Stereocontrol of intramolecular Diels–Alder reactions by an allylic diphenylcyclopropyl group†

Regis Tripoli,[a] Tory N. Cayzer,[a] Anthony C. Willis,‡[a] Michael S. Sherburn*[a,b] and Michael N. Paddon-Row*[c]

Received 1st June 2007, Accepted 19th June 2007
First published as an Advance Article on the web 13th July 2007
DOI: 10.1039/b708324f

Intramolecular Diels–Alder reactions of ester-linked 1,3,8-nonatrienes carrying a diphenylcyclopropyl substituent attached to C1 proceed with high levels of stereoselectivity. The stereochemical outcomes of these reactions are explained by reference to B3LYP/6-31G(d) transition structures. Experimentally, the diphenylcyclopropane rings remain intact through these IMDA reactions, notwithstanding their predicted extremely high degree of asynchronicity (the B3LYP-computed lengths in the IMDA transition structures differ by as much as 1.1 Å), providing support to the notion that these reactions are concerted processes.

Introduction

The intramolecular Diels–Alder (IMDA) reaction is a powerful synthetic transformation. Over the years, many methods have been devised to steer the stereochemical outcome of the reaction.[1] Recently, we demonstrated that allylic stereocontrolling substituents attached to the terminus of the diene can give high levels of π-diastereofacial selectivity in IMDA reactions. The key experimental findings of this work, along with a theoretical model based upon computational investigations, are summarised in Fig. 1.[2] The *unlike* π-diastereofacial selectivity observed in these reactions comes about through the preference for a reactive conformation about the bond connecting the diene and the stereocentre in which the silyloxy group adopts an *inside* orientation. The dienophile reacts at the more accessible π-face of the diene; in the absence of overriding electronic effects, this will be on the side of the diene in which the smaller substituent resides. The present work describes an investigation into IMDA precursors **1**, **2** and **3**, containing the diphenylcyclopropyl group at the diene terminus (Fig. 2).

We studied these IMDA reactions for two reasons. Firstly, and more importantly, we were interested in learning whether the cyclopropyl group could exert strong remote stereochemical control in the IMDA reaction. This enquiry is a logical extension of our earlier investigations into allylic stereocontrol by a chiral C1-substituent of the type –CHR′(O***SiR***$_3$) (Fig. 1). Thus, can a compact chiral, purely hydrocarbon, cyclopropyl group exert strong stereochemical control in the IMDA reaction and, if so, what is the most favourable diastereoisomeric transition structure (TS) for the reaction? In addition to providing additional mechanistic insights into remote allylic stereocontrol in IMDA reactions, diphenylcyclopropyl substituents could be of synthetic utility, given their susceptibility to ring-opening reactions with acids,[3]

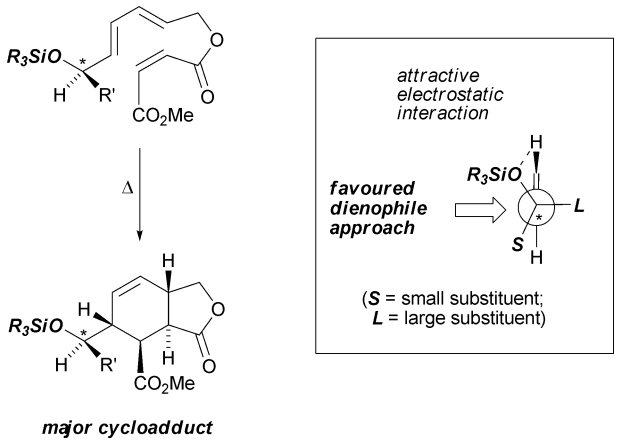


Fig. 1 Theoretical model for π-diastereofacial selectivity in addition reactions to chiral allylic silyloxy systems.

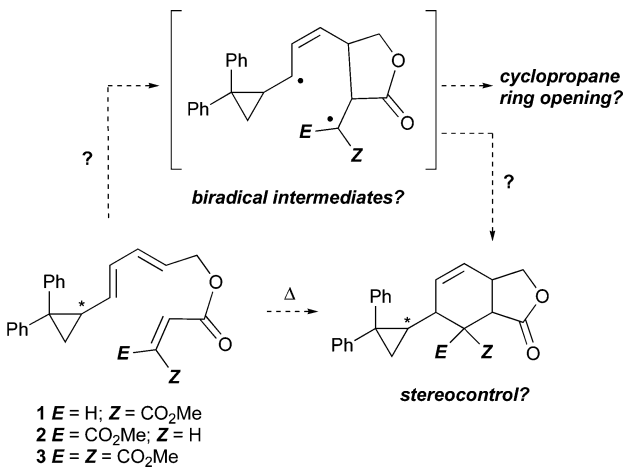


Fig. 2 Can a diphenylcyclopropyl group induce stereoselectivity or trap biradical intermediates in Diels–Alder reactions?

[a]*Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia. E-mail: sherburn@rsc.anu.edu.au (synthetic)*
[b]*ARC Centre of Excellence for Free Radical Chemistry and Biotechnology*
[c]*School of Chemistry, The University of New South Wales, Sydney, NSW 2052, Australia. E-mail: m.paddonrow@unsw.edu.au (computational)*

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all compounds prepared, 2D NMR spectra of **19a** and **17b**, thermal ellipsoid plots for **17a**, **18b**, and **17c**, geometries, scf energies, enthalpies and free energies of the TSs. See DOI: 10.1039/b708324f

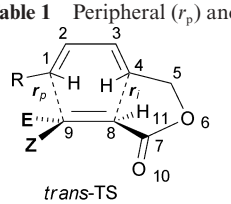
‡ Author to whom correspondence should be addressed regarding X-ray crystal structures. E-mail: willis@rsc.anu.edu.au

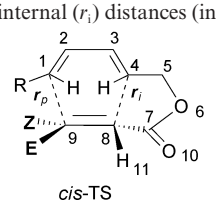
lithium metal,[4] and weak nucleophiles under photochemical conditions.[5]

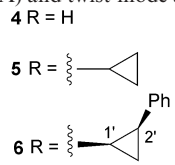
The second reason for our studying C1-substituted-cyclopropyl IMDA reactions is the finding that quantum chemical computed TSs of IMDA reactions of 9-substituted, ester linked 1,3,8-nonatrienes—in which the 9-substituent is π-conjugating—show remarkable asynchronicity in their forming bonds. Consider, for example, the restricted B3LYP/6-31+G(d) *cis* and *trans* IMDA TSs for the series **4a–4f**. The bond asynchronicity, Δr_{as}, is defined as the numerical difference between the lengths of the forming peripheral bond, r_p, and the forming internal bond, r_i and their values are given in Table 1. We focus attention on Δr_{as} values for the *trans* IMDA TSs since they are somewhat larger than the corresponding Δr_{as} values for the *cis* TSs. For the 9-unsubstituted system, **4a**, the bond asynchronicity of 0.2 Å is small and falls within the range for DA reactions involving acrylate dienophiles. However, upon introduction of a conjugating substituent at C9, the bond asynchronicity increases significantly to 0.53 and 0.72 Å for the 9-*E*-CO_2Me TS, *trans*-**4b-TS**, and 9-*Z*-CO_2Me TS, *trans*-**4c-TS**, respectively. This increase in bond asynchronicity appears to be accumulative because it increases to 1.0 Å in the 9,9-diester TS, *trans*-**4d-TS** and to 1.1 Å in the 9,9-dicyano TS, *trans*-**4e-TS**. It is even larger—1.3 Å—for the 9,9-diethynyl TS, *trans*-**4e-TS**. These rather astonishing bond asynchronicity values are the result of strong increases in the forming peripheral bond length, ranging from 2.56 Å, for *trans*-**4d-TS**, to extraordinarily large values of 2.94–3.20 Å for the 9,9-disubstituted *trans* TSs. Such large Δr_{as} values raise the mechanistic question of concertedness of these IMDA reactions, particularly that of 9,9-disubstituted systems.[6] Forming bonds of lengths >2.9 Å can hardly contribute significant energetic advantage towards lowering the activation barrier of a concerted process and it is possible, therefore, that some of the IMDA reactions of **4a–4f** might proceed by a non-concerted pathway. However, additional DFT calculations on the IMDA *trans* TSs for **4a–4f** suggest that these reactions *are* concerted. Detailed intrinsic reaction coordinate analyses show that all of these TSs smoothly lead to adducts without passing through any intermediate. Also, wavefunction stability calculations[7] show that the B3LYP/6-31+G(d) wavefunctions for the *trans* TSs of **4a–4e** are stable with respect to allowing the restricted wavefunction to become unrestricted. Thus, at the level of theory used, for these TSs, the closed-shell singlet configuration is stable and the TS has no biradical character. In contrast, the restricted DFT wavefunction for *trans*-**4f-TS** displayed a restricted → unrestricted instability. Optimisation of the stable unrestricted singlet wavefunction gave a new, open-shell, singlet state with a non-zero expectation value $<S^2> = 0.36$. This suggests biradical character in *trans*-**4f-TS**.

These results, while not confirming that some of the IMDA reactions of **4a–f** might proceed *via* non-concerted pathways, do predict very large calculated bond asynchronicities—particularly for the 9,9-disubstituted TSs—which indicate that these reactions may be on the borderline between concertedness and non-concertedness. Perhaps the introduction of a judiciously chosen substituent might tip the balance in favour of non-concertedness and the presence of the resulting biradical intermediate[8] could be signalled by its intramolecular trapping by that substituent. It seemed reasonable, therefore, to probe the possibility of non-concertedness in these IMDA reactions by attaching a diphenylcyclopropyl group at C1 of such 1,3,8-nonatrienes, as depicted by structures **1**, **2** and **3** (Fig. 2). This group is known to intercept and trap radical intermediates on a very short time-scale (estimated rate of ring opening at 25 °C = 4×10^{11} s^{-1}).[9] Values of salient geometrical parameters for

Table 1 Peripheral (r_p) and internal (r_i) distances (in Å) and twist-mode asynchronicities, θ_{as} (in degrees), for IMDA TSs of compounds **4**, **5** and **6**[a]







a ***E*** = H; ***Z*** = H
b ***E*** = CO_2Me; ***Z*** = H
c ***E*** = H; ***Z*** = CO_2 Me
d ***E*** = CO_2Me; ***Z*** = CO_2Me
e ***E*** = CN; ***Z*** = CN
f ***E*** = C≡CH; ***Z*** = C≡CH

$\Delta r_{as} = | r_p - r_i |$
$\theta_{as} = \angle$ C1–C4–C8–C9

	trans TS				*cis* TS			
	r_p	r_i	Δr_{as}	θ_{as}	r_p	r_i	Δr_{as}	θ_{as}
4a-TS[b,c]	2.355	2.159	0.196	−8.8	2.310	2.226	0.084	5.9
4b-TS[b,c]	2.559	2.026	0.533	−9.6	2.479	2.094	0.385	4.0
4c-TS[b,c]	2.703	1.983	0.72	−21.2	2.566	2.048	0.518	15.6
4d-TS[b]	2.942	1.923	1.019	−18.3	2.960	1.961	0.999	14.7
4e-TS[b]	3.044	1.914	1.13	−21.0	2.804	1.952	0.852	8.7
4f-TS[b]	3.198	1.880	1.318	−23.0	2.858	1.920	0.938	10.2
5a-TS[d]	2.400	2.089	0.311	−9.6	2.345	2.160	0.185	6.2
5b-TS[d]	2.708	1.968	0.74	−11.8	2.651	1.997	0.654	6.0
5c-TS[d]	2.948	1.904	1.044	−25.4	2.716	1.983	0.733	15.7
5d-TS[d]	3.158	1.962	1.196	−19.0	3.144	1.995	1.149	17.0
***ul*-6a-TS**[d]	2.403	2.087	0.316	−9.8	2.345	2.159	0.186	6.2
***ul*-6b-TS**[d]	2.786	1.919	0.867	−11.3	2.706	1.966	0.74	5.6
***ul*-6c-TS**[d]	2.937	1.908	1.029	−26.7	2.728	1.977	0.751	15.5
***ul*-6d-TS**[d]	3.169	1.966	1.203	−21.0	3.174	2.007	1.167	16.0

[a] Values for compounds **5** and **6** are for the most stable TS conformation about the C1–cyclopropyl bond. [b] B3LYP/6-31+G(d). [c] ref. 2. [d] B3LYP/6-31G(d).

IMDA TSs for 1-cyclopropyl-1,3,8-nonatrienes, **5a–5d**, and 1-(2′-phenylcyclopropyl)-1,3,8-nonatrienes, **6a–6d**—the latter series serving as models for the diphenylcyclopropyl systems **1**, **2** and **3**—are given in Table 1. The Δr_{as} values for **5-TS**s and **6-TS**s are actually slightly larger than the corresponding values for the C1-unsubstituted *trans*-**4-TS**s.

Computational methods

Gas phase transition structures (TSs) for intramolecular Diels–Alder reactions of **5a–5d** and **6a–6d** were optimised using the B3LYP functional[10] and, unless stated otherwise, the 6-31G(d) basis set.[11] Restricted B3LYP calculations were employed throughout because, for all TSs located in this study, the restricted Kohn–Sham wavefunction was calculated to be stable, thereby indicating zero biradical character in the TSs. Conformational TSs about the C1–cyclopropyl bond were obtained following relaxed potential energy scans (using redundant coordinates). In some instances, the PE scans revealed only a two-fold rotational barrier, thereby indicating that there are only two conformationally stable TSs, the third one presumably being destabilised by steric congestion. Harmonic vibrational frequencies were carried out to characterise the TSs and to calculate TS free energies at 298.15 K and 1 atm pressure. *cis* : *trans* Ratios and *lk* : *ul* product ratios were calculated from the free energies at the aforementioned temperature and pressure using standard methods.[12] Because the purpose of the calculations was to gain qualitative insights into mechanistic aspects of the systems under study, experimental temperatures were not used to calculate the TS free energies. The TS free energies, *cis* : *trans* ratios and *lk* : *ul* ratios for the IMDA reactions of **5a–5d** and **6a–6d** are given in Tables 2 and 3, respectively. Geometries, scf energies, enthalpies and free energies of the TSs are given in the ESI†. The Gaussian 03 program was used throughout.[13]

Justification of the theoretical model

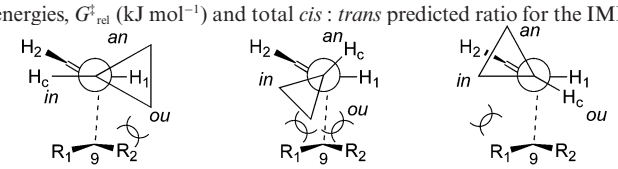
The B3LYP functional, in conjunction with the 6-31G(d) basis set, is known to give acceptable relative energies and geometries for a broad variety of Diels–Alder reactions.[2,14,15] Importantly, we have shown that the B3LYP/6-31G(d) method correctly predicts *cis* : *trans* ratios for the IMDA reactions of several 9-substituted pentadienyl acrylates, often with an accuracy of 1 kJ mol^{-1}.[16] This level of theory is, therefore, adequate for this study. We have used *gas phase* DFT calculations. The excellent agreement found in previous studies between gas phase B3LYP predicted IMDA *cis* : *trans* and *lk* : *ul* ratios and the experimental ratios, obtained using weakly polar solvents, such as toluene, chlorobenzene or 1,2-dichlorobenzene suggests that weakly polar solvents—which are often used in IMDA reactions—have no significant influence on *cis* : *trans* and *lk* : *ul*[15] selectivities. Ideally, calculations should be carried out on the IMDA reactions of the experimental 1-(2′-diphenylcyclopropyl) systems **1**, **2** and **3** (Fig. 2). However, exploratory calculations on maleate **1** failed to achieve convergence in geometry optimisations within a reasonable time, owing to failure in obtaining simultaneously stable conformations of both phenyl groups. Replacement of the *trans*-phenyl substituent with a hydrogen atom, to give the series **6a–6d**, removed this difficulty and so this series was used as models for **1**, **2** and **3**. These models should be quite reliable because the *cis*-phenyl substituent is retained in **6a–6d** and it is this substituent, being directed towards the reaction centre, which should have the major influence on IMDA stereoselectivity, with the *trans*-phenyl substituent, being directed away from the reaction centre, playing only a minor, indirect role by modifying the conformation of the *cis*-phenyl group.

Results and discussion

Various earlier computational studies[2,17,18] involving the location of TSs for addition reactions to alkenes carrying an allylic stereocentre (C*) reveal an approximate staggered arrangement of the C* substituents with respect to the developing C1–C9 bond, with the allylic substituents distributed among the *inside* (*in*), *anti* (*an*), and *outside* (*ou*) positions in TSs, as depicted schematically in Fig. 3

The π-diastereofacial selectivity is determined by the positional preferences of the C* substituents for the *in*, *an* and *ou* sites in the TS. Steric effects play an important role because of the quite different volumes of the *an*, *in* and *an* spaces, with *an* being the

Table 2 B3LYP/6-31G(d) relative free energies, $G^{\ddagger}_{rel}$ (kJ mol^{-1}) and total *cis* : *trans* predicted ratio for the IMDA TSs of compounds **5a–5d** at 298.15 K[a]



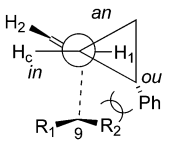
5-*in* **5-*an*** **5-*ou***

	5a ($R_1 = R_2 = H$)	**5b** ($R_1 = H$, $R_2 = CO_2Me$)	**5c** ($R_1 = CO_2Me$, $R_2 = H$)	**5d** ($R_1 = R_2 = CO_2Me$)
cis TSs				
in	0	5.96	12.9	12.3
an	12.0	—[b]	23.4	21.7
ou	4.26	7.09	21.0	—[b]
trans TSs				
in	1.18	0	0	0
an	12.7	16.8	—[b]	15.4
ou	6.44	6.94	7.43	9.68
cis : *trans*	63 : 37	12 : 88	0.5 : 99.5	0.7 : 99.3

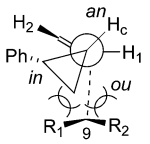
[a] Structures of **5a–5d** are defined in Table 1. [b] No TS could be found for this conformation; see Computational Methods.

Table 3 B3LYP/6-31G(d) relative free energies,[a] $G^{\ddagger}_{rel}$ (kJ mol^{-1}) for the IMDA TSs of compounds **6a–6d** and total *cis* : *trans* and *lk* : *ul* predicted product ratios at 298.15 K and 1 atm[b]

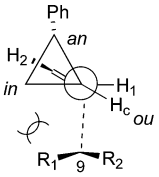
***lk* TSs**



lk*-6-*in

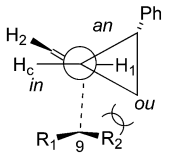


lk*-6-*an

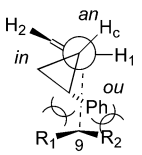


lk*-6-*ou

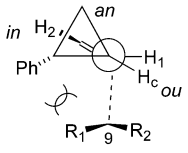
***ul* TSs**



ul*-6-*in



ul*-6-*an



ul*-6-*ou

	6a ($R_1 = R_2 = H$)		**6b** ($R_1 = H$, $R_2 = CO_2Me$)		**6c** ($R_1 = CO_2Me$, $R_2 = H$)		**6d** ($R_1 = R_2 = CO_2Me$)	
	lk	*ul*	*lk*	*ul*	*lk*	*ul*	*lk*	*ul*
cis TSs								
in	3.05	0	—[c]	7.56	10.7	7.71	34.3	10.7
an	22.5	—[c]	25.4	—[c]	—[c]	—[c]	—[c]	—[c]
ou	8.99	15.3	11.3	15.2	20.9	—[c]	19.6	30.2
trans TSs								
in	5.48	0.74	5.89	0	—[c]	0	16.9	0
an	23.0	—[c]	—[c]	—[c]	18.5	—[c]	—[c]	—[c]
ou	10.8	15.8	10.8	21.0	7.58	10.8	9.39	17.5
cis : *trans*	60.4 : 39.6		5.1 : 94.9		5.2 : 94.8		1.3 : 98.7	
cis lk : *ul*	24.2 : 75.8		17.2 : 82.8		23.0 : 77.0		2.7 : 97.3	
trans lk : *ul*	14.1 : 85.9		9.6 : 90.4		4.5 : 95.5		2.3 : 97.7	

[a] Relative free energies for each system include both *lk* and *ul* IMDA TSs. [b] Structures of **6a–6d** are defined in Table 1. [c] No TS could be found for this conformation; see Computational Methods.

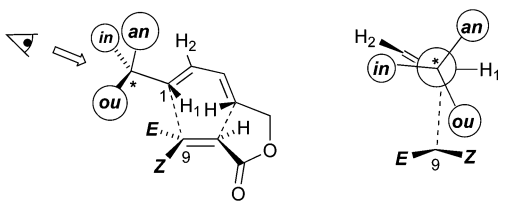
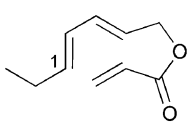


Fig. 3 Schematic representations of an IMDA *trans* TS. The Newman projection formula on the right depicts a view along the C*–C1 bond of the structure on the left.

largest and *ou* being the smallest. Thus, for example, it has been found that the positional preference of the methyl substituent in the IMDA TS of the 1-ethyl pentadienyl acrylate system (**7**, Fig. 4) is *an* > *in* > *ou*.[2]



7

Fig. 4

Electrostatic effects can also influence positional preferences.[15b] Thus, the silyloxy group ($OSiR_3$) has the greatest preference for the *in* position, which is probably due to a combination of a stabilising electrostatic interaction between the silyloxy oxygen atom and H-2 of the diene (Fig. 3) and to a destabilising four-electron interaction between a lone pair on oxygen and the diene π HOMO electrons.[2,15b]

It is expected that stereocontrol by a C1-cyclopropyl substituent should be determined mainly by steric factors. Consider, first of all, the IMDA TSs for systems **5a–5d**, which are achiral. For each system there are two diastereoisomeric TSs, namely *cis* and *trans*, each of which may exist as three different conformations of the cyclopropyl substituent about the C1–C(cyclopropyl) bond. These three conformational TSs—**5**-*in*, **5**-*an* and **5**-*ou*—are schematically depicted at the top of Table 2, the label *in*, *an*, and *ou* referring to the position of the cyclopropyl methine hydrogen, H_c.

The calculations predict *cis* stereoselectivity for the IMDA reaction of the 9-unsubstituted system, **5a** (*cis* : *trans* = 63 : 37 at 298 K) and this is in accord with experimentally observed moderate *cis* stereoselectivity for a variety of IMDA reactions lacking 9-ester substituents.[16a] Introduction of ester groups into the 9-position causes a reversal of stereoselectivity, favouring formation of the *trans* adduct. The *trans* selectivity is weaker for the 9-*E*-ester, **5b**, than for the 9-*Z*-ester, **5c**, and the 9,9-diester, **5d**, presumably for reasons given in detail elsewhere for related systems.[16b,19] Our DFT calculations predict the most stable TS conformation to be **5**-*in*—in which the cyclopropyl methine hydrogen, H_c, adopts the *in* position—for both *cis* and *trans*

modes of addition and for all systems. This conformation strongly resembles the most stable conformation observed experimentally for vinylcyclopropane, in which the vinyl double bond is *transoid* to the cyclopropane ring.[20] In general, the **5**-*an* conformation is the least favourable because the two cyclopropyl methylene groups occupy the less favourable *in* and *ou* positions. As expected from steric arguments, the introduction of 9-ester groups further destabilises the **5**-*an* TS relative to the **5**-*in* TS, and the magnitude of this destabilisation is approximately the same for both *E* and *Z* ester groups because the cyclopropyl vertex which is pointing towards the C9 substituents in the **5**-*an* conformation is roughly equidistant from the *E* and *Z* ester groups. The C9-substituent effect on the relative energies of the **5**-*ou* and **3**-*in* TSs is also explicable in terms of steric effects. In the case of the *cis* TSs, introduction of an *E* ester group causes almost complete loss of the stabilisation energy of **5**-*in* relative to **5**-*ou* (*cf.* 4.3 kJ mol^{-1} in **5a** and 1.1 kJ mol^{-1} for **5b**) because, in the *cis* TS, replacing $R_1 = H$ with $R_1 = CO_2Me$ introduces a steric clash which adversely affects the energy of *cis*-**5b**-*in* relative to that of *cis*-**5b**-*ou*. The reverse holds for 9-*Z*-ester substitution in the *cis* TS ($R_1 = CO_2Me$, $R_2 = H$) and, indeed, such substitution leads to enhanced stabilisation of the *in* TS (*cf.* 4.3 kJ mol^{-1} in **5a** and 8 kJ mol^{-1} for **5c**). The stabilisation of the *in* TS conformation over the *ou* conformation in the 9,9-diester is roughly additive (10 kJ mol^{-1}).[21] In the case of the *trans* TSs, 9-ester substitution brings about a moderately enhanced stabilisation of the *in* TS, compared to the *ou* TS, which appears odd in the case of 9-*Z* substitution ($R_1 = H$, $R_2 = CO_2Me$), for which the *in* TS should be destabilised. Taking twist-mode asynchronicity[16b,19] into account resolves this problem. Twist-mode asynchronicity is defined by the dihedral angle, θ_{as} = C1–C4–C8–C9 and values of θ_{as} for the IMDA TSs of **4–6** are given in Table 1. Two significant features of θ_{as} are (1) they have a positive sign for *cis* TSs and a negative sign for *trans* TSs, and (2) the magnitude of θ_{as} is substantially larger for 9-*Z*-substituted TSs than for 9-*E*-substituted TSs, a feature which has been explained elsewhere.[16b] These features are illustrated in Fig. 5 for the *cis* and *trans* TSs for **5c**. Thus, twist-mode asynchronicity causes C9 and its attendant 9-*Z* ester substituent to be driven deeper into the *endo* region, thereby further raising the energy of *cis*-**5**-*ou*, relative to the *in* TS. In contrast, the 9-*Z*-CO_2Me substituent is markedly displaced in the *exo* direction in the *trans* TS. This should lead to a reduction in adverse steric interactions between the ester and the cyclopropane vertex occupying the *ou* position and, therefore, to an undiminished stabilisation of the *in* TS compared to the *ou* TS, as is found.

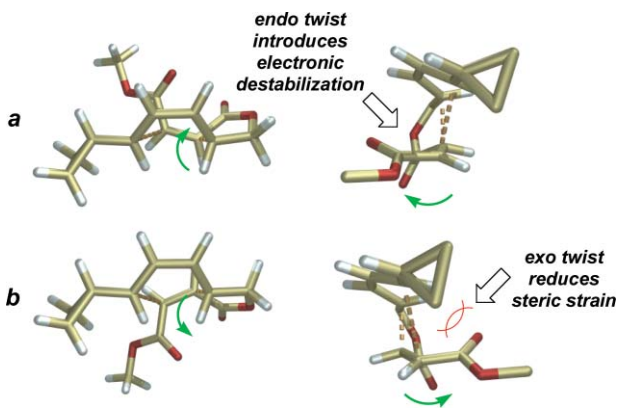


Fig. 5 Optimised TS geometries of (*a*) *cis*-**5c**-*in* and (*b*) *trans*-**5b**-*in*. The direction of dienophile twisting is depicted with green arrows. Some hydrogens are omitted from the right hand structures for clarity.

Insights gained from our calculations for the IMDA TSs for **5a–5d** may be used to predict the most favourable IMDA TS for chiral trienes **6a–6d** bearing the 1-(*cis*-2′-phenylcyclopropyl) substituent. In these systems, the presence of the two stereocentres on the cyclopropane ring discriminates the two π-faces of the diene, thereby leading to *like* (*lk*) and *unlike* (*ul*) stereoselectivity for each mode of addition, *cis* and *trans*. The possible TSs for these reactions are depicted in Table 3. The favoured TS should be *ul*-**6**-*in*, in which H_c adopts the *in* position and the bulky CHPh group occupies the *an* position—this position being less sterically congested than the *ou* region. The B3LYP-computed relative free energies of the IMDA TSs (298 K) for **6a–6d** are presented in Table 3.

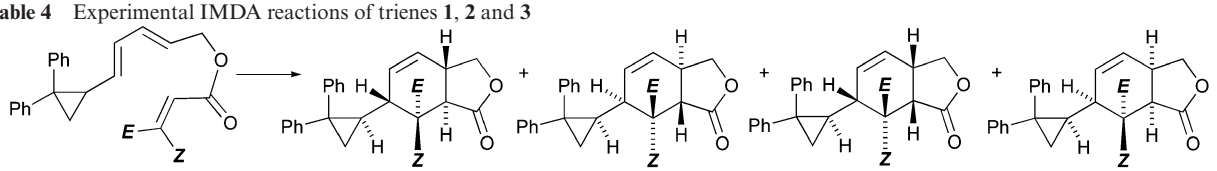
Four predictions may be drawn from the data of Table 3. These are: (1) *cis* stereoselectivity is predicted for the parent system **6a** and *trans* selectivity for the 9-ester systems, being the greatest for the 9,9-diester **6d**. This trend has been explained elsewhere for other 1,3,8-nonatriene IMDA reactions.[16] (2) As anticipated from the above discussion on the IMDA reactions of **5a–5d**, *ul* facial selectivity is predicted for both *cis* and *trans* modes of addition and the *ul* TS with the lowest free energy is **6**-*in*. (3) The *ul* selectivity is stronger for *trans* addition than for *cis* addition. (4) For both *cis* and *trans* modes of addition, *ul* selectivity increases with progressive 9-ester substitution becoming greater than 97% for the 9,9-diester. These predictions were tested experimentally. Trienes **1**, **2** and **3** were prepared from dienol **15**, which in turn was accessed from benzophenone hydrazone **8** in 6 steps and 44% overall yield (Scheme 1).

Oxidation of benzophenone hydrazone **8**[22] with nickel peroxide gave diphenyl diazomethane **9**,[23] which underwent cycloaddition with methyl acrylate at room temperature[24] to afford cyclopropane ester **10**.[25] Reduction to primary alcohol **11** with lithium aluminium hydride followed by Swern oxidation afforded aldehyde **12** in 75% yield over 4 steps. Horner–Wadsworth–Emmons reaction of aldehyde **12** with the lithium salt of phosphonate **13** afforded the *E*,*E*-dienoic ester **14** in 62% yield. DIBALH reduction of ester **14** at −78 °C[26] furnished the desired dienol **15** in 95% yield. The three IMDA precursors **1**, **2** and **3** were easily accessed from dienol **15** by esterification reactions. Thus, reaction with maleic anhydride gave the half ester of maleic acid, which was converted into methyl ester **1** by reaction with diazomethane at −78 °C. Union of **15** with methyl fumaroyl chloride gave triene ester **2**. Finally, 9,9-diester triene **3** was accessed by reaction of dienol **15** with the acyl chloride of known carboxylic acid **16**.[27] The results from the experimental IMDA reactions of the three trienes are listed in Table 4.

The relative stereochemistries of three of the five isolated cycloadducts, namely **17a**, **18b** and **17c**, were secured through single crystal X-ray analyses (Table 5, Fig. 6).§ The stereochemistries of the remaining two structures—**19a** and **17b**—were tentatively assigned through 2D NMR techniques (see ESI for details†). In each case, the relative stereochemistry about the newly

§ CCDC reference numbers 644828–644830. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708324f

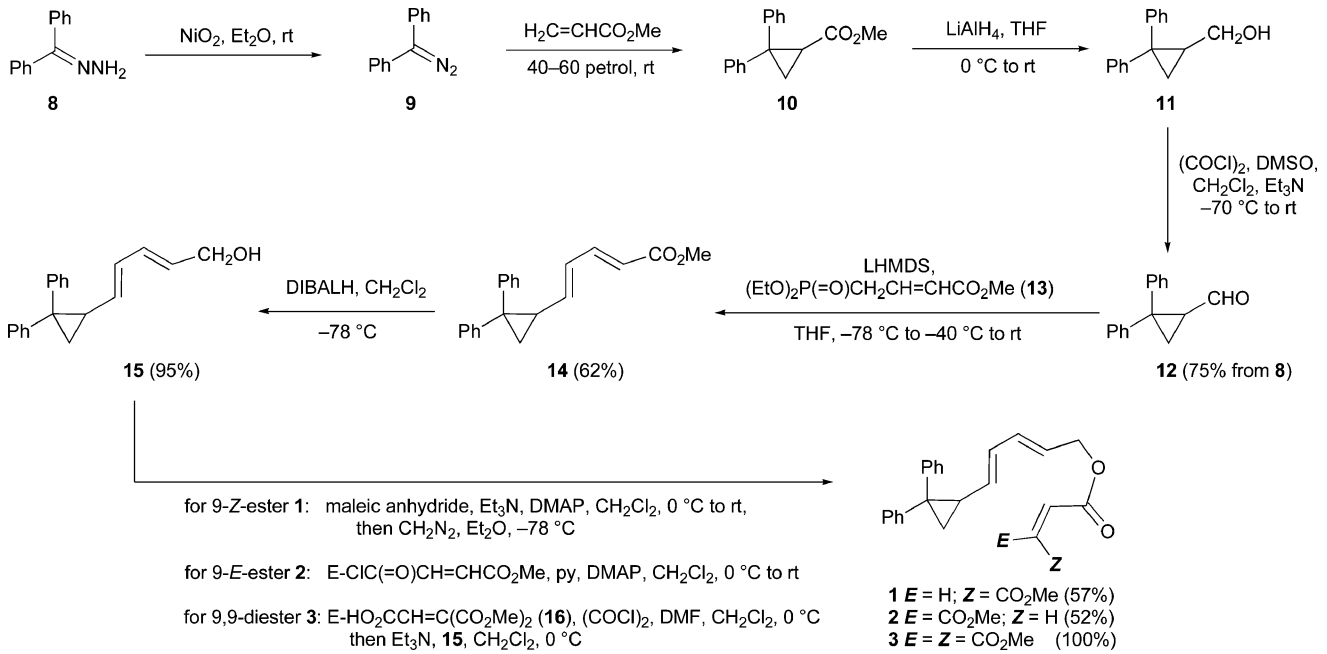
Table 4 Experimental IMDA reactions of trienes **1**, **2** and **3**



1 ***E*** = H; ***Z*** = CO_2Me **17** ***trans, unlike*** **18** ***trans, like*** **19** ***cis, unlike*** **20** ***cis, like*** **a** ***E*** = H; ***Z*** = CO_2Me
2 ***E*** = CO_2Me; ***Z*** = H **b** ***E*** = CO_2Me; ***Z*** = H
3 ***E*** = ***Z*** = CO_2Me **c** ***E*** = ***Z*** = CO_2Me

Triene substrate	***E*/*Z***	Solvent	Reaction time[a]/h	Isolated yield[b] (%)	*Experimental* adduct ratio[c,d] **17** : **18** : **19** : **20**	*Calculated* adduct ratio[e] **17** : **18** : **19** : **20**
1	H/CO_2Me	PhMe	5	75	82 : 0 : 18 : 0	86 : 9 : 4 : 1
2	CO_2Me/H	PhCl	12	63	86 : 14 : 0 : 0	91 : 4 : 4 : 1
3	CO_2Me/CO_2Me	PhH	3	72	>99 : 0 : 0 : 0	97 : 2 : 1 : 0

[a] Time required for >95% conversion, as judged by ^{1}H NMR. [b] Combined isolated yield after chromatography. [c] Determined from ^{1}H NMR spectra of crude reaction mixtures. [d] Kinetic product ratios are reported: control experiments confirmed that all cycloadducts were stable to the reaction conditions. [e] Calculated values based upon the *cis*-2′-phenylcyclopropyl model systems **6b–d** (Table 3).



Scheme 1

formed bicyclic system is secure but the sense of π-diastereofacial selectivity is not. We assign stereostructures to these compounds on the basis of the computational findings described herein.

Two conclusions can immediately be drawn upon inspection of the data in Table 4: (1) all three IMDA reactions are highly stereoselective; and (2) no ring opened products are observed. The latter observation leads us to conclude that *if* these cycloadditions have biradicaloid character, then their closure to form IMDA adducts is significantly faster than 4×10^{11} s^{-1}, the rate of ring opening of the diphenylcyclopropylmethyl radical.[9]

Experimental stereoselectivities for the three reactions involving the C1-diphenylcyclopropyl substituent are in very good agreement with computed values for the mono-phenylcyclopropyl model system. It is particularly noteworthy that the predicted increase in stereoselection through the model series maleate **6c** → fumarate **6b** → 9,9-diester **6d** is mirrored in the experimental results with trienes **1**, **2** and **3** respectively. These results demonstrate, once again, the value of DFT as a predictive tool for stereoselective synthesis. Thus, hydrocarbon substituents around a stereocentre *can* induce high levels of π-diastereofacial selectivity in intramolecular cycloadditions. This is all the more remarkable when the length of the developing peripheral (C1–C9) bond in the TS is taken into account. These findings raise interesting questions. Will high stereoselectivities also be witnessed in intermolecular addition processes to diphenylcyclopropyl-substituted dienes? Will other substituted ring systems give similar outcomes? Answers to these questions are currently being sought.

Table 5 X-ray crystallographic data for compounds **17a**, **18b** and **17c**

	17a	**18b**	**17c**
CCDC No.	644828	644830	644829
Formula	$C_{25}H_{24}O_4$	$C_{25}H_{24}O_4$	$C_{27}H_{26}O_6$
M	388.46	388.46	446.5
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/a$	$P2_1$	*Pbca*
a/Å	13.9345(2)	11.0190(4)	15.0402(3)
b/Å	8.7920(2)	7.6264(3)	15.3235(3)
c/Å	16.3108(3)	12.1306(5)	19.7863(5)
β/°	96.0142(11)	91.3965(17)	—
V/Å^3	1987.27(6)	1019.10(7)	4560.12(17)
Z	4	2	8
T/K	200	200	200
Measured reflections	41962	12952	40672
Independent reflections	4543	1943	4046
Reflections in refinement	3260 [$I > 2\sigma(I)$]	1460 [$I > 1.5\sigma(I)$]	2621 [$I > 2\sigma(I)$]
R	0.0325	0.0353	0.0325
Rw	0.0351	0.0391	0.0361
S	1.1283	1.0875	1.0664

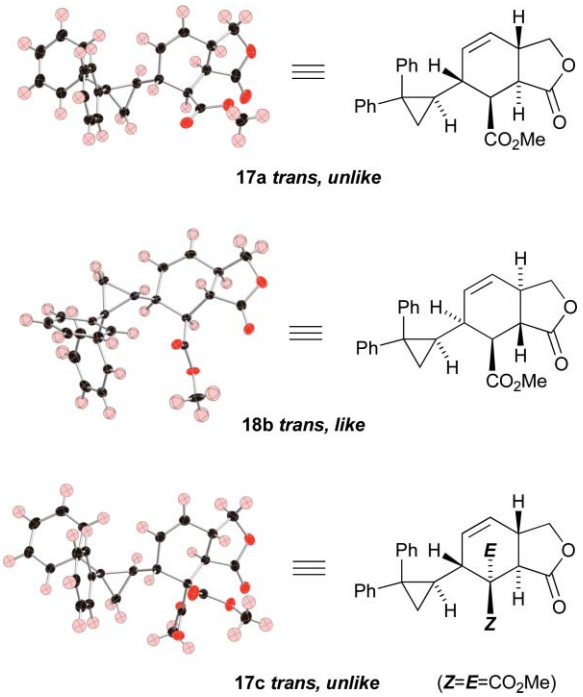


Fig. 6 Molecular structures from single crystal X-ray analyses of cycloadducts. Thermal ellipsoids are shown at 30% probability levels.

Experimental

General

NMR spectra were recorded at 298 K using a Varian Unity INOVA 300 MHz spectrometer. Residual protio-chloroform (δ 7.26 ppm) was used as an internal reference for ^{1}H NMR spectra. The ^{13}C NMR resonance of chloroform (δ 77.1 ppm) was used as an internal reference for ^{13}C NMR spectra. Assignment of proton signals was assisted by ^{1}H–^{1}H COSY and NOESY experiments when necessary; assignment of carbon signals was assisted by DEPT experiments. IR spectra were recorded on a Perkin-Elmer 1600 F.T.I.R. or Perkin-Elmer Spectrum One spectrometer as neat films on NaCl plates for oils or as KBr pellets for solid products. Low resolution mass spectra were recorded on a Finnigan PolarisQ ion trap mass spectrometer using electron impact (EI) ionisation mode at 40 or 70 eV. High resolution mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Microanalyses were performed at the Research School of Chemistry, Australian National University. Melting points were measured on a Reichert melting point stage and are uncorrected. Analytical TLC was performed with Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm). Flash chromatography employed Merck Kiesegel 60 (230–400 mesh) silica gel. Reactions were conducted under a positive pressure of dry argon or nitrogen. Diethyl ether, toluene and THF were dried over sodium wire and distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Commercially available chemicals were purified by standard procedures or used as purchased.

Methyl 2,2-diphenylcyclopropanecarboxylate (10)

Compound **10** was prepared following literature procedures.[22–24] A mixture of benzophenone (13.31 g, 73 mmol, 1 equiv.) and anhydrous hydrazine (8.6 mL, 274 mmol, 3.75 equiv.) in ethanol (50 mL) was heated to reflux overnight, affording benzophenone hydrazone (**8**) as white needles after recrystallisation from ethanol (12.03 g, 84% yield).[22] Careful oxidation of **8** (0.200 g, 1.02 mmol, 1 equiv.) was quantitatively achieved using nickel peroxide in excess (12 g) in Et_2O (50 mL) at rt.[23] After evaporation of the reaction solvent *in vacuo* at rt, diazo compound **9** was obtained as a deep purple liquid. Reaction of **9** (1.02 mmol, 1 equiv.) with methyl acrylate (0.24 mL, 2.69 mmol, 2.64 equiv.) in petroleum spirit (20 mL) at rt afforded the cyclopropane ester **10**.[24] No purification was necessary in this three step preparation. Compound **10**[25] was obtained in quantitative yield from **8** as an off-white solid: mp 41–42 °C (lit.,[25] 40 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07–7.28 (m, 10H), 3.42 (s, 3H), 2.48 (dd, J = 8.1, 6.0 Hz, 1H), 2.10 (dd, J = 6.0, 4.8 Hz, 1H), 1.54 (dd, J = 8.1, 4.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 145.0, 140.5, 129.8, 128.7, 128.6, 127.8, 127.3, 126.8, 52.0, 40.2, 29.1, 20.4 ppm. IR (KBr disc): ν_{max} 3084, 3059, 3026, 2950, 1732, 1495, 1383, 1270 cm^{-1}. EIMS: *m*/*z*

(%): 252 (M^+, 14), 237 (7), 221 (19), 192 (100). HRMS: calcd for $C_{17}H_{16}O_2$: 252.1150; found 252.1149. All characterisation data matched those reported.[25]

(2,2-Diphenylcyclopropyl)methanol (11)[28,29]

A solution of compound **10** (0.26 g, 1.02 mmol, 1 equiv.) in THF was treated with $LiAlH_4$ at 0 °C under N_2 atm. The reaction mixture was kept at this temperature for 10 min, then warmed to rt and stirred for 1 h. On completion of the reaction, the remaining hydride species was quenched with a mixture of THF and iced water (1 : 1) at 0 °C and stirred until a white precipitate formed. The solvent was removed under reduced pressure and the residue dissolved in methanol. The resulting mixture was filtered through Celite and the solvent evaporated *in vacuo*. Column chromatography (petroleum ether 40–60–ethyl acetate, 3 : 1) of the crude material afforded pure **11** as a yellow oil (0.227 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.43 (m, 10H), 3.48 (dd, $J = 11.7$, 6.6 Hz, 1H), 3.38 (dd, $J = 11.7$, 7.8 Hz, 1H), 1.97–2.04 (m, 1H), 1.71 (bs, 1H), 1.40 (dd, $J = 5.4$, 4.8 Hz, 1H), 1.30 (dd, $J = 8.7$, 4.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 141.4, 130.4, 128.8, 128.6, 128.1, 127.0, 126.3, 64.0, 35.9, 28.0, 18.2 ppm. IR (thin film): ν_{max} 3401, 3059, 3024, 2930, 2879, 1642, 1495, 1035 cm^{-1}. EIMS: m/z (%): 224 (M^+, 47), 207 (69), 206 (99), 194 (73), 193 (100). HRMS: calcd for $C_{16}H_{16}O$: 224.1201; found 224.1201.

2,2-Diphenylcyclopropanecarbaldehyde (12)[28,29]

DMSO (0.145 mL, 2.04 mmol, 2 equiv.) was added dropwise to a solution of oxalyl chloride (0.11 mL, 1.22 mmol, 1.2 equiv.) in CH_2Cl_2 at −78 °C under N_2 atm and stirred at this temperature for 10 min. A solution of **11** (0.228 g, 1.02 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was added and stirring continued at −70 °C for 30 min. Triethylamine (0.567 mL, 4.08 mmol, 4 equiv.) was then added dropwise, the mixture stirred at −65 °C for a further 30 min and then allowed to warm to rt overnight. Water was then added and the mixture extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petroleum ether 40–60–ethyl acetate, 9 : 1) afforded **12** (0.1699 g, 75% over 4 steps from **8**) as a yellow solid: mp 75–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, $J =$ 6.6, 1H), 7.07–7.34 (m, 10H), 2.17–2.49 (m, 1H), 2.17 (dd, $J =$ 5.4, 5.1 Hz, 1H), 1.78 (dd, $J = 8.4$, 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 144.1, 139.6, 130.3, 129.2, 128.9, 127.7, 127.6, 127.2, 41.2, 37.0, 20.5 ppm. IR (KBr disc): ν_{max} 3058, 3026, 2835, 2764, 1705, 1495, 1447, 1170 cm^{-1}. EIMS: m/z (%): 222 (M^+, 72), 221 (28), 193 (96), 192 (61), 178 (55), 165 (55), 115 (100). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.15; H, 6.37. HRMS: calcd for $C_{16}H_{14}O$: 222.1045; found 222.1045.

(2*E*,4*E*)-Methyl 5-(2,2-diphenylcyclopropyl)penta-2,4-dienoate (14)

To a stirred solution of LHMDS (0.818 mmol, 1.07 equiv.) in THF (10 mL) was added phosphonate **13** (0.18 g, 0.764 mmol, 1 equiv.) in THF (4 mL) at −78 °C under N_2 atm. After 5 min the mixture was warmed to −40 °C and a solution of **12** (0.169 g, 0.764 mmol, 1 equiv.) in THF (5 mL) was added dropwise. The reaction was allowed to warm to rt overnight. Water, HCl (1 M) and Et_2O were then added. Extraction was carried out with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petroleum ether 40–60–ethyl acetate, 95 : 5) afforded **14** as a 9 : 1 mixture of *E* : *Z* isomers at the newly formed bond (0.144 g, 62%). The pure (*E*,*E*)-diene was isolated after three recrystallisations: mp 100–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.33 (m, 10H), 7.10 (dd, $J = 15.3$, 11.1 Hz, 1H), 6.35 (dd, $J = 15.0$, 11.1 Hz, 1H), 5.76 (d, $J = 15.3$ Hz, 1H), 5.37 (dd, $J = 15.0$, 10.2 Hz, 1H), 3.71 (s, 3H), 2.31–2.40 (m, 1H), 1.76 (dd, $J = 8.7$, 5.1 Hz, 1H), 1.63 (dd, $J = 5.4$, 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 146.0, 145.7, 145.1, 140.9, 130.9, 128.8, 128.6, 127.7, 127.5, 127.2, 126.4, 118.2, 51.7, 39.3, 31.2, 23.6 ppm. IR (KBr disc): ν_{max} 3025, 3061, 2909, 1714, 1634, 1495, 1309, 1260, 1144 cm^{-1}. EIMS: m/z (%): 304 (M^+, 69), 244 (39), 205 (88), 191 (37), 167 (62), 165 (96), 111 (48), 91 (100). HRMS: calcd for $C_{21}H_{20}O_2$: 304.1463; found 304.1462.

(2*E*,4*E*)-5-(2,2-Diphenylcyclopropyl)penta-2,4-dien-1-ol (15)

Compound **14** (0.193 g, 0.634 mmol, 1 equiv.) was stirred in CH_2Cl_2 (40 mL) at −78 °C under N_2 atm. DIBALH (2.12 mL, 3.17 mmol, 5 equiv., 1.5 M in toluene) was then added and the temperature kept at −78 °C until complete disappearance of the starting material. Ethyl acetate (15 mL), then methanol (15 mL) were added dropwise at −78 °C. A solution of sodium potassium tartrate (5.219 g, 15.9 mmol, 25 equiv.) in water (30 mL) was then added at −78 °C and the mixture allowed to warm to rt overnight. Aqueous HCl (2 M, 5 mL) was added to reduce the precipitates in the mixture. Extraction was carried out using CH_2Cl_2 (40 mL). The organic phase was washed with aqueous $NaHCO_3$ (40 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was subjected to chromatography on silica (ethyl acetate–hexanes 20 : 80) to give **15** (141.9 mg, 0.514 mmol, 81%) as a colourless viscous oil: $R_f = 0.24$ (ethyl acetate–hexanes 20 : 80). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02–7.35 (m, 10H), 6.15 (dd, $J = 15.0$, 10.5 Hz, 1H), 5.97 (dd, $J =$ 15.0, 10.5 Hz, 1H), 5.61 (ddd, $J = 15.0$, 6.0, 6.0 Hz, 1H), 4.86 (dd, $J = 15.0$, 9.6 Hz, 1H), 4.01 (d, $J = 5.4$ Hz, 2H), 2.15–2.27 (m, 1H), 1.57 (dd, $J = 8.7$, 5.1 Hz, 1H), 1.42 (dd, $J = 5.7$, 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 146.4 (C), 141.2 (C), 135.8 (CH), 131.7 (CH), 130.9 (CH), 129.1 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 126.6 (CH), 125.9 (CH), 63.4 (CH_2), 37.8 (C), 30.6 (CH), 22.9 (CH_2). IR (thin film): ν_{max} 3368 (br, OH), 3057, 3024 (m, CH), 2924, 2860 (m, Ar–H), 1688, 1654 (m, C=C) cm^{-1}. EIMS (70 eV): m/z (%): 276 (M^+, 40), 258 ([M − H_2O]$^+$, 50), 245 (50), 217 (40), 205 (50), 191 (50), 167 (90), 165 (80), 115 (50), 91 (100). HRMS (EI$^+$): calcd for $C_{20}H_{20}O$: 276.1514; found 276.1514.

Methyl (2*E*,4*E*)-5-(2,2-diphenylcyclopropyl)penta-2,4-dienyl maleate (1)

To a solution of **15** (0.224 g, 0.811 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) at 0 °C under N_2 atm were added Et_3N (0.181 mL, 1.30 mmol, 1.6 equiv.), maleic anhydride (0.179 g, 1.82 mmol, 2.25 equiv.) and DMAP (10 mg, 0.081 mmol, 0.1 equiv.). The solution was stirred for 10 min, then Et_2O (40 mL) was added and the mixture washed with aqueous HCl (2 M, 2 × 50 mL) and brine (1 × 50 mL). The organic fraction was then dried (Na_2SO_4) and evaporated to dryness. The crude mixture (288 mg)

was diluted in THF (3 mL) and cooled to −78 °C under N_2 atm. A solution of diazomethane in Et_2O was added dropwise until TLC showed no starting material. N_2 was bubbled into the mixture for 30 min to remove the unreacted diazomethane and the solvent was then evaporated under reduced pressure. Column chromatography (CH_2Cl_2–pentane, 60 : 40) afforded **1** as a yellow oil (0.181 g, 57% over two steps from the dienol **15**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14–7.3 (m, 10H), 6.24 (s, 2H), 6.10–6.30 (m, 2H), 5.65 (ddd, J = 14.4, 6.9, 6.9 Hz, 1H), 5.01 (dd, J = 14.4, 9.9 Hz, 1H), 4.65 (d, J = 6.9 Hz, 2H), 3.76 (s, 3H), 2.25–2.33 (m, 1H), 1.68 (dd, J = 8.4, 4.8 Hz, 1H), 1.53 (dd, J = 5.4, 4.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 165.2, 146.5, 141.4, 137.6, 135.5, 131.1, 130.1, 130.0, 128.8, 128.7, 128.6, 127.5, 127.0, 126.3, 123.2, 66.0, 52.4, 38.2, 30.9, 23.7 ppm. IR (thin film): ν_{max} 3057, 3025, 2951, 1730, 1650, 1495, 1437, 1391, 1212, 1162 cm^{-1}. EIMS: m/z (%): 388 (M^+, 35), 357 (38), 342 (46), 329 (28), 328 (100). HRMS: calcd for $C_{25}H_{24}O_4$: 388.1675; found 388.1678.

rel-(3a*R*,4*S*,5*S*,7a*S*,1′*R*)-Methyl 1,3,3a,4,5,7a-hexahydro-3-oxo-5-(2,2-diphenylcyclopropyl)isobenzofuran-4-carboxylate (17a) and *rel*-(3a*R*,4*R*,5*S*,7a*S*,1′*R*)-methyl 1,3,3a,4,5,7a-hexahydro-3-oxo-5-(2,2-diphenylcyclopropyl)isobenzofuran-4-carboxylate (19a)

A solution of **1** (0.457 g, 1.17 mmol, 1 equiv.) and 2,6-di-*tert*-butyl-4-methylphenol (3 mg, 14 μmol, 0.01 equiv.) in toluene (250 mL) was heated at reflux under N_2 atm for 5 h. The solvent was then evaporated under reduced pressure and ^{1}H NMR analysis revealed the presence of two cycloadducts. The two adducts **17a** and **19a** were isolated by column chromatography (petroleum ether 40–60–ethyl acetate–triethylamine, 96 : 2 : 2) in a ratio of 82 : 18 (340.9 mg, 75% combined yield).

17a. White solid (279.5 mg, 61%): mp 161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08–7.28 (m, 10H), 5.71 (ddd, J = 9.9, 1.5, 1.5 Hz, 1H), 5.67 (ddd, J = 9.9, 3.0, 3.0 Hz, 1H), 4.47 (dd, J = 14.5, 7.5 Hz, 1H), 3.86 (dd, J = 11.5, 7.5 Hz, 1H), 3.55 (s, 3H), 3.27 (d, J = 3.6 Hz, 1H), 3.09–3.14 (m, 1H), 2.44 (dd, J = 13.6, 3.6 Hz, 1H), 1.88 (d, J = 10.5, 1H), 1.65–1.74 (m, 1H), 1.55 (dd, J = 5.4, 5.1 Hz, 1H), 1.13 (dd, J = 8.7, 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 172.3, 146.4, 140.7, 132.5, 129.9, 129.1, 128.8, 128.6, 126.9, 126.6, 123.9, 70.9, 52.4, 42.6, 42.3, 39.9, 38.7, 36.6, 32.2, 18.5 ppm. IR (KBr disc): ν_{max} 2917, 1785, 1732, 1495, 1445, 1379, 1177, 1090 cm^{-1}. EIMS: m/z (%): 388 (M^+, 12), 357 (27), 356 (5), 330 (11), 329 (24), 328 (100). Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 77.34; H, 6.25. HRMS: calcd for $C_{25}H_{24}O_4$: 388.1675; found 388.1672.

19a. White solid (61.4 mg, 14%): mp 159–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07–7.26 (m, 10H), 5.92 (ddd, J = 9.9, 2.7, 2.7 Hz, 1H), 5.59 (ddd, J = 9.9, 2.7, 2.7 Hz, 1H), 4.40 (dd, J = 8.7, 8.7 Hz, 1H), 4.10 (dd, J = 8.4, 8.4 Hz, 1H), 3.61 (s, 3H), 3.14 (dd, J = 5.8, 5.8 Hz, 1H), 2.97–3.00 (m, 1H), 2.88 (dd, J = 10.6, 5.8 Hz, 1H), 1.61–1.68 (m, 1H), 1.50–1.58 (m, 1H), 1.38 (dd, J = 5.4, 5.4 Hz, 1H), 1.24 (dd, J = 8.6, 5.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 171.6, 146.3, 140.5, 133.3, 130.6, 129.7, 128.7, 128.6, 128.4, 126.7, 123.1, 70.5, 52.1, 43.5, 42.1, 40.9, 38.3, 35.4, 28.6, 18.5 ppm. IR (KBr disc): ν_{max} 3025, 2923, 1765, 1730, 1494, 1445, 1385, 1173, 1019 cm^{-1}. EIMS: m/z (%): 388 (M^+, 23), 357 (38), 339 (12), 198 (10), 197 (59), 194 (77), 193 (100). HRMS: calcd for $C_{25}H_{24}O_4$: 388.1675; found 388.1676.

Methyl (2*E*,4*E*)-5-(2,2-diphenylcyclopropyl)penta-2,4-dienyl fumarate (2)

To a solution of **15** (1.674 g, 6.06 mmol, 1 equiv.) in CH_2Cl_2 (50 mL) at 0 °C under N_2 atm were added pyridine (1.18 mL, 14.54 mmol, 2.4 equiv.) and 4-dimethylaminopyridine (74 mg, 0.606 mmol, 0.1 equiv.). (*E*)-Methyl 3-(chlorocarbonyl)acrylate (1.08 g, 7.27 mmol, 1.2 equiv.) was then added dropwise at 0 °C. The reaction was stirred at this temperature for 10 min then allowed to warm to rt. After 1.5 h, water was added. The organic phase was then collected and washed with 1 M aqueous HCl, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petroleum ether 40–60–ethyl acetate, 95 : 5) afforded **2** as a yellow oil (1.22 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12–7.36 (m, 10H), 6.86 (s, 2H), 6.10–6.29 (m, 2H), 5.65 (ddd, J = 14.5, 6.9, 6.9 Hz, 1H), 5.02 (dd, J = 14.5, 9.7 Hz, 1H), 4.66 (d, J = 6.9 Hz, 2H), 3.80 (s, 3H), 2.25–2.33 (m, 1H), 1.67 (dd, J = 8.7, 4.8 Hz, 1H), 1.53 (dd, J = 5.7, 4.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 164.9, 146.5, 141.3, 137.8, 135.5, 133.9, 133.6, 131.0, 128.7, 128.6, 128.5, 127.5, 126.9, 126.2, 122.9, 66.1, 52.6, 38.2, 30.8, 23.1 ppm. IR (thin film): ν_{max} 3058, 3025, 2951, 1723, 1652, 1495, 1445, 1301, 1259, 1153, 986 cm^{-1}. EIMS: m/z (%): 388 (M^+, 7), 259 (42), 258 (96), 217 (50), 206 (54), 205 (56), 191 (75), 167 (100). HRMS: calcd for $C_{25}H_{24}O_4$: 388.1675; found 388.1673.

rel-(3a*R*,4*R*,5*S*,7a*S*,1′*R*)-Methyl 1,3,3a,4,5,7a-hexahydro-3-oxo-5-(2,2-diphenylcyclopropyl)isobenzofuran-4-carboxylate (17b) and *rel*-(3a*S*,4*S*,5*R*,7a*R*,1′*R*)-methyl 1,3,3a,4,5,7a-hexahydro-3-oxo-5-(2,2-diphenylcyclopropyl)isobenzofuran-4-carboxylate (18b)

A solution of **2** (0.244 g, 0.63 mmol, 1 equiv.) and 2,6-di-*tert*-butyl-4-methylphenol (2 mg, 9 μmol, 0.01 equiv.) in chlorobenzene (125 mL) was heated to reflux under N_2 atm for 12 h. The solvent was then removed under reduced pressure and ^{1}H NMR analysis of the crude mixture revealed the presence of two cycloadducts. The two adducts **17b** and **18b** were isolated from a fraction of the crude mixture by column chromatography (petroleum ether 40–60–ethyl acetate, 98 : 2, with 2% triethylamine) in a ratio of 86 : 14 (154.2 mg, 63% combined yield).

17b. White solid (132.6 mg, 54%): mp 188–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10–7.20 (m, 10H), 5.71 (ddd, J = 9.9, 1.6, 1.6 Hz, 1H), 5.62 (ddd, J = 9.9, 3.0, 3.0 Hz, 1H), 4.39 (dd, J = 8.1, 6.3 Hz, 1H), 3.92 (dd, J = 11.1, 8.1 Hz, 1H), 3.73 (s, 3H), 2.83 (dd, J = 11.4, 7.5 Hz, 1H), 2.70 (dd, J = 13.5, 11.4 Hz, 1H), 2.60–2.71 (m, 1H), 1.85–1.95 (m, 1H), 1.61–1.71 (m, 1H), 1.42–1.50 (m, 1H), 1.02 (dd, J = 8.5, 5.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 171.6, 146.4, 140.5, 133.3, 129.7, 129.6, 128.6, 128.4, 126.8, 126.7, 123.2, 70.5, 52.1, 43.6, 42.1, 40.9, 38.3, 35.8, 28.6, 18.5 ppm. IR (KBr disc): ν_{max} 2950, 2918, 2849, 1787, 1738, 1494, 1445, 1321, 1273, 1178, 1087. EIMS: m/z (%): 388 (M^+, 11), 258 (14), 220 (16), 217 (9), 194 (68), 193 (100). HRMS: calcd for $C_{25}H_{24}O_4$: 388.1675; found 388.1674.

18b. White solid (21.6 mg, 9%): mp 185–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04–7.27 (m, 10H), 5.82 (ddd, J = 9.6, 2.1, 2.1 Hz, 1H), 5.72 (ddd, J = 9.6, 2.8, 2.8 Hz, 1H), 4.38 (dd, J = 8.2, 6.6 Hz, 1H), 3.90 (dd, J = 11.1, 8.2, 1H), 3.51 (s, 3H), 2.86 (dd, J = 11.1, 7.8 Hz, 1H), 2.72 (dd, J = 13.5, 11.1 Hz, 1H), 2.48–2.66 (m,

1H), 1.84–1.93 (m, 2H), 1.37 (dd, $J = 9.0, 5.1$ Hz, 1H), 1.23 (dd, $J = 9.0, 5.1$ Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 172.8, 146.4, 140.7, 134.6, 130.9, 128.6, 128.4, 127.8, 127.1, 126.1, 124.7, 70.5, 52.3, 44.5, 42.6, 40.7, 37.5, 37.1, 28.6, 19.6 ppm. IR (KBr disc): ν_{max} 2917, 2849, 1784, 1736, 1495, 1262, 1178, 1087 cm^{-1}. EIMS: m/z (%): 388 (M^+, 8), 258 (9), 220(11), 194 (48), 193 (100). HRMS: calcd for $C_{25}H_{24}O_4$: 388.1675; found 388.1675.

1,1-Dimethyl 2-(2*E*,4*E*)-5-(2,2-diphenylcyclopropyl)penta-2,4-dienyl ethene-1,1,2-tricarboxylate (3)

1,1-Dimethyl 2-hydrogen ethylenetricarboxylic acid (**16**)[27a] was prepared from 2-*tert*-butyl 1,1-dimethyl ethylenetricarboxylate using the procedure of Snider.[27b] Oxalyl chloride (258.7 mg, 2.038 mmol, 2.0 equiv.) and DMF (1.5 mg, 0.0204 mmol, 0.02 equiv.) were added to a solution of **16** (191.7 mg, 1.019 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL) and stirred at 0 °C under N_2 atm for 30 min until the evolution of gas ceased. The mixture was then concentrated *in vacuo*, diluted with CH_2Cl_2 (0.8 mL) and added to a solution of **15** (172.7 mg, 0.6249 mmol, 1.0 equiv.) and triethylamine (0.127 mL, 1.250 mmol, 2.0 equiv.) in CH_2Cl_2 (0.8 mL) at 0 °C under N_2 atm. The solution was stirred at this temperature for 10 min then water (10 mL) was added and the mixture extracted with CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4), filtered, and evaporated to dryness to give the crude IMDA precursor **3** (280 mg, quantitative yield) as a yellow oil. Due to its propensity to cyclise, this material was used without further purification.

rel-(3a*R*,5*S*,7a*S*,1′*R*)-Dimethyl 1,3,3a,7a-tetrahydro-3-oxo-5-(2,2-diphenylcyclopropyl)isobenzofuran-4,4-(5*H*)-dicarboxylate (17c)

A solution of IMDA precursor **3** (280 mg) in benzene (62 mL) was stirred at 25 °C under N_2 atm for 3 h. The solvent was then evaporated under reduced pressure and ^{1}H NMR analysis revealed the presence of a single cycloadduct. Column chromatography (hexanes–ethyl acetate–triethylamine, 70 : 28 : 2, absorption load onto silica using ethyl acetate) afforded **17c** as a white solid (201.6 mg, 72%): mp 196–198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11–7.24 (m, 10H), 5.63 (ddd, $J = 9.9, 1.5, 1.5$ Hz, 1H), 5.54 (ddd, $J = 9.9, 3.6, 2.4$ Hz, 1H), 4.40 (dd, $J = 8.1, 6.9$ Hz, 1H), 3.86 (dd, $J = 11.4, 8.1$ Hz, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 2.95 (d, $J = 14.1$ Hz, 1H), 2.58–2.63 (m, 2H), 1.59–1.66 (m, 1H), 1.53–1.59 (m, 1H), 1.02 (dd, $J = 8.4, 4.8$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 169.4, 168.3, 146.3, 140.1, 132.6, 129.9, 129.4, 128.6, 128.5, 126.9, 126.8, 122.7, 69.7, 57.9, 53.5, 53.1, 44.6, 42.4, 38.0, 35.8, 28.8, 18.4 ppm. IR (KBr disc): ν_{max} 3026, 2954, 1795, 1739, 1737, 1496, 1434, 1265, 1088 cm^{-1}. EIMS: m/z (%): 446 (M^+, 30), 414 (19), 258 (24), 220 (22), 197 (28), 193 (100). Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.43; H, 6.10. HRMS: calcd for $C_{27}H_{26}O_6$: 446.1729; found 446.1727.

Acknowledgements

Funding from the Australian Research Council (ARC) is gratefully acknowledged, as are computing time allocations from the Australian Partnership for Advanced Computing and the Australian Centre for Advanced Computing and Communications.

Notes and references

1 (*a*) *The Diels–Alder Reaction: Selected Practical Methods*, ed. F. Fringuelli and A. Taticchi, Wiley, New York, 2002; (*b*) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668–1698.
2 M. J. Lilly, N. A. Miller, A. J. Edwards, A. C. Willis, P. Turner, M. N. Paddon-Row and M. S. Sherburn, *Chem.–Eur. J.*, 2005, **11**, 2525–2536.
3 S. Oudeyer, E. Léonel, J. P. Paugam and J.-Y. Nédélec, *Tetrahedron*, 2003, **59**, 1073–1081.
4 A. Maerckera, K. S. Oeffner and U. Girreser, *Tetrahedron*, 2004, **60**, 8245–8256.
5 J. P. Dinnocenzo, H. Zuilhof, D. R. Lieberman, T. R. Simpson and M. W. McKechney, *J. Am. Chem. Soc.*, 1997, **119**, 994–1004.
6 The Δr_{as} values for the corresponding *cis* TSs for these systems (not given in Table 1) are slightly smaller than those for the respective *trans* TSs. The *cis* TSs are not discussed because, with the exception of **4a**, the *trans* TS is lower in energy than the *cis* TS.
7 (*a*) R. Seeger and J. A. Pople, *J. Chem. Phys.*, 1977, **66**, 3045–3050; (*b*) R. Bauernschmitt and R. Ahlrichs, *J. Chem. Phys.*, 1996, **104**, 9047–9052.
8 (*a*) For representative examples of experimental and computational investigations into biradical Diels–Alder mechanisms, see: L. K. Montgomery, K. Schueller and P. D. Bartlett, *J. Am. Chem. Soc.*, 1964, **86**, 622–628; (*b*) P. D. Bartlett and L. K. Montgomery, *J. Am. Chem. Soc.*, 1964, **86**, 628–631; (*c*) P. D. Bartlett, G. E. H. Wallbillich, A. S. Wingrove, J. S. Swenton, L. K. Montgomery and B. D. Kramer, *J. Am. Chem. Soc.*, 1968, **90**, 2049–2056; (*d*) J. S. Swenton and P. D. Bartlett, *J. Am. Chem. Soc.*, 1968, **90**, 2056–2058; (*e*) P. D. Bartlett, C. J. Dempster, L. K. Montgomery, K. E. Schueller and G. E. H. Wallbillich, *J. Am. Chem. Soc.*, 1969, **91**, 405–409; (*f*) P. D. Bartlett and G. E. H. Wallbillich, *J. Am. Chem. Soc.*, 1969, **91**, 409–414; (*g*) P. D. Bartlett and J. J.-B. Mallett, *J. Am. Chem. Soc.*, 1976, **98**, 143–151; (*h*) V. Branchadell, J. Font, A. G. Moglioni, C. Ochoa de Echagüen, A. Oliva, R. M. Ortuño, J. Veciana and J. Vidal-Gancedo, *J. Am. Chem. Soc.*, 1997, **119**, 9992–10003; (*i*) K. Mikami, S. Matsumoto, Y. Okubo, M. Fujitsuka, O. Ito, T. Suenobu and S. Fukuzumi, *J. Am. Chem. Soc.*, 2000, **122**, 2236–2243; (*j*) S. Sakai and T. Okumura, *J. Mol. Struct. (THEOCHEM)*, 2004, **685**, 89–95.
9 M. Newcomb, C. C. Johnson, M. B. Manek and T. R. Varick, *J. Am. Chem. Soc.*, 1992, **114**, 10915–10921.
10 (*a*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter*, 1988, **37**, 785–789; (*b*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652; (*c*) For reviews of density-functional methods see: T. Ziegler, *Chem. Rev.*, 1991, **91**, 651–667; (*d*) *Density Functional Methods in Chemistry*, ed. J. K. Labanowski and J. W. Andzelm, Springer-Verlag, New York, 1991; (*e*) R. G. Parr and W. Yang, *Density-Functional Theory of Atoms and Molecules*, Oxford University Press, New York, 1989; (*f*) W. Koch and M. C. Holthausen, *A Chemist's Guide to Density Functional Theory*, Wiley-VCH, Weinheim, 2000.
11 (*a*) W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, John Wiley & Sons, Inc., New York, 1986; (*b*) *The Encyclopedia of Computational Chemistry*, ed. P. v. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer, III and P. R. Schreiner, John Wiley & Sons. Ltd., Chichester, 1998.
12 J. W. Moore, R. G. Pearson, *Kinetics and Mechanism*, John Wiley & Sons Inc., New York, 3rd edn, 1981, ch. 7.
13 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian*, 2003, Revision D.01, Gaussian, Inc., Pittsburgh, PA, 2003.
14 O. Wiest, D. C. Montiel and K. N. Houk, *J. Phys. Chem. A*, 1997, **101**, 8378–8388.

15 (*a*) M. J. Lilly, M. N. Paddon-Row, M. S. Sherburn and C. I. Turner, *Chem. Commun.*, 2000, 2213–2214; (*b*) M. N. Paddon-Row and M. S. Sherburn, *Chem. Commun.*, 2000, 2215–2216; (*c*) C. I. Turner, R. M. Williamson, M. N. Paddon-Row and M. S. Sherburn, *J. Org. Chem.*, 2001, **66**, 3963–3969; (*d*) T. N. Cayzer, M. N. Paddon-Row and M. S. Sherburn, *Eur. J. Org. Chem.*, 2003, 4059–4068; (*e*) T. N. Cayzer, M. J. Lilly, R. M. Williamson, M. N. Paddon-Row and M. S. Sherburn, *Org. Biomol. Chem.*, 2005, **3**, 1302–1307.
16 (*a*) T. N. Cayzer, M. N. Paddon-Row, D. Moran, A. D. Payne, M. S. Sherburn and P. Turner, *J. Org. Chem.*, 2005, **70**, 5561–5570; (*b*) M. N. Paddon-Row, D. Moran, G. A. Jones and M. S. Sherburn, *J. Org. Chem.*, 2005, **70**, 10841–10853.
17 (*a*) P. Caramella, N. G. Rondan, M. N. Paddon-Row and K. N. Houk, *J. Am. Chem. Soc.*, 1981, **103**, 2438–2440; (*b*) M. N. Paddon-Row, N. G. Rondan and K. N. Houk, *J. Am. Chem. Soc.*, 1982, **104**, 7162–7166; (*c*) M. N. Paddon-Row, N. G. Rondan, K. N. Houk and K. D. Jordan, *J. Am. Chem. Soc.*, 1982, **104**, 1143–1145; (*d*) K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, C. C. Spellmeyer, J. T. Metz, Y. Li and R. J. Loncharich, *Science*, 1986, **231**, 1108–1117; (*e*) X. Wang, Y. Li, Y.-D. Wu, M. N. Paddon-Row, N. G. Rondan and K. N. Houk, *J. Org. Chem.*, 1990, **55**, 2601–2609; (*f*) S. S. Wong and M. N. Paddon-Row, *J. Chem. Soc., Chem. Commun.*, 1990, 456–458; (*g*) S. S. Wong and M. N. Paddon-Row, *J. Chem. Soc., Chem. Commun.*, 1991, 327–330.
18 (*a*) K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880–3882; (*b*) K. N. Houk, H.-Y. Duh, Y.-D. Wu and S. R. Moses, *J. Am. Chem. Soc.*, 1986, **108**, 2754–2755; (*c*) L. Raimondi, Y.-D. Wu, F. K. Brown and K. N. Houk, *Tetrahedron Lett.*, 1992, **33**, 4409–4412; (*d*) R. Annunziata, M. Benaglia, M. Cinquinu, F. Cozzi and L. Raimondi, *J. Org. Chem.*, 1995, **60**, 4697–4706; (*e*) L. Raimondi and M. Benaglia, *Eur. J. Org. Chem.*, 2001, 1033–1043; (*f*) J. A. R. Luft, K. Meleson and K. N. Houk, *Org. Lett.*, 2007, **9**, 555–558.
19 (*a*) F. K. Brown and K. N. Houk, *Tetrahedron Lett.*, 1985, **26**, 2297–2300; (*b*) L. Raimondi, F. K. Brown, J. Gonzalez and K. N. Houk, *J. Am. Chem. Soc.*, 1992, **114**, 4796–4804.
20 L. A. Carreira, T. G. Towns and T. B. Malloy, Jr., *J. Am. Chem. Soc.*, 1978, **100**, 385–388.
21 In fact, no *cis* TS corresponding to the *ou* conformation for **5c** could be found. Relaxed potential energy scans revealed only a point of inflection for this type of conformation which lies about 10 kJ mol^{-1} above the *in* conformation.
22 L. I. Smith and M. M. Falkof, *Org. Synth.*, 1955, **coll. vol. III**, 350–351.
23 K. Nakagawa, H. Onoue and K. Minami, *Chem. Commun. (London)*, 1966, 730–731.
24 W. M. Jones, T. H. Glenn and D. G. Baarda, *J. Org. Chem.*, 1963, **28**, 2887–2889.
25 S. Sengmany, E. Léonel, J. P. Paugam and J.-Y. Nédélec, *Synthesis*, 2002, **4**, 533–537.
26 Attempts to carry the reduction at higher temperatures resulted in products of cyclopropane ring-opening.
27 (*a*) T. R. Kelly, *Tetrahedron Lett.*, 1973, **14**, 437–440; (*b*) B. B. Snider, D. M. Roush and T. A. Killinger, *J. Am. Chem. Soc.*, 1979, **101**, 6023–6027.
28 H. M. Walborsky, L. Barash, A. E. Young and F. J. Impastato, *J. Am. Chem. Soc.*, 1961, **83**, 2517–2525.
29 M. Schmittel, A. A. Mahajan, G. Bucher and J. W. Bats, *J. Org. Chem.*, 2007, **72**, 2166–2173.

