Optimising Stereoselectivity in Intramolecular Diels–Alder Reactions of Pentadienyl Acrylates: Synthetic and Computational Investigations into the "Steric Directing Group" Approach

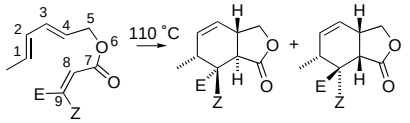
Tory N. Cayzer,[a] Leon S.-M. Wong,[a] Peter Turner,[a] Michael N. Paddon-Row,*[b] and Michael S. Sherburn*[a]

Abstract: Experimental conditions for the intramolecular cycloaddition of four related pentadienyl acrylates **3**, **4**, **5** and **6** are reported. In contrast with several previous reports, pentadienyl acrylates *do* undergo synthetically useful intramolecular Diels–Alder reactions: **3**, **4**, **5** and **6** cyclise at reasonable rates at temperatures of 132–180 °C at atmospheric pressure in moderate to good yields. The stereochemical outcome of each of these reactions was accurately measured and the results are in good agreement with transition structure populations predicted using B3LYP/6-31+G(d) theory. The parent system **3** cyclises with moderate *endo* selectivity; the presence of *either* a C5-methyl substituent *or* a C3-bromine atom results in a slight shift towards the *trans*-fused *exo* stereoisomer but—overall—a less selective reaction. The presence of *both* C3-Br and C5-CH_3 substituents results in a marked improvement in stereoselectivity with the *exo*,*lk*-product predominating. Interpretation of B3LYP/6-31+G(d) transition structures allows insights into the improvement in stereoselectivity obtained by incorporating a removable "steric directing group" into a 5-methyl-1,3,8-nonatriene precursor.

Keywords: cycloaddition · density functional calculations · diastereoselectivity · synthetic methods

Introduction

The intramolecular Diels–Alder (IMDA) reaction has proven to be a remarkably popular reaction in synthesis[1] and evidence for a biological version is growing.[2] Despite the existence of an enormous body of experimental results[1] and a large amount of computational modelling,[3–7] accurate predictions of the stereochemical outcome of many IMDA reactions are not available. In studies directed towards this end, we have calculated transition structures (TSs) for ester tethered 1,3,8-nonatrienes[8] that are fully optimised at the B3LYP/6-31G(d) level of theory and found a remarkably close correlation with experimentally determined stereoselectivities.[9] Both *endo*/*exo*- and π-diastereofacial attributes of the stereoselectivity are accurately predicted by DFT calculations on ester-linked diene–dienophile systems. Our investigations have thus far been limited to the more reactive, terminally-substituted alkenic dienophile precursors which predominantly furnish *trans*-fused bicyclic systems (**1** and **2**, Scheme 1). Herein we disclose our findings on a combined synthetic/computational study into *acrylate* esters of four related pentadienols **3**–**6**. We confirm that, despite several literature reports of unsuccessful reactions of this type,[10–19] pentadienyl acrylates *do* undergo synthetically useful IMDA reactions. We also report the use of bromine as a very effective



1 (E = H, Z = CO_2Me) ***exo*** ***endo***

synthetic product ratio (PhMe, 2h, 79%)	***exo*:*endo*** = 79:21
computed product ratio (gas phase)	***exo*:*endo*** = 97:3

2 (E = CO_2Me; Z = H) ***exo*** ***endo***

synthetic product ratio (PhMe, 23h, 85%)	***exo*:*endo*** = 65:35
computed product ratio (gas phase)	***exo*:*endo*** = 55:45

Scheme 1. B3LYP/6-31G(d) theory correctly predicts both the preference for *trans*-fused *exo* cycloadducts in IMDA reactions of "doubly activated dienophile" precursors **1** and **2** and a lower *exo*/*endo* selectivity for *E*-dienophile precursor **2** than *Z*-dienophile precursor **1**.

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Supporting Information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. ^{1}H and ^{13}C NMR spectra of all cycloadducts, energies and final optimised coordinates for stationary points of all transition structures, and crystal structure analysis details.

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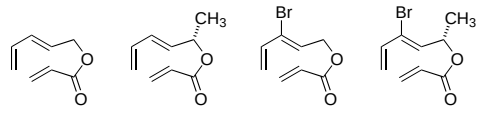
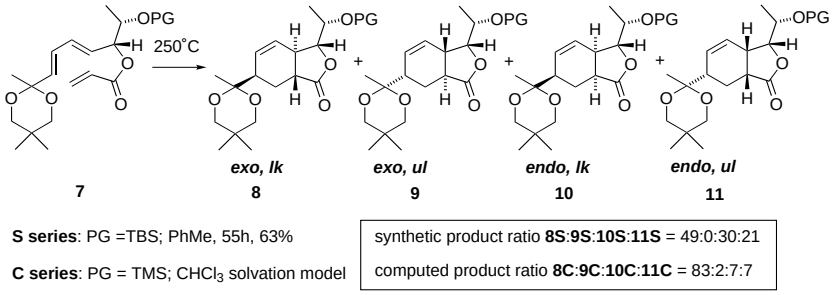


3 4 5 6

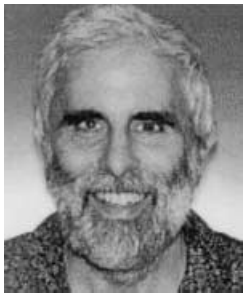
"steric directing group"[20–26] in IMDA reactions of 5-substituted 1,3,8-nonatrienes, and we demonstrate that B3LYP/6-31+G(d) theory models these reactions with a remarkable degree of accuracy. In addition, we expose the attributes of IMDA TSs which are responsible for the observed stereoselectivities: new information which will promote future synthetic applications of IMDA reactions such as these.

While representing key C–C bond forming steps in proposed biosyntheses of the natural products zeylena[27] and ligulaverin[28] the literature contains a significant number of reports of unsuccessful IMDA reactions of pentadienyl acrylates. Thus, in their seminal studies on the IMDA reaction, House and Cronin were discouraged from investigating the intramolecular cycloaddition chemistry of the parent ester-linked 1,3,8-nonatriene system **3** due to its alleged propensity for polymerisation (see below, however).[10, 29] Subsequent to the House/Cronin study, the literature contains several reports of unsuccessful IMDA reactions of acrylate esters.[11, 13–18] Substrates demonstrating a reluctance to cyclise include tether substituted triene **4** (no reaction in refluxing xylene over 18 h)[16] whereas other pentadienyl acrylate precursors decomposed on heating in toluene[13] or benzene.[14] A major obstacle to IMDA reaction of ester tethered trienes appears to be an equilibrium disfavouring the necessary *E*-conformation of the ester linkage,[30] although, at least with the furan diene and more activated dienophiles, this problem can be overcome by carrying out the reaction in a more polar solvent.[31] Indeed, the IMDA reaction of pentadienyl acrylates is so synthetically unattractive that ingenious alternative methods involving temporary metal connections[32] and diester tethers[33] have been developed to prepare pentadienyl acrylate adducts.

Of the six reports of successful IMDA reactions of pentadienyl acrylates,[29, 34–38] two describe the cycloaddition of activated cyclic dienes[37, 38] and two report very low yielding ($\leq$13%) reactions of unactivated acyclic dienes.[29, 36] The remaining two papers detail White's elegant synthetic approach towards pillaromycinone.[34, 35] Thus, upon heating to 250 °C in a sealed vessel, a solution of acrylate **7** (Scheme 2) provided a mixture of three of the four possible stereoisomeric cycloadducts **8**–**11** in the key step of the pillaromycinone synthesis. White and Snyder recently disclosed their findings on experimental and computational aspects of this IMDA reaction,[34] with transition structures leading to the four IMDA adducts being located using the MM2* procedure[6] and single point energies for these TSs calculated at the B3LYP/6-31+G(d) level (e.g. B3LYP/6-31G(d)//MM2*). The MM2*-optimised TSs for IMDA reaction of **7** exhibit a longer developing *internal* bond and shorter developing *peripheral* bond,[34] the reverse of that found by us in *fully optimised* B3LYP/6-31G(d) TSs for related IMDA reactions.[9] This difference in developing bond lengths notwithstanding, the combined B3LYP/6-31G*//MM2* method correctly identifies *exo,like*[39] adduct **8** as the major product.



Scheme 2. Synthetic and B3LYP/6-31G(d)//MM2* computational results reported by White and Snyder.[34]



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In light of these decidedly mixed results of attempts to carry out IMDA reactions of pentadienyl acrylates, we felt that a more thorough investigation into reactions of this type was needed. A group of four pentadienyl acrylate IMDA precursors **3**–**6** was chosen as the focus of both synthetic and computational investigations such that salient aspects of *endo*/*exo* stereoselectivity and π-diastereoselectivity might be delineated.

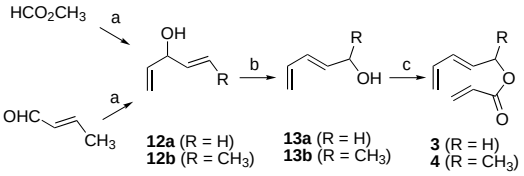
The influence of C3-substituents upon the stereochemical outcome of IMDA reactions has received considerable attention over the past 20 years.[1] 3,7-Disubstituted 1,3,8-

0947-6539/02/0803-0740 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 3

nonatriene substrates undergo IMDA reactions which preferentially form *trans*-fused bicyclic products,[24, 40] a transformation which has enjoyed application in the synthesis of the CD ring system of steroids. With some substrates, however, the *cis*/*trans* selectivity is negligible;[41] with others, the *cis*-fused product is dominant.[42] In a recent report, the stereoselectivity of a 3-methyl-1,3,8-nonatriene IMDA reaction was reversed as the tether substituents were altered.[43] These results clearly demonstrate that the various stereodirecting influences are finely balanced in reactions of this type. Independent studies by the Boeckman[20] and Roush[21] groups led to the development of *removable* C3-substituents for controlling the stereochemical outcome of both 1,3,8-nonatriene and 1,3,9-decatriene IMDA reactions. This "steric directing group" strategy, with its origins in the work of Wilson[22] (and a timely contribution by Marshall[23]) involves the temporary placement of a TMS or Br substituent at C3 of a 5-substituted-1,3,9-decatriene. The strategy has enjoyed application in the 1,3,9-decatriene series by the Roush group[25] and others[26] in several successful total syntheses, with an improvement in IMDA stereoselectivity of a 5-substituted-1,3,9-decatriene invariably being seen upon incorporation of a heteroatom-based group at C3. In view of the modest *exo*/*endo* stereoselectivity witnessed in the cyclisation of pentadienyl acrylate **7** by White (Scheme 2),[34, 35] the use of a C3-bromine substituent as a stereocontrolling element in 5-substituted-1,3,8-nonatriene precursor **6** was an attractive proposition. Such a study would complement results obtained in the 1,3,9-decatriene series[44] and promote future applications in stereoselective synthesis.

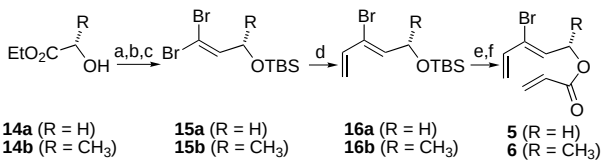
Results and Discussion

The preparation of the four IMDA precursors is shown in Schemes 3 and 4. Non-brominated precursors **3** and **4** were prepared by acid-catalysed transposition reactions of doubly allylic alcohols **12a** and **12b** to the corresponding conjugated dienols **13a** and **13b**[45] followed by esterification with acryloyl chloride (Scheme 3). Brominated trienes **5** and **6** were



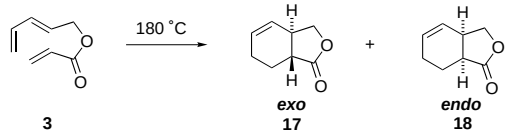
Scheme 3. Synthesis of pentadienyl acrylates **3** and **4**: a) CH_2=CHMgBr, THF, 0–25 °C, **12a**: 53 %; **12b**: 87 %; b) 1 % H_2SO_4/H_2O, 30 °C, **13a**: 74 %; **13b**: 64 %; c) CH_2=CHCOCl, Et_3N, CH_2Cl_2, 0 °C, **3**: 55 %; **4**: 61 %.

prepared through six step sequences commencing from ethyl glycolate **14a** and ethyl lactate **14b**, respectively (Scheme 4). The alcohol functionality of the hydroxy ester starting material was first protected as the silyl ether, the ester group was then reduced to the corresponding aldehyde before Corey–Fuchs reaction to form the *gem*-dibromoolefins **15a** and **15b**.[46] Stille couplings under modified Farina conditions[47] gave the *Z*-bromodienes **16a** and **16b** in >20:1 selectivity over the *E*-bromodiene regioisomer.[48] Deprotection of the silyl ether and esterification of the resulting bromodienols with acryloyl chloride gave the requisite IMDA precursors **5** and **6**. In our hands, none of these four IMDA precursors were particularly susceptible to polymerisation. However, the parent precursor **3** was found to have poor solubility at room temperature in several common organic solvents (benzene, toluene, THF, diethyl ether), and it might have been this unexpected property which led House and Cronin to their (apparently erroneous) conclusion that **3** undergoes facile polymerisation.[10]



Scheme 4. Synthesis of pentadienyl acrylates **5** and **6**: a) TBSCl, imidazole, DMAP, CH_2Cl_2, 0–25 °C, **a**: 100 %; **b**: 86 %; b) DIBALH, CH_2Cl_2, −78 °C, **a**: 87 %; **b**: 87 %; c) PPh_3, CBr_4, CH_2Cl_2, 0–25 °C, **15a**: 86 %; **15b**: 67 %; d) CH_2=$CHSnBu_3$, Pd_2dba_3, $AsPh_3$, THF, 50 °C, **16a**: 83 %; **16b**: 85 %; e) TBAF, THF, 0–25 °C, **a**: 84 %; **b**: 77 %; f) CH_2=CHCOCl, Et_3N, CH_2Cl_2, 0 °C, **5**: 79 %; **6**: 83 %.

The results of IMDA reactions of the four pentadienyl acrylates are depicted in Schemes 5–8, along with predicted Boltzmann populations from DFT calculations. All calculations were carried out using the GAUSSIAN 98 program.[49]



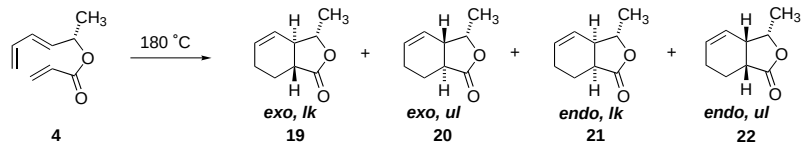
synthetic product ratio
(1,2-$C_6H_4Cl_2$, 190 h, 10 mol % BHT, 56%) **17**:**18** = 30:70

computed product ratio
(populations at B3LYP/6-31+G(d) level):

a) based on electronic energies (incl. zpe)	**17**:**18** = 38:62
b) based on enthalpies	**17**:**18** = 39:61
c) based on free energies	**17**:**18** = 36:64

Scheme 5. Synthetic and computed product ratios for the IMDA reaction of **3**. Synthetic product ratios are based on GC and NMR analyses of crude reaction mixtures; computed product ratios refer to the gas phase.

The hybrid B3LYP functional was used throughout, with the 6-31G(d) and 6-31+G(d) basis sets. It is well known that the B3LYP/6-31G(d) and B3LYP/6-31+G(d) models give excellent transition structures and energies for pericyclic reactions.[3, 50, 51] All transition structures were fully optimised using both basis sets and they were characterised by harmonic frequency calculations using the same level of theory. Zero-point energy (zpe) corrections to the energies of the transition structures were unscaled. The diastereomeric product distribution for each reaction was assumed to be identical to the Boltzmann populations of the respective transition structures and these were calculated using the same temperature that was used in the experiment. Three different Boltzmann populations were calculated for each IMDA reaction, depending on the type of (relative) transition structure energy being



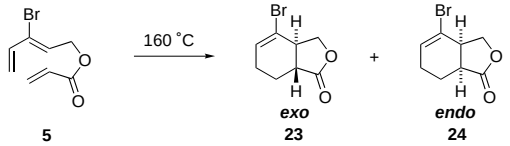
4 19 20 21 22

synthetic product ratio (1,2-$C_6H_4Cl_2$, 146 h, 5 mol % BHT, 59%) **19**:**20**:**21**:**22** = 28:12:30:30

computed product ratio (populations at B3LYP/6-31+G(d) level):

a) based on electronic energies (incl. zpe) **19**:**20**:**21**:**22** = 45:8:25:22
b) based on enthalpies **19**:**20**:**21**:**22** = 42:9:25:24
c) based on free energies **19**:**20**:**21**:**22** = 47:7:27:19

Scheme 6. Synthetic and computed product ratios for the IMDA reaction of **4**. Synthetic product ratios are based on GC and NMR analyses of crude reaction mixtures; computed product ratios refer to the gas phase.



5 23 24

synthetic product ratio (1,2-$C_6H_4Cl_2$, 87 h, 5 mol % BHT, 71%) **23**:**24** = 50:50

computed product ratio (populations at B3LYP/6-31+G(d) level):

a) based on electronic energies (incl. zpe) **23**:**24** = 73:27
b) based on enthalpies **23**:**24** = 72:28
c) based on free energies **23**:**24** = 76:24

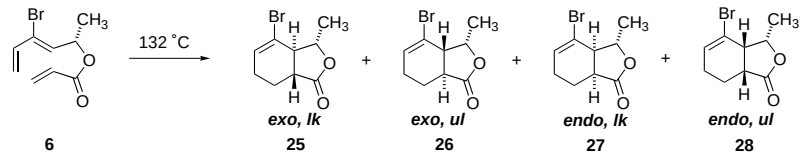
Scheme 7. Synthetic and computed product ratios for the IMDA reaction of **5**. Synthetic product ratios are based on GC and NMR analyses of crude reaction mixtures; computed product ratios refer to the gas phase.

considered: relative electronic energies (including zpe), relative enthalpies and relative free energies. These energy values, which refer to gas phase transition structures, are given in Table 1.

Table 1. B3LYP/6-31+G(d) relative energies (E_{rel}) of transition structures.

Transition structure	E_{rel} [kJ mol^{-1}][a]
3-*exo*	1.88
3-*endo*	0.00
4-*exo*,*lk*	0.00
4-*exo*,*ul*	6.42
4-*endo*,*lk*	2.22
4-*endo*,*ul*	2.63
5-*exo*	0.00
5-*endo*	3.53
6-*exo*,*lk*	0.00
6-*exo*,*ul*	19.8
6-*endo*,*lk*	8.17
6-*endo*,*ul*	16.5

[a] Including B3LYP/6-31+G(d) zero-point energy correction.



6 25 26 27 28

synthetic product ratio (PhCl, 156 h, 5 mol % BHT, 83%) **25**:**26**:**27**:**28** = 81:0:19:0

computed product ratio (populations at B3LYP/6-31+G(d) level):

a) based on electronic energies (incl. zpe) **25**:**26**:**27**:**28** = 91:0:8:1
b) based on enthalpies **25**:**26**:**27**:**28** = 91:0:8:1
c) based on free energies **25**:**26**:**27**:**28** = 92:0.5:7:0.5

Scheme 8. Synthetic and computed product ratios for the IMDA reaction of **6**. Synthetic product ratios are based on GC and NMR analyses of crude reaction mixtures; computed product ratios refer to the gas phase.

The B3LYP/6-31+G(d) transition structures are shown in Figures 1–4, together with the lengths of the forming bonds (those optimised using the 6-31G(d) are shown in parentheses). We found that both 6-31+G(d) and 6-31G(d) basis sets gave very similar geometries for all transition structures and the computed Boltzmann populations were also quite similar, although those using the 6-31+G(d) basis set are in slightly better agreement (by about 2%) with the experimental product distribution data than those using the 6-31G(d) basis set. Accordingly, we present only the results using the 6-31+G(d) basis set. Geometric details of the optimised transition structures and their energies are provided in the Supporting Information.

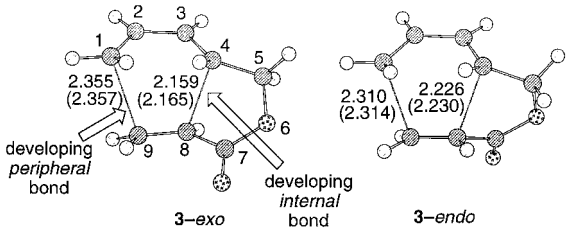


Figure 1. IMDA TS geometries for **3** at the B3LYP/6-31+G(d) level of theory. Distances shown are in Å (distances in parentheses refer to the B3LYP/6-31G(d) basis set).

Reactions were conducted at atmospheric pressure in dilute solutions in 1,2-dichlorobenzene or chlorobenzene in the presence of a small amount of antioxidant and the progress of each reaction was monitored by GC.[52] Interestingly, the parent compound **3** required a longer time for cyclisation than its 5-methyl analogue **4** which, in turn, was less reactive than the 3-bromodiene compounds. Of the brominated precursors, the compound possessing the 5-methyl tether substituent **6** underwent IMDA reaction significantly more readily than its *des*-methyl analogue **5**. Evidently, the presence of either a 3-bromo substituent or a 5-methyl group (or both) accelerates the rate of the IMDA reaction. The observation of a faster reaction upon C5-substitution is in qualitative agreement with Jung's observations with related IMDA reactions of the furan diene, which were interpreted as a manifestation of the reactive rotamer effect.[31] With the exception of the 3-bromo-5-methyl precursor **6**, the trienes furnished mixtures of all possible stereoisomeric products. With precursor **6**, only two of the four possible isomers were formed, within the limits of detection.[53, 54] All ten cycloadducts were found to be stable to the reaction conditions used to

0947-6539/02/0803-0742 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 3

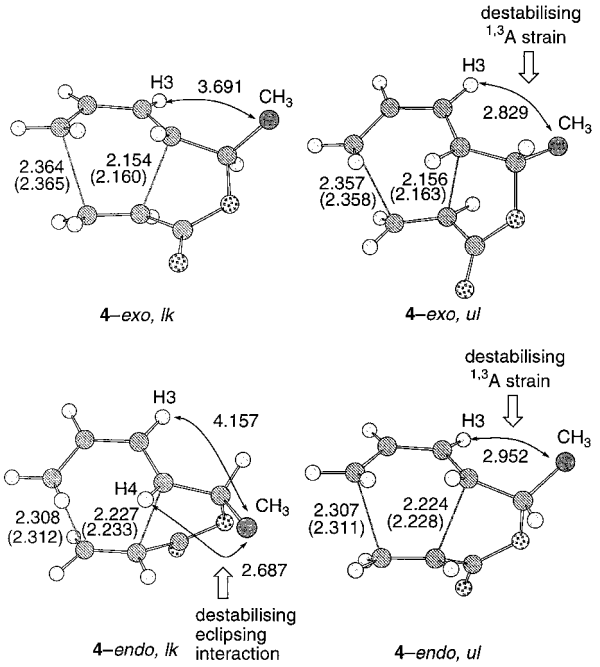


Figure 2. IMDA TS geometries for **4** at the B3LYP/6-31+G(d) level of theory. Distances shown are in Å (distances in parentheses refer to the B3LYP/6-31G(d) basis set). Hydrogens are omitted from the C5 methyl group (darkened) for clarity.

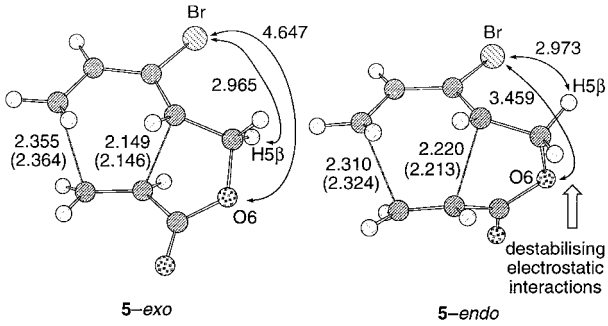


Figure 3. IMDA TS geometries for **5** at the B3LYP/6-31+G(d) level of theory. Distances shown are in Å (distances in parentheses refer to the B3LYP/6-31G(d) basis set).

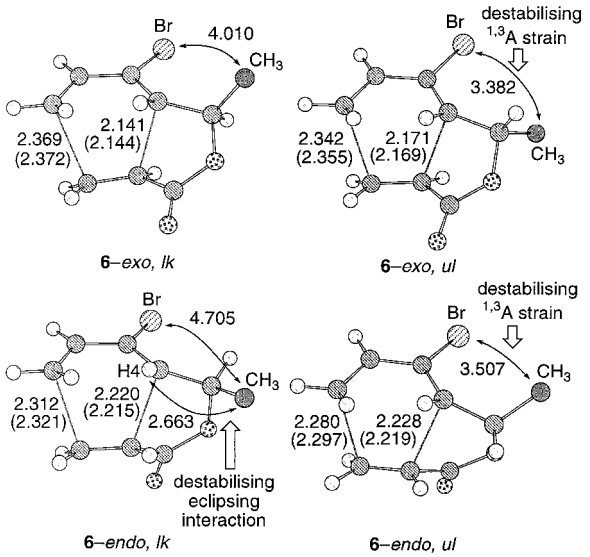
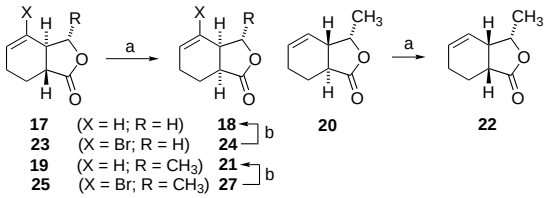


Figure 4. IMDA TS geometries for **6** at the B3LYP/6-31+G(d) level of theory. Distances shown are in Å (distances in parentheses refer to the B3LYP/6-31G(d) basis set). Hydrogens are omitted from the C5 methyl group (darkened) for clarity.



Scheme 9. IMDA cycloadduct structure correlation experiments: a) DBU (1.25 equiv), CH_2Cl_2, 40 °C, 1.5 h; b) $HSnBu_3$ (2.9 equiv), AIBN (0.1 equiv), PhMe, 80 °C, 18 h.

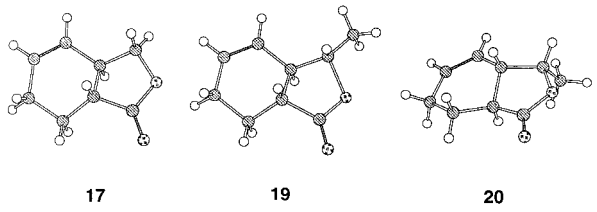


Figure 5. Chem 3D renderings of X-ray coordinates of *exo* cycloadducts **17**, **19**, and **20**.

form them, demonstrating that the reactions were under kinetic control. Initial assignments of product stereochemistries were based upon the results of NMR experiments. These assignments were augmented by the following cross-correlation studies (Scheme 9). Firstly, each *trans*-fused *exo* adduct was converted cleanly in essentially quantitative yield into the *cis*-fused congener by treatment with a slight excess of DBU in dichloromethane. Secondly, reductive debromination of the bromine-containing cycloadducts with tributylstannane/AIBN in hot toluene gave the corresponding non-halogenated congener as a single stereoisomer. The stereochemistry of each of the *trans*-fused *exo*-IMDA adducts **17**, **19** and **20** was confirmed by single crystal X-ray analysis (Figure 5).[55] The corresponding *cis*-fused bicyclic *endo* adducts are oils at ambient temperature.

The observed *exo*:*endo* product ratio[56] for the parent compound **3** in refluxing 1,2-dichlorobenzene (30:70) is in very good agreement with the calculated Boltzmann population (38:62) for the fully optimised B3LYP/6-31+G(d) TSs in the gas phase at 180 °C.[57] The calculated product distribution is essentially the same irrespective of whether relative electronic energies, relative enthalpies or relative free energies of transition structures were used.

The presence of the tether (C5) methyl substituent tilts the product distribution marginally towards the *exo*-product stereochemistry (*exo*:*endo* = 40:60), yet even this subtle difference is predicted by our calculations (e.g. Scheme 6, a) *exo*:*endo* = 53:47). Interestingly, the *exo*,*lk* isomer **19** is preferred over its *ul* congener **20**, whereas there is no such preference between the two *endo* isomers **21** and **22**.[58] These observations are reproduced in our DFT calculations (Scheme 6, a)–c)). The incorporation of the 3-bromo substituent into the parent triene structure (Scheme 7 versus Scheme 5) causes a slightly more pronounced shift towards

the *exo* isomer than does the incorporation of a tether methyl group (Scheme 6 versus Scheme 5). Again, this trend is reflected in the DFT calculations, although they predict a larger *exo*:*endo* ratio of 73:27 than the observed one of 50:50. This discrepancy may be due to the neglect of solvation effects in the calculations: Whereas the B3LYP/6-31G(d) dipole moments of the *exo* and *endo* TSs for **3** are essentially the same (4.4 D), that for the **5**-*endo* TS (5.2 D) is significantly larger than that for **5**-*exo* TS (3.4 D). It is therefore expected that **5**-*endo* TS will be stabilised relative to **5**-*exo* TS by polar solvents such as *ortho*-dichlorobenzene, the solvent used in the IMDA reaction of **5**. This proposition receives support from, albeit, crude self-consistent reaction field (SCRF) calculations based on the solvation continuum Onsager model.[59, 60] The B3LYP/6-31G(d) *exo* and *endo* TSs for the IMDA reaction of **5** were optimised using a solvent dielectric corresponding to *ortho*-dichlorobenzene ($\varepsilon = 9.93$). The resulting Boltzmann distribution gave an *exo*:*endo* product ratio of 44:56. This ratio is in remarkable (but fortuitous) agreement with the experimental ratio of 50:50.[61]

It is the 3-bromo-5-methyl substrate **6**, however, which displays the most dramatic change in product stereoselection. Only products of *lk* π-facial selectivity are seen, and the *exo*,*lk* stereoisomer **25** is by far the more dominant of this *exo*/*endo* pair. Moreover, there is good agreement between the observed product distribution and the Boltzmann distributions of the DFT TSs.

Interpretation of the Results

Dienophile moieties of IMDA precursors can be activated by the attachment of an electron acceptor to either the peripheral or the internal dienophile carbon. With 1,3,8-nonatrienes, the presence of a peripheral (i.e., C9) acceptor group leads to advanced *internal* (C4–C8) bond development in IMDA transition states. The stereocontrolling influences upon these IMDA transition states are like those at play in the formation of 1,2-disubstituted five-membered rings: Greater steric interference is felt in the transition state leading to the *cis*-isomer than the *trans*-isomer. Thus, *trans*-fused bicyclo[4.3.0]-nonanes are the dominant products in IMDA reactions of terminally-activated 1,3,8-nonatrienes.[40b] With internally-activated 1,3,8-nonatrienes the IMDA transition state asynchronicity is reversed, with *peripheral* (C1–C9) bond formation being advanced. In this scenario the transition states are nine-membered ring-like, a situation which favours the *cis*-fused bicyclo[4.3.0]nonane cycloadduct.[40b]

On the basis of this argument, the experimental *cis*- (i.e., *endo*-) preference of the parent triene **3**, carrying an internal acceptor (the ester tether carbonyl group), is expected. *The surprising aspect of the present work is that B3LYP/6-31G+(d) theory shows advanced internal (C4–C8) bond formation in both* **3**-*exo and* **3**-*endo TSs* (Figure 1). Such an arrangement would usually be expected to give rise to the *trans*-fused *exo* product. The likely reason for this unexpected TS bond length asynchronicity is reduced overlap between the C7 carbonyl group and the dienophile (C8–C9) π bond. Thus, for diene and dienophile to dock in a reactive conformation, the linking chain between the two reacting moieties is conformationally constrained to such an extent that C=C-C=O conjugation is disrupted. Indeed, the non-coplanarity of the C=C-C=O bond is evident in all IMDA TSs for **3**, **4**, **5** and **6** (Figure 6; C9-C8-C7-C=O dihedral angles range from 30 – 32°). This TS feature explains the necessity for unexpectedly high temperatures in the promotion of IMDA reactions of pentadienyl acrylates:

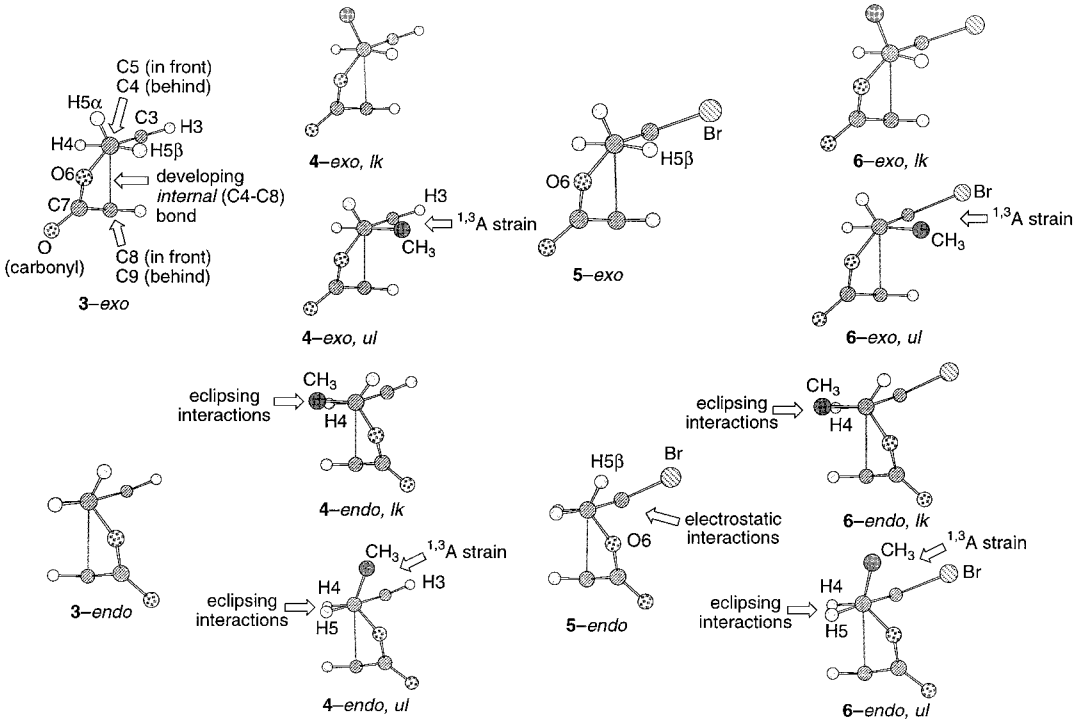


Figure 6. Profile views of B3LYP/6-31+G(d) IMDA TSs for **3**, **4**, **5** and **6**. A key is provided in the **3**-*exo* TS. Important interactions are highlighted. Hydrogens are omitted from the C5 methyl group (darkened) for clarity.

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the dienophile moieties in these substrates are poorly served by the C7 carbonyl "activating" group. Indeed, it is probably no coincidence that **3** indergoes IMDA reaction with a similar *endo*:*exo* selectivity to the parent *trimethylene*-tethered 1,3,8-nonatriene.[4]

The increase in *exo* selectivity upon the introduction of C3 and C5 substituents into **3** could, a priori, have its origin in the twist-asynchronicity model of Brown and Houk.[7] In this model, any substitution in a 1,3,8-nonatriene-type system which leads to shorter developing *internal* (C4–C8) bonds in IMDA TSs favours *trans*-fused *exo* products over the *cis*-fused *endo* products. This preference arises from conformational requirements about the developing *internal* bond which results in a twist of the dienophile about this axis: This twist-asynchronicity is more readily accommodated in *exo* TSs than in *endo* TSs. In the absence of substitution, the *endo* TS is preferred. A dramatic example of this effect is provided by **29** (Figure 7), in which an ester substituent is located at C9. Whereas unsubstituted **3** gives an experimental *exo*:*endo* ratio of 30:70 (see above), **29** gives almost exclusively *exo* product, with an *exo*:*endo* ratio of 95:5.[9, 62] The increased asynchronicity in the *exo* and *endo* TSs for the IMDA reaction of **29**, compared with **3**, as measured by the difference in the lengths, Δr, of the developing bonds is apparent. Thus Δr is 0.1 – 0.2 Å, for **3** (Figure 1), compared to 0.5 – 0.7 Å for **29** (Figure 7). In addition, the twist-asynchronicity in the *exo* TSs, as measured by θ_1 (C3-C4-C8-C9 dihedral angle) is much larger in C9-substituted ester **29** (73.8°) than in unsubstituted **3** (61.5°).[63]

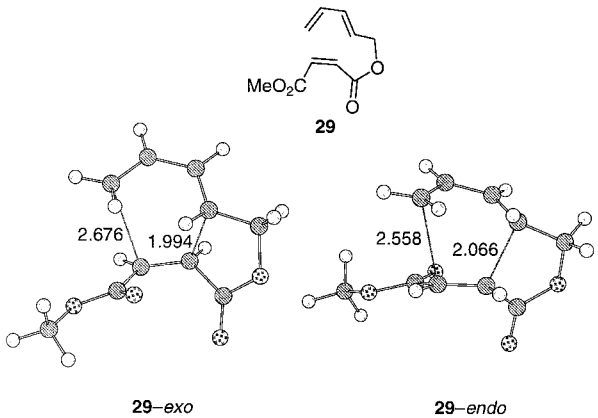

Figure 7. IMDA TS geometries for **29** at the B3LYP/6-31G(d) level of theory. Distances shown are in Å.

Inspection of the TSs for **4**–**6** (Figures 2 – 4) reveal no increased bond length asynchronicity relative to **3** with the Δr values remaining remarkably similar throughout the series ($\Delta r \approx 0.2$ Å for the *exo* TSs and ≈ 0.1 Å for the *endo* TSs). In addition, the level of twist-asynchronicity in the *exo* TSs of **4**–**6** are either the same as or *less* than that in **3** ($\theta_1 = 55.4 - 61.6°$ in **4**–**6** versus 61.5° in **3**). *Twist asynchronicity clearly does not explain the observed increase in exo product along the series* **3** < **4** < **5** < **6**.

The enhanced *exo* selectivity observed and calculated for the IMDA reaction of **4**, relative to that for **3**, is most likely due to torsional effects involving the disposition of the C5-methyl group about the C4–C5 bond. The C1–C5 fragment, together with the C5-methyl group, may be modelled by 1,3-hexadiene. Referring to the profiles of the IMDA TSs for the IMDA reaction of **4**, depicted in Figure 6, the conformations of both **4**-*endo*,*lk* and **4**-*endo*,*ul* TSs about the C4–C5 bond correspond approximately to B3LYP/6-31G(d) conformational energy maxima for 1,3-hexadiene since both suffer eclipsing interactions between a C5-group and the C4–H bond. In addition, there is a repulsive interaction between C5-methyl and the double bond in **4**-*endo*,*ul* (this may be more clearly seen using the "bent-bond" representation[64] for the double bond). In contrast, the conformations of both **4**-*exo*,*lk* and **4**-*exo*,*ul* TSs correspond approximately to B3LYP/6-31G(d) energy minima for 1,3-hexadiene. Thus, the presence of the C5-methyl substituent has the effect of accentuating the *exo*/*endo* energy difference by way of this additional steric and torsional strain.

The enhanced *exo* selectivity observed and calculated for the IMDA reaction of **5**, relative to that for **3**, is probably *not* due to ^{1,3}A strain involving the C3-Br substituent since the distance between Br and H5β is about the same in both **5**-*exo* and **5**-*endo* TSs (Figure 3). We favour an electrostatic explanation: The Br substituent is 1 Å closer to O6 in the **5**-*endo* TS, compared with the **5**-*exo* TS. (One of O6's lone pairs in the **5**-*endo* TS point towards the Br atom.[65]) In addition, the C3–Br bond dipole has a less favourable alignment in the **5**-*endo* TS with both the C5–O6 and C7 carbonyl dipoles, compared with the **5**-*exo* TS, resulting in the aforementioned higher dipole moment for the **5**-*endo* TS (5.2 D) than for the **5**-*exo* TS (3.4 D).

Quantitative estimates of the preferences that the C3-Br and C5-methyl substituents have for *exo* over *endo* docking modes may be obtained from the relative energies of the TSs, presented in Table 1. For unsubstituted **3** the B3LYP/6-31+G(d) *endo* TS is 1.9 kJ mol^{-1} lower in energy than the *exo* TS (including zpe). For **4**, the *exo*,*lk* TS is 2.2 kJ mol^{-1} lower in energy than the *endo*,*lk* TS. The introduction of a C5-methyl group therefore causes a stabilisation of the *exo* TS over the *endo* TS by 4.1 kJ mol^{-1}. The **5**-*exo* TS is calculated to be 3.5 kJ mol^{-1} lower in energy than the **5**-*endo* TS. Thus, the introduction of a C3-Br group leads to a lowering of the *exo* TS energy of 5.4 kJ mol^{-1} relative to the *endo* TS. Assuming an additive *exo* directing effect of the C3-Br and C5-methyl groups, the **6**-*exo*,*lk* TS should be favoured over the **6**-*endo*,*lk* TS by about 9.5 kJ mol^{-1}. In fact the B3LYP/6-31+G(d) preference is 8.2 kJ mol^{-1} which is close to the estimated value based on additivity.

The IMDA reactions of **4** and **6** each gives the predominant stereoisomeric product resulting from *like* approach of the dienophile to the diene. This preference for *like* over *unlike* adducts may be explained in terms of minimisation of developing ^{1,3}A strain in the IMDA transition structure.[66] Specifically, dienophile approach to one π diastereoface of the diene incurs a penalty caused by destabilising steric interactions between the C5-methyl group and H3 (with **4**) or Br (with **6**). Consider first the IMDA reaction involving **4**. This destabilising interaction is clearly seen in the **4**-*exo*,*ul* TS (Figures 2 and 6), in which the H3-(C5)methyl distance is 2.83 Å. This interaction, which is absent in the **4**-*exo*,*lk* TS, results in a 6.4 kJ mol^{-1} energetic preference for the **4**-*exo*,*lk*

TS over the **4**-*exo*,*ul* TS (Table 1). With regard to the *endo*,*lk* and *ul* TSs, the destabilising ^{1,3}A interaction is less pronounced in the **4**-*endo*,*ul* TS, compared to the **4**-*exo*,*ul* TS, because the H3-(C5)methyl distance in the former TS is 0.12 Å greater than that in the latter. However, the **4**-*endo*,*lk* TS also suffers an energetic penalty that is due, not to ^{1,3}A strain, but to an eclipsing (C4)H-(C5)methyl interaction (these groups are 2.69 Å apart). The consequence of both **4**-*endo*,*lk* and **4**-*endo*,*ul* TSs suffering destabilising interactions seems to be that both TSs have similar energies (Table 1), thereby resulting in equal amounts of *like* and *unlike* adducts, as observed experimentally. Introduction of Br at C3 of **4**, to give **6**, leads to a significant increase in ^{1,3}A strain in both *unlike* TSs, namely **6**-*exo*,*ul* and **6**-*endo*,*ul*, for the IMDA reaction of **6**, owing to the fairly short (C3)Br-(C5)methyl distances of 3.38 and 3.51 Å, respectively, in these TSs (Figures 4, 6). In both TSs the Br and methyl substituents probably lie within the sum of their van der Waals radii (e.g. the Pauling van der Waals radii for Br and methyl are 1.95 and 2.0 Å, respectively.[67]). This large destabilising ^{1,3}A interaction is reflected in the significant increase in the energies of the *unlike* TSs, compared with the respective *like* TSs, namely 19.8 kJ mol^{-1} for **6**-*exo*,*ul* TS, relative to **6**-*exo*,*lk* TS, and 8.3 kJ mol^{-1} for **6**-*endo*,*ul* TS, relative to **6**-*endo*,*lk* TS (Table 1). The smaller energy difference calculated between the two *endo* TSs, compared to that between the two *exo* TSs, is due to the presence of the additional eclipsing (C4)H-(C5)methyl interaction in the **6**-*endo*,*lk* TS.

Conclusion

This work demonstrates that, in contrast with the majority of literature on this transformation, intramolecular Diels–Alder reactions of pentadienyl acrylates *are* synthetically useful reactions. The parent triene **3** undergoes a moderately *endo*-selective IMDA reaction upon thermolysis. Interestingly, both C3-Br and C5-CH_3 substituents have an *exo*-directing influence on the stereochemical outcome of IMDA reactions of 1,3,8-nonatrienes. When both C3-Br and C5-CH_3 substituents are present in the same precursor, a highly stereoselective reaction ensues. Thus, bromine serves as an effective, removable C3 "steric directing group" in this class of IMDA reaction.

Importantly, the stereochemical outcome of these reactions can be predicted to a level that is unprecedented for IMDA processes. Thus, DFT at the B3LYP/6-31+G(d) level of theory is a useful qualitative *and* quantitative predictor of stereoselectivity in IMDA reactions. Theory has also given useful insights into the origin of the observed stereoselectivities. Thus, a shift towards *exo* cycloadducts upon incorporation of a tether (C5) methyl substituent arises not through increased TS asynchronicity, but instead through destabilising eclipsing interactions between substituents about the C4–C5 bond in IMDA TSs. A shift towards *exo* cycloadducts upon incorporation of a C3-Br comes about through unfavourable electrostatic interactions in the *endo* TS. π-Diastereofacial selectivity in these reactions is dominated by the development of ^{1,3}A strain in TSs leading to the minor isomers. DFT also provides clues to the lack of reactivity of pentadienyl acrylates and, as such, is strongly recommended for those planning to use IMDA reactions in future synthetic endeavours.

Experimental Section

General methods: NMR spectra were recorded using a Bruker DPX/DRX 400 MHz spectrometer. Residual acetone ($\delta = 2.04$), benzene ($\delta = 7.15$), chloroform ($\delta = 7.26$), and methanol ($\delta = 3.31$) were used as internal references for ^{1}H NMR spectra measured in these solvents. Residual acetone ($\delta = 29.8$), benzene ($\delta = 128.1$), chloroform ($\delta = 77.1$), and methanol ($\delta = 49.0$) were used as internal references for ^{13}C NMR spectra. Assignment of proton signals was assisted by ^{1}H/^{1}H COSY, tppi COSY, 1D NOE and NOESY experiments when necessary; assignment of carbon signals was assisted by DEPT experiments. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer as thin films on NaCl plates or as KBr pellets for solid products. Mass spectra were recorded by the Mass Spectrometry Facility at the Research School of Chemistry, Australian National University, Canberra, Australia. Optical rotations were measured with an Optical Activity Polaar 2001 optical polarimeter. Microanalyses were performed at the Campbell Microanalytical Laboratory at the Department of Chemistry, University of Otago, New Zealand. Melting points were measured on a Reichert melting point stage and are uncorrected. HPLC was performed using a Waters 510 EF chromatograph pump and Waters U6 K injector monitored by an ISCO 226 UV spectrophotometer at $\lambda = 254$ nm and a Waters R403 refractive index detector. GC measurements were recorded on a Hewlett Packard 5890 A gas chromatograph with a split/splitless capillary inlet and FID detector. GC data was processed using Hewlett Packard ChemStation software.

Reactions were conducted under a positive pressure of dry argon or nitrogen in flame-dried glassware, protected from light with aluminium foil. Diethyl ether, toluene and THF were dried over sodium wire and distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. Chlorobenzene and 1,2-dichlorobenzene were purified by the methods of Perrin and Armarego.[68] Commercially available chemicals were purified by standard procedures or used as purchased. Dienol **13a** was prepared from commercially available 1,4-pentadien-3-ol **12a** by slightly modifying the literature procedure[45] and dienol **13b** was prepared from **12b**[16] according to the literature procedure.[45] Aldehyde precursors to **15a**[46c] and **15b**[46a,b] were synthesised according to literature procedures. Analytical TLC was performed with Merck plates, precoated with silica gel 60 F254 (0.2 mm). Flash chromatography employed Merck Kiesegel 60 (230–400 mesh) silica gel.

Synthesis of the pentadienyl acrylates

(2*E*)-Penta-2,4-dien-1-yl acrylate (3):[10, 29] Triethylamine (8.239 g, 81.43 mmol, 2.5 equiv) and acryloyl chloride (5.897 g, 65.15 mmol, 2 equiv) were added to a stirred solution of dienol **13a**[45] (2.740 g, 32.57 mmol, 1 equiv) in dichloromethane (70 mL) at 0 °C. The mixture was stirred at this temperature for 10 min. The solution was allowed to warm to room temperature before being diluted with diethyl ether (230 mL). The mixture was washed with 2 M HCl (2 × 110 mL), sat. aq. $NaHCO_3$ (2 × 110 mL), brine (110 mL), dried (Na_2SO_4) and concentrated in vacuo. After column chromatography on silica (pentane/diethyl ether 95:5), the acrylate **3** (2.494 g, 18.05 mmol, 55 %) was obtained as a colourless oil. $R_f = 0.58$ (diethyl ether/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 6.43$ (dd, $J = 17.3$, 1.5 Hz, 1H; CHH′), 6.40–6.27 (m, 2H; CHH′, CH), 6.14 (dd, $J = 17.4$, 10.4 Hz, 1H; CH), 5.84 (dd, $J = 10.4$, 1.5 Hz, 1H; CHH′), 5.84–5.77 (m, 1H; CH), 5.31–5.22 (m, 1H; CHH′), 5.15 (m, 1H; CHH′), 4.70 (d, $J = 6.1$ Hz, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 165.8$ (C), 135.9 (CH), 134.8 (CH), 130.9 (CH_2), 128.3 (CH), 127.0 (CH), 118.7 (CH_2), 64.5 (CH_2); IR (neat): $\nu = 3089$, 3041 (C-H), 1728 (C=O), 1635, 1620, 1606 cm^{-1} (C=C); MS (70 eV, EI): m/z (%): 138 (10) $[M]^+$, 93 (25) $[C_7H_9]^+$, 67 (55) $[C_3H_3O_2]^+$, 55 (100) $[C_3H_3O]^+$; HRMS: calcd for $C_8H_{10}O_2$ $[M]^+$: 138.0681; found: 138.0680.

(±)-(1*S*,2*E*,4*E*)-1-Methylpenta-2,4-dien-1-yl acrylate (4):[16] Compound **4** was prepared from dienol **13b**[45] in 61 % isolated yield (4.0 g scale) using the procedure described above for **3**. Acrylate **4** was obtained as a colourless oil. $R_f = 0.64$ (pentane/diethyl ether 96:4); ^{1}H NMR (400 MHz,

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$CDCl_3$, 25 °C): $\delta = 6.40$ (dd, $J = 17.3$, 1.5 Hz, 1H; CHH′), 6.36–6.21 (m, 1H; 2 × CH), 6.11 (dd, $J = 17.3$, 10.4 Hz, 1H; CH), 5.81 (dd, $J = 10.4$, 1.5 Hz, 1H; CHH′), 5.71 (ddd, $J = 13.9$, 6.6, 0.6 Hz, 1H; CH), 5.47 (dq, $J =$ 6.5, 0.9 Hz, 1H; CH), 5.24 (dd, $J = 15.9$, 1.8 Hz, 1H; CHH′), 5.12 (dd, $J =$ 9.8, 2.1 Hz, 1H; CHH′), 1.37 (d, $J = 6.5$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 165.5$ (C), 136.1 (CH), 132.7 (CH), 132.2 (CH), 130.6 (CH_2), 128.8 (CH), 118.5 (CH_2), 70.7 (CH), 20.2 (CH_3); IR (neat): $\nu = 3087$, 2980, 2932 (C-H), 1718 (C=O), 1636, 1618, 1606 cm^{-1} (C=C); MS (70 eV, EI): *m*/*z* (%): 152 (10) $[M]^+$, 81 (90) $[C_6H_9]^+$, 55 (100) $[C_3H_3O]^+$; HRMS: calcd for $C_9H_{12}O_2$ $[M]^+$: 152.0837; found: 152.0836.

[*tert*-Butyldimethylsilyl]oxy-3,3-dibromoprop-2-ene (15a): A solution of carbon tetrabromide (9.57 g, 28.9 mmol, 2.00 equiv) in dichloromethane (22 mL) was added at 0 °C over 15 min to a solution of triphenylphosphine (15.13 g, 57.68 mmol, 4.00 equiv) in dichloromethane (45 mL). The resulting solution was allowed to warm to room temperature for 30 min before cooling to 0 °C and the dropwise addition of a solution of [*tert*-butyldimethylsilyl]oxy ethanal[46c] (2.513 g, 14.40 mmol, 1 equiv) in dichloromethane (5 mL). After 30 min the solution was diluted slowly, with vigorous stirring, with hexanes (100 mL) and the resulting suspension was stirred for 15 min. The precipitated triphenylphosphine oxide/phosphonium salts were filtered off and the filtrate was evaporated in vacuo. The resulting solid was dissolved in the minimum amount of dichloromethane before the addition of hexanes (100 mL) with stirring. After 15 min the resulting precipitate was filtered off and solvent was removed from the filtrate in vacuo. The resulting solid was then passed through a short plug of silica, eluting with diethyl ether/hexanes (5:95) before distillation to give the pure product as a colourless oil (3.169 g, 9.600 mmol, 67%). $R_f = 0.66$ (diethyl ether/hexanes 5:95); b.p. 59–61 °C/0.2 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 6.56$ (t, $J = 5.7$ Hz, 1H; CH), 4.18 (d, $J =$ 5.8 Hz, 2H; CH_2), 0.90 (s, 9H, C_4H_9), 0.09 (s, 6H, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 138.4$ (CH), 88.8 (C), 63.7 (CH_2), 25.8 (CH_3), 18.2 (C), −5.3 (CH_3); IR (neat): $\nu = 2954$, 2929 (C-H), 1623 (C=C), 838, 778 cm^{-1} (Si-CH_3); MS (70 eV, EI): *m*/*z* (%): 317 (6) $[M(^{81}Br)_2 - CH_3]^+$, 315 (15) $[M(^{79}Br^{81}Br) - CH_3]^+$, 313 (6) $[M(^{79}Br)_2 - CH_3]^+$, 55 (100) $[C_3H_3O]^+$; HRMS: calcd for $C_5H_9OSi^{81}Br_2$ $[M - C_4H_9]^+$: 274.8748; found: 274.8738; calcd for $C_5H_9OSi^{81}Br^{79}Br$ $[M - C_4H_9]^+$: 272.8769; found: 272.8764; calcd for $C_5H_9OSi^{79}Br_2$ $[M - C_4H_9]^+$: 270.8789; found: 270.8786.

[*tert*-Butyldimethylsilyl]oxy-3-bromo-2,4-pentadiene (16a): Triphenylarsine (288.2 mg, 0.941 mmol, 0.100 equiv) was added to a solution of dibromoolefin **15a** (3.106 g, 9.409 mmol, 1 equiv) in THF (50 mL) before twice degassing by the freeze/thaw method. To the resulting solution was added tris(dibenzylideneacetone)dipalladium(**0**) (107.9 mg, 0.118 mmol, 0.0125 equiv) and the solution was degassed once again. The solution was then warmed to 50 °C before the addition of vinyltributyltin (2.95 mL, 9.967 mmol, 1.06 equiv). The mixture was stirred at 50 °C for 10 h then diluted with diethyl ether (200 mL) and filtered through a short pad of silica. The filtrate was washed with 25% aq. NH_3 (3 × 50 mL) and dried (Na_2SO_4), the solvent was removed under reduced pressure and the residue was immediately purified by flash chromatography (gradient elution, hexanes to ethyl acetate/hexanes 3:97) to give a mixture of **16a** and triphenylarsine (91:9 ratio by NMR) as a yellow oil (2.44 g, 85%). This mixture was used directly in the next step.

3-Bromo-2,4-pentadienol: A solution of tetrabutylammonium fluoride (1M in THF, 13.2 mL, 13.2 mmol, 1.50 equiv) was added dropwise, with stirring, at 0 °C to a solution of **16a** (2.440 g, 8.800 mmol, 1 equiv) in THF (44 mL). The resulting solution was stirred for 30 min at room temperature before quenching with sat. aq. NH_4Cl (100 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL), and the combined organic layers were washed with brine (100 mL) and dried (Na_2SO_4) before reducing in vacuo. The crude product was purified by flash chromatography (ethyl acetate/hexanes 30:70) to give the title compound as an unstable yellow oil (1.101 g, 6.754 mmol, 77%) which was converted directly into the acrylate derivative. $R_f = 0.27$ (ethyl acetate/hexanes 30:70); ^{1}H NMR (400 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 6.47$ (dd, $J = 16.3$, 10.5 Hz, 1H; CH), 6.30 (t, $J =$ 5.6 Hz, 1H; CH), 5.52 (d, $J = 16.3$ Hz, 1H; CHH′), 5.23 (d, $J = 10.4$ Hz, 1H; CHH′), 4.33 (d, $J = 5.3$ Hz, 2H; CH_2), 4.16 (br s, 1H; -OH); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 136.5$ (CH), 135.2 (CH), 124.4 (C), 118.4 (CH_2), 62.4 (CH_2); IR (neat): $\nu = 3332$ (OH), 1634, 1604, 1026, 985, 915 cm^{-1} (C=C).

(2*Z*)-3-Bromopenta-2,4-dien-1-yl acrylate (5): Compound **5** was prepared from 3-bromo-2,4-pentadienol in 83% isolated yield (1.0 g scale) using the procedure described above for **3**. Acrylate **5** was obtained as a colourless oil. $R_f = 0.26$ (ethyl acetate/hexanes 5:95); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 6.43$ (dd, $J = 17.4$, 1.3 Hz, 1H; CH_2), 6.33 (dd, $J = 16.3$, 10.4 Hz, 1H; CH), 6.16 (t, $J = 6.1$ Hz, 1H; CH), 6.13 (dd, $J = 17.2$, 10.3 Hz, 1H; CH), 5.85 (dd, $J = 10.5$, 1.5 Hz, 1H; CH_2), 5.65 (d, $J = 16.0$ Hz, 1H; CH_2), 5.30 (d, $J = 10.6$ Hz, 1H; CH_2), 4.92 (d, $J = 6.2$ Hz, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 165.8$ (C), 134.9 (CH), 131.3 (CH_2), 128.0 (C), 128.0 (CH), 120.2 (CH_2), 63.9 (CH_2); IR (neat): $\nu = 1728$ (C=O), 1181 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 218 (17) $[M(^{81}Br)]^+$, 216 (17) $[M(^{79}Br)]^+$, 137 (15) $[M - Br]^+$, 65 (64) $[C_5H_5]^+$, 55 (100) $[C_3H_3O]^+$; HRMS: calcd for $C_8H_9O_2{}^{81}Br$ $[M]^+$: 217.9765; found: 217.9757; calcd for $C_8H_9O_2{}^{79}Br$ $[M]^+$: 215.9786; found: 215.9781.

(*S*)-2-{[*tert*-Butyldimethylsilyl]oxy}-4-bromo-3,5-hexadiene (16b): Compound **16b** was prepared from dibromoalkene **15b**[46a,b] in 83% isolated yield (2.7 g scale) using the procedure described above for **16a**. Bromodiene **16b** was obtained as a yellow oil. $R_f = 0.60$ (ethyl acetate/hexanes 5:95); $[\alpha]_D^{25} = +38.3$ ($c = 0.3$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 6.29$ (dd, $J = 16.3$, 10.4 Hz, 1H; CH), 6.00 (d, $J = 7.5$ Hz, 1H; CH), 5.59 (d, $J = 16.3$ Hz, 1H; CH_2), 5.24 (d, $J = 10.3$ Hz, 1H; CH_2), 4.79 (dq, $J = 7.6$, 6.3 Hz, 1H; CH), 1.26 (d, $J = 6.3$ Hz, 3H; CH_3), 0.89 (s, 9H; *t*Bu), 0.07 (d, $J = 11.2$ Hz, 6H; 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 139.8$ (CH), 136.2 (CH), 123.2 (C), 119.3 (CH_2), 69.7 (CH), 26.5 (CH_3), 23.8 (CH_3), 18.8 (C), −3.9 (CH_3), −4.1 (CH_3); IR (neat): $\nu = 2956$, 2929 (C-H), 1606, 1078, 831 (C=C), 1256, 776 cm^{-1} (Si-CH_3); MS (70 eV, EI): *m*/*z* (%): 277 (24) $[M(^{81}Br) - CH_3]^+$, 275 (23) $[M(^{79}Br) - CH_3]^+$, 235 (81) $[M(^{81}Br) - C_4H_9]^+$, 233 (80) $[M(^{79}Br) - C_4H_9]^+$, 75 (100) $[C_2H_7OSi]^+$; HRMS: calcd for $C_{11}H_{20}O^{81}BrSi$ $[M - CH_3]^+$: 277.0446; found: 277.0450; calcd for $C_{11}H_{20}O^{79}BrSi$ $[M - CH_3]^+$: 275.0467; found: 275.0464.

(*S*)-4-Bromo-3,5-hexadien-2-ol: This compound was prepared from **16b** in 84% isolated yield (1.2 g scale) using the procedure described above for 3-bromo-2,4-pentadienol. (*S*)-4-Bromo-3,5-hexadien-2-ol was obtained as a colourless oil. $R_f = 0.30$ (ethyl acetate/hexanes 30:70); $[\alpha]_D^{25} = -10.2$ ($c =$ 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 6.33$ (dd, $J = 16.3$, 10.4 Hz, 1H; CH), 6.06 (d, $J = 7.5$ Hz, 1H; CH), 5.66 (d, $J = 16.3$ Hz, 1H; CH_2), 5.31 (d, $J = 10.4$ Hz, 1H; CH_2), 4.90–4.82 (m, 1H; CH), 2.34 (br s, 1H; OH), 1.36 (d, $J = 6.4$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 137.5$ (CH), 135.2 (CH), 124.9 (C), 119.4 (CH_2), 67.7 (CH), 22.0 (CH_3); IR (neat): $\nu = 3332$ (OH), 2974 (C-H), 1634, 1603, 970 (C=C), 1126, 1060 cm^{-1} (C-O); MS (70 eV): *m*/*z* (%): 178 (8) $[M(^{81}Br)]^+$, 176 (9) $[M(^{79}Br)]^+$, 163 (35) $[M(^{81}Br) - CH_3]^+$, 161 (42) $[M(^{79}Br) - CH_3]^+$, 97 (66) $[M - Br]^+$, 82 (100) $[C_5H_6O]^+$; HRMS: calcd for $C_6H_9O^{81}Br$ $[M]^+$: 177.9816; found: 177.9809; calcd for $C_6H_9O^{79}Br$ $[M]^+$: 175.9837; found: 175.9845.

(1*S*,2*Z*)-3-Bromo-1-methylpenta-2,4-dien-1-yl acrylate (6): Compound **6** was prepared from (*S*)-4-bromo-3,5-hexadien-2-ol in 84% isolated yield (1.2 g scale) using the procedure described above for **3**. Acrylate **6** was obtained as a colourless oil. $R_f = 0.27$ (ethyl acetate/hexanes 5:95); $[\alpha]_D^{26} =$ +39.3 ($c = 0.9$ in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 6.41$ (dd, $J = 17.3$, 1.5 Hz, 1H; CH_2), 6.29 (dd, $J = 16.3$, 10.4 Hz, 1H; CH), 6.10 (dd, $J = 17.3$, 10.4 Hz, 1H; CH), 6.04 (d, $J = 7.7$ Hz, 1H; CH), 5.85 (dq, $J = 7.7$, 6.5 Hz, 1H; CH), 5.82 (dd, $J = 10.4$, 1.4 Hz, 1H; CH_2), 5.66 (d, $J = 16.3$ Hz, 1H; CH_2), 5.29 (d, $J = 10.4$ Hz, 1H; CH_2), 1.40 (d, $J = 6.5$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 165.3$ (C), 135.1 (CH), 133.4 (CH), 131.0 (CH_2), 128.5 (CH), 126.2 (C), 120.1 (CH_2), 71.0 (CH), 19.5 (CH_3); IR (neat): $\nu = 1727$, 1191 (C=O), 1636, 1047, 970, 917, 809 cm^{-1} (C=C); MS (70 eV, EI): *m*/*z* (%): 231 (22 $[M(^{81}Br)]^+$, 229 (19) $[M(^{79}Br)]^+$, 161 (63) $[C_5H_4{}^{81}BrO]^+$, 159 (67) $[C_5H_4{}^{79}BrO]^+$, 55 (100) $[C_3H_3O]^+$; HRMS: calcd for $C_9H_{11}O_2{}^{81}Br$ $[M]^+$: 231.9922; found: 231.9929; calcd for $C_9H_{11}O_2{}^{79}Br$ $[M]^+$: 229.9942; found: 229.9946.

IMDA reactions of the pentadienyl acrylates

IMDA reaction of acrylate 3: A solution of acrylate **3** (223.3 mg, 1.616 mmol, 1 equiv) and BHT (35.7 mg, 0.162 mmol, 0.1 equiv) in freshly distilled 1,2-dichlorobenzene (323 mL) was stirred at 180 °C for 190 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography on silica (diethyl ether/pentane 30:70) to give cycloadduct **17** (38.1 mg, 0.276 mmol, 17%) followed by cycloadduct **18** (86.0 mg, 0.622 mmol, 39%).

(±)-(3a*R*,7a*R*)-3,3a,6,7,7a-Hexahydroisobenzofuran-1-one (17): white crystalline solid after recrystallisation from a 3:1 mixture of hexanes/*tert*-butyl methyl ether. $R_f = 0.54$ (diethyl ether/pentane 30:70); m.p. 56–58 °C; ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 5.26$ (m, 1H; CH), 5.16 (m, 1H; CH),

3.71 (dd, $J = 7.2$, 7.2 Hz, 1H; CHH′), 3.14 (ddd, $J = 11.5$, 7.9, 0.7 Hz, 1H; CHH′), 2.08 (m, 1H; CH), 1.94 (m, 1H; CH), 1.78 – 1.61 (m, 2H; CH_2), 1.57 (ddd, $J = 12.6$, 12.6, 2.2 Hz, 1H; CHH′), 1.19 (dddd, $J = 12.6$, 12.6, 10.6, 7.3 Hz, 1H; CHH′); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 176.7$ (C), 130.6 (CH), 123.6 (CH), 71.1 (CH_2), 43.2 (CH), 41.3 (CH), 26.1 (CH_2), 21.2 (CH_2); IR (KBr): $\nu = 3028$, 2896 (C-H), 1777 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 138 (10) $[M]^+$, 94 (45) $[C_7H_{10}]^+$, 79 (100) $[C_6H_7]^+$; elemental analysis calcd (%) for $C_8H_{10}O_2$: C 69.54, H 7.30; found: C 69.82, H 7.17.

(±)-(3a*R*,7a*S*)-3,3a,6,7,7a-Hexahydroisobenzofuran-1-one (18): colourless oil. $R_f = 0.36$ (diethyl ether/pentane 30:70); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 5.93 – 5.86$ (m, 1H; CH), 5.60 – 5.55 (m, 1H; CH), 4.34 (dd, $J =$ 8.9, 6.6 Hz, 1H; CHH′), 4.02 (dd, $J = 8.9$, 2.5 Hz, 1H; CHH′), 3.08 – 3.01 (m, 1H; CH), 2.83 – 2.79 (m, 1H; CH), 2.09 – 1.93 (m, 3H; 2 × HH′, 1 × CHH′), 1.81 – 1.71 (m, 1H; CHH′); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 178.6$ (C), 130.5 (CH), 125.2 (CH), 72.1 (CH_2), 37.9 (CH), 35.2 (CH), 20.9 (CH_2), 19.6 (CH_2); IR (neat): $\nu = 3024$, 2922 (C-H), 1776 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 138 (40) $[M]^+$, 93 (70) $[C_7H_9]^+$, 80 (100) $[C_6H_8]^+$; elemental analysis calcd (%) for $C_8H_{10}O_2$: C 69.54, H 7.30; found: C 69.31, H 7.58.

IMDA reaction of acrylate 4: A solution of acrylate **4** (2.246 g, 14.77 mmol, 1 equiv) and BHT (162.7 mg, 0.738 mmol, 0.05 equiv) in freshly distilled 1,2-dichlorobenzene (2.90 L) was stirred at 180 °C for 146 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography on silica (ethyl acetate/hexanes 20:80) to give a mixture (930 mg, 6.12 mmol, 41 %) of cycloadducts **19**, **20**, and **21** followed by cycloadduct **22** (440 mg, 2.89 mmol, 20 %). The mixture of cycloadducts **19**, **20** and **21** was separated by HPLC [Whatman Partisil column, eluting with ethyl acetate/hexanes 15:85, 13.5 mL min^{-1}] to give **19** at $t_R = 35.2$ min (362 mg, 2.38 mmol, 16 %), **20** at $t_R = 38.0$ min (132 mg, 0.868 mmol, 6 %), and **21** at $t_R = 39.5$ min (389 mg, 2.56 mmol, 17 %).

(±)-(3*S*,3a*R*,7a*R*)-3-Methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (19): white crystalline solid after recrystallisation from THF/hexanes 1:9. $R_f = 0.29$ (ethyl acetate/hexanes 20:80); m.p. 76 – 78 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 5.75$ (m, 2H; CH), 4.15 (dq, $J = 10.6$, 6.1 Hz, 1H; CH), 1.66 – 1.53 (m, 1H), 2.37 – 2.15 (m, 5H), 1.43 (d, $J =$ 6.1 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 175.9$ (C), 130.4 (CH), 122.9 (CH), 79.6 (CH), 48.1 (CH), 44.2 (CH), 25.7 (CH_2), 21.1 (CH_2), 18.1 (CH_3); IR (KBr): $\nu = 3028$, 2978, 2943, 2875 (C-H), 1770 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 152 (10) $[M]^+$, 124 (20) $[C_8H_{12}O]^+$, 80 (100) $[C_6H_8]^+$; elemental analysis calcd (%) for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 70.88, H 7.99.

(±)-(3*S*,3a*S*,7a*S*)-3-Methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (20): white crystalline solid after recrystallisation from hexanes. $R_f = 0.29$ (ethyl acetate/hexanes 20:80); m.p. 63 – 65 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 5.85 – 5.81$ (m, 1H; CH), 5.77 – 5.71 (m, 1H; CH), 4.76 (m, 1H; CH), 2.98 – 2.88 (m, 1H; CH), 2.50 (ddd, $J = 13.6$, 12.3, 2.9 Hz, 1H; CH), 2.29 – 2.22 (m, 2H; CH_2), 2.15 – 2.08 (m, 1H; CHH′), 1.56 (dddd, $J = 12.3$, 12.3, 9.7, 7.9 Hz, 1H; CHH′), 1.22 (d, $J = 6.6$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 176.5$ (C), 131.2 (CH), 125.5 (CH), 78.0 (CH), 44.2 (CH), 39.8 (CH), 26.7 (CH_2), 22.6 (CH_2), 14.8 (CH_3); IR (KBr): $\nu = 3028$, 2983, 2940, 2915, 2836 (C-H), 1779 (C=O), 1629 cm^{-1} (C=C); MS (70 eV, EI): *m/z* (%): 152 (20) $[M]^+$, 137 (5) $[M - CH_3]^+$, 108 (60) $[C_8H_{12}]^+$, 80 (100) $[C_6H_8]^+$; elemental analysis calcd (%) for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 71.19, H 7.98.

(±)-(3*S*,3a*R*,7a*S*)-3-Methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (21): colourless oil. $R_f = 0.29$ (ethyl acetate/hexanes 20:80); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 5.88$ (dddd, $J = 9.9$, 4.0, 4.0, 1.9 Hz, 1H; CH), 5.60 (dddd, $J = 10.1$, 3.8, 2.1, 2.1 Hz, 1H; CH), 4.28 (dq, $J = 6.4$, 4.8 Hz, 1H; CH), 2.62 (m, 1H; CH), 2.11 – 1.75 (m, 4H; 2 × H_2), 1.39 (d, $J = 6.4$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 178.3$ (C), 129.8 (CH), 124.4 (CH), 80.7 (CH), 41.6 (CH), 37.7 (CH), 21.7 (CH_2), 19.9 (CH_2), 19.8 (CH_3); IR (neat): $\nu = 3025$, 2975, 2930, 2846 (C-H), 1767 (C=O), 1651 cm^{-1} (C=C); MS (70 eV, EI): *m/z* (%): 152 (15) $[M]^+$, 124 (15) $[C_8H_{12}O]^+$, 107 (10) $[C_8H_{11}]^+$, 80 (100) $[C_6H_8]^+$; elemental analysis calcd (%) for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 70.67, H 8.26.

(±)-(3*S*,3a*S*,7a*R*)-3-Methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (22): colourless oil. $R_f = 0.21$ (ethyl acetate/hexanes 20:80); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 5.63$ (m, 1H; CH), 5.16 (m, 1H; CH), 3.89 (m, 1H; CH), 2.29 (ddd, $J = 7.1$, 3.5, 3.5 Hz, 1H; CH), 2.16 (m, 1H; CH), 2.06 – 1.94 (m, 2H; CHH′), 1.65 – 1.55 (m, 1H; CHH′), 1.35 – 1.22 (m, 1H; CHH′), 0.95 (d, $J = 6.5$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 178.2$ (C), 131.7 (CH), 121.9 (CH), 78.1 (CH), 40.1 (CH), 38.7 (CH), 20.6 (CH_2), 19.7 (CH_2), 16.0 (CH_3); IR (neat): $\nu = 3027$, 2981, 2929, 2847 (C-H), 1767 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 152 (20) $[M]^+$, 124 (20) $[C_8H_{12}O]^+$, 107 (20) $[C_8H_{11}]^+$, 80 (100) $[C_6H_8]^+$; elemental analysis calcd (%) for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 70.94, H 7.84.

IMDA reaction of acrylate 5: A solution of acrylate **5** (108.9 mg, 0.502 mmol, 1 equiv) and BHT (5.8 mg, 26 μmol) in freshly distilled 1,2-dichlorobenzene (92 mL) was stirred at 160 °C for 87 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography on silica (ethyl acetate/hexanes 30:70) to give cycloadduct **23** (41.4 mg, 0.191 mmol, 38 %) followed by cycloadduct **24** (37.1 mg, 0.171 mmol, 34 %).

(±)-(3a*R*,7a*R*)-4-Bromo-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (23): white crystalline solid. $R_f = 0.35$ (ethyl acetate/hexanes, 30:70); m.p. 107 – 110 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 6.09$ (m, 1H; CH), 4.40 (dd, $J = 7.9$, 6.9 Hz, 1H; CHH′), 3.98 (dd, $J = 11.3$, 8.0 Hz, 1H; CHH′), 3.28 – 3.13 (m, 1H; CH), 2.64 (dt, $J = 12.7$, 2.8 Hz, 1H; CHH′), 2.44 – 2.30 (m, 2H; CH, CHH′), 2.23 – 2.12 (m, 1H; CHH′), 1.70 – 1.56 (m, 1H; CHH′); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 175.3$ (C), 131.7 (CH), 116.9 (C), 70.7 (CH_2), 46.4 (CH), 45.3 (CH), 28.9 (CH_2), 20.8 (CH_3); IR (KBr): $\nu = 1772$, 1338 (C=O), 1633, 1075, 983, 770 cm^{-1} (C=C); MS (70 eV, EI): *m/z* (%): 218 (47) $[M(^{81}Br)]^+$, 216 (48) $[M(^{79}Br)]^+$, 160 (20) $[M - C_2H_2O_2]^+$, 158 (22) $[M - C_2H_2O_2]^+$, 137 (18) $[M - Br]^+$, 79 (100) $[C_6H_7]^+$; HRMS: calcd for $C_8H_9O_2{}^{81}Br$ $[M]^+$: 217.9765; found: 217.9769; calcd for $C_8H_9O_2{}^{79}Br$ $[M]^+$: 215.9786; found: 215.9792.

(±)-(3a*R*,7a*S*)-4-Bromo-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (24): colourless oil. $R_f = 0.26$ (ethyl acetate/hexanes 30:70); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 5.73 – 5.68$ (m, 1H; CH), 4.01 (dd, $J = 9.3$, 2.4 Hz, 1H; CHH′), 3.51 (dd, $J = 9.3$. 6.6 Hz, 1H; CHH′), 2.40 – 2.32 (m, 1H; CH), 2.03 – 1.96 (m, 1H; CH), 1.75 – 1.62 (m, 2H; 2 × CHH′), 1.38 – 1.28 (m, 1H; CHH′), 1.12 – 1.02 (m, 1H; CHH′); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): $\delta = 176.2$ (C), 132.9 (CH), 121.4 (C), 70.1 (CH_2), 43.1 (CH), 40.0 (CH), 23.8 (CH_2), 19.1 (CH_2); IR (neat): $\nu = 2922$ (C-H), 1774, 1209 (C=O), 1146, 983, 809 cm^{-1} (C=C); MS (70 eV): *m/z* (%): 218 (45) $[M(^{81}Br)]^+$, 216 (45) $[M(^{79}Br)]^+$, 173 (63) $[M - CO_2H]^+$, 171 (62) $[M - CO_2H]^+$, 160 (28) $[M - C_2H_2O_2]^+$, 158 (30) $[M - C_2H_2O_2]^+$, 137 (43) $[M - Br]^+$, 79 (100) $[C_6H_7]^+$; HRMS: calcd for $C_8H_9O_2{}^{81}Br$ $[M]^+$: 217.9765; found: 217.9766; calcd for $C_8H_9O_2{}^{79}Br$ $[M]^+$: 215.9786; found: 215.9785.

IMDA reaction of acrylate 6: A solution of acrylate **6** (54 mg, 0.23 mmol, 1 equiv) and BHT (2.5 mg, 11 μmol) in freshly distilled chlorobenzene (24 mL) was stirred at 132 °C for 140 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography on silica (ethyl acetate/hexanes 30:70) to give an 81:19 mixture of **25** and **27** as a white solid (45 mg, 0.19 mmol, 84 %). A pure sample of major cycloadduct **25** was obtained after two recrystallisations of this mixture from dichloromethane/hexanes. A pure sample of cycloadduct **27** was obtained by epimerisation of the 81:19 mixture of **25** and **27** with DBU (see following section for experimental details).

(3*S*,3a*R*,7a*R*)-4-Bromo-3-methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (25): white crystalline solid. $R_f = 0.32$ (ethyl acetate/hexanes 30:70); m.p. 112 – 115 °C; $[\alpha]_D^{29} = +19.1$ ($c = 0.8$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 5.47$ (m, 1H; CH), 3.79 (m, 1H; CH), 2.03 – 1.93 (m, 1H; CH), 1.84 – 1.75 (m, 2H; CH, CHH′), 1.59 – 1.43 (m, 2H; CH_2), 1.34 (d, $J =$ 6.0 Hz, 3H, CH_3), 1.10 – 0.97 (m, 1H; CHH′); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): $\delta = 173.5$ (C), 132.4 (CH), 116.9 (C), 79.4 (CH), 52.4 (CH), 46.8 (CH), 28.8 (CH_2), 21.3 (CH_2), 20.3 (CH_3); IR (KBr): $\nu = 1780$, 1393, 1172 (C=O), 988, 768 cm^{-1} (C=C); MS (70 eV, EI): *m/z* (%): 232 (19) $[M(^{81}Br)]^+$, 230 (20) $[M(^{79}Br)]^+$, 160 (78) $[M - C_3H_4O_2]^+$, 158 (82) $[M - C_3H_4O_2]^+$, 79 (100) $[C_6H_7]^+$; HRMS: calcd for $C_9H_{11}O_2{}^{81}Br$ $[M]^+$: 231.9922; found: 231.9924; calcd for $C_9H_{11}O_2{}^{79}Br$ $[M]^+$: 229.9942; found: 229.9946.

(3*S*,3a*R*,7a*S*)-4-Bromo-3-methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (27): white crystalline solid. $R_f = 0.32$ (ethyl acetate/hexanes 30:70); m.p. 55 – 57 °C; $[\alpha]_D^{28} = +134.0$ ($c = 1.0$, CH_2Cl_2); ^{1}H NMR (400 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 6.36 – 6.25$ (m, 1H; CH), 4.65 (dq, $J = 6.5$, 2.8 Hz, 1H; CH), 3.31 – 3.21 (m, 1H; CH), 3.14 – 3.05 (m, 1H; CH), 2.22 – 1.95 (m, 3H; CH_2, CHH′), 1.87 – 1.75 (m, 1H; CHH′), 1.46 (d, $J = 6.5$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, 25 °C): $\delta = 176.8$ (C), 133.0 (CH), 122.2 (C), 79.8 (CH), 49.3 (CH), 40.0 (CH), 24.5 (CH_2), 20.7 (CH_2), 19.8 (CH_3); IR (neat): $\nu = 1770$, 1227, 1153 (C=O), 1091, 806 cm^{-1} (C=C); MS (70 eV, EI): *m/z* (%): 232 (22) $[M(^{81}Br)]^+$, 230 (22) $[M(^{79}Br)]^+$, 160 (68)

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$[M - C_3H_4O_2]^+$, 158 (70) $[M - C_3H_4O_2]^+$, 79 (100) $[C_6H_7]^+$; HRMS: calcd for $C_9H_{11}O_2{}^{81}Br$ $[M]^+$: 231.9922; found: 231.9921; calcd for $C_9H_{11}O_2{}^{79}Br$ $[M]^+$: 229.9942; found: 229.9946.

Cycloadduct structure correlation experiments

***trans*-Bicycle → *cis*-bicycle isomerisation reactions**: The epimerisation of **25** to **27** is representative. A mixture of cycloadducts **25** and **27** (101.2 mg, 0.433 mmol, 1 equiv) was dissolved in dichloromethane (6 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 72 μL, 0.48 mmol, 1.1 equiv) was added and the resulting solution was stirred at reflux for 90 min. Filtration of the cooled solution through a plug of silica and concentration in vacuo gave *cis*-isomer **27** as a colourless oil (99.7 mg, 0.431 mmol, 99 %).

Reductive debromination reactions: The radical debromination of **24** is representative. To a solution of cycloadduct **24** (13.8 mg, 63.6 μmol, 1 equiv) in toluene (640 μL) at room temperature was added tributyltin hydride (49 μL, 182 μmol, 2.9 equiv) and AIBN (1.1 mg, 6.7 μmol, 0.1 equiv) before warming to 80 °C for 3 h. The solution was then diluted with dichloromethane (25 mL) before washing with 25 % aq. NH_3 solution (3×20 mL). The combined aqueous layers were extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$) before removal of solvent in vacuo. The crude product was passed through a short pad of silica to furnish **18** as a colourless oil, spectroscopically identical to the major product obtained upon IMDA reaction of 3.

Acknowledgement

The authors thank The Australian Research Council for the award of a Senior Research Fellowship (to M.N.P.-R.) and a project grant (to M.S.S.) and the New South Wales ac3 Parallel Computing Facility for allocation of CPU time (to M.N.P.-R.). We also thank Dr. Ian Luck for assistance with NMR experiments and Dr. Kelvin Picker for assistance with GC monitoring and HPLC separations.

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[54] Product ratios were calculated from GC traces of reaction mixtures (direct injection of reaction solutions), NMR spectra of evaporated crude reaction mixtures and isolated quantities of products (after chromatographic purification). No significant differences were seen between the ratios calculated by the three different methods.

[55] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-172249 – 172251. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[56] We use the terms *endo* and *exo* to describe the orientation of the dienophile tether connection with respect to the diene. An *endo* orientation of the dienophile tether "substituent" affords the *cis*-fused bicycle; an *exo* orientation of the dienophile tether furnishes the *trans*-fused cycloadduct.

[57] This ratio differs slightly from that reported in an earlier paper (ref. [9]) since the latter was calculated using the 6-31G(d) basis set.

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[62] A direct synthetic comparison with this computational result is not available. The C1-methyl analogue of precursor **29**, triene **1** (Scheme 1) gives predominantly the *exo* adduct (*exo*:*endo* = 79:21).

[63] The *E*-dienophile congener **2** (Scheme 1) is less stereoselective than its *Z*-dienophile counterpart but the general trend still holds (i.e., substitution of C9 with an activating group promotes more *trans*-fused product). Our modified Houk twist asynchronicity model[9] accounts for the difference in *exo*:*endo* stereoselectivity witnessed with the two C9-substituted dienophile stereoisomers (Scheme 1).

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Received: July 26, 2001 [F3444]

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