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Palladium catalysed reactions of allene with active methylene pronucleophiles. *C*-1,3-Dienylmethyl derivatives and their Diels–Alder reactions

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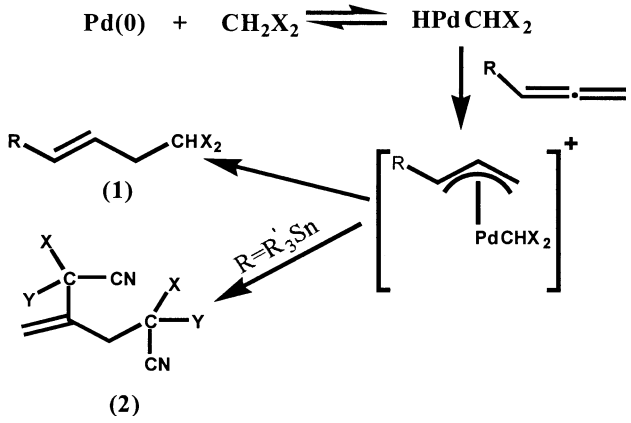
Abstract—A 2-step 100% atom economic sequence is reported whereby active methylene pronucleophiles react with 2 mol equiv. of allene to give bis-1,3-dienylmethyl derivatives of the pronucleophiles. Subsequent double Diels–Alder reactions furnish 1,1′-linked cyclohexenes with a 3-carbon spacer. © 2001 Published by Elsevier Science Ltd.

In a previous paper[1] we reported a 3-step 100% atom economic sequence involving phenols and 2 mol equiv. of allene leading, via phenoxymethyl-1,3-dienes, to the formation of a 4:1 mixtures of chromans and dihydrobenzofurans. Although there have been a number of publications concerning the reactions of substituted allenes with active methine and methylene pronucleophiles, reactions with the parent allene have been largely neglected. Substituted allenes (Scheme 1, R=alkyl, aryl, R^1O, R^1S) generally react by what appears to be addition of $HPdCHX_2$ to the allene generating a π-allylpalladium (II) species (Scheme 1)[2–4] to afford allylated derivatives **1**.

Allenylstannanes react with pronucleophiles of the type CH(CN)XY to give double alkylation products **2** (Scheme 1) in good yield.[2] Intramolecular versions of these processes have also been reported[2,5] leading to 3–6 membered ring formation. In all the foregoing processes the substituted allenes and the active methine/methylene pronucleophiles react in a 1:1 molar ratio. We now report processes involving 2:1, 3:1 and 4:1 molar ratios of allene to active methylene pronucleophiles which generate 1,3-dienylmethyl derivatives of the active methylene compounds. Subsequent Diels–Alder reactions of these products proceed in good yield to afford a range of unusual 1,1′-dicyclohexyl derivatives linked by three carbon bridges.

A range of active methylene compounds was reacted with allene (1.5 bar) in THF in a Schlenk tube at 80°C (oil bath temperature) in the presence of 5 mol% $Pd(PPh_3)_4$ to afford bis-alkylated products **4**–**7** in 47–92% yield (Table 1). However, in the case of dimethyl malonate only the monoalkylated product **3** (Table 1, entry 1) was obtained. Interestingly when 1,3-dimethyl barbituric acid and malononitrile were employed as pronucleophiles using the standard (Table 1) conditions they afforded 4:1 and 5:1 mixtures, respectively, of bis-1,3-dienylmethyl and allyl-1,3-dienylmethyl products (Scheme 2).

Coulsen[6] has reported some examples of this type of reaction. He employed bis(triphenylphosphine) (maleic



Scheme 1.

Keywords: atom economy; π-allylpalladium (II) species; allene dimerisation; chromans; bis-allylation.

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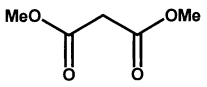
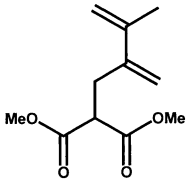
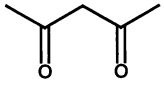
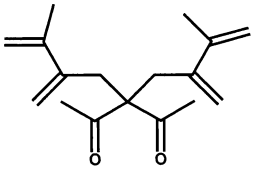
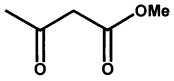
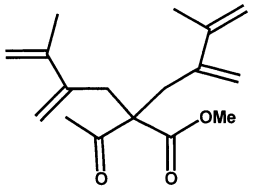
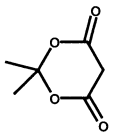
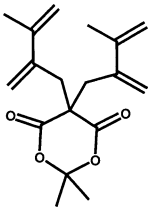
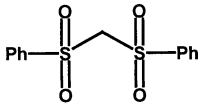
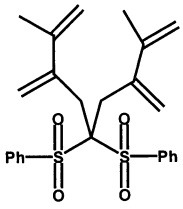
Table 1. Mono- and bis-1,3-dienylmethyl derivatives of active methylene pronucleophiles

Entry	Pronucleophile	Product	Yield (%)[a]
1		 (3)	89[b]
2		 (4)	90
3		 (5)	92
4		 (6)	61
5		 (7)	47

All reactions were carried out with 5 mol% $Pd(PPh_3)_4$ in a Schlenk tube for 16 h at 80°C (oil bath temperature) with allene (1.5 bar) in THF.
[a] Isolated yield.
[b] Oil bath temperature 90°C.

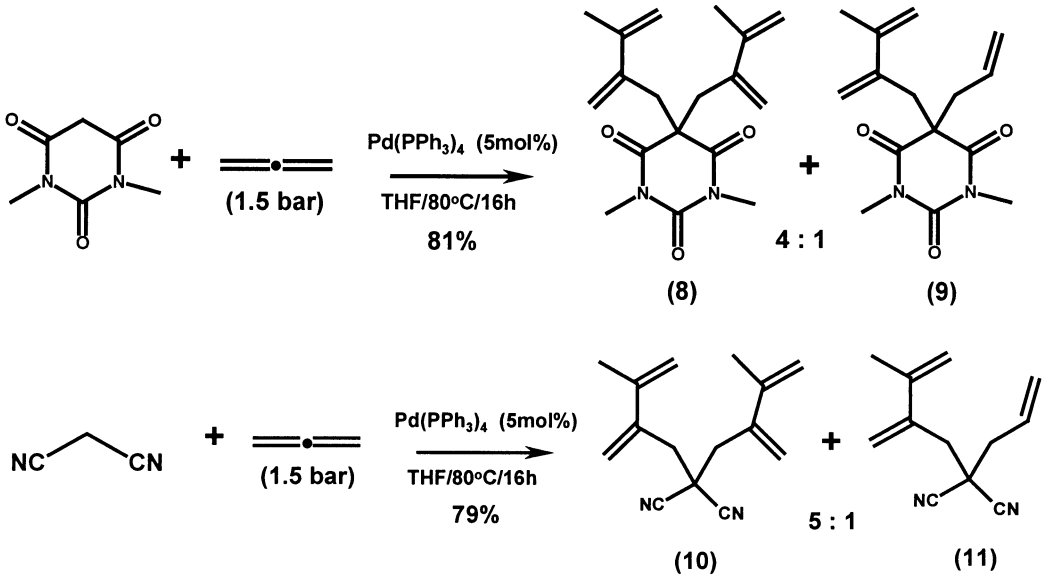
anhydride)Pd(0) as catalyst and obtained mainly the mono-1,3-dienylmethyl products in variable yield. No allyl derivatives were reported in this work.

When dimedone was reacted with allene under analogous conditions it produced a further variation in products (Scheme 3) affording a separable 5:9:1 mixture of **12**, **13** and **14**, respectively. Decreasing the reaction temperature to 60°C (oil bath) afforded a 10:10:1 mixture of **12**, **13** and **14**.

In contrast to dimedone the reaction of 4-hydroxycoumarin with allene under our standard conditions afforded **16** (34%) (Scheme 4), presumably via **15**. This type of cyclisation process has been previously observed by us.[1] Compound **15** could originate by direct C(3)-alkylation of 4-hydroxycoumarin or via *O*-alkylation–Claisen rearrangement.[1]

1. Mechanism

The formation of monoallyl products **9** and **11** and bis-allyl product **12** as well as bis-1,3-dienylmethyl derivatives **8** and **10** and products **13** and **14** derived from the undetected mono-1,3-dienylmethyl derivative of dimedone is capable of a number of interpretations. Clearly two catalytic cycles (Scheme 5) are operating whose relative rates are dependent on the nature of the pronucleophile.

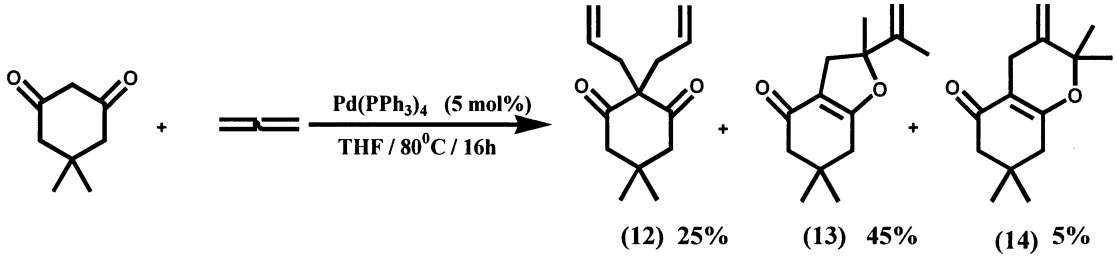


Scheme 2.

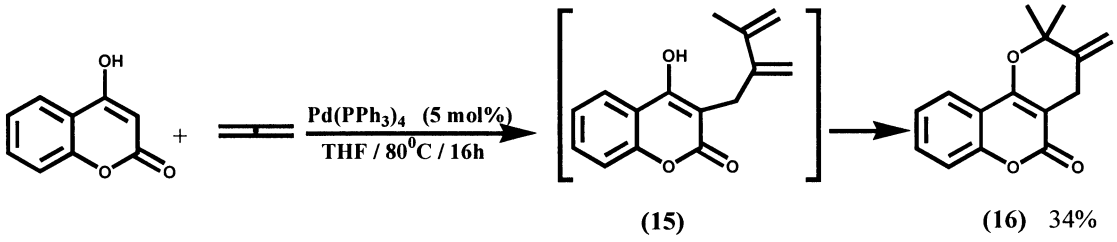
The reaction of allene with Pd(0) to form complex **17** (Scheme 5, path a) was first suggested by Coulsen.[6] The reductive dimerisation of alkenes and alkynes to form 5-membered metallocycles is well documented.[7] The observation that monosubstituted allenes react with most pronucleophiles in a 1:1 ratio to give the corresponding allyl derivatives (Scheme 1) rather than 1,3-dienylmethyl derivatives could then be interpreted as steric retardation of palladacycle formation (Scheme 6).

Examples of reductive dimerisation of allenes are also known. For example a recent paper[8] describe the formation of such a product (Scheme 7), where the tether strongly influences the regioselectivity.

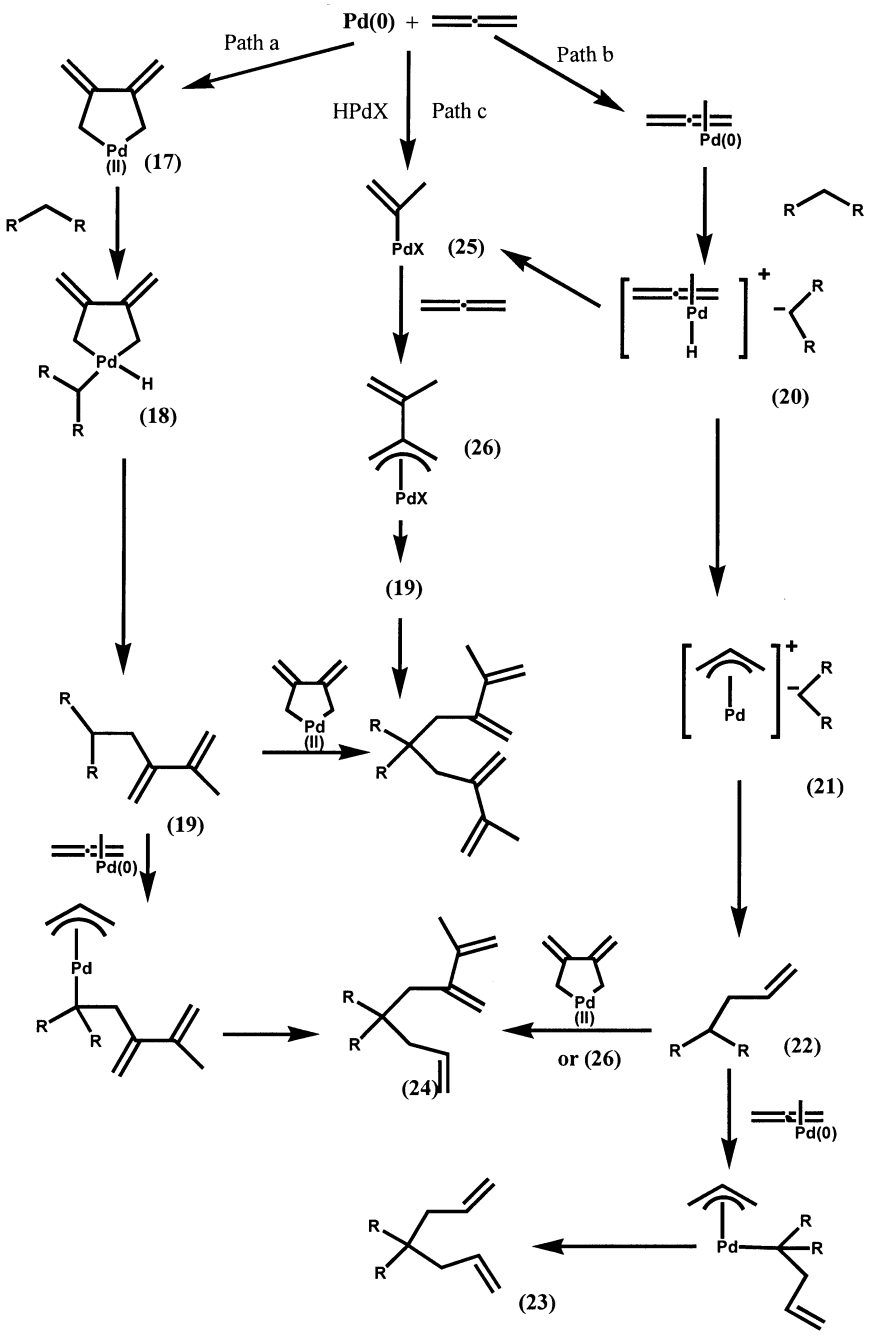
Any proposed mechanism must account for Coulsen's deuterium labelling studies using CD_2XY which showed the label was regioselectively located in the methyl group of the 1,3-dienylmethyl products. Both Pd(IV) species **18** and Pd(II) species **25** (Scheme 5) could give rise to this labelling pattern. Formation of the bis-allylated product **23** presumably arises via **21** and **22**, (Scheme 5, path b) which conforms to mechanistic suggestions made by others.[2–4] The monoallyl mono-1,3-dienylmethyl product **24** could arise by a combination of either path a and path b, or a combination of path b and path c via **19** or **22** (Scheme 5). In order to probe the efficacy of **22** as a precursor for **24** we prepared monoallylated species **27** and the mono-1,3-dienylmethyl species **3** and subjected them to the standard catalytic conditions. While **27** afforded **11** in 82% yield, **3** was recovered unchanged i.e. no conversion to **28** or **29** was observed.



Scheme 3.



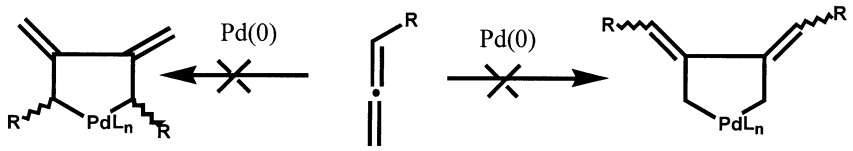
Scheme 4.



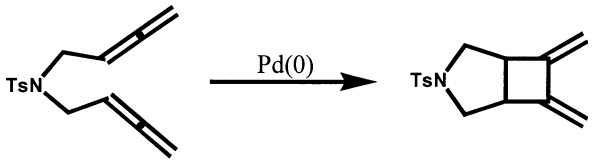
Scheme 5.

Whilst path a, via **17** and **18** is attractive, the requirement that the rate of processes involving the Pd(IV) species **18** should normally be substantially faster than those proceeding via a Pd(II) species such as **21** is less appealing. In a sequence involving only Pd(II) species (Scheme 5, paths b and c) the crux of the mechanistic problem is summarised in Scheme 8. What are the features of the substrates that control the regiochemistry of the hydropalladation to give **25** or **21** whilst carbo- and acyl-palladation are highly regioselective for **30** and **31**?

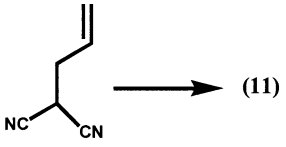
Prior work with monosubstituted allenes show products



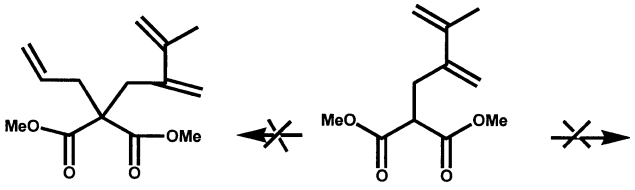
Scheme 6.



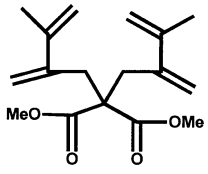
Scheme 7.



(27)

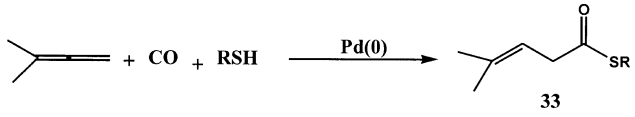


(29) (3)



(28)

(Scheme 1) derived from **21** are favoured in these cases whereas related work on carbonylation (1 bar) by our group shows that both allene and monosubstituted allenes appear to proceed via **25** to give amides **32** (Scheme 9).[9]



Scheme 10.

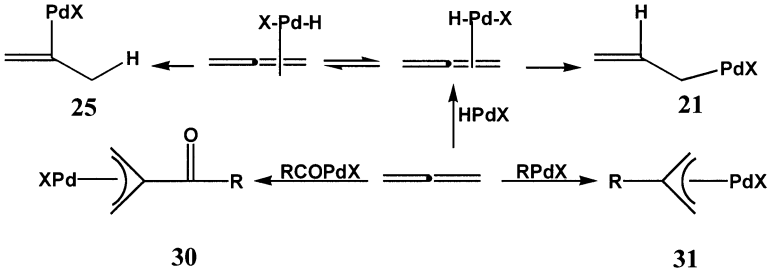
However, in contrast to Scheme 9, 1,1-dimethyl allene reacts with thiols and CO (400 psi) via **21** to give terminal acylation products **33** (Scheme 10).[10]

A further not unrelated case is the linear versus branched hydroformylation of alkenes.[11]

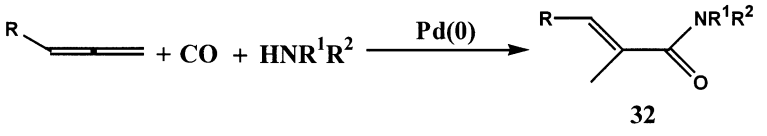
Bearing in mind that H, R and RCO groups migrate from Pd(II) to the coordinated alkene/allene whereas soft nucleophiles [amines, malonate anions, alcohols, thiols(?)][12] attack the palladium complexed alkene/allene externally we propose these various processes are controlled by stereoelectronic factors. Cazes et al. observed formation of both mono- and dimeric products when deca-1,2-diene was reacted with a sterically hindered pronucleophile (Scheme 11).[3]

Thus (i) formation of **25** in preference to **21** (Scheme 8) is favoured by coordination of π^*-acceptor ligands such as CO or an additional allene which render the Pd(II) centre more electrophilic (electrophiles preferentially attack the central carbon of allenes).[13] (ii) In certain cases, such as 4-hydroxycoumarin, where acidic enols are present the process is likely to procede via O-alkylation or *O*-1,3-dienylallylation followed by Claisen rearrangement.[1,14] (iii) Sterically hindered pronucleophiles react slowly and permit dimerisation of mono-substituted allene to become dominant.[3] (iv) The rates of allylation and dienylmethylation of the pronucleophile are finely balanced in some cases (Schemes 2 and 3).

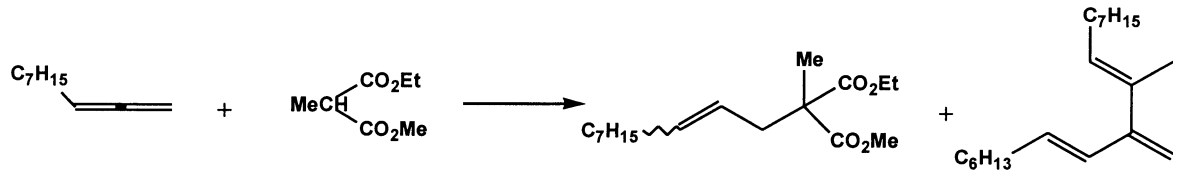
Taking all these factors into consideration we favour either a combination of paths b and c (Scheme 5) or of path b (Scheme 5) with Scheme 12 for the formation of the mixed allyl-dienylmethyl products **9** and **11**. The conversion



Scheme 8.



Scheme 9.



Scheme 11.

of **27→11** and the failure of **3** to react further to either **28** or **29** suggests the origin of **9** and **11** is more likely to be via **21** (Scheme 5) with the increased steric hindrance in pronucleophile **22** slowing the rate of a second allylation sufficiently to allow **17** (Scheme 12) or **26** (Scheme 5) to compete.

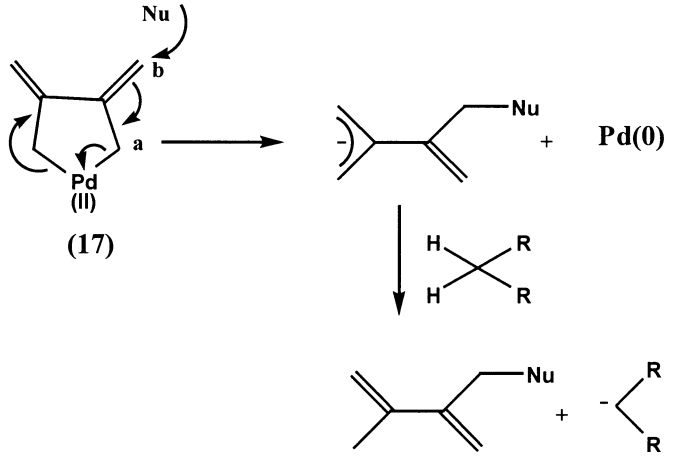
It should be noted that a further alternative (Scheme 12) to Scheme 5, path a, involving only Pd(II) intermediates deserves consideration.

The nucleophile can attack **17** at a or b to generate Pd(0) and an allylic anion which deprotonates more of the pronucleophile.

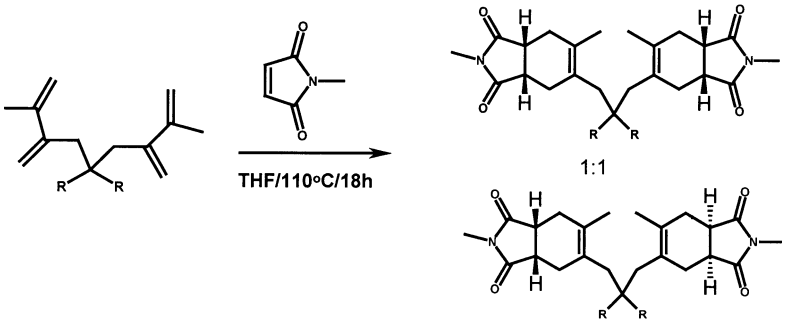
Although the p*K*a's of the three pronucleophiles which give rise to some allylation products, as opposed to bis-dienylmethyl products, differ widely (*N*,*N*′-dimethyl barbituric acid, p*K*a 4.7; dimedone, p*K*a 5.25 and malononitrile, p*K*a 11.2) they share two common features in that they are unable to form cyclic H-bonded enolates and their enols or deprotonated species pose considerably less steric hindrance than the other pronucleophiles by virtue of the 6-membered rings or linearity of the CN groups. For example the ring C atoms of the enol of dimedone are essentially coplanar except for C(5).[15] This would promote a faster rate of attack of the nucleophile on the π-complexed allene **20** (Scheme 5, path b).

2. Diels–Alder reactions

The mono- and bis-1,3-dienylmethyl derivatives generated from the palladium catalysed reactions undergo Diels–Alder reactions with *N*-methyl maleimide to give 1:1 mixtures of *syn*- and *anti*-cycloadducts in good yield (Scheme 13, Table 2).

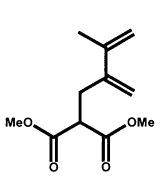
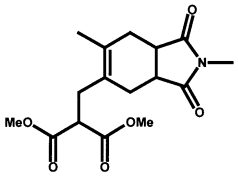
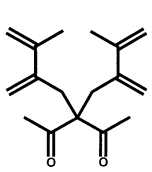
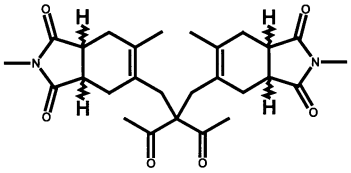
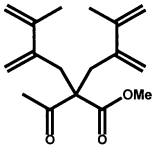
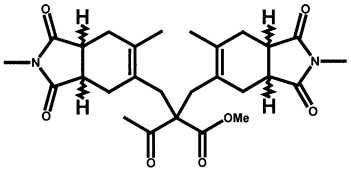
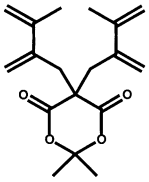
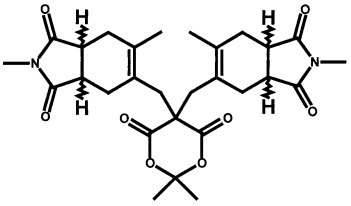
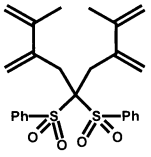
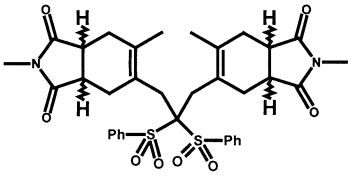
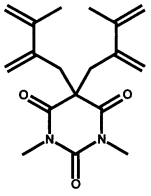
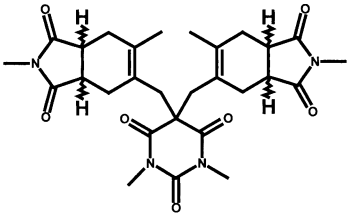
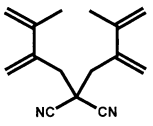
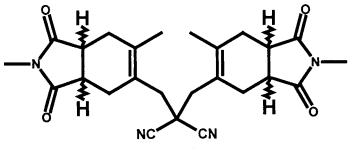


Scheme 12.



Scheme 13.

Table 2. Diels–Alder products

Entry	Diene	Product[a]	Yield (%)[b]
1	 (3)	 (34)	79
2	 (4)	 (35a, b)	56
3	 (5)	 (36a, b)	81
4	 (6)	 (37a, b)	64
5	 (7)	 (38a, b)	83
6	 (8)	 (39a, b)	87
7	 (10)	 (40a, b)	94

All reactions carried out in THF at 100°C in a Schlenk tube for 18 h.
[a] All products except **34** (entry 1) comprise 1:1 mixtures of diastereoisomers.
[b] Isolated yield.

3. Experimental

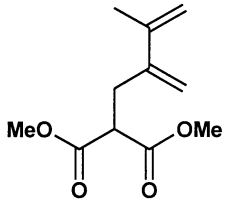
Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Mass spectral data were obtained on an Autospec instrument at 70 eV. Accurate mass measurements were determined on an electrospray LCT-Micromass instrument. Nuclear magnetic resonance spectra were recorded at 250 MHz on a Brucker AM 250.

Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants are given in Hertz (Hz). Unless otherwise specified deuteriochloroform was used as solvent. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, dt=double triplet. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. The term 'ether' refers to diethyl ether and petroleum ether refers to that fraction of petroleum ether with boiling point between 40–60°C. Column chromatography was performed with flash silica gel (Merck 9385).

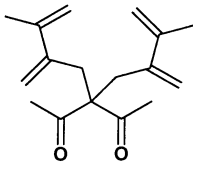
3.1. General procedure for alkylation active methylene pronucleophiles with allene

The dicarbonyl compound (2 mmol) and $Pd(PPh_3)_4$ (5 mol%) were mixed in dry THF (10 ml) in a Schlenk tube. The solution was degassed before addition of allene (1.5 bar). The reaction mixture was heated and stirred at 80°C for 16 h, then cooled. The excess pressure was vented from the Schlenk tube and the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography.

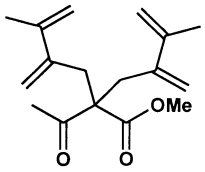
3.1.1. 2-(3-Methyl-2-methylene-but-3-enyl)-malonic acid dimethyl ester (3). Column chromatography eluting with 1:2 v/v petroleum ether–ether afforded the product (89%) as a colourless oil. (Found: C, 62.35; H, 7.5. $C_{11}H_{16}O_4$ requires: C, 62.25; H, 7.6%); δ_H 1.89 (s, 3H, Me), 2.92 (d, 2H, J=7.6 Hz, CH_2), 3.65 (t, 1H, J=7.6 Hz, CH), 3.73 (s, 6H, 2×OCH_3), 5.01(s, 2H, C=CH_2), and 5.09 and 5.14 (2×s, 2×1H, C=CH_2); *m/z* (%): 212 (M^+, 3), 180 (7), 152 (39), 121 (38), 93 (100), 77 (24), 59 (19), and 41 (17).



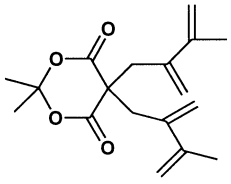
3.1.2. 3,3-Bis-(3-methyl-2-methylene-but-3-enyl)-pentane-2,4-dione (4). Column chromatography eluting with 49:1 v/v hexane–ether afforded the product (90%) as a colourless oil. (Found: C, 78.3; H, 9.0. $C_{17}H_{24}O_2$ requires: C, 78.4; H, 9.3%); δ_H 1.87 (s, 6H, 2×CH_3–C=), 2.11 (s, 6H, 2×CH_3CO), 3.02 (s, 4H, 2×CH_2) and 4.79, 4.94, 5.06 and 5.18 (4×s, 4×2H, 4×C=CH_2); *m/z* (%): 261 (M^++1, 1), 203 (4), 189 (4), 149 (7), 91 (74) and 439 (100).



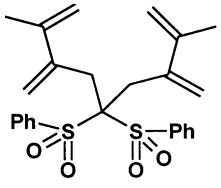
3.1.3. 2-Acetyl-5-methyl-4-methylene-2-(3-methyl-2-methylene-but-3-enyl)-hex-5-enoic acid methyl ester (5). Column chromatography eluting with 49:1 v/v petroleum ether–ether afforded the product (92%) as a colourless oil. (Found: C, 73.95; H, 8.7. $C_{17}H_{24}O_3$ requires: C, 73.9; H, 8.75%); δ_H 1.87 (s, 6H, 2×CH_3C=), 2.13(s, 3H, CH_3CO), 2.91 and 3.02 (2×d, 2×2H, J=15.6 Hz, 2×CH_2), 3.64 (s, 3H, OCH_3), 4.91, 4.93, 5.03 and 5.19 (4×s, 4×2H, 4×C=CH_2); *m/z* (%): 276 (M^+, 5), 235 (9), 217 (15), 147 (34), 93 (22), 73 (100) and 55 (51).



3.1.4. 2,2-Dimethyl-5,5-bis-(3-methyl-2-methylene-but-3-enyl-[1,3]dioxane-4,6-dione (6). Column chromatography eluting with 49:1 v/v petroleum ether–ether afforded the product (61%) as a colourless amorphous powder, mp 56–57°C. (Found: C, 71.1; H, 8.15. $C_{18}H_{24}O_4$ requires: C, 71.05; H, 7.95%); δ_H 1.56 (s, 6H, 2×Me), 1.86 (s, 6H, 2×CH_3C=), 3.10 (s, 4H, 2×CH_2) and 5.04, 5.12, 5.20 and 5.28 (4×s, 4×2H, 4×C=CH_2); *m/z* (%): 246 (M^+ – $(CH_3)_2CO$, 9), 201 (41), 187 (38), 159 (41), 147 (36), 105 (40), 91 (100), 77 (60) and 41 (73).



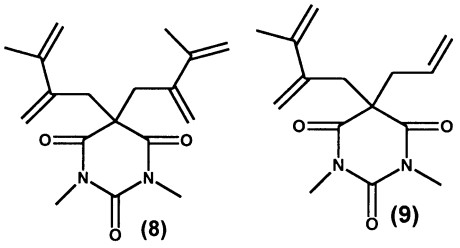
3.1.5. Bis-(3-methyl-2-methylene-but-3-enyl)-bis-(phenylsulfonyl)-methane (7). Column chromatography eluting with 9:1 v/v petroleum ether–ether afforded the product (47%) as colourless prisms, mp 105–106°C. (Found: C, 65.5; H, 6.2; S, 14.2. $C_{25}H_{28}O_4S_2$ requires: C, 65.75; H, 6.2; S, 14.05%); δ_H 1.87 (s, 6H, 2×CH_3), 3.43 (s, 4H, 2×CH_2), 4.97, 4.99, 5.33 and 5.54 (4×s, 4×2H, 4×C=CH_2), 7.53 (m, 4H, ArH), 7.65 (m, 2H, ArH) and 8.10 (d, 4H, J=7.3 Hz, ArH); *m/z* (%): 456 (M^+, 4), 315 (26), 253 (33), 173 (100), 133 (49), 91 (81) and 73 (68).



3.1.6. 1,3-Dimethyl-5,5-bis-(3-methyl-2-methylene-but-3-enyl)-pyrimidine-2,4,6-trione (8) and 5-allyl-1,3-dimethyl-5-(3-methyl-2-methylene-but-3-enyl)-pyrimidine-2,4,6-trione (9). Column chromatography eluting with 19:1 v/v petroleum ether–ether afforded 4:1 mixture of **8** and **9** (81%) as a colourless oil.

Major isomer **8** (Found: C, 68.2; H, 7.6; N, 8.95. $C_{18}H_{24}N_2O_3$ requires: C, 68.35; H, 7.65; N, 8.85%); δ_H 1.80 (s, 6H, 2×CH_3), 3.03 (s, 4H, 2×CH_2), 3.16 (s, 6H, 2×NCH_3) and 4.73, 4.91, 4.95 and 5.07 (4×s, 4×2H, 4×C=CH_2); *m/z* (%): 317 (M^++1, 8), 316 (M^+, 4), 281 (10), 221 (14), 147 (31) and 73 (100).

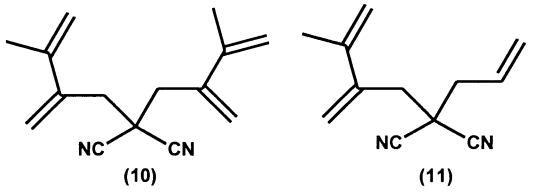
Minor isomer **9**: (Found: C, 65.35; H, 7.45; N, 10.3. $C_{15}H_{20}N_2O_3$ requires: C, 65.2, H, 7.3, N, 10.15%); δ_H 1.77 (s, 3H, CH_3), 2.82 (d, 2H, J=7.2 Hz, CH_2CH=), 2.93 (s, 2H, CH_2C=), 3.18 (s, 6H, 2×NCH_3), 4.86–5.09 (m, 6H, 3×C=CH_2) and 5.5 (m, 1H, CH_2–CH=CH_2); *m/z* (%): 277 (M^++1, 80), 276 (M^+, 27), 221 (28), 169 (34), 147 (22), 69 (48) and 57 (100).



3.1.7. 2,2-Bis-(3-methyl-2-methylene-but-3-enyl)-malononitrile (10) and 2-allyl-2-(3-methyl-2-methylene-but-3-enyl)-malononitrile (11). Column chromatography eluting with 49:1 v/v petroleum ether–ether of the 5:1 mixture of **10** and **11** afforded the separated isomers (79% combined yield) each of which was a colourless oil.

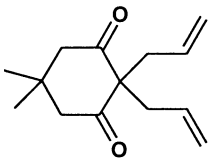
Major isomer **10** (Found: C, 79.7; H, 7.9; N, 12.5. $C_{15}H_{18}N_2$ requires: C, 79.6; H, 8.0; N, 12.4%); δ_H 1.99 (s, 6H, 2×Me), 2.93 (s, 4H, 2×CH_2), 5.13 (s, 4H, 2×C=CH_2) and 5.41 and 5.52 (2×s, 2×2H, 2×C=CH_2); *m/z* (%): 226 (M^+, 22), 217 (23), 165 (22), 147 (33), 136 (90), 73 (100), 69 (59) and 57 (67).

Minor isomer **11** δ_H 1.99 (s, 3H, Me), 2.71 (d, 2H, J=7.2 Hz, CH_2–CH=), 2.91 (s, 2H, CH_2–C=), 5.15 (s, 2H, C=CH_2), 5.38–5.52 (m, 4H, 2×C=CH_2) and 5.8 (m, 1H, CH_2–CH=CH_2); *m/z* (%): 186 (M^+, 3), 158 (24), 93 (27), 79 (45), 53 (52) and 41 (100).

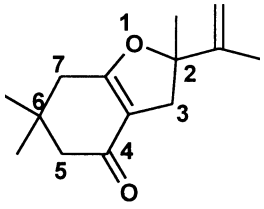


3.1.8. 2-Allyl-2-(3-methyl-2-methylene-but-3-enyl)-malononitrile (11). Prepared from allylmalononitrile[16] by the general procedure. Work up followed by column chromatography offered the product (82%) as a colourless oil. HRMS: 186.1150. $C_{12}H_{14}N_2$ requires: 186.1157. The ^{1}H NMR and mass spectra were identical to those given above.

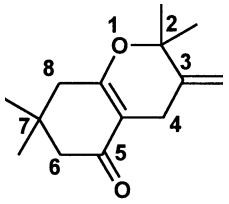
3.1.9. 2,2-Diallyl-5,5-dimethyl-cyclohexane-1,3-dione (12). Column chromatography eluting with 49:1 v/v petroleum ether–ether afforded the product (40%) as a colourless amorphous powder, mp 39–40°C. (Found: C, 76.1; H, 9.35. $C_{14}H_{20}O_2$ requires: C, 76.35; H, 9.15%); δ_H 0.98 (s, 6H, 2×Me), 2.5 (d, 4H, J=7.3 Hz, 2×CH_2–CH=), 2.54 (s, 4H, 2×CH_2CO), 5.05–5.13 (m, 4H, 2×CH=CH_2) and 5.6 (m, 2H, 2×CH=CH_2); *m/z* (%): 220 (M^+, 4), 179 (18), 83 (100), 79 (34), 55 (38) and 41 (79).



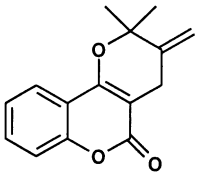
3.1.10. 2-Isopropenyl-2,6,6-trimethyl-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one (13). Column chromatography eluting with 17:3 v/v hexane–ether afforded the product (45%) as a colourless oil. (Found: C, 76.05; H, 9.2. $C_{14}H_{20}O_2$ requires: C, 76.35; H, 9.15%); δ_H 1.10 and 1.12 (2×s, 2×3H, 6-Me), 1.51 (s, 3H, 2-Me), 1.77 (s, 3H, Me–C=), 2.24 (s, 2H, 7-CH_2), 2.31 (s, 2H, CH_2CO), 2.63 and 2.85 (2×dt, 2×1H, J=14 and 1.8 Hz, 3-CH_2), and 4.84 and 4.91 (2×s, 2×1H, C=CH_2); *m/z* (%): 220 (M^+, 48), 205 (79), 192 (42), 177 (41), 149 (42), 136 (100), 121 (73) and 43 (53).



3.1.11. 2,2,7,7-Tetramethyl-3-methylene-2,3,4,6,7,8-hexahydro-chromen-5-one (14). Column chromatography eluting with 17:3 v/v hexane–ether afforded the product (5%) as a colourless oil. δ_H 1.05 (s, 6H, 2×7-Me), 1.44 (s, 6H, 2×2-Me), 2.22 (s, 2H, 8-CH_2), 2.24 (s, 2H, CH_2CO), 3.01 (s, 2H, 4-CH_2) and 5.0 and 5.03 (2×s, 2×1H, C=CH_2); *m/z* (%): 220 (M^+, 65), 205 (75), 177 (31), 149 (26), 136 (100), 121 (48) and 55 (29).



3.1.12. 2,2-Dimethyl-3-methylene-3,4-dihydro-2*H*-pyrano-[3,2-*c*]chromen-5-one (16). Column chromatography eluting with 16:1 v/v petroleum ether–ether afforded the product (34%) which crystallised from hexane as colourless needles, mp 150–151°C. (Found: C, 74.5; H, 6.1. $C_{15}H_{14}O_3$ requires: C, 74.35; H, 5.8%); δ_H 1.61 (s, 6H, Me), 3.36 (t, 2H, J=1.5 Hz, CH_2), 5.17 (t, 2H, J=1.5 Hz, C=CH_2), 7.3 (m, 2H, ArH) and 7.49 and 7.8 (2×m, 2×1H, ArH); *m/z* (%): 243 (M^++1, 92), 221 (41), 207 (13), 175 (15), 147 (35) and 73 (100).

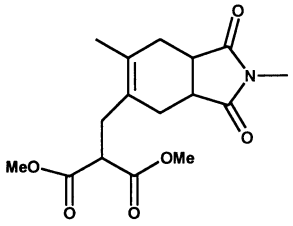


3.2. General procedure for Diels–Alder reactions

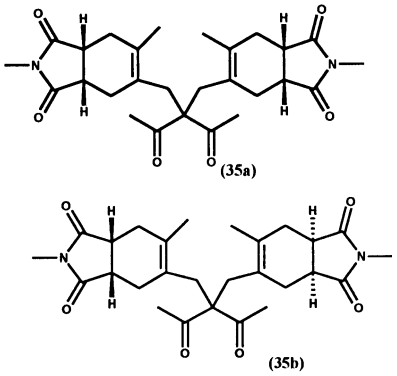
The diene (0.2 g) and *N*-methylmaleimide (1.5 equiv.) or

bis-dienes (0.2 g) and *N*-methylmaleimide (3 equiv.) were mixed in dry THF (10 ml) in a Schlenk tube. The solution was stirred at 110°C for 18 h, then cooled, vented and the solvent evaporated under reduced pressure. The residue was purified by column chromatography. The low melting products were difficult to obtain free of small amounts of water of crystallisation.

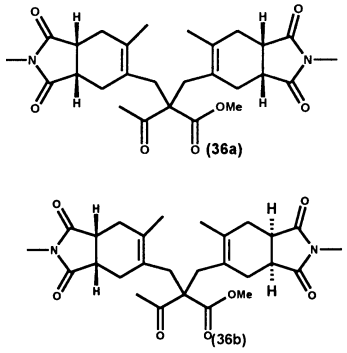
3.2.1. 2-(2,6-Dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-ylmethyl)-malonic acid dimethyl ester (34). Column chromatography eluting with 19:1 v/v dichloromethane–ethyl acetate afforded the product (79%) as an amorphous colourless solid, mp 73–74°C. (Found: C, 59.2; H, 6.75; N, 4.3. $C_{16}H_{21}NO_6$ requires: C, 59.45; H, 6.55; N, 4.35%); δ_H 1.67 (s, 3H, Me), 2.25 and 2.45 (2× 2H, 2× $=CCH_2$), 2.58 (dd, 1H, J=6.5 and 14.1 Hz, 1H of exocyclic CH_2), 2.68(dd, 1H, J=8.9 and 14.1 Hz, 1H of exocyclic CH_2), 2.95 (s, 3H, NMe), 3.05 (m, 2H, ring junction protons), 3.55 (dd, 1H, J=6.5 and 8.9 Hz, COCHCO) and 3.67 and 3.70 (2×s, 2×3H, OMe); *m/z* (%): 323 (M^+, 8), 231 (100), 192 (49), 107 (54) and 91 (83).



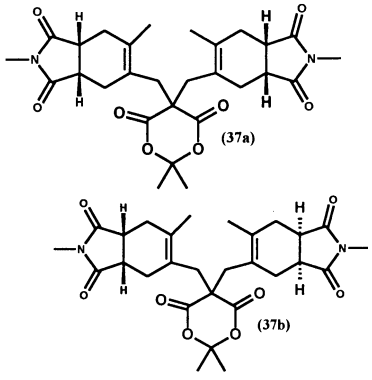
3.2.2. 3,3-Bis-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-ylmethyl)-pentane-2,4-dione (35a,b). Column chromatography eluting with 3:16:1 v/v/v petroleum ether–ether–methanol afforded a 1:1 mixture of **35a** and **35b** (56%) as a colourless amorphous powder, mp 64–65°C. (Found: C, 66.05; H, 7.05; N, 5.8. $C_{27}H_{34}N_2O_6{\cdot}0.5H_2O$ requires: C, 66.0; H, 7.15; N, 5.7%); HRMS (found): 505.2315. $C_{27}H_{34}N_2O_6Na$ requires 505.2296; δ_H 1.7, 1.74, 1.92 and 1.98 (4×s, 4×3H, 4× $CH_3C=$), 2.19(s, 3H, CH_3CO), 2.21 (s, 9H, 3×CH_3CO), 2.23–2.49 (m, 16H, CH and CH_2), 2.83–2.89 (m, 4H, CH and CH_2), 2.93 (s, 9H, 3×NCH_3), 2.94 (s, 3H, NCH_3) and 2.99–3.06 (m, 12H, CH and CH_2); *m/z* (%): 483 (M^++1, 12), 439 (5), 292 (14), 192 (34), 83 (40), 73 (70) and 69 (100).



3.2.3. 2,2-Bis-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a,hexahydro-1*H*-isoindol-5-ylmethyl)-3-oxo-butyric acid methyl ester (36a,b). Column chromatography eluting with 3:16:1 v/v/v petroleum ether–ether–methanol afforded a 1:1 mixture of **36a** and **36b** (81%) as a colourless amorphous powder, mp 62–64°C. (Found: C, 64.3; H, 6.9; N, 5.6. $C_{27}H_{34}N_2O_7{\cdot}0.25H_2O$ requires: C, 64.5; H, 6.85; N, 5.55%); HRMS (found): 521.2285. $C_{27}H_{34}N_2O_7Na$ requires 521.2264; δ_H 1.65 (s, 6H, 2×$CH_3C=$), 1.67 (s, 3H, $CH_3C=$), 1.78 (m, 3H, CH_3–C=), 2.16 and 2.17 (2×s, 2× 3H, 2×CH_3CO), 2.23–2.8 (m, 20H, CH and CH_2), 2.89 (s, 3H, NCH_3), 2.94 (s, 9H, 3×NCH_3), 2.99 (m, 12H, CH and CH_2) and 3.65 and 3.69 (2×s, 2×3H, 2×OCH_3); *m/z* (%): 499 (M^++1, 100), 498 (M^+, 7), 276 (30), 192 (31) and 57 (36).

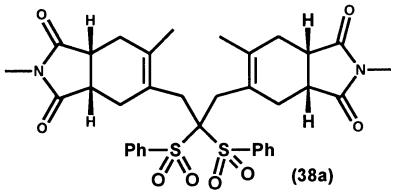


3.2.4. 2,2-Dimethyl-5,5-bis-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-ylmethyl)-[1,3]-dioxane-4,6-dione (37a,b). Column chromatography eluting with 3:16:1 v/v/v petroleum ether–ether–methanol afforded a 1:1 mixture of **37a** and **37b** (64%) as a colourless amorphous powder, mp 89–90°C. (Found: C, 62.45; H, 6.35; N, 4.9. $C_{28}H_{34}N_2O_8{\cdot}0.75H_2O$ requires: C, 62.3; H, 6.6; N, 5.2%); δ_H 1.57 (s, 12H, 4×Me), 1.68 (s, 3H, CH_3–C=), 1.71 (s, 9H, 3×CH_3–C=), 2.1–2.16 (m, 8H, CH and CH_2), 2.42–2.59 (m, 12H, CH and CH_2), 2.93 (s, 12H, 4× NCH_3), 2.97 (m, 8H, CH and CH_2) and 3.12–3.18 (m, 4H, CH and CH_2); *m/z* (%): 424 ($M^+-(CH_3)_2CCO_2$, 2), 232 (4), 182 (65), 113 (56), 55 (82) and 41 (100).

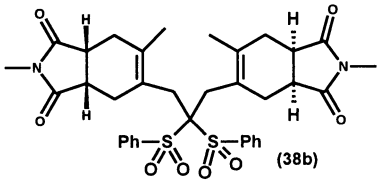


3.2.5. Bis-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-ylmethyl)-bis-(phenylsulpfonyl)-methane (38a,b). Column chromatography eluting with 3:16:1 v/v/v petroleum ether–ether–methanol afforded a 1:1 mixture of **38a** and **38b** (83%) as a colourless amorphous powder, mp 204–205°C. (Found: C, 59.5; H, 5.55; N, 3.8; S, 9.6. $C_{35}H_{38}N_2O_8S_2{\cdot}0.5H_2O$ requires: C, 61.15; H, 5.65; N, 4.05; S, 9.3%); HRMS (found): 701.1954. $C_{35}H_{38}N_2O_8S_2Na$ requires 701.1967; δ_H 1.62 (s, 6H, 2× Me), 1.75 (s, 6H, 2×Me), 1.85 (m, 2H, CH and CH_2), 2.0–2.3 (m, 6H, CH and CH_2), 2.4–2.5 (m, 4H, CH and CH_2), 2.7–2.85 (m, 4H, CH and CH_2), 2.92 and 2.93 (2×s,

2×6H, 4×NCH_3), 2.94–3.1 (m, 12H, CH and CH_2), 3.2 and 3.6 (2×d, 2×2H, J=15 Hz, 2×CH_2), 7.5–7.7 (m, 12H, ArH) and 7.93 and 8.03 (2×d, 2×4H, J=7.6 Hz, ArH); *m/z* (%): 536(M^+−$PhSO_2H$, 2), 365 (96), 216 (71), 202 (100), 91 (68) and 77 (74).

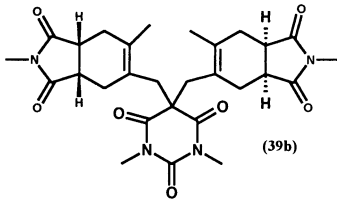


(38a)

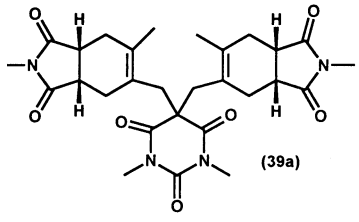


(38b)

3.2.6. 5,5-Bis-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-ylmethyl)-1,3-dimethyl-pyrimidine-2,4,6-trione (39a,b). Column chromatography eluting with 4:15:1 v/v/v petroleum ether–ether–methanol afforded a 1:1 mixture of **39a** and **39b** (87%) as a colourless amorphous powder, mp 88–89°C. (Found: C, 61.6; H, 6.45; N,10.35. $C_{28}H_{34}N_4O_7{\cdot}0.5H_2O$ requires: C, 61.4; H, 6.4; N, 10.25%); HRMS (found): 561.2307. $C_{28}H_{34}N_4O_7Na$ requires 561.2325; δ_H 1.68 (s, 9H, 3×Me), 1.7 (s, 3H, Me), 1.9 (m, 4H, CH and CH_2), 2.19 (m, 4H, CH and CH_2), 2.28–2.45 (m, 8H, CH and CH_2), 2.65 (dd, 4H, J=4 and 13.5 Hz, 2×CH_2), 2.87 (s, 12H, 4×NCH_3), 2.94 (m, 12H, CH and CH_2), 3.24 (s, 3H, NCH_3), 3.27 (s, 6H, 2×NCH_3) and 3.3 (s, 3H, NCH_3); *m/z* (%): 538 (M^+, 0.2), 346 (100), 192 (58), 107 (52) and 91 (44).

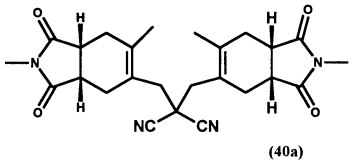


(39b)

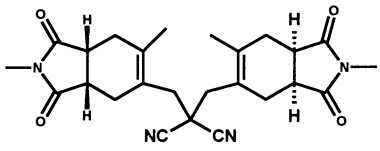


(39a)

3.2.7. 2,2-Bis-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-ylmethyl)-malononitrile (40a,b). Column chromatography eluting with 5:14:1 v/v/v petroleum ether–ether–methanol afforded a 1:1 mixture of **40a** and **40b**) (94%) as a colourless amorphous powder, mp 75–77°C. (Found: C, 65.65; H, 6.05; N, 12.1. $C_{25}H_{28}N_4O_4{\cdot}0.5H_2O$ requires: C, 65.65; H, 6.35; N, 12.25%); HRMS (found): 471.2009. $C_{25}H_{28}N_4O_4Na$ requires 471.2008; δ_H 1.83 (s, 12H, 4×Me), 2.35–2.65 (m, 16H, CH and CH_2), 2.74 (m, 4H, CH and CH_2), 2.95 (s, 9H, 3×NCH_3), 2.96 (s, 3H, NCH_3), 3.0 (m, 2H, 2×CH) and 3.13 (m, 10H, CH and CH_2); *m/z* (%): 448 (M^+, 6), 193 (100), 135 (63), 107 (97), 91 (68) and 79 (53).



(40a)



(40b)

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