Stereocontrol in the intramolecular Buchner reaction of diazoketones

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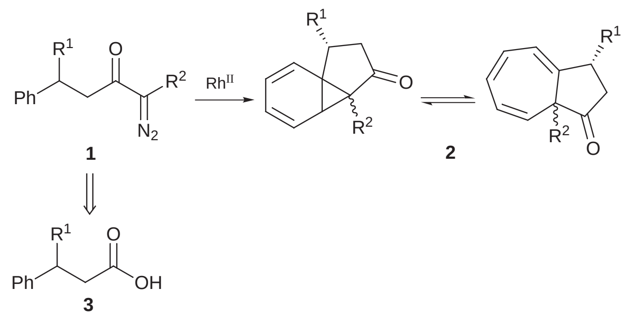
Rhodium(II) acetate catalysed intramolecular Buchner cyclisation of a series of diazoketones **1** proceeds with excellent diastereoselectivity to produce the *trans* substituted azulenones **2**, which exist as a rapidly equilibrating cycloheptatriene–norcaradiene system, from which the norcaradiene tautomers can be efficiently trapped as PTAD cycloadducts **4**. The cyclisation–cycloaddition sequence can be conducted in either a stepwise or a tandem process, leading to the pentacyclic systems **4** as a single diastereomer in each case. In the reaction of diazoketone **1f** intramolecular cyclopropanation competes with cyclisation to the aromatic ring.

Introduction

The addition of carbenes to aromatic rings provides a very useful route to seven membered carbocycles; rhodium(II) carboxylate catalysed decomposition of α-diazocarbonyl derivatives offers a particularly efficient method of effecting this ring expansion, both intermolecularly and intramolecularly.[1] The intramolecular Buchner reaction has attracted considerable attention in recent years from both a synthetic[2–4] and a mechanistic point of view.[2–5] The proposed mechanism for the cyclisation involves initial cyclopropanation of the aromatic ring to form a norcaradiene derivative (NCD) which is in dynamic equilibrium with the cycloheptatriene (CHT), as illustrated in eqn. (1). The norcaradiene–cycloheptatriene equilibrium has been widely investigated.[6] While the cycloheptatriene is generally the more stable tautomer, systems in which the norcaradiene form is preferred following the Buchner addition have been reported.[2,5,6]

There have been few reports of stereocontrol in the Buchner cyclisation; moderate enantioselection has been reported through use of asymmetric rhodium(II) catalysts.[1,2g] Zaragoza[4a] reported good diastereoselection in the cyclisation of a diazoamide derivative as illustrated in eqn. (2) (the relative stereochemistry of the minor diastereomer was not specified), while Julia[4b,c] reported formation in low yield of two lactones in the copper catalysed cyclisation of diazomalonate derivatives as illustrated in eqn. (3) with no diastereoselection. Both Doyle[4d] and Saba[5d] have reported cyclisation of systems in which the formation of diastereomeric products were possible but no comment on the stereoselectivity was made in either case. Doyle's work involved reaction of a diazoester derivative as illustrated in eqn. (4), while Saba had reacted diazoketone derivatives as shown in eqn. (5) which are more closely related to the research described below. Eqn. (6) illustrates an intramolecular cyclisation reported by Sonawane and co-workers in 1992 to proceed without any diastereoselection, forming an equimolar mixture of diastereomers.[3f] Diastereoselective cyclisation of the diazoketone derivative (R = Me) illustrated in eqn. (7) to form the *cis* substituted cycloheptafuranone has been reported, while the cyclisation of the phenyl substituted diazoketone produced a mixture of diastereomers.[4f] *Trans* diastereoselectivity in intramolecular Buchner cyclisation of diazoesters has been recently described.[4g]

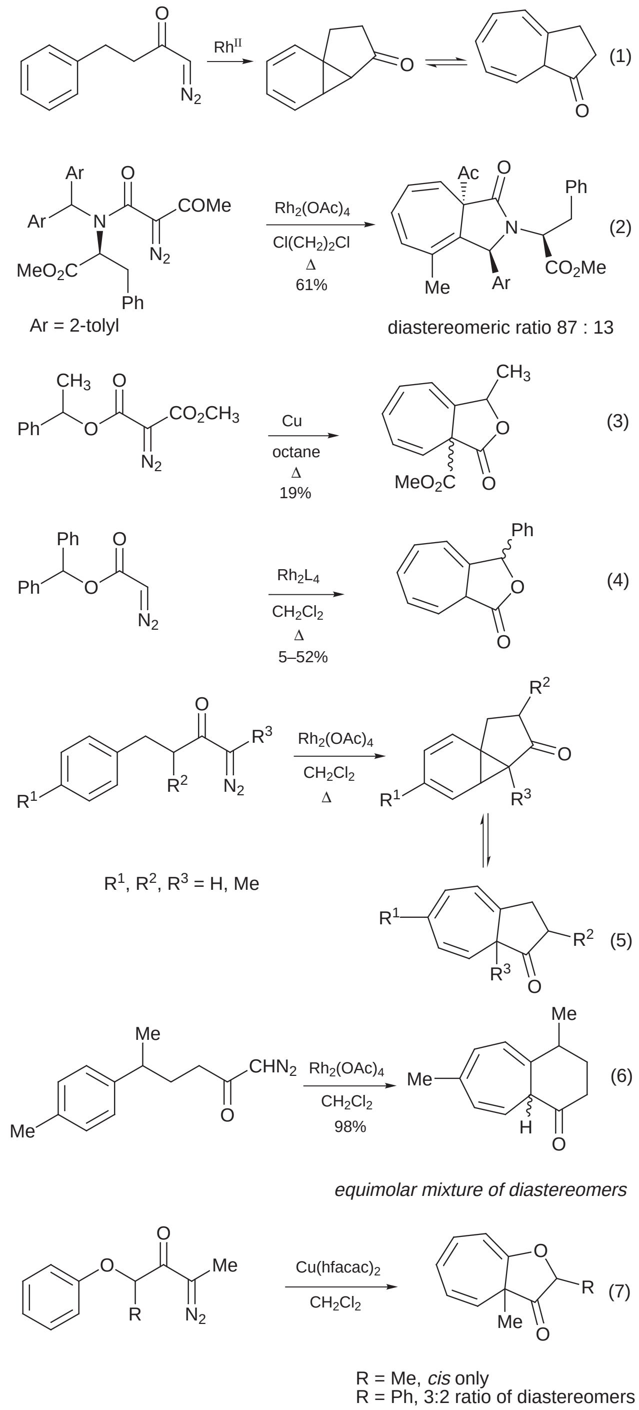
Investigation of intramolecular cyclisation of α-diazoketone derivatives of general structure **1** was proposed to establish if efficient internal asymmetric induction from the single stereogenic centre in **1** to the newly formed quaternary centre in the azulenone derivatives **2** could be obtained during the rhodium catalysed cyclisation, as illustrated in Scheme 1. We were particularly interested in these diazoketone derivatives as they could be readily obtained from the corresponding carboxylic acids **3**, which are in turn readily available with high enantiopurities, for example *via* stereoselective conjugate addition of organocuprate reagents.[7] Accordingly, provided efficient diastereocontrol is obtained in the key cyclisation step, extension of this methodology to the enantiomerically enriched series is readily envisaged leading to efficient asymmetric synthesis of bicyclo[5.3.0]decane derivatives. While there was little precedent for diastereoselective Buchner cyclisation as outlined above, it was hoped that by variation of the ligands on the rhodium catalyst it would be possible to control the diastereofacial selectivity of the addition of the rhodium carbenoid to the aromatic ring. In the event, excellent diastereoselectivity was observed in the rhodium(II) acetate catalysed cyclisation of racemic diazoketones **1**.[8] Subsequent to our preliminary report in this area we became aware of related studies by Moody's group, described in the preceding paper,[9] employing diazoester and diazoamide derivatives in place of the diazoketones in our work.

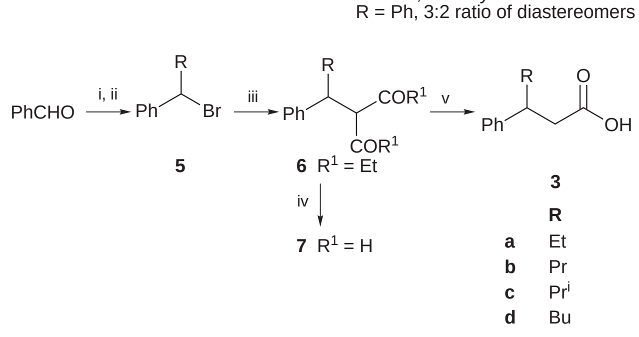


Scheme 1

Results and discussion

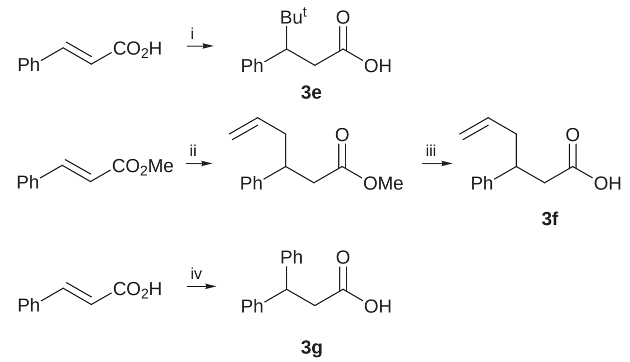
A series of 3-phenylpropanoic acids bearing alkyl substituents at the 3-position **3a–f** was readily prepared, as summarised in





Scheme 2 *Reagents and conditions*: i, **a** EtMgBr, **b** PrMgCl, **c** Pr^iMgCl, **d** BuMgCl, Et_2O, 85–89%; ii, PBr_3, Et_2O, 77–81%; iii, $CH_2(CO_2Et)_2$, NaOEt, EtOH, 80–86%; iv, KOH, EtOH, Δ, then HCl, 73–77%; v, 190–200 °C, 69–77%.

Schemes 2 and 3.[10] Benzaldehyde was readily transformed to a series of 3-alkylphenylpropanoic acids by sequential Grignard addition, bromination, alkylation of diethyl malonate, hydrolysis and decarboxylation following a modification of a sequence



Scheme 3 *Reagents and conditions*: i, Bu^tMgCl, THF, 0 °C, 53%; ii, trimethylallylsilane, TBAF, HMPA, THF, DMF, molecular sieves, 85%; iii, NaOH, aq. EtOH, 70%; iv, $AlCl_3$, PhH, 90%.

reported by Kuchař and co-workers.[10a] While this five step sequence is rather long, the individual steps are easily conducted and very reliable, providing ready access to synthetically useful amounts of the acids **3a**–**d**. Most importantly the route is synthetically versatile allowing introduction of a range of 3-alkyl substituents *via* the Grignard reagent. Reaction of a solution of *tert*-butylmagnesium chloride (2 M) with cinnamic acid as described by Wotiz and co-workers[10d] furnished the *tert*-butyl substituted acid **3e** in moderate yield (53%); the efficiency of the transformation was sensitive to both the concentration of the Grignard solution (use of solutions more dilute than 2 M resulted in reduced yields) and the reaction temperature (best results were obtained by slow addition of the cinnamic acid to the solution of the Grignard reagent at 0 °C and removing the reaction mixture from the ice-bath once the addition was complete). Conjugate addition of trimethylallylsilane to methyl cinnamate in the presence of TBAF as described by Majetich *et al.*[10e] proceeded efficiently; ester hydrolysis produced the allyl substitued carboxylic acid **3f**. 3,3-Diphenylpropanoic acid **3g** was readily prepared by aluminium trichloride catalysed Friedel–Crafts alkylation of benzene with cinnamic acid following a procedure reported by Dippy and Young.[10f]

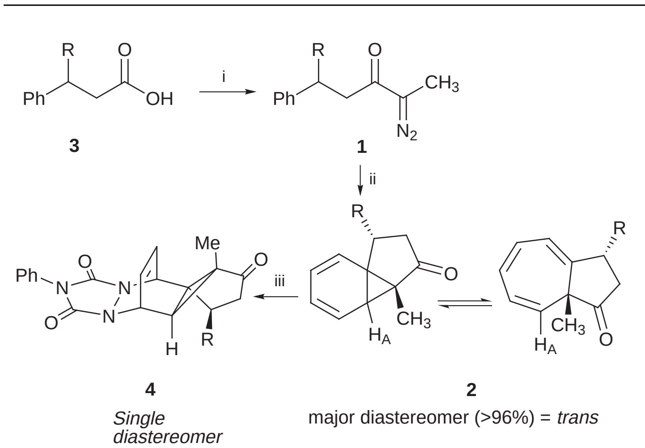
The 3-phenylpropanoic acids **3a**–**h** were transformed under standard conditions to the diazoketones **1a**–**h** by treatment with either oxalyl chloride or thionyl chloride followed by excess ethereal diazoethane as shown in Scheme 4 and Table 1. In most cases the yields of diazoketones recovered were quite good (70–85% from the analogous carboxylic acids) except for the diphenyl substituted derivative **1g**. The previously reported derivative without any substituent at the 3-position, 2-diazo-5-phenylpentan-3-one **1h**,[2d] was included in the study for comparison with the novel 3-substituted compounds **1a**–**g**. Significantly the 3-substituted diazoketones **1a**–**f** were noticeably more stable than the unsubstituted derivative **1h**, and were readily purified by chromatography and stored in a freezer for several weeks without decomposition. The diazoketone bearing the sterically demanding *tert*-butyl substituent **1e** was particularly stable. In contrast the diphenyl derivative **1g** was very labile, decomposing rapidly on silica gel, accounting for the low yield recovered, and an analytically pure sample of this diazoketone could not be obtained. The instability of this compound is believed to be due to the very labile hydrogen atom at the 5-position which may be susceptible to hydride abstraction[4a,d] forming a highly stabilised benzylic carbocation.

Rhodium(II) acetate catalysed decomposition of the α-diazoketones **1** resulted in efficient carbenoid addition to the benzene ring as shown in Scheme 4 and Table 1. Interestingly the presence of the β-alkyl substituent in **1a**–**e** facilitates the cyclisation resulting in increased efficiency in the formation of the products of Buchner cyclisation compared to the unsubstituted diazoketone **1h**, presumably by favouring the conformation required for the cycloaddition process. The transformation is conducted by slow addition (typically 1 h) of a solution of the diazoketone

Table 1 Synthesis, rhodium(II) acetate catalysed intramolecular Buchner reaction of α-diazoketones **1** and PTAD cycloaddition to the azulenones **2**

	R	Yield (%)[a] of **1**	Dr of **2** *trans* : *cis*[b]	Yield (%)[c] of **2**	Yield (%) of **4**		
					Method A[d]	Method B[d]	Method C[d]
a	Et	70	96:4	79	95	—	68
b	Pr	80	97:3	74	98	74	70
c	Pr^i	85	>98:2	74	98	78	74
d	Bu	78	98:2	70	98	79	71 (64[e])
e	Bu^t	85	>98:2	72	97	73	75
f	allyl	76	>98:2	46[f]	98	79	—
g	Ph	24	*cis* not identified	33	98	67	29
h	H	77	—	59	94	77	54

[a] Yields of diazoketones **1** based on the carboxylic acids **3**. [b] The diastereomeric ratios in the azulenones **2** were determined by integration of ^{1}H NMR spectra of the crude products; when the minor *cis* diastereomer could not be detected a ratio of >98:2 is quoted. [c] Yield of *trans* azulenones **2** isolated as single diastereomers following chromatography on silica gel, except for **2a** which was isolated as a mixture of diastereomers (96:4) in the experiment quoted; however, the two diastereomers of **2a** are chromatographically separable. [d] Method A: PTAD (1 equiv.) was added to a solution of the azulenone **2** in CH_2Cl_2 at 0 °C; yield of cycloadduct **4** quoted following recrystallisation or chromatography on silica gel. Method B: PTAD (1 equiv.) was generated *in situ* by lead tetraacetate oxidation of phenylurazole in a CH_2Cl_2 solution of the azulenone **2** at 0 °C; yield of cycloadducts **4** quoted following passage of the reaction mixture through a short column of silica gel. Method C (one-pot procedure): Diazoketone **1** was added dropwise over 0.5–1 h to a dilute refluxing solution of rhodium(II) acetate (1 mol%) in CH_2Cl_2. The solution was cooled to 0 °C and PTAD (1 equiv.) was added; yield of cycloadducts **4** quoted following chromatography on silica gel, except for **4a** which was purified by recrystallisation instead of chromatographically. [e] Yield when *in situ* generation of PTAD was employed in the one-pot synthesis of the cycloadduct **4d**. [f] The product of intramolecular cyclopropanation **5** was also isolated in 44% yield.



	R
a	Et
b	Pr
c	Pr^i
d	Bu
e	Bu^t
f	allyl
g	Ph
h	H

Scheme 4 *Reagents and conditions*: i, (a) $(COCl)_2$ or $SOCl_2$; (b) excess CH_3CHN_2 (5–10 equiv.), Et_2O, −20 °C; ii, $Rh_2(OAc)_4$, CH_2Cl_2, Δ; iii, Method A: PTAD, CH_2Cl_2, 0 °C; Method B: $Pb(OAc)_4$, phenylurazole, CH_2Cl_2, 0 °C; Method C (one-pot procedure): PTAD added directly to the azulenone **2** in CH_2Cl_2, 0 °C following rhodium acetate catalysed cyclisation of the diazoketone **1** without isolation.

in dichloromethane to a refluxing dilute solution of rhodium(II) acetate (1 mol%) in the same solvent. The cyclisations occur very rapidly; usually reaction is finished once the diazoketone addition has been completed. Most importantly, in contrast to literature precedent,[3f,4a,b] the cyclisation is highly diastereoselective. In many cases only the *trans* diastereomer of the product **2** could be detected by ^{1}H NMR spectroscopy; even in those cases where the minor *cis* diastereomer was detected, only 2–4% of it was present in the crude product mixture. Chromatographic purification on silica gel gave the azulenones **2** as single diastereomers where the R substituent is disposed *trans* to the bridgehead methyl group.

While the precise mechanism of the rhodium catalysed carbenoid addition is unknown, the observed stereocontrol of the intramolecular cycloaddition can be rationalised as illustrated in Fig. 1. Approach of the carbenoid to the aromatic

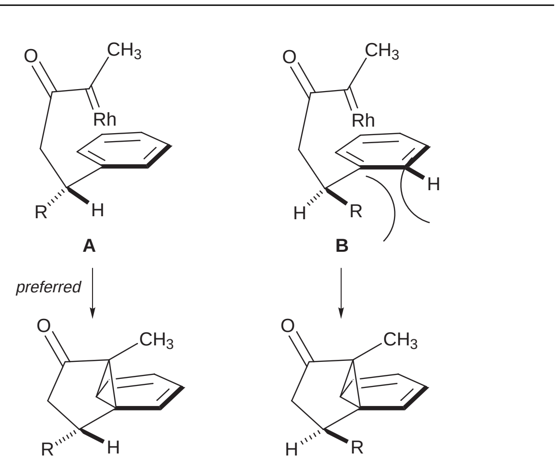


Fig. 1 Diastereoselection in the rhodium catalysed intramolecular cyclisation.

ring *via* conformation A is preferred over conformation B in which the alkyl substituent experiences $A^{1,3}$ strain. The slight increase in diastereoselection as the R group increases in size from ethyl (96:4) to the more bulky alkyl groups (>98:2) is consistent with this interpretation. The Moody group have observed similar diastereoselection in the cyclisation of diazomalonate derivatives.[9]

The phenyl substituted diazoketone **1g** did not undergo efficient cyclisation on exposure to rhodium(II) acetate and only a modest yield (33%) of the azulenone **2g** was recovered; the low efficiency of cyclisation is again believed to be associated with the very labile hydrogen at C5.[4a,d] Signals associated with the *cis* isomer in this case could not be identified in crude NMR spectra.

In the case of the allyl substituted diazoketone **1f** excellent diastereoselection was obtained in both the intramolecular cyclisation to give the azulenone **2f** and the competing intramolecular cyclopropanation to form **5**, as illustrated in Scheme 5. Chemoselectivity in the rhodium(II) acetate catalysed process was low, resulting in formation of essentially equal amounts of the products of the two pathways. Only a single diastereomer of each of the products, the azulenone **2f** and the cyclopropane derivative **5**, could be detected. X-Ray analysis of the cyclopropanation product as its 2,4-dinitrophenylhydrazone derivative **6** established the relative stereochemistry at C2 and C5, as shown in Fig. 2.

The azulenones **2** produced are clearly a rapidly equilibrating

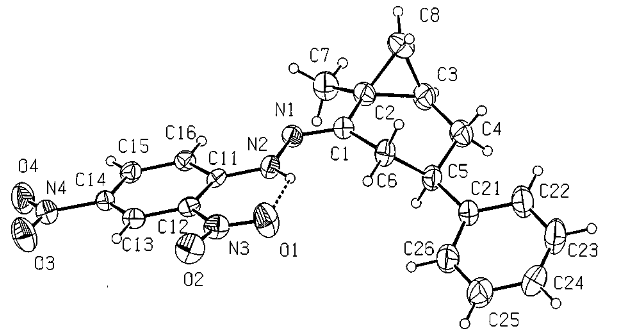
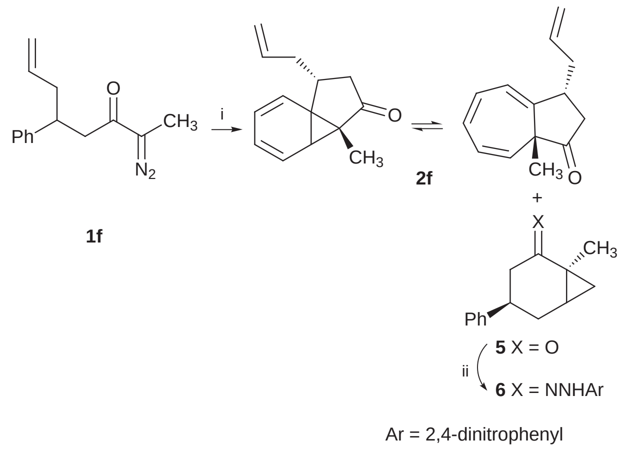


Fig. 2 A view of **6** showing the structure and stereochemistry. Thermal ellipsoids are drawn at the 30% probability level. The six-membered ring C1–C6 adopts a half-chair conformation. The X-ray analysis also shows an intramolecular N–H · · · O bond between the N2H and the nitro O [N · · · O 2.608(4) Å].



Scheme 5 *Reagents and conditions*: i, $Rh_2(OAc)_4$, CH_2Cl_2, Δ, (**2f** 46%, **5** 44%); ii, $ArNHNH_2$, H_2SO_4, EtOH, Δ, 2–3 min (73%).

mixture of the norcaradiene and cycloheptatriene forms.[6] The chemical shift of the proton at C8 labelled as H_A in Scheme 4 is particularly sensitive to the position of equilibrium, and indicates that for each of the *trans* substituted azulenones **2** the norcaradiene tautomer (NCD) is quite significant at equilibrium at room temperature, while the position of equilibrium in the minor *cis* isomers of the azulenones lies more towards the cycloheptatriene form (CHT). For example, for *trans* azulenone **2d** (R = Bu) the doublet for H_A appears at δ_H 3.69 (*J* 7 Hz) indicating that at equilibrium at room temperature in $CDCl_3$ the azulenone **2d** exists as approximately 70–75% NCD, 25–30% CHT, while for the *cis* isomer the signal is seen at δ_H 4.89 (*J* 10 Hz). As the distinctive H_A signals for the two diastereomers are clearly resolved, accurate estimation of the diastereomeric ratio is possible on the basis of the ^{1}H NMR spectra of the crude products.

Cycloadditions to norcaradiene and cycloheptatriene equilibrating mixtures have been reported;[11] most importantly for this work, it has been reported that the norcaradiene form can be trapped as a cycloadduct with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD).[5d,11,12] As a crystalline derivative of the azulenones **2** was required to allow crystallographic determination of the relative stereochemistry, investigation of cycloaddition with PTAD was explored.

The norcaradienes/cycloheptatrienes **2a**–**h** (**2a** as a 96:4 diastereomeric mixture, **2b**–**g** as the *trans* diastereomers only) reacted rapidly and efficiently with PTAD in dichloromethane solution at 0 °C resulting in decolouration of the brick-red solution of PTAD and formation of the cycloadducts **4a**–**h**, stable white crystalline solids, in good yield (94–98%) as shown in Scheme 4 and Table 1 (Method A).[8] While reaction of PTAD with most of the azulenones (**2a**,**b**,**d**,**f**,**g**,**h**) was complete within

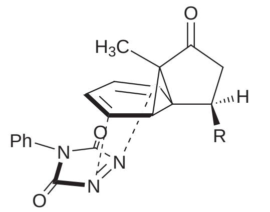


Fig. 3 Stereochemistry of PTAD cycloaddition.

10 min, reaction of the azulenone derivative bearing the bulky Bu^t substituent **2e** was noticeably slower, requiring 30–35 min for complete reaction under the same conditions, with **2c** (R = Pr^i) displaying intermediate reactivity, requiring approximately 20 min. This influence of the nature of the substituent R on the rate of the cycloaddition indicates that approach of the dienophile is hindered by the bulky Pr^i or Bu^t group. While the crude products of these reactions were shown to be essentially pure by NMR spectroscopy, analytically pure samples could be easily obtained either by recrystallisation or passage through a short column of silica gel. As the PTAD adducts are isolated in excellent yields it is clear that the cycloaddition process traps out very efficiently the norcaradiene form of the azulenones **2**. Most importantly only a single diastereomer of the cycloadducts **4** could be detected, indicating that the cycloaddition to **2** is stereospecific. The relative stereochemistry of the cycloadduct **4d** was determined by X-ray crystallography,[8] establishing not only the stereochemistry of the cycloaddition of **2d** with PTAD, but also the stereochemistry of the rhodium(II) acetate catalysed diazoketone cyclisation to form **2d** as the *trans* diastereomer. The stereochemistry of each of the remaining cycloadducts **4** was assigned by analogy to **4d**.

Thus the pentacyclic systems **4** are formed extremely efficiently as single stereoisomers; the excellent diastereocontrol in the rhodium(II) acetate catalysed cyclisation to form **2** essentially as a single diastereomer with *trans* stereochemistry has already been discussed above (Fig. 1). This step fixes the stereochemistry of the norcaradiene as shown in Fig. 3, and, in particular, the relative stereochemistry of the alkyl substituent R and the bridgehead methyl group. Approach of the dienophile to the norcaradiene takes place from the less hindered face only (opposite to the bridgehead methyl substituent) as illustrated in Fig. 3 producing the cycloadducts **4** stereospecifically. Only the *exo* adduct has been observed in these reactions.

An alternative method for preparation of the adducts **4** was also investigated involving *in situ* generation of PTAD by lead tetraacetate oxidation of phenylurazole[13] in the presence of the azulenones **2**. As can be seen in Table 1 (Method B), this method was also successful in producing the cycloadducts **4**, but resulted in lower yields than the reactions using PTAD directly. However, it is notable that the azulenones **2**, which are quite labile compounds, survive the conditions employed for the *in situ* generation of PTAD.

As the transformation of the α-diazoketones **1** to the complex pentacyclic systems involved two reactions, both occurring under mild conditions, it seemed possible to link these transformations into a tandem cyclisation–cycloaddition process which could be conducted in a single pot. Transition metal-catalysed cyclisations are ideally suited for use in tandem processes due to the mild reaction conditions and selectivity usually associated with such reactions.[14] The synthetically powerful combination of transition metal-catalysed cyclisation followed by cycloaddition has been elegantly demonstrated by Padwa and co-workers,[15] where the initial cyclisation involves rhodium catalysed decomposition of diazocarbonyl compounds to form ylides which subsequently undergo cycloaddition reactions. As shown in Scheme 4 and Table 1 (Method C), combination of the rhodium catalysed aromatic cyclisation and cycloaddition into a one-pot procedure proved very successful; for example, when the diazoketone **1d** (R = Bu^n) was firstly treated with rhodium(II) acetate (*ca.* 1 mol%) in refluxing dichloromethane, then the resulting solution of the azulenone **2d** was cooled to 0 °C prior to addition of PTAD (1 mol), the cycloadduct **4d** was isolated in 71% yield. As the isolated yield of **2d** from rhodium(II) acetate catalysed decomposition of **1d** is 70% it can be clearly seen that the tandem process is extremely efficient for the stereospecific formation of the cycloadducts **4**. When *in situ* generation of the dienophile was employed in the tandem sequence, the cycloadduct **4d** was obtained in 64% yield following recrystallisation. It is interesting to note that the PTAD cycloaddition was extremely efficient despite the conditions of high dilution (concentration of the azulenone **2** and PTAD were each approximately 2 mM) employed for the rhodium catalysed cyclisation. Thus, due to the mild conditions associated with both the rhodium catalysed cyclisation and PTAD cycloaddition it is possible to conduct the two steps in tandem without any adverse effects. This tandem process has been extended successfully to the other diazoketones **1** as shown in Table 1 (Method C). This process is an extremely rapid (from **1** to **4** in approximately 90 min) and efficient method for the conversion of a simple precursor stereospecifically into a complex polycyclic system. Most importantly the stereochemistry of each of the newly formed stereocentres in **4a**–**g** is ultimately controlled by that of the single stereocentre present in the diazoketone **1a**–**g**. Therefore this tandem process results in an enormous increase in complexity (one relatively easily controlled stereocentre in **1** to a total of six asymmetric carbon atoms in **4** with excellent stereocontrol) in a single reaction flask. Furthermore, the process displays a high degree of atom economy: less than 1 mol% of rhodium(II) acetate is required to effect the first cyclisation while in the second step addition of just one equivalent of PTAD is required to lead to the cycloadduct **4**. Extension of this methodology to the enantiomerically enriched series of diazoketones **1** is underway.

When the PTAD cycloaddition was conducted using a sample of azulenone **2d** which was a mixture of diastereomers (*trans* : *cis* = 83 : 17), there were additional signals visible in the ^{1}H NMR spectrum of the crude product mixture; however, following recrystallisation only a single diastereomer of the adduct **4d** could be isolated (53%) and all attempts to isolate and identify the other diastereomer proved unsuccessful. Therefore the adducts **4** can be synthesised stereospecifically even if the starting azulenone **2** is a mixture of diastereomers.

This very simple stereospecific synthesis of the polycycles **4** has considerable synthetic potential. The rigid pentacyclic framework is envisaged to allow further stereospecific transformation of the compound to lead to carbocyclic intermediates for use in synthesis. Stereospecific modification of **4** is currently under investigation to establish the scope of their potential in synthesis. Use of alternative dienophiles, especially carbon based systems, is also under investigation.

Conclusions

Rhodium(II) acetate catalysed cyclisation of diazoketones **1** proceeds with excellent diastereocontrol to produce the *trans* substituted azulenones **2**. The norcaradiene tautomers of the azulenones, which exist in dynamic equilibrium with the cycloheptatriene tautomers, can be efficiently and stereospecifically trapped as PTAD cycloadducts. The cyclisation–cycloaddition sequence can be conducted in either a sequential or tandem process.

Experimental

All solvents were dried and distilled before use. Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 F_{254}); preparative thin layer chromatography was conducted using Merck silica gel 60 PF_{254}; column chromatography was conducted using Merck silica gel 60.

Elemental analyses were performed in the Microanalysis Laboratory at University College Cork on a Perkin-Elmer 240 elemental analyser. Melting points were determined on a Uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

^{1}H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a JEOL GSX 270 NMR spectrometer in $CDCl_3$, unless otherwise specified, using TMS as internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants in hertz (Hz). Infrared spectra were recorded as KBr discs (solids) or thin films on NaCl plates (oils) on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Mass spectra were recorded on a Kratos Profile HV-4 double focusing high resolution mass spectrometer (E.I.).

Ether refers to diethyl ether.

Synthesis of 1-arylalkyl alcohols

1-Phenylpropanol.[10a] Benzaldehyde (10.00 g, 9.43×10^{-2} mol) in dry ether (30 ml), was added dropwise over 30 min to a solution of ethylmagnesium bromide [freshly prepared from magnesium (2.43 g, 0.10 mol) and ethyl bromide (10.89 g, 0.10 mol)] in dry ether (30 ml) at 0 °C, while stirring under nitrogen. After stirring for 20 min at 0 °C, the reaction was quenched by slow addition of the reaction mixture to a saturated solution of ammonium chloride (100 ml) at 0 °C. The layers were separated and the aqueous layer was extracted with ether (3 × 50 ml). The combined ether extracts were dried over magnesium sulfate and evaporated under reduced pressure to give the crude product. Distillation gave the *alcohol* (11.41 g, 89%) as a colourless oil, bp 68–70 °C at 1.0 mmHg (lit.,[10a] 100–101 °C at 11 mmHg); ν_{max}(film)/cm^{-1} 3360, 1604, 1493, 1453; δ_H($CDCl_3$) 0.86–0.92 [3H, t, *J* 7, C(3)H_3], 1.62–1.81 [2H, m, C(2)H_2], 2.44 (1H, br s, O*H*), 4.47–4.53 [1H, t, *J* 6, C(1)*H*], 7.23–7.34 (5H, m, Ar*H*).

1-Phenylbutanol.[10a] This was obtained following the procedure described for 1-phenylpropanol, from benzaldehyde (8.00 g, 7.55×10^{-2} mol) in dry ether (30 ml) and *n*-propylmagnesium chloride [freshly prepared from magnesium (2.02 g, 8.30×10^{-2} mol) and *n*-propyl chloride (6.52 g, 8.30×10^{-2} mol)] in dry ether (30 ml). Distillation gave the *alcohol* (9.85 g, 87%) as a colourless oil, bp 62–63 °C at 0.8 mmHg (lit.,[10a] 119–120 °C at 15 mmHg); ν_{max}(film)/cm^{-1} 3373, 1604, 1494; δ_H($CDCl_3$) 0.77–0.82 [3H, t, *J* 7, C(4)H_3], 1.49–1.78 [4H, m, C(3)H_2, C(2)H_2], 3.87 (1H, br s, O*H*), 4.40–4.47 [1H, t, *J* 6, C(1)*H*], 7.11–7.24 (5H, m, Ar*H*); δ_C($CDCl_3$) 13.71 (CH_3-4), 18.71 (CH_2-3), 40.93 (CH_2-2), 73.83 (*C*H-1), 125.74, 126.93, 127.96 (3 × *C*H), 144.82 (*C*).

1-Phenyl-2-methylpropanol.[10a] This was obtained following the procedure described for 1-phenylpropanol, from benzaldehyde (12.00 g, 0.11 mol) in dry ether (50 ml) and isopropylmagnesium chloride [freshly prepared from magnesium (2.92 g, 0.12 mol) and isopropyl chloride (9.42 g, 0.12 mol)] in dry ether (40 ml). Distillation gave the *alcohol* (14.92 g, 88%) as a colourless oil, bp 55–56 °C at 1.0 mmHg (lit.,[10a] 103–104 °C at 10 mmHg); ν_{max}(film)/cm^{-1} 3386, 1604, 1493; δ_H($CDCl_3$) 0.85–0.87 [3H, d, *J* 7, one of CH(CH_3)$_2$], 1.08–1.10 [3H, d, *J* 7, one of CH(CH_3)$_2$], 1.96–2.12 [1H, m, C(2)*H*], 2.81 (1H, br s, O*H*), 4.39–4.42 [1H, d, *J* 8, C(1)*H*], 7.35–7.48 (5H, m, Ar*H*).

1-Phenylpentanol.[16] This was obtained following the procedure described for 1-phenylpropanol, from benzaldehyde (10.00 g, 9.43×10^{-2} mol) in dry ether (30 ml) and *n*-butylmagnesium chloride [freshly prepared from magnesium (2.43 g, 0.10 mol) and *n*-butyl chloride (9.25 g, 0.10 mol)] in dry ether (30 ml). Distillation gave the *alcohol* (13.15 g, 85%) as a colourless oil, bp 80–81 °C at 1.5 mmHg (lit.,[16] 137 °C at 21 mmHg);

ν_{max}(film)/cm^{-1} 3362, 1603, 1494; δ_H(CDCl$_3$) 0.82–0.87 [3H, t, *J* 7, C(5)H_3], 1.10–1.36 [4H, m, C(3)H_2, C(4)H_2], 1.53–1.77 [2H, m, C(2)H_2], 3.29 (1H, br s, O*H*), 4.47–4.52 [1H, t, *J* 6, C(1)*H*], 7.16–7.29 (5H, m, Ar*H*).

Synthesis of 1-arylalkyl bromides

1-Phenylpropyl bromide 5a.[10a] Phosphorus tribromide (3.62 ml, 4.04×10^{-2} mol) was added dropwise to a solution of 1-phenylpropanol (11.00 g, 8.09×10^{-2} mol) and pyridine (0.5 ml) in ether (20 ml) while stirring under nitrogen at 0 °C. After stirring for 2.5 h at room temperature, the reaction was quenched by slow addition of the reaction mixture onto ice (100 g). Following separation of the layers, the aqueous layer was extracted with ether (3 × 75 ml). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (5%, 2 × 100 ml) and water (2 × 75 ml), dried with magnesium sulfate, and evaporated under reduced pressure. The crude product was distilled to give the *bromide* **5a** (12.87 g, 80%) as a colourless oil, bp 58–60 °C at 1.0 mmHg (lit.,[10a] 96–97 °C at 12 mmHg); ν_{max}(film)/cm^{-1} 1600, 1494, 1454, 695; δ_H(CDCl$_3$) 0.86–0.92 [3H, t, *J* 7, C(3)H_3], 1.95–2.27 [2H, m, C(2)H_2], 4.76–4.81 [1H, t, *J* 6, C(1)*H*], 7.11–7.31 (5H, m, Ar*H*); δ_C(CDCl$_3$) 12.95 (CH$_3$-3), 33.05 (CH$_2$-2), 56.98 (*C*H-1), 126.47, 128.30, 128.91 (3 × *C*H), 141.84 (*C*).

1-Phenylbutyl bromide 5b.[10a] This was obtained following the procedure described for **5a**, from 1-phenylbutanol (17.30 g, 1.20×10^{-1} mol) and pyridine (0.5 ml) in ether (30 ml), and phosphorus tribromide (5.17 ml, 5.75×10^{-2} mol). The crude product was distilled to give the *bromide* **5b** (19.40 g, 79%) as a colourless oil, bp 65–67 °C at 1.5 mmHg (lit.,[10a] 110–112 °C at 11 mmHg); ν_{max}(film)/cm^{-1} 1604, 1493, 1454, 697; δ_H(CDCl$_3$) 0.81–0.95 [3H, t, *J* 7, C(4)H_3], 1.22–1.59 [2H, m, C(3)H_2], 2.05–2.35 [2H, m, C(2)H_2], 4.92–5.02 [1H, t, *J* 6, C(1)*H*], 7.25–7.46 (5H, m, Ar*H*); δ_C(CDCl$_3$) 13.64 (CH$_3$-4), 21.71 (CH$_2$-3), 42.54 (CH$_2$-2), 55.41 (*C*H-1), 127.10, 127.54, 128.86 (3 × *C*H), 142.36 (*C*).

1-Phenyl-2-methylpropyl bromide 5c.[10a] This was obtained following the procedure described for **5a**, from 1-phenyl-2-methylpropanol (14.80 g, 9.84×10^{-2} mol) and pyridine (0.5 ml) in ether (30 ml), and phosphorus tribromide (4.43 ml, 4.92×10^{-2} mol). Distillation gave the *bromide* **5d** (15.85 g, 81%) as a colourless oil, bp 93–95 °C at 6.0 mmHg (lit.,[10a] 104–105 °C at 10 mmHg); ν_{max}(film)/cm^{-1} 1492, 1453, 697; δ_H(CDCl$_3$) 0.84–0.86 [3H, d, *J* 6, one of CH(CH_3)$_2$], 1.17–1.20 [3H, d, *J* 6, one of CH(CH_3)$_2$], 2.23–2.38 [1H, m, C(2)*H*], 4.69–4.72 [1H, d, *J* 8, C(1)*H*], 7.22–7.40 (5H, m, Ar*H*).

1-Phenylpentyl bromide 5d. This was obtained following the procedure described for **5a**, from 1-phenylpentanol (15.50 g, 9.45×10^{-2} mol) and pyridine (0.5 ml) in ether (30 ml), and phosphorus tribromide (4.25 ml, 4.73×10^{-2} mol). The crude product was distilled to give the *bromide* **5d** (15.49 g, 77%) as a colourless oil, bp 79–80 °C at 2.0 mmHg; ν_{max}(film)/cm^{-1} 1602, 1455, 1494; δ_H(CDCl$_3$) 0.84–0.91 [3H, t, *J* 7, C(5)H_3], 1.18–1.52 [4H, m, C(3)H_2, C(4)H_2], 2.04–2.33 [2H, m, C(2)H_2], 4.89–4.95 [1H, t, *J* 8, C(1)*H*], 7.13–7.38 (5H, m, Ar*H*).

Synthesis of 1-arylalkylpropanedioic acid diethyl esters

Diethyl (1-phenylpropyl)propanedioate 6a.[10a] Sodium (1.16 g, 5.03×10^{-2} mol) was slowly added to ethanol (30 ml) while stirring under nitrogen at room temperature. Once all of the sodium had dissolved, diethyl malonate (8.04 ml, 5.03×10^{-2} mol) was added and stirring was continued for 10 min. 1-Phenylpropyl bromide **5a** (10.00 g, 5.04×10^{-2} mol) was then added dropwise over 20 min. The reaction mixture tended to solidify on addition of the bromide and it was necessary to warm the solution gently to ensure adequate stirring. The reaction mixture was then refluxed for 12 h while stirring under nitrogen. After cooling to room temperature, ethanol was removed under reduced pressure and the residue was diluted with water (100 ml), and extracted with ether (3 × 100 ml). The combined organic extracts were washed with water (2 × 100 ml), dried with magnesium sulfate, and evaporated under reduced pressure. The crude product was distilled to give the *malonate ester* **6a** (11.33 g, 81%) as a colourless sweet smelling oil, bp 90–92 °C at 0.8 mmHg (lit.,[10a] 113–114 °C at 0.5 mmHg); ν_{max}(film)/cm^{-1} 1732, 1604, 1496, 1454; δ_H(CDCl$_3$) 0.68–0.74 [3H, t, *J* 7, C(3)H_3], 0.87–0.93, 1.23–1.29 (2 × 3H, 2 × t, *J* 8, 2 × OCH$_2$CH_3), 1.54–1.83 [2H, m, C(2)H_2], 3.23–3.37 (1H, dt, *J* 11, 4, C(1)*H*], 3.63–3.67 [1H, d, *J* 11, C*H*(CO$_2$Et)$_2$], 3.80–3.88, 4.17–4.25 (2 × 2H, 2 × q, *J* 8, 2 × OCH_2CH$_3$), 7.14–7.28 (5H, m, Ar*H*).

Diethyl (1-phenylbutyl)propanedioate 6b.[10a] This was obtained following the procedure described for **6a**, from 1-phenylbutyl bromide **5b** (15.40 g, 7.23×10^{-2} mol), diethyl malonate (11.57 g, 7.23×10^{-2} mol) and sodium (1.66 g, 7.23×10^{-2} mol) in ethanol (50 ml). The crude product was distilled to give the *malonate ester* **6b** (17.52 g, 83%) as a colourless sweet smelling oil, bp 108–109 °C at 0.2 mmHg (lit.,[10a] 141–142 °C at 1.8 mmHg); ν_{max}(film)/cm^{-1} 1736, 1603, 1494, 1438; δ_H(CDCl$_3$) 0.78–0.84 [3H, t, *J* 8, C(4)H_3], 0.86–0.92 (3H, t, *J* 7, one of OCH$_2$CH_3), 1.03–1.21 [2H, m, C(3)H_2], 1.24–1.29 (3H, t, *J* 7, one of OCH$_2$CH_3), 1.56–1.69 [2H, m, C(2)H_2], 3.34–3.43 [1H, dt, *J* 11, 5, C(1)*H*], 3.62–3.66 [1H, d, *J* 11, C*H*(CO$_2$Et)$_2$], 3.80–3.88, 4.17–4.26 (2 × 2H, 2 × q, *J* 8, 2 × OCH_2CH$_3$), 7.14–7.32 (5H, m, Ar*H*); δ_C(CDCl$_3$) 13.36, 13.50, 13.69 (CH$_3$-4 and 2 × OCH$_2$$CH_3$), 19.59 ($CH_2$-3), 35.36 ($CH_2$-2), 44.78 (*C*H-1), 57.97 (*C*H(CO$_2$Et)$_2$), 60.26, 60.94 (2 × OCH$_2$CH$_3$), 125.92, 127.52, 128.41 (3 × *C*H), 140.70 (*C*), 167.40, 168.02 (2 × *C*=O).

Diethyl (2-methyl-1-phenylpropyl)propanedioate 6c.[10a] This was obtained following the procedure described for **6a**, from 1-phenyl-2-methylpropyl bromide **5c** (12.75 g, 5.99×10^{-2} mol), diethyl malonate (9.58 g, 5.99×10^{-2} mol) and sodium (1.38 g, 5.99×10^{-2} mol) in ethanol (50 ml). The crude product was distilled to give the *malonate ester* **6c** (15.04 g, 86%) as a colourless oil, bp 117–119 °C at 0.5 mmHg (lit.,[10a] 132–133 °C at 1 mmHg); ν_{max}(film)/cm^{-1} 1736, 1602, 1495, 1452; δ_H(CDCl$_3$) 0.79–0.81 [3H, d, *J* 7, one of CH(CH_3)$_2$], 0.82–0.84 [3H, d, *J* 7, one of CH(CH_3)$_2$], 0.88–0.94, 1.26–1.31 (2 × 3H, 2 × t, *J* 7, 2 × OCH$_2$CH_3), 1.92–2.17 [1H, m, C(2)*H*], 3.36–3.42 [1H, dd, *J* 12, 5, C(1)*H*], 3.78–3.87 (2H, q, *J* 7, OCH_2CH$_3$), 3.93–3.97 [1H, d, *J* 12, C*H*(CO$_2$Et)$_2$], 4.14–4.29 (2H, q, *J* 7, OCH_2CH$_3$), 7.14–7.29 (5H, m, Ar*H*).

Diethyl (1-phenylpentyl)propanedioate 6d.[10a,c] This was obtained following the procedure described for **6a**, from 1-phenylpentyl bromide **5d** (11.50 g, 6.15×10^{-2} mol), diethyl malonate (9.85 g, 6.15×10^{-2} mol) and sodium (1.41 g, 6.15×10^{-2} mol) in ethanol (50 ml). The crude product was distilled to give the *malonate ester* **6d** (15.06 g, 80%) as a colourless sweet smelling oil, bp 113–115 °C at 0.3 mmHg; ν_{max}(film)/cm^{-1} 1734, 1603, 1495, 1440; δ_H(CDCl$_3$; 60 MHz) 0.8–0.9 [2 × 3H, 2 × t, C(5)H_3 and one of OCH$_2$CH_3], 1.0–1.3 [4H, m, C(3)H_2, C(4)H_2], 1.3–1.4 (3H, t, one of OCH$_2$CH_3), 1.6–1.7 [2H, m, C(2)H_2], 3.4–3.5 [1H, dt, C(1)*H*], 3.6–3.8 [1H, d, C*H*(CO$_2$Et)$_2$], 3.8–4.1, 4.1–4.3 (2 × 2H, 2 × q, 2 × OCH_2CH$_3$), 7.1–7.3 (5H, m, Ar*H*).

Synthesis of 1-arylalkylpropanedioic acids

(1-Phenylpropyl)propanedioic acid 7a.[10a] A solution of the malonate ester **6a** (10.50 g, 3.79×10^{-2} mol) in ethanol (20 ml) and aqueous potassium hydroxide (2.5 M, 20 ml) was refluxed for 3 h. The reaction mixture was then cooled to room temperature and ethanol was evaporated at reduced pressure. The residue was diluted with water (50 ml) and extracted with ethyl acetate (50 ml). The layers were separated, acidified to pH 2 (using dilute hydrochloric acid) and extracted with ethyl acetate (3 × 75 ml). The organic extracts were dried with magnesium sulfate and evaporated under reduced pressure to give the *malonic acid* **7a** (6.39 g, 76%) as a white solid; ν_{max}(KBr)/cm^{-1} 3550–2585, 1709, 1604, 1495, 1454; δ_H(CD_3OD) 0.66–0.71 [3H, t, *J* 7, C(3)H_3], 1.51–1.68 [1H, m, one of C(2)H_2], 1.75–1.86 [1H, m, one of C(2)H_2], 3.14–3.24 [1H, dt, *J* 11, 4, C(1)*H*], 3.63–3.67 [1H, d, *J* 11, C*H*(CO_2H)$_2$], 7.15–7.29 (5H, m, Ar*H*).

(1-Phenylbutyl)propanedioic acid 7b.[10a] This was obtained following the procedure described for **7a**, from the malonate ester **6b** (17.25 g, 5.91 × 10^{-2} mol), aqueous potassium hydroxide (2.5 M, 24 ml) and ethanol (30 ml), to give the *malonic acid* **7b** (10.32 g, 74%) as a white solid; ν_{max}(KBr)/cm^{-1} 3625–2573, 1718, 1602, 1496, 1456; δ_H(CD_3OD) 0.74–0.86 [3H, t, *J* 8, C(4)H_3], 0.99–1.15 [2H, m, C(3)H_2], 1.55–1.79 [2H, m, C(2)H_2], 3.24–3.39 [1H, m, C(1)*H*], 3.60–3.68 [1H, d, *J* 11, C*H*(CO_2H)$_2$], 7.14–7.35 (5H, m, Ar*H*); δ_C(CD_3OD) 14.23 (CH_3-4), 21.23 (CH_2-3), 37.28 (CH_2-2), 46.59 (*C*H-1), 60.22 [*C*H(CO_2H)$_2$], 127.75, 129.27, 129.51 (3 × *C*H), 142.80 (*C*), 171.64, 172.05 (2 × *C*=O).

(2-Methyl-1-phenylpropyl)propanedioic acid 7c.[10a] This was obtained following the procedure described for **7a**, from the malonate ester **7c** (15.0 g, 5.14 × 10^{-2} mol), aqueous potassium hydroxide (2.5 M, 20 ml) and ethanol (30 ml), to give the *malonic acid* **7c** (8.85 g, 73%) as a white solid; ν_{max}(KBr)/cm^{-1} 3650–2570, 1710, 1604, 1495, 1454; δ_H(CD_3OD) 0.78–0.80 [3H, d, *J* 7, one of CH(CH_3)$_2$], 0.83–86 [3H, d, *J* 7, one of CH(CH_3)$_3$], 2.01–2.07 [1H, m, C(2)*H*], 3.28–3.34 [1H, dd, *J* 11, 5, C(1)*H*], 3.97–4.01 [1H, d, *J* 11, C*H*(CO_2H)$_2$], 7.10–7.25 (5H, m, Ar*H*), 11.04 (1H, br s, O*H*).

(1-Phenylpentyl)propanedioic acid 7d. This was obtained following the procedure described for **7a**, from the malonate ester **6d** (13.10 g, 4.28 × 10^{-2} mol), aqueous potassium hydroxide (2.5 M, 20 ml) and ethanol (30 ml), to give the *malonic acid* **7d** (8.24 g, 77%) as a white solid; ν_{max}(KBr)/cm^{-1} 3612–2571, 1714, 1496, 1455; δ_H(CD_3OD) 0.74–0.80 [3H, t, *J* 8, C(5)H_3], 0.99–1.28 [4H, m, C(3)H_2, C(4)H_2], 1.55–1.79 [2H, m, C(2)H_2], 3.25–3.34 [1H, dt, *J* 11, 4, C(1)*H*], 3.63–3.68 [1H, d, *J* 11, C*H*(CO_2H)$_2$], 7.14–7.28 (5H, m, Ar*H*).

Synthesis of 3-alkyl-3-arylpropanoic acids

3-Phenylpentanoic acid 3a.[10a,b] (1-Phenylpropyl)propanedioic acid **7a** (9.00 g, 4.05 × 10^{-2} mol) was heated at 180–185 °C with stirring for 20 min. The reaction mixture was allowed to cool to 50 °C and dissolved in sodium hydroxide (1 M, 50 ml). This was then diluted with water (50 ml), treated with charcoal, filtered and washed with ethyl acetate (2 × 50 ml). The aqueous layer was acidified to pH 2 (with dilute aqueous hydrochloric acid) and extracted with ethyl acetate (3 × 75 ml). The organic layer was dried with magnesium sulfate and evaporated under reduced pressure to give the *acid* **3a** (4.98 g, 69%) as a white solid; mp 47–49 °C [lit.,[10a] 47–48 °C]; ν_{max}(KBr)/cm^{-1} 3320–2540 (br), 1708; δ_H($CDCl_3$) 0.75–0.81 [3H, t, *J* 8, C(5)H_3], 1.49–1.80 [2H, m, C(4)H_2], 2.52–2.71 [2H, m, C(2)H_2], 2.91–3.04 [1H, m, C(3)*H*], 7.11–7.32 (5H, m, Ar*H*), 11.17 (1H, br s, COO*H*); δ_C($CDCl_3$) 12.08 (CH_3-5), 29.37 (CH_2-4), 41.13, 43.53 (CH_2-2, *C*H-3), 127.74, 128.12, 129.91 (3 × *C*H), 143.64 (*C*), 178.77 (*C*=O).

3-Phenylhexanoic acid 3b.[10a] This decarboxylation was conducted following the procedure described for **3a**, from (1-phenylbutyl)propanedioic acid **7b** (5.30 g, 2.14 × 10^{-2} mol) by heating at 190–200 °C for 20 min while stirring under nitrogen. The *acid* **3b** (3.13 g, 77%) was isolated as a white solid, mp 33–34.5 °C [lit.,[10a] 33–34 °C]; ν_{max}(KBr)/cm^{-1} 3371–2650 (br), 1712, 1604; δ_H($CDCl_3$) 0.72–0.78 [3H, t, *J* 7, C(6)H_3], 1.05–1.11 [2H, m, C(5)H_2], 1.42–1.51 [2H, m, C(4)H_2], 2.43–2.73 [2H, m, C(2)H_2], 3.05–3.18 [1H, m, C(3)*H*], 7.11–7.37 (5H, m, Ar*H*); δ_C($CDCl_3$) 13.87 (CH_3-6), 20.40 (CH_2-5), 38.48 (CH_2-4), 40.75 (*C*H-3), 50.27 (CH_2-2), 126.16, 127.48, 128.89 (3 × *C*H), 144.71 (*C*), 178.65 (*C*=O).

3-Phenyl-4-methylpentanoic acid 3c.[10a] This decarboxylation was conducted following the procedure described for **3a**, from (2-methyl-1-phenylpropyl)propanedioic acid **7c** (6.25 g, 2.61 × 10^{-2} mol) by heating at 180–185 °C for 20 min while stirring under nitrogen. The *acid* **3c** (3.76 g, 75%) was isolated as a white solid, mp 46–48 °C [lit.,[10a] 46–47 °C]; ν_{max}(KBr)/cm^{-1} 3250–2575 (br), 1708, 1496; δ_H($CDCl_3$) 0.73–0.76 [3H, d, *J* 6, one of CH(CH_3)$_2$], 0.91–0.94 [3H, d, *J* 6, one of CH(CH_3)$_2$], 1.81–1.86 [1H, m, C(4)*H*], 2.59–2.89 [3H, m, C(2)H_2, C(3)*H*], 7.11–7.29 (5H, m, Ar*H*); δ_C($CDCl_3$) 20.14 [one of CH(CH$_3$)$_2$], 20.49 [one of CH(CH$_3$)$_2$], 33.23 (*C*H-4), 38.51 (CH_2-2), 48.51 (*C*H-3), 126.54, 128.30, 128.52 (3 × *C*H), 142.57 (*C*), 178.86 (*C*=O).

3-Phenylheptanoic acid 3d.[10c] This decarboxylation was conducted following the procedure described for **3a**, from (1-phenylpentyl)propanedioic acid **7d** (23.40 g, 9.30 × 10^{-2} mol) by heating at 190–200 °C for 20 min while stirring under nitrogen. The *acid* **3d** (13.67 g, 71%) was isolated as a white solid, mp 41–43 °C [lit.,[10c] 42–43 °C]; ν_{max}(KBr)/cm^{-1} 3371–2650 (br), 1712, 1604; δ_H($CDCl_3$) 0.76–0.81 [3H, t, *J* 7, C(7)H_3], 1.12–1.26 [4H, m, C(6)H_2, C(5)H_2], 1.56–1.71 [2H, m, C(4)H_2], 2.54–2.57 [2H, m, C(2)H_2], 3.03–3.06 [1H, m, C(3)*H*], 7.11–7.23 (5H, m, Ar*H*); δ_C($CDCl_3$) 13.63 (CH_3-7), 22.32 (CH_2-6), 29.47 (CH_2-5), 36.67 (CH_2-4), 41.67 (CH_2-2), 42.13 (*C*H-3), 126.01, 127.42, 128.19 (3 × *C*H), 144.26 (*C*), 178.42 (*C*=O).

3-Phenyl-4,4-dimethylpentanoic acid 3e.[10d] Cinnamic acid (5.00 g, 3.38 × 10^{-2} mol) in dry ether (50 ml) was added dropwise over 15 min to a solution of *tert*-butylmagnesium chloride in ether (2 M, 42 ml, 8.40 × 10^{-2} mol), at 0 °C while stirring under nitrogen. The reaction mixture was stirred for 4 h while slowly returning to room temperature. The reaction mixture was then added slowly with stirring, to concentrated hydrochloric acid (20 ml) in ice (60 g). The layers were separated and the aqueous layer was washed with ether (3 × 50 ml). The combined ether extracts were dried and evaporated under reduced pressure to give the crude product. Purification by chromatography on silica gel with gradient ether–hexane as eluant gave the *acid* **3e** (3.69 g, 53%), as a white solid, mp 114–116 °C [lit.,[10d] 115–116 °C]; ν_{max}(KBr)/cm^{-1} 3284–2568, 1702, 1603, 1494; δ_H($CDCl_3$) 0.87 (9H, s, 3 × CH_3), 2.66–2.82 [2H, m, C(2)H_2], 2.89–2.95 [1H, m, C(3)*H*], 7.11–7.27 (5H, m, Ar*H*); δ_C($CDCl_3$) 27.90 (3 × CH_3 of Bu^t), 33.69 (*C* of Bu^t), 35.41 (CH_2-2), 51.90 (*C*H-3), 126.43, 127.64, 129.26 (3 × *C*H), 141.36 (*C*), 178.45 (*C*=O).

Methyl 3-phenylhex-5-enoate.[10e] A reaction vessel containing 4 Å molecular sieves (2.00 g) was flamed dried under vacuum (5 min), and placed under nitrogen. A solution of tetrabutylammonium fluoride (1 M in THF, 1.5 ml, 1.50 × 10^{-3} mol) in dry DMF (20 ml) was added. Methyl cinnamate **2** (2.00 g, 1.23 × 10^{-2} mol) in dry DMF (20 ml) was then added dropwise over 5 min while stirring. A solution of HMPA (6.63 g, 3.70 × 10^{-2} mol) and allylsilane (4.22 g, 3.70 × 10^{-2} mol) in dry DMF (40 ml) was added slowly over 10 min. An immediate colour change from yellow to black was observed on addition of the allylsilane solution. The reaction was monitored by TLC and was complete after 10 min. After methanolysis of the reaction mixture using a methanol–hydrochloric acid solution (20 ml) (9:1), the reaction mixture was diluted with water (100 ml). The aqueous layer was extracted with dichloromethane

(3 × 100 ml) and the combined organic extracts were dried over magnesium sulfate and evaporated under reduced pressure. Purification by chromatography on silica gel with gradient dichloromethane–hexane as eluant gave the *ester* (2.13 g, 85%) as a colourless oil; ν_{max}(film)/cm^{-1} 1738, 1640; δ_H(CDCl$_3$) 2.38–2.43 (2H, overlapping dd, appears as t, CH_2), 2.53–2.75 (2H, m, CH_2), 3.18–3.29 [1H, m, C(3)H], 3.58 (3H, s, OCH_3), 4.93–5.08 [2H, m, C(6)H_2], 5.59–5.75 [1H, m, C(5)H], 7.13–7.35 (5H, m, ArH); δ_C(CDCl$_3$) 40.40, 40.57 (CH$_2$-2, CH$_2$-4), 41.76 (OCH$_3$), 51.40 (CH-3), 116.83 (CH$_2$-6), 126.53, 127.39, 128.41 (3 × CH), 135.91 (CH-5), 143.60 (C), 172.56 (C=O).

3-Phenylhex-5-enoic acid 3f. A solution of methyl 3-phenylhex-5-enoate (5.00 g, 1.96 × 10^{-2} mol) in ethanol (30 ml), and sodium hydroxide (2.5 M, 20 ml) was refluxed for 12 h. The reaction mixture was then cooled to room temperature and the ethanol was evaporated at reduced pressure. The crude reaction mixture was diluted with water (50 ml) and the solution was washed with ethyl acetate (3 × 50 ml). The aqueous layer was then acidified to pH 2 (using dilute aqueous hydrochloric acid) and washed with ethyl acetate (3 × 75 ml). The organic layer was dried with magnesium sulfate and evaporated under reduced pressure to give the *acid* **3f** (2.83 g, 70%) isolated as a white solid, mp 53–55 °C; ν_{max}(KBr)/cm^{-1} 3520–2780 (br), 1707, 1495; δ_H(CDCl$_3$) 2.27–2.39 [2H, m, C(4)H_2], 2.52–2.75 [2H, m, C(2)H_2], 3.14–3.26 [1H, m, C(3)H], 4.95–5.02 [2H, m, C(6)H_2], 5.53–5.72 [1H, m, C(5)H], 7.14–7.61 (5H, m, ArH); δ_C(CDCl$_3$) 40.18, 40.60 (CH$_2$-2, CH$_2$-4), 41.45 (CH-3), 117.04 (CH$_2$-6), 127.31, 128.29, 128.85 (3 × CH), 135.68 (CH-5), 143.25 (C).

3,3-Diphenylpropanoic acid 3g.[10f] Powdered anhydrous aluminium chloride (25.00 g, 0.188 mol) was added slowly over 5 min to cinnamic acid (15.00 g, 0.101 mol) in dry benzene (220 ml), while stirring at 0 °C under nitrogen. Once the aluminium chloride was added, the ice-bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then added slowly with stirring to concentrated hydrochloric acid (20 ml) in ice (50 g). The aqueous layer was extracted with ethyl acetate (3 × 50 ml) and the combined organic layers were then washed with aqueous sodium hydroxide (20%, 2 × 100 ml). The acid was isolated by acidifying the aqueous layer to pH 2 and extracting with ethyl acetate (3 × 75 ml). The organic extract was dried with magnesium sulfate and evaporated under reduced pressure to give the *acid* **3g** (20.32 g, 90%) isolated as a white solid, mp 154–156 °C [lit.,[10f] 154–155 °C]; ν_{max}(KBr)/cm^{-1} 3250–2550, 1702, 1603, 1494; δ_H (CDCl$_3$) 3.06–3.09 [2H, d, J 8, C(2)H_2], 4.49–4.55 [1H, t, J 8, C(3)H], 7.15–7.30 (10H, m, ArH).

Synthesis of diazoketones †

3-Phenylpentanoyl chloride. 3-Phenylpentanoic acid **3a** (2.91 g, 1.75 × 10^{-2}) in freshly distilled thionyl chloride (20 ml) was refluxed for 2.5 h while stirring under nitrogen. Excess thionyl chloride was evaporated under reduced pressure and any remaining traces were removed as an azeotrope with dry toluene (2 × 20 ml). Distillation gave the *acid chloride* (2.94 g, 91%) as a colourless oil, bp 113–115 °C at 0.5 mmHg; ν_{max}(film)/cm^{-1} 1799, 1603.

2-Diazo-5-phenylheptan-3-one 1a. Oxalyl chloride (0.67 ml, 7.6 × 10^{-3} mol) was added dropwise over 5 min to 3-phenylpentanoic acid **3a** (1.232 g, 6.92 × 10^{-3} mol) in dry ether (15 ml), while stirring at 0 °C under nitrogen. The solution was allowed to slowly return to room temperature while stirring for 18 h. The solvent and residual reagent were removed under reduced pressure to give the acyl chloride which was used without purification. An ethereal diazoethane solution was prepared from *N*-ethyl-*N*-nitrosourea[17] (7.48g, 6.83 × 10^{-2} mol) and cooled to −20 °C using a salt–ice bath. The crude acyl chloride in dry ether (20 ml) was added dropwise over 20 min to the diazoethane solution while stirring under nitrogen. The solution was then allowed to slowly return to room temperature while stirring for 2.5 h. The ether and residual diazoethane were evaporated under reduced pressure. Purification by chromatography on silica gel, using ethyl acetate–hexane (5:95) as eluant, gave the *diazoketone* **1a** (1.04 g, 70%) as a yellow oil (Found: C, 72.43; H, 7.50; N, 12.97. $C_{13}H_{16}N_2O$ requires C, 72.19; H, 7.46; N, 12.95%); ν_{max}(film)/cm^{-1} 2071, 1632; δ_H(CDCl$_3$) 0.78 [3H, t, J 7, C(7)H_3], 1.35–2.05 [5H, m, contains s at 1.90 for C(1)H_3, C(6)H_2], 2.58–2.76 [2H, m, C(4)H_2], 3.01–3.12 [1H, m, C(5)H], 7.12–7.31 (5H, m, ArH); δ_C(CDCl$_3$) 7.98 (CH$_3$-1), 11.91 (CH$_3$-7), 28.78 (CH$_2$-6), 44.09 (CH-5), 44.67 (CH$_2$-4), 126.36 (CH), 127.48 (2 × CH), 128.01 (2 × CH), 143.96 (C), 193.36 (C=O); *m/z* 215 (M$^+$ − H, 29%), 208 (20%), 196 (21%), 188 (M$^+$ − N$_2$, 9%), 119 (PhC$_3$H$_6$$^+$, 41%), 105 (PhC$_2H_4$$^+$, 57%), 91 (PhCH$_2$$^+$, 100%).

3-Phenylhexanoyl chloride. This was prepared following the procedure described for 3-phenylpentanoyl chloride, from 3-phenylhexanoic acid **3b** (3.12 g, 1.63 × 10^{-2} mol) and freshly distilled thionyl chloride (20 ml). Distillation gave the *acid chloride* (3.17 g, 92%) as a colourless oil, bp 116–117 °C at 0.9 mmHg; ν_{max}(film)/cm^{-1} 1800, 1603, 1495.

2-Diazo-5-phenyloctan-3-one 1b. 3-Phenylhexanoyl chloride (2.20 g, 1.05 × 10^{-2} mol) in dry ether (20 ml) was added dropwise over 20 min to a freshly distilled ethereal diazoethane solution [prepared from *N*-ethyl-*N*-nitrosourea[17] (12.29 g, 0.105 mol)], at −20 °C while stirring under nitrogen. The solution was then allowed to slowly return to room temperature while stirring for 3 h. The ether and residual diazoethane were evaporated under reduced pressure. Purification by chromatography on silica gel, using ethyl acetate–hexane (5:95) as eluant, gave the *diazoketone* **1b** (2.10 g, 87%) as an orange oil (Found: C, 73.53; H, 7.31. $C_{14}H_{18}N_2O$ requires C, 73.01; H, 7.88%); ν_{max}(film)/cm^{-1} 2070, 1638; δ_H(CDCl$_3$) 0.82–0.87 [3H, t, J 7, C(8)H_3], 1.09–1.26 [2H, m, C(7)H_2], 1.53–1.71 [2H, m, C(6)H_2], 1.83 [3H, s, C(1)H_3], 2.68–2.77 [2H, m, C(4)H_2], 3.11–3.20 [1H, m, C(5)H], 7.15–7.31 [5H, m, ArH]; δ_C(CDCl$_3$) 7.98 (CH$_3$-1), 13.91 (CH$_3$-8), 20.51 (CH$_2$-7), 38.11 (CH$_2$-6), 42.14 (CH-5), 44.99 (CH$_2$-4), 126.36, 127.42, 128.08 (3 × CH), 144.18 (C) [Found (HRMS, EI): 202.13597 (M$^+$ − N$_2$). $C_{14}H_{18}O$ requires M$^+$ 202.13577]; *m/z* 202 (7%), 159 (14%), 132 (64%), 91 (100%).

3-Phenyl-4-methylpentanoyl chloride. This was prepared following the procedure described for 3-phenylpentanoyl chloride, from 3-phenyl-4-methylpentanoic acid **3c** (3.20 g, 1.67 × 10^{-2} mol) and freshly distilled thionyl chloride (20 ml), while refluxing for 3 h. Distillation gave the *acid chloride* (3.10 g, 95%) as a colourless oil, bp 90–94 °C at 0.08 mmHg; ν_{max}(film)/cm^{-1} 1801, 1602, 1494.

2-Diazo-5-phenyl-6-methylheptan-3-one 1c. This was prepared following the procedure described for **1b**, using 3-phenyl-4-methylpentanoyl chloride (4.00 g, 1.91 × 10^{-2} mol) in ether (40 ml) and freshly distilled ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea[17] (22.35 g, 0.191 mol)]. Purification by chromatography on silica gel, using ethyl acetate–hexane (2:98) as eluant, gave the *diazoketone* **1c** (3.91 g, 89%) as an orange oil; ν_{max}(film)/cm^{-1} 2071, 1633, 1494; δ_H(CDCl$_3$) 0.73–0.75 [3H, d, J 7, one of CH(CH_3)$_2$], 0.96–0.99 [3H, d, J 7, one of CH(CH_3)$_2$], 1.76 [3H, s, C(1)H_3], 1.82–1.95 [1H, m, CH(CH$_3$)$_2$], 2.77–2.81 [2H, m, C(4)H_2], 2.92–3.02 [1H, m, C(5)H], 7.11–7.30 (5H, m, ArH); δ_C(CDCl$_3$) 8.32 (CH$_3$-1), 20.50, 20.90 [2 × CH$_3$, CH(CH$_3$)$_2$], 33.08 (CH-6), 41.84 (CH$_2$-4), 49.30 (CH-5),

† The diazo carbon was not detected in the ^{13}C NMR spectra of any of the diazoketones **1**.

126.41, 128.20, 128.53 (3 × *C*H), 143.31 (*C*), 194.21 (*C*=O) (Found (HRMS, EI): 202.13508 ($M^+ - N_2$). $C_{14}H_{18}O$ requires M^+ 202.13577]; *m*/*z* 202 (11%), 159 (24%), 132 (67%), 91 (100%).

3-Phenylheptanoyl chloride. This was prepared following the procedure described for 3-phenylpentanoyl chloride, from 3-phenylheptanoic acid **3d** (4.51 g, 2.18×10^{-2} mol) and freshly distilled thionyl chloride (20 ml). Distillation gave the *acid chloride* (4.33 g, 88%) as a colourless oil, bp 109–112 °C at 0.2 mmHg; ν_{max}(film)/cm^{-1} 1802, 1604, 1495.

2-Diazo-5-phenylnonan-3-one 1d. This was prepared following the procedure described for **1b**, using 3-phenylheptanoyl chloride (4.00 g, 1.78×10^{-2} mol) in ether (40 ml) and freshly distilled ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea[17] (20.83 g, 0.178 mol)]. Purification by chromatography on silica gel, using ethyl acetate–hexane (3:97) as eluant, gave the *diazoketone* **1d** (3.87 g, 89%) as an orange oil; ν_{max}(film)/cm^{-1} 2069, 1637, 1560, 1494; δ_H($CDCl_3$) 0.80–0.86 [3H, t, *J* 7, C(9)H_3], 1.05–1.40 [4H, m, C(7)H_2 and C(8)H_2], 1.59–2.01 [2H, m, C(6)H_2], 1.84 [3H, s, C(1)H_3], 2.63–2.78 [2H, m, C(4)H_2], 3.12–3.34 [1H, m, C(5)*H*], 7.14–7.35 (5H, m, Ar*H*); δ_C($CDCl_3$) 8.03 (CH_3-1), 13.92 (CH_3-9), 22.59 (CH_2-8), 29.61 (CH_2-7), 35.65 (CH_2-6), 42.43 (*C*H-5), 45.09 (CH_2-4), 126.41, 127.47, 128.44 (3 × *C*H), 144.29 (*C*), 193.44 (*C*=O) [Found (HRMS, EI): 244.15769. $C_{15}H_{20}N_2O$ requires M^+ 244.15756]; *m*/*z* 216 (21%), 159 (54%), 132 (86%), 104 (78%), 91 (100%).

3-Phenyl-4,4-dimethylpentanoyl chloride. This was prepared following the procedure described for 3-phenylpentanoyl chloride, from 3-phenyl-4,4-dimethylpentanoic acid **3e** (2.00 g, 9.71×10^{-3} mol) and freshly distilled thionyl chloride (20 ml), while refluxing for 3 h. Distillation gave the *acid chloride* (1.98 g, 91%) as a colourless oil, bp 123–125 °C at 0.1 mmHg; ν_{max}(film)/cm^{-1} 1798, 1603, 1495.

2-Diazo-5-phenyl-6,6-dimethylheptan-3-one 1e. This was prepared following the procedure described for **1b**, using 3-phenyl-4,4-dimethylpentanoyl chloride (1.00 g, 4.45×10^{-3} mol) in ether (10 ml) and freshly distilled ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea[17] (5.21 g, 4.45×10^{-2} mol)]. Purification by chromatography on silica gel, using ethyl acetate–hexane (2:98) as eluant, gave the *diazoketone* **1e** (1.01 g, 93%) as an orange oil which solidified on cooling; ν_{max}(film)/cm^{-1} 2070, 1644, 1494; δ_H($CDCl_3$) 0.91 (9H, s, 3 × CH_3), 1.75 [3H, s, C(1)H_3], 2.77–2.82 [1H, m, one of C(4)H_2], 2.91–3.15 [2H, m, one of C(4)H_2 and C(5)*H*], 7.15–7.29 (5H, m, Ar*H*); δ_C($CDCl_3$) 8.07 (CH_3-1), 28.09 (3 × CH_3), 33.87 (*C*-6), 38.74 (CH_2-4), 51.91 (*C*H-5), 126.33, 127.69, 129.18 (3 × *C*H), 141.85 (*C*), 193.87 (*C*=O) [Found (HRMS, EI): 244.15526. $C_{15}H_{20}N_2O$ requires M^+ 244.15756]; *m*/*z* 204 (12%), 163 (14%), 144 (28%), 121 (100%), 104 (46%).

3-Phenylhex-5-enoyl chloride. This was prepared following the procedure described for 3-phenylpentanoyl chloride, from 3-phenylhex-5-enoic acid **3f** (2.81 g, 1.48×10^{-2} mol) and freshly distilled thionyl chloride (20 ml). Distillation gave the *acid chloride* (2.82 g, 90%) as a colourless oil, bp 116–115 °C at 0.8 mmHg; ν_{max}(film)/cm^{-1} 1799, 1604, 1495.

2-Diazo-5-phenyloct-7-en-3-one 1f. *(a) Reaction with distilled 3-phenylhex-5-enoyl chloride.* This was prepared following the procedure described for **1b**, using 3-phenylhex-5-enoyl chloride (2.20 g, 1.06×10^{-2} mol) in ether (20 ml) and freshly distilled ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea[17] (11.70 g, 0.10 mol)]. Purification by chromatography on silica gel, using ethyl acetate–hexane (5:95) as eluant, gave the *diazoketone* **1f** (2.03 g, 83%) as an orange oil (Found: C, 73.74; H, 7.76; N, 12.29. $C_{14}H_{16}N_2O$ requires C, 73.66; H, 7.06; N, 12.27%); ν_{max}(film)/cm^{-1} 2072, 1639; δ_H($CDCl_3$) 1.76 [3H, s, C(1)H_3], 2.21–2.35 [2H, m, C(6)H_2], 2.50–2.71 [2H, m, C(4)H_2], 3.17–3.33 [1H, m, C(5)*H*], 4.72–5.02 [2H, m, C(8)H_2], 5.50–5.58 [1H, m, C(7)*H*], 7.06–7.33 (5H, m, Ar*H*); δ_C($CDCl_3$) 8.02 (CH_3-1), 40.27 (CH_2-6), 41.87 (*C*H-5), 43.70 (CH_2-4), 116.72 (CH_2-8), 126.53 127.44, 128.43 (3 × *C*H), 135.91 (*C*H-7), 143.71 (*C*) [Found (HRMS, EI): 228.12637. $C_{14}H_{16}N_2O$ requires M^+ 228.12626]; *m*/*z* 228 (1%), 200 (2%), 158 (38%), 131 (92%), 104 (42%), 91 (100%).

(b) Reaction with oxalyl chloride generated 3-phenylhex-5-enoyl chloride. Oxalyl chloride (1.61 g, 1.26×10^{-3} mol) in dry ether (10 ml) was added dropwise over 5 min to 3-phenylhex-5-enoic acid **3f** (2.00 g, 1.05×10^{-2} mol) in dry ether (10 ml), while stirring at 0 °C under nitrogen. The solution was allowed to slowly return to room temperature while stirring over 12 h. The solvent and residual reagent were removed under reduced pressure to give the acyl chloride which was used without purification. An ethereal diazoethane solution was prepared from *N*-ethyl-*N*-nitrosourea[17] (24.34 g, 0.208 mol) and cooled to −20 °C using a salt–ice bath. The crude acyl chloride in dry ether (20 ml) was added dropwise over 20 min to the diazoethane solution while stirring under nitrogen. The solution was then allowed to slowly return to room temperature while stirring for 2.5 h. Purification by radial chromatography on silica gel, using ethyl acetate–hexane (2:98) as eluant, gave the *diazoketone* **82** (1.84 g, 76%) as an orange oil with spectral characteristics identical to those described above.

3,3-Diphenylpropanoyl chloride. This was prepared following the procedure described for 3-phenylpentanoyl chloride, from 3,3-diphenylpropanoic acid **3g** (4.41 g, 1.95×10^{-2} mol) and freshly distilled thionyl chloride (25 ml). Distillation gave the *acid chloride* (3.96 g, 83%) as a low melting white solid, bp 135–138 °C at 0.2 mmHg; ν_{max}(KBr)/cm^{-1} 1800, 1603, 1496.

2-Diazo-5,5-diphenylpentan-3-one 1g. *(a) Reaction with distilled 3,3-diphenylpropanoyl chloride.* This was prepared following the procedure described for **1b**, using 3,3-diphenylpropanoyl chloride (2.60 g, 1.06×10^{-2} mol) in ether (20 ml) and freshly distilled ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea[17] (12.40 g, 0.106 mol)]. The diazoketone decomposed rapidly on exposure to silica, however quick passage through a very short column of silica gel, using ethyl acetate as eluant, removed the major impurities and gave the *diazoketone* **1g** (533 mg, 19%) as an orange oil; ν_{max}(film)/cm^{-1} 2075, 1636, 1494; δ_H($CDCl_3$) 1.60 [3H, s, C(1)H_3], 3.07–3.10 [2H, d, *J* 7, C(4)H_2], 4.61–4.68 [1H, t, *J* 7, C(5)*H*], 7.06–7.33 (10H, m, Ar*H*); δ_C($CDCl_3$) 7.67 (CH_3-1), 43.87 (CH_2-4), 46.27 (*C*H-5), 125.85, 127.13, 127.88 (*C*H), 142.91, 143.45 (2 × *C*), 191.87 (*C*=O) [Found (HRMS, EI): 236.12005 ($M^+ - N_2$). $C_{17}H_{16}O$ requires M^+ 236.12012]; *m*/*z* 236 (8%), 209 (12%), 193 (20%), 167 (100%), 132 (93%), 104 (47%).

(b) Reaction with oxalyl chloride generated 3,3-diphenylpropanoyl chloride. This was prepared following procedure (*b*) described for **1f**, using 3,3-diphenylpropanoic acid **3g** (3.50 g, 1.55×10^{-2} mol) in ether (30 ml), oxalyl chloride (2.36 g, 1.86×10^{-2} mol) in dry ether (10 ml) and freshly distilled ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea[17] (18.14 g, 0.155 mol)]. The crude product was passed quickly through a very short column of silica gel, using ethyl acetate as eluant, to gave the *diazoketone* **1g** (0.98 g, 24%) as an orange oil with spectral characteristics identical to those described above.

3-Phenylpropanoyl chloride.[3b] This was prepared following the procedure described for 3-phenylpentanoyl chloride, from 3-phenylpropanoic acid (5.0 g, 3.33×10^{-2} mol) and freshly distilled thionyl chloride (25 ml). Distillation gave the *acid chloride* (4.89 g, 87%) as a colourless oil, bp 106–108 °C at 11 mmHg (lit.,[3b] 43–48 °C at 0.04 mmHg); ν_{max}(film)/cm^{-1} 1804, 1604.

2-Diazo-5-phenylpentan-3-one 1h.[2d] This was prepared following the procedure described for **1b**, using 3-phenylpropanoyl chloride (2.00 g, 1.19×10^{-2} mol) in ether (20 ml) and freshly distilled ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea[17] (11.70 g, 0.10 mol)]. Purification by chromatography on silica gel, using ethyl acetate–hexane (2:98) as eluant, gave the *diazoketone* **1h** (1.96 g, 88%) as an orange oil; ν_{max}(film)/cm^{-1} 2072, 1639; δ_H(60 MHz, $CDCl_3$) 1.9 [3H, s, C(1)H_3], 2.2–2.9 [4H, m, C(4)H_2, C(5)H_2], 7.2–7.3 (5H, m, Ar*H*).

Rhodium(II) acetate catalysed decomposition of α-diazoketones: synthesis of azulenones

***trans*-(3*R**,8a*R**)-3,8a-Dihydro-3-*n*-propyl-8a-methylazulen-1(2*H*)-one 2b.** 2-Diazo-5-phenyloctan-3-one **1b** (75 mg, 3.26×10^{-4} mol) in dichloromethane (100 ml) was added dropwise over 1 h to a refluxing solution of rhodium(II) acetate (0.5 mg) in dichloromethane (150 ml), while stirring under nitrogen. The reaction was monitored by TLC and was complete once the diazoketone had been added. Evaporation of the solvent at reduced pressure gave the crude product as a yellow oil. A ^{1}H NMR spectrum of the crude product was recorded to determine the efficiency of the cyclisation and the diastereomeric ratio of the azulenones formed: *trans*:*cis* = 97:3 (by ^{1}H NMR integration). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave a single diastereomer of the *azulenone* **2b** (49 mg, 74%) as a colourless oil (Found: C, 83.12; H, 8.89. $C_{14}H_{18}O$ requires C, 83.12; H, 8.97%); ν_{max}(film)/cm^{-1} 1748, 1715, 1603; δ_H($CDCl_3$) 0.70 [3H, s, C(8a)CH_3], 0.87–0.92 (3H, t, *J* 7, CH_2CH_3), 1.19–1.37 (3H, m, one of $CH_2CH_2CH_3$ and $CH_2CH_2CH_3$), 1.42–1.56 (1H, m, one of $CH_2CH_2CH_3$), 1.87–1.97 [1H, dd, *J* 18, 9, one of C(2)H_2], 2.47–2.57 [1H, dd, *J* 18, 9, one of C(2)H_2], 2.71–2.83 [1H, m, C(3)*H*], 3.66–3.69 [1H, d, *J* 7, C(8)*H*], 6.01–6.13 [2H, m, C(4)*H* and C(7)*H*], 6.25–6.32 [2H, m, C(5)*H* and C(6)*H*]; δ_C($CDCl_3$) 9.76 (C-8aCH_3), 14.09 (CH_3-3′), 20.69 (CH_2-2′) 37.43 (CH_2-1′), 39.17 (*C*H-3), 40.34 (CH_2-2), 75.46 (*C*H-8), 123.89, 124.78, 125.98, 126.78 (4 × *C*H, *C*H-4–*C*H-7), 218.33 (*C*=O), C-3a and C-8a not detected [Found (HRMS, EI): 202.13868. $C_{14}H_{18}O$ requires M$^+$ 202.13577]; *m/z* 202 (23%), 187 (15%), 132 (100%), 91 (95%).

The minor diastereomer *cis*-(3*R**,8a*S**)-3,8a-dihydro-3-*n*-propyl-8a-methylazulen-1(2*H*)-one could be detected in the ^{1}H NMR spectrum of the crude product mixture at δ_H 4.88–4.91 [d, *J* 9, C(8)H].

***trans*-(3*R**,8a*R**)-3,8a-Dihydro-3-ethyl-8a-methylazulen-1(2*H*)-one 2a.** This was prepared following the procedure described for **2b** from 2-diazo-5-phenylheptan-3-one **1a** (100 mg, 4.63×10^{-4} mol) in dichloromethane (100 ml) and using rhodium(II) acetate (0.5 mg) as catalyst in dichloromethane (100 ml). The diastereomeric ratio was estimated as *trans*:*cis* = 96:4 (by integration of the ^{1}H NMR spectrum of the crude product mixture). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave *azulenone* **2a** (*trans*:*cis* = 96:4) (69 mg, 79%) as a clear oil (the diastereomers can be separated chromatographically) (Found: C, 82.99; H, 8.73. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%); ν_{max}(film)/cm^{-1} 1748, 1715; δ_H($CDCl_3$) 0.71 [3H, s, C(8a)CH_3], 0.89 (3H, t, *J* 8, CH_2CH_3), 1.20–1.39, 1.52–1.68 (2 × 1H, 2 × m, CH_2CH_3), 1.82–1.98 [1H, dd, *J* 18, 8, one of C(2)H_2], 2.48–2.60 [1H, dd, *J* 18, 9, one of C(2)H_2], 2.61–2.75 [1H, m, C(3)*H*], 3.75 [1H, d, *J* 8, C(8)*H*], 6.01–6.12, 6.25–6.31 [2 × 2H, 2 × br m, C(4)*H*, C(5)*H*, C(6)*H*, C(7)*H*]; δ_C($CDCl_3$) 10.20 (C-8aCH_3), 11.72 (CH_2CH_3), 28.01 (CH_2-1′), 40.26 (CH_2-2), 40.93 (*C*H-3), 79.18 (br, *C*H-8), 123.72, 124.86, 126.10, 126.91 (4 × *C*H, *C*H-4–*C*H-7), 218.30 (*C*=O), C-3a and C-8a not detected [Found (HRMS, EI): 188.11954. $C_{13}H_{16}O$ requires M$^+$ 188.12012]; *m/z* 188 (M$^+$,10%), 173 (M$^+$ − CH_3, 5%), 159 (M$^+$ − C_2H_5, 5%), 145 (4%), 131 (M$^+$ − C_2H_5 − CO, 14).

The minor diastereomer *cis*-(3*R**,8a*S**)-3,8a-dihydro-3-ethyl-8a-methylazulen-1(2*H*)-one could be detected in the ^{1}H NMR spectrum of the crude product mixture at δ_H 4.86 [d, *J* 9, C(8)*H*].

***trans*-(3*R**,8a*S**)-3,8a-Dihydro-3-isopropyl-8a-methylazulen-1(2*H*)-one 2c.** This was prepared following the procedure described for **2b**, from 2-diazo-5-phenyl-6-methylheptan-3-one **1c** (98 mg, 4.26×10^{-4} mol) in dichloromethane (100 ml) and using rhodium(II) acetate (0.5 mg) as catalyst in dichloromethane (150 ml). The diastereomeric ratio was estimated as *trans*:*cis* > 98:2 (by integration of the ^{1}H NMR spectrum of the crude product mixture). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave a single diastereomer of the *azulenone* **2c** (64 mg, 74%) as a colourless oil; ν_{max}(film)/cm^{-1} 1746, 1714; δ_H($CDCl_3$) 0.73 [3H, s, C(8a)CH_3], 0.76–0.78 [3H, d, *J* 7, one of CH(CH_3)$_2$], 0.87–0.90 [3H, d, *J* 7, one of CH(CH_3)$_2$], 1.63–1.71 [1H, m, C*H*(CH_3)$_2$], 2.00–2.10 [1H, dd, *J* 18, 9.5, one of C(2)H_2], 2.48–2.58 [1H, dd, *J* 18, 9.5, one of C(2)H_2], 2.67–2.72 [1H, m, C(3)*H*], 3.96–3.99 [1H, d, *J* 8, C(8)*H*], 6.09–6.12 [2H, m, C(4)*H*, C(7)*H*], 6.28–6.30 [2H, m, C(5)*H*, C(6)*H*]; δ_C($CDCl_3$) 11.61 (C-8aCH_3), 18.52 (one of CH_3 of Pr^i), 20.98 (one of CH_3 of Pr^i), 32.42 (*C*H of Pr^i), 38.05 (CH_2-2), 41.40 (*C*-8a), 45.84 (*C*H-3), 87.90 (*C*H-8), 124.24, 124.94, 126.11, 127.38 (4 × *C*H, *C*H-4–*C*H-7), 218.33 (*C*=O), C-3a not detected [Found (HRMS, EI): 202.13616. $C_{14}H_{18}O$ requires M$^+$ 202.13577]; *m/z* 202 (42%), 187 (30%), 132 (100%), 118 (52%), 104 (40%).

The signal for the minor diastereomer *cis*-(3*R**,8a*R**)-3,8a-dihydro-3-isopropyl-8a-methylazulen-1(2*H*)-one which appears at δ_H 4.63–4.66 [d, *J* 9, C(8)*H*] could not be detected in the ^{1}H NMR spectrum of the crude product mixture.

***trans*-(3*R**,8a*R**)-3,8a-Dihydro-3-*n*-butyl-8a-methylazulen-1(2*H*)-one 2d.** This was prepared following the procedure described for **2b**, from 2-diazo-5-phenylnonan-3-one **1d** (160 mg, 6.56×10^{-4} mol) in dichloromethane (150 ml) and using rhodium(II) acetate (0.5 mg) as catalyst in dichloromethane (200 ml). The diastereomeric ratio was estimated as *trans*:*cis* = 98:2 (by integration of the ^{1}H NMR spectrum of the crude product mixture). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave a single diastereomer of the *azulenone* **2d** (99 mg, 70%) as a colourless oil (Found: C, 83.70; H, 9.6. $C_{15}H_{20}O$ requires C, 83.70; H, 9.33%); ν_{max}(film)/cm^{-1} 1748, 1714; δ_H($CDCl_3$) 0.70 [3H, s, C(8a)CH_3], 0.85–0.90 (3H, t, *J* 7, CH_2CH_3), 1.25–1.28 (5H, m, one of $CH_2CH_2CH_2CH_3$ and $CH_2CH_2CH_2CH_3$), 1.52–1.55 (1H, m, one of $CH_2CH_2CH_2CH_3$), 1.87–1.97 [1H, dd, *J* 18, 9, one of C(2)H_2], 2.48–2.58 [1H, dd, *J* 18, 9, one of C(2)H_2], 2.68–2.75 [1H, m, C(3)*H*], 3.68–3.71 [1H, d, *J* 7, C(8)*H*], 6.05–6.11 [2H, m, C(4)*H*, C(7)*H*], 6.27–6.30 [2H, m, C(5)*H*, C(6)*H*]; δ_C($CDCl_3$) 9.58 (C-8aCH_3), 13.85 (CH_3-4′), 22.43 (CH_2-3′), 29.66 (CH_2-2′), 34.77 (CH_2-1′), 36.77 (*C*-8a), 39.30 (*C*H-3), 40.35 (CH_2-2), 74.71 (*C*H-8), 91.80 (*C*-3a), 123.85, 124.69, 125.87, 127.08 (4 × *C*H, *C*H-4–*C*H-7), 218.26 (*C*=O) [Found (HRMS, EI): 216.15036. $C_{15}H_{20}O$ requires M$^+$ 216.15142]; *m/z* 216 (95%), 199 (25%), 174 (40%), 159 (100%).

The minor diastereomer *cis*-(3*R**,8a*S**)-3,8a-dihydro-3-*n*-butyl-8a-methylazulen-1(2*H*)-one could be detected in the ^{1}H NMR spectrum of the crude product mixture at δ_H 4.87–4.91 [d, *J* 10, C(8)H].

***trans*-(3*R**,8a*S**)-3,8a-Dihydro-3-*tert*-butyl-8a-methylazulen-1(2*H*)-one 2e.** This was prepared following the procedure described for **2b**, from 2-diazo-5-phenyl-6,6-dimethylheptan-3-one **1e** (100 mg, 4.10×10^{-4} mol) in dichloromethane (100 ml) and using rhodium(II) acetate (0.5 mg) as catalyst in dichloromethane (150 ml). The diastereomeric ratio was estimated as *trans*:*cis* > 98:2 (by integration of the ^{1}H NMR spectrum of the crude product mixture). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave a single diastereomer of the *azulenone* **2e** (64 mg, 72%) as a colourless oil (Found: C, 83.27; H, 9.51. $C_{15}H_{20}O$ requires C, 83.27; H, 9.33%); ν_{max}(film)/cm^{-1} 1747, 1714; δ_H($CDCl_3$) 0.72 [3H, s, C(8a)CH_3], 0.83 (9H, s, 3 × CH_3 of Bu^t), 2.20–2.29 [1H, dd, *J* 17, 6, one of C(2)H_2], 2.52–2.62 [1H, dd, *J* 17, 9.5, one of C(2)H_2], 2.66–2.72 [1H, dd, *J* 9.5, 6, C(3)*H*], 4.11–4.14 [1H, d, *J* 8, C(8)*H*], 6.07–6.36 [4H, m, C(4)*H*, C(5)*H*, C(6)*H*, C(7)*H*]; δ_C($CDCl_3$) 11.03 (*C*H_3, C-8aCH_3), 27.72 (3 × *C*H_3 of Bu^t), 33.83 (*C* of Bu^t), 37.70 (*C*H_2-2) 38.63 (*C*-8a), 49.98 (*C*H-3), 84.02 (*C*H-8), 96.39 (*C*-3a), 124.39, 125.47, 126.02, 127.53 (4 × *C*H, *C*H-4–*C*H-7), 218.56 (*C*=O) [Found (HRMS, EI): 216.15241. $C_{15}H_{20}O$ requires M$^+$ 216.15142]; *m*/*z* 216 (20%), 160 (42%), 145 (30%), 132 (38%).

The signal for the minor diastereomer *cis*-(3*R**,8a*S**)-3,8a-dihydro-3-*tert*-butyl-8a-methylazulen-1(2*H*)-one which appears at δ_H 5.06–5.09 [d, *J* 10, C(8)*H*] could not be detected in the ^{1}H NMR spectrum of the crude product mixture.

***trans*-(3*R**,8a*R**)-3,8a-Dihydro-3-allyl-8a-methylazulen-1(2*H*)-one 2f and *trans*-(1*R**,4*S**)-1-methyl-4-phenylbicyclo-[4.1.0]heptan-2-one 5.** These were prepared following the procedure described for **2b**, from 2-diazo-5-phenyloctan-7-en-3-one **1f** (110 mg, 4.83 × 10^{-4} mol) in dichloromethane (100 ml) and using rhodium(II) acetate (0.5 mg) as catalyst in dichloromethane (150 ml). The product ratio **2f**:**5** was estimated as 1:1.1 (by integration of the ^{1}H NMR spectrum of the crude product mixture). The diastereomeric ratio of **2f** was estimated as *trans*:*cis* > 98:2 (by integration of the ^{1}H NMR spectrum of the crude product mixture). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave *trans*-(1*R**,4*S**)-methyl-4-phenylbicyclo[4.1.0]heptan-2-one **5** (43 mg, 44%) as a white solid, with spectral characteristics as described below, and *trans*-(3*R**,8a*R**)-3,8a-dihydro-3-allyl-8a-methylazulen-1(2*H*)-one **2f** (44 mg, 46%) as a colourless oil.

Spectral characteristics of **2f** (Found: C, 83.86; H, 7.99. $C_{14}H_{18}O$ requires C, 83.94; H, 8.05%); ν_{max}(film)/cm^{-1} 1748, 1717; δ_H($CDCl_3$) 0.72 [3H, s, C(8a)CH_3], 1.94–2.04 [1H, dd, *J* 18, 9, one of C(2)H_2], 2.03–2.07 (1H, m, one of CH_2CH=CH$_2$), 2.23–2.40 (1H, m, one of CH_2CH=CH$_2$), 2.47–2.57 [1H, dd, *J* 18, 9, one of C(2)H_2], 2.81–2.83 [1H, m, C(3)*H*], 3.81–3.83 [1H, d, *J* 7, C(8)*H*], 4.99–5.06 (2H, m, CH=CH_2), 5.64–5.76 (1H, m, C*H*=CH$_2$), 6.05–6.14 [2H, m, C(4)*H*, C(7)*H*], 6.27–6.32 [2H, m, C(5)*H*, C(6)*H*]; δ_C($CDCl_3$) 10.29 (C-8a*C*H$_3$), 38.30 (*C*-8a), 38.96 (*C*H-3), 39.37, 40.08 (*C*H$_2$-1′, *C*H$_2$-2), 79.45 (*C*H-8), 116.96 (*C*H$_2$-3′), 123.58, 124.90, 126.26, 127.27 (4 × *C*H, *C*H-4–*C*H-7), 135.50 (*C*H-2′), 218.26 (*C*=O), C-3a not detected [Found (HRMS, EI): 200.11995. $C_{14}H_{16}O$ requires M$^+$ 200.12012]; *m*/*z* 200 (30%), 104 (72%), 96 (100%), 68 (90%).

Spectral characteristics of **5** (Found: C, 83.51; H, 8.35. $C_{14}H_{18}O$ requires C, 83.96; H, 8.05%); ν_{max}(KBr)/cm^{-1} 1688, 1467, 1392; δ_H($CDCl_3$) 1.14–1.17 [2H, d, *J* 7, C(7)H_2], 1.28 [3H, s, C(1)CH_3], 1.62–1.83 [2H, m, C(6)*H* and one of C(5)H_2], 2.34–2.52 [3H, m, C(3)H_2 and one of C(5)H_2], 3.02–3.15 [1H, m, C(4)*H*], 7.14–7.34 (5H, m, Ar*H*); δ_C($CDCl_3$) 19.45 (C-1*C*H$_3$), 27.25 (*C*H$_2$-7), 27.99 (*C*H-6), 28.95 (*C*-1), 33.19, 43.58 (*C*H$_2$-3, *C*H$_2$-5), 45.25 (*C*H-4), 126.54, 128.29, 128.64 (3 × *C*H), 143.64 (*C*), 210.39 (*C*=O) [Found (HRMS, EI): 200.12022. $C_{14}H_{16}O$ requires M$^+$ 200.12012]; *m*/*z* 200 (40%), 128 (31%), 104 (95%), 96 (97%), 68 (100%).

The signal for the minor diastereomer *cis*-(3R*,8aS*)-3,8a-dihydro-3-allyl-8a-methylazulen-1(2*H*)-one which appears at δ_H 4.78–4.82 [d, *J* 9, C(8)*H*] could not be detected in the ^{1}H NMR spectrum of the crude product mixture. No evidence for formation of a second diastereomer of the cyclopropanation product **5** was observed in the ^{1}H NMR spectra of the crude or purified products.

***trans*-(3*R**,8a*S**)-3,8a-Dihydro-3-phenyl-8a-methylazulen-1(2*H*)-one 2g.** This was prepared following the procedure described for **2b**, from 2-diazo-5,5-diphenylpentan-3-one **1g** (103 mg, 3.90 × 10^{-4} mol) in dichloromethane (100 ml) and using rhodium(II) acetate (0.5 mg) as catalyst in dichloromethane (100 ml). Purification by preparative thin layer chromatography, using ethyl acetate–hexane (25:75) as eluant, gave a single diastereomer of the *azulenone* **2g** (31 mg, 33%) as a colourless oil; ν_{max}(film)/cm^{-1} 1745, 1712; δ_H($CDCl_3$) 0.85 [3H, s, C(8a)CH_3], 2.33–2.43 [1H, dd, *J* 18, 10, one of C(2)H_2], 2.81–2.91 [1H, dd, *J* 18, 9, one of C(2)H_2], 4.06–4.08 [1H, d, *J* 8, C(8)*H*], 4.06–4.13 [1H, m, C(3)*H*], 5.97–5.99 [1H, d, *J* 7, C(4)*H*], 6.13–6.19 [1H, overlapping dd appears as t, *J* 8, 8, C(7)H], 6.25–6.37 [2H, m, C(5)*H*, C(6)*H*], 7.12–7.41 (5H, m, Ar*H*); δ_C($CDCl_3$) 10.78 (C-8a*C*H$_3$), 39.24 (*C*-8a), 43.86 (*C*H$_2$-2), 44.90 (*C*H-3), 84.07 (*C*H-8), 101.68 (*C*-3a), 124.68 (*C*H), 125.25 (*C*H), 126.63 (*C*H), 126.81 (*C*H), 127.17 (*C*H), 127.75 (*C*H), 128.70 (*C*H), 142.32 (*C*), 217.46 (*C*=O) [Found (HRMS, EI): 236.12031. $C_{17}H_{16}O$ requires M$^+$ 236.12012]; *m*/*z* 236 (5%), 165 (30%), 103 (15%), 73 (75%).

The minor diastereomer *cis*-(3*R**,8a*R**)-3,8a-dihydro-3-phenyl-8a-methylazulen-1(2*H*)-one could not be identified in the ^{1}H NMR spectrum of the crude product mixture.

3,8a-Dihydro-8a-methylazulen-1(2*H*)-one 2h.[2d] This was prepared following the procedure described for **2b**, from 2-diazo-5-phenylpentan-3-one **1h** (150 mg, 7.97 × 10^{-4} mol) in dichloromethane (100 ml) and using rhodium(II) acetate (0.5 mg) as catalyst in dichloromethane (150 ml). Purification by preparative thin layer chromatography, using ethyl acetate–hexane as eluant, gave the *azulenone* **2h** (75 mg, 59%) as a colourless oil; ν_{max}(film)/cm^{-1} 1743, 1710; δ_H($CDCl_3$) 0.89 [3H, s, C(8a)CH_3], 2.08–3.05 [4H, m, C(2)H_2C(3)H_2], 4.30–4.33 [1H, d, *J* 8, C(8)*H*], 6.00–6.25 [4H, m, C(4)*H*–C(7)*H*].

Trapping of the NCD tautomer of azulenones *via* cycloaddition with PTAD

The numbering scheme used for the cycloadducts **4** is shown in Fig. 4. The substituents on the side chain, R, are numbered 1′, 2′, 3′, *etc.*

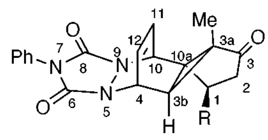


Fig. 4

(1*R,3a*R**,3b*S**)-1,2,3b,4-Tetrahydro-1-*n*-propyl-3a-methyl-7-phenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa-[1,2-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4b.** *Method A: Cycloaddition with PTAD.* 4-Phenyl-1,2,4-triazoline-3,5-dione (50 mg, 2.86 × 10^{-4} mol) in dichloromethane (10 ml) was added dropwise over 5 min to *trans*-(3*R**,8a*R**)-3,8a-dihydro-3-*n*-propyl-8a-methylazulen-1(2*H*)-one **2b** (55 mg, 2.72 × 10^{-4} mol) in dichloromethane (10 ml), while stirring at 0 °C, under nitrogen. Immediate decolorisation of the brick-red dienophile was observed on mixing with the azulenone. Once all of the dienophile had been added, the ice-bath was removed and stirring was continued for 10 min. Evaporation of solvent at reduced pressure gave the adduct as an off-white solid. Passage through a short column of silica gel, with dichloromethane as eluant, gave the adduct **4b** (100 mg, 98%) as a white solid. Recrystallisation from hot ethanol gave a white crystalline solid, mp 169–171 °C (Found: C, 69.62; H, 6.34; N, 10.98. $C_{22}H_{23}N_3O_3$ requires C, 70.01; H, 6.14; N, 11.13%); ν_{max}(KBr)/cm^{-1} 1787 (w), 1720, 1498, 1412; δ_H($CDCl_3$) 0.93–0.99 (3H, t, *J* 7, CH$_2$CH_3), 1.21–1.43 (3H, m, CH$_2$CH_2CH$_3$ and one of CH_2CH$_2$CH$_3$), 1.26 [3H, s, C(3a)CH_3], 1.73–1.90 [1H, dd, *J* 18, 9, one of C(2)H_2], 1.90–1.92 [1H, d, *J* 5, C(3b)*H*], 2.03–2.13 (1H, m, one of CH_2CH$_2$CH$_3$), 2.33–2.43 [1H, dd, *J* 18, 8, one of C(2)H_2], 2.63–2.73 [1H, m, C(1)*H*], 5.30–5.38 [2H, m, C(4)*H*, C(10)*H*], 6.27–6.42 [2H, m, C(11)*H*, C(12)*H*], 7.33–7.47 (5H, m, Ar*H*); δ_C(CDCl$_3$) 11.71, 14.11 (C-3a*C*H$_3$, *C*H$_3$-3′), 21.13 (*C*H$_2$-2′), 24.32 (*C*H-3b), 33.31 (*C*H$_2$-1′), 38.00 (*C*H-1), 39.10 (*C*H$_2$-2), 39.43, 41.06 (*C*-3a, *C*-10a), 53.88, 56.41 (*C*H-4, *C*H-10), 125.37 (2 × Ar*C*H), 128.30, 128.40 (2 signals for 3 carbons: Ar*C*H, *C*H-11, *C*H-12), 129.04 (2 × Ar*C*H), 131.22 (*C*), 156.43, 157.09, 211.31 (3 × *C*=O) [Found (HRMS, EI): 377.17471. $C_{22}H_{23}N_3O_3$ requires M$^+$ 377.17394]; *m*/*z* 202 (34%), 187 (21%), 131 (100%), 104 (50%).

Method B: Cycloaddition with in situ *generated PTAD.* Lead tetraacetate (241 mg, 5.45×10^{-4} mol) in dichloromethane (10 ml) was added dropwise over 5 min to a solution of *trans*-(3*R**,-8a*R**)-3,8a-dihydro-3-*n*-propyl-8a-methylazulen-1(2*H*)-one **2b** (100 mg, 4.95×10^{-4} mol) and phenylurazole (96 mg, 5.45×10^{-4} mol), in dichloromethane (10 ml), while stirring at 0 °C, under nitrogen. The brick-red colour of the dienophile PTAD was observed only fleetingly as the cycloaddition reaction occurred rapidly upon generation of the dienophile. After completion of addition of the lead tetraacetate, the ice-bath was removed and after stirring for 10 min at room temperature, the reaction was complete, based on monitoring by TLC. Purification by chromatography on silica gel, using dichloromethane as eluant, gave the *adduct* **4b** (138 mg, 74%) as a white solid, with spectral characteristics identical to those described above.

Method C: Tandem synthesis of PTAD adduct. 2-Diazo-5-phenyloctan-3-one **1b** (39 mg, 1.70×10^{-4} mol) in dichloromethane (50 ml) was added dropwise over 30 min to a refluxing solution of rhodium(II) acetate (0.5 mg) in dichloromethane (50 ml), while stirring under nitrogen. The reaction was monitored by TLC and was complete once all of the diazoketone had been added. The reaction mixture was then cooled to 0 °C, and 4-phenyl-1,2,4-triazoline-3,5-dione (33 mg, 1.87×10^{-4} mol) in dichloromethane (10 ml) was added dropwise over 5 min. The ice-bath was removed after addition of the dienophile and, after stirring for 10 min at room temperature, the reaction was complete, based on reaction monitoring by TLC. Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave the *adduct* **4b** (45 mg, 70%) as a white solid, with spectral characteristics identical to those described above.

(1*R,3a*R**,3b*S**)-1,2,3b,4-Tetrahydro-1-ethyl-3a-methyl-7-phenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa[1,2-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4a.** *Method A: Cycloaddition with PTAD.* This was prepared following the procedure (Method A) described for **4b**, from 4-phenyl-1,2,4-triazoline-3,5-dione (51 mg, 2.9×10^{-4} mol) in dichloromethane (10 ml), and (3*R**,8a*R**)-3,8a-dihydro-3-ethyl-8a-methylazulen-1(2*H*)one **2a** (55 mg, 2.9×10^{-4} mol, *trans* : *cis* = 96 : 4) in dichloromethane (10 ml). Passage through a short column of silica gel, with dichloromethane as eluant, gave the *adduct* **4a** (102 mg, 96%) as a single diastereomer as a white solid. Recrystallisation from hot ethanol gave the *adduct* **4a** as a white crystalline solid (101 mg, 95%); mp 179–81 °C (Found C, 69.30; H, 5.65; N, 11.65. $C_{21}H_{21}N_3O_3$ requires C, 69.41; H, 5.82; N, 11.56%); ν_{max}(KBr)/cm^{-1} 1770 (w), 1714; δ_H(CDCl$_3$) 0.94 (3H, t, *J* 8, CH$_2$C*H*$_3$), 1.25 [3H, s, C(3a)C*H*$_3$], 1.28–1.48 (1H, m, one of C*H*$_2$CH$_3$), 1.77–1.94 [2H, contains dd, *J* 18, 9, one of C(2)*H*$_2$, and d at 1.91, *J* 4, C(3b)*H*], 2.08–2.24 (1H, m, one of C*H*$_2$CH$_3$), 2.30–2.45 [1H, dd, *J* 18, 9, one of C(2)*H*$_2$], 2.54–2.69 [1H, m, C(1)*H*], 5.29–5.41 [2H, m, C(4)*H* and C(10)*H*], 6.26–6.34, 6.36–6.44 [2 × 1H, 2 × m, C(11)*H*, C(12)*H*], 7.32–7.50 (5H, m, ArH); δ_C(CDCl$_3$) 11.58, 12.18 (C-3a*C*H$_3$, *C*H$_3$-2′), 24.25 (*C*H-3b, *C*H$_2$-1′), 38.92 (*C*H$_2$-2), 39.36 (one of C-3a, C-10a), 39.81 (CH-1), 41.13 (one of C-3a, C-10a), 53.80, 56.33 (*C*H-4, *C*H-10), 125.30 (2 × Ar*C*H), 127.92, 128.30, 128.36 (Ar*C*H, *C*H-11, *C*H-12), 128.58 (2 × Ar*C*H), 131.18 (Ar*C*), 156.30, 156.94, 211.10 (3 × *C*=O) [Found (HRMS, EI): 363.15861. $C_{21}H_{21}N_3O_3$ requires M$^+$ 363.15829]; *m*/*z* 363 (M$^+$, 3%), 188 (M$^+$ − PTAD, 20%), 159 (M$^+$ − PTAD − C_2H_5, 12%), 145 (23%), 131 (M$^+$ − PTAD − C_2H_5 − CO, 100%), 115 (37%).

Method C: Tandem synthesis of PTAD adduct. This was prepared following the procedure (Method C) described for **4b**, using 2-diazo-5-phenylheptan-3-one **1a** (63 mg, 2.9×10^{-4} mol) in dichloromethane (100 ml), rhodium(II) acetate (0.5 mg) in dichloromethane (100 ml), and 4-phenyl-1,2,4-triazoline-3,5-dione (51 mg, 2.9×10^{-4} mol) in dichloromethane (10 ml). Purification by recrystallisation from ethanol gave the *adduct* **4a** as a white solid (72mg, 68%) with spectral characteristics identical to those described above.

(1*R,3a*S**,3b*R**)-1,2,3b,4-Tetrahydro-1-isopropyl-3a-methyl-7-phenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa[1,2-*d*]-[1,2,4]triazolo[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4c.** *Method A: Cycloaddition with PTAD.* This was prepared following the procedure (Method A) described for **4b**, using 4-phenyl-1,2,4-triazoline-3,5-dione (49 mg, 2.81×10^{-4} mol) in dichloromethane (10 ml), and *trans*-(3*R**,8a*S**)-3,8a-dihydro-3-isopropyl-8a-methylazulen-1(2*H*)-one **2c** (54 mg, 2.67×10^{-4} mol) in dichloromethane (10 ml), with stirring for 20 min. Passage through a short column of silica gel with dichloromethane as eluant gave the *adduct* **4c** (99 mg, 98%) as a white solid. Recrystallisation from hot ethanol gave a white crystalline solid, mp 151–153 °C (Found: C, 69.80; H, 6.31; N, 10.87. $C_{22}H_{23}N_3O_3$ requires C, 70.01; H, 6.14; N, 11.13%); ν_{max}(KBr)/cm^{-1} 1774 (w), 1715, 1496, 1408; δ_H(CDCl$_3$) 0.95–1.00 [2 × 3H, 2 × d (appears as t), *J* 6, 6, CH(C*H*$_3$)$_2$], 1.25 [3H, s, C(3a)C*H*$_3$], 2.07–2.09 [1H, d, *J* 4, C(3b)*H*], 2.11–2.15 [2H, m, C(2)*H*$_2$], 2.48–2.54 [1H, m, C*H*(CH$_3$)$_2$], 2.67–2.74 [1H, m, C(1)*H*], 5.32–5.40 [2H, m, C(4)*H*, C(10)*H*], 6.28–6.42 [2H, m, C(11)*H*, C(12)*H*], 7.33–7.46 (5H, m, Ar*H*); δ_C(CDCl$_3$) 11.36, 16.24, 22.85 (C-3a*C*H$_3$, 2 × *C*H$_3$ of Pr^i), 24.73, 27.62, (*C*H-1′, *C*H-3b), 32.65 (*C*H$_2$-2), 38.86, 39.71 (*C*-3a, *C*-10a), 44.07 (*C*H-1), 54.06, 56.28 (*C*H-4, *C*H-10), 125.17 (2 × Ar*C*H), 128.19, 128.56 (Ar*C*H, *C*H-11, *C*H-12), 128.76 (2 × Ar*C*H), 131.70 (*C*), 156.65, 157.13, 210.63 (3 × *C*=O) [Found (HRMS, EI): 377.17324. $C_{22}H_{23}N_3O_3$ requires M$^+$ 377.17394]; *m*/*z* 377 (2%), 202 (83%), 187 (55%), 132 (100%), 91 (79%).

Method B: Cycloaddition with in situ *generated PTAD.* This was prepared following the procedure (Method B) described for **4b**, using lead tetraacetate (69 mg, 1.56×10^{-4} mol) in dichloromethane (5 ml), *trans*-(3*R**,8a*S**)-3,8a-dihydro-3-isopropyl-8a-methylazulen-1(2*H*)-one **2c** (30 mg, 1.49×10^{-4} mol) and phenylurazole (28 mg, 1.56×10^{-4} mol) in dichloromethane (5 ml), with stirring at room temperature for 20 min. Purification by preparative thin layer chromatography on silica gel, using ethyl acetate–hexane (3 : 7) as eluant, gave the *adduct* **4c** (44 mg, 78%) as a white solid, with spectral characteristics identical to those described above.

Method C: Tandem synthesis of PTAD adduct. This was prepared following the procedure (Method C) described for **4b**, using 2-diazo-5-phenyl-6-methylheptan-3-one **1c** (73 mg, 3.17×10^{-4} mol) in dichloromethane (100 ml), rhodium(II) acetate (0.5 mg) in dichloromethane (100 ml), and 4-phenyl-1,2,4-triazoline-3,5-dione (58 mg, 3.33×10^{-4} mol) in dichloromethane (10 ml), with stirring at room temperature for 20 min. Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave the *adduct* **4c** (88 mg, 74%) as a white solid, with spectral characteristics identical to those described above.

(1*R,3a*R**,3b*S**)-1,2,3b,4-Tetrahydro-1-*n*-butyl-3a-methyl-7-phenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa[1,2-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4d.** *Method A: Cycloaddition with PTAD.* This was prepared following the procedure (Method A) described for **4b**, from 4-phenyl-1,2,4-triazoline-3,5-dione (62 mg, 3.55×10^{-4} mol) in dichloromethane (10 ml), and *trans*-(3*R**,8a*R**)-3,8a-dihydro-

3-*n*-butyl-8a-methylazulen-1(2*H*)-one **2d** (73 mg, 3.38×10^{-4} mol) in dichloromethane (10 ml). Passage through a short column of silica gel, with dichloromethane as eluant, gave the *adduct* **4d** (129 mg, 98%) as a white solid. Recrystallisation from hot ethanol gave a white crystalline solid; mp 174–176 °C (Found: C, 70.43; H, 6.42; N, 11.12. $C_{23}H_{25}N_3O_3$ requires C, 70.57; H, 6.44; N, 10.73%); ν_{max}(KBr)/cm^{-1} 1787 (w), 1721, 1497, 1412; δ_H($CDCl_3$) 0.89–0.94 (3H, t, *J* 7, CH_2CH_3), 1.26–1.38 (5H, m, $CH_2CH_2CH_2CH_3$ and one of $CH_2CH_2CH_2CH_3$), 1.27 [3H, s, C(3a)CH_3], 1.81–1.91 [1H, dd, *J* 18, 10, one of C(2)H_2], 1.90–1.91 [1H, d, *J* 4, C(3b)*H*], 2.08–2.11 (1H, m, one of $CH_2CH_2CH_2CH_3$), 2.33–2.43 [1H, dd, *J* 18, 8, one of C(2)H_2], 2.64–2.73 [1H, m, C(1)*H*], 5.30–5.38 [2H, m, C(4)*H*, C(10)*H*], 6.27–6.41 [2H, m, C(11)*H*, C(12)*H*], 7.35–7.46 (5H, m, Ar*H*); δ_C($CDCl_3$) 11.79, 14.12 (C-3aCH_3, CH_3-4′), 22.96 (CH_2-3′), 24.41 (*C*H-3b), 30.24 (CH_2-2′), 30.99 (CH_2-1′), 38.30 (*C*H-1), 39.28 (CH_2-2), 39.53, 41.16 (*C*-3a, *C*-10a), 53.96, 56.47 (*C*H-4, *C*H-10), 125.27 (2 × Ar*C*H), 128.24, 128.48, 128.75 (Ar*C*H, *C*H-11, *C*H-12), 129.12 (2 × Ar*C*H), 131.30 (*C*), 156.48, 157.16, 211.39 (3 × *C*=O) [Found (HRMS, EI): 391.18653. $C_{23}H_{25}N_3O_3$ requires M^+ 391.18959]; *m*/*z* 392 (2%), 216 (24%), 201 (18%), 132 (100%), 119 (93%), 91 (95%).

Method B: Cycloaddition with in situ *generated PTAD.* This was prepared following the procedure (Method B) described for **4b**, using lead tetraacetate (819 mg, 1.85×10^{-3} mol) in dichloromethane (20 ml), *trans*-(3*R**,8a*R**)-3,8a-dihydro-3-*n*-butyl-8a-methylazulen-1(2*H*)-one **2d** (380 mg, 1.76×10^{-3} mol) and phenylurazole (327 mg, 1.85×10^{-3} mol) in dichloromethane (20 ml). Purification by chromatography on silica gel, using dichloromethane as eluant, gave the *adduct* **4d** (544 mg, 79%) as a white solid, with spectral characteristics identical to those described above.

Method C: Tandem synthesis of PTAD adduct. This was prepared following the procedure (Method C) described for **4b**, using 2-diazo-5-phenylnonan-3-one **1b** (111 mg, 4.55×10^{-4} mol) in dichloromethane (100 ml), rhodium(II) acetate (0.5 mg) in dichloromethane (100 ml), and 4-phenyl-1,2,4-triazoline-3,5-dione (84 mg, 4.78×10^{-4} mol) in dichloromethane (10 ml). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave the *adduct* **4d** (126 mg, 71%) as a white solid, with spectral characteristics identical to those described above.

(1*R,3a*S**,3b*R**)-1,2,3b,4-Tetrahydro-1-*tert*-butyl-3a-methyl-7-phenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa[1,2-*d*]-[1,2,4]triazolo[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4e.** *Method A: Cycloaddition with PTAD.* This was prepared following the procedure (Method A) described for **4b**, using 4-phenyl-1,2,4-triazoline-3,5-dione (127 mg, 7.23×10^{-4} mol) in dichloromethane (20 ml), and *trans*-(3*R**,8a*S**)-3,8a-dihydro-3-*tert*-butyl-8a-methylazulen-1(2*H*)-one **2e** (150 mg, 6.94×10^{-4} mol) in dichloromethane (20 ml), with stirring at room temperature for 30 min. Passage through a short column of silica gel, with dichloromethane as eluant, gave the *adduct* **4e** (263 mg, 97%) as a white solid. Recrystallisation from hot ethanol gave a white crystalline solid, mp 144–146 °C (Found: C, 70.37; H, 6.39; N, 10.70. $C_{23}H_{25}N_3O_3$ requires C, 70.57; H, 6.44; N, 10.73%); ν_{max}(KBr)/cm^{-1} 1771 (w), 1714, 1496, 1405; δ_H($CDCl_3$) 1.12 (9H, s, 3 × CH_3), 1.27 [3H, s, C(3a)CH_3], 2.06–2.16 [1H, dd, *J* 18, 11, one of C(2)H_2], 2.16–2.17 [1H, d, *J* 5, C(3b)*H*], 2.20–2.30 [1H, dd, *J* 18, 8, one of C(2)H_2], 2.53–2.60 [1H, dd, *J* 11, 8, C(1)*H*], 5.34–5.38 [2H, m, C(4)*H*, C(10)*H*], 6.25–6.30 [1H, overlapping dd, *J* 6, 6, C(11)*H*], 6.37–6.42 [1H, ddd, *J* 6, 6, 2, C(12)*H*], 7.34–7.50 (5H, m, Ar*H*); δ_C($CDCl_3$) 13.04 (C-3aCH_3), 25.65 (*C*H-3b), 25.80 (3 × CH_3 of Bu^t), 34.16 (*C* of Bu^t), 36.76 (CH_2-2), 39.26, 40.32 (*C*-3a, *C*-10a), 49.12 (*C*H-1), 54.02, 56.71 (*C*H-4, *C*H-10), 125.29, 129.08 (4 × Ar*C*H), 128.53, 129.45 (2 signals for 3 carbons: Ar*C*H, C-11, C-12), 131.25 (*C*), 156.61, 157.54, 210.97 (3 × *C*=O) [Found (HRMS, EI): 391.18691. $C_{23}H_{25}N_3O_3$ requires M^+ 391.18959]; *m*/*z* 391 (2%), 216 (30%), 160 (75%), 119 (100%), 91 (73%).

Method B: Cycloaddition with in situ *generated PTAD.* This was prepared following the procedure (Method B) described for **4b**, using lead tetraacetate (215 mg, 4.86×10^{-4} mol) in dichloromethane (10 ml), *trans*-(3*R**,8a*S**)-3,8a-dihydro-3-*tert*-butyl-8a-methylazulen-1(2*H*)-one **2e** (100 mg, 4.63×10^{-4} mol) and phenylurazole (86 mg, 4.86×10^{-4} mol) in dichloromethane (10 ml). Purification by preparative thin layer chromatography on silica gel, using ethyl acetate–hexane (3:7) as eluant, gave the *adduct* **4e** (132 mg, 73%) as a white solid, with spectral characteristics identical to those described above.

Method C: Tandem synthesis of PTAD adduct. This was prepared following the procedure (Method C) described for **4b**, using 2-diazo-5-phenyl-6,6-dimethylheptan-3-one **1b** (50 mg, 2.05×10^{-4} mol) in dichloromethane (50 ml), rhodium(II) acetate (0.5 mg) in dichloromethane (50 ml), and 4-phenyl-1,2,4-triazoline-3,5-dione (39 mg, 2.25×10^{-4} mol) in dichloromethane (10 ml). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave the *adduct* **4e** (60 mg, 75%) as a white solid, with spectral characteristics identical to those described above.

(1*R,3a*R**,3b*S**)-1,2,3b,4-Tetrahydro-1-allyl-3a-methyl-7-phenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa-[1,2-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4f.** *Method A: Cycloaddition with PTAD.* This was prepared following the procedure (Method A) described for **4b**, using 4-phenyl-1,2,4-triazoline-3,5-dione (54 mg, 3.10×10^{-4} mol) in dichloromethane (10 ml), and *trans*-(3*R**,8a*R**)-3,8a-dihydro-3-allyl-8a-methylazulen-1(2*H*)-one **2f** (59 mg, 2.95×10^{-4} mol) in dichloromethane (15 ml). Passage through a short column of silica gel, with dichloromethane as eluant, gave the *adduct* **4f** (108 mg, 98%) as a white solid. Recrystallisation from ether–hexane gave a white crystalline solid, mp 158–161 °C (Found: C, 69.82; H, 5.61; N, 11.21. $C_{22}H_{21}N_3O_3$ requires C, 70.28; H, 5.64; N, 11.19%); ν_{max}(KBr)/cm^{-1} 1773 (w), 1718, 1496, 1406; δ_H($CDCl_3$) 1.27 [3H, s, C(3a)CH_3], 1.88–1.98 [1H, dd, *J* 18, 10, one of C(2)H_2], 1.92–1.93 [1H, d, *J* 5, C(3b)*H*], 2.14–2.25 (1H, m, one of CH_2CH=CH_2), 2.28–2.38 [1H, dd, *J* 18, 8, one of C(2)H_2], 2.73–2.89 [2H, m, C(1)*H* and one of CH_2CH=CH_2], 5.05–5.14 [2H, m, C(4)*H*, C(10)H], 5.33–5.40 (2H, m, CH=CH_2), 5.73–5.89 (1H, m, C*H*=CH_2), 6.29–6.43 [2H, m, C(11)*H*, C(12)*H*], 7.34–7.49 (5H, m, Ar*H*); δ_C($CDCl_3$) 11.50 (C-3aCH_3), 24.10 (*C*H-3b), 35.40, 36.71 (CH_2-2, CH_2-1′), 38.70, 38.88 (*C*-10a, *C*-3a), 41.01 (*C*H-1), 53.51, 56.31 (*C*H-4, CH-10), 117.00 (CH_2-3′), 125.00 (2 × Ar*C*H), 127.35, 128.25 (Ar*C*H, *C*H-11, *C*H-12), 128.42 (2 × Ar*C*H), 131.16 (*C*), 135.56 (*C*H-2′), 156.41, 157.00, 210.71 (3 × *C*=O).

Method B: Cycloaddition with in situ *generated PTAD.* This was prepared following the procedure (Method B) described for **4b**, using lead tetraacetate (349 mg, 7.88×10^{-4} mol) in dichloromethane (10 ml), *trans*-(3*R**,8a*R**)-3,8a-dihydro-3-allyl-8a-methylazulen-1(2*H*)-one **2f** (150 mg, 7.50×10^{-4} mol) and phenylurazole (139 mg, 7.88×10^{-4} mol) in dichloromethane (10 ml). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave the *adduct* **4f** (222 mg, 79%) as a white solid, with spectral characteristics identical to those described above.

(1*R,3a*S**,3b*R**)-1,2,3b,4-Tetrahydro-3a-methyl-1,7-diphenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa-[1,2-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4g.** *Method A: Cycloaddition with PTAD.* This was prepared following the procedure (Method A) described for **4b**, using 4-phenyl-1,2,4-triazoline-3,5-dione (54 mg, 3.10×10^{-4} mol) in dichloromethane (10 ml), and *trans*-(3*R**,8a*S**)-3,8a-dihydro-3-phenyl-8a-methylazulen-1(2*H*)-one **2g** (70 mg, 2.95×10^{-4}

mol) in dichloromethane (15 ml), with stirring for 20 min. Passage through a short column of silica gel, with dichloromethane as eluant, gave the *adduct* **4g** (119 mg, 98%) as a white solid. Recrystallisation from ether–hexane gave a white crystalline solid, mp 158–160 °C (decomp.) (Found: C, 73.16; H, 5.50; N, 9.98. $C_{25}H_{21}N_3O_3$ requires C, 72.98; H, 5.14; N, 10.21%); ν_{max}(KBr)/cm^{-1} 1787 (w), 1720, 1498, 1412; δ_H($CDCl_3$) 1.32 [3H, s, C(3a)CH_3], 2.31–2.33 [1H, d, *J* 5, C(3b)*H*], 2.52–2.62 [1H, dd, *J* 17, 10, one of C(2)H_2], 2.62–2.69 [1H, dd, appears as t, *J* 17, 10, one of C(2)H_2], 3.79–3.86 [1H, dd, appears as t, *J* 10, 10, C(1)*H*], 5.24–5.27 (1H, dd, *J* 5, 2) and 5.33–5.37 (1H, m) [C(4)*H*, C(10)*H*], 6.25–6.39 [2H, m, C(11)*H*, C(12)*H*], 7.16–7.48 (10H, m, Ar*H*); δ_C($CDCl_3$) 11.30 (C-3aCH_3), 24.17 (*C*H-3b), 39.92 (one of *C*-3a and *C*-10a), 40.36 (CH_2-2), 40.54 (one of *C*–3a and *C*-10a), 43.49 (*C*H-1), 53.16, 55.10 (*C*H-4, *C*H-10), 125.25, 127.31, 127.62, 128.11, 128.26, 128.68 (6 signals for 8 × *C*H), 131.30, 138.75 (2 × *C*), 154.24, 155.86, 210.24 (3 × *C*=O).

Method B: Cycloaddition with in situ *generated PTAD.* This was prepared following the procedure (Method B) described for **4b**, using lead tetraacetate (66 mg, 1.49×10^{-4} mol) in dichloromethane (10 ml), *trans*-(3*R**,8a*S**)-3,8a-dihydro-3-phenyl-8a-methylazulen-1(2*H*)-one **2g** (32 mg, 1.36×10^{-4} mol) and phenylurazole (26 mg, 1.49×10^{-4} mol), in dichloromethane (10 ml). Purification by preparative thin layer chromatography on silica gel, using ethyl acetate–hexane (3:7) as eluant, gave the *adduct* **4g** (37 mg, 67%) as a white solid, with spectral characteristics identical to those described above.

Method C: Tandem synthesis of PTAD adduct. This was prepared following the procedure (Method C) described for **4b**, using 2-diazo-5,5-diphenylpentan-3-one **1g** (57 mg, 2.05×10^{-4} mol) in dichloromethane (50 ml), rhodium(II) acetate (0.5 mg) in dichloromethane (50 ml), and 4-phenyl-1,2,4-triazoline-3,5-dione (36 mg, 2.06×10^{-4} mol) in dichloromethane (10 ml). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave the *adduct* **4g** (24 mg, 29%) as a white solid, with spectral characteristics identical to those described above.

(3a*R,3b*S**)-1,2,3b,4-Tetrahydro-3a-methyl-7-phenyl-4,10-etheno-6*H*,10*H*-cyclopenta[1,3]cyclopropa[1,2-*d*][1,2,4]triazolo-[1,2-*a*]pyridazine-3,6,8(3a*H*,7*H*)-trione 4h.**[5d] *Method A: Cycloaddition with PTAD.* This was prepared following the procedure (Method A) described for **4b**, using 4-phenyl-1,2,4-triazoline-3,5-dione (40 mg, 2.3×10^{-4} mol) in dichloromethane (10 ml), and 3,8a-dihydro-8a-methylazulen-1(2*H*)-one **2h** (35 mg, 2.19×10^{-4} mol) in dichloromethane (10 ml), with stirring at room temperature for 10 min. Passage through a short column of silica gel, with dichloromethane as eluant, gave the *adduct* **4h** (69 mg, 94%) as a white solid. Recrystallisation from hot ethanol gave a white crystalline solid, mp 166–167 °C [lit.,[5d] 166–167 °C]; ν_{max}(KBr)/cm^{-1} 1775 (w), 1718, 1501, 1406; δ_H($CDCl_3$) 1.25 [3H, s, C(3a)CH_3], 1.62–1.64 [1H, d, *J* 5, C(3b)*H*], 2.14–2.48 [4H, m, C(1)H_2C(2)H_2], 5.19–5.22 (1H, dd, *J* 5, 2) and 5.29–5.36 (1H, m) [C(4)*H*, C(10)*H*], 6.31–6.40 [2H, m, C(11)*H*, C(12)*H*], 7.33–7.49 (5H, m, Ar*H*) [Found (HRMS, EI): 335.12482. $C_{19}H_{17}N_3O_3$ requires M^+ 335.12699]; *m*/*z* 335 (3%), 177 (11%), 160 (10%), 117 (78%), 91 (100%).

Method B: Cycloaddition with in situ *generated PTAD.* This was prepared following the procedure (Method B) described for **4b**, using lead tetraacetate (52 mg, 3.43×10^{-4} mol) in dichloromethane (20 ml), 3,8a-dihydro-8a-methylazulen-1(2*H*)-one **4h** (50 mg, 3.12×10^{-4} mol) and phenylurazole (61 mg, 3.43×10^{-4} mol) in dichloromethane (20 ml), with stirring for 10 min. Purification by preparative thin layer chromatography on silica gel, using ethyl acetate–hexane (3:7) as eluant, gave the *adduct* **4h** (80 mg, 77%) as a white solid, with spectral characteristics identical to those described above.

Method C: Tandem synthesis of PTAD adduct. This was prepared following the procedure (Method C) described for **4b**, using 2-diazo-5-phenylpentan-3-one **1h** (41 mg, 2.18×10^{-4} mol) in dichloromethane (50 ml), rhodium(II) acetate (0.5 mg) in dichloromethane (50 ml), and 4-phenyl-1,2,4-triazoline-3,5-dione (42 mg, 2.40×10^{-4} mol) in dichloromethane (10 ml), with stirring at room temperature for 10 min. Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave the *adduct* **4h** (39 mg, 54%) as a white solid, with spectral characteristics identical to those described above.

2,4-Dinitrophenylhydrazone derivative of (1*R,4*S**)-1-methyl-4-phenylbicyclo[4.1.0]heptan-2-one 6.** Concentrated sulfuric acid (4 ml, 3 M) was added slowly to a solution of 2,4-dinitrophenylhydrazine (2 g, 1.01×10^{-2} mol) in methanol (30 ml) and water (10 ml), while stirring at room temperature. A portion of this solution (2 ml) of 2,4-dinitrophenylhydrazine was added dropwise to *trans*-(1*R**,4*S**)-1-methyl-4-phenylbicyclo[4.1.0]-heptan-2-one **5** (100 mg, 5.00×10^{-4} mol) in ethanol (1 ml), while stirring at room temperature. The solution was then heated for 2 min, until an orange solid precipitated. The crude reaction mixture was then cooled to 0 °C, filtered and washed with cold ethanol (2 × 0.5 ml). Recrystallisation from hot ethanol gave the *hydrazone* **6** (139 mg, 73%) as an orange crystalline solid, mp 173–174 °C; ν_{max}(KBr)/cm^{-1} 1617, 1459, 1331; δ_H($CDCl_3$) 0.79–0.83 [1H, dd appears as t, *J* 5, one of C(7)H_2], 1.09–1.14 [1H, dd, *J* 9, 5, one of C(7)H_2], 1.47 [3H, s, C(1)CH_3], 1.49–1.72 [2H, m, C(6)*H*, one of C(5)H_2], 2.05–2.16 [1H, dd, *J* 14, 2, one of C(5)H_2], 2.34–2.51 [1H, m, one of C(3)H_2], 2.81–2.89 [2H, m, C(4)*H*, one of C(3)H_2], 7.17–7.37 (5H, m, Ar*H*), 8.01–8.05 (1H, d, *J* 10, Ar*H*), 8.30–8.34 (1H, dd, *J* 10, 3, Ar*H*), 9.10 (1H, d, *J* 2), 11.26 (1H, br s, *NH*); δ_C($CDCl_3$) 22.54 (C-1CH_3), 23.07 (*C*-1), 24.74 (*C*H-6), 25.33, 30.57, 33.34 (CH_2-3, CH_2-5, CH_2-7), 42.64 (*C*H-4), 116.39, 123.59, 126.56, 127.08, 128.84, 129.97 (6 × *C*H), 143.65, 145.23 (2 × *C*), 162.56 (*C*=N) [Found (HRMS, EI): 380.14779. $C_{20}H_{20}N_4O_4$ requires M^+ 380.14846]; *m*/*z* 380 (12%), 202 (10%), 177 (28%), 139 (100%), 91 (67%).

X-Ray crystallographic data for 6

$C_{20}H_{20}N_4O_4$, $M = 380.40$, triclinic, space group $P\bar{1}$, $a = 7.943(5)$, $b = 8.000(3)$, $c = 16.237(3)$ Å, $\alpha = 101.63(2)$, $\beta = 93.12(3)$, $\gamma = 112.79(3)°$, $V = 921.6(6)$ Å^3, $Z = 2$, $F(000) = 400$, $D_c = 1.371$ g cm^{-3}, $\mu = 0.098$ mm^{-1}. 3248 reflections in the range $2 < \theta < 25°$ were collected with graphite monochromated Mo radiation; of these, 3248 were unique and 1274 had $I > 2\sigma(I)$. The structure was solved using SHELXS-86[18a] and refined with all non-H atoms allowed anisotropic vibration, with NRCVAX[18b] and SHELXL-93[18c] using F^2 and all data. H atoms allowed for as riding atoms. Final R_{obs}, R_w, gof values are 0.054, 0.137, 0.83 respectively.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/279. See http://www.rsc.org/suppdata/perkin1/1998/4077/ for crystallographic files in .cif format.

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