Pergamon

Tetrahedron 57 (2001) 10335–10345

TETRAHEDRON

Palladium catalysed tandem cyclisation–anion capture. Part 8: Cascade hydrostannylation—cyclisation–anion capture and cascade hydroboration—cyclisation–anion capture on solid phase

Ronald Grigg,[a,*] William S. MacLachlan,[b] David T. MacPherson,[b] Visuvanathar Sridharan[a] and Selvaratnam Suganthan[a]

[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, University of Leeds, Leeds LS2 9JT, UK*
[b]*GlaxoSmithKline, New Frontiers Science Park, Harlow, Essex CM19 5AW, UK*

Received 14 August 2001; revised 21 September 2001; accepted 18 October 2001

Abstract—Up to four bonds and five stereocentres are created, in five component processes (five point diversity), utilising resin bound aryl iodides by hydroboration or hydrostannylation of alkynes, followed by cyclisation–anion capture involving Suzuki or Stille reactions. Three small libraries were prepared to validate the chemistry.

1. Introduction

Solid phase synthesis is now established as a powerful tool for the preparation of combinatorial libraries of small molecules for drug lead discovery.[1] The molecular diversity of these libraries is the key element in their usefulness and this is enhanced by incorporating a variety of chemistries and diverse building blocks.

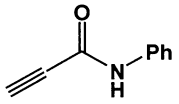
We have been developing palladium catalysed cyclisation–anion capture cascades as powerful protocols for the assembly of complex heterocycles.[2] We now report applications of this chemistry to solid phase synthesis. In this paper we focus on organostannanes and organoboranes as anion capture agents.

2. Results and discussion

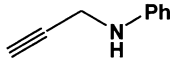
2.1. Cascade hydrostannylation—cyclisation–anion capture

Palladium catalysed hydrostannylation of terminal alkynes followed by insertion of palladium(0) into an aryl iodide and cyclisation onto a proximate alkene terminating in an intermolecular Stille reaction potentially provides a wide range of diverse compounds.[3] It has been established that excellent regioselectivity in the hydrostannylation of terminal alkynes can be achieved by the incorporation of a β- or γ-heteroatom.[4]

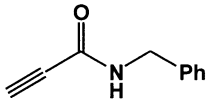
Initially we prepared a series of terminal alkynes **1a**–**p**.



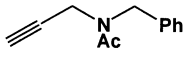
1a



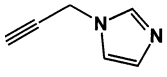
1b



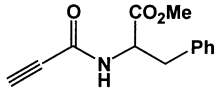
1c



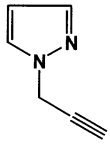
1d



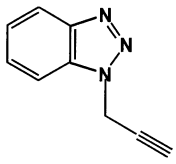
1e



1f



1g

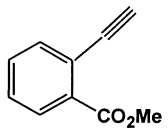


1h

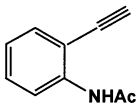
Keywords: cascade reactions; palladium catalysis; hydrostannylation; hydroboration; Stille coupling; Suzuki coupling; cyclisation.

* Corresponding author. Tel./fax: +44-113-233-6501; e-mail: r.grigg@chem.leeds.ac.uk

0040–4020/01/$ - see front matter
PII: S0040-4020(01)01061-4

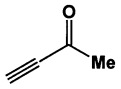


1i

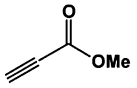


1j

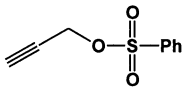
1k



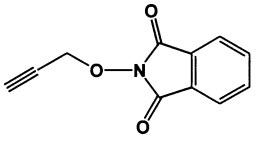
1l



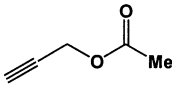
1m



1n

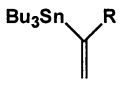


1o

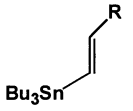


1p

The alkynes **1a**–**m** were allowed to react with Bu_3SnH (2 equiv.) in the presence of 5 mol% $Pd_2(dba)_3$ and 20 mol% $(2\text{-furyl})_3P$ over 2 h at 0°C to rt at which time hydrostannylation was judged complete by ^1H NMR monitoring. The hydrostannylation was highly regioselective (Table 1) affording **2** as the sole isomer in the majority of cases.

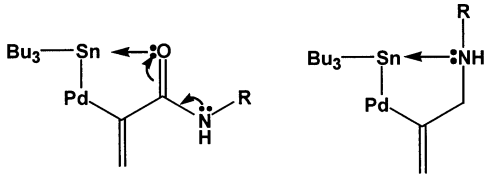


2



3

The propynamides are believed to undergo regiospecific hydrostannylation due to the stronger coordination of the carbonyl oxygen with tin compared to the coordination of nitrogen in propynamines (Scheme 1).

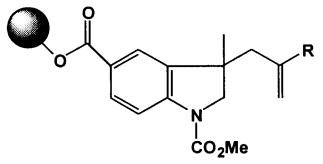


Scheme 1.

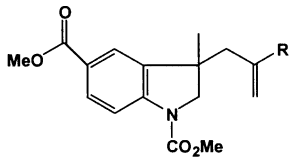
In the case of alkynes, **1n**–**p**, fragmentation to allene via allenylpalladium complex **4** renders them unsuitable substrates (Scheme 2).

The resin bound starter species **7** was prepared from methyl 3-iodo-4-aminobenzoate **5** as shown in Scheme 3 using Wang resin.

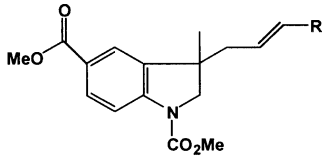
Heating the resin bound aryl iodide (1 mol equiv.) with vinylstannanes derived from **1a**–**m** (2 mol equiv.) in toluene (110°C, 8 h) induced cyclisation–anion capture furnishing **8**. Transesterification of the resin bound **8** using NaCN, Et_3N and 1:3 v/v MeOH–THF (50°C, 2 days) gave **9** and in some cases mixtures of **9** and **10** (Table 1).



8

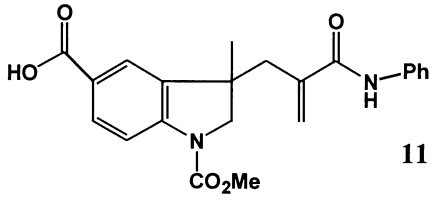


9



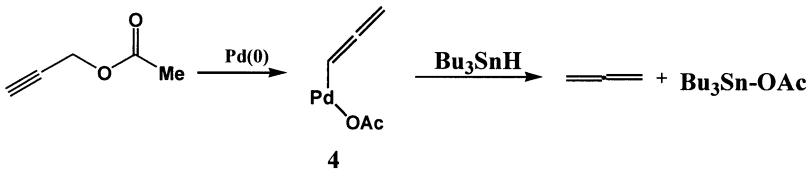
10

Cleavage of resin bound **8a** using 20% TFA in CH_2Cl_2 gave **11** in 85% yield. Thus allowing two variants (CO_2Me and CO_2H) of the 'stub'.



11

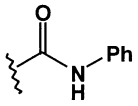
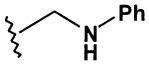
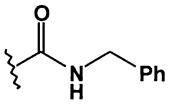
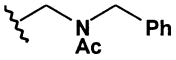
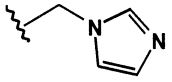
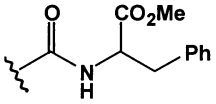
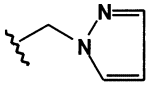
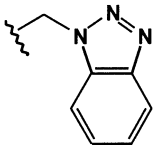
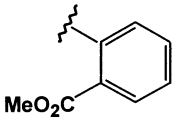
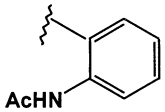
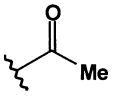
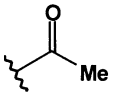
Interestingly for entries 2, 5 and 11 (Table 1) the ratio of **9**/**10** is higher than the precursor α- and β-vinylstannane ratio indicating that β-vinylstannanes are more reactive than the α-vinylstannanes. However another possibility for the variation in the ratio of **9**/**10** is rearrangement analogous to that observed by Busacca.[5]



4

Scheme 2.

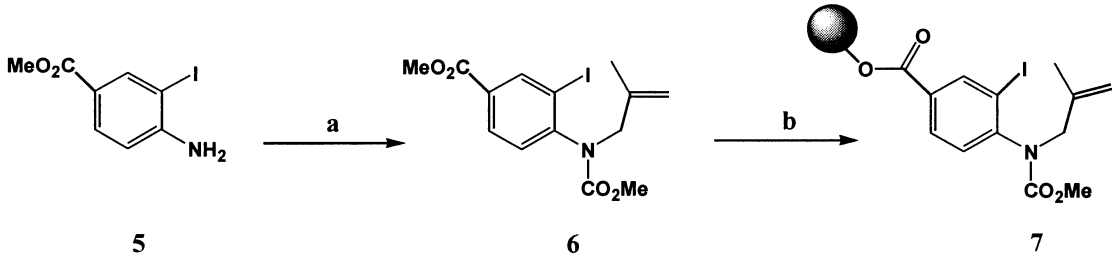
Table 1. Regioselectivity of formation of stannanes **2a–m** and **3a–m** and the products of their cyclisation-anion capture **9a–k/10a–k**

Entry	Alkynes	Ratio of **2/3**	R	Ratio of **9/10**	Yield[a] (%)
1	**1a**	100:0		100:0	65
2	**1b**	85:15		75:25	86
3	**1c**	100:0		100:0	72
4	**1d**	100:0		100:0	59
5	**1e**	85:15		75:25	65
6	**1f**	100:0		100:0	62[b]
7	**1g**	100:0		100:0	74
8	**1h**	100:0		100:0	79
9	**1i**	100:0		100:0	70
10	**1j**	100:0		100:0	58
11	**1k**	80:20		29:71	84
12	**1l**	91:10		–	–
13	**1m**	100:0		–	–

[a] Isolated yield.
[b] 1:1 mixture of diastereoisomers.

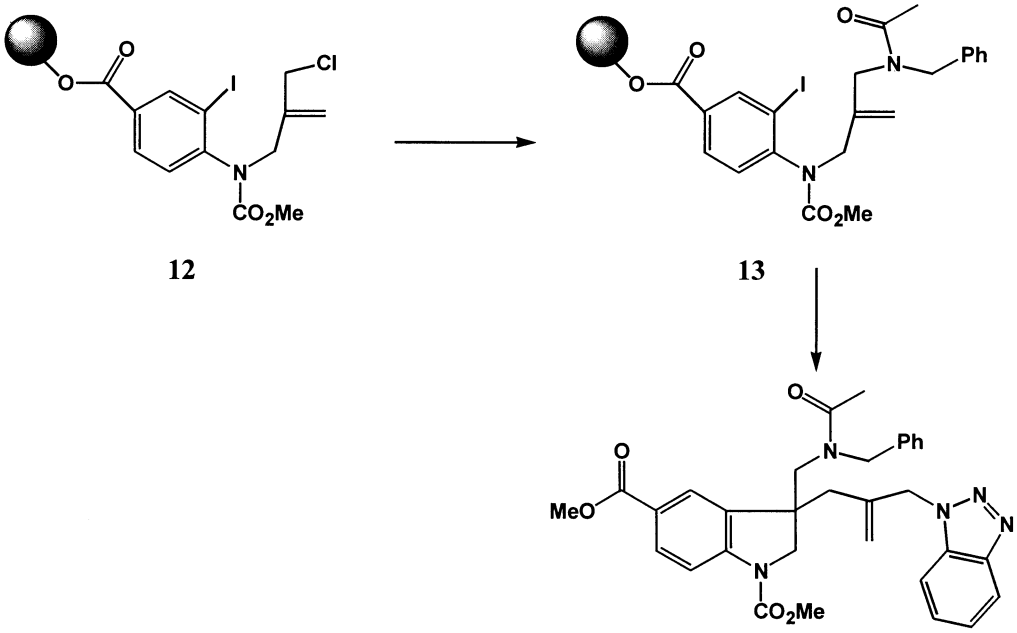
When vinylstannanes **2l** and **2m** derived in situ from **1l** and **1m** were heated with resin bound aryl iodide **7** followed by transesterification they gave complex mixtures (Table 1, entries 12 and 13). The literature reports[5] that reaction between iodobenzene and vinylstannane **2m** gave methyl cinnamate as the major product while the expected Stille product was only present in trace amounts. Busacca proposed that methyl cinnamate was formed via a palladium carbene intermediate.

Further structural variation is required in this cascade to make a diverse library. An illustrative example of how this can be achieved is shown in Scheme 4. Resin bound allyl chloride **12** was reacted with excess of benzylamine (4 equiv.) followed by acetylation to give **13** (Scheme 4). This sequence of reactions allows three site variations for library synthesis. Palladium catalysed cyclisation–Stille coupling using vinylstannane **2h** and finally transesterification gave **14** in 70% yield (Scheme 4).



5 6 7

Scheme 3. (a) (i) $ClCO_2Me$ (1.2 equiv.), pyridine (2 equiv.) rt, 15 h, 95%, (ii) NaH (1.1 equiv.), DMF methallyl chloride (1.5 equiv.), rt, 87%; (b) (i) 2N NaOH, THF, 45°C, 15 h, 94%, (ii) Wang resin (loading 1.2 mmol/g), DIPCDI (2 equiv.), DMAP (5 mol%), DCM, rt, 24 h.



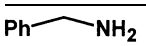
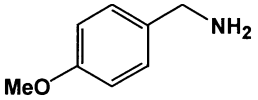
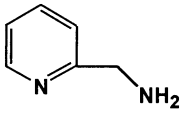
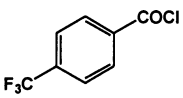
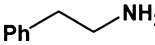
12 13 14

70%

Scheme 4.

Having achieved these cascade reactions on solid support we extended the technology to the preparation of two small libraries using split and mix methodology. For this purpose resin bound allyl chloride **12** was split into five equal parts (5.7 g×5) and displacement of allyl chloride with an excess of five different primary amines was carried out separately (Table 2). These five resin bound compounds were mixed and split into five equal parts (5.5 g×5) and each of these was acylated using an excess of five different acylating reagents (Table 2). The resin beads (25 compounds) were then mixed and the resin pool was split into two equal parts (9.2 g×2) and palladium catalysed cyclisation–Stille coupling with two different vinylstannanes generated in situ from the corresponding alkynes (Table 2) was carried out. The products were cleaved from the resin by transesterification and filtered through a short plug of silica to give L1 (5.0 g), L2 (5.0 g). Each library was shown to comprise a mixture of 25 compounds as expected by HPLC/MS. The libraries were analysed by LC/MS: a Waters Symmetry® C_{18} (2.1×150 mm) column eluting (0.2 ml/min) with mixtures of water (0.1% TFA) and acetonitrile (0.1% TFA); gradient decreasing linearly from 100% water

Table 2. Split and mix libraries derived from **12** via amination/acylation/cyclisation—Stille coupling

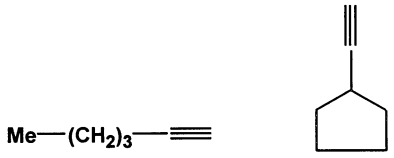
Amines[a]	Acylating agents	Alkynes
	$TsCl$, Et_3N, DCM, rt, 24 h	**1d** and **1h**
	Ac_2O, pyridine, MeCN, 50°C, 24 h	
	 Et_3N, rt, 24 h	
$BuNH_2$	EtNCO, DCM, rt, 24 h	
	PhNCO, DCM, rt, 24 h	

[a] MeCN, K_2CO_3 (2 equiv.), 80°C, 24 h.

(0.1% TFA) to 20% water (0.1% TFA) over 20 min with maintenance of the mobile phase at 20% water (0.1% TFA) for 10 min; UV detection 214 mm; MS Finnigan LCQ or Micromass ZMD 2000 using electrospray positive ionisation.

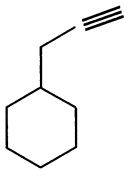
2.2. Cascade hydroboration—cyclisation–anion capture

Hydroboration of terminal alkynes followed by insertion of palladium(0) into an aryl iodide and cyclisation onto a proximate alkene terminating in an intermolecular Suzuki reaction potentially provides a wide range of diverse compounds. Here we report examples of this cascade on solid phase.

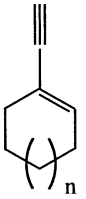


15a

15b

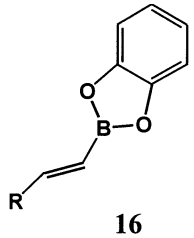


15c



15d n=1
15e n=0

The terminal alkynes **15a–e**, **1k** and **1d** were allowed to react with catecholborane (1 mol equiv.) at 70°C for 1.5 h in the absence of solvent[6] and the crude products were examined by ^{1}H NMR. In the case of **15a–e** and **1k** the *E*-2-alkenyl-1,3,2-benzodioxaborates **16a–e** and **16k** were obtained stereo- and regio-specifically. In the case of **1d** starting material was recovered.



16

Attempted Suzuki coupling of zipper **7** using alkenylborates **16a** and **16k** derived from **15a** and **1k** in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Na_2CO_3 (2 equiv.)/ K_3PO_4 (2 equiv.) failed to give the desired product. Only starting material was recovered.

The literature reports[7] that relatively strong bases such as NaOR or NaOH were required for the coupling of alkenyl borates with aryl halides. These bases are strong enough to cleave **7** from the resin. However, there are some literature reports[8] that Na_2CO_3, or K_2CO_3 suspended in alcoholic solvents are effective bases for these reactions, but alcoholic solvents are not suitable for resin chemistry. We have demonstrated[9] palladium catalysed cyclisation–anion capture methodology employing boronic acids as anion transfer reagents, which employed Na_2CO_3 as base. Therefore after hydroboration water was added to the reaction mixture and the resulting mixture was stirred for 1 h at 80°C to effect hydrolysis of **16a–e** and **16k** to the corresponding boronic acids. Subsequent addition of resin bound zipper **7**, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Na_2CO_3 (3 mol equiv.), Et_4NCl (1 mol equiv.) and toluene and heating (110°C, 15 h) gave **17a–c** and **17k**. Transesterification gave **18a–c** and **18k** in good yields (Table 3). Hydride ion capture product **19** (<10%) was also formed in most reactions (Table 3).

Hydroboration, using catecholborane only works well for simple alkyl and aryl alkynes. Heteroatom functionalised alkynes fail to hydroborate, because of the coordination of the heteroatom to boron.

To illustrate viable approaches to diverse libraries, resin bound allyl chloride **12** was reacted with excess benzylamine followed by reaction with ethyl isocyanate. The resulting resin bound product was then subjected to palladium catalysed cyclisation–Suzuki coupling with **16c** and finally cleaved from the resin by transesterification to give **20** in 52% yield.

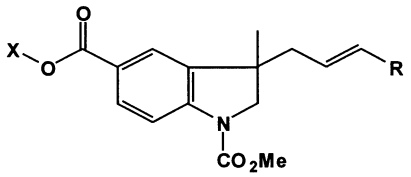
A further variant is illustrated by the reaction between resin bound allyl chloride **12** and excess butylamine followed by reaction with phenyl isocyanate. Palladium catalysed cyclisation–Suzuki coupling of this resin bound product with **16d** and finally Diels–Alder reaction with *N*-methylmaleimide (*endo* transition state) and subsequent cleavage from the resin by methanolysis gave **21** in 30% yield over five steps. ^{1}H NMR spectroscopy showed **21** to comprise a 2:1 mixture of diastereoisomers. The overall sequence generates four C–C bonds, five stereocentres and employs five reactants. This illustrates the potential for achieving considerable diversity in the libraries.

Using split and mix methodology another small library was assembled. For this purpose resin bound allyl chloride **12** was split into four equal parts (1.7 g×4) and displacement of the chloride with excess of four different primary amines was carried out separately (Table 4). For the purpose of making the library these four resin bound compounds were mixed. The resin 'pool' was split into two equal parts (3.3 g×2) and each of these was acylated using excess of two different acylating reagents (Table 4). The resin beads (eight compounds) were then mixed. The resin pool was split into two equal parts (3.5 g×2) and palladium catalysed cyclisation–Suzuki coupling with two different

Table 3. Split and mix libraries derived from **7** via cyclisation—Suzuki coupling with in situ generated boronates.

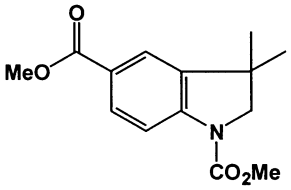
Entry	Alkyne	R	**18** (%)[a]	**19** (%)[b]
1	**15a**	*n*-Bu	84	5
2	**15b**	*c*-C_5H_9	71	5
3	**15c**	*c*-$C_6H_{11}CH_2$	93	–
4	**1k**	Ph	81	8

[a] Isolated yield.
[b] Determined from the ^{1}H NMR spectrum of the reaction mixture.



X =  17

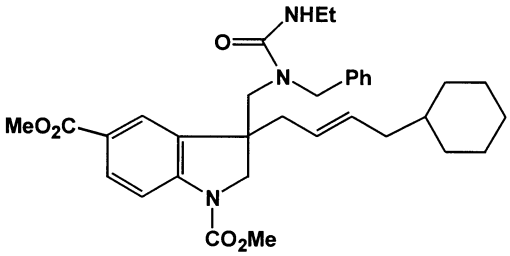
X = Me 18



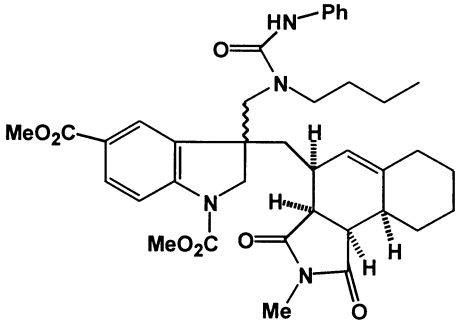
19

in situ generated boronates (Table 4) was carried out. The resin beads (16 compounds) were then mixed and the resin pool (5.6 g) subjected to the Diels–Alder reaction with dimethyl maleate. The products were cleaved from the resin by transesterification and filtered through a short plug of silica to give the library (2.4 g) which was shown to comprise a mixture of the expected 16 compounds by HPLC/MS as previously discussed.

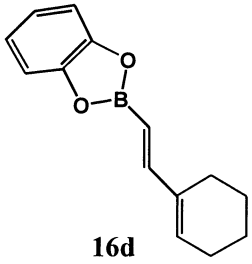
In summary, three libraries have been prepared to demonstrate the efficiency and power of the new cascade technology. The new technology offers unique series of compounds. It effects major increases in molecular complexity and occurs in excellent yield. It is capable of substantial further development in many directions including parallel synthesis of single compounds.



20



21



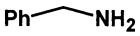
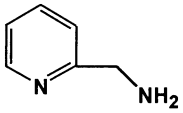
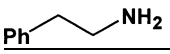
16d

3. Experimental

3.1. General

Melting points were determined on a Kofler 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 QE 300 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. Non-commercially available alkynes were synthesised according to literature methods.[10]

Table 4. Split and mix libraries derived from **12** via amination/acylation/cylisation—Suzuki coupling (in situ generated boronates)./Diels–Alder reactions

Amine[a]	Acylating agent	Alkyne	Dienophile[b]
	Ac_2O, Pyridine, MeCN, 50°C, 24 h and PhNCO, DCM, rt, 24 h	**15d** and **15e**	
			
$BuNH_2$			
			

[a] MeCN, K_2CO_3 (2 equiv.), 80°C, 24 h.
[b] Toluene, 110°C, 36 h.

3.1.1. Methyl 3-iodo-4[(methoxycarbonyl)(2-methyl-2-propenyl)amino]benzoate 6. Methyl chloroformate (4 g, 0.043 mol) was added dropwise with stirring to a solution of the methyl 3-iodo-4-aminobenzoate **5** (10 g, 0.036 mol) and pyridine (5.6 g, 0.072 mol) in dry DCM (200 ml) at 0°C. The resulting mixture was stirred at room temperature for 15 h. Water (100 ml) was then added and the mixture extracted with DCM (2×150 ml). The combined organic layers were dried ($MgSO_4$) and evaporated and the residual crude product (11.5 g, 95%) was used directly for the next stage without further purification. δ ($CDCl_3$, 300 MHz): 8.43 (d, 1H, J=1.8 Hz, ArH), 8.19 (dd, 1H, J=1.8 and 8.1 Hz, ArH), 7.95 (d, 1H, J=8.1 Hz, ArH), 7.22 (br, 1H, NH), 3.92 and 3.81 (2×s, 2×3H, 2×OMe); m/z (%): 335 (M^+, 4), 304 (100), 276 (56) and 91 (12). A solution of methyl 3-iodo-4(*N*-methoxycarbonyl)aminobenzoate (9.6 g, 0.045 mol) in DMF (75 ml) was added dropwise at 0°C to a stirred suspension of sodium hydride (50% dispersion in mineral oil, 4.44 g, 0.09 mol) in dry DMF (75 ml) and the resulting solution was stirred at room temperature for 1 h. Methallyl chloride (4.17 g, 0.045 mol) was added dropwise at 0°C to this stirred solution and the stirring continued at room temperature for 15 h. The solvent was then evaporated, water (75 ml) was added and the mixture extracted with DCM (2×100 ml). The combined organic layers were dried ($MgSO_4$), the solvent evaporated and the residual oil purified by flash chromatography eluting with 5:1 v/v hexane–ethyl acetate to give the ester **6** (9.6 g, 87%) as a pale yellow gum. (Found: C, 42.8; H, 4.1; N, 3.55; $C_{14}H_{16}INO_4$ requires: C, 43.2; H, 4.15; N, 3.6%.) δ ($CDCl_3$, 300 MHz): 8.55 (d, 1H, J=1.7 Hz, ArH), 8.0 (dd, 1H, J=1.7 and 8.2 Hz, ArH), 7.22 (d, 1H, J=8.2 Hz, ArH), 4.86 and 4.75 (2×s, 2×1H, =CH_2), 4.63 and 3.61 (2×d, 2×1H, J= 13.2 Hz, NCH_2), 3.94 and 3.65 (2×s, 2×3H, 2×OMe), and 1.81 (s, 3H, Me); m/z (%): 389 (M^+, 8), 358 (100), 330 (70) and 299 (12).

3.1.2. Hydrolysis of methyl ester 6 and attachment to the resin 7. Ester **6** (6.25 g, 0.016 mol) was treated with 2 M NaOH (35 ml) in THF (35 ml) and stirred for 15 h at 45°C. The THF was removed under reduced pressure, the aqueous mixture neutralised with 2N HCl (35 ml) and extracted with ether (3×75 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give acid (5.66 g, 94%) as colourless solid which was used for the next step without further purification. δ ($CDCl_3$, 300 MHz): 8.59 (s, 1H, ArH), 8.05 and 7.2 (2×d, 2×1H, J=8.1 Hz, ArH), 4.83 and 4.77 (2×s, 2×1H, =CH_2), 4.61 and 3.6 (2×d, 2×1H, J=14.2 Hz, NCH_2), 3.67 (s, 3H, OMe), and 1.8 (s, 3H, Me). DCM (30 ml) was added to Wang resin (loading 1.2 mmol/g) (6.25 g, 7.5 mmol) and the resin allowed to swell for 5 min. Acid (5.62 g, 0.015 mol) in DCM (40 ml) and diisopropylcarbodiimide (DIPCDI) (1.92 g, 0.015 mol) were then added followed by DMAP (0.045 g, 0.37 mmol) after 10 min. The mixture was stirred slowly for 24 h, then filtered and washed successively with MeOH, DCM and ether and dried under vacuum to give the resin bound aryl iodide **7** (8.85 g).

3.2. General procedure for palladium catalysed cascade hydrostannylation—cyclisation–anion capture

A solution of terminal alkyne (1.69 mmol), tris(dibenzylideneacetone) dipalladium(0) (0.0423 mmol) and tris-(2-furyl)phosphine (0.169 mmol) in dry toluene (20 ml) was stirred and cooled at 0°C and tributyltin hydride (1.69 mmol) added. After 5 min the cooling bath was removed and stirring continued for 2 h at room temperature. The vinylstannane was readily detected in the ^1H NMR spectrum (presence of olfinic protons) of the crude product. After addition of resin bound aryl iodide **7** (1 g, 0.84 mmol) the mixture was heated at 110°C for 8–12 h. The resin was then filtered off, washed thoroughly with MeOH, DCM and ether and dried under vaccum. Transesterification was carried out using NaCN (0.4 g, 0.84 mmol) and Et_3N (0.57 g, 5.9 mmol) in 1:3 v/v MeOH–THF (10 ml) and the mixture was heated at 50°C for 2 days. Following removal of the resin by filtration, evaporation of the filtrate afforded the product.

3.2.1. 3-Methyl-3-(2-phenylcarbamoyl-allyl)2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9a. Prepared from alkyne **1a** by the general procedure. Hydrostannylation gave only α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with 2:1 v/v ether–hexane to afford the product **9a** (65%) as colourless prisms, mp 154–157°C. (Found: C, 67.5; H, 5.85; N, 6.55; $C_{23}H_{24}N_2O_5$ requires: C, 67.65; H, 5.9; N, 6.85%.) δ ($CDCl_3$, 300 MHz): 7.92–7.12 (m, 8H, ArH), 5.47 and 4.95 (2×s, 2×1H, =CH_2), 4.58 and 4.18 (2×d, 2×1H, J=11.8 Hz, NCH_2), 3.82 and 3.5 (2×s, 2×3H, 2×OMe), 2.88 and 2.51 (2×d, 2×1H, J= 13.2 Hz, CH_2–C=) and 1.42 (s, 3H, Me); m/z (%): 408 (M^+, 1), 377 (7), 248 (84), 216 (51) and 161 (100).

3.2.2. 3-Methyl-3-(2-phenylaminomethyl-allyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethylester 9b and 3-methyl-3-((*E*)-4-phenylamino-but-2-enyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 10b. Prepared from alkyne **1b** by the general procedure. Hydrostannylation gave 85:15 ratio of α- and β-vinylstannanes. After cyclisation and transesterification the crude product comprised a 3:1 mixture of **9b** and **10b**. Flash chromatography eluting with 1:2 v/v ether–hexane gave **9b** as colourless prisms, mp 109–112°C, and the minor isomer **10b** contaminated with **9b**. The total yield was 86%.

9b: (found: C, 69.75; H, 6.75; N, 7.0; $C_{24}H_{26}N_2O_4$ requires: C, 70.05; H, 6.65; N, 7.1%). δ ($CDCl_3$, 300 MHz): 7.96 (d, 2H, J=7.3 Hz, ArH), 7.84 (s, 1H, ArH), 7.1 (t, 2H, J= 7.6 Hz, ArH), 6.65 (t, 1H, 7.5 Hz, ArH), 6.41 (d, 2H, J= 6.5 Hz, ArH), 5.12 and 4.8 (2×s, 2×1H, =CH_2), 4.13 and 3.71 (2×d, 2×1H, J=11.1 Hz, NCH_2), 3.87 and 3.83 (2×s, 2×3H, 2×OMe), 3.65 (br, 1H, NH), 3.25 (br, 2H, NCH_2), 2.55 and 2.4 (2×d, 2×1H, J=13.9 Hz, CH_2–C=) and 1.12 (s, 3H, Me); m/z (%): 394 (M^+, 56), 363 (12), 248 (55), 216 (31) and 146 (100).

10b: δ ($CDCl_3$, 300 MHz): 7.95 (d, 2H, J=7.3 Hz, ArH), 7.75 (s, 1H, ArH), 7.15 (t, 2H, J=7.6 Hz, ArH), 6.65 (t, 1H, 7.5 Hz, ArH), 6.55 (d, 2H, J=6.5 Hz, ArH), 5.55 (m, 2H, 2×=CH), 3.84 and 3.8 (2×s, 2×3H, 2×OMe), 3.6 (m, 4H, 2×NH_2), 3.25 (br, 2H, NCH_2), 2.32 (m, 2H, CH_2–C=) and 1.31 (s, 3H, Me).

3.2.3. 3-(2-Benzylcarbamoyl-allyl)-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9c. Prepared from alkyne **1c** by the general procedure. Hydrostannylation gave only α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with ether to afford the product **9c** (72%) as colourless prisms, mp 52–55°C. (Found: C, 67.95; H, 6.25; N, 6.45; $C_{24}H_{26}N_2O_5$ requires: C, 68.25; H, 6.2; N, 6.65%.) δ ($CDCl_3$, 300 MHz): 7.9 (d, 1H, *J*=7.8 Hz, ArH), 7.76 (s, 1H, ArH), 7.29 (m, 6H, ArH), 6.14 (br, 1H, NH), 5.44 and 4.98 (2×s, 2×1H, $=CH_2$), 4.27 (t, 2H, *J*=5.8 Hz, CH_2Ph), 4.1 and 3.61 (2×d, 2×1H, *J*=11.2 Hz, NCH_2), 3.84 and 3.77 (2×s, 2×3H, 2×OMe), 2.78 and 2.59 (2×d, 2×1H, *J*=13.3 Hz, CH_2–C=) and 1.35 (s, 3H, Me); *m/z* (%): 422 (M^+, 1), 391 (7), 248 (55), 216 (41), 175 (100) and 91 (37).

3.2.4. 3-{2-[(Acetyl-benzyl-amino)-methyl]-allyl}-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9d. Prepared from alkyne **1d** by the general procedure. Hydrostannylation gave only α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with ether to afford the product **9d** (59%) as a pale yellow gum. (Found: C, 68.8; H, 6.55; N, 5.85; $C_{26}H_{30}N_2O_5$ requires: C, 69.3; H, 6.7; N, 6.2%.) δ ($CDCl_3$, 300 MHz). An asterisk indicates the presence of a pair of signals of almost equal intensity which represent the same proton(s) of the amide rotamers: 7.84–7.0 (m, 8H, ArH), 5.91 and 4.78 (2×s, 2×1H, $=CH_2$, 4.86* and 4.72*), 4.15–4.34 (m, 2H, CH_2Ph), 3.8 and 3.82 (2×s, 2×3H, 2×OMe), 3.51–3.72 (m, 2H, NCH_2), 3.15 and 3.38 (2×d, 2×1H, *J*=13.2 Hz, NCH_2), 2.37 (m, 2H, CH_2–C=), 2.14 (s, 3H, $COCH_3$, 1.84*) and 1.4 (s, 3H, Me); *m/z* (%): 451 (M^++1, 2), 419 (20), 248 (91), 203 (90) and 91 (100).

3.2.5. 3-(2-Imidazol-1-ylmethyl-allyl)-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9e and 3-((*E*)-4-imidazol-1-yl-but-2-enyl)-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 10e. Prepared from alkyne **1e** by the general procedure. Hydrostannylation gave 87:13 ratio of α- and β-vinylstannane (^1H NMR). After cyclisation and transesterification the crude product comprised a 3:1 mixture of **9e** and **10e**. Flash chromatography eluting with 95:5 v/v ethyl acetate–methanol gave the products **9e** and **10e** in 65% combined yield as pale yellow gums.

9e: (found: C, 64.7; H, 5.95; N, 10.95; $C_{20}H_{23}N_3O_4$ requires: C, 65.0; H, 6.25; N, 11.35%). δ ($CDCl_3$, 300 MHz): 8.05 (d, 2H, *J*=7.9 Hz, ArH), 7.81, 7.25, 7.05 and 6.68 (4×s, 4×1H, ArH), 4.98 and 4.77 (2×s, 2×1H, $=CH_2$), 4.1 and 3.75 (2×d, 2×1H, *J*=13.1 Hz, NCH_2), 3.92 (s, 3H, OMe), 3.82 (m, 5H, OMe and NCH_2), 2.3 (s, 2H, CH_2–C=) and 1.41 (s, 3H, Me); *m/z* (%): 369 (M^+, 7), 338 (11), 248 (81), 216 (53) and 122 (100).

10e: δ ($CDCl_3$, 300 MHz): 7.97 (d, 2H, *J*=8.0 Hz, ArH), 7.75, 7.41, 7.02 and 6.78 (4×s, 4×1H, ArH), 5.6 and 5.4 (2×m, 2×1H, 2×=CH), 4.41 (d, 1H, 7.5 Hz, NCH_2), 3.91 and 3.84 (2×s, 2×3H, 2×OMe), 3.86 and 3.65 (2×d, 2H, *J*=13.5 Hz, NCH_2), 2.38 (m, 2H, CH_2–C=) and 1.39 (s, 3H, Me); *m/z* (%): 369 (M^+, 6), 338 (11), 262 (12), 248 (81), 122 (100) and 59 (32).

3.2.6. 3-[2-(1-Methoxycarbonyl-2-phenyl-ethylcarbamoyl)-allyl]-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9f. Prepared from alkyne **1f** by the general procedure. Hydrostannylation gave only α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with ether to afford the product **9f** (62%) as colourless prisms, mp 65–68°C (1:1 mixture of diastereoisomers). (Found: C, 65.3; H, 6.0; N, 5.5; $C_{27}H_{30}N_2O_7$ requires: C, 65.55; H, 6.10; N, 5.65%.) δ ($CDCl_3$, 300 MHz): 7.89 (m, 3H, ArH), 7.3–7.05 (m, 5H, ArH), 6.2 and 6.15 (2×d, 1H, *J*=7.6 Hz, NH, isomers), 5.43, 5.42, 5.07 and 5.02 (4×s, 2H, $=CH_2$, isomers), 4.8 and 4.79 (2×q, 1H, *J*=7.9 Hz, NCH, isomers), 4.05 (dd, 1H, *J*=11.3 and 5 Hz, CHPh), 3.88 and 3.87 (2×s, 3H, 2×OMe, isomers), 3.81 (s, 3H, OMe), 3.73 and 3.72 (2×s, 3H, 2×OMe, isomers), 3.59 (t, 1H, *J*=11.5 Hz, CHPh), 3.15 (m, 2H, NCH_2), 2.81 2.69, 2.67 and 2.5 (4×d, 2H, *J*=13.4 Hz, CH_2–C=, isomers), 1.31 and 1.3 (2×s, 3H, Me, isomers); *m/z* (%): 494 (M^+, 5), 463 (10), 248 (100), 216 (35), 144 (30) and 91 (40).

3.2.7. 3-Methyl-3-(2-pyrazol-1-ylmethyl-allyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9g. Prepared from alkyne **1g** by the general procedure. Hydrostannylation gave only the α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with 3:1 v/v ether–hexane to afford the product **9g** (74%) as a pale yellow gum. (Found: C, 64.7; H, 6.15; N, 10.9; $C_{20}H_{23}N_3O_4$ requires: C, 65.0; H, 6.25; N, 11.35%.) δ ($CDCl_3$, 300 MHz): 7.9 (d, 2H, *J*=7.8 Hz, ArH), 7.8, 7.45, 7.18 and 6.21 (4×s, 4×1H, ArH), 4.92 and 4.8 (2×s, 2×1H, $=CH_2$), 4.27 (s, 2H, NCH_2), 4.1 and 3.71 (2×d, 2×1H, *J*=11.2 Hz, NCH_2), 3.9 and 3.82 (2×s, 2×3H, 2×OMe), 2.78 (s, 2H, CH_2–C=) and 1.41 (s, 3H, Me); *m/z* (%): 370 (M^++1, 12), 338 (7), 248 (35), 216 (26), 122 (100) and 59 (22).

3.2.8. 3-(2-Benzotriazol-1-ylmethyl-allyl)3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9h. Prepared from alkyne **1h** by the general procedure. Hydrostannylation gave only the α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with 2:1 v/v ether–hexane to afford the product **9h** (79%) as colourless prisms, mp 120–123°C. (Found: C, 65.7; H, 5.9; N, 13.35; $C_{23}H_{24}N_4O_4$ requires: C, 65.7; H, 5.75; N, 13.3%.) δ ($CDCl_3$, 300 MHz): 8.0 (m, 3H, ArH), 7.8 (s, 1H, ArH), 7.21–7.47 (m, 3H, ArH), 4.96–4.7 (m, 4H, NCH_2 and $=CH_2$), 4.18 and 3.77 (2×d, 2×1H, *J*=11.2 Hz, NCH_2), 3.9 (s, 6H, 2×OMe), 2.4 (s, 2H, CH_2–C=) and 1.41 (s, 3H, Me); *m/z* (%): 420 (M^+, 12), 389 (6), 248 (60), 216 (36), 173 (100) and 59 (16).

3.2.9. 3-[2-(2-Methoxycarbonyl-phenyl)allyl]-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9i. Prepared from alkyne **1i** by the general procedure. Hydrostannylation gave only the α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with 2:1 v/v ether–hexane to afford the product **9i** (70%) as colourless prisms, mp 135–138°C. (Found: C, 67.8; H, 6.1; N, 3.2; $C_{24}H_{25}NO_6$ requires: C, 68.05; H, 5.95; N, 3.3%.) δ

($CDCl_3$, 300 MHz): 7.8 (m, 3H, ArH), 7.6 (s, 1H, ArH), 7.25 (m, 2H, ArH), 6.95 (d, 1H, J=6.8 Hz, ArH), 5.03 and 5.0 (2×s, 2H, =CH_2), 3.9 (m, 7H, NCH and 2×OMe), 3.8 (s, 3H, OMe), 3.57 (d, 1H, J=13.2 Hz, NCH), 2.85 and 2.78 (2×d, J=13.5 Hz, 2H, CH_2–C=) and 1.3 (s, 3H, Me); *m/z* (%): 423 (M^+, 2), 248 (100), 216 (40), 145 (26) and 130 (11).

3.2.10. 3-[2-(2-Acetylamino-phenyl)-allyl]-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9j. Prepared from alkyne **1j** by the general procedure. Hydrostannylation gave only the α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with 2:1 v/v ether–hexane to afford the product **9j** (58%) as a colourless gum. (Found: C, 68.0; H, 6.1; N, 6.6; $C_{24}H_{26}N_2O_5$ requires: C, 68.25; H, 6.2; N, 6.65%.) δ ($CDCl_3$, 300 MHz): 8.1 (d, 1H, J=7.2 Hz, ArH), 7.85 (m, 2H, ArH and NH), 7.62 (s, 1H, ArH), 7.2–7.0 (m, 4H, ArH), 5.2 and 5.02 (2×s, 2H, =CH_2), 3.9 (s, 3H, OMe), 3.75 (m, 4H, NCH and OMe), 3.5 (d, 1H, J=13.0 Hz, NCH), 2.87 and 2.8 (2×d, J=13.0 Hz, 2H, CH_2–C=), 2.0 (s, 3H, COMe) and 1.4 (s, 3H, Me); *m/z* (%): 422 (M^+, 2), 391 (5), 248 (100), 216 (40), 132 (76) and 84 (60).

3.2.11. 3-Methyl-3-((*E*)-3-phenyl-allyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 10k and 3-methyl-3-(2-phenyl-allyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 9k. Prepared from alkyne **1k** by the general procedure. Hydrostannylation gave an 80:20 ratio of a α- and β-vinylstannanes (^1H NMR). After cyclisation and transesterification the crude product comprised a 71:29 mixture of **10k** and **9k**. Flash chromatography eluting with 1:1 v/v ethyl acetate–hexane gave the products **10k** and **9k** in 84% combined yield as pale yellow gums.

10k: colourless prisms from ether, mp 99–102°C. (Found: C, 72.1; H, 6.4; N, 3.5; $C_{22}H_{23}NO_4$ requires: C, 72.3; H, 6.3; N, 3.85%.) δ ($CDCl_3$, 300 MHz): 7.95–7.8 (m, 3H, ArH), 7.31–7.12 (m, 5H, ArH), 6.05 (d, 1H, J=16.5 Hz, PhCH=), 6.0 (m, 1H, CH=), 4.03 and 3.7 (2×d, 2H, 13.5 Hz, NCH_2), 3.91 and 3.8 (2×s, 2×3H, 2×OMe), 2.48 (m, 2H, CH_2–C=) and 1.41 (s, 3H, Me); *m/z* (%): 365 (M^+, 6), 298 (6), 248 (100), 216 (35) and 59 (32).

9k: δ ($CDCl_3$, 300 MHz): 7.95–7.8 (m, 3H, ArH), 7.31–7.12 (m, 5H, ArH), 5.15 and 4.81 (2×s, 2×1H, =CH_2), 3.75 and 3.42 (2×d, 2×1H, J=13.1 Hz, NCH_2), 3.91 and 3.8 (2×s, 2×3H, 2×OMe), 2.82 and 2.76 (2×d, 2H, J=12.5 Hz, CH_2–C=) and 1.41 (s, 3H, Me); *m/z* (%): 365 (M^+, 1), 276 (7), 248 (100), 189 (24) and 59 (20).

3.2.12. 3-Methyl-3-(2-phenylcarbamoyl-allyl)-2,3-dihydro-indole-1,5-dicarboxylic acid 1-methyl ester 11. Prepared by the general procedure. Hydrostannylation gave only the α-vinylstannane. After cyclisation the product was cleaved from the resin using 20% TFA in CH_2Cl_2 at room temperature over 3 h. After the normal work up the crude product was purified by flash chromatography eluting with 4:1 v/v ether–hexane to afford the product (85%) as colourless prisms, mp 89–91°C. (Found: C, 67.0; H, 5.6; N, 7.1; $C_{22}H_{22}N_2O_5$ requires: C, 66.85; H, 5.7; N, 7.05%.) δ (CD_3COCD_3, 300 MHz): 9.05 (br, 1H, OH), 7.82 (m, 3H, ArH), 7.63 (d, 2H, J=7.6 Hz, ArH), 7.28 (t, 2H, J=7.8 Hz, ArH), 7.02 (t, 1H, J=7.8 Hz, ArH), 5.77 and 5.21 (2×s, 2×1H, =CH_2), 4.2 and 3.62 (2×d, 2×1H, J=11.2 Hz, NCH_2), 3.6 (s, 3H, OMe), 2.94 and 2.68 (2×d, 2×1H, J=12.8 Hz, CH_2–C=) and 1.41 (s, 3H, Me); *m/z* (%): 394 (M^+, 2), 302 (3), 234 (65), 161 (100), 131 (40) and 77 (15).

3.2.13. Resin bound allyl chloride 12. A solution of methyl 3-iodo-4(*N*-methoxycarbonyl)aminobenzoate (1.69 g, 0.005 mol) in DMF (25 ml) was added dropwise at 0°C to a stirred suspension of sodium hydride (50% dispersion in mineral oil, 0.242 g, 0.01 mol) in dry DMF (25 ml) and the resulting solution was stirred at room temperature for 1 h. 3-Chloro-2-chloromethyl-1-propene (1.26 g, 0.01 mol) was added dropwise at 0°C to this stirred solution and the stirring continued at room temperature for 15 h. The solvent was then evaporated, water (25 ml) added and the mixture extracted with DCM (2×50 ml). The combined organic layers were dried ($MgSO_4$), the solvent evaporated and the residual oil purified by flash chromatography eluting with 2:1 v/v hexane–ether to give the ester (1.8 g, 85%) as a pale yellow gum. (Found: C, 39.5; H, 3.5; N, 3.2; I, 30.0; $C_{14}H_{15}ClINO_4$ requires: C, 39.7; H, 3.55; N, 3.3; I, 29.95%.) δ ($CDCl_3$, 300 MHz): 8.55 (d, 1H, J=1.7 Hz, ArH), 8.0 (dd, 1H, J=1.7 and 8.2 Hz, ArH), 7.25 (d, 1H, J=8.2 Hz, ArH), 5.3 and 5.03 (2×s, 2×1H, =CH_2), 4.62 and 3.95 (2×d, 2×1H, J=13.1 Hz, NCH_2), 4.2 and 4.13 (2×d, 2H, J=12.9 Hz, CH_2Cl), 3.9 and 3.65 (2×s, 2×3H, 2×OMe); *m/z* (%): 423 (M^+, 8), 388 (34), 392 (100), and 364 (12).

Hydrolysis of methyl ester and attachment to the resin were carried out as described for resin bound aryl iodide **7**.

3.2.14. 3-[(Acetyl-benzyl-amino)-methyl]-3,2-(2-benzotriazol-1-ylmethyl-allyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 14. Benzylamine (0.45 g, 4.2 mmol) and K_2CO_3 (0.58 g, 4.2 mmol) were added to a stirred suspension of the resin bound allyl chloride **5** (12 g, 1.05 mmol) (loading 0.87 mmol/g) in MeCN (15 ml) under a nitrogen atmosphere. The resulting mixture was heated at 80°C for 12 h. The resin was then filtered off, washed thoroughly with water, MeOH, DCM and ether and dried under vaccum. Ac_2O (0.43 g, 4.2 mmol) and pyridine (0.33 g, 4.2 mmol) were added to a stirred suspension of the solid support in MeCN (15 ml) under nitrogen atmosphere. The resulting mixture was heated at 50°C for 12 h. The resin was then filtered off, washed throughly with MeOH, DCM and ether and dried under vacuum. Compound **14** was then prepared from this resin by the general procedure. Hydrostannylation gave only the α-vinylstannane. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with 2:1 v/v ether–hexane to afford the product **14** (70%) as a pale yellow gum. (Found: C, 67.55; H, 5.7; N, 12.4; $C_{32}H_{33}N_5O_5$ requires: C, 67.7; H, 5.8; N, 12.35%.) δ ($CDCl_3$, 300 MHz): 8.1 (m, 3H, ArH), 7.8 (s, 1H, ArH), 7.5–7.25 (m, 6H, ArH), 6.91 (m, 2H, ArH), 5.05 and 4.8 (2×s, 2H, =CH_2), 4.85 and 4.75 (2×d, 2×1H, J=13.8 Hz, NCH_2), 4.34 and 4.1 (2×d, 2×1H, J=13.5 Hz, NCH_2), 4.3 (d, 1H, J=13.2 Hz, NCH), 3.95–3.72 (m, 8H, 2×NCH and 2×OMe), 3.22 (d, 1H, J=13.7 Hz, NCH), 2.55 and 2.42 (2×d, J=13.5 Hz, 2H, CH_2–C=) and 2.1 (s, 3H, COMe); *m/z* (%): 567 (M^+, 2), 536 (4), 405 (37), 373 (100), 120 (86) and 91 (85).

3.3. General procedure for cascade hydroboration—palladium catalysed cyclisation–anion capture

A mixture of terminal alkyne (5 equiv., 4.23 mmol) and catecholborane (5 equiv., 4.23 mmol) was stirred under nitrogen in the absence of solvent at 70°C for 1.5 h. Water (3 ml) was then added and the mixture was stirred for a further 1 h at 80°C. After addition of resin bound aryl iodide **7** (1 equiv., 0.84 mmol), $Pd(OAc)_2$ (10 mol%, 0.084 mmol), PPh_3 (20 mol%, 0.16 mmol), Na_2CO_3 (3 equiv., 2.5 mmol) Et_4NCl (1 equiv., 0.84 mmol) and toluene (15 ml) the mixture was heated at 110°C for 12 h. The resin was then filtered off, washed throughly with H_2O, MeOH, DCM and ether and dried under vaccum. After transesterification as described earlier and following removal of the resin by filtration, evaporation of the filtrate afforded the product.

3.3.1. 3-(*E*)-Hept-2-enyl-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 18a. Prepared from alkyne **15a** by the general procedure. The crude product was purified by flash chromatography eluting with 1:5 v/v ether–petroleum ether to afford the product **18a** (84%) as a colourless gum. (Found: C, 69.4; H, 8.0; N, 4.05; $C_{20}H_{27}NO_4$ requires: C, 69.55; H, 7.85; N, 4.05%.) δ ($CDCl_3$, 300 MHz): 7.9–7.76 (m, 3H, ArH), 5.42 and 5.2 (2×m, 2×1H, 2×=CH), 3.95 and 3.61 (2×d, 2×1H, J=11.1 Hz, NCH_2), 3.9 and 3.81 (2×s, 2×3H, 2×OMe), 2.28 (m, 2H, CH_2–C=), 1.9 (m, 2H, CH_2–C=), 1.38 (s, 3H, Me), 1.25 (m, 4H, 2×CH_2) and 0.82 (t, 3H, J=6.7 Hz, Me); *m/z* (%): 346 (M^++1, 5), 314 (4), 248 (100), 216 (50), 130 (25) and 77 (6).

3.3.2. 3-((*E*)-3-Cyclopentyl-allyl)-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 18b. Prepared from alkyne **15b** by the general procedure. The crude product was purified by flash chromatography eluting with 1:5 v/v ether–petroleum ether to afford the product **18b** (71%) as a colourless gum. (Found: C, 70.6; H, 7.2; N, 3.65; $C_{21}H_{27}NO_4$ requires: C, 70.5; H, 7.6; N, 3.9%.) δ ($CDCl_3$, 300 MHz): 7.9–7.75 (m, 3H, ArH), 5.4 (dd, 1H, J=16.2 and 7.4 Hz, =CH), 5.15 (m, 1H, =CH), 3.95 and 3.6 (2×d, 2×1H, J=11.0 Hz, NCH_2), 3.9 and 3.82 (2×s, 2×3H, 2×OMe), 2.3 (m, 3H, CH_2–C= and CH–C=), 1.8–1.5 (m, 6H, 3×CH_2), 1.39 (s, 3H, Me) and 1.2 (m, 2H, CH_2); *m/z* (%): 357 (M^+ 5), 326 (10), 248 (100), 216 (35), 189 (24) and 145 (30).

3.3.3. 3-((*E*)-4-Cyclohexyl-but-2-enyl)-3-methyl-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 18c. Prepared from alkyne **15c** by the general procedure. The crude product was purified by flash chromatography eluting with 1:5 v/v ether–petroleum ether to afford the product **18c** (93%) as a pale yellow thick oil. (Found: C, 71.15; H, 7.9; N, 3.35; $C_{23}H_{31}NO_4$ requires: C, 71.65; H, 8.1; N, 3.65%.) δ ($CDCl_3$, 300 MHz): 7.9–7.7 (m, 3H, ArH), 5.4 and 5.1 (2×m, 2×1H, 2×=CH), 3.95 and 3.61 (2×d, 2×1H, J= 11.3 Hz, NCH_2), 3.9 and 3.8 (2×s, 2×3H, 2×OMe), 2.28 (m, 2H, CH_2–C=), 1.8 (t, 2H, J=6.8 Hz, CH_2–C=), 1.7–1.5 (m, 5H, 2×CH_2 and CH), 1.38 (s, 3H, Me), 1.18 (m, 4H, 2×CH_2) and 0.8 (m, 2H, CH_2); *m/z* (%): 385 (M^+ 10), 354 (71), 248 (100), 216 (30), 189 (15) and 145 (20).

3.3.4. 3-Methyl-3-((*E*)-3-phenyl-allyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 18k. Prepared from alkyne **1k** by the general procedure. The crude product was purified by flash chromatography eluting with 1:4 v/v ether–petroleum ether to afford the product **18k** (81%) as colourless prisms from ether, mp 100–103°C. (Found: C, 71.8; H, 6.55; N, 3.4; $C_{22}H_{23}NO_4$ requires: C, 72.3; H, 6.35; N, 3.85%.) δ ($CDCl_3$, 300 MHz): 7.95–7.81 (m, 3H, ArH), 7.3–7.1 (m, 5H, ArH), 6.05 (d, J=15.1 Hz, 1H, =CH), 6.0 (m, 1H, =CH), 4.0 and 3.61 (2×d, 2×1H, J=13.5 Hz, NCH_2), 3.85 and 3.77 (2×s, 2×3H, 2×OMe), 2.48 (m, 2H, CH_2–C=) and 1.4 (s, 3H, Me); *m/z* (%): 366 (M^++1, 9), 334 (4), 248 (100), 216 (28), 145 (25) and 77 (10).

3.3.5. 3-(1-Benzyl-3-ethyl-ureidomethyl)-3-((*E*)-4-cyclohexyl-but-2-enyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 20. Benzylamine (0.45 g, 4.2 mmol) and K_2CO_3 (0.58 g, 4.2 mmol) were added to a stirred suspension of the resin bound allyl chloride **12** (12 g, 1.05 mmol) (loading 0.87 mmol/g) in MeCN (15 ml) under a nitrogen atmosphere. The resulting mixture was heated at 80°C for 12 h. The resin was then filtered off, washed throughly with water, MeOH, DCM and ether and dried under vaccum. Ethyl isocyanate (0.29 g, 4.2 mmol) was added to a stirred suspension of the solid support in DCM (15 ml) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 24 h. The resin was then filtered off, washed throughly with MeOH, DCM and ether and dried under vacuum. Compound **20** was then prepared from this resin by the general procedure using alkyne **15c**. After cyclisation and transesterification the crude product was purified by flash chromatography eluting with 1:1 v/v ethyl acetate–hexane to afford the product **20** (52%) as colourless prisms from ether, mp 55–58°C. (Found: C, 70.3; H, 7.70; N, 7.3; $C_{33}H_{43}N_3O_5$ requires: C, 70.55; H, 7.70; N, 7.5%.) δ ($CDCl_3$, 300 MHz): 7.92 (m, 2H, ArH), 7.81 (s, 1H, ArH), 7.25 (m, 3H, ArH), 6.95 (d, 2H, J=6.9 Hz, ArH), 5.44 and 5.1 (2×m, 2×1H, 2×=CH_2), 4.4 and 4.04 (m, 5H, 2×NCH_2 and NCH), 3.91 and 3.85 (2×S, 2×3H, 2×OMe), 3.43 (d, 1H, J=14.5 Hz, NCH), 3.22 (q, 2H, J=6.9 Hz, NCH_2CH_3), 2.4 (m, 2H, CH_2–C=), 1.81 (t, 2H, J=6.8 Hz, CH_2–C=), 1.42–1.7 (m, 5H, 2×CH_2 and CH), 1.1–1.25 (m, 4H, 2×CH_2), 0.95 (t, 3H, J=6.9 Hz, CH_3) and 0.8 (m, 2H, CH_2); *m/z* (%): 561 (M^+, 6), 530 (5), 457 (15), 234 (15), 120 (100) and 91 (85).

3.3.6. 3-(1-Butyl-3-phenyl-ureidomethyl)-3-(2-methyl-1,3-dioxo-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo(*E*) isoindol-4-ylmethyl)-2,3-dihydro-indole-1,5-dicarboxylic acid dimethyl ester 21. *n*-Butylamine (0.30 g, 4.2 mmol) and K_2CO_3 (0.58 g, 4.2 mmol) were added to a stirred suspension of the resin bound allyl chloride **12** (12 g, 1.05 mmol) (loading 0.87 mmol/g) in MeCN (15 ml) under a nitrogen atmosphere. The resulting mixture was heated at 80°C for 12 h. The resin was then filtered off, washed throughly with water, MeOH, DCM and ether and dried under vaccum. Phenyl isocyanate (0.5 g, 4.2 mmol) was added to a stirred suspension of the solid support in DCM (15 ml) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 24 h. The resin was then filtered off, washed throughly with MeOH, DCM and ether and dried under vaccum. Hydroboration of **15d** and Suzuki coupling were carried out according to the general procedure. *N*-Methylmaleimide (0.46 g, 4.2 mmol)

was added to a stirred suspension of the solid support in toluene (15 ml). The resulting mixture was heated at 110°C for 24 h. The resin was then filtered off, washed thoroughly with MeOH, DCM and ether and dried under vacuum. After transesterification the crude product was purified by flash chromatography eluting with 2:1 v/v ethyl acetate–hexane to afford the product **21** (2:1 mixture diastereoisomers) (52%) as pale yellow prisms. mp 80–83°C. (Found: C, 67.7; H, 6.8; N, 8.3; $C_{38}H_{46}N_4O_7$ requires: C, 68.0; H, 6.90; N, 8.35%.) δ ($CDCl_3$, 300 MHz). An asterisk indicates the presence of a pair of signals (2:1) which represent the same proton(s) of the minor diastereoisomer. 8.10–7.90 (m, 3H, ArH), 7.18–7.31 (m, 4H, ArH), 7.10 (m, 1H, ArH), 6.35 (br, 1H, CONH), 5.22 (d, 1H, J= 3.5 Hz, CH═, 5.05*), 4.3 (m, 3H, 3×NCH), 3.95 (m, 1H, NCH), 3.87 (s, 3H, OMe, 3.85*), 3.75 (brs, 3H, OMe), 3.17 (m, 1H, NCH), 2.85 (s, 3H, NMe, 3.94*), 2.81 (m, 1H, NCH), 2.71–2.31 (m, 4H), 2.2–1.62 (m, 7H), 1.45–1.05 (m, 7H), 0.98–0.7 (m, 4H); *m/z* (%): 671 (M^++1, 5), 447 (4), 246 (6), 133 (20), 95 (38) and 55 (100).

Acknowledgements

We thank GlaxoSmithKline, Leeds University and the EPSRC for support.

References

1. Thomson, A. L.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600. Fruchthel, S. J.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17–42.
2. Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65–87. Brown, S.; Clarkson, S.; Grigg, R. *Tetrahedron* **2001**, *57*, 1347–1359. Anwar, U.; Casaschi, A.; Grigg, R. *Tetrahedron* **2001**, *57*, 1361–1367.
3. Casaschi, A.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525–7539. Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2000**, *56*, 7541–7551. Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2000**, *56*, 7553–7560.
4. Guibe, F.; Balavoine, G.; Zhang, H. X. *J. Org. Chem.* **1990**, *55*, 1857–1867.
5. Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Muzza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553–7556.
6. Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5225–5249.
7. Miyaura, N.; Ishiyama, J.; Suzuki, H.; Ishikawa, M.; sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.
8. Yanagi, T.; Ohe, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn* **1989**, *62*, 3892–3895.
9. Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Ravishankar, T.; Thorton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803–11826.
10. (a) Coppola, R. A.; Damon, R. E. *Synth. Commun.* **1993**, 2003–2010. (b) Nilsson, B. M.; Vargas, M. H.; Ringdhl, B. *J. Med. Chem.* **1992**, *35*, 285–294. (c) Papanastassion, Z. B. *J. Med. Chem.* **1967**, *10*, 701–706. (d) Capella, L.; Montevecchi, P. C.; Nanni, D. *J. Org. Chem.* **1994**, *59*, 3368–3374. (e) Barra, E. D.; de la Hoz, A.; Loupy, A.; Migallon, A. S. *Heterocycles* **1994**, *38*, 1367–1374. (f) Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *57*, 4940–4949. (g) Davini, E.; Giongo, M.; Riocci, M. *Org. Prep. Proced. Int.* **1995**, *27*, 586–589.