

# On the Diels–Alder reactions of pentadienyl maleates and citraconates†

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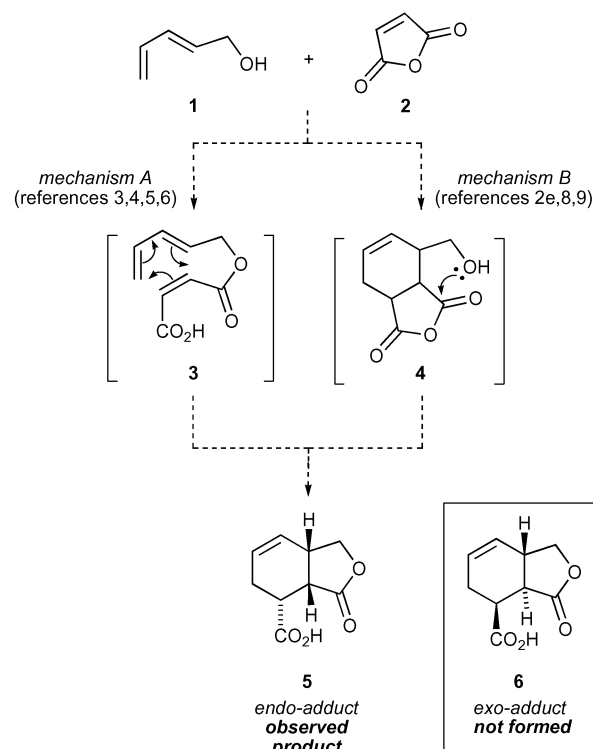
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Reactions between conjugated dienols and maleic anhydride provide *either cis*-fused or *trans*-fused bicyclic products as major products, depending upon how the reaction is carried out. Simply mixing the two reactants together generally leads to *cis*-fused lactone acids in thermal reactions which proceed *via* intermolecular Diels–Alder reaction followed by intramolecular esterification. Pre-forming the maleate half ester derivative followed by heating affords predominantly *trans*-fused lactone acids in good yields by way of an intramolecular Diels–Alder (IMDA) reaction. Sorbyl citraconate half esters undergo a rapid thermolytic fragmentation in refluxing toluene to form the dienol and citraconic anhydride. The resulting diene–dienophile pair undergo an intermolecular cycloaddition followed by a rapid intramolecular esterification to give *cis*-fused bicyclic lactone acids as major products. The IMDA reaction of citraconic half esters is sufficiently rapid in DMSO to dominate over fragmentation: the *exo*-cycloadduct is formed almost exclusively. Nine literature reports of *endo*-selective IMDA reactions of triene acids are erroneous; the cycloadditions proceed in an intermolecular manner.

## Introduction

The reaction of 2,4-pentadien-1-ols with maleic anhydride to form *cis*-fused lactone acids (Scheme 1), first reported sixty years ago,<sup>1</sup> has enjoyed wide application in synthesis.<sup>2</sup> The stereochemical outcome of this transformation is well documented but the mechanism is the subject of some controversy. Thus, in studies with electron rich dienes<sup>3–5</sup> and simple chiral dienols,<sup>6</sup> the reaction was assumed to proceed *via* formation of an unisolable<sup>4</sup> half ester derivative of maleic acid **3** followed by an *endo*-selective intramolecular Diels–Alder (IMDA)<sup>7</sup> reaction (Scheme 1, mechanism A). Evidence presented for this esterification–IMDA pathway involved observations with the corresponding pentadienyl acetate, which underwent cycloaddition at higher temperature<sup>3</sup> and in comparatively low yield.<sup>4</sup> On the other hand, in studies with chiral acyclic dienols and derivatives, other groups<sup>2e,8,9</sup> contend that the formation of *cis*-fused lactone acids occurs *via* an *endo*-selective intermolecular Diels–Alder reaction with maleic anhydride to form an unisolable hydroxy anhydride **4**, which undergoes a rapid intramolecular esterification (Scheme 1, mechanism B). Evidence presented for this sequence of events centred on observations of a gradual improvement in  $\pi$ -diastereofacial selectivity with progressively larger silyl ether derivatives of chiral dienols.<sup>8</sup>

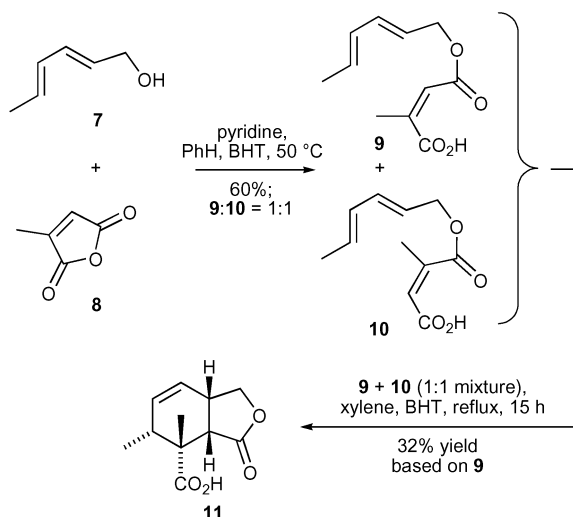
Perhaps the most convincing support for the IMDA route in Scheme 1 is the exclusive formation of *cis*-fused lactone acids from pre-formed half ester derivatives of substituted maleic anhydrides.<sup>10–14</sup> Thus, White and Sheldon<sup>10,11</sup> reported that heating a 50 : 50 mixture of citraconate half esters **9** and **10** in xylene at reflux produces a single crystalline product **11** in low yield along with a substantial quantity of polymer



**Scheme 1** Literature reports of the reaction between dienols and maleic anhydride to form *cis*-fused lactone acids.

(Scheme 2). No evidence for other cycloadducts was reported, thus the authors concluded that half ester **9** produces *cis*-lactone acid **11**, with regioisomeric half ester **10** destroyed through ‘autocatalytic polymerisation’. The corresponding methyl ester of triene acid **9** gave exclusively the *trans*-fused *exo*-cycloadduct in 40% yield. Initially, it was proposed that the stereoselectivity

† Electronic supplementary information (ESI) available: synthetic procedures, characterisation details, selected time lapse <sup>1</sup>H NMR stacked plots and Cartesian coordinates and energies of B3LYP/6-31 +G(d) optimised TS geometries. See <http://www.rsc.org/suppdata/ob/b5/b501446h/>



**Scheme 2** Preparation and cycloaddition of sorbyl citraconate esters as carried out by White and Sheldon.<sup>11</sup>

of the reaction depicted in Scheme 2 could be rationalised by an intramolecular hydrogen bond between the carboxylic acid hydrogen and the ester carbonyl oxygen in **9**, thereby permitting a sterically undemanding *endo*-transition structure (TS) that is favoured since it accommodates secondary orbital overlap.<sup>10</sup> Later, it was postulated that the lactone carbonyl of the IMDA cycloadducts might be protonated by the proximate carboxylic acid, thereby facilitating retro-cycloaddition under the reaction conditions, a circumstance that would be expected to favour the thermodynamic *cis*-fused product **11** over the less stable *trans*-fused *exo*-cycloadduct.<sup>11</sup> In a later study, Batchelor and Mellor<sup>12,13</sup> reported a similar, exclusive *endo*-stereoselectivity in a reaction of a dienol ester of dichloromaleic anhydride. These authors subscribed to the former theory, noting that the internal protonation of the ester carbonyl in **9** by the carboxylic acid group might be facilitating the *endo*-transition state in a kinetically-controlled process.

The conversions **3** → **5** (Scheme 1) and **9** → **11** (Scheme 2) are discussed in the major reviews on the IMDA reaction.<sup>7</sup> Roush<sup>7f</sup> postulated that an intramolecular hydrogen bond in triene acid **9** might cause a shift in the electronic characteristics of the dienophile such that the stereoelectronics of the asynchronous transition state are acting in the opposite direction in the carboxylic acid *versus* the corresponding methyl ester, which undergoes an *exo*-selective IMDA reaction.<sup>11</sup> These explanations for the unusual *endo*-selectivity for citraconate half ester **9** would apply to the maleate (**3**; Scheme 1) and dichloromaleate half esters, of course.

To summarise previous findings in this area: (1) two different mechanisms have been proposed for the reaction between dienols and maleic anhydride to form *cis*-lactone acids, one involving an IMDA reaction, the other involving an intermolecular Diels–Alder reaction (Scheme 1); (2) pentadienyl citraconates and related half esters give *endo*-cycloadducts on heating (Scheme 2) whereas the corresponding methyl esters give *exo*-adducts. The research described herein addresses the former mechanistic issue and explains the latter. *Crucial to the interpretation of these results in terms of an IMDA reaction is the assumption that the half esters, such as 9 and 10, are stable to fragmentation into the dienol 7 and anhydride 8, under the reaction conditions.* As we shall see, this assumption is incorrect for certain reaction conditions.

## Results and discussion

Our attempts to resolve the mechanistic issue (Scheme 1) by carrying out reactions in NMR tubes were unsuccessful, with

a mixture of unreacted starting materials **1** and **2** and bicyclic lactone acid **5** the only components detected in the reaction mixture. Evidently, triene **3** and/or hydroxy anhydride **4** are formed only fleetingly.

We turned to computational methods to corroborate the conversions **3** → **5** (Scheme 1) and **9** → **11** (Scheme 2). Gas phase Density Functional Theory (DFT) calculations were carried out to locate and analyse the transition structures (TSs) for the IMDA reactions of triene acid **3**. All calculations were carried out with the Gaussian 03 program,<sup>15</sup> using the hybrid B3LYP functional<sup>16</sup> in conjunction with the 6-31 + G(d) basis set [B3LYP/6-31 + G(d)],<sup>17</sup> a combination which is known to give acceptable relative energies and geometries for pericyclic reactions.<sup>18–21</sup> *Endo*- and *exo*-TSs for the IMDA reaction of **3** were located for four conformations of the –CO<sub>2</sub>H substituent (Fig. 1). Relative energies of the TSs shown in Fig. 1 refer to 0 K and include zero-point energy correction.

	$E_{\text{rel}}(\text{exo-endo})/\text{kJ mol}^{-1}$	exo:endo ratio
 <b>3-s-cis-syn</b>	–8.48	93:7
 <b>3-s-trans-syn</b>	–9.37	95:5
 <b>3-s-cis-anti</b>	–9.18	95:5
 <b>3-s-trans-anti</b>	+1.39	39:61

**Fig. 1** The four conformations of the carboxylic acid group, B3LYP/6-31 + G(d) *endo*- and *exo*-TS relative energies and predicted kinetic product ratios (Boltzmann populations at 383 K).

A detailed analysis of the geometries of these and related TSs is reported elsewhere.<sup>22</sup> Here we focus on the predicted stereoselectivity of the IMDA reaction of **3**.

The data listed in Fig. 1 show that three of the four conformations about the –CO<sub>2</sub>H group are predicted to display strong *exo*-selectivity. The *s-trans-anti* conformation, however, is calculated to be predominantly *endo*-selective. The origin of *endo*-selectivity in the *s-trans-anti* acid conformation can be traced to the impact of an intramolecular hydrogen bond between the *anti* hydroxy proton of the –CO<sub>2</sub>H group and the tether carbonyl group (Fig. 2) upon the geometries of the *exo*- and *endo*-TSs. None of the other six TSs (two of which are reproduced in Fig. 2) can accommodate such a bond; hence these TS geometries are analogous to those with –CO<sub>2</sub>Me groups, and IMDA stereoselectivities are similarly highly *exo*-selective.<sup>22</sup>

Whilst these computational findings for the IMDA reactions involving the **3-s-trans-anti** TSs, which exhibit H-bonding, validate White's important early work,<sup>10</sup> these TSs are significantly

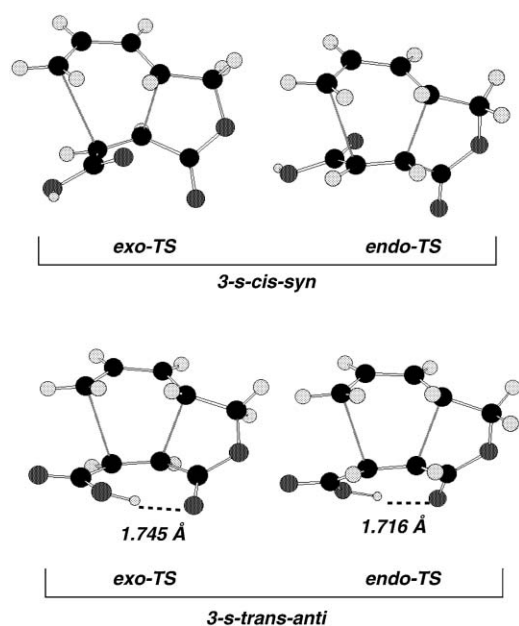


Fig. 2 Optimised 3-*s-cis-syn* and 3-*s-trans-anti* endo- and exo-TSs. H-bonds are shown as dashed lines.

higher in energy than any of the four corresponding *syn* TSs, by as much as 24 kJ mol<sup>-1</sup>. The 3-*s-trans-anti* TSs are, therefore, unlikely to play a noticeable role in the IMDA reaction of triene acid **3**, which is expected to be strongly *exo*-selective. Indeed, the calculated product ratio at 383 K (110 °C) from a Boltzmann population of the eight TSs is *exo* : *endo* = 94 : 6, a finding that is in sharp contrast with literature reports on experimental studies in this area (Schemes 1 and 2).

In light of the proven reliability of our level of theory in predicting stereoselectivities of IMDA reactions of this general type,<sup>21,23–26</sup> we were disturbed by this discrepancy between theory and experiment. A synthetic investigation into the IMDA

reactions of *pre-formed* triene acids **3** was clearly warranted. Furthermore, a comparison between the outcomes of these processes and reactions carried out by heating mixtures of pentadienols with maleic anhydride might settle the mechanistic issue depicted in Scheme 1. To this end, reactions between eight dienols with varying steric and electronic demands (Fig. 3) and maleic anhydride were carried out, both by heating mixtures of the two reactants<sup>1–6,8,9</sup> in toluene and by pre-forming the maleate half ester **3** prior to heating. The maleate half ester derivatives of dienols **1**, **7**, **12–17** were prepared at or below room temperature by reaction with maleic anhydride, Et<sub>3</sub>N and DMAP.<sup>27</sup> Triene acids **3** were sufficiently stable to allow full characterisation.

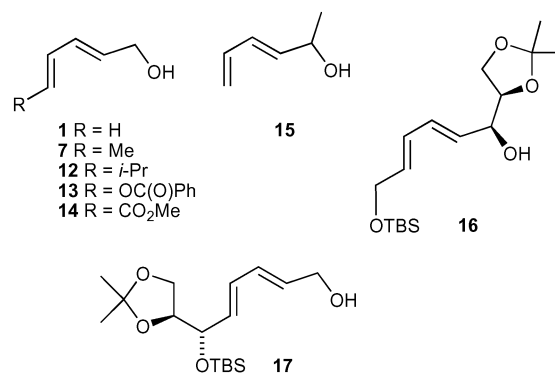


Fig. 3 The eight pentadienols treated with maleic anhydride.

The results of the two sets of reactions are listed in Table 1, along with the results of IMDA reactions of the methyl ester derivatives of triene acids **3**, *i.e.* **18**. As expected, lactone acids were produced under both sets of conditions. The stereochemical outcomes of these reactions, however, were very different. Whereas the much-used ‘mix and heat’ conditions generally gave *cis*-fused lactone products **5** (*via* *endo*-selective Diels–Alder reactions) in high selectivity, heating the maleate half esters **3** resulted in mixtures rich in the *trans*-fused bicycle **6** (resulting

Table 1 Results of reactions between dienols and maleic anhydride, with and without prior formation of the half ester derivative **3**. IMDA reactions of methyl esters **18**<sup>26</sup> are shown for comparison

Et <sub>3</sub> N, DMAP, CH <sub>2</sub> Cl <sub>2</sub> , 0 °C										
Entry	Dienol	Mix and heat method <sup>a</sup>			IMDA reaction of <b>3</b> <sup>b</sup>			IMDA reaction of <b>18</b> <sup>b</sup>		
		<i>Endo</i> : <i>exo</i>	Time/h	Yield <sup>c</sup> (%)	<i>Endo</i> : <i>exo</i>	Time/h	Yield <sup>c</sup> (%)	<i>Endo</i> : <i>exo</i>	Time/h	Yield (%)
1	<b>1</b>	97 : 3	2	56	21 : 79	5	47	17 : 83	4	97
2	<b>7</b>	96 : 4	1	90	31 : 69	2	83	21 : 79	2	79
3	<b>12</b>	88 : 12	2	88	15 : 85	3	49	18 : 82	5	92
4	<b>13</b>	>99 : 1	2	35	60 : 40	4	50	40 : 60	6	75
5	<b>14</b>	— <sup>d</sup>	—	—	27 : 73	10	40	22 : 78	7	86
6	<b>14</b> <sup>e</sup>	>99 : 1	2	57	—	—	—	—	—	—
7	<b>15</b>	94 : 6	2	71	16 : 84	3	46	13 : 87	3	94
8	<b>16</b>	>99 : 1	30	79 <sup>f</sup>	14 : 86	7	66	14 : 86	19	100
9	<b>17</b>	54 : 46	67	45	1 : >99	17	62	1 : >99	15	80

<sup>a</sup> A 1 : 1 mixture of the dienol and maleic anhydride in toluene (0.3–0.5 mol L<sup>-1</sup>) was heated to reflux under Ar in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (0.1 equiv.) until no starting dienol remained by TLC and <sup>1</sup>H NMR. <sup>b</sup> A solution of **3** or **18** in toluene (0.005–0.010 mol L<sup>-1</sup>) was heated to reflux under Ar in the presence of BHT (0.1 equiv.) until no triene remained by TLC and <sup>1</sup>H NMR. <sup>c</sup> Isolated yield of the corresponding methyl esters after treatment with CH<sub>2</sub>N<sub>2</sub> and chromatographic purification. <sup>d</sup> Complex mixture produced. <sup>e</sup> TBS ether of alcohol **14** employed. <sup>f</sup> Bis-lactones were isolated in this case. See the ESI† for details.

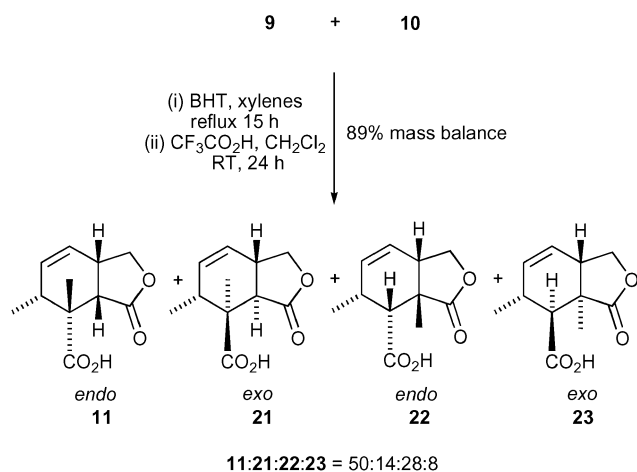
from *exo*-selective reactions). Furthermore, IMDA reactions of the triene acids **3** gave remarkably similar stereochemical outcomes to those of the corresponding methyl esters **18**.<sup>26</sup> Thus, thermal reactions between 2,4-dien-1-ols and maleic anhydride carried out by simply mixing the reactants together proceed by initial *endo*-selective intermolecular Diels–Alder reaction followed by intramolecular esterification (Scheme 1, pathway B). It must be concluded, therefore, that some previous reports of IMDA reactions<sup>3–6</sup> actually involve intermolecular cycloaddition processes.

From a practical standpoint, this work demonstrates that it is possible to control the stereochemical outcome of reactions between dienols and maleic anhydride by effecting the cycloaddition step either *inter*- or *intra*-molecularly; a result of significance in the light of the synthetic importance of the Diels–Alder reaction.

When the ‘mix and heat’ reaction is carried out with less reactive dienes (Table 1, entries 5 and 9), increasing amounts of *trans*-fused *exo*-adducts are observed. When these reactions are analysed prior to complete conversions, significant amounts of triene acids **3** are detected. We therefore attribute the poor *endo*-selectivity of these reactions to the competing esterification–intramolecular cycloaddition pathway, *i.e.* Scheme 1, mechanism B. An exception to the general IMDA stereoselectivity trend is seen with the triene acid derived from dienol **13**, which undergoes IMDA reaction with only modest *exo*-preference (Table 1, entry 4).

The general *exo*-selectivity observed in the IMDA reactions of maleate half esters is consistent with calculations at the B3LYP/6-31 + G(d) level of theory. Thus, for triene acid **3**, the calculated ratio (*exo* : *endo* = 94 : 6; 110 °C, gas phase) compares favourably with the experimental ratio (*exo* : *endo* = 79 : 21; 110 °C, toluene solution; Table 1, entry 1). The *exclusively endo*-selective IMDA reactions of citraconate esters reported in seminal studies by White<sup>10,11</sup> (Scheme 2) and Mellor,<sup>12,13</sup> however, are not consistent with these findings. This conclusion led us to reinvestigate the work of White and Sheldon.

As discussed in the introduction, White and Sheldon<sup>10,11</sup> reported that a 1 : 1 mixture of citraconate half esters **9** and **10** in xylene at reflux produces cycloadduct **11** in low yield along with a polymer (Scheme 2). We heated a 1 : 1 mixture of regioisomeric citraconate half acids **9** and **10** in xylene under the reported conditions,<sup>11</sup> the solvent was removed and a <sup>1</sup>H NMR spectrum was recorded. A complex mixture of products was observed comprising the four expected cycloadducts **11**, **21**, **22** and **23** and hydroxy anhydrides of general structure **4**. We did not detect significant amounts of polymer. Upon treatment with trifluoroacetic acid in dichloromethane,<sup>28</sup> our complex mixture was reduced to the four lactone acids in good overall yield (Scheme 3).

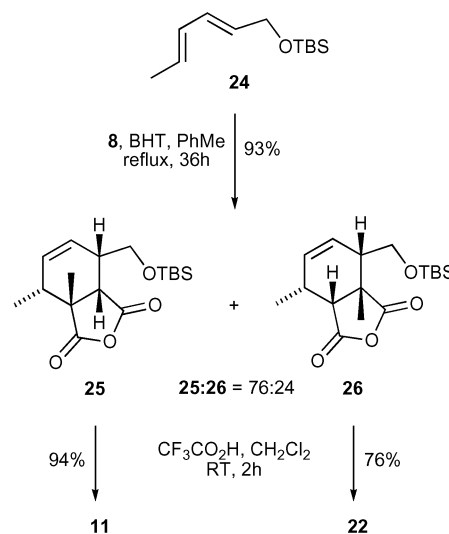


Scheme 3

The presence of a complicated product mixture, from which the major product **11** could be isolated by crystallisation, understandably led White and Sheldon to conclude that decomposition of half ester **10** was occurring under the reaction conditions, whereas half ester **9** was undergoing IMDA reaction to give **11**.<sup>11</sup>

We confirmed the presence of the two regioisomeric *endo*-cycloadducts (**11** and **22**) and the two regioisomeric *exo*-cycloadducts (**21** and **23**) by comparison with authentic samples, which were prepared as follows.

The two *endo*-cycloadducts **11** and **22** were prepared by intermolecular Diels–Alder reaction between sorbyl alcohol *tert*-butyldimethylsilyl (TBS) ether and citraconic anhydride, separation of the two regioisomeric adducts **25** and **26**, then treatment with trifluoroacetic acid, which caused desilylation and concomitant lactonisation (Scheme 4). The Diels–Alder reaction was clean, high yielding, completely *endo*-selective and moderately regioselective.



Scheme 4

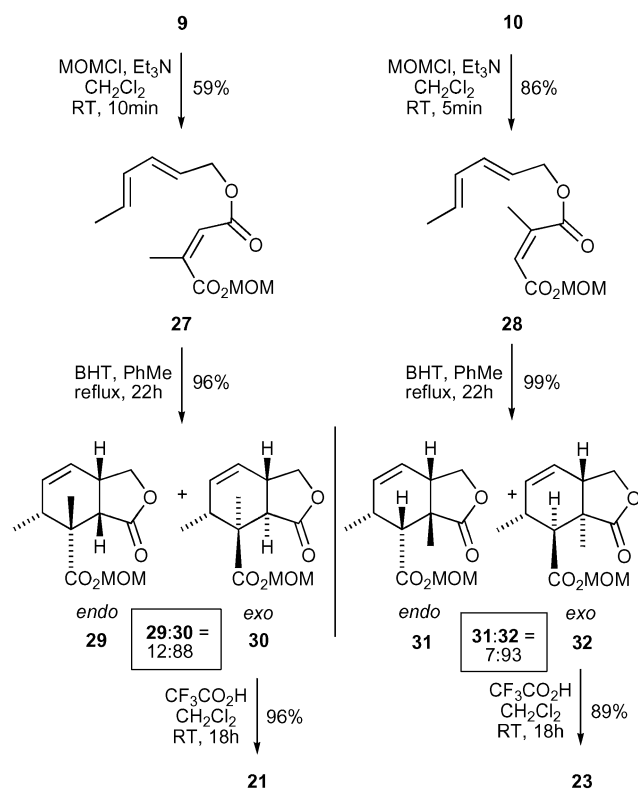
*Exo*-adducts **21** and **23** were accessed from IMDA reactions of the methoxymethyl (MOM) esters of **9** and **10**, **27** and **28** respectively, followed by hydrolysis of the MOM ester cycloadducts to the corresponding acids, as shown in Scheme 5. These two IMDA reactions were clean, very high yielding, highly *exo*-selective and, of course, completely regioselective. The methyl esters derived from acids **11** and **21** were identical in all respects to the compounds reported by White and Sheldon.<sup>11</sup>

Pure samples of each of the four carboxylic acid cycloadducts **11**, **21**, **22** and **23** were found to be stable in refluxing xylenes for 15 h. These experiments disprove the reversible IMDA theory for the formation of thermodynamically more stable *cis*-fused lactone acids<sup>11</sup> (see Introduction).

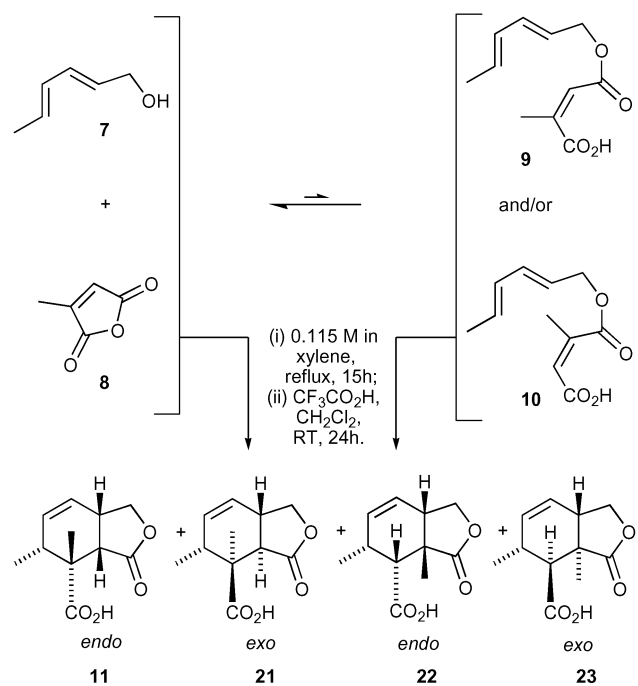
On face value, the result depicted in Scheme 3 confirms the original proposal that sorbyl citraconate half esters undergo *endo*-selective IMDA reactions, since *endo* adducts are favoured over *exo* adducts (*endo* : *exo* = 78:22). That this is *not* the case was proven by the experiments depicted in Scheme 6. Exposure of separate samples of the two triene precursors **9** and **10** to the same reaction conditions used with the 1 : 1 mixture of **9** and **10** (xylene, reflux) led to the formation of essentially the same product mixture, as did heating a 1 : 1 mixture of sorbyl alcohol **7** and citraconic anhydride **8**.

These results are consistent with a mechanism involving heterolysis of the ester linkage of triene acids **9** and **10** to citraconic anhydride and sorbyl alcohol, followed by an *endo*-selective intermolecular Diels–Alder reaction to give hydroxy anhydrides **33** and **34**, and finally intramolecular ester formation to give *cis*-fused lactone acids (Scheme 7). This last step can be sluggish, and is accelerated by the addition of trifluoroacetic acid.





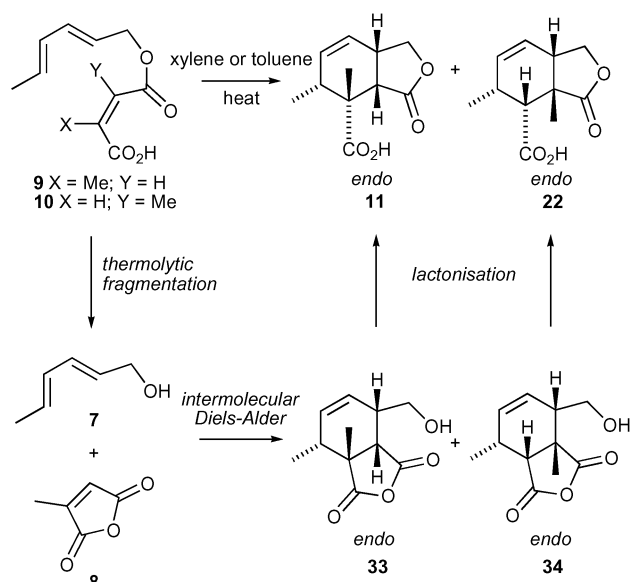
Scheme 5



	product ratio	mass balance
from <b>9</b>	<b>11:21:22:23</b> = 52:12:29:7	90%
from <b>10</b>	<b>11:21:22:23</b> = 53:11:29:7	91%
from <b>7+8</b>	<b>11:21:22:23</b> = 58:7:29:7	95%

Scheme 6

Support for this proposal comes from carrying out experiments in NMR tubes. After heating separate samples of **9** and **10** dissolved in d<sub>8</sub>-toluene at 110 °C for 15 min, 50% of each triene acid precursor is converted into citraconic anhydride and sorbyl



Scheme 7

alcohol within 15 min. We assume that the *intermolecular* Diels-Alder reaction between **7** and **8** is completely *endo*-selective and modestly regioselective; the result obtained with the TBS ether of sorbyl alcohol (Scheme 4) supports this proposal. The production of small amounts (*ca.* 20% of the product mixture) of *trans*-fused *exo*-adducts **21** and **23** is the result of the IMDA pathway. The stereoselectivity of the IMDA reactions of **9** and **10** in aromatic solvents cannot be elucidated from these experiments but it is fairly safe to assume that they are strongly *exo*-selective, in line with maleate half esters **3** (Table 1) and citraconate diesters (Scheme 5), and the result of the following experiment.

For pentadienyl maleate and citraconate half esters, the competition between fragmentation and IMDA reaction is due to the two processes having similar activation energies. For substituted maleates, the IMDA activation energies in toluene and xylene are higher than those for fragmentation, whereas the reverse is true for unsubstituted maleate half esters. To disfavour fragmentation, citraconate half ester **9** was dissolved in DMSO, a solvent that is known to lower the activation energies of IMDA reactions of ester-tethered precursors.<sup>29</sup> Upon heating at 120 °C for 16 h, **9** underwent a highly stereoselective IMDA reaction, giving rise to **21** and **11** as a 92 : 8 *exo* : *endo* mixture of cycloadducts in 58% isolated yield.<sup>30</sup> The high *exo*-IMDA stereoselectivity exhibited by acid **9** in DMSO is remarkably similar to that of the corresponding MOM ester **27** (Scheme 5), and also follows the general trend for maleate esters and acids (Table 1) and is strongly supported by calculations (Fig. 1).

Studies with other precursors<sup>31</sup> demonstrate that the heat-promoted fragmentation of citraconate half esters to form an alcohol and citraconic anhydride (*i.e.* **9/10** → **7** + **8**; Scheme 6) appears to be a general reaction. Surprisingly, we could not find a single report of this fragmentation reaction in the literature. It is striking that monoesters of citraconic acid react this way, whereas monoesters of maleic acid are stable. We presume that half esters of other *substituted* maleic acids behave in a similar manner to those of the monoesters of citraconic acid. We suspect that the *endo*-selective Diels-Alder reactions reported by Mellor and Batchelor<sup>12,13</sup> are also the result of *intermolecular* cycloadditions.

Although it may be reasonable to interpret the experimental observation that triene acid **9** gives bicyclic lactone acid **11** upon heating in terms of a one-step IMDA mechanism (Scheme 2), our findings demonstrate that this is not the case and that an alternative, three-step mechanistic sequence prevails.

## Acknowledgements

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