoothly at 110°C (5×10^{-3} M solutions in toluene) over 12 h furnishing 5/N-macrocycles **19**. With these substrates it was also possible to obtain a medium size spirocyclic product **19a** (Table 3, entry 1) in moderate yield.

A fourth, and final series of bridged-ring forming macrocyclisation employing **22**, obtained as outlined in Scheme 6, afforded the desired products **23** (Table 4). Monitoring the hydrostannylation reaction (0.05 M solutions in toluene at 0–25°C over 1 h) by ^1H NMR indicated only the α-vinylstannane was formed. In these cases the preferred catalyst system comprises 10 mol% Pd_2dba_3/80 mol% tri(2-furyl)phosphine and an additive depending on the size of macrocycle (Scheme 6 and Table 4). The bis-cyclisations employed 5×10^{-3} M solutions in toluene and were completed in 2–4 h at 110°C.

In this last series a variety of reactions conditions were evaluated, which demonstrated the superior effectiveness of lithium chloride[11] and silver carbonate,[12] when compared to Cu(I)[13] and tetraalkylammonium salts[11,13] which did not improve the yields (see Table 4).

In summary, we have demonstrated the synthetic potential of hydrostannylation-intramolecular anion capture cascades for the preparation of both small and large bridged- and spirocyclic-rings.

Experimental

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec 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 with tetramethylsilane as internal standard. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. 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). Anhydrous DMF was commercially available (Aldrich), THF and toluene were sodium dried under a nitrogen atmosphere and *n*-hexane was distilled prior to use. Petroleum ether refers to the fraction with boiling point 40–60°C.

General method for 4a–d

The N-protected propargylamine or propargyl alcohol (10 mmol) in dry DMF (10 ml) was added over 0.25 h to a stirred suspension of NaH (0.400 g, 10 mmol, 60% dispersion in mineral oil) in dry DMF (5 ml) under a nitrogen atmosphere at 0°C. The mixture was allowed to warm to room temperature and stirred for a further 0.5 h, then cooled to 0°C and the allyl chloride **3** (2.5 g, 8.1 mmol) in DMF (10 ml) added dropwise over 0.5 h. After stirring for a further 16 h at room temperature the solvent was removed in vacuo, the residue dissolved in ether (70 ml), washed with water (30 ml), brine (30 ml) and dried ($MgSO_4$). Filtration and evaporation of the solvent followed by column chromatography of the residue, eluting with mixtures of ether/petroleum ether, afforded the **products 4a–d** (66–87%).

4a. Colourless needles (87%), mp 45–46°C from ether/petroleum ether. (Found: C, 55.9; H, 3.9; N, 3.5. $C_{20}H_{18}INO_2$ requires: C, 55.7; H, 4.2; N, 3.3%); δ 2.29 (m, 1H, $C{\equiv}CH$), 4.62–4.06 (m, 6H, OCH_2 and 2×NCH_2), 5.57–5.27 (m, 2H, $C{=}CH_2$), 6.71 (t, *J*=7.0 Hz, 1H, ArH), 6.82 (m, 1H, ArH), 7.60–7.30 (m, 6H, ArH) and 7.78 (m, 1H, ArH); *m/z* (%) 432 (M^++1, 5), 401 (19), 392 (16), 212 (100), 105 (81) and 77 (45).

4b. Colourless needles (85%), mp 91–93°C from ether/petroleum ether. (Found: C, 48.9; H, 3.8; N, 2.9. $C_{19}H_{18}INO_3S$ requires: C, 48.9; H, 3.9; N, 3.0%); δ 1.98 (t, *J*=2.0 Hz, 1H, $C{\equiv}CH$), 3.98 (s, 2H, $C{=}CH_2N$), 4.15 (d, *J*=2.0 Hz, 2H, $C{\equiv}CCH_2$), 4.57 (s, 2H, CH_2O), 5.35, 5.65 (2×s, 2H, $C{=}CH_2$), 6.79 (m, 2H, ArH), 7.26–7.53 (m, 4H, ArH), 7.83 (dd, *J*=9 and 2.0 Hz, 1H, ArH) and 7.87 (m, 2H, ArH); *m/z* (%) 467 (M^+, 7), 326 (21), 248 (51), 141 (47), 106 (60) and 77 (100).

4c. Colourless oil (85%). (Found: C, 47.4; H, 3.9. $C_{13}H_{13}IO_2$ requires: C, 47.6; H, 3.9%); δ 2.45 (t, *J*=2.0 Hz, 1H, $C{\equiv}CH$), 4.23, 4.20 [2s, 4H, $(CH_2)_2O$], 4.61 (s, 2H, $ArOC\mathit{H}_2$), 5.35, 5.49, (s, 2H, $C{=}CH_2$), 6.72 (t, *J*=8.0 Hz, 1H, ArH), 6.82 (d, *J*=8.0 Hz, 1H, ArH), 7.29 (t, *J*=8.0 Hz, 1H, ArH) and 7.78 (d, *J*=8.0 Hz, 1H, ArH); *m/z* (%) (FAB) 328 (M^+, 36), 273 (14), 202 (13), 146 (100) and 131 (47).

4d. Colourless oil (66%). (HRMS found: 342.0118. $C_{15}H_{15}IO_2$ requires: 342.0117); δ 1.97 (t, *J*=2.0 Hz, 1H, $C{\equiv}CH$), 2.49 (m, 2H, $C{\equiv}CCH_2$), 3.60 (t, *J*=7.0 Hz, 2H, $CH_2C\mathit{H}_2O$), 4.18 (s, 2H, $OCH_2C{=}C$), 4.60 (s, 2H, $ArOC\mathit{H}_2$), 5.32, 5.45 (s, 2H, $C{=}CH_2$), 6.72 (t, *J*=8.0 Hz, 1H, ArH), 6.83 (d, *J*=8.0 Hz, 1H, ArH), 7.30 (t, *J*=8.0 Hz, 1H, ArH) and 7.77 (d, *J*=8.0 Hz, 1H, ArH); *m/z* (%) 342 (M^+, 32), 272 (14), 220 (55), 92 (95), 77 (84) and 53 (100).

Synthesis of compound 4e

Propiolic anhydride[14] (0.35 g, 2.9 mmol) was added over 0.25 h to a stirred solution of amine **5** (1.1 g, 2.9 mmol) in ether (40 ml) at 0°C and the mixture stirred for 16 h at room temperature. The solvent was removed and the residue purified by column chromatography eluting with 1:1 (v/v) ether:petroleum ether to afford the *product* (1.29 g, 98%) as colourless oil. (Found: C, 55.5; H, 4.1; N, 3.3. $C_{20}H_{18}INO_2$ requires: C, 55.7; H, 4.2; N, 3.3%); δ (mixture of rotomers) 3.05, 3.17 (2×s, 1H, $C{\equiv}CH$), 4.09, 4.31 (2×s, 2H, CH_2N), 4.49, 4.53 (2×s, 2H, $C\mathit{H}_2OAr$), 4.63, 4.80 (2×s, 2H, $NC\mathit{H}_2Ph$), 5.13, 5.21, 5.53, 5.55 (4×s, 2H, $C{=}CH_2$), 6.70–6.80 (m, 2H, ArH), 7.24–7.37 (m, 6H, ArH) and 7.35–7.78 (m, 1H, ArH); *m/z* (%) 431 (M^+, 6), 340 (43), 212 (94), 131 (62) and 91 (100).

General method for 4f and 4g

A mixture of amine **5** (1.2 g, 3.2 mmol), DCC (0.65 g, 3.2 mmol) and the appropriate carboxylic acid (3.2 mmol) in THF (40 ml) was stirred at 20°C for 16 h. The solvent was then removed in vacuo, the residue dissolved in ether (50 ml) and washed successively with water (2×40 ml) and brine (40 ml) and dried ($MgSO_4$). Filtration followed by evaporation of the filtrate and column chromatography of the residue eluting with mixtures of ether:petroleum ether afforded the products.

4f. Colourless oil (45%). (Found: C, 56.9; H, 4.4; N, 3.2. $C_{21}H_{20}INO_2$ requires: C, 56.7; H, 4.5; N, 3.2%); δ (mixture of rotomers) 2.26 (t, *J*=3.0 Hz, 1H, $C{\equiv}CH$), 3.66, 4.02 (2×s, 2H, $C{\equiv}CCH_2N$), 4.21, 4.49 (2×s, 2H, $C{=}CCH_2N$), 4.49 (m, 2H, $C\mathit{H}_2OAr$), 4.66, 5.19 (2×br s, 2H, $NC\mathit{H}_2Ph$), 5.19 (s, 1H, $C{=}CH_2$), 5.45–5.53 (m, 1H, $C{=}CH_2$), 6.72–6.80 (m, 2H, ArH), 7.18–7.38 (m, 6H, ArH) and 7.74–7.79 (m, 1H, ArH); *m/z* (%) 445 (M^+, 1), 220 (11), 209 (41), 127 (64) and 91 (100).

4g. Colourless oil (41%). (Found: C, 57.7; H, 5.0; N, 3.1. $C_{22}H_{22}INO_2$ requires: C, 57.6; H, 4.8; N, 3.1 %); δ (mixture of rotomers) 1.94 (s, 1H, $C{\equiv}CH$), 2.62 (m, 4H, CH_2CH_2CO), 4.07, 4.20 (2×s, 2H, $C{=}CCH_2N$), 4.49 (m, 2H, $C\mathit{H}_2OAr$), 4.60 (m, 2H, $NC\mathit{H}_2Ph$), 5.14, 5.17 (2×s, 1H, $C{=}CH_2$), 5.42, 5.52 (2×s, 1H, $C{=}CH_2$) and 6.71–7.78 (m, 9H, ArH); *m/z* (%) 459 (M^+, 4), 368 (3), 240 (100), 186 (44) and 91 (100).

General procedure for the synthesis of small polycycles by cyclisation–anion capture of 4a–c and 4e

A mixture of palladium acetate (0.011 g, 0.05 mmol), triphenylphosphine (0.026 g, 0.1 mmol) and 4 (0.5 mmol) in toluene (5 ml) was stirred at 0°C under nitrogen whilst tributyltin hydride (0.160 g, 0.5 mmol, 0.148 ml) was added dropwise over 5 min. The reaction was then allowed to warm to room temperature over 1 h before being heated at 100°C for 16 h. After cooling to room temperature, a saturated aqueous solution of potassium fluoride (5 ml) was added and the mixture stirred for 1 h, filtered, the organic phase dried (Na_2SO_4), filtered and the filtrate evaporated. The residue was purified by column chromatography (SiO_2) eluting with mixtures of ether:petroleum ether.

Spirocycle 7a. Colourless needles from petroleum ether/ether (67%), mp 85–86°C. (HRMS found: 305.1368. $C_{20}H_{19}NO_2$ requires: 305.1371); δ 2.49, 2.64 (2×d, J=8.0 Hz, 2H, $CH_2C{=}C$), 3.58, 3.80 (2×m, 2H, CH_2N), 4.21 (br s, 2H, $ArOCH_2$), 4.21, 4.61 (2×br s, 2H, $C{=}CCH_2N$), 4.94, 5.20 (2×br s, 2H, $C{=}CH_2$) and 6.75–7.77 (m, 9H, ArH); *m/z* (%) 305 (M^+, 37), 200 (31), 174 (61), 131 (42), 105 (100) and 77 (86).

Spirocycle 7b. Colourless needles from petroleum ether/ether (70%), mp 104–105°C. (Found: C, 66.1; H, 5.7; N, 4.1. $C_{19}H_{19}NO_3S$ requires: C, 66.5; H, 5.6; N, 4.1%); δ 2.38 (s, 2H, $CH_2C{=}C$), 3.05, 3.68 (2×d, J=12.0 Hz, 2H, CH_2N), 3.56, 4.15 (2×d, J=11.0 Hz, 2H, $C{=}CCH_2N$), 4.22, 4.54 (2×d, J=8.0 Hz, 2H, $ArOC\mathit{H}_2$), 4.45, 5.10 (2×s, 2H, $C{=}CH_2$), 6.85 (t, J=9.0 Hz, 2H, ArH), 7.01 (dd, J=7 and 2.0 Hz, 1H, ArH), 7.18 (dt, J=8 and 3.0 Hz, ArH) and 7.55–7.80 (m, 5H, ArH); *m/z* (%) 341 (M^+, 11), 200 (100), 170 (32), 131 (59) and 77 (58).

Spirocycle 7c. Colourless oil (53%). (Found: C, 77.3; H, 7.1. $C_{13}H_{14}O_2$ requires: C, 77.3; H, 7.0%); δ 2.45, 2.66 (2×d, J=13.0 Hz, 2H, $CH_2C{=}C$), 3.62, 3.77 (2×d, J=11.0 Hz, 2H, CCH_2O), 4.05, 4.19 (2×d, J=12.0 Hz, 2H, $C{=}CCH_2O$), 4.25, 4.54 (2×d, J=9.0 Hz, 2H, $ArOC\mathit{H}_2$), 4.88, 4.96 (2×s, 2H, $C{=}CH_2$), 6.81 (d, J=8.0 Hz, 1H, ArH), 6.88 (t, J=7.0 Hz, 1H, ArH) and 7.14–7.20 (m, 2H, ArH); *m/z* (%) 202 (M^+, 100), 170 (63) and 131 (89).

Spirocycle 7e. Colourless oil (56%). (HRMS found: 305.1418. $C_{20}H_{19}NO_2$ requires 305.1416); δ 2.75, 2.99 (2×d, J=15.0 Hz, 2H, $CH_2C{=}C$), 3.28, 3.55 (2d, J=12.0 Hz, 2H, CH_2NCO), 4.19, 4.25 (2×d, J=9.0 Hz, 2H, $NC\mathit{H}_2Ph$), 4.50, 4.85 (2×d, J=14.0 Hz, 2H, $ArOC\mathit{H}_2$), 5.44, 6.45 (2×s, 2H, $C{=}CH_2$), 6.78 (d, J=8.0 Hz, 1H, ArH), 7.07 (d, J=7.0 Hz, 1H, ArH), 7.17 (t, J=8.0 Hz, 1H, ArH) and 7.28 (m, 5H, ArH); *m/z* (%) 305 (M^+, 98), 186 (100), 158 (51), 131 (49), 118 (85) and 91 (86).

Preparation of 8a–d

The diol (2 mmol) in DMF (15 ml) was added over 0.5 h to a stirred suspension of NaH (0.08 g, 2 mmol, 60% in mineral oil) in DMF (5 ml) under a nitrogen atmosphere at 0°C. The mixture was allowed to warm to room temperature and stirred for 0.5 h, then cooled to 0°C followed by addition of allyl chloride **3** (0.61 g, 2 mmol) in DMF (15 ml) dropwise over 0.5 h. The resulting mixture was stirred at room temperature for 16 h before removal of the solvent in vacuo. The residue was dissolved in ether, washed with water and brine, dried ($MgSO_4$), filtered and the filtrate evaporated. The residue was purified by column chromatography (SiO_2) eluting with mixtures of ether:petroleum ether to afford the intermediate alcohols which (1 mmol) were added to a stirred solution of tributylphosphine (0.30 g, 1.5 mol), 1,1′-(azodicarbonyl)dipiperidine (ADDP) (0.374 g, 1.5 mmol) and propargylamine (0.08 g, 1.5 mmol) in benzene (20 ml) at 0°C. The mixture was stirred at the same temperature for 10 min and at room temperature for 24 h. The solvent was then removed and the residue purified by column chromatography (SiO_2) eluting with mixtures of ether:petroleum ether to afford **8a–d**.

8a (n=2). Colourless viscous oil (40%). (Found: C, 51.5; H, 4.7; N, 2.6. $C_{23}H_{26}INO_4S$ requires: C, 51.3; H, 4.8; N, 2.6%); δ 1.68 (m, 4H, 2×CH_2), 1.97 (t, J=2.0 Hz, 1H, $C{\equiv}CH$), 3.23 (t, J=6.0 Hz, 2H, CH_2N), 3.48 (t, J=5.0 Hz, 2H, $OC\mathit{H}_2CH_2$), 4.11 (s, 4H, $C{=}CCH_2O$ and $NCH_2C{\equiv}C$), 4.59 (s, 2H, $ArOC\mathit{H}_2$), 5.29, 5.41 (2×s, 2H, $C{=}CH_2$), 6.71 (t, J=8.0 Hz, 1H, ArH), 6.83 (d, J=8.0 Hz, 1H, ArH), 7.26 (m, 1H, ArH), 7.46–7.56 (m, 3H, ArH) and 7.76–7.85 (m, 3H, ArH); *m/z* (%) 539 (M^+, 1), 398 (95), 250 (55), 208 (67), 141 (89), 108 (95), 77 (100) and 55 (83).

8b (n=3). Colourless viscous oil (45%). (Found: C, 52.1; H, 5.1; N, 2.8. $C_{24}H_{28}INO_4S$ requires: C, 52.1; H, 5.1; N, 2.6%); δ 1.39, 1.62 (2×m, 6H, 3×CH_2), 1.97 (t, J=2.0 Hz, 1H, $C{\equiv}CH$), 3.19 (t, J=7.0 Hz, 2H, CH_2N), 3.46 (t, J=6.0 Hz, 2H, $OC\mathit{H}_2CH_2$), 4.13 (m, 4H, $C{=}CCH_2O$ and $NCH_2C{\equiv}C$), 4.60 (s, 2H, $ArOC\mathit{H}_2$), 5.30, 5.43 (2×s, 2H, $C{=}CH_2$), 6.71 (t, J=8.0 Hz, 1H, ArH), 6.84 (d, J=8.0 Hz, 1H, ArH), 7.28 (t, J=8.0 Hz, 1H, ArH), 7.46–7.58 (m, 3H, ArH), 7.77 (dd, J=7 and 1.0 Hz, 1H, ArH) and 7.84 (d, J=8.0 Hz, 2H, ArH); *m/z* (%) 553 (M^+, 1), 412 (19), 208 (27), 141 (58) and 77 (100).

8c (n=4). Colourless viscous oil (47%). (Found: C, 52.9; H, 5.3; N, 2.3. $C_{25}H_{30}INO_4S$ requires: C, 52.9; H, 5.3; N, 2.5%); δ 1.36, 1.55 (2×m, 8H, 4×CH_2), 1.97 (t, J=2.0 Hz, 1H, $C{\equiv}CH$), 3.19 (t, J=7.0 Hz, 2H, CH_2N), 3.45 (t, J=6.0 Hz, 2H, $OC\mathit{H}_2CH_2$), 4.11 (s, 4H, $C{=}CCH_2O$ and $NCH_2C{\equiv}C$), 4.60 (s, 2H, $ArOC\mathit{H}_2$), 5.29, 5.43 (2×s, 2H, $C{=}CH_2$), 6.71 (t, J=7.0 Hz, 1H, ArH), 6.83 (d, J=8.0 Hz, 1H, ArH), 7.28 (m, 1H, ArH), 7.47–7.57 (m, 3H, ArH), 7.77 (dd, J=7 and 1.0 Hz, 1H, ArH) and 7.84 (d, J=7.0 Hz, 2H, ArH); *m/z* (%) 567 (M^+, 4), 426 (43), 348 (56), 208 (86), 141 (91), 131 (50) and 77 (100).

8d (n=5). Colourless viscous oil (52%). (Found: C, 53.9; H, 5.6; N, 2.6. $C_{26}H_{32}INO_4S$ requires: C, 53.8; H, 5.5; N, 2.4%); δ 1.39, 1.61 (2×m, 10H, 5×CH_2), 1.97 (t, J=1.0 Hz, 1H, $C{\equiv}CH$), 3.19 (t, J=7.0 Hz, 2H, CH_2N), 3.46 (t, J=6.0 Hz, 2H, $OC\mathit{H}_2CH_2$), 4.13 (m, 4H, $C{=}CCH_2O$ and $NCH_2C{\equiv}C$), 4.60 (s, 2H, $ArOC\mathit{H}_2$), 5.30, 5.44 (2×s, 2H, $C{=}CH_2$), 6.71 (t, J=8.0 Hz, 1H, ArH), 6.84 (d, J=8.0 Hz, 1H, ArH), 7.27 (t, J=8.0 Hz, 1H, ArH), 7.47–7.57 (m, 3H, ArH), 7.47–7.58 (m, 3H, ArH), 7.77 (d, J=7.0 Hz, 1H, ArH) and 7.84 (d, J=8.0 Hz, 2H, ArH); *m/z* (%) 581 (M^+, 1), 362 (29), 208 (76), 141 (82), 77 (100) and 55 (65).

General procedure for spiro-macrocycles 10b–d

Method A: A mixture of palladium acetate (0.011 g, 0.05 mmol), triphenylphosphine (0.028 g, 0.1 mmol) and aryl iodide **8** (0.5 mmol) in dry toluene (10 ml) was stirred at 0°C under nitrogen whilst tributyltin hydride (0.140 g, 0.5 mmol) was added over 5 min. The reaction mixture was allowed to warm to room temperature over 1 h before being diluted with toluene (90 ml) to an aryl iodide **9** concentration of 5×10^{-3} M and then heated at 100°C for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure and, following workup as described for **7**, the residue was purified by column chromatography (SiO_2) eluting with mixtures of ether:petroleum ether.

Method B: A mixture of palladium acetate (0.011 g, 0.05 mmol), triphenylphosphine (0.028 g, 0.1 mmol) and aryl iodide **8** (0.5 mmol) in dry toluene (10 ml) was stirred at 0°C under nitrogen whilst tributyltin hydride (0.140 g, 0.5 mmol) was added over 5 min. The reaction mixture was allowed to warm to room temperature over 1 h. The mixture containing **9** was taken up into a syringe (10 ml) and added, over 20 h via syringe pump, to a mixture of palladium acetate (0.011 g, 0.05 mmol) and triphenylphosphine (0.028 g, 0.1 mmol) in toluene (90 ml) stirred and heated at 100°C. The mixture was stirred at the same temperature for a further 6 h before the solvent was removed in vacuo, followed by workup as described for Method A.

Spiro-macrocycle 10b (n=3). Obtained by Methods A and B (39 and 59% yield, respectively) as colourless prisms from petroleum ether/ether, mp 140–142°C. (Found: C, 67.4; H, 6.9; N, 3.1. $C_{24}H_{28}NO_4S$ requires: C, 67.6; H, 6.6; N, 3.3%); δ 1.43, 1.80 (m, 6H, $3\times CH_2$), 2.36, 2.92 (2×d, J=16.0 Hz, 2H, $CH_2C{=}C$), 3.04, 3.97 (2×m, 2H, CH_2N), 3.32, 3.47 (2×m, 2H, OCH_2), 3.47, 3.61 (2×d, J=9.0 Hz, 2H, CCH_2O), 3.87, 4.08 (2×d, J=16.0 Hz, 2H, $NCH_2C{=}C$), 4.41, 4.45 (2×d, J=9.0 Hz, 2H, $\mathrm{ArOC}H_2$), 4.79, 5.04 (2×s, 2H, $CH_2{=}C$), 6.79 (d, J=8.0 Hz, 1H, ArH), 6.88 (td, J=7 and 1.0 Hz, 1H, ArH), 7.15 (td, J=6 and 1.0 Hz, 1H, ArH), 7.24 (dd, J=6 and 1.0 Hz, 1H, ArH), 7.48–7.58 (m, 3H, ArH) and 7.80–7.83 (m, 2H, ArH); m/z (%) 427 (M^+, 7), 286 (100), 131 (55) and 77 (36).

Spiro-macrocycle 10c (n=4). Obtained by Method A in 44% yield as colourless prisms from petroleum ether/ether, mp 137–139°C. (Found: C, 68.0; H, 7.0; N, 3.0. $C_{25}H_{31}NO_4S$ requires: C, 68.0; H, 7.0; N, 3.2%); δ 1.43, 1.71 (m, 8H, $4\times CH_2$), 2.40, 2.95 (2×d, J=10.0 Hz, 2H, $CH_2C{=}C$), 2.99, 3.42 (2×m, 2H, CH_2N), 3.42 (m, 2H, OCH_2), 3.42, 3.62 (2×d, J=9.0 Hz, 2H, CCH_2O), 3.42, 3.87 (2×d, J=15.0 Hz, 2H, $NCH_2C{=}C$), 4.42 (s, 2H, $\mathrm{ArOC}H_2$), 4.77, 5.05 (2×s, 2H, $CH_2{=}C$), 6.79 (d, J=8.0 Hz, 1H, ArH), 6.86 (t, J=7.0 Hz, 1H, ArH), 7.15 (t, J=8.0 Hz, 1H, ArH), 7.25 (d, J=8.0 Hz, 1H, ArH), 7.48–7.57 (m, 3H, ArH) and 7.78–7.81 (m, 2H, ArH); m/z (%) 441 (M^+, 12), 300 (100), 178 (8), 131 (16) and 77 (8).

Spiro-macrocycle 10d (n=5). Obtained by Method A in 53% yield as viscous colourless oil. (Found: C, 68.3; H, 7.3; N, 3.1. $C_{26}H_{33}NO_4S$ requires: C, 68.6; H, 7.3; N, 3.1%); δ 1.26–1.66 (m, 10H, $5\times CH_2$), 2.39, 2.89 (2×d, J=17.0 Hz, 2H, $CH_2C{=}C$), 3.10, 3.45 (2×m, 4H, CH_2N and OCH_2), 3.44, 3.61 (2×d, J=8.0 Hz, 2H, CCH_2O), 3.65, 3.75 (2×d, J=16.0 Hz, 2H, $NCH_2C{=}C$), 4.41, 4.47 (2×d, J=9.0 Hz, 2H, $ArOCH_2$), 4.74, 5.06 (2×s, 2H, $CH_2{=}C$), 6.78 (d, J=8.0 Hz, 1H, ArH), 6.86 (t, J=7.0 Hz, 1H, ArH), 7.15 (t, J=8.0 Hz, 1H, ArH), 7.22 (d, J=8.0 Hz, 1H, ArH), 7.47–7.56 (m, 3H, ArH) and 7.80 (d, J=7.0 Hz, 2H, ArH); m/z (%) 455 (M^+, 7), 314 (100), 170 (29), 131 (48), 77 (8) and 55 (23).

Bis-sulfonamide (12). Allylic chloride **11** (448 mg, 1 mmol), [readily available by reaction of sodium *N*-(2-iodophenyl)phenylsulfonamide with 2-chloromethyl-3-chloro-1-propene in DMF over 24 h], was stirred and reacted with potassium phthalimide (222 mg, 1.2 mmol) in dry DMF (8 ml) at 90°C for 2 h. The DMF was then removed under reduced pressure and dichloromethane (10 ml) added. The organic layer was separated and washed with water (10 ml), dried (Na_2SO_4), filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in methanol (10 ml) and treated with hydrazine monohydrate (150 μl, 3 mmol). The resulting mixture was boiled under reflux for 1 h, cooled to 0°C and filtered. The filtrate was evaporated, the crude amine dissolved in dichloromethane (10 ml) and triethylamine (209 μl, 1.5 mmol) and phenylsulfonyl chloride (0.212 g, 1.2 mmol) added and stirring continued at room temperature for 4 h. The solvent was then evaporated under reduced pressure and the residue purified by column chromatography (SiO_2) eluting with 1:1 (v/v) *n*-hexane:ether furnishing bis-sulfonamide **12** (0.454 g, 80%) as colourless needles from *n*-hexane/ether, mp 99–100°C. (Found: C, 46.8; H, 3.6; N, 4.8; S, 11.3. $C_{22}H_{21}IN_2O_4S_2$ requires: C, 46.5; H, 3.7; N, 4.45; S, 11.3%); δ 3.74–4.02 (m with d at 3.77, J=14.3 Hz, 3H, CH_2NH and 1H of $\mathrm{C}H_2\mathrm{NAr}$), 4.20 (d, J=14.3 Hz, 1H, $\mathrm{C}H_2\mathrm{NAr}$), 4.68, 5.03 (2×s, 2H, $CH_2{=}C$), 5.15 (m, 1H, NH), 6.81–8.00 (m, 14H, ArH); m/z (%) 568 (M^+, 3), 285 (33), 159 (32), 141 (43), 130 (41) and 77 (86).

Alkyne 14 (n=8). Sodium hydride (0.288 g, 1.2 mmol, 60% dispersion in mineral oil) was added to a stirred solution of **12** (3.41 g, 6 mmol) in dry DMF (18 ml) cooled at 0°C. The mixture was stirred at room temperature for 30 min and then added dropwise over 30 min to a solution of 1,8-dibromooctane (1.36 g, 5 mmol) in dry DMF (18 ml). The resulting suspension was stirred at room temperature for 4 h, the DMF evaporated under reduced pressure and dichloromethane (20 ml) added. The mixture was washed with water (20 ml), dried (Na_2SO_4), filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography eluting with mixtures of *n*-hexane/ether affording the monobromide (79–83%). A solution of this bromide (2 mmol) in DMF (3 ml) was added to a solution of sodium *N*-propargyl-phenylsulfonamide (2 mmol) in DMF (3 ml) [previously prepared from *N*-propargylphenylsulfonamide (2 mmol) and sodium hydride (2 mmol)]. The resulting mixture was stirred for 1.5 h at room temperature, DMF was removed under reduced pressure and the residue dissolved in water (10 ml) and extracted with dichloromethane (2×10 ml). The organic layer was dried (Na_2SO_4), filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2) eluting with mixtures of *n*-hexane/ether to afford **product 14** (77% yield) as a pale yellow sticky oil. (Found: C, 54.0; H, 4.8; N, 4.75; S, 11.0. $C_{39}H_{44}IN_3O_6S_3$ requires: C, 53.75; H, 4.85; N, 4.8; S, 11.05%); δ 1.14–1.56 (m, 12H, $6\times CH_2$), 2.00 (t, J=2.0 Hz, 1H, $C{\equiv}CH$), 3.05, 3.19 (2×t, J=7.5 Hz, 4H, $2\times \mathrm{CH_2C}H_2\mathrm{N}$), 3.84, 3.91 (2×d, J=16.5 Hz, 2H, $\mathrm{C{=}CC}H_2\mathrm{NCH_2}$), 4.05 (d, J=15.0 Hz, 1H, $\mathrm{C}H_2\mathrm{NAr}$), 4.13 (d, J=2.0 Hz, 2H, $CH_2C{\equiv}C$), 4.30 (d, J=15.0 Hz, 1H, $\mathrm{C}H_2\mathrm{NAr}$), 5.08, 5.14 (2×s, 2H, $CH_2{=}C$) and 7.00–7.89 (m, 19H, ArH); m/z (%) 873 (M^+, 0.3), 732 (36), 537

928), 412 (26), 359 (88), 272 (81), 270 (34), 218 (34), 184 (24), 144 (49), 143 (32), 141 (53), 130 (34), 78 (28), 77 (100) and 32 (28).

Spiro-macrocycle 15. Obtained according to Method A as described previously in 15% yield as colourless prisms from *n*-hexane/ether, mp 110–115°C. (Found: C, 62.5; H, 6.2; N, 5.65; S, 12.7. $C_{39}H_{45}N_3O_6S_3$ requires: C, 62.6; H, 6.05; N, 5.6; S, 12.85%); δ 1.20–1.76 (m, 12H, $6{\times}CH_2$), 2.41 (d, J=13.5 Hz, 1H, $CCH_2C{=}C$), 2.85–3.23 (m, 7H, 1H of $CCH_2C{=}C$ and $3{\times}CH_2N$), 3.50 (d, J=15.0 Hz, 1H, CH_2N), 3.50 (d, J=14.0 Hz, 1H, CH_2N), 4.13, 4.33 (2×d, J=11.0 Hz, 2H, $C{=}CCH_2N$), 4.39, 4.72 (2×s, 2H, $CH_2{=}C$) and 7.02–7.97 (m, 19H, ArH); *m/z* (%) 747 (M^+, 0.2), 606 (13), 361 (18), 359 (13), 146 (14), 87 (100), 79 (11), 77 (22), 57 (11), 43 (41) and 41 (18).

Allyl alcohol 16. A suspension of chloride **11** (0.224 g, 0.5 mmol) and sodium acetate (0.164 g, 2.0 mmol) in DMF (3 ml) was stirred at 80°C for 2 d. The DMF was evaporated under reduced pressure, ethyl acetate (10 ml) and water (10 ml) were added, the organic layer decanted, dried (Na_2SO_4), filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in an 8:3 (v/v) mixture of MeOH-3 M hydrochloric acid[15] (5.5 ml) and the solution stirred at room temperature for 1 d. After the usual work-up the residue was purified by column chromatography (SiO_2) eluting with 7:3 (v/v), *n*-hexane–ether affording alcohol **16** (0.168 g, 78%) as colourless needles from *n*-hexane/ether, mp 93–94°C. (Found: C, 44.55; H, 3.8; N, 3.25; S, 7.5. $C_{16}H_{16}INO_3S$ requires: C, 44.75; H, 3.75; N, 3.25; S, 7.5%); δ 2.76 (br s, 1H, OH), 4.04 (d, J=14.3 Hz, 1H, CH_2N), 4.28 (s, 2H, CH_2O), 4.36 (d, J=14.3 Hz, 1H, CH_2N), 4.71, 5.05 (2×s, 2H, $CH_2{=}C$), 6.93–7.04, 7.28–7.31 and 7.48–7.88 (3×m, 9H, ArH); *m/z* (%) 429 (M^+, 11), 360 (46), 359 (44), 288 (54), 232 (35), 230 (55), 203 (42), 143 (55), 141 (29), 130 (83), 78 (24), 77 (100) and 51 (34).

General procedure for propargylic esters 17

A solution of alcohol **16** (0.644 g, 1.5 mmol), diacid (4.5 mmol), DMAP (10 mg) and DCC (0.464 g, 2.3 mmol) in DMF (15 ml) was stirred at room temperature for 12 h. The suspension was filtered and the DMF evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2) eluting with 3:2 (v/v) *n*-hexane–ethyl acetate giving the pure monoacid monoester. This material (1 mmol) was dissolved in THF (10 ml) and treated with triphenylphosphine (0.393 g, 1.5 mmol), propargyl alcohol (90 μl, 1.5 mmol) and ADDP (0.378 g, 1.5 mmol). The resulting solution was stirred at room temperature for 1 d and then filtered. The filtrate was evaporated and the residue purified by column chromatography (SiO_2) eluting with mixtures of *n*-hexane/ether affording diesters **17** (48–53%).

Diester 17a (*n*=2). Sticky colourless oil (51%). (Found: C, 48.6; H, 4.25; N, 2.25; S, 5.5. $C_{23}H_{22}INO_6S$ requires: C, 48.7; H, 3.9; N, 2.5; S, 5.65%); δ 2.49 (t, J=2.0 Hz, 1H, $C{\equiv}CH$), 2.67–2.71 (m, 4H, $2{\times}CH_2CO$), 4.09, 4.34 (2×d, J=14.5 Hz, 2H, CH_2N), 4.67 (d, J=13.4 Hz, 1H, $C{=}CCH_2O$), 4.69 (d, J=2.0 Hz, 2H, $CH_2C{\equiv}C$), 4.77 (d, J=13.4 Hz, 1H, $C{=}CCH_2O$), 4.90, 5.10 (2×s, 2H, $CH_2{=}C$) and 7.00–7.89 (m, 9H, ArH); *m/z* (%) 567 (M^+, 1), 427 (26), 426 (100), 288 (32), 286 (22), 285 (25), 284 (73), 270 (32), 230 (24), 144 (43), 143 (84), 142 (49), 141 (38), 139 (56), 130 (32), 111 (26), 77 (62), 55 (28) and 39 (71).

Diester 17b (*n*=3). Sticky colourless oil (49%). (Found: C, 49.5; H, 4.15; N, 2.6; S, 5.5. $C_{24}H_{24}INO_6S$ requires: C, 49.6; H, 4.15; N, 2.4; S, 5.5%); δ 1.96 (m, 2H, CH_2CH_2CO), 2.36–2.46 (m, 4H, $2{\times}CH_2CO$), 2.48 (t, J=2.2 Hz, 1H, $C{\equiv}CH$), 4.11, 4.34 (2×d, J=14.4 Hz, 2H, CH_2N), 4.65 (d, J=13.2 Hz, 1H, $C{=}CCH_2O$), 4.68 (d, J=2.2 Hz, 2H, $CH_2C{\equiv}C$), 4.75 (d, J=13.2 Hz, 1H, $C{=}CCH_2O$), 4.91, 5.10 (2×s, 2H, $CH_2{=}C$) and 7.00–7.89 (m, 9H, ArH); *m/z* (%) 581 (M^+, 0.5), 441 (30), 440 (81), 288 (41), 284 (83), 270 (42), 230 (33), 153 (61), 144 (71), 143 (100), 142 (72), 141 (56), 130 (51), 125 (54), 83 (47), 77 (91), 55 (63), 51 (37), 42 (32), 41 (36) and 39 (76).

Diester 17c (*n*=4). Colourless prisms (58%) from *n*-hexane/ether, mp 78–79°C. (Found: C, 50.7; H, 4.6; N, 2.35; S, 5.4. $C_{25}H_{26}INO_6S$ requires: C, 50.4; H, 4.4; N, 2.35; S, 5.4%); δ 1.67 (m, 4H, $2{\times}CH_2$), 2.33–2.38 (m, 4H, $2{\times}CH_2CO$), 2.49 (t, J=2.2 Hz, 1H, $C{\equiv}CH$), 4.11, 4.34 (2×d, J=14.4 Hz, 2H, CH_2N), 4.64 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.67 (d, J=2.2 Hz, 2H, $CH_2C{\equiv}C$), 4.73 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.90, 5.10 (2×s, 2H, $CH_2{=}C$) and 7.00–7.89 (m, 9H, ArH); *m/z* (%) 595 (M^+, 0.5), 454 (90), 288 (46), 284 (77), 270 (30), 144 (54), 143 (100), 142 (59), 141 (40), 130 (37), 111 (67), 77 (76), 55 (74), 41 (25) and 39 (55).

Diester 17d (*n*=5). Viscous colourless oil (53%). (Found: C, 51.6; H, 4.8; N, 2.4; S, 5.0. $C_{26}H_{28}INO_6S$ requires: C, 51.25; H, 4.6; N, 2.3; S, 5.25%); δ 1.31–1.41 (m, 2H, CH_2), 1.58–1.68 (m, 4H, $2{\times}CH_2CH_2CO$), 2.36 (m, 4H, $2{\times}CH_2CO$), 2.50 (t, J=2.0 Hz, 1H, $C{\equiv}CH$), 4.10, 4.35 (2×d, J=14.4 Hz, 2H, CH_2N), 4.65 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.68 (d, J=2.0 Hz, 2H, $CH_2C{\equiv}C$), 4.74 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.90, 5.09 (2×s, 2H, $CH_2{=}C$) and 7.00–7.88 (m, 9H, ArH); *m/z* (%) 609 (M^+, 0.4), 469 (33), 468 (100), 288 (55), 286 (31), 284 (85), 144 (51), 143 (84), 142 (57), 141 (44), 125 (36), 77 (60), 69 (50), 55 (49) and 39 (44).

Diester 17e (*n*=6). Colourless prisms (50%) from *n*-hexane/ether, mp 49–51°C. (Found: C, 52.25; H, 5.05; N, 2.5; S, 5.0. $C_{27}H_{30}INO_6S$ requires: C, 52.0; H, 4.85; N, 2.25; S, 5.15%); δ 1.32–1.35 (m, 4H, $2{\times}CH_2$), 1.61–1.69 (m, 4H, $2{\times}CH_2CH_2CO$), 2.28–2.48 (m, 4H, $2{\times}CH_2CO$), 2.50 (t, J=2.0 Hz, 1H, $C{\equiv}CH$), 4.10, 4.34 (2×d, J=14.4 Hz, 2H, CH_2N), 4.64 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.67 (d, J=2.0 Hz, 2H, $CH_2C{\equiv}C$), 4.73 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.90, 5.09 (2×s, 2H, $CH_2{=}C$) and 7.00–7.89 (m, 9H, ArH); *m/z* (%) 623 (M^+, 0.3), 482 (79), 288 (43), 284 (67), 156 (65), 144 (41), 143 (66), 141 (90), 98 (38), 83 (55), 82 (39), 77 (50), 69 (52), 67 (45), 56 (78), 55 (100), 41 (71) and 39 (69).

Diester 17f (*n*=7). Colourless needles (53%) from *n*-hexane/ether, mp 55–58°C. (Found: C, 52.7; H, 5.35; N, 2.25; S, 4.9. $C_{28}H_{32}INO_6S$ requires: C, 52.75; H, 5.05; N, 2.2; S, 5.05%); δ 1.32 (m, 6H, $3{\times}CH_2$), 1.56–1.78 (m, 4H, $2{\times}CH_2CH_2CO$), 2.26–2.37 (m, 4H, $2{\times}CH_2CO$), 2.50 (t,

J=2.0 Hz, 1H, $C{\equiv}CH$), 4.12, 4.34 (2×d, J=14.4 Hz, 2H, CH_2N), 4.64 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.67 (d, J=2.0 Hz, 2H, $CH_2C{\equiv}C$), 4.73 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.91, 5.10 (2×s, 2H, $CH_2{=}C$) and 7.00–7.89 (m, 9H, ArH); m/z (%) 637 (M^+, 0.2), 495 (56), 284 (55), 170 (35), 144 (36), 143 (56), 142 (38), 141 (77), 98 (34), 97 (47), 77 (42), 69 (37), 67 (42), 56 (66), 55 (100), 43 (40), 41 (64) and 39 (57).

Diester 17g (*n*=8). Colourless needles (52%) from *n*-hexane/ether, mp 64–67°C. (Found: C, 53.6; H, 5.2; N, 2.3; S, 4.8. $C_{29}H_{34}INO_6S$ requires: C, 53.45; H, 5.25; N, 2.15; S, 4.9%); δ 1.30 (m, 8H, 4×CH_2), 1.56–1.78 (m, 4H, 2×CH_2CH_2CO), 2.27–2.37 (m, 4H, 2×CH_2CO), 2.49 (t, J=1.8 Hz, 1H, $C{\equiv}CH$), 4.10, 4.33 (2×d, J=14.4 Hz, 2H, CH_2N), 4.64 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.67 (d, J=1.8 Hz, 2H, $CH_2C{\equiv}C$), 4.73 (d, J=13.5 Hz, 1H, $C{=}CCH_2O$), 4.90, 5.09 (2×s, 2H, $CH_2{=}C$) and 7.00–7.88 (m, 9H, ArH); m/z (%) 651 (M^+, 0.5), 510 (97), 288 (64), 284 (89), 270 (33), 144 (56), 143 (100), 142 (55), 141 (37), 77 (61), 55 (55), 41 (31) and 39 (36).

General procedure for spiro-macrolides 19a–g

The diesters **17a–g** (0.25 mmol) were hydrostannylated and cyclised using the same procedure as that described for the synthesis of **10** but with a catalyst system comprising Pd_2dba_3 (5 mol%) and tri(2-furyl)phosphine (20 mol%). Product yields are collected in Table 3.

Macrolide 19a (*n*=2). Colourless needles from *n*-hexane/ether, mp 46–49°C. (Found: C, 62.7; H, 5.1; N, 3.1; S, 7.0. $C_{23}H_{23}NO_6S$ requires: C, 62.55; H, 5.25; N, 3.15; S, 7.25%); δ 2.3 (d, J=15.3 Hz, 1H, $CCH_2C{=}C$), 2.53–2.66 (m, 5H, 2×CH_2CO and 1H of $CCH_2C{=}C$), 3.60 (d, J=10.7 Hz, 1H, CCH_2O), 3.80, 3.98 (2×d, J=11.0 Hz, 2H, CH_2N), 4.01 (d, J=10.7 Hz, 1H, CCH_2O), 4.35, 4.85 (2×d, J=12.0 Hz, 2H, $C{=}CCH_2O$), 4.93, 5.31 (2×s, 2H, $CH_2{=}C$) and 7.00–7.83 (m, 9H, ArH); m/z (%) 441 (M^+, 8), 441 (26), 271 (29), 270 (100), 167 (28), 149 (46) and 77 (22).

Macrolide 19b (*n*=3). Colourless needles from *n*-hexane/ether, mp 48–50°C. (Found: C, 63.6; H, 5.9; N, 2.7; S, 6.8. $C_{24}H_{25}NO_6S$ requires: C, 63.3; H, 5.55; N, 3.05; S, 7.05%); δ 1.65–1.78 (m, 2H, CH_2CH_2CO), 2.41–2.52 (m, 6H, 2×CH_2CO and $CCH_2C{=}C$), 3.64 (d, J=11.0 Hz, 1H, CCH_2N), 3.80, 3.88 (2×d, J=11.5 Hz, 2H, CCH_2O), 3.92 (d, J=11.0 Hz, 1H, CCH_2N), 4.60 (br s, 3H, $C{=}CCH_2O$ and 1H of $C{=}CH_2$), 5.13 (s, 1H, $CH_2{=}C$) and 7.00–7.88 (m, 9H, ArH); m/z (%) 455 (M^+, 7), 270 (100), 169 (38), 141 (25), 130 (27), 77 (35), 41 (15) and 39 (30).

Macrolide 19c (*n*=4). Colourless needles from *n*-hexane/ether, mp 134–138°C. (Found: C, 64.0; H, 6.0; N, 2.8; S, 6.8. $C_{25}H_{27}NO_6S$ requires: C, 63.95; H, 5.8; N, 3.0; S, 6.85%); δ 1.71–1.81 (m, 4H, 2×CH_2CH_2CO), 2.31–2.57 (m, 6H, 2×CH_2CO and $CCH_2C{=}C$), 3.83–3.96 (m, 4H, CCH_2O and CH_2N), 4.26 (d, J=12.5 Hz, 1H, $C{=}CCH_2O$), 4.32 (s, 1H, $CH_2{=}C$), 4.69 (d, J=12.5 Hz, 1H, $C{=}CCH_2O$), 4.85 (s, 1H, $CH_2{=}C$) and 7.04–7.85 (m, 9H, ArH); m/z (%) 469 (M^+, 21), 272 (10), 271 (25), 270 (100), 141 (14), 130 (12) and 77 (13).

Macrolide 19d (*n*=5). Colourless needles from *n*-hexane/ether, mp 61–63°C. (Found: C, 64.7; H, 6.1; N, 2.85; S, 6.6. $C_{26}H_{29}NO_6S$ requires: C, 64.6; H, 6.05; N, 2.9; S, 6.65%); δ 1.34–1.43 (m, 2H, CH_2), 1.73 (m, 4H, 2×CH_2CH_2CO), 2.36–2.46 (m, 6H, 2×CH_2CO and $CCH_2C{=}C$), 3.67 (d, J=11.0 Hz, 1H, CH_2N), 3.70–3.96 (m, 3H, CCH_2O and 1H of CH_2N), 4.09 (s, 1H, $CH_2{=}C$), 4.33, 4.48 (2×d, J=12.5 Hz, 2H, $C{=}CCH_2O$), 4.76 (s, 1H, $CH_2{=}C$) and 7.04–7.85 (m, 9H, ArH); m/z (%) 483 (M^+, 10), 271 (27), 270 (100), 168 (15), 167 (11), 141 (26), 130 (27), 129 (12), 77 (33), 55 (16) and 41 (10).

Macrolide 19e (*n*=6). Colourless needles from *n*-hexane/ether, mp 31–34°C. (Found: C, 65.2; H, 6.3; N, 2.7; S, 6.5. $C_{27}H_{31}NO_6S$ requires: C, 65.15; H, 6.25; N, 2.8; S, 6.45%); δ 1.26–1.43 (m, 4H, 2×CH_2), 1.70–1.75 (m, 4H, 2×CH_2CH_2CO), 2.36–2.45 (m, 6H, 2×CH_2CO and $CCH_2C{=}C$), 3.73 (d, J=11.0 Hz, 1H, CH_2N), 3.88 (br s, 2H, CCH_2O), 3.97 (d, J=11.0 Hz, CH_2N), 4.11, 4.24 (2×d, J=10.0 Hz, 2H, $C{=}CCH_2O$), 4.26 (s, 1H, $CH_2{=}C$), 4.65 (d, J=2.8 Hz, 1H, $CH_2{=}C$) and 7.02–7.84 (m, 9H, ArH); m/z (%) 497 (M^+, 27), 272 (33), 271 (65), 270 (100), 168 (40), 167 (25), 141 (62), 130 (81), 129 (25), 78 (28), 77 (74), 55 (39) and 41 (25).

Macrolide 19f (*n*=7). Colourless sticky oil. (Found: C, 65.45; H, 6.35; N, 2.5; S, 6.3. $C_{28}H_{33}NO_6S$ requires: C, 65.75; H, 6.5; N, 2.75; S, 6.3%); δ 1.27–1.45 (m, 6H, 3×CH_2), 1.66–1.73 (m, 4H, 2×CH_2CH_2CO), 2.34–2.47 (m, 4H, 2×CH_2CO), 2.47, 2.59 (2×d, J=16.0 Hz, 2H, $CCH_2C{=}C$), 3.72 (d, J=11.0 Hz, 1H, CH_2N), 3.78–3.94 (m, 3H, CCH_2O and 1H of CH_2N), 4.02 (d, J=12.0 Hz, 1H, $C{=}CCH_2O$), 4.26 (s, 1H, $CH_2{=}C$), 4.28 (d, J=12.0 Hz, 1H, $C{=}CCH_2O$), 4.80 (s, 1H, $CH_2{=}C$) and 7.02–7.85 (m, 9H, ArH); m/z (%) 511 (M^+, 7), 272 (17), 271 (33), 270 (100), 168 (19), 149 (21), 141 (29), 130 (35), 77 (43), 55 (29) and 41 (21).

Macrolide 19g (*n*=8). Colourless sticky oil. (Found: C, 66.0; H, 6.6; N, 2.5; S, 6.0. $C_{29}H_{35}NO_6S$ requires: C, 66.25; H, 6.7; N, 2.65; S, 6.1%); δ 1.26–1.36 (m, 8H, 4×CH_2), 1.67 (m, 4H, 2×CH_2CH_2CO), 2.19–2.37 (m, 4H, 2×CH_2CO), 2.42, 2.56 (2×d, J=15.0 Hz, 2H, $CCH_2C{=}C$), 3.72 (d, J=11.0 Hz, 1H, CH_2N), 3.76–3.94 (m, 3H, CCH_2O and 1H of CH_2N), 4.02, 4.18 (2×d, J=11.5 Hz, 2H, $C{=}CCH_2O$), 4.38, 4.81 (2×s, 2H, $CH_2{=}C$) and 7.00–7.83 (m, 9H, ArH); m/z (%) 525 (M^+, 24), 523 (17), 272 (36), 271 (61), 270 (100), 168 (26), 141 (40), 130 (50), 77 (47) and 55 (26).

General procedure for alkynes 21a–d

Methacryloyl chloride (2.4 g, 23 mmol) was added to a stirred solution of 2-iodoaniline (5 g, 23 mmol) and triethylamine (2.3 g, 23 mmol) in dichloromethane (50 ml) cooled at 0°C. After 10 min the cooling bath was removed, the mixture was stirred for 3 h at room temperature, then diluted with CH_2Cl_2 (50 ml) and washed with water. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was crystallised from benzene to afford **20** (74%) as colourless prisms, mp 49°C. Sodium hydride (0.351 g, 60% dispersion in mineral oil, 13.9 mmol) was added slowly to a solution of **20** (4 g, 13.9 mmol) in dry DMF (10 ml). After 2 h at room temperature the reaction mixture was added to a solution of the appropriate α,ω-dibromide (41.7 mmol, 3 mol equiv.) in DMF (10 ml) and stirred at room temperature for further 2 h. The mixture was then diluted with ether (100 ml) and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo to yield a pale yellow oil which was purified by column chromatography (SiO_2) eluting with 7:3 (v/v) petroleum ether–ether to afford the *N*-ω-bromoalkyl derivatives of **20**. Sodium hydride (0.200 g, 60% dispersion in mineral oil, 5 mmol) was added slowly to a solution of *N*-propargylsulfonamide (0.98 g, 5 mmol) in dry DMF (5 ml). After 2 h at room temperature a solution of the appropriate *N*-ω-bromoalkyl compound (5 mmol) in DMF (5 ml) was added to the reaction mixture and stirring continued at room temperature for a further 2 h. The mixture was then diluted with ether (50 ml) and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residual oil was purified by column chromatography (SiO_2) eluting with 2:3 (v/v) petroleum ether–ether to afford **21a–d**.

21a. Obtained (78%) as colourless prisms from ether, mp 78°C. (Found: C, 53.2; H, 4.9; N, 5.0; S, 5.9; I, 22.2. $C_{25}H_{29}IN_2O_3S$ requires: C, 53.2; H, 5.2; N, 4.9; S, 5.7; I, 22.5%); δ 1.30–1.80 (m, 8H, 4×CH_2), 1.81 (s, 3H, CH_3), 2.00 (s, 1H, $C{\equiv}CH$), 3.17 (t, J=7.0 Hz, 3H, CH_2NSO_2Ph and ArNC*H*), 4.10 (br s, 3H, $CH_2C{\equiv}C$ and ArNC*H*), 4.94, 5.00 (2×s, 2H, $C{=}CH_2$) and 7.00–7.81(m, 9H, ArH); *m*/*z* (%) 564 (M^+, 45), 437 (100) and 423 (60).

21b. Obtained (79%) as colourless prisms from ether, mp 60°C. (Found: C, 54.1; H, 5.3; N, 4.9; S, 5.6; I, 21.9. $C_{26}H_{31}IN_2O_3S$ requires: C, 54.0%; H, 5.4; N, 4.8; S, 5.5; I, 21.9%); δ 1.30–1.70 (m, 10H, 5×CH_2), 1.82 (s, 3H, CH_3); 2.00 (s, 1H, $C{\equiv}CH$), 3.19 (m, 3H, CH_2NSO_2Ph and ArNC*H*), 4.12 (br s, 3H, $CH_2C{\equiv}C$ and ArNC*H*), 4.95 and 5.01 (2×s, 2H, $C{=}CH_2$) 7.00–7.82 (m, 9H, ArH); *m*/*z* (%) 578 (M^+, 0.3), 451 (100) and 437 (44).

21c. Obtained (75%) as a colourless oil. (Found: C, 54.4; H, 5.6; N, 4.8; S, 5.6; I, 21.3. $C_{27}H_{33}IN_2O_3S$ requires: C, 54.7; H, 5.6; N, 4.7; S, 5.4; I, 21.4%); δ 1.30–1.70 (m, 12H, 6xCH_2), 1.81 (s, 3H, CH_3), 1.98 (s, 1H, $C{\equiv}CH$), 3.18 (t, 3H, J=7.2 Hz, CH_2NSO_2Ph and ArNC*H*), 4.11 (br s, 3H, $CH_2C{\equiv}C$ and ArNC*H*), 4.94, 5.00 (2×s, 2H, $C{=}CH_2$), 7.00–7.84 (m, 9H, ArH); *m*/*z* (%) 592 (M^+, 0.1), 465 (64), 451 (21).

21d. Obtained (70%) as a colourless oil. (Found: C, 56.1; H, 5.8; N, 4.5; S, 5.4; I, 20.6. $C_{29}H_{37}IN_2O_3S$ requires: C, 56.1; H, 6.0; N, 4.5; S, 5.1; I, 20.4%); δ 1.05–1.60 (m, 16H, 8×CH_2), 1.80 (s, 3H, CH_3), 2.00 (s, 1H, $C{\equiv}CH$), 3.18 (m, 3H, CH_2NSO_2Ph and ArNC*H*), 4.17 (m, 3H, $CH_2C{\equiv}C$ and ArNC*H*), 4.95, 5.02 (2×s, 2H, $C{=}CH_2$) and 7.00–7.90 (m, 9H, ArH). *m*/*z* (%) 620 (M^+, 0.1), 493 (7) and 479 (1).

General procedure for bridged-macrocycles 23

The hydrostannylation and cyclisation–anion capture process was performed as described for the synthesis of spiro-macrocycles **10** (Method A) using a catalyst comprised of Pd_2dba_3 (10 mol%) and tri(2-furyl)phosphine (80 mol%) together with the appropriate additive shown in Table 4. Yields are collected in Table 4.

23a. Obtained as colourless prisms, mp 174°C. (Found: C, 68.3; H, 6.9; N, 6.2; S, 7.3. $C_{25}H_{30}N_2O_3S$ requires: C, 68.5; H, 6.9; N, 6.4; S, 7.3%). δ 1.00–1.20 (m, 8H, 4×CH_2), 2.52 (d, J=13.8 Hz, 1H, $CH_2C{=}C$), 2.63 (m, 1H, CH_2NSO_2Ph), 2.69 (d, J=13.8 Hz, 1H, $CH_2C{=}C$), 3.20 (m, 1H, CH_2NS), 3.30 (m, 1H, ArNC*H*), 3.41 (d, J=18.4 Hz, 1H, $NCH_2C{=}C$), 3.83 (d, J=18.4 Hz, 1H, $NCH_2C{=}C$), 4.03 (m, 1H, ArNC*H*), 4.60, 4.80 (2×s, 2H, $C{=}CH_2$) and 6.81–7.74 (m, 9H, ArH); *m*/*z* (%) 438 (M^+, 1), 297 (100) and 277 (9).

23b. Obtained as colourless prisms, mp 137°C. (Found: C, 68.8; H, 7.2; N, 5.9; S, 7.2. $C_{26}H_{32}N_2O_3S$ requires: C, 69.0; H, 7.1; N, 6.2; S, 7.1%); δ 1.0–1.2 (m, 10H, 5×CH_2), 2.42 (d, J=14.2 Hz, 1H, $CH_2C{=}C$), 2.69 (d, J=14.2 Hz, 1H, $CH_2C{=}C$), 2.90, 3.00 (2×m, 2H, CH_2NSO_2SPh), 3.35 (m, 1H, ArNC*H*), 3.48 (d, J=18.3 Hz, 1H, $NCH_2C{=}C$), 3.83 (d, J=18.4 Hz, $NCH_2C{=}C$), 4.02 (m, 1H, ArNC*H*), 4.50, 4.90 (2×s, 2H, $C{=}CH_2$) and 6.82–7.74 (m, 9H, ArH); *m*/*z* (%) 452 (M^+, 3) and 311 (100).

23c. Obtained as colourless prisms, mp 153°C. (Found: C, 68.6; H, 7.4; N, 5.8. $C_{27}H_{34}N_2O_3S$ requires: C, 69.5; H, 7.3; N, 6.0%); δ 1.00–1.20 (m, 12H, 6×CH_2), 2.90 (m, 1H, CH_2NSO_2Ph), 2.47 (d, J=15 Hz, 1H, $CH_2C{=}C$), 2.72 (d, J=15.0 Hz, 1H, $CH_2C{=}C$), 2.98 (m, 1H, CH_2NSO_2Ph), 3.50 (d, J=18 Hz, $NCH_2C{=}C$), 3.35 (m, 1H, ArNC*H*), 3.56 (d, J=18 Hz, 1H, $NCHC{=}C$), 4.15 (m, 1H, ArNC*H*), 4.76, 5.14 (2×s, 2H, $C{=}CH_2$) and 6.87–7.75 (m, 9H, ArH); *m*/*z* (%) 466 (M^+, 2) and 325 (100).

23d. Obtained as a pale yellow oil. (Found: C, 70.4; H, 7.9; N, 5.6; S, 6.6. $C_{29}H_{38}N_2O_3S$ requires: C, 70.4; H, 7.7; N, 5.6; S, 6.5%); δ 1.00–1.20 (m, 16H, 8×CH_2), 2.38 (d, J=15.0 Hz, 1H, $CH_2C{=}C$), 2.77 (d, J=15.0 Hz, $CH_2C{=}C$), 2.76, 3.25 (2×m, 2H, CH_2NSO_2Ph), 3.28 (d, J=15.0 Hz, $NCH_2C{=}C$), 3.32 (m, 1H, ArNC*H*), 3.75 (d, J=15.0 Hz, 1H, $NCH_2C{=}C$), 4.11 (m, 1H, ArNC*H*), 4.49, 4.87 (2×s, 2H, $C{=}CH_2$) and 6.86–7.78 (m, 9H, ArH); *m*/*z* (%) 494 (M^+, 1) and 353 (100).

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References

1. Part 4. Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525–7539.

2. (a) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235–1246. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–669.

3. (a) Stille, J. K.; Tanaka, M. J. *J. Am. Chem. Soc.* **1987**, *109*,

3785–3786. (b) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883–2894.

4. Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120–4122.

5. Some examples of sp^2–sp, allylic sp^3–sp^2 and sp^2–sp^2 Stille couplings are: (a) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *Tetrahedron* **1992**, *48*, 2957–2976. (b) Pattenden, G.; Thom, S. M. *Synlett* **1993**, 215–216. (c) Nicolau, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertino, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420. (d) Finch, H.; Pegg, N. A.; Evans, B. *Tetrahedron Lett.* **1993**, *34*, 8353–8356. (e) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755–3757. (f) Barret, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1881–1882. (g) Boden, C.; Pattenden, G. *Synlett* **1991**, 181–182. (h) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1721–1723. (i) Critcher, D. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9107–9110. (j) McDermott, T. S.; Mortlock, A. A.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 700–709. (k) Taber, D. F.; Wang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 22–26. (l) Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* **1997**, 381–383. (m) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948. (n) Kim, Y.; Singer, R. A.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1261–1263. (o) Jyojima, T.; Miyamoto, N.; Katohno, M.; Nakata, M.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **1998**, *39*, 6007–6010. (p) Entwistle, D. A.; Jordan, S. I.; Montgomery, J.; Pattenden, G. *Synthesis* **1998**, 603–612. (q) Masse, C. E.; Yang, M.; Solomon, J.; Panek, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4123–4134.

6. Preliminary communication: Casaschi, A.; Grigg, R.; Sansano, J. M.; Wilson, D.; Redpath, J. *Tetrahedron Lett.* **1996**, *37*, 4413–4416.

7. (a) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65–87. (b) Grigg, R.; Sridharan, V. In *Transition Metal Catalysed Reaction*; Davies, S. G., Murahashi, S.-I., Eds.; IUPAC Monograph, Blackwell Science, 1999; pp. 81–97.

8. (a) Guibé, F.; Balavoine, G.; Zhang, H. X. *J. Org. Chem.* **1990**, *55*, 1857–1867. (b) Ito, Y.; Inouye, M.; Yakata, H.; Murakami, M. *J. Org. Chem.* **1990**, *55*, 2567–2568.

9. Tsunodo, T.; Yoshico, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642.

10. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

11. Kimura, E. *Tetrahedron* **1992**, *48*, 6175–6217.

12. Grigg, R.; Sridharan, V.; Xu, L. -H. *J. Chem. Soc., Chem. Commun.* **1995**, 1903–1904.

13. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.

14. Straus, F.; Voss, W. *Ber.* **1926**, *59*, 1681–1691.

15. Alonso, D. A.; Nájera, C.; Sansano, J. M. *Tetrahedron* **1994**, *50*, 6603–6620.