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Three-component Heck–Diels–Alder cascade processes involving alkylallenes, aryl iodides and dienophiles

Stephen Brown,[a] Ronald Grigg,[b,*] Joanne Hinsley,[b] Stewart Korn,[c] Visuvanathar Sridharan[b] and Michael D. Uttley[b]

[a]*Syngenta, Process Technology Department, Huddersfield Works, Huddersfileld HD2 1FF, UK*
[b]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK*
[c]*Avecia Lifesciences Molecules, P. O. Box 521, Leeds Road, Huddersfield HD2 1GA, UK*

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Abstract—A wide variety of aryl/heteroaryl iodides undergo an intermolecular Heck reaction with alkylallenes to furnish 1,3-dienes. These subsequently react in situ with various dienophiles to give Diels–Alder adducts. The chemistry has been extended to incorporate cyclisation-anion capture methodology and the stereochemistry of the products has been determined. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Appropriately designed cascade reactions allow complex carbo- and heterocyclic skeletons to be assembled in an atom and waste efficient manner. They offer significant economies when incorporated into manufacturing processes and maximise the use of available chemical plant. As part of our continuing research into multicomponent reaction methodology, we report full details of a novel three-component (alkyl allene, aryl iodide, *N*-methylmaleimide (NMM)) intermolecular Heck–Diels–Alder cascade.[1,2] A number of cascade reactions involving consecutive Heck and Diels–Alder reactions have been developed during recent years[3–7] but none have adopted the strategy of employing allenes.[8] Depending on the types of allene and dienophile employed, further rings can be incorporated into the product, thereby further increasing molecular complexity. All three components can be varied which provide access to a substantial number of analogues.

2. Results and discussion

The reaction sequence is shown in Scheme 1. Oxidative addition of Pd(0) to the aryl/heteroaryl iodide results in regiospecific reaction of ArPdI with the alkylallene to create the π-allylpalladium (II) species **1**. The absence of a suitable nucleophile allows an inherently slow β-hydride elimination reaction to occur, generating the 1,3-diene **2** which undergoes Diels–Alder cycloaddition with the dienophile to furnish the product **3**. The basic cascade (Scheme 1) results in the formation of three bonds and one ring.

Dimethylallene and NMM were initially selected to explore the cascade process. They were reacted with a range of aryl iodides (Scheme 2, Table 1).

Catalyst systems comprising either 10 mol% $Pd(OAc)_2$/20 mol% PPh_3 (catalyst A) or 5 mol% $Pd_2(dba)_3$/20 mol% PPh_3 (catalyst B) were found to be effective.

Optimum conditions for the reaction were found to depend on substituents present in the aryl iodide. With electron withdrawing groups present in the aryl iodide a temperature of 120°C for 48 h gave the best yield. In contrast, when employing aryl iodides bearing electron donating groups a temperature of 90°C gave the best yield probably due to the reduced stability of the ArPdI complex. Non-polar solvents were preferred to maintain the stereoselectivity of the Diels–Alder reaction and toluene proved suitable. Silver carbonate was employed as the base although thallium carbonate gave comparable results. The reaction, as expected, proved tolerant to a wide range of functionality in the aryl iodide component and aryl iodides bearing strongly electron withdrawing substituents or electron donating substituents gave excellent yields (Table 1, entries 5–7 and 9).

The low yield of compound **11** is ascribed to the bulkier aryl group's steric interaction with the methyl group on the diene which substantially raises the energy of the *S-cis* diene conformation rendering the Diels–Alder reaction less effective. In this case inspection of the ^1H NMR spectrum of the crude reaction mixture indicated olefinic signals arising from unreacted diene.

Keywords: palladium catalysis; 1,3-dienes; Diels–Alder; allenes.

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

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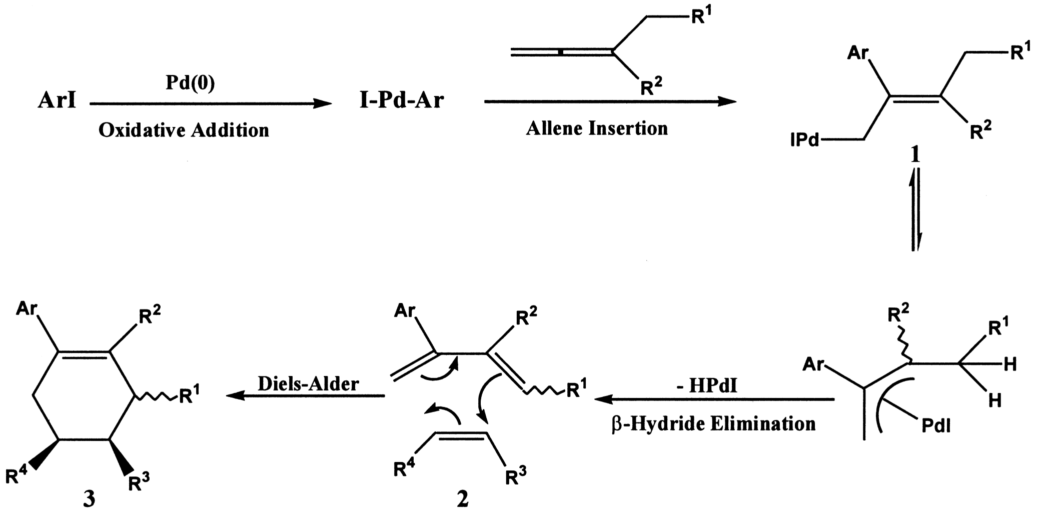
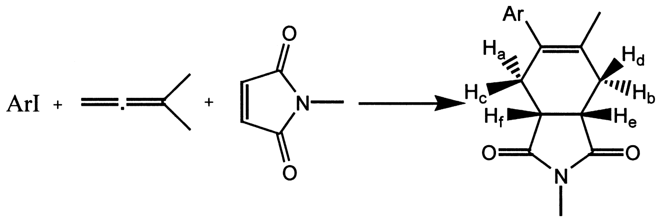


Scheme 1.



Scheme 2.

The second phase of our study of the new cascade involved a survey of the suitability of the heteroaryl/vinyl iodides as substrates (Table 2).

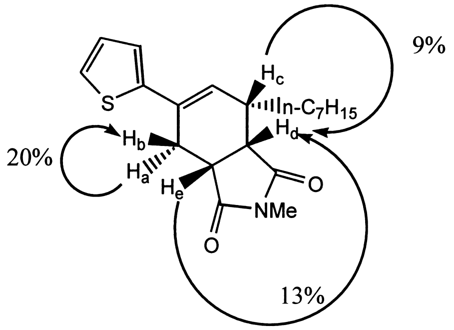
Both electron rich and electron deficient heteroaryl iodides gave good yields of cascade product as did the vinyl iodide (Table 2, entry 4). The reason for the lower yield of product **27** (Table 2, entry 3) may be due to the sensitivity of the electron rich indole ring to oxidative/thermal degradation at 120°C. We have not attempted to optimise this reaction.

In order to explore the diastereoselectivity of the Diels–Alder reaction *n*-octylallene was employed as the diene precursor to probe selectivity for formation of the *cis* and *trans* diene isomers since the diene stereochemistry is retained in the cycloadduct product.

Under the usual conditions but employing *n*-octylallene and 2-iodothiophene a 4:1 mixture of diastereomers was produced in a combined yield of 80% (Scheme 3).

nOe Studies determined that the major diastereomer was **36**, where the *n*-heptyl group and H_d display a *trans* relationship. Thus irradiation of H_e gave a 13% enhancement of H_d, whilst irradiation of H_a effected enhancement of H_b by 20% and irradiation of H_c gave a 9% enhancement of H_d.

An *endo* transition state in the cycloaddition reaction would lead to the major isomer, provided that the stereochemistry of the 1,2-double bond of the diene is *trans* (Scheme 4).



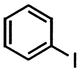
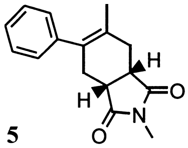
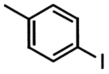
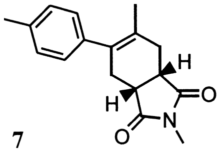
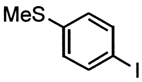
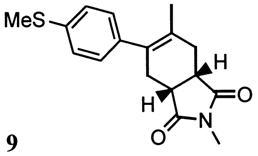
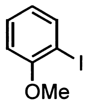
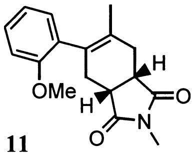
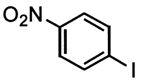
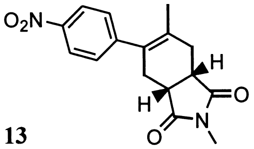
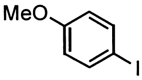
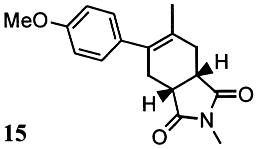
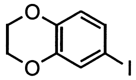
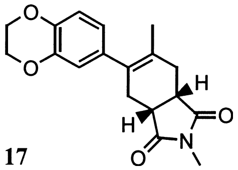
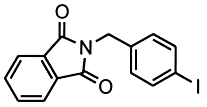
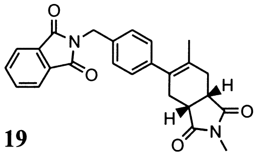
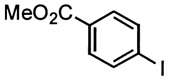
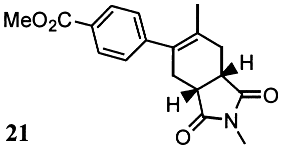
36

In the minor isomer there is a *syn* relationship between the *n*-heptyl group and H_d of the product as determined by nOe studies. This situation could arise from the *trans* diene via an *exo* transition state or via the *cis* diene and an *endo* transition state.

The use of an allene such as vinylidenecyclohexane **37** would determine whether or not the selectivity observed is due to *endo*/*exo* transition states or diene stereoisomers, since only one double bond isomer of the diene is possible in this case (Scheme 5).

Employment of iodobenzene and vinylidenecyclohexane produced a tricyclic cascade product **38** in 48% yield (Scheme 6). Inspection of the ^1H NMR spectrum of the reaction mixture indicated a 4:1 mixture of inseparable diastereomers. This result suggested that the diene produced from *n*-octylallene is the *trans*-isomer as depicted in

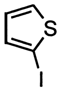
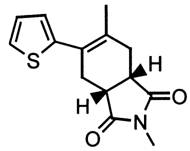
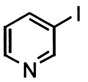
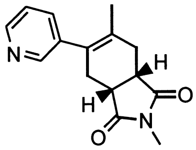
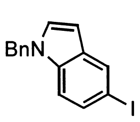
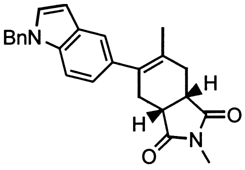
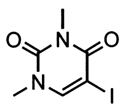
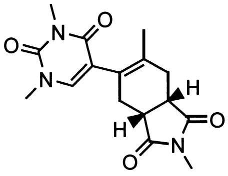
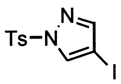
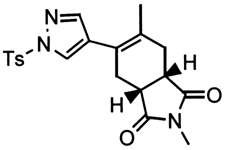
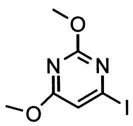
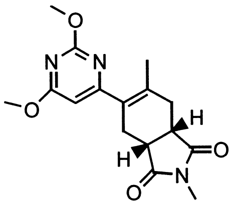
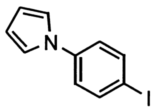
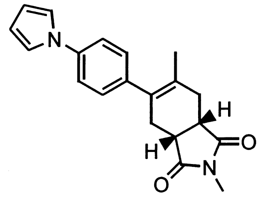
Table 1. Pd(0) catalysed cascade reactions of aryl iodides, dimethylallene and *N*-methylmaleimide

Entry	Aryl iodide	Catalyst	Product	Yield (%)[a]
1	 **4**	A	 **5**	76
2	 **6**	A	 **7**	71
3	 **8**	A	 **9**	56
4	 **10**	A	 **11**	40
5	 **12**	B	 **13**	78
6	 **14**	B	 **15**	89
7	 **16**	B	 **17**	79
8	 **18**	B	 **19**	76
9	 **20**	B	 **21**	90

All reactions were carried out in toluene at 90–120°C for 48 h. The catalyst system comprised either $Pd(OAc)_2/PPh_3$ (catalyst A) or $Pd(dba)_3/PPh_3$ (catalyst B).

[a] Isolated yield.

Table 2. Reaction of heteroaryl/vinyl iodides, dimethylallene and *N*-methylmaleimide

Entry	Heteroaryl iodide	Catalyst	Product	Yield (%)[a]
1	 **22**	A	 **23**	84
2	 **24**	A	 **25**	78
3	 **26**	A	 **27**	41
4	 **28**	A	 **29**	65
5	 **30**	A	 **31**	50
6	 **32**	B	 **33**	71
7	 **34**	B	 **35**	86

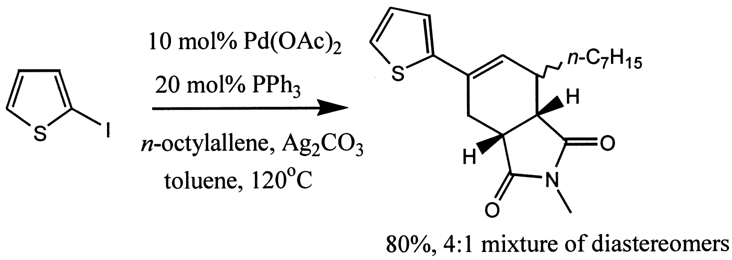
All reactions were carried out in toluene at 90–120°C for 48 h. The catalyst system comprised either $Pd(OAc)_2/PPh_3$ (catalyst A) or $Pd(dba)_3/PPh_3$ (catalyst B).

[a] Isolated yields.

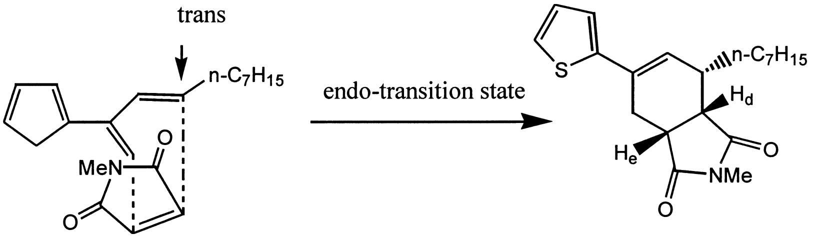
Scheme 4 and that the diastereomer mixtures arise from *endo*- and *exo*-transition states.

The stereochemistry of the major diastereoisomer of **38** was established from 2D nOesy and 1D nOe experiments. The 2D nOesy data indicates a correlation between H_b and H_c and, additionally, both of these protons show a correlation with H_d and H_e. Irradiation of H_c gave a 5% enhancement of H_d and irradiation of H_b effects enhancement of H_a by 20% and H_e by 6%.

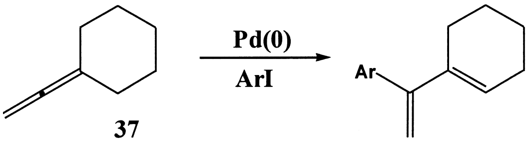
Maleic anhydride was also evaluated as a dienophile under the standard reaction conditions with vinylidenecyclohexane and iodobenzene as co-reactants. Cycloadduct **39** was isolated in 48% yield (Scheme 7). The ^1H NMR spectrum of **39** suggested it was almost exclusively one



Scheme 3.



Scheme 4.

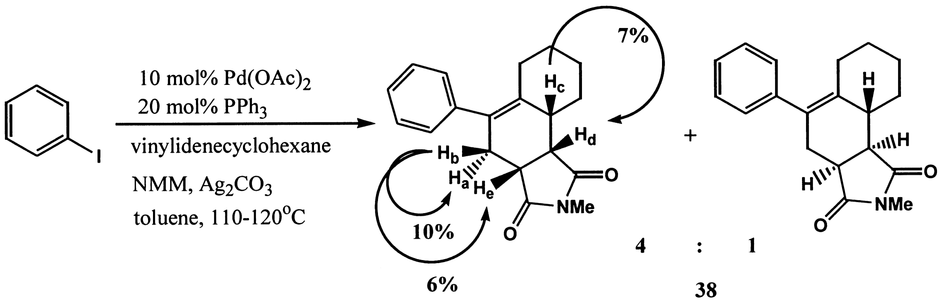


Scheme 5.

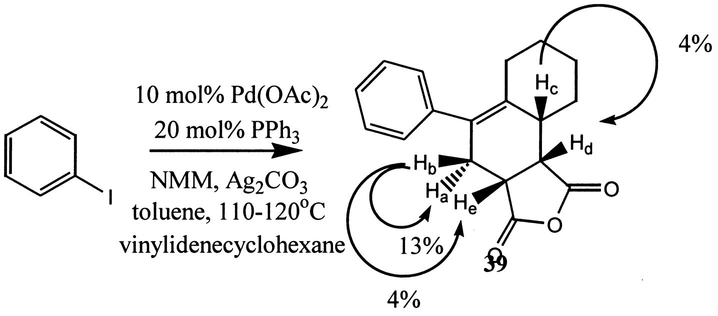
diastereomer and 2D nOesy indicated a correlation between H$_b$ and H$_c$. Irradiation of H$_c$ gave a 4% enhancement of H$_d$ and irradiation of H$_b$ effected enhancement of H$_a$ by 13% and H$_e$ by 4%.

Dimethyl fumarate was next employed as the dienophile with dimethylallene. Under the usual reaction conditions, the desired product **40** was isolated in 72% yield (Scheme 8).

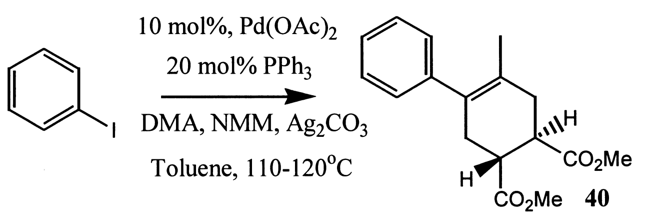
To further explore the scope of this cascade, it was decided to interface it with our palladium catalysed cascade cyclisation-anion capture methodology.[9,10] When **41** and vinylidenecyclohexane were reacted under the usual conditions, product **44** was obtained in 58% yield as a 2.3:1 mixture of diastereomers (Scheme 9). After initial oxidative addition of palladium(0) to the aryl iodide **41**, a subsequent 5-*exo*-trig cyclisation occurs to generate intermediate **42**.



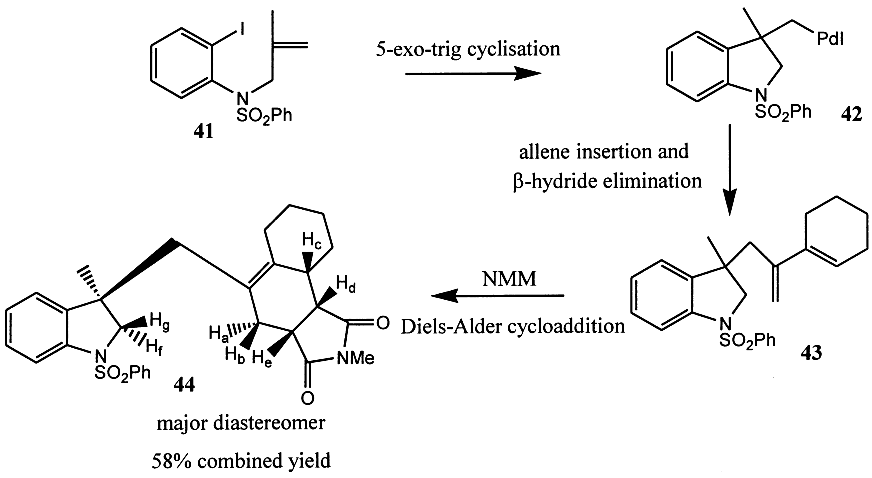
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

Regiospecific reaction of this intermediate with vinylidenecyclohexane followed by β-hydride elimination generates diene **43**. Finally, Diels–Alder cycloaddition with *N*-methylmaleimide furnishes **44** (Scheme 9).

The 2D nOesy spectra indicate that the major diastereomer is **44**. Thus H_c showed a correlation with H_b, H_e and H_d and H_b showed a correlation with H_a, H_c and H_e whilst H_a showed a correlation with H_b and H_g. Proton H_f showed a correlation with the indoline C(3)-Me. The minor isomer is that which is epimeric at the C(3) centre of the indoline.

In summary, the intermolecular Heck–Diels–Alder cascade reaction provides novel methodology which allows a high degree of molecular diversity to be incorporated into the products. Vinylidenecyclohexane allows an additional ring to be incorporated.

3. Experimental

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Mass spectra were obtained from VG Autospec and VG7070 instruments at 70 eV. Nuclear magnetic resonance spectra were recorded at 300 MHz (Bruker) unless otherwise stated. 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, br s=broad singlet. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. Infrared spectra were recorded on an Avator 360 FT-IR and are recorded as nujol mulls unless otherwise stated.

The term ether refers to diethyl ether and petroleum ether refers to the fraction boiling at 40–60°C.

Flash column chromatography was performed using flash silica gel (Merck 9385).

3.1. General method for the palladium catalysed Heck–Diels–Alder cascade

The aryl/heteroaryl iodide (1 mmol), *N*-methylmaleimide (1.00 mmol, 0.11 g), 1,1-dimethylallene (5.00 mmol, 0.50 ml), silver carbonate (2.00 mmol, 0.55 g) and freshly distilled toluene (10 ml) were combined in a Schlenk tube under nitrogen. The catalyst system, comprising either $Pd_2(dba)_3$ (0.05 mmol, 0.05 g) or $Pd(OAc)_2$ (0.10 mmol, 0.02 g) and triphenylphosphine (0.20 mmol, 0.05 g) was then added and the mixture heated to 90–120°C for 48 h, diluted with dichloromethane (10 ml), filtered, concentrated and purified by flash column chromatography.

Some of the products proved to be hygroscopic. Therefore, in some cases, accurate mass data is given in lieu of microanalyses.

3.1.1. 2,5-Dimethyl-6-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (5). The general method was used with iodobenzene and a catalyst system comprising palladium acetate and triphenylphosphine. The reagents were stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography eluting with 2:3 v/v ether/petroleum ether afforded the product (76%) as a pale yellow oil. Found HRMS: 255.1263; $C_{16}H_{17}NO_2$ requires: 255.1259. Found: N, 5.3; $C_{16}H_{17}NO_2$ requires: N, 5.5%. δ (300 MHz): 7.08–7.32 (5H, m, ArH), 3.19 (2H, m, H_e and H_f), 3.00 (3H, s, NMe), 2.90 (1H, d, J=14.6 Hz, H_a), 2.67 (1H, d, J=14.6 Hz, H_b), 2.60 (1H, m, H_c), 2.41 (1H, m, H_d), 1.78 (3H, s, =CMe). *m*/*z* (%) 255 (M^+, 100), 170 (87), 155 (95), 77 (65).

3.1.2. 2,5-Dimethyl-6-*p*-tolyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7). The general method was used with

4-iodotoluene and a catalyst system comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 2:3 v/v ether/petroleum ether afforded the product (71%) as a pale yellow viscous oil. Found: HRMS: 269.1409; $C_{17}H_{19}NO_2$ requires: 269.1415. δ (300 MHz): 7.11 (2H, d, J=8.0 Hz, ArH), 6.98 (2H, d, J=8.0 Hz, ArH), 3.17 (2H, m, H_e and H_f), 2.96 (3H, s, NMe), 2.87 (1H, d, J=14.5 Hz, H_a), 2.64 (1H, d, J=14.6 Hz, H_b), 2.54 (1H, m, H_c), 2.36 (1H, m, H_d), 2.32 (3H, s, ArMe), 1.77 (3H, s, J=1.7 Hz, =CMe). *m/z* (%) 269 (M^+, 100), 184 (52), 169 (62), 91 (38).

3.1.3. 2,5-Dimethyl-6-(4-methylthiophenyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (9). The general method was used with 4-iodothioanisole and a catalyst system comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (56%) as a pale yellow viscous oil. Found HRMS: 301.1127; $C_{17}H_{19}NO_2S$ requires: 301.1136. δ (300 MHz): 7.20 (2H, d, J=8.3 Hz, ArH), 7.02 (2H, d, J=8.3 Hz, ArH), 3.18 (2H, m, H_e and H_f), 2.97 (3H, s, NMe), 2.87 (1H, d, J=17.1 Hz, H_a), 2.65 (1H, d, J=13.1 Hz, H_b), 2.52 (1H, m, H_c), 2.48 (3H, s, SMe), 2.39 (1H, m, H_d), 1.70 (3H, s, =CMe). *m/z* (%) 301 (M^+, 100), 169 (31), 143 (28), 91 (34).

3.1.4. 5-(2-Methoxyphenyl)-2,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (11). The general method was used with 2-iodoanisole (0.13 ml) and a catalyst system comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (40%) as a pale yellow viscous oil. Found HRMS: 285.1362. $C_{17}H_{19}NO_3S$ requires: 285.1364. δ (300 MHz): 6.83–7.26 (4H, m, ArH), 3.76 (3H, s, OMe), 3.13 (2H, m, H_e and H_f), 3.00 (3H, s, NMe), 2.97 (1H, m, H_a), 2.62–2.67 (2H, m, H_b and H_c), 2.40 (1H, m, H_d), 1.64 (3H, s, =CMe). *m/z* (%) 285 (M^+, 100), 199 (60), 185 (46), 121 (26).

3.1.5. 5-(4-Nitrophenyl)-2,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (13). The general method was used with 4-iodonitrobenzene and a catalyst system comprising $Pd_2(dba)_3$ and triphenylphosphine. The mixture was stirred and heated for 20 h at 120°C. Work up followed by column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (78%) as hygroscopic pale yellow rods, mp 137–138°C. Found: C, 63.8; H, 5.65; N, 9.0; $C_{16}H_{16}N_2O_4$ requires C, 64.0; H, 5.4; N, 9.3% δ (300 MHz): 8.19 (2H, d, J=8.9 Hz, ArH), 7.24 (2H, d, J=8.9 Hz, ArH), 3.24 (2H, m, H_e and H_f), 2.99 (3H, s, NMe), 2.88 (1H, d, J=14.4 Hz, H_a), 2.62 (1H, d, J=14.4 Hz, H_b), 2.58 (1H, m, H_c), 2.42 (1H, m, H_d), 1.79 (3H, s, =CMe). *m/z* (%) 300 (M^+, 100), 283 (48), 215 (49), 198 (34), 168 (30), 154 (31), 71 (34), 57 (51), 43 (39). ν_{max}/cm^{-1} (KBr): 859 (2 adjacent aromatic C–H), 1353 (NO_2), 1520 (NO_2), 1694 (C=O).

3.1.6. 5-(4-Methoxyphenyl)-2,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (15). The general method was used employing 4-iodoanisole and a catalyst system comprising $Pd_2(dba)_3$ and triphenylphosphine. The mixture was stirred and heated to 90°C for 48 h. Work up followed by column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (89%) as hygroscopic pale yellow rods, mp 83–84°. Found: C, 71.6; H, 6.95; N, 4.8; $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.7; N, 4.9% δ (300 MHz): 7.01 (2H, d, J=8.8 Hz, ArH), 6.84 (2H, d, J=8.8 Hz, ArH), 3.79 (3H, s, OMe), 3.16 (2H, m, H_e and H_f), 2.96 (3H, s, NMe), 2.85 (1H, d, J=14.7 Hz, H_a), 2.60 (1H, d, J=14.8 Hz, H_b), 2.56 (1H, m, H_c), 2.41 (1H, m, H_d), 1.76 (3H, s, =CMe). *m/z* (%) (FAB): 285 (M^+, 100), 109 (23), 95 (36), 83 (45), 69 (69). ν_{max}/cm^{-1} 840 (2 adjacent aromatic C–H), 1691 (C=O), 2821 (OMe).

3.1.7. 5-(2,3-Dihydrobenzo-[1,4]-dioxin-6-yl)-2,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (17). The general method was used, employing 3,4-ethylenedioxyiodobenzene and $Pd_2(dba)_3$ and triphenylphosphine as the catalyst system. The mixture was stirred and heated to 90°C for 48 h. Work up followed by column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (79%) as very hygroscopic pale yellow prisms, mp 70–72°C. Found: C, 68.75; H, 6.15; N, 4.25; $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.11; N, 4.47% δ (300 MHz): 6.77 (1H, d, J=8.2 Hz, ArH), 6.55 (2H, m, ArH), 4.23 (4H, s, CH_2), 3.15 (2H, m, H_e and H_f), 2.95 (3H, s, NMe), 2.80 (1H, d, J=14.2 Hz, H_a), 2.63 (1H, d, J=14.2 Hz, H_b), 2.53 (1H, m, H_c), 2.33 (1H, m, H_d), 1.76 (3H, s, =CMe). *m/z* (%) 313 (M^+, 100). ν_{max}/cm^{-1} 1177 (C–O), 1698 (C=O).

3.1.8. 2-[3-(2,6-Dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-yl)-benzyl]-isoindole-1,3-dione (19). The general method was used, employing 4-iodobenzyl phthalimide and $Pd_2(dba)_3$ and triphenylphosphine as the catalyst system. The mixture was stirred and heated to 90°C for 48 h. Work up followed by column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (76%) as hygroscopic pale yellow prisms, mp 126–127°C. Found: C, 71.7; H, 5.6; N, 6.15; $C_{25}H_{22}N_2O_4 \cdot 0.25H_2O$ requires C, 71.65; H, 5.4; N, 6.7%. HRMS: 415.1651. $C_{25}H_{22}N_2O_4$+H (M+1) requires 415.1658. δ (300 MHz): 7.84 (2H, m, ArH), 7.70 (2H, m, ArH), 7.25 (2H, m, ArH), 7.14 (1H, m, ArH), 6.98 (1H, m, ArH), 4.83 (2H, s, CH_2), 3.16 (2H, m, H_e and H_f), 2.95 (3H, s, NMe), 2.85 (1H, d, J=14.1 Hz, H_a), 2.61 (1H, d, J=14.1 Hz, H_b), 2.56 (1H, m, H_c), 2.39 (1H, m, H_a), 1.72 (3H, s, =CMe). *m/z* (%) 414 (M^+, 100), 267 (61), 182 (53), 160 (71). ν_{max}/cm^{-1} 1651 (C=O), 1698 (C=O).

3.1.9. 4-(2,6-Dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-yl)-benzoic acid methyl ester (21). The general method was used employing methyl 4-iodobenzoate and a catalyst system comprising $Pd_2(dba)_3$ and triphenylphosphine. The mixture was stirred and heated for 48 h at 90°C. Work up followed by column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (90%) as very hygroscopic pale yellow prisms, mp 76–78°C. Found: C, 68.95; H, 6.1; N, 4.6; $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.11; N, 4.47%. δ (300 MHz): 7.99 (2H, d, J=8.2 Hz, ArH), 7.17 (2H, d, J=8.2 Hz, ArH), 3.90 (3H, s, OMe), 3.19 (2H, m, H_e and H_f), 2.97 (3H, s, NMe), 2.85 (1H, d, J=14.3 Hz, H_a), 2.64 (1H, d, J=14.3 Hz, H_b), 2.59

(1H, m, H_c), 2.41 (1H, m, H_d), 1.77 (3H, s, =CMe). *m*/*z* (%) (FAB): 314 (M+1, 100), 282 (64), 149 (52), 95 (34), 83 (45), 69 (65). ν_{max}/cm^{-1} 843 (2 adjacent aromatic C–H), 1692 (C=O), 1721 (aryl ester).

3.1.10. 2,5-Dimethyl-6-thiophen-2-yl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (23). The general method was used with 2-iodothiophene and a catalyst comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (84%) as a pale yellow viscous oil. Found HRMS: 261.0817. $C_{14}H_{15}NO_2S$ requires: 261.0823. δ (300 MHz): 6.87–7.23 (3H, m, ArH), 3.15 (2H, m, H_e and H_f), 2.99 (1H, m, H_a), 2.97 (3H, s, NMe), 2.68 (1H, d, J=15.5 Hz, H_b), 2.57 (1H, m, H_c), 2.43 (1H, dd, J=14.8, 5.30 Hz, H_d), 1.96 (3H, s, =CMe). *m*/*z* (%) 261 (M^+, 100), 246 (19), 176 (47), 161 (43), 135 (32).

3.1.11. 2,5-Dimethyl-6-pyridin-3-yl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (25). The general method was used with 3-iodopyridine and a catalyst system comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 3:2 v/v ethyl acetate:ether afforded the product (78%) as a pale yellow gum. Found HRMS: 256.1210. $C_{15}H_{16}N_2O_2$ requires: 256.1211. δ (300 MHz): 7.40–8.46 (4H, m, ArH), 3.21 (2H, m, H_e and H_f), 2.98 (3H, s, NMe), 2.85 (1H, d, J=14.5 Hz, H_a), 2.69 (1H, d, J=14.5 Hz, H_b), 2.58 (1H, m, H_c), 2.44 (1H, m, H_d), 1.77 (3H, d, J=1.7 Hz, =CMe). *m*/*z* (%) 256 (M^+, 100), 170 (50), 156 (41), 77 (18).

3.1.12. 5-(1-Benzyl-1*H*-indol-5-yl)-2,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (27). The general method was used with 5-iodo-*N*-benzylindole and a catalyst system comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (42%) as a pale yellow foam. Found HRMS: 384.1843. $C_{25}H_{24}N_2O_2$ requires: 384.1837. δ (300 MHz): 6.87–7.37 (9H, m, ArH), 6.53 (1H, d, J=3.1 Hz, NCH=C*H*), 5.29 (2H, s, NCH_2Ph), 3.16 (2H, m, H_e and H_f), 2.99 (3H, s, NMe), 2.97 (1H, m, H_a), 2.84 (1H, d, J=14.6 Hz, H_b), 2.61 (1H, m, H_c), 2.41 (1H, m, H_d), 1.81 (3H, s, =CMe). *m*/*z* (%) 384 (M^+, 73), 255 (31), 91 (100).

3.1.13. 5-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (29). The general method was used with *N*,*N'*-dimethyl-5-iodouracil and a catalyst system comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 2:3 v/v ether/petroleum ether afforded the product (65%) as a pale yellow solid, mp 168–170°C. Found C, 60.45; H, 6.15; N, 13.1. $C_{16}H_{19}N_3O_4$ requires: C, 60.55; H, 6.05; N, 13.25%. δ (300 MHz): 6.84 (1H, s, uracil H), 3.40 and 3.34 (2×3H, 2×s, 2×NMe), 3.14 (2H, m, H_e and H_f), 3.00 (3H, s, NMe), 2.38–2.62 (4H, m, H_a, H_b, H_c and H_d), 1.70 (3H, s, =CMe). *m*/*z* (%) 317 (M^+, 65), 277 (100), 231 (48), 140 (23).

3.1.14. 2,5-Dimethyl-6-[1-toluene-4-sulphonyl)-1*H*-pyrazol-4-yl]-3a,4,7,7a-tetrahydroisoindole-1,3-dione (31). The general method was used with 4-iodo-*N*1-tosylpyrazole and a catalyst system comprising palladium acetate and triphenylphosphine. The mixture was stirred and heated for 48 h at 120°C. Work up followed by flash column chromatography, eluting with 1:1 v/v ethyl acetate:ether afforded the product (50%) as an off-white solid, mp 74–76°C. Found: C, 59.8; H, 5.25; N, 10.5. $C_{20}H_{21}N_3O_4S$ requires: C, 60.15, H, 5.3; N, 10.5%. δ (300 MHz): 7.31–7.90 (6H, m, ArH), 3.12 (2H, m, H_e and H_f), 2.90 (3H, s, NMe), 2.78 (1H, d, J=15.5 Hz, H_a), 2.64 (1H, d, J=14.6 Hz, H_b), 2.37–2.49 (2H, m, H_c and H_d), 2.40 (3H, s, ArMe), 1.81 (3H, s, =CMe). *m*/*z* (%) 399 (M^+, 32), 259 (35), 201 (100), 91 (46).

3.1.15. 5-(2,4-Dimethoxypyrimidin-5-yl)-2,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (33). The general method was used employing 5-iodo-2,4-dimethoxypyrimidine and a catalyst system comprising $Pd_2(dba)_3$ and triphenylphosphine. The mixture was stirred and heated for 48 h at 90°C. Work up followed by column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (71%) as hygroscopic pale yellow prisms, mp 78–79°C. Found: C, 60.8; H, 5.85; N, 13.0; $C_{16}H_{19}N_3O_4$ requires C, 60.55; H, 6.05; N, 13.25%. δ (300 MHz): 7.82 (1H, s, ArH), 3.98 (3H, s, OMe), 3.94 (3H, s, OMe), 3.17 (2H, m, H_e and H_f), 2.99 (3H, s, NMe), 2.68 (1H, d, J=13.8 Hz, H_a), 2.61 (1H, d, J=14.3 Hz, H_b), 2.50 (1H, m, H_c), 2.42 (1H, m, H_d), 1.68 (3H, s, =CMe). *m*/*z* (%) (FAB): 318 (M+1, 100), 95 (49), 81 (55), 69 (79). ν_{max}/cm^{-1} 1698 (C=O), 2853 (OMe).

3.1.16. 2,5-Dimethyl-6-(4-pyrrol-1-ylphenyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (35). The general method was used, employing 1-(4-iodophenyl)pyrrole and $Pd_2(dba)_3$ and triphenylphosphine as the catalyst system. The mixture was stirred and heated to 90°C for 48 h. Work up followed by column chromatography, eluting with 1:1 v/v ether/petroleum ether afforded the product (86%) as hygroscopic pale yellow prisms, mp 89–90°C. Found: C, 74.3; H, 6.45; N, 8.6; $C_{20}H_{20}N_2O_2\cdot0.125H_2O$ requires C, 74.45; H, 6.33; N, 8.68% δ (300 MHz): 7.31 (2H, d, J=8.6 Hz, ArH), 7.12 (2H, d, J=8.6 Hz, ArH), 7.07 (2H, m, ArH), 6.33 (2H, m, ArH), 3.17 (2H, m, H_e and H_f), 2.97 (3H, s, NMe), 2.87 (1H, d, J=14.5 Hz, H_a), 2.64 (1H, d, J=14.1 Hz, H_b), 2.57 (1H, m, H_c), 2.39 (1H, m, H_d), 1.78 (3H, s, =CMe). *m*/*z* (%): 320 (M^+, 100). ν_{max}/cm^{-1} 728 (4 adjacent aromatic C–H), 843 (2 adjacent aromatic C–H), 1692 (C=O).

3.1.17. 4-Heptyl-2-methyl-6-thiophen-2-yl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (36). Prepared from 2-iodothiophene (1.00 mmol), *N*-methylmaleimide (1.00 mmol), *n*-octylallene (2.00 mmol), silver carbonate (2.00 mmol) and a catalytic system comprising palladium acetate (0.10 mmol) and triphenylphosphine (0.20 mmol), with stirring for 48 h at 120°C. Work up followed by flash column chromatography eluting with 2:3 v/v ether/petroleum ether gave a 4:1 mixture of two separable diastereomers each as a pale yellow gum (80% combined yield).

Major product. Obtained in 64% yield. HRMS: 345.1766.

$C_{16}H_{16}NO_3S_2$ requires: 345.1762. δ (300 MHz): 6.97–7.26 (3H, m, ArH), 6.17 (1H, s, H_f), 3.61 (1H, m, H_e), 3.18 (1H, m, H_d), 2.94 (3H, s, NMe), 2.55 (1H, dd, J=16.7, 3.9 Hz, H_a), 2.25 (1H, m, H_b), 2.05 (1H. m. H_c), 0.83–1.87 (15H, m, alkyl H). *m/z* (%) EI: 345 (M^+, 54), 246 (97), 161 (100), 128 (34).

Minor product. Obtained in 16% yield. HRMS 345.1766. $C_{16}H_{16}NO_3S_2$ requires: 345.1762. δ (300 MHz): 6.94–7.14 (3H, m, ArH), 5.99 (1H, s, H_f), 3.13–3.25 (3H, m, H_a, H_d, H_e), 2.87 (3H, s, NMe), 2.35–2.53 (2H, m, H_b, H_c), 0.83–1.96 (15H, m, alkyl H). *m/z* (%): 345 (M^+, 26), 246 (100), 161 (61), 111 (20).

3.1.18. 2-Methyl-5-phenyl-3a,4,6,7,8,9,9a,9b-octahydrobenzo[*e*]isoindole-1,3-dione (38). Iodobenzene (1.00 mmol), *N*-methylmaleimide (1.00 mmol), vinylidenecyclohexane (5.00 mmol), silver carbonate (2.00 mmol) and a catalytic system comprising palladium acetate (0.10 mmol) and triphenylphosphine (0.20 mmol) were added to dry toluene (10 ml) in a Schlenk tube. The reaction mixture was stirred and heated to 120°C for 48 h, then cooled, diluted with dichloromethane and filtered. The filtrate was evaporated in vacuo and the residue purified by flash column chromatography, eluting with 1:1 v/v ether/petroleum ether to give the product (48%) as a pale yellow viscous oil. HRMS: 295.1576. $C_{19}H_{21}NO_2$ requires 295.1572. δ (500 MHz): 7.05–7.32 (5H, m, ArH), 3.15 (2H, m, H_d, H_e), 2.94 (3H, s, NMe), 2.93 (1H, m, H_a), 2.55 (1H, m, H_b), 2.43 (1H, m, H_c), 0.82–2.25 (8H, m, cyclohexyl H). *m/z* (%): 295 (M^+, 100), 253 (17), 167 (51), 112 (84), 77 (36).

3.1.19. 5-Phenyl-3a,4,6,7,8,9,9a,9b-octahydronaptho[1,2-*c*]furan-1,3-dione (39). Iodobenzene (1.00 mmol), maleic anhydride (1.00 mmol), vinylidenecyclohexane (5.00 mmol), silver carbonate (2.00 mmol) and a catalytic system comprising palladium acetate (0.10 mmol) and triphenylphosphine (0.20 mmol) were added to dry toluene (10 ml) in a Schlenk tube. The reaction mixture was stirred and heated to 120°C for 48 h, then diluted with dichloromethane (10 ml) and filtered. The filtrate was evaporated in vacuo and the residue purified by flash column chromatography, eluting with 1:2 v/v ether/petroleum ether to afford the product (40%) as a pale yellow viscous oil. HRMS: 282.1250. $C_{18}H_{18}O_3$ requires 282.1255. δ (500 MHz): 7.09–7.47 (5H, m, ArH), 3.45 (2H, m, H_d, H_e), 2.93 (1H, dd, J=16.3, 1.9 Hz, H_a), 2.61 (1H, m, H_b), 2.50 (1H, m, H_c), 0.85–2.25 (8H, m, cyclohexyl H). *m/z* (%): 282 (M^+, 63), 254 (40), 167 (100), 91 (96), 77 (46).

3.1.20. Dimethyl 4-methyl-5-phenylcyclohex-4-ene-1,2-dicarboxylate (40). Iodobenzene (1.00 mmol), dimethyl fumarate (1.00 mmol), 1,1-dimethylallene (5.00 mmol), silver carbonate (2.00 mmol) and a catalytic system comprising palladium acetate (0.10 mmol) and triphenylphosphine (0.20 mmol) were added to dry toluene (10 ml) in a Schlenk tube. The reaction mixture was stirred and heated to 120°C for 48 h, diluted with dichloromethane (10 ml) and filtered. The filtrate was evaporated in vacuo and the residue purified by flash column chromatography, eluting with 1:3 v/v ether/petroleum ether to give the product (72%) as a colourless oil. Found: C, 70.55; H, 6.7. $C_{17}H_{20}O_4$ requires: C, 70.8; H, 7.0%). δ (400 MHz): 7.10–7.41 (5H, m, ArH), 3.73 and 3.69 (2×3H, 2×s, 2×OMe), 3.00 (2H, m, H_e, H_f), 2.27–2.66 (4H, m, H_a, H_b, H_c, H_d), 1.58 (3H, s, =CMe). *m/z* (%): 288 (M^+, 3), 228 (60), 169 (100).

3.1.21. 5-(1-Benzenesulphonyl-3-methyl-2,3-dihydro-1*H*-indol-3-ylmethyl)-2-methyl-3a,4,6,7,8,9a,9b-octahydrobenzo[*e*]isoindole-1,3-dione (44). Prepared from **41** (1.00 mmol), *N*-methylmaleimide (1.00 mmol), vinylidenecyclohexane (5.00 mmol), silver carbonate (2.00 mmol) and a catalytic system comprising palladium acetate (0.10 mmol) and triphenylphosphine (0.20 mmol) in toluene. The reaction mixture was stirred for 48 h at 120°C, diluted with dichloromethane (10 ml), filtered and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 1:1 v/v ether/petroleum ether to give the product (58%) (2:3:1 mixture of diastereomers) as a pale yellow solid. HRMS: 504.2093. $C_{29}H_{32}N_2O_4S$ requires 504.2082. δ (500 MHz) (diastereomer mixture): 6.95–7.86 (9H, m, ArH), 3.77 (1H, d, J=9.8 Hz, H_g), 3.37 (1H, d, J=9.8 Hz, H_f), 2.92 (1H, d, J=13.7 Hz, H_a), 2.86–3.05 (2H, m, H_d, H_e), 2.84 (3H, s, NMe), 1.18–2.26 (12H, m, H_b, H_c, $C(Me)CH_2$, cyclohexyl H), 1.17 (3H, s, C(**Me**)CH_2). *m/z* (%) (diastereomer mixture):504 (M^+, 0.2), 272 (100), 141 (36), 130 (57), 77 (60).

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