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Sequential decarboxylative azomethine ylide cycloaddition—palladium catalysed hydrostannylation–cyclisation-anion capture processes

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Abstract—A novel tactical combination of the iminium ion induced decarboxylative generation of azomethine ylides, from secondary acyclic and cyclic α-amino acids, and their 1,3-dipolar cycloaddition, with regioselective palladium catalysed hydrostannylation of terminal alkynes, and subsequent cyclisation-anion capture of the organostannane is described. A major increase in molecular complexity results with the formation of 5 bonds, 5 stereocentres, 2 rings and 1 tetra-substituted carbon centre. © 2001 Elsevier Science Ltd. All rights reserved.

We have been engaged in developing tactical combinations of novel 1, 3-dipolar cycloaddition chemistry and palladium catalysed reactions, for the synthesis of complex heterocycles and have previously reported examples of such processes, which combine azomethine-ylide—cycloaddition cascades with palladium-catalysed cyclisation reactions,[1–5] or with rhodium-catalysed reactions.[6] A similar approach was employed by our group in the synthesis of bicyclic β-lactams.[7]

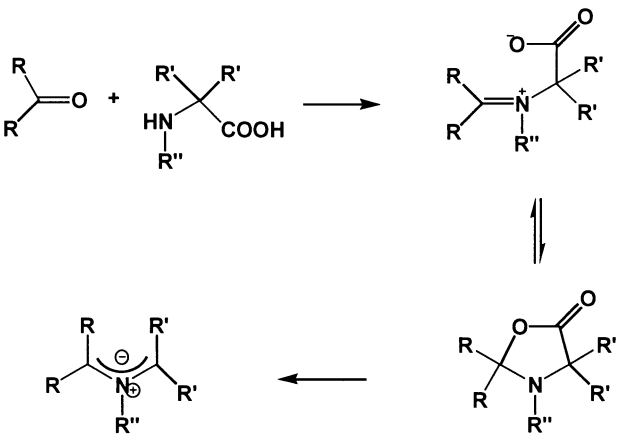
As part of our continuing interest in this type of tactical combination, we explored the decarboxylative generation of azomethine ylides from amino acids and aryl aldehydes.

Primary and secondary α-amino acids (acyclic and cyclic) react with aldehydes and ketones with concomitant decarboxylation to give non-stabilised azomethine ylides via an oxazolidine-5-one intermediate (Scheme 1).[8–11] In the presence of a suitable dipolarophile these ylides undergo a highly stereoselective cycloaddition reaction to produce cycloadducts in high yield.

Our group has also reported extensively on palladium catalysed cyclisation-anion capture processes.[12–14] This process has been developed into a powerful method for the construction of fused, bridged and spiro heterocycles. In these reactions a capture agent is required in order to form the final bond (C–C, C–N, C–H etc.) and this allows regeneration of the Pd(0) catalyst. Recently we have employed a range of such reagents in palladium catalysed molecular queuing processes.[15]

Organotin (IV) reagents are particularly attractive anion capture reagents due to their ease of preparation and tolerance of air and moisture. Recently we have described the successful implementation of palladium catalysed cascade hydrostannylation–cyclisation-anion capture processes[16–18] to synthesise novel complex heterocycles in good yield with in situ generation of organostannanes, achieved by palladium catalysed hydrostannylation of terminal alkynes bearing a β-heteroatom. The β-heteroatom ensures high regioselectivity for the α-vinylstannane.[19]

We sought to link these two disparate ring-forming reactions ie decarboxylative 1,3-dipolar cycloaddition and



Scheme 1.

Keywords: cascade reactions; palladium catalysis; Stille coupling; hydrostannylation; 13-dipolar cycloaddition.

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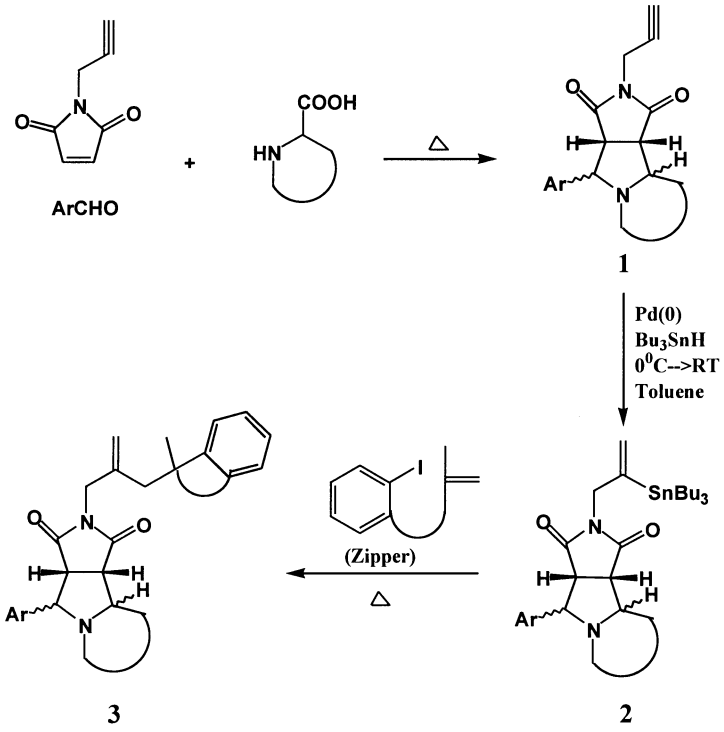
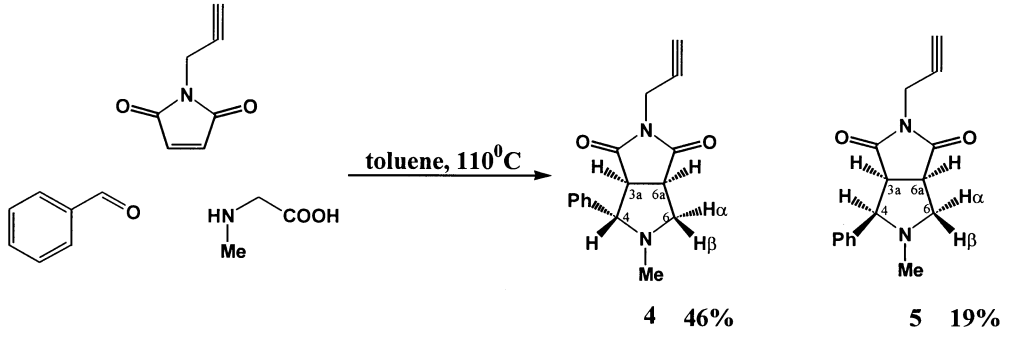


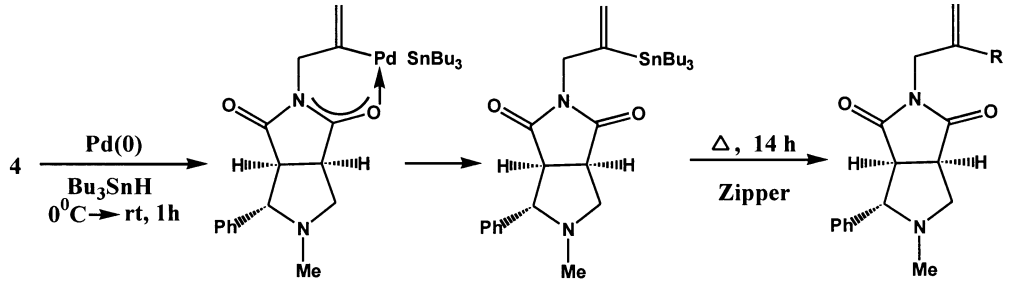
Scheme 2.

palladium catalysed cascade hydrostannylation–cyclisation-anion capture to create complex heterocycles. Our proposed reaction is summarised in Scheme 2.

Treatment of *N*-propargylmaleimide, which we have recently introduced as a dipolarophile,[6] with an aldehyde and a secondary α-amino acid should give cycloadduct **1**. Palladium catalysed hydrostannylation of the terminal acetylene bearing a β-heteroatom ensures the formation of α-vinylstannane **2**. At this stage the zipper molecule is added to the reaction to initiate cyclisation-anion capture to the polycyclic product **3**. Each cycloadduct **2** would be expected to give a 1:1 mixture of diastereoisomers in the sequence **2**→**3** due to the formation of a new stereocentre upon cyclisation in the absence of any proximate controlling stereocentres. Overall, the successful implementation of



Scheme 3.



Scheme 4.

Table 1.

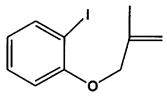
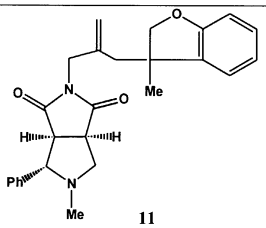
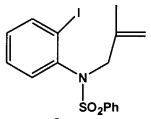
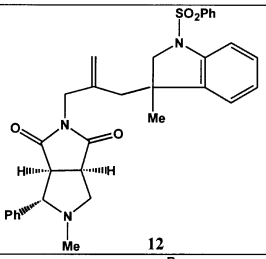
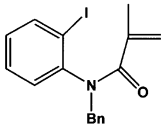
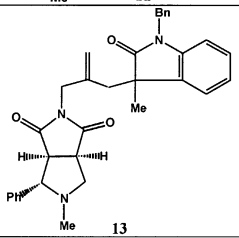
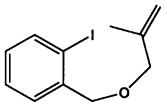
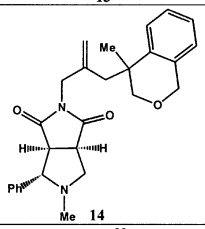
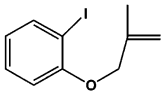
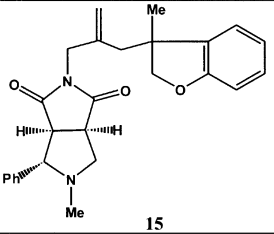
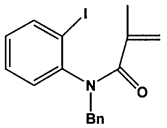
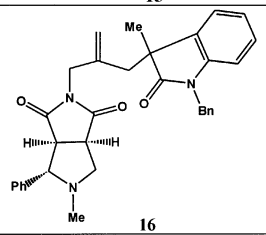
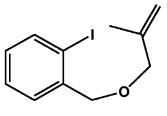
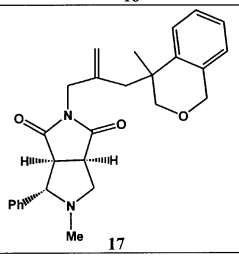
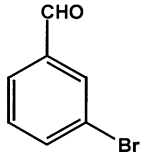
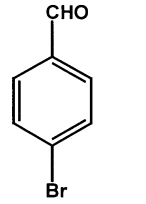
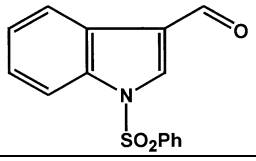
Cycloadduct	Zipper molecule	R	Yield (%)
4	 7	 11	66
4	 8	 12	45
4	 9	 13	55
4	 10	 14	46
5	 7	 15	55
5	 9	 16	42
5	 10	 17	49

Table 2.

Aldehyde	*endo/exo* **18**:**19**	Combined yield (%)
18 	2:1	59
19 	5:2	56
20 	1:0	68

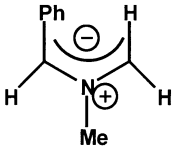
Scheme 2 would result in the formation of 5 bonds, 2 rings, 5 stereocentres and one tetra-substituted carbon centre.

1. Sarcosine as the azomethine ylide precursor

N-Propargylmaleimide was reacted with benzaldehyde and sarcosine (toluene, 110°C, 20 h) to give a 3:1 mixture of cycloadducts from which **4** and **5** were isolated in 46 and 19% yield, respectively (Scheme 3).

The stereochemistry of **4** and **5** was determined by n.O.e. experiments (see Section 4). The vicinal coupling constants between 4-H and 3a-H in **4** and **5** are 6 and 9 Hz, respectively, with the larger coupling (9 Hz) when these hydrogens are *cis*-related.

Cycloadducts **4** and **5** are presumed to arise from *endo*- and *exo*-cycloaddition respectively of the *N*-propargylmaleimide to dipole **6**.

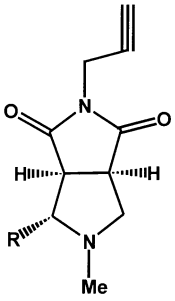


6

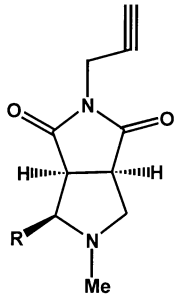
Cycloadduct **4** was then hydrostannylated (Pd(0), Bu_3SnH, toluene, 0°C to rt, 1 h). After 1 h proton NMR indicated that all of **4** had been consumed. The appropriate zipper molecule **7**–**10** was immediately added and the mixture heated at reflux (14 h) (Scheme 4), giving products **11**–**14** in 45–60% (Table 1) as inseparable 1:1 mixtures of diastereoisomers. The presence of 2 diastereoisomers was obvious by ^{1}H NMR in the case of **11**, **13** and **14** where 2 sets of signals were observed whereas in **12** the 300 MHz ^{1}H NMR spectrum ($CDCl_3$) failed to separate the signals for the diastereoisomers. Exo-adduct **5** reacted likewise with **7**, **9** and **10** under analogous conditions to give **15**–**17** as inseparable 1:1 mixtures of diastereoisomers in 42–55% yield.

The hydrostannylation step (Scheme 4) proceeded regiospecifically. No evidence for the generation of the (*E*)-β-substituted isomer was observed by ^{1}H NMR and no product from Stille coupling of the (*E*)-β-substituted stannane was detected.

Next we varied the aldehyde component in the cycloaddition step. Results are summarised in Table 2.



21

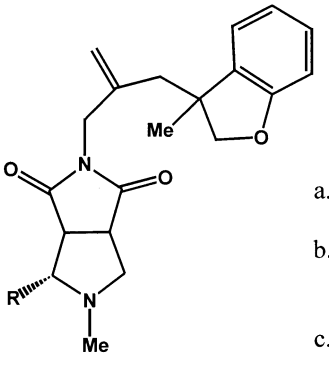


22

a. R = 3-BrC_6H_4
b. R = 4- BrC_6H_4
c. R = 3-(N-sulphonyl)indolyl

Reaction of sarcosine and *N*-propargylmaleimide (toluene, 110°C, 17–24 h) with aryl aldehydes **18**–**20** gave the expected cycloadducts **21a**–**b** and **22a**–**b** as mixtures of *endo*- and *exo*- isomers in 56–68% combined yield. The cycloaddition involving *N*-phenylsulphonyl-indole 3-carboxaldehyde **20** gave only endo isomer **21c** in 68% yield. This together with the increased reaction time (48 h) is a reflection of the steric bulk of the indole moiety.

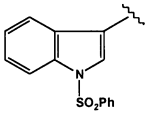
endo-Cycloadducts **21a**–**c** were hydrostannylated in situ as previously described, giving only the corresponding α-substituted stannanes which were reacted with zipper molecule **7** to give **23a**–**c** in 60–71% yield as 1:1 mixtures of diastereoisomers.



23

a. R = 3-BrC_6H_4 60%

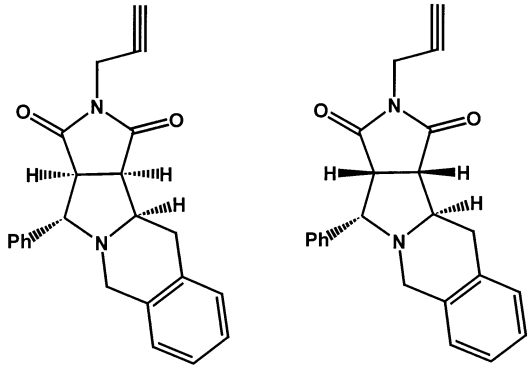
b. R = 4-BrC_6H_4 71%

c. R =  62%

2. Cyclic α-amino acids as azomethine ylide precursors

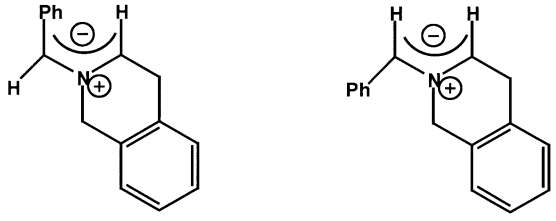
1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid reacted

with *N*-propargylmaleimide and benzaldehyde (DMF, 110°C, 20 h) to afford a 1:1 mixture of cycloadducts **24** and **25** in 44% yield. DMF was used as the solvent in this case to counteract the insolubility of the tetrahydroisoquinoline carboxylic acid in toluene.



24 **25**

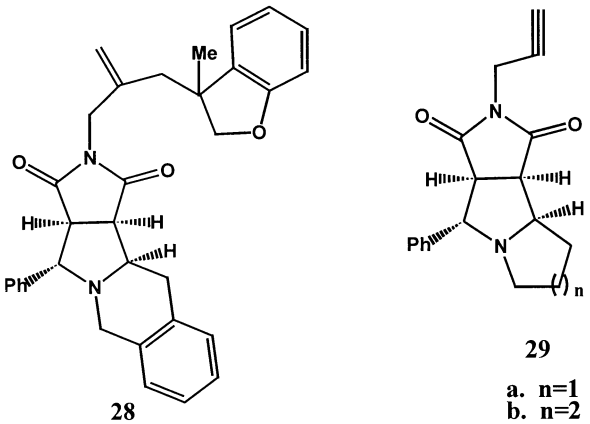
The stereochemistry of the cycloadducts was determined by comparison of the spectral data with the corresponding *N*-methylmaleimide adducts.[9] These studies indicated that both cycloadducts arose from *anti*-dipole **26**. No cycloadducts were observed from the reaction of the alternative *syn*-dipole **27**.



26 **27**

Stereoselective formation of *anti*-azomethine ylide from carbonyl compounds and α-amino acids has previously been reported and discussed by our group.[9]

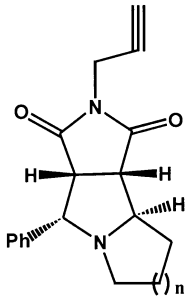
endo-Isomer **24** was hydrostannylated to give solely the α-substituted stannane (established by ^{1}H NMR) which was treated with zipper molecule **7** (toluene, reflux) to give the expected anion-capture product **28** in 57% yield as a 1:1 mixture of diastereoisomers.



28

29

a. n=1
b. n=2

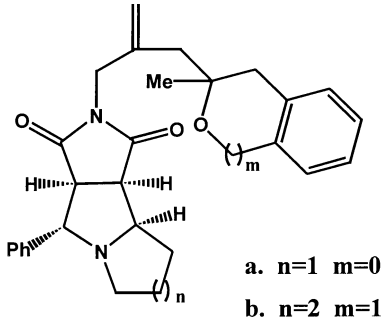


30

a. n=1
b. n=2

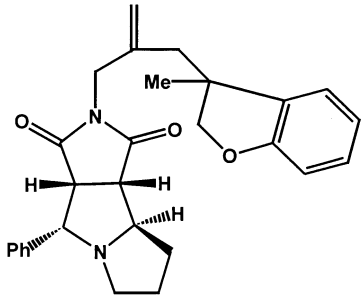
Proline and pipecolinic acid reacted with *N*-propargylmaleimide and benzaldehyde (toluene, reflux, 20 h) to afford **29a/30a** and **29b/30b** respectively (via the respective *anti*-dipoles) in a 3:1 ratio and combined yields of 69 and 45%, respectively.

endo-Adduct **29a** was then hydrostannylated and reacted with zippers **7** and **9**, respectively to give **31a** and **31b**, each as a 1:1 mixture of diastereoisomers, in 49 and 48% yield, respectively. *Endo*-adduct **29b** was treated identically with **7** and **9** to give **31c** and **31d** in 52 and 49% yield, respectively.



31

a. n=1 m=0
b. n=2 m=1
c. n=2 m=0
d. n=2 m=1



32

Likewise *exo*-adduct **30a** was hydrostannylated successfully and reacted with **7** to produce **32** in 49% yield as a 1:1 mixture of diastereoisomers.

3. One-pot process

The synthetic potential of any reaction sequence is

significantly enhanced if it can be carried out as a one-pot procedure. We briefly studied one such process with toluene as the common solvent. The cycloaddition with *N*-sulphonyl-indole-3-carboxaldehyde, *N*-propargylmaleimide and sarcosine was allowed to proceed for 48 h at reflux, after which time the mixture was cooled to 0°C, before addition of the palladium catalyst, phosphine and tributyl tin hydride. The mixture was left to warm up to room temperature over 1 h to allow the regiospecific hydrostannylation. Then the zipper **7** was added and the mixture heated at reflux overnight. Product **23c** was isolated in 40% yield. Disappointingly the yield of the one-pot process was approximately the same as the overall yield for the two-pot process (42%). Nevertheless, this study indicates that the workup for the cycloaddition stage in this case is not required, therefore saving time and resources.

4. Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec mass spectrometer operating at 70 eV. Nuclear magnetic resonance spectra were recorded on Brucker QE300 and AM400 machines operating at 300 and 400 MHz, respectively. Unless otherwise specified, deuterochloroform was used as solvent with tetramethyl silane as internal standard. Micro analyses were obtained using a Carlo Erba MOD 11016 instrument. Thin layer chromatography was carried out on Whatman PESIL G/UV polyester plates coated with 0.2 mm layer of silica. Column chromatography was performed with silica gel 60 (Merk 9385). Petroleum ether refers to the fraction with bp 40–60°C. Anhydrous DMF and THF were commercially available (Aldrich). Compounds **7**–**10** have been previously prepared by us.[20]

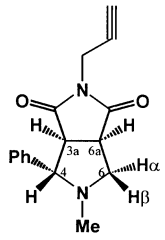
4.1. General procedure for decarboxylative cycloaddition reactions

A solution of the aldehyde (10.0 mmol), *N*-propargylmaleimide (10.0 mmol) and amino acid (10.0 mmol) in dry toluene or DMF (12 ml) was heated at 110°C. When the reaction was complete (TLC analysis), the solvent was removed in vacuo to yield the crude product (usually as a mixture of isomers), which was separated by flash chromatography.

The isomer ratio was determined from the ^{1}H NMR spectrum of the crude product.

4.1.1. 5-Methyl-4-phenyl-2-prop-2-ynyl-1,3,3aα,4β,6αβ,6aα-hexahydro-pyrrolo[3,4-*c*] pyrrole-1,3-dione (4) and 5-methyl-4-phenyl-2-prop-2-ynyl-1,3,3aα,4α,6αβ,6aα-hexahydro-pyrrolo [3,4-*c*] pyrrole-1,3-dione (5). Prepared from benzaldehyde (1.6 g, 15.0 mmol), *N*-propargylmaleimide (2.0 g, 15.0 mmol) and sarcosine (1.3 g, 15.0 mmol) in boiling toluene (18 ml) over 20 h. Evaporation of the solvent in vacuo provided a brown gum comprising a 3:1 mixture of cycloadducts. Flash chromatography eluting with 1:1 v/v ether–petroleum ether, yielded the major isomer **4** (1.83 g, 46%) as a pale orange gum and the minor isomer **5** (0.76 g, 19%) as colourless plates from ether–petroleum ether, mp 138–140°C.

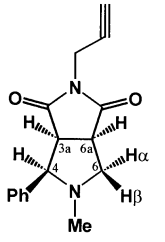
Major endo-isomer **4**: (Found: C, 71.7; H, 6.0; N, 10.45. $C_{16}H_{16}N_2O_2$ requires: C, 71.6; H, 6.0; N, 10.45%); *m/z* (%) 268 (M^+, 48), 191 (35), 132 (100), 118 (32) and 91 (24). δ_H ($CDCl_3$): 7.12 (m, 5H, ArH), 3.90 (s, 2H, NCH_2), 3.23 (d, 1H, *J*=6 Hz, 4-H), 2.92 (t, 1H, *J*=9 Hz, 6-H$_\alpha$), 2.67 (dt, 1H, *J*=9 and 7 Hz, 6a-H), 2.56 (dd, 1H, *J*=9 and 6 Hz, 3a-H), 2.18 (dd, 1H, *J*=9 and 7 Hz, 6-H$_\beta$), 1.77 (m, 1H, C≡CH) and 1.64 (s, 3H, NMe).



4 *% enhancement*

irradiated hydrogen	3a-H	4-H	6-H$_\alpha$	6-H$_\beta$	6a-H	NMe	Ph
3a-H	-	4	-	-	4	-	5
4-H	-	-	-	2	-	3	11
6-H$_\alpha$	-	-	-	28	8	-	-
6-H$_\beta$	-	5	27	-	5	2	-
6a-H	3	-	7	-	-	-	-

Minor endo-isomer **5**: (Found: C, 71.4; H, 5.9; N, 10.3. $C_{16}H_{16}N_2O_2$ requires: C, 71.6; H, 6.0; N, 10.45%); *m/z* (%) 268 (M^+, 48), 191 (35), 132 (100), 118 (32) and 91 (24). δ_H ($CDCl_3$): 7.35 (m, 3H, ArH), 7.23 (m, 2H, ArH), 4.18 (d, 2H, *J*=2 Hz, NCH_2), 3.65 (d, 1H, *J*=9.5 Hz, 6-H$_\beta$), 3.51 (d, 1H, *J*=9 Hz, 4-H), 3.40 (dd, 1H, *J*=9 and 8 Hz, 3a-H), 3.24 (dd, 1H, *J*=7 and 8 Hz, 6a-H), 2.57 (dd, 1H, *J*=7 and 9.5 Hz, 6-H$_\alpha$), 2.21 (m, 1H, C≡CH) and 2.16 (s, 3H, NMe).



5 *% enhancement*

irradiated hydrogen	3a-H	4-H	6-H$_\alpha$	6-H$_\beta$	6a-H	NMe	Ph
3a-H	-	5	-	-	6	-	3
4-H	1	-	-	-	3	3	15
6-H$_\alpha$	-	8	-	30	14	3	-
6-H$_\beta$	-	-	24	-	1	2	3
6a-H	9	-	4	4	-	-	-

4.1.2. 4-(3-Bromo-phenyl)-5-methyl-2-prop-2-ynyl-1,3,3aα,4β,6αβ,6aα-hexahydro-pyrrolo[3,4-*c*]pyrrole-1,3-dione (21a) and 4-(3-bromo-phenyl)-5-methyl-2-prop-2-ynyl-1,3,3aα,4α,6αβ,6aα-hexahydro-pyrrolo[3,4-*c*]-pyrrole-1,3-dione (22a). Prepared from *m*-bromobenzaldehyde (0.88 g, 4.8 mmol), *N*-propargylmaleimide

(0.66 g, 4.8 mmol) and sarcosine (0.43 g, 4.8 mmol) in refluxing toluene (20 ml) over 17 h. Evaporation of the solvent in vacuo afforded a brown gum comprising a 2:1 mixture of cycloadducts. Flash chromatography on silica eluting with 1:1 v/v ether–petroleum ether, yielded the major isomer **21a** (0.67 g, 40%) as a colourless gum and the minor isomer **22a** (0.31 g, 19%) as a colourless amorphous solid.

Major endo-isomer **21a**: (Found: C, 55.4; H, 4.55; N, 7.9. $C_{16}H_{15}N_2O_2Br$ requires: C, 55.35; H, 4.35; N, 8.05%); *m/z* (%) 348 (M^+, ^{81}Br, 45), 346 (M^+, ^{79}Br, 45), 212 (^{81}Br, 56), 210 (^{79}Br, 56), 191 (100), 82 (64) and 43 (45). δ_H: 7.53 (s, 1H, ArH), 7.44 (d, 1H, *J*=7 Hz, ArH), 7.26 (m, 2H, ArH), 4.25 (d, 2H, *J*=2.5 Hz, $CONCH_2$), 3.51 (m, 2H, 4-H and 6-H_α), 3.40 (d, 1H, *J*=6.5 Hz, 3a-H), 3.23 (dt, 1H, *J*=8 and 6.5 Hz, 6a-H), 2.21 (m, 1H, 6-H_β), 2.21 (t, 1H, *J*=2.5 Hz, C≡CH) and 2.13 (s, 3H, NMe).

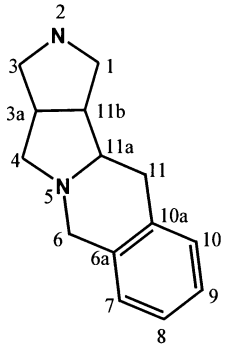
Minor exo-isomer **22a**: Mp 128–130°C. (Found: C, 55.4; H, 4.4; N, 7.85. $C_{16}H_{15}N_2O_2Br$ requires: C, 55.35; H, 4.35; N, 8.05%); *m/z* (%) 348 (M^+, ^{81}Br, 48), 346 (M^+, ^{79}Br, 49), 212 (^{81}Br, 100), 210 (^{79}Br, 98), 191 (94), 132 (40) and 82 (52). δ_H: 7.43 (m, 2H, ArH), 7.21 (m, 2H, ArH), 4.18 (d, 2H, *J*=2.5 Hz, $CONCH_2$), 3.65 (d, 1H, *J*=9.5 Hz, 6-H_β), 3.49 (d, 1H, *J*=7.5 Hz, 4-H), 3.40 (t, 1H, *J*=7.5 Hz, 3a-H), 3.24 (t, 1H, *J*=7.5 Hz, 6a-H), 2.58 (dd, 1H, *J*=9.5 and 7.5 Hz, 6-H_α), 2.27 (t, 1H, *J*=2.5 Hz, C≡CH) and 2.16 (s, 3H, NMe).

4.1.3. 4-(4-Bromo-phenyl)-5-methyl-2-prop-2-ynyl-1,3,3aα,4β,6αβ,6aα-hexahydro-pyrrolo[3,4-*c*]pyrrole-1,3-dione (21b) and 4-(4-bromo-phenyl)-5-methyl-2-prop-2-ynyl-1,3,3aα,4α,6αβ,6aα-hexahydro-pyrrolo[3,4-*c*]-pyrrole-1,3-dione (22b). Prepared from *p*-bromobenzaldehyde (1.35 g, 7.3 mmol), *N*-propargylmaleimide (1.00 g, 7.3 mmol) and sarcosine (0.86 g, 7.3 mmol) in refluxing toluene (9 ml) over 17 h. Evaporation of the solvent in vacuo afforded a brown gum comprising a 3:2 mixture of cycloadducts. Flash chromatography on silica eluting with 1:1 v/v ether–petroleum ether, yielded the major isomer **21b** (1.02 g, 40%) as a colourless amorphous solid and the minor isomer **22b** (0.41 g, 16%) as colourless amorphous solid.

Major endo-isomer **21b**: Mp 165–167°C. (Found: C, 55.35; H, 4.4; N, 7.95. $C_{16}H_{15}N_2O_2Br$ requires: C, 55.35; H, 4.35; N, 8.05%); *m/z* (%) 348 (M^+, ^{81}Br, 64), 346 (M^+, ^{79}Br, 63), 212 (^{81}Br, 59), 210 (^{79}Br, 58), 191 (54), 81 (35) and 43 (100). δ_H: 7.51 and 7.25 (2×d, 4H, *J*=8 Hz, ArH), 4.26 (d, 2H, *J*=2 Hz, $CONCH_2$), 3.52 (m, 2H, 4-H and 6-H_α), 3.40 (d, 1H, *J*=6.5 Hz, 3a-H), 3.23 (dt, 1H, *J*=8 and 6.5 Hz, 6a-H), 2.56 (m, 1H, 6-H_β), 2.22 (t, 1H, *J*=2 Hz, C≡CH) and 2.13 (s, 3H, NMe).

Minor exo-isomer **22b**: Mp 170–172°C. (Found: C, 55.25; H, 4.35; N, 7.9. $C_{16}H_{15}N_2O_2Br$ requires: C, 55.35; H, 4.35; N, 8.05%); *m/z* (%) 348 (M^+, ^{81}Br, 40), 346 (M^+, ^{79}Br, 40), 212 (^{81}Br, 100), 210 (^{79}Br, 99), 191 (47) and 82 (31). δ_H: 7.45 and 7.13 (2×d, 4H, *J*=8 Hz, ArH), 4.18 (d, 2H, *J*=2.5 Hz, $CONCH_2$), 3.64 (d, 1H, *J*=9.5 Hz, 6-H_β), 3.47 (t, 1H, *J*=7.5 Hz, 4-H), 3.40 (t, 1H, *J*=7.5 Hz, 3a-H), 3.25 (t, 1H, *J*=7.5 Hz, 6a-H), 2.58 (dd, 1H, *J*=9.5 and 7.5 Hz, 6-H_α), 2.22 (t, 1H, *J*=2.5 Hz, C≡CH) and 2.13 (s, 3H, NMe).

4.1.4. 4-(1-Benzenesulphonyl-1*H*-indol-3-yl)-5-methyl-2-prop-2-ynyl-1,3,3aα,4β,6αβ,6aα-hexahydro-pyrrolo-[3,4-*c*]pyrrole-1,3-diene (21c). Prepared from *N*-phenylsulphonylindole-3-carboxaldehyde (0.63 g, 2.2 mmol), *N*-propargylmaleimide (0.30 g, 2.2 mmol) and sarcosine (0.20 g, 2.2 mmol) in refluxing toluene (20 ml) over 24 h. Evaporation of the solvent in vacuo afforded the crude cycloadduct as a brown gum. Flash chromatography eluting with 1:1 v/v ether–petroleum ether, yielded the cycloadduct **21c** (0.53 g, 68%) as a colourless amorphous solid, mp 130–132°C. Found: C, 64.4; H, 4.85; N, 9.55. $C_{24}H_{21}N_3O_4S$ requires: C, 64.4; H, 4.75; N. 9.4%); *m/z* (%) 447 (M^+, 14), 306 (100), 171 (72), 130 (17) and 77 (34). δ_H: 7.98 (m, 1H, ArH), 7.89 (d, 2H, *J*=8 Hz, ArH), 7.76 (d, 1H, *J*=8 Hz, ArH), 7.38 (m, 6H, ArH), 4.28 (d, 2H, *J*=2 Hz, $CONCH_2$), 3.92 (d, 1H, *J*=5.5 Hz, 4-H), 3.56 (dt, 1H, *J*=8.5 and 6 Hz, 6a-H), 3.43 (m, 2H, 6-H_α and 3a-H), 2.66 (dd, 1H, *J*=10 and 6Hz, 6-H_β), 2.23 (t, 1H, *J*=2 Hz, C≡CH) and 2.12 (s, 3H, Me).

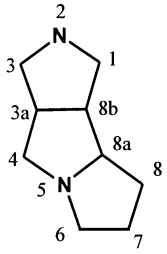


4.1.5. 4-Phenyl-2-prop-2-ynyl-3aα,4β,6,11,11aα,11bα-hexahydro-pyrrolo[3′,4′:3,4] pyrrolo [1,2-*b*] isoquinoline-1,3-dione (24) and 4-phenyl-2-prop-2-ynyl-3aα,4α,6,11,11aβ,11bα-hexahydro-pyrrolo[3′,4′:3,4]pyrrolo-[1,2-*b*]isoquinoline-1,3-dione (25). Prepared from benzaldehyde (0.62 g, 5.8 mmol), *N*-propargylmaleimide (0.80 g, 5.8 mmol) and (*S*)-(−)-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid (1.03 g, 5.8 mmol) in boiling DMF (7 ml) over 20 h. Evaporation of the solvent in vacuo afforded a brown gum comprising a 1:1 mixture of cycloadducts. Flash chromatography on silica eluting with 1:1 v/v ether–petroleum ether, yielded the major isomer **24** (0.45 g, 20%) as a pale yellow amorphous solid and the minor isomer **25** (0.50 g, 22%) as a pale yellow amorphous solid.

Endo-isomer **24**: Mp 79–81°C. (Found: C, 77.3; H, 5.9; N, 7.8. $C_{23}H_{20}N_2O_2$ requires: C, 77.5; H, 5.65; N, 7.85%); *m/z* (%) 356 (M^+, 65), 220 (58), 130 (53), 115 (34) and 104 (100). δ_H: 7.43–6.90 (m, 9H, ArH), 4.79 (s, 1H, 4-H), 4.30 (d, 2H, *J*=2.5 Hz, $CONCH_2$), 3.80 (m, 2H, 1×6-H and 11b-H), 3.47 (m, 2H, 3a-H and 11a-H), 3.25 (d, 1H, *J*=15 Hz, 1×6-H), 3.08 (dd, 1H, *J*=16 and 3 Hz, 1×11-H), 2.68 (dd, 1H, *J*=16 and 11 Hz, 1×11-H), and 2.19 (t, 1H, *J*=2.5 Hz, C≡CH).

Exo-isomer **25**: Mp 179–181°C. (Found: C, 77.45; H, 5.9; N, 7.7. $C_{23}H_{20}N_2O_2$ requires: C, 77.5; H, 5.65; N, 7.85%);

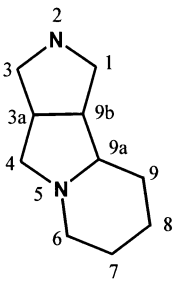
m/z (%) 356 (M^+, 69), 221 (65), 130 (39), 115 (29) and 104 (100). δ_H: 7.38 (m, 5H, ArH), 7.17 (m, 3H, ArH), 6.87 (d, 1H, *J*=8 Hz, ArH), 4.35 (d, 1H, *J*=9 Hz, 4-H), 4.18 (m, 4H, $CONCH_2$, 1×6-H and 11a-H), 3.61 (d, 1H, *J*=18 Hz, 1×6-H), 3.53 (t, 1H, *J*=9 Hz, 3a-H), 3.18 (d, 1H, *J*=9 Hz, 11b-H), 2.86 (d, 2H, *J*=8 Hz, 11-H) and 2.23 (t, 1H, *J*= 2.5 Hz, C≡CH).



4.1.6. 4-Phenyl-2-prop-2-ynyl-1,2,3,3aα,4β,6,7,8,8aα,8bα-decahydropyrrolo[3,4-*a*]pyrrolizine-1,3-dione (29a) and 4-phenyl-2-prop-2-ynyl-1,2,3,3aα,4α,6,7,8,8aβ,8bα-decahydropyrrolo[3,4-*a*]pyrrolizine-1,3-dione (30a). Prepared from benzaldehyde (0.95 g, 8.9 mmol), *N*-propargylmaleimide (1.23 g, 8.9 mmol) and proline (1.03 g, 8.9 mmol) in refluxing toluene (11 ml) over 20 h. Evaporation of the solvent in vacuo afforded a brown gum comprising a 3:1 mixture of cycloadducts. Flash chromatography eluting with 1:1 v/v ether–petroleum ether, yielded the major isomer **29a** (1.00 g, 47%) as colourless prisms from ether–petroleum ether and the minor isomer **30a** (0.37 g, 22%) as colourless prisms from ether–petroleum ether.

Major endo-isomer **29a**: Mp 93–95°C. (Found: C, 73.15; H, 6.3; N, 9.7. $C_{18}H_{18}N_2O_2$ requires: C, 73.45; H, 6.15; N, 9.5%); *m/z* (%) 294 (M^+, 30), 159 (100), 131 (29), 104 (27), 91 (13), and 39 (18). δ_H: 7.48 (d, 2H, *J*=8 Hz, ArH), 7.32 (m, 3H, ArH), 4.27 (d, 2H, *J*=2.5 Hz, $CONCH_2$), 4.25 (d, 1H, 5.5 Hz, 4-H), 3.95 (d, 1H, *J*=9 Hz, 8a-H), 3.58 (t, 1H, *J*=9 Hz, 8b-H), 4.48 (dd, 1H, *J*=5.5 and 9 Hz, 3a-H), 3.06 and 2.62 (2×m, 2H, 6-H), 2.22 (t, 1H, *J*=2.5 Hz, C≡CH) and 1.94 (m, 4H, 7-H and 8-H).

Minor exo-isomer **30a**: Mp 130–132°C. (Found: C, 73.3; H, 6.05; N, 9.8. $C_{18}H_{18}N_2O_2$ requires: C, 73.45; H, 6.15; N, 9.5%); *m/z* (%) 294 (M^+, 47), 159 (100), 131 (31), 104 (29) and 77 (12). δ_H: 7.31 (m, 5H, ArH), 4.14 (d, 2H, *J*=2.5 Hz, $CONCH_2$), 4.09 (d, 1H, *J*=9.5 Hz, 4-H), 3.81 (dd, 1H, *J*=9.5 and 8 Hz, 8a-H), 3.54 (t, 1H, *J*=8 Hz, 3a-H), 3.32 (d, 1H, *J*=8 Hz, 8b-H), 2.92 and 2.85 (2×m, 2H, 6-H), 2.16 (t, 1H, *J*=2.5 Hz, C≡CH), 2.10 (m, 2H, 7-H) and 1.74 (m, 2H, 8-H).



4.1.7. 8-Phenyl-2-prop-2-ynyl-1,2,3,3aα,4β,6,7,8,9,9aα,9bα-decahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3-dione (29b) and 8-phenyl-2-prop-2-ynyl-1,2,3,3aα,4α,6,7,8,9,9aβ,9bα-decahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3-dione (30b). Prepared from benzaldehyde (0.80 g, 7.6 mmol), *N*-propargylmaleimide (1.04 g, 7.6 mmol) and DL-pipecolinic acid (0.98 g, 7.6 mmol) in boiling toluene (9 ml) over 20 h. Evaporation of the solvent in vacuo afforded a brown gum comprising a 3:1 mixture of cycloadducts. Flash chromatography eluting with 1:1 v/v ether–petroleum ether, yielded the major isomer **29b** (0.77 g, 33%) as pale yellow gum and the minor isomer **30b** (0.26 g, 12%) as colourless prisms from ether.

Major endo-isomer **29b**: (Found: C, 74.05; H, 6.75; N, 9.2. $C_{19}H_{20}N_2O_2$ requires: C, 74.0; H, 6.55; N, 9.1%); *m/z* (%) 308 (M^+, 96), 172 (100), 115 (30), 55 (20), and 39 (22). δ_H: 7.40 (m, 3H, ArH), 7.10 (d, 2H, *J*=7 Hz, ArH), 4.61 (s, 1H, 2-H), 4.30 (d, 2H, *J*=2 Hz, $CONH_2$), 3.50 (t, 1H, *J*=8 Hz, 9b-H), 3.42 (d, 1H, *J*=8 Hz, 3a-H), 2.81 (m, 2H, 1×6-H and 9a-H), 2.21 (t, 1H, *J*=2.5 Hz, C≡CH), 2.00 (dd, 1H, *J*=11 and 1 Hz, 1×6-H) and 1.74–0.85 (m, 6H, 7-H, 8-H and 9-H).

Minor exo-isomer **30b**: Mp 129–131°C. (Found: C, 73.7; H, 6.6; N, 9.1. $C_{19}H_{20}N_2O_2$ requires: C, 74.0; H, 6.55; N, 9.1%); *m/z* (%) 308 (M^+, 75), 231 (51), 173 (100), 115 (20) and 32 (85). δ_H: 7.8 (m, 5H, ArH), 4.62 (d, 1H, *J*= 9 Hz, 4-H), 4.14 (d, 2H, *J*=2 Hz, $CONCH_2$), 3.81 (m, 1H, 9a-H), 3.47 (t, 1H, *J*=8 Hz, 9b-H), 2.94 (d, 1H, *J*=8 Hz, 3a-H), 2.73 (m, 2H, 6-H), 2.19 (t, 1H, *J*=2 Hz, C≡CH) and 1.89–1.11 (m, 6H, 7-H, 8-H and 9-H).

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

Tributyltin hydride (1.0 mmol) was added to a solution of cycloadduct (1 mmol), $Pd_2(dba)_3$ (0.062 mmol) and *tris*-(2-furylphosphine) (0.025 mmol) in toluene (15 ml) at 0°C under a nitrogen atmosphere. The resulting solution was allowed to warm to room temperature and stirred for 1.5 h. The 'zipper' molecule of choice (1.0 mmol) in toluene (1 ml) was then added and the reaction mixture heated at reflux for 14 h. The solvent was removed in vacuo, the residue dissolved in DCM, filtered and the solvent evaporated. The residue was then purified by flash chromatography.

4.2.1. 5-Methyl-2-[2-(3-methyl-2,3-dihydro benzofuran-3-yl methyl)-allyl]-4-phenyl-1,3,3aα,4β,6αβ,6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (11). Prepared from cycloadduct **4** (0.31g, 1.2 mmol) and compound **7** (0.33 g, 1.2 mmol) in dry toluene (8 ml). Work up in the normal manner followed by flash chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product (0.33 g, 66%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 74.85; H, 6.9; N, 6.55. $C_{26}H_{28}N_2O_3$ requires: C, 75.0; H, 6.8; N, 6.75%); *m/z* (%) 416 (M^+, 18), 284 (68), 158 (60), 133 (100), 105 (96) and 91 (49). δ_H: 7.40 (m, 5H, ArH), 7.15 (m, 2H, ArH), 6.89 (m, 1H, ArH), 6.81 (d, 1H, *J*=8 Hz, ArH), 4.83 and 4.88 (2×s, 2H, $=CH_2$), 4.53 and 4.19 (2×d, 2H, *J*=9 Hz, OCH_2), 3.81 (s, 2H, NCH_2), 3.56 (d, 1H, *J*=6 Hz, 4-H), 3.46 (m, 2H, 6-H_α and 6a-H), 3.29 (dd, 1H, *J*=8 and 6 Hz, 3a-H), 2.61 (dd, 1H, *J*=8 and

4 Hz, 6-H_β), 2.42 and 2.45 (2×d, 2H, J=14 Hz, CH_2C=), 2.11 (s, 3H, CMe) and 1.43 (s, 3H, NMe).

4.2.2. 2-[2-(1-Benzenesulphonyl-3-methyl-2, 3-dihydro-1*H*-indole-3-ylmethyl)-allyl]-5-methyl-4-phenyl-1,3,3aα, 4β,6αβ,6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (12). Prepared from cycloadduct **4** (0.35g, 1.3 mmol) and compound **8** (0.54 g, 1.3 mmol) in toluene (9 ml). Work up in the normal manner followed by flash chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product (0.32 g, 45%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 69.0; H, 6.1; N, 7.35. $C_{33}H_{35}N_3O_4S$ requires: C, 69.15; H, 6.0; N, 7.6%); *m/z* (%) 554 ($M-H^+$, 1), 414 (70), 272 (100), 132 (47) and 77 (51). δ_H(diastereomer mixture): 7.86–6.98 (m, 28H, ArH), 4.81 and 4.65 (2×s, 4H, $=CH_2$), 4.00 (d, 4H, J=10 Hz, 2×NC*H*H), 3.80 (s, 4H, CH_2NSO_2Ph), 3.50 (m, 10H, 4×NCH*H*, 2×6-H_α, 2×4-H and 2×6a-H), 3.30 (dd, 2H, J= 7 and 4 Hz, 2×3a-H), 2.61 (dd, 2H, J=9 and 6 Hz, 2×6-H_β), 2.24 and 2.16 (2×d, 4H, J=14 Hz, 2×CH_2C=), 2.16 and 2.10 (2×s, 6H, 2×NMe) and 1.22 (s, 6H, 2×CMe).

4.2.3. 2-[2-(1-Benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-ylmethyl)-allyl]-5-methyl-4-phenyl-1,3,3aα,4β,6α β,6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (13). Prepared from cycloadduct **4** (0.31g, 1.1 mmol) and compound **9** (0.41 g, 1.1 mmol) in toluene (7 ml). Work up in the normal manner followed by flash chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product **13** (0.32 g, 55%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 76.0; H, 6.3; N, 8.05. $C_{33}H_{33}N_3O_3$ requires: C, 76.25; H, 6.4; N, 8.1%); *m/z* (%) 520 (M+1, 25), 283 (70), 236 (45), 132 (36) and 91 (100). δ_H: 7.32 (m, 22H, ArH), 7.18 (m, 2H, ArH), 7.07 (m, 2H, ArH), 6.71 (m, 2H, ArH), 4.98 and 5.00 (2×d, 2H, 2×NC*H*HPh), 4.83 and 4.85 (2×d, 2H, 2×NCH*H*Ph), 4.66 (m, 4H, 2×$=CH_2$), 3.71 and 3.73 (2×d, 2H, 2×NC*H*HC=), 3.48 (m, 8H, 4×NCH*H*C=, 2×3-H and 2×6-H_α), 3.25 (dt, 2H, J=9 and 5 Hz, 2×6a-H), 2.75 and 2.77 (2×d, 2H, 2×C*H*HCMe), 2.60 (m, 4H, CH*H*CMe) and 2×6-H_β), 2.09 (s, 6H, 2×NMe) and 1.45 and 1.47 (2×s, 6H, 2×CMe).

4.2.4. 5-Methyl-2-[2-(4-methyl-isochroman-4-ylmethyl)-allyl]-4-phenyl-1,3,3aα,4β,6αβ,6aα-hexahydropyrrolo-[3,4-*c*]pyrrole-l,3-dione (14). Prepared from cycloadduct **4** (0.31 g, 1.2 mmol) and compound **10** (0.34 g, 1.2 mmol) in toluene (8 ml). Work up in the normal manner followed by flash chromatography eluting with 1:2 v/v petroleum ether–ether afforded the product (0.25 g, 46%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 75.35; H, 6.85; N, 6.45. $C_{27}H_{30}N_2O_3$ requires: C, 75.3; H, 7.0; N, 6.5%); *m/z* (%) 430 (M^+, 38), 283 (100), 147 (98), 119 (79) and 91 (36). δ_H: 7.38 (m, 5H, ArH), 7.20 (m, 2H, ArH), 6.96 (d, 1H, J=8 Hz, ArH), (m, 18H, ArH), 4.85 (m, 8H, 2×CH_2Ph and 2×$=CH_2$), 3.95 and 3.97 (2×d, 2H, J= 11.5 Hz, 2×OC*H*H), 3.87 (broad s, 4H, 2×NCH_2C=), 3.48 (m, 8H, 2×OCH*H*, 2×4-H, 2×6-H_α and 1×6a-H), 3.29 (m, 2H, 2×3a-H), 2.60 (m, 2H, 2×6-H_β), 2.10 (s, 6H, 2×NMe) and 1.28 and 1.29 (2×s, 6H, 2×CMe).

4.2.5. 5-Methyl-2-[2-(4-methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-4-phenyl-1,3,3aα,4α,6αβ,6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (15). Prepared from cycloadduct **5** (0.31 g, 1.1 mmol) and compound **7** (0.41 g, 1.1 mmol) in toluene (7 ml). Work up in the normal manner followed by flash chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product (0.32 g, 55%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 74.8; H, 6.5; N, 7.0. $C_{26}H_{28}N_2O_3$ requires: C, 75.0; H, 6.8; N, 6.75%); *m/z* (%) 417 (M+1, 10), 248 (81), 133 (100), 105 (82), 91 (60) and 77 (52). δ_H: 7.18 (m, 7H, ArH), 6.80 (m, 2H, ArH), 5.00 and 4.82 (2×s, 2H, $=CH_2$), 4.48 and 4.16(2×d, 2H, J=9 Hz, OCH_2), 3.73 and 3.82 (2×d, 2H, J=13 Hz, NCH_2C=), 3.60 (d, 1H, J=9.5 Hz, 6-H_β), 3.47 (d, 1H, J=8 Hz, 4-H), 3.56 (m, 1H, 3a-H), 3.19 (m, 1H, 6a-H), 2.55 (t, 1H, J=9.5 Hz, 6-H_α), 2.38 (s, 2H, $CMeCH_2C$=), 2.16 (s, 3H, NMe) and 1.30 (s, 3H, CMe).

4.2.6. 2-[2-(1-Benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-ylmethyl)-allyl]-5-methyl-4-phenyl-1,3,3aα,4α,6α β,6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (16). Prepared from cycloadduct **5** (0.23 g, 8.7 mmol) and compound **9** (0.33 g, 8.7 mmol) in toluene (6 ml). Work up in the normal manner followed by flash chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product (0.19 g, 42%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 76.15; H, 6.7; N, 7.95. $C_{33}H_{33}N_3O_3$ requires: C, 76.0; H, 6.75; N, 8.05%); *m/z* (%) 519 (M−2, 40), 283 (43), 236 (45), 132 (50) and 91 (100). δ_H: 7.18 (m, 12H, ArH), 6.64 (d, 2H, J=8 Hz, ArH), 4.95 and 4.67 (2×d, 2H, J=16 Hz, CH_2Ph), 4.73 and 4.70 (2×s, 2H, $=CH_2$), 3.56 (d, 1H, J=10 Hz, 6-H_β), 3.55 and 3.46 (2×d, 2H, J=13 Hz, NCH_2C=), 3.46 (d, 1H, J=8 Hz, 4-H), 3.33 (t, 1H, J=8 Hz, 3a-H), 3.17 (t, 1H, J=8 Hz, 6a-H), 2.70 and 2.60 (2×d, 2H, $CMeCH_2C$=), 2.52 (dd, 1H, J=10 and 8 Hz, 6-H_α), 2.14 (s, 3H, NMe) and 1.44 (s, 3H, CMe).

4.2.7. 5-Methyl-2-[2-(4-methyl-isochroman-4-ylmethyl)-allyl]-4-phenyl-1,3,3aα,4α,6αβ,6aα-hexahydropyrrolo-[3,4-*c*]pyrrole-l,3-dione (17). Prepared from cycloadduct **5** (0.24 g, 0.89 mmol) and compound **10** (0.26 g, 0.89 mmol) in toluene (6 ml). Work up in the normal manner followed by flash chromatography eluting with 1:2 v/v petroleum ether–ether afforded the product (0.19 g, 49%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 75.6; H, 6.9; N, 6.6. $C_{27}H_{30}N_2O_3$ requires: C, 75.3; H, 7.0; N, 6.5%); *m/z* (%) 430 (M^+, 34), 284 (49), 147 (100), 132 (97), 119 (71) and 91 (34). δ_H: 7.32 (m, 16H, ArH), 6.96 (d, 2H, J=8 Hz, ArH), 4.95 and 4.67 (2×d, 4H, J=16 Hz, CH_2Ph), 3.91 and 3.95 (2×d, 4H, J=13 Hz, 2×NC*H*HC=), 3.61 (d, 2H, J=10 Hz, 2×6-H_β), 3.47 (m, 4H, 2×4-H and 2×NCH*H*C=), 3.52 and 3.56 (2×t, 2H, J=8 Hz, 2×3a-H), 3.19 and 3.20 (2×t, 2H, J=8 Hz, 2×6a-H), 2.52 (m, 8H, 2×6-H_α and 4×C*H*HC=), 2.32 (d, 4H, J=14 Hz, 2× CH*H*C=), 2.14 and 2.15 (2×s, 6H, 2×NMe) and 1.25 and 1.26 (2×s 6H, 2×CMe).

4.2.8. 4-(3-Bromophenyl)-5-methyl-2-[2-(3-methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-1,3,3aα,4β,6αβ, 6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (23a). Prepared from cycloadduct **21a** (0.35 g, 0.99 mmol) and compound **7** (0.27 g, 0.99 mmol) in toluene (6.5 ml). Work up in the normal manner followed by flash chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product (0.35 g, 71%, 1:1 mixture of diastereoisomers),

as a colourless gum. (Found: C, 63.3; H, 5.5; N, 5.4. $C_{26}H_{27}BrN_2O_3$ requires: C, 63.05; H, 5.50; N, 5.65%); *m/z* (%) 496 (M^+, ^{81}Br, 2), 494 (M^+, ^{79}Br, 2), 364 (^{81}Br, 16), 362 (^{79}Br, 16), 133 (100), 105 (64) and 82 (24). δ_H: 7.52 (s, 1H, ArH), 7.45 (d, 1H, *J*=8 Hz, ArH), 7.36 (m, 2H, ArH), 7.18 (m, 2H, ArH), 6.90 (m, 1H, ArH), 6.81 (d, 1H, *J*=8 Hz, ArH), 4.84 and 4.86 (2×s, 2H, =CH_2), 4.19 and 4.52 (2×d, 2H, *J*=9 Hz), OCH_2), 3.80 (s, 2H, $CONCH_2$), 3.48 (m, 3H, 4-H, 3a-H and 6-H_a), 3.24 (dt, 1H, *J*=8 and 6.5 Hz, 6a-H), 2.57 (m, 1H, 6-H_β), 2.45 and 2.18 (2×d, 2H, *J*= 14 Hz, CMeCH_2C=), 2.13 (s, 3H, NMe) and 1.43 (s, 3H, CMe).

4.2.9. 4-(4-Bromophenyl)-5-methyl-2-[2-(3-methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-1,3,3aα,4β,6αβ, 6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (23b). Prepared from cycloadduct **21b** (0.31 g, 0.9 mmol) and compound **7** (0.25 g, 0.9 mmol) in toluene (6 ml). Work up in the normal manner followed by flash chromatography eluting with 1:1 v/v petroleum ether–ether afforded the product (0.27 g, 60%, 1:1 mixture of diastereoisomers), as a colourless amorphous solid. (Found: C, 63.3; H, 5.9; N, 5.7. $C_{26}H_{27}BrN_2O_3$ requires: C, 63.05; H, 5.50; N, 5.4%); *m/z* (%) 496 (M^+, ^{81}Br, 1), 494 (M^+, ^{79}Br, 1), 364 (^{81}Br, 16), 362 (^{79}Br, 16), 133 (100) and 105 (52). δ_H: 7.51 (d, 2H, *J*=8 Hz, ArH), 7.18 (m, 4H, ArH), 6.86 (m, 1H, ArH), 6.79 (d, 1H, *J*=8 Hz, ArH), 4.83 and 4.85 (2×s, 2H, =CH_2), 4.51 and 4.18 (2×d, 2H, OCH_2), 3.79 (s, 2H, $CONCH_2$), 3.43 (m, 3H, 4-H, 3a-H and 6-H_α), 3.20 (dt, 1H, *J*=8 and 6.5 Hz, 6a-H), 2.55 (m, 1H, 6-H_β), 2.41 and 2.38 (2×d, 2H, *J*=14 Hz, $CMeCH_2C$=), 2.10 (s, 3H, NMe) and 1.42 (s, 3H, CMe).

4.2.10. 4-(1-Benzenesulphonyl-1*H*-indole-3-yl)-5-methyl-2-[2-(3-methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-1,3,3aα,4β,6αβ,6aα-hexahydropyrrolo[3,4-*c*]pyrrole-l,3-dione (23c). Prepared from cycloadduct **21c** (0.30 g, 0.67 mmol) and compound **7** (0.17 g, 0.67 mmol) in toluene (6.5 ml). Work up in the normal manner followed by flash chromatography eluting with 1:2 v/v petroleum ether–ether afforded the product (0.25 g, 62%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 68.65; H, 5.9; N, 6.9. $C_{34}H_{33}N_3O_5S$ requires: C, 68.55; H, 5.6; N, 7.05%); *m/z* (%) 595 (M^+, 6), 171 (28), 133 (100), 105 (34) and 43 (25). δ_H: 8.00 (d, 1H, *J*=8 Hz, ArH), 7.98 (d, 2H, *J*=8 Hz, ArH), 7.71 (d, 1H, *J*=8 Hz, ArH), 7.28 (m, 7H, ArH), 6.88 (m, 1H, ArH), 6.80 (d, 1H, *J*=8 Hz, ArH), 6.80 (m, 13H, ArH), 4.84 and 4.88 (2×s, 4H, =CH_2), 4.53 and 4.20 (2×d, 4H, OCH_2), 4.01 (d, 2H, *J*=4.5 Hz, 4-H), 3.82 (s, 4H, $CONCH_2$), 3.50 (m, 2H, 6a-H), 3.37 (m, 2H, 6-H_α and 3a-H), 2.70 (dd, 2H, *J*=9.5 and 5.5 Hz, 6-H_β), 2.43 (d, 4H, *J*=2 Hz, $CMeCH_2C$=), 2.10 (s, 6H, NMe) and 1.44 (s, 6H, CMe).

4.3. One-pot procedure for 23c

A solution of *N*-phenylsulphonylindole-3-carboxaldehyde (1.0 mmol), *N*-propargylmaleimide (1.0 mmol) and sarcosine (1.0 mmol) in toluene (12 ml) were heated at reflux under an atmosphere of dry nitrogen for 48 h, after which time the reaction was shown to be complete by ^{1}H NMR. The reaction mixture was allowed to cool to room temperature, followed by the addition of $Pd_2(dba)_3$ (0.05 mmol) and *tris*(2-furyl)phosphine (0.1 mmol) and then cooled further to 0°C. Tributyltin hydride (1.0 mmol) was added dropwise to the reaction mixture which then was allowed warm to room temperature over 1.5 h. Compound **7** (1.0 mmol) in toluene (1 ml) was then added, and the solution heated at reflux under nitrogen over 14 h. The solvent was removed in vacuo, the residue dissolved in dichloromethane, filtered and evaporated to give the crude product which was purified by flash chromatography as described above to afford the product (39%) as a 1:1 mixture of diastereoisomers.

4.3.1. 2-[2-(3-Methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]4-phenyl-3aα,4β,6,11,11aα,11bα-hexahydro-pyrrolo[3′,4′:3,4] pyrrolo [1,2-*b*] isoquinoline-1,3-dione (28). Prepared from cycloadduct **24** (0.30 g, 0.78 mmol) and compound **7** (0.22 g, 0.78 mmol) in toluene (5 ml). Work up in the normal manner followed by flash chromatography eluting with 3:2 v/v petroleum ether–ether afforded the product (0.22 g, 57%, 1:1 mixture of diastereoisomers), as a colourless amorphous solid, mp 151–152°C. (Found: C, 78.35; H, 6.45; N, 5.35. $C_{33}H_{32}N_2O_3$ requires: C, 78.55; H, 6.4; N, 5.55%); *m/z* (%) 504 (M^+, 21), 371 (66), 220 (25), 133 (100) and 105 (45). δ_H: 7.25 (m, 2×20H, ArH), 6.82 (m, 2×3H, ArH), 4.91 (s, 2H, 2×=C*H*H), 4.79 (s, 2H, 2-H), 4.75 (s, 2H, 2×=CH*H*), 4.48 and 4.49 (2×d, 2H, 2×OC*H*H), 4.16 (d, 2H, 2 OCH*H*), 3.80 (m, 8H, 2×$CONCH_2$, 2×NC*H*HPh and 2×6a-H), 3.46 (m, 4H, 2×3a-H and 2×1-H), 3.21 (d, 2H, 2×NCH*H*Ph), 3.06 (dd, 2H, *J*=16 and 3 Hz, 2×CHC*H*HPh), 2.68 (m, 2H, 2×CH*H*Ph), 2.41 (s, 4H, 2×$CMeC H_2C$=) and 1.40 (s, 6H, 2×CMe).

4.3.2. 2-[2-(3-Methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-4-phenyl-1,2,3,3aα,4β,6,7,8,8aα,8bα-decahydro-pyrrolo[3,4-*a*]pyrrolizine-1,3-dione (31a). Prepared from cycloadduct **29a** (0.34 g, 1.2 mmol) and compound **7** (0.33 g, 1.2 mmol) in toluene (8 ml). Work up in the normal manner followed by flash chromatography eluting with 1:2 v/v petroleum ether–ether afforded the product (0.26 g, 49%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 75.8; H, 6.85; N, 6.1. $C_{28}H_{30}N_2O_3$ requires: C, 76.0; H, 6.85; N, 6.35%); *m/z* (%) 442 (M^+, 10), 309 (39), 159 (57), 133 (100) and 105 (36). δ_H: 7.50–6.79 (m, 2×9H, ArH), 4.93 and 4.84 (2×s, 4H, 2×=CH_2), 4.17 and 4.18 (2×d, 4H, *J*=9 Hz, 2×OCH_2), 4.06 (d, 2H, *J*=6 Hz, 2×3-H), 3.90 (m, 2H, 2×1-H), 3.81 (s, 4H, 2×NCH_2C=), 3.58 (t, 2H, *J*=9 Hz, 2×6a-H), 3.36 (dd, 2H, *J*=9 and 6 Hz, 2×3a-H), 2.98 and 2.64 (2×m, 4H, NCH_2CH_2), 2.41 (s, 4H, 2×$CHMeC H_2C$=), 1.60–2.05 (8H, $NCH_2CH_2CH_2$) and 1.42 and 1.43 (2×s, 6H, 2×CMe).

4.3.3. 2-[2-(4-Methyl-isochroman-4-ylmethyl)-allyl]-4-phenyl-1,2,3,3aα,4β,6,7,8,8aα,8bα-decahydropyrrolo-[3,4-*a*]pyrrolizine-1,3-dione (31b). Prepared from cycloadduct **29a** (0.25 g, 0.84 mmol) and compound **10** (0.24 g, 0.84 mmol) in toluene (5.5 ml). Work up in the normal manner followed by flash chromatography eluting with 1:2 v/v petroleum ether–ether afforded the product (0.19 g, 48%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 76.4; H, 7.35; N, 6.0. $C_{29}H_{32}N_2O_3$ requires: C, 76.3; H, 7.05; N, 6.15%); *m/z* (%) 456 (M^+, 15), 309 (99), 159 (100), 147 (52) and 91 (50). δ_H: 7.49 (d, 2×2H, *J*=8 Hz, ArH), 7.25 (m, 12H, *J*=8 Hz, ArH), 6.99 (d, 2×1H, *J*=8 Hz, ArH), 4.92 (d, 2H, *J*=5 Hz, 2×C*H*HPh),

4.83 (m, 6H, 2×CH*H*Ph and 2×CH_2=), 4.07 (d, 2H, *J*= 6.5 Hz, 2×3-H), 3.98 (m, 8H, 2×NCH_2C=, 2×OC*H*H and 2×1-H), 3.59 and 3.60 (2×t, 2H, *J*=9 Hz, 2×6a-H), 3.50 (d, 2H, *J*=11.5 Hz, 2×OCH*H*), 3.37 (dd, 2H, *J*=9 and 6.5 Hz, 2×3a-H), 2.98 and 2.63 (2×m, 4H, 2×NCH_2CH_2), 2.50 and 2.51 (2×d, 2H, *J*=13.5 Hz, C*H*HC=) and 2.36 (d, 2H, CH*H*C=), 1.83 (m, 8H, 2×NCH_2CH_2 and 2×$NCHCH_2$) and 1.28 and 1.29 (2×s, 6H, 2×CMe).

4.3.4. 2-[2-(1-Methyl-1,3-dihydro-isobenzofuran-1-ylmethyl)-allyl]-8-phenyl-1,2,3,3aα,4β,6,7,8,9,9aα,9bα-decahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3-dione (31c). Prepared from cycloadduct **29b** (0.29 g, 0.95 mmol) and compound **7** (0.26 g, 0.95 mmol) in toluene (6 ml). Work up in the normal manner followed by flash chromatography eluting with 3:2 v/v petroleum ether–ether afforded the product (0.23 g, 52%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 76.2; H, 7.25; N, 5.9. $C_{29}H_{32}N_2O_3$ requires: C, 76.3; H, 7.1; N, 6.15%); *m*/*z* (%) 456 (M^+, 10), 324 (38), 172 (35), 133 (100) and 105 (31). δ_H (CDCl3): 7.36 (m, 2×3H, ArH), 7.10 (m, 2×4H, ArH), 6.88 (m, 2×1H, ArH), 6.80 (d, 2×1H, ArH), 5.05 (s, 2H, 2×=CHH), 4.82 and 4.83 (2×s, 2H, 2×=CHH), 4.60 (s, 2H, 2×3-H), 4.53 and 4.54 (2×d, 2H, 2×OC*H*H), 4.21 (d, 2H, 2×OCH*H*), 3.89 (s, 4H, 2×NCH_2C=), 3.45 (t, 2H, *J*= 7.5 Hz, 2×6a-H), 3.37 and 3.38 (2×d, 2H, *J*=7.5 Hz, 3a-H), 2.80 (broad s, 4H, 2×$NCHHCH_2$ and 2×1-H), 2.17 (s, 4H, 2×$CMeCH_2C$=), 1.44 (s, 6H, 2×CMe) and 2.01–0.84 (m, 14H, NCH*H*CH_2CH_2CH_2).

4.3.5. 2-[2-(4-Methyl-isochroman-4-ylmethyl)-allyl]-8-phenyl-2,3,3aα,4β,6,7,8,9,9aα,9bα-decahydro-1*H*-pyrrolo-[3,4-*a*]indolizine-1,3-dione (31d). Prepared from cycloadduct **29b** (0.25 g, 0.8 mmol) and compound **10** (0.23 g, 0.8 mmol) in toluene (6 ml). Work up in the normal manner followed by flash chromatography eluting with 3:2 v/v petroleum ether–ether afforded the product (0.19 g, 49%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 76.35; H, 7.25; N, 5.65. $C_{30}H_{34}N_2O_3$ requires: C, 76.55; H, 7.3; N, 5.95%); *m*/*z* (%) 470 (M^+, 15), 323 (100), 172 (58), 147 (38) and 119 (38). δ_H: 7.10–7.40 (m, 2×8H, ArH), 6.99 (d, 2×1H, *J*=8 Hz, ArH), 5.03 (s, 2H, 2×=C*H*H), 4.82 (m, 6H, 2×CH_2Ph and 2×=CH*H*), 4.60 (s, 2H, 2×2-H), 3.99 and 4.00 (2×d, 2H, *J*=11 Hz, 2× OC*H*HCMe), 3.91 (s, 4H, 2×NCH_2C=), 3.52 (d, 2H, *J*=11 Hz, 2×OCH*H*CMe), 3.44 (t, 2H, *J*=8 Hz, 2×6a-H), 3.38 (d, 2H, *J*=8 Hz, 2×3a-H), 2.81 (m, 4H, 2×NC*H*HCH_2 and 2×1-H), 2.57 and 2.58 (2×d, 2H, *J*=10 Hz, 2× CMeC*H*HC=), 2.38 and 2.39 (2×d, 2H, *J*=10 Hz, 2× CMeCH*H*C=), 2.01 (m, 2H, 2×NCH*H*CH_2), 1.30 (s, 6H, 2×CMe) and 0.83–1.71 (2×6H, $NCH_2CH_2CH_2CH_2$).

4.3.6. 2-[2-(Methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-4-phenyl-1,3,3aα,4α,6,7,8,8aβ,8bα-decahydro-pyrrolo[3,4-*a*]pyrrolizine-1,3-dione (32). Prepared from cycloadduct **30a** (0.14 g, 0.46 mmol) and compound **7** (0.13 g, 0.046 mmol) in toluene (3 ml). Work up in the normal manner followed by flash chromatography eluting with 1:2 v/v petroleum ether–ether afforded the product (0.10 g, 49%, 1:1 mixture of diastereoisomers), as a colourless gum. (Found: C, 75.95; H, 6. 5; N, 6.3. $C_{28}H_{30}N_2O_3$ requires: C, 76.15; H, 6.6; N, 6.35%); *m*/*z* (%) 442 (M^+, 4), 159 (78), 133 (100) and 105 (72). δ_H: 7.31 (broad s, 2×5H, ArH), 7.11 (d, 2×2H, ArH), 6.93 (t, 2×1H, *J*= 8 Hz, ArH), 6.78 (m, 2×1H, *J*=8 Hz, ArH), 4.93 and 4.78 (2×d, 4H, *J*=9 and 4 Hz, 2×=CH_2), 4.46 and 4.48 (2×d, 2H, *J*=9 Hz, 2×OC*H*H), 4.14 and 4.15 (2×d, 2H, *J*=9 Hz, 2×OCH*H*), 4.10 (d, 2H, *J*=8 Hz, 2×3-H), 3.74 (m, 6H, 2×NCH_2C= and 2×1-H), 3.49 and 3.50 (2×t, 2H, *J*= 8 Hz, 2×3a-H), 3.27 and 3.28 (2×d, 2H, *J*=8 Hz, 2×6a-H), 2.86 and 2.74 (2×m, 4H, 2×NCH_2CH_2), 2.35 (s, 4H, $CMeCH_2C$=), 2.10 (m, 4H, 2×NCH_2CH_2), 1.73 (m, 4H, 2×$NCHCH_2$) and 1.37 (s, 6H, 2×CMe).

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References

1. Grigg, R.; Coulter, T. *Tetrahedron Lett.* **1991**, *32*, 1359–1362.
2. Grigg, R.; Sridharan, V.; Suganthan, S.; Bridge, A. N. *Tetrahedron* **1995**, *51*, 295–306.
3. Fielding, M. R.; Grigg, R.; Sridharan, V.; Thorton-Pett, M.; Urch, C. *Tetrahedron* **2001**, *57*, 7737–7748.
4. Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7125–7128.
5. Grigg, R.; Liu, A.; Suganthan, S.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7129–7132.
6. Grigg, R.; Sridharan, V.; Wang, J.; Xu, J. *Tetrahedron* **2000**, *56*, 8967–8976.
7. Burwood, M.; Davies, B.; Diaz, I.; Grigg, R.; Molina, P.; Sridharan, V.; Hughes, M. *Tetrahedron Lett.* **1995**, *36*, 9053–9056.
8. Grigg, R.; Ali, M. F.; Sridharan, V.; Thianpatanagal, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182–183. Grigg, R.; Thianpatanagal, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180–181.
9. Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703–2713.
10. Wang, C. J.; Ripka, W. C.; Confalone, P. A. *Tetrahedron Lett.* **1984**, *25*, 4613–4616. Inazumi, T.; Yamada, K.; Kuroki, Y.; Kakehi, A.; Noguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 557–564. Mahmud, H.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2001**, *57*, 4095–4105.
11. Eschenmoser; *Chem. Soc. Rev.* **1976**, *5*, 377–410.
12. For a review see: Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65–87.
13. Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 2381–2382.
14. Fielding, M. R.; Grigg, R.; Urch, C. J. *J. Chem. Soc., Chem. Commun.* **2000**, 2239–2240.
15. Brown, S.; Clarkson, S.; Grigg, R.; Thomas, W. A.; Sridharan, V.; Wilson, D. M. *Tetrahedron* **2001**, *57*, 1347–1359.
16. Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *27*, 1361–1367.
17. Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 607–615.
18. Casaschi, A.; Grigg, R.; Sansano, J. M.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7541–7551.
19. Zhang, H. X.; Guibe, F. *J. Org. Chem.* **1990**, *55*, 1857–1867.
20. Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanantham, R.; Thornton-Pett, M.; Wilson, D. M. *Tetrahedron* **1997**, *53*, 11803–11826.