Stereocontrol of the Intramolecular Diels−Alder Reaction by Internal Hydrogen Bonding

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A novel approach for *exo*/*endo* stereocontrol of intramolecular Diels–Alder reactions is described. Substrates carrying a hydroxymethyl group attached to the diene and an ester group attached to the dienophile participate in hydrogen bonding in the transition state. This non-covalent interaction causes either a significant enhancement or diminution in the observed kinetic *endo*/*exo* product ratio. Thus, the parent pentadienyl maleate **12** undergoes intramolecular Diels–Alder reaction to give an approx. 5:1 mixture of *trans*- and *cis*-fused bicyclic cycloadducts, whereas the *C*2-hydroxymethyl analogue **1** delivers a 1:1 ratio of products. In contrast, the parent pentadienyl fumarate **13** gives a 3:2 *trans*:*cis* ratio, which is improved to 9:1 in the *C*2-hydroxymethyl analogue **4**. These stereoselectivities are accurately predicted from transition structure populations calculated using B3LYP/6-31+G(d) theory. The presence of an intramolecular H-bond confers a transannular Diels–Alder-like appearance upon the transition states of these reactions.

Introduction

Diels−Alder reactions are amongst the most powerful and versatile of synthetic transformations, with two new covalent bonds and up to four contiguous stereocentres being formed in each reaction.[1] Intermolecular,[1] intramolecular[2] and transannular[3] variants are well documented. Given its importance, it is not surprising that the control of stereoselectivity of Diels−Alder reactions continues to be an active area of research. Despite an enormous body of experimental and theoretical data on the Diels−Alder reaction, however, the origins of stereoselectivity are poorly understood.[4]

Previous studies (Figure 1) have described the influence of hydrogen bonding upon π-*facial* stereoselectivity in intermolecular Diels−Alder reactions; processes with inherent kinetic *endo*-selectivity.[5,6] Furthermore, there are numerous reports of catalysts[7] and solvents[8] impacting upon the rates and stereoselectivities of Diels−Alder reactions through hydrogen bonding. In this paper we describe the use of intramolecular hydrogen bonds to control the *endo*/*exo*-stereoselectivity of intramolecular Diels−Alder (IMDA) reactions.

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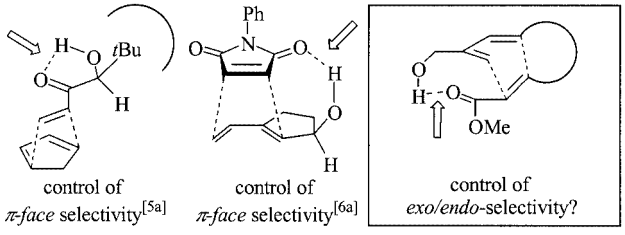


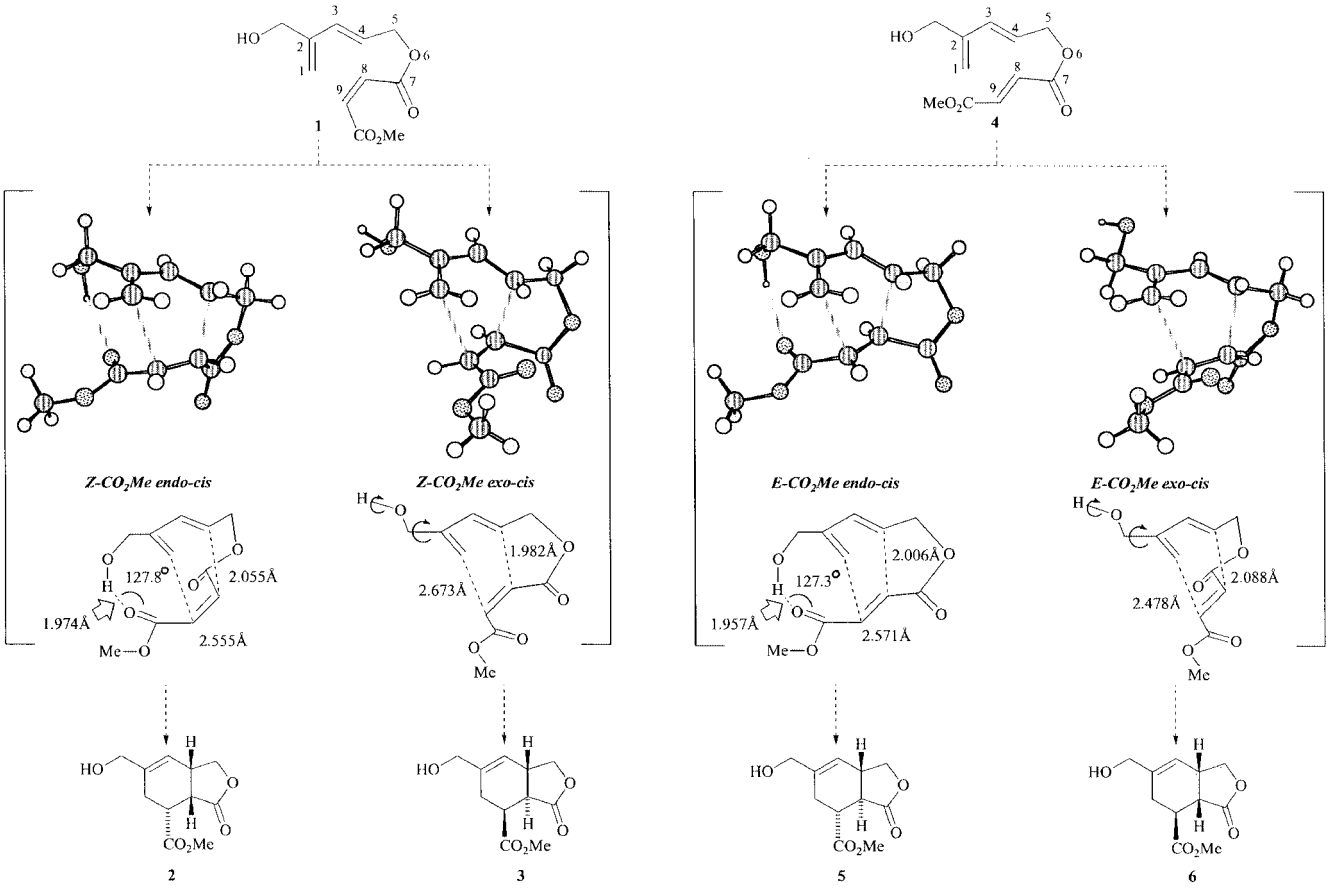
Figure 1. Promoting and controlling Diels−Alder reactions through H-bonds

Results and Discussion

Suitable candidate structures to test this theory are depicted in Scheme 1, which contain an alcohol group appended to the diene and an ester group attached to the dienophile. For the (*Z*)-dienophile system **1**, intramolecular H-bonding should occur in the CO_2Me *endo* mode of addition and would be necessarily absent in the CO_2Me *exo* mode.

Thus, the *cis*-fused bicycle **2** would be favoured over its *trans*-fused congener **3**, the opposite stereochemical outcome to that seen in substrates that lack the *C*2-hydroxymethyl group.[6] With the (*E*)-dienophile system **4**, intramolecular H-bonding in the CO_2Me *endo* mode would favour the formation of the *trans*-fused product **5**, a reaction that usually gives roughly equal amounts of the two stereoisomers.[6]

These reactions were examined computationally using the hybrid B3LYP functional together with the 6-31+G(d) basis set. It is generally accepted that B3LYP/6-31+G(d) models give reliable geometries of transition structures



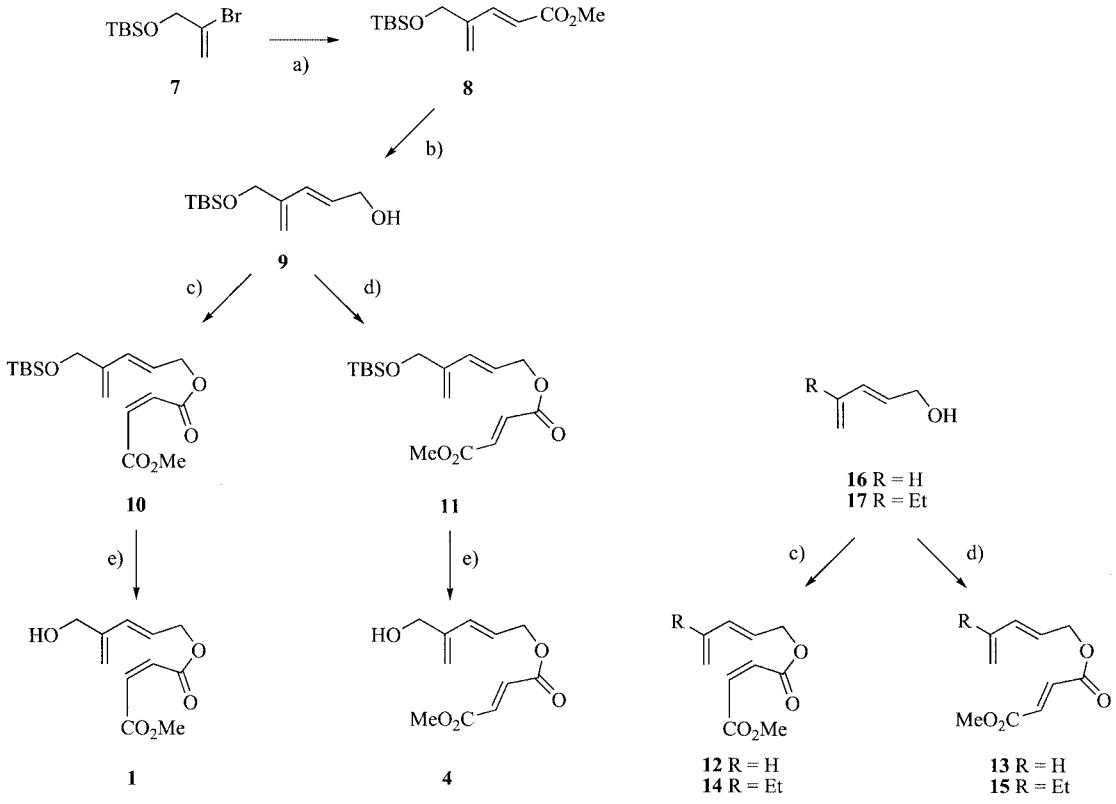
Scheme 1. Intramolecular H-bond-assisted IMDA reactions under scrutiny; B3LYP/6-31+G(d) TSs for favoured *s-cis* (O=C−C9=C8) conformations are depicted, along with C=O···H bond angles, H-bond lengths, and developing internal and peripheral bond lengths

(TSs) and activation energies for pericyclic reactions.[9,10,11a,12] A thorough treatment of *exo*/*endo* selectivity for IMDA reactions of **1** and **4** requires the location of 72 TSs, since the carbonyl group attached to C9 can be either *transoid* or *cisoid* with respect to the C8=C9 dienophile and nine different conformers about the hydroxymethyl group can be identified. In the event, a total of 36 TSs were located since non-H-bonded *CO_2Me endo* conformations were found to be considerably less stable than their intramolecular H-bonded analogues. The computational methods used are described in detail in the Computational Studies Sect.[13]

Eight triene substrates were synthesized to examine these predictions (Scheme 2): the maleate and fumarate esters of the parent pentadienol along with systems carrying *C*2-ethyl, hydroxymethyl and *tert*-butyldimethylsilyloxymethyl substituents. The silyloxymethyl-appended dienol **9** was prepared by Heck reaction between the bromoalkene **7**[14] and methyl acrylate, followed by reduction.[15] Standard esterification reactions gave the silyloxymethyl-substituted maleate and fumarate IMDA precursors **10** and **11**,[12] from which the hydroxymethyl compounds **1** and **4** were obtained by buffered TBAF deprotection. The parent IMDA precursors **12** and **13** and the *C*2-ethyl-substituted systems **14** and **15** were prepared by esterifying the known dienols **16**[16] and **17**,[17] respectively.

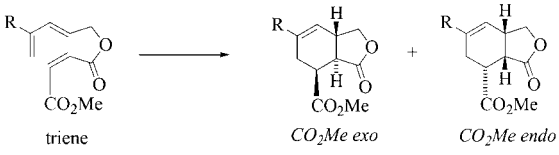
IMDA reactions of the trienes **1**, **4**, **10**, **11**, **12, 13, 14,** and **15** were carried out in dilute solutions in refluxing toluene. The results of these experiments, along with predicted stereoisomer ratios based upon calculated Boltzmann distributions, are listed in Table 1 and 2. That these experimentally-determined ratios are the outcome of kinetically controlled IMDA reactions was shown by exposing isolated cycloadducts to the reaction conditions used to form them: in all cases, no change was observed.

In results consistent with earlier findings,[11a] the parent maleate and fumarate precursors exhibited a preference for the formation of *trans*-fused bicycles, with the maleate undergoing a much more *trans*-selective IMDA reaction than the fumarate (compare Table 1, Entry 1 vs. Table 2, Entry 1). A comparison of the cycloaddition results of the ethyl-substituted dienes **14** and **15** with their unsubstituted counterparts **12** and **13** shows that the ethyl group instills a very slight *CO_2Me endo*-directing influence upon the reaction (compare Entry 1 vs. Entry 2). As expected, no significant difference is seen in IMDA stereoselectivity upon replacement of a C2−CH_2CH_3 group by a C2−CH_2OTBS group (compare Entry 2 vs. Entry 3). A significant change in stereochemical outcome is witnessed for the C2−CH_2OH compounds, however, with the maleate undergoing a non-stereoselective IMDA reaction and the fumarate undergoing a highly *trans*-selective IMDA reaction (Entry 4).



Scheme 2. Reagents and conditions: a) $Pd(OAc)_2$ (4 mol %), LiCl, Bu_4NCl, K_2CO_3, $H_2C{=}CHCO_2Me$, DMF, 85 °C, 5 h, 55%. b) DIBAL-H (2.2 equiv.), Et_2O, −78 °C, 30 min, 89%. c) *i.* Et_3N, maleic anhydride, DMAP (10 mol %), 0 °C, 10 min. *ii.* CH_2N_2, Et_2O, −78 °C, 10 min, 60−64%. d) (*E*)-$MeO_2CHC{=}CHCO_2H$, DCC, DMAP, room temp., 2 h, 69−81%. e) AcOH, TBAF, THF, room temp., 3 h, 82−85%

Table 1. Pentadienyl maleate IMDA reactions



Entry	R	Triene	Solvent	Temp. (°C)	Time (h)[a]	Yield (%)	CO_2Me *exo*/CO_2Me *endo* Product	Exp.[b]	Theory[c]
1	H	**12**	PhMe	110	4	97	**18/19**	83:17	94:6
2	CH_2CH_3	**14**	PhMe	110	4	89	**20/21**	73:27	–
3	CH_2OTBS	**10**	PhMe	110	4	92	**22/23**	72:28	–
4	CH_2OH	**1**	PhMe	110	3	94	**2/3**	49:51	54:46

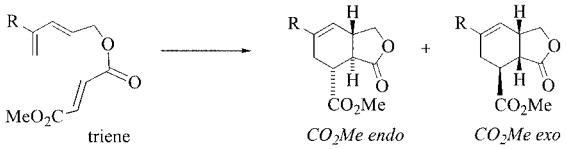
[a] Time taken for > 95% conversion of starting triene. [b] The mean of the ratios measured from GC of the crude reaction mixture, ^1H NMR of the crude reaction mixture, and the isolated yields after purification. The difference between the three sets of ratios was at most ±2%. [c] Estimated value based upon a restricted set of 36 out of 72 possible TSs: see Exp. Sect. for full details.

Furthermore, the experimental *cis*:*trans* cycloadduct ratios are remarkably close to those predicted by theory. The dramatic shift in reaction outcome upon incorporation of the C2−CH_2OH substituent is thus attributed to stabilization of *CO_2Me endo* TSs with respect to *CO_2Me exo* TSs by an internal H-bond, which confers a transannular Diels−Alder-like appearance upon the *CO_2Me endo* TSs (Scheme 1).

In summary, this work shows that substrate-based internal hydrogen bonds have a significant impact upon *exo*/*endo* stereoselectivity of Diels−Alder reactions, with improvements in *exo*:*endo* stereoselectivity from 2:1 (C2−CH_2OTBS fumarate) to 9:1 (C2−CH_2OH fumarate) being realized. The deployment of non-covalent interactions in this way should enjoy wider application.

Computational Studies: All calculations were carried out using the GAUSSIAN 98 program.[18] The hybrid B3LYP functional was used throughout, together with the 6-31+G(d) basis set. It is generally accepted that B3LYP/6-31+G(d) models give reliable geometries of transition

Table 2. Pentadienyl fumarate IMDA reactions



Entry	R	Triene	Solvent	Temp. (°C)	Time (h)[a]	Yield (%)	CO_2Me *endo*/CO_2Me *exo* Product	Exp.[b]	Theory[c]
1	H	**13**	PhMe	110	205	77	**24/25**	58:42	55:45
2	CH_2CH_3	**15**	PhMe	110	44	74	**26/27**	65:35	–
3	CH_2OTBS	**11**	PhMe	110	45	77	**28/29**	68:32	–
4	CH_2OH	**4**	PhMe	110	11	83	**5/6**	91:9	98:2

[a] Time taken for > 95% conversion of starting triene. [b] The mean of the ratios measured from GC of the crude reaction mixture, ^1H NMR of the crude reaction mixture, and the isolated yields after purification. The difference between the three sets of ratios was at most ±4%. [c] Estimated value based upon a restricted set of 36 out of 72 possible TSs: see Exp. Sect. for full details.

structures (TSs) and activation energies for pericyclic reactions.[9,10][11a,12] All TSs were fully characterised by carrying out harmonic frequency calculations. Intrinsic reaction coordinate calculations were also carried out on three representative TSs to confirm that each of them did, indeed, connect the respective triene reactant and intramolecular Diels–Alder (IMDA) product. This analysis also confirms that the IMDA reactions are concerted but asynchronous processes. Product distributions were calculated with zero point energy corrections included.

The *exo*/*endo* selectivities for the IMDA reactions of the (*E*)- and (*Z*)-2-hydroxymethylene-9-ester systems, **1** and **4**, were estimated by locating appropriate gas phase TSs for the *exo* and *endo* modes and carrying out a Boltzmann population analysis at the same temperature as was used experimentally. Solvation effects were not investigated. Cartesian coordinates for the significant TSs are given in the Supporting Information.

A thorough treatment of the *exo*/*endo* selectivity for the IMDA reactions of **1** and **4** requires the location of 72 TSs. Thus, for each mode (*exo* or *endo*), the disposition of the 9-ester carbonyl group may be either *transoid* or *cisoid* with respect to the dienophile C8=C9 double bond (hereafter referred to as *trans* and *cis*, respectively). Furthermore, nine different conformations associated with the 2-CH_2OH group may be realised, i.e. three conformations about the C2–C(H_2OH) bond and three about the (HOH_2)C–O(H) bond. The calculation of such a large number of TSs at the high level of theory employed in this study [B3LYP/6-31+G(d)] is not feasible and, indeed, is not necessary since the purpose of the DFT calculations in this study was to provide an indication of whether *exo*/*endo* selectivity in the IMDA reactions of **1** and **4** could be significantly strengthened, in the case of the (*E*)-isomer, or even reversed, in the case of the (*Z*)-isomer, by intramolecular H-bonding. In this spirit, 36 TSs were calculated, including the four possible intramolecularly-H-bonded TSs which are depicted graphically in Figure 2.

Intramolecular H-bonding occurs in the *CO_2Me endo* mode of addition and is necessarily absent in the *CO_2Me exo* mode. Two distinct H-bonded conformations were found for both (*Z*) and (*E*) systems; in one conformation,

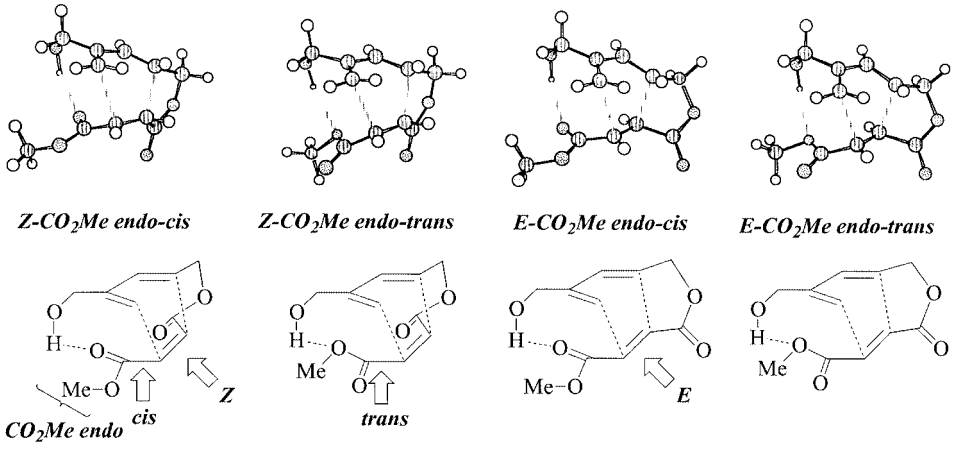


Figure 2. H-bonded transition structures

the H-bond involves the carbonyl oxygen atom as the acceptor (the ester adopts the *cis* conformation) and in the other, it is the methoxy oxygen atom which acts as the acceptor (the ester adopts the *trans* conformation). In each case [(*E*) or (*Z*)], the *cis* conformation is substantially more stable than the *trans* conformation. However, we find that, for a given TS configuration, the *cis* conformation is inherently more stable than the *trans* conformation — by about 8 kJ/mol for the (*E*)-isomer, and 5 kJ/mol for the (*Z*)-isomer — even in the absence of intramolecular H-bonding.

The intramolecular H-bonding to the carbonyl oxygen atom, with the ester group adopting the *cis* conformation, is essentially π-hydrogen bonding, with the angle between the hydroxy H atom and the C=O bond being about 127° in both (*Z*)-*CO_2Me endo-cis* and (*E*)-*CO_2Me endo-cis* TSs. The H-bond length is 1.974 Å and 1.957 Å in the (*Z*)-*CO_2Me endo-cis* and (*E*)-*CO_2Me endo-cis* TSs, respectively. The H-bonding in the TS in which the ester group adopts the *trans* conformation is likewise π-type, but with the H-bond being slightly longer than that calculated for the respective *cis* conformer, specifically 2.098 Å for the (*Z*)-*CO_2Me endo-trans* TS and 2.056 Å for the (*E*)-*CO_2Me endo-trans* TS.

Using simple molecular models, the four most stable non-H-bonded TSs which give products having the *opposite exo/endo* stereoselectivity to those resulting from the H-bonded TSs are displayed in Figure 3.

Considering the (z.p.e. corrected) energies of only the eight TSs shown in Figure 2 and Figure 3 gives the following *exo*/*endo* selectivities (110 °C):

1: *CO_2Me exo*/*CO_2Me endo* = 13:87 (1)

4: *CO_2Me endo*/*CO_2Me exo* = 99:1 (2)

These selectivities are biased in favour of those products arising from configurations containing the intramolecularly H-bonded forms because only a restricted set of TSs were considered. Each TS depicted in Figure 2 and Figure 3 is just one member of a set of nine TSs arising from various conformations of the C2−CH_2OH group. Rigid rotor calculations suggest that the H-bonded TSs shown in Figure 2 are by far the most stable (> 8 kJ/mol) conformations associated with rotations within the C2−CH_2OH group in their respective sets. Consequently, the exclusion of the non-H-bonded conformations associated with the (*E*)-*CO_2Me endo-cis*, (*E*)-*CO_2Me endo-trans*, (*Z*)-*CO_2Me endo-cis* and (*Z*)-*CO_2Me endo-trans* TSs (Figure 2) from the *exo*/*endo* selectivity calculations is a reasonable approximation. This is not the case for the four sets of TSs (*E*)-*CO_2Me exo-cis*, (*E*)-*CO_2Me exo-trans*, (*Z*)-*CO_2Me exo-cis* and (*Z*)-*CO_2Me exo-trans* (Figure 3), for which no intramolecular H-bonding is possible; consequently, it is expected that many of the nine conformational isomers associated with rotations within the C2−CH_2OH group for each set of TSs have similar energies.

An over-corrected estimate for the *exo*/*endo* selectivities for the IMDA reaction of 1 and 4 may be obtained by assuming that, for each type of TS, namely (*E*)-*CO_2Me exo-cis*, (*E*)-*CO_2Me exo-trans*, (*Z*)-*CO_2Me exo-cis* and (*Z*)-*CO_2Me exo-trans*, the nine conformations associated with the C2−CH_2OH group have the same energy as that conformation depicted for the respective TS shown in Figure 3. The following *exo*/*endo* selectivities are now calculated (110 °C):

1: *CO_2Me exo*/*CO_2Me endo* = 54:46 (3)

4: *CO_2Me endo*/*CO_2Me exo* = 98:2 (4)

The *exo*/*endo* selectivity is unchanged in the case of **4** whereas that for the (*Z*) stereoisomer becomes stereorandom. Twenty eight additional transition structures, differing in their conformations with respect to the C2−CH_2OH group, were calculated, but the *exo*/*endo* selectivities for **1** and **4** were found to be nearly the same as those estimated above [Equations (3) and (4)].

In the case of the IMDA reactions of the parent 9-esters, **12** and **13**, all eight possible transition structures (i.e. *exo*/*endo*, *E*/*Z*, *cis*/*trans*) were calculated and so the resulting calculated *exo*/*endo* selectivities are complete.

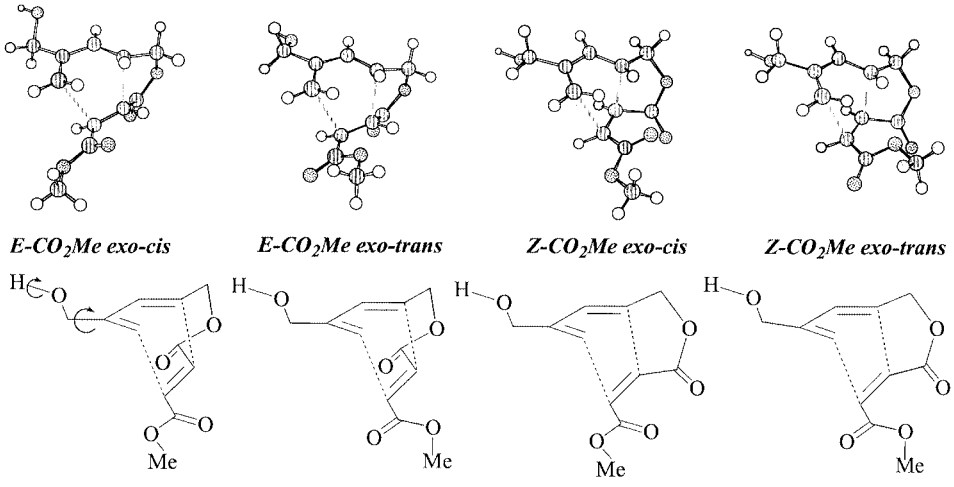


Figure 3. Non-H-bonded transition structures; nine discrete conformations of each TS are possible, arising from depicted bond rotations

Experimental Section

General Synthetic Methods: NMR spectra were recorded at 298 K using a Varian Unity INOVA 500 MHz, Bruker DPX/DRX 400 MHz or Varian Unity INOVA 300 MHz spectrometer. Residual benzene (δ = 7.15), chloroform (δ = 7.26), and methanol (δ = 3.31) were used as internal references for ^{1}H NMR spectra measured in these solvents. Residual benzene (δ = 128.1), chloroform (δ = 77.1), and methanol (δ = 49.0) were used as internal references for ^{13}C NMR spectra. Assignment of proton signals was assisted by ^{1}H-^{1}H COSY and NOESY experiments when necessary; assignment of carbon signals was assisted by DEPT experiments; Q = quaternary carbon atom. IR spectra were recorded with a Perkin−Elmer 1600 FT-IR. or Perkin−Elmer Spectrum One spectrometer as neat films on NaCl plates for oils or as KBr pellets for solid products. Mass spectra were recorded by the Mass Spectrometer Facility of the Research School of Chemistry, Australian National University, Canberra. Microanalyses were performed at the Campbell Microanalytical Laboratory at the Department of Chemistry, University of Otago, New Zealand. Melting points were measured with a Reichert melting point stage and are uncorrected. HPLC was performed using a Waters 510EF chromatograph pump and Waters U6 K injector monitored by a Waters Lambda-Max 481 UV spectrophotometer at λ = 254 nm and an Erma ERC-7512 refractive index detector. GC measurements were recorded with a Agilent 6850 gas chromatograph with a split/splitless capillary inlet and FID detector. GC data were processed using Hewlett Packard ChemStation software. Analytical TLC was performed with Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm). Flash chromatography employed Merck Kieselgel 60 (230−400 mesh) silica gel.

Reactions were conducted under a positive pressure of dry argon or nitrogen. Diethyl ether, toluene and THF were dried over sodium wire and distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Commercially available chemicals were purified by standard procedures or used as purchased. The dienols **16**[16] and **17**[17] were prepared according to the literature procedures.

Synthesis of the Triene Substrates

Methyl (2*E*)-Penta-2,4-dien-1-yl Maleate (12): Triethylamine (560.3 mg, 5.537 mmol, 1.6 equiv.), maleic anhydride (763.6 mg, 7.787 mmol, 2.25 equiv.) and DMAP (42.3 mg, 0.346 mmol, 0.1 equiv.) were added to a stirred solution of the dienol **16**[16] (291.1 mg, 3.461 mmol, 1.0 equiv.) in dichloromethane (16 mL) at 0 °C. The mixture was stirred at this temperature for 10 min. The solution was warmed to room temperature before being diluted with diethyl ether (62 mL). The mixture was washed with 2 M HCl (32 mL), brine (32 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted with toluene (8 mL) and stirred at −78 °C. An ethereal solution of diazomethane was added dropwise until TLC confirmed the reaction had gone to completion. Excess diazomethane was removed by bubbling N_2 gas through the solution. The solution was concentrated in vacuo then subjected to column chromatography on silica (20% ethyl acetate/hexanes) to give the maleate **12** (457.0 mg, 2.329 mmol, 67%) as a colourless oil. R_f = 0.43 (20% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37−6.25 (m, 2 H), 6.24 (m, 2 H), 5.77 (m, 1 H), 5.24 (m, 1 H), 5.13 (d, *J* = 9.1 Hz, 1 H), 4.69 (d, *J* = 6.2 Hz, 2 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.6 (Q), 164.9 (Q), 135.8 (CH), 135.3 (CH), 129.9 (CH), 129.6 (CH), 126.3 (CH), 119.0 (CH_2), 65.3 (CH_2), 52.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2953 (C−H), 1732 (C=O), 1644 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 197 (10) $[M + 19]^+$, 196 (15) $[M^+]$, 131 (30) $[M - C_5H_5]^+$, 114 (100) $[M - C_5H_8O]^+$, 67 (70) $[M - C_5H_5O_4]^+$. HRMS: calcd. $C_{10}H_{13}O_4$ $[M + H]^+$: 197.0814; found 197.0811.

Methyl (2*E*)-4-Ethylpenta-2,4-dien-1-yl Maleate (14): The dienol **17**[17] (306 mg, 2.73 mmol) was converted into the maleate **14** (366 mg, 1.63 mmol, 60%) using the procedure described above for maleate **12**. The maleate **14** was obtained as a colourless oil. R_f = 0.36 (20% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.32 (d, *J* = 16.0 Hz, 1 H), 6.23 (s, 2 H), 5.76 (dt, *J* = 15.7, 6.7 Hz, 1 H), 5.00 (s, 2 H), 4.70 (d, *J* = 6.6 Hz, 2 H), 3.73 (s, 3 H), 2.18 (q, *J* = 7.6 Hz, 2 H), 1.06 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6 (C), 164.9 (C), 146.5 (C), 137.1 (CH), 129.8 (CH), 129.7 (CH), 121.4 (CH), 115.9 (CH_2), 65.9 (CH_2), 52.1 (CH_3), 24.4 (CH_2), 12.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3081, 3039, 2969, 2881 (C−H), 1732 (C=O), 1647, 1610 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 224 (15) $[M^+]$, 164 (5) $[M - C_2H_4O_2]^+$, 114 (100) $[M - C_7H_{10}O]^+$. HRMS: calcd. $C_{12}H_{16}O_4$: 224.1049; found 224.1049.

2-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]prop-2-ene (7): 2-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]prop-2-ene (**7**)[14] was prepared from a modified literature procedure.[19] Dry hydrogen bromide gas (9.115 g, 112.6 mmol, 1.1 equiv.) was bubbled into tetraethylammonium bromide (2.582 g, 122.9 mmol, 1.2 equiv.) and dry dichloromethane (150 mL) at 0 °C. After stirring the reaction mixture at room temp. for 10 min, propargyl alcohol (5.738 g, 102.4 mmol, 1.0 equiv.) was added slowly and the reaction mixture stirred at room temp. for 1 h followed by reflux for 2 h. After allowing to cool, the mixture was poured into diethyl ether (125 mL), the precipitate was filtered through a short pad of silica washing with diethyl ether (50 mL). The filtrate washings were concentrated in vacuo, diluted into dry dichloromethane (40 mL), and stirred at room temp. Imidazole (1.394 g, 204.8 mmol, 2.0 equiv.), TBSCl (23.15 g, 153.6 mmol, 1.5 equiv.), and DMAP (2.297 g, 20.48 mmol, 0.2 equiv.) were added and the mixture stirred for 40 min. The mixture was diluted into diethyl ether (200 mL) before being washed with 2 M HCl (2 × 200 mL), brine (200 mL), and dried ($NaSO_4$). The filtrate was passed through a short plug of silica (eluting with pentanes) and concentrated in vacuo to give compound **7** (9.889 g, 39.36 mmol, 38%) as a colourless oil: R_f = 0.26 (pentanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (ddd, *J* = 3.7, 2.0, 2.0 Hz, 1 H), 5.53 (ddd, *J* = 3.4, 1.7, 1.7 Hz, 1 H), 4.21 (dd, *J* = 1.7, 1.7 Hz, 2 H), 0.92 (s, 9 H), 0.10 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.9 (C), 114.7 (CH_2), 67.5 (CH_2), 25.9 (CH_3), 18.4 (C), −5.3 (CH_3), −5.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2955, 2930, 2886, 2857 (C−H), 1640 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 195 (80) $[M - C_4H_9]^+$, 193 (78) $[M - C_4H_9]^+$, 139 (100) $[M - C_6H_{11}Si]^+$, 137 (98) $[M - C_6H_{11}Si]^+$. HRMS: calcd. for $C_5H_{10}O^{79}BrSi$: 192.9684; found 192.9693. HRMS: calcd. $C_5H_{10}O^{81}BrSi$: 194.9664; found 194.9671.

Methyl (2*E*)-4-[(*tert*-Butyldimethylsilyl)oxymethyl]penta-2,4-dienoate (8): This compound was prepared from modified literature procedures for a similar substrate.[15,20] DMF (400 mL) was added to a mixture of $Pd(OAc)_2$ (353.3 mg, 1.574 mmol, 0.04 equiv.), nBu$_4$NCl (10.94 g, 39.36 mmol, 1.0 equiv.), LiCl (1.668 g, 39.36 mmol, 1.0 equiv.), and K_2CO_3 (13.60 g, 98.4 mmol, 2.5 equiv.). To this solution was added the bromoalkene **7** (9.889 g, 39.36 mmol, 1.0 equiv.) in DMF (100 mL) and methyl acrylate (20.33 g, 236.2 mmol, 6.0 equiv.). The mixture was heated at 85 °C for 5 h. After allowing to cool to room temp. the mixture was diluted into a mixture of diethyl ether and water (1200 mL each). The organic phase was washed with water (3 × 600 mL) and the aqueous phase was ex-

tracted once with diethyl ether (600 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo then subjected to column chromatography on silica (5% diethyl ether/pentanes) to give compound **8** (5.330 g, 20.79 mmol, 55%) as a colourless oil: R_f = 0.20 (5% diethyl ether/pentanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 16.4 Hz, 1 H), 5.88 (d, *J* = 16.4 Hz, 1 H), 5.66 (ddd, *J* = 3.4, 1.7, 1.7 Hz, 1 H), 5.47 (m, 1 H), 4.32 (2 H, dd), 3.76 (s, 3 H), 0.92 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5 (C), 144.2 (CH), 143.4 (C), 122.4 (CH_2), 117.5 (CH), 62.3 (CH_2), 51.7 (CH_3), 25.9 (CH_3), 18.4 (C), −5.3 (CH_3), −5.4 (CH_3) ppm. IR (neat): ṽ = 2953, 2930, 2885, 2857 (C−H), 1723 (C=O), 1636, 1608 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 257 (0.5) $[M + H]^+$, 241 (10) $[M - CH_3]^+$, 225 (20) $[M - CH_3O]^+$, 199 (60) $[M - C_4H_9]^+$, 167 (25) $[M - C_4H_9O_2]^+$, 89 (100) $[M - C_9H_{15}OSi]^+$. HRMS: calcd. $C_{12}H_{21}O_3Si$ $[M - CH_3]^+$: 241.1260; found 241.1265.

(2*E*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]penta-2,4-dien-1-ol (9): A solution of the methyl dienoate **8** (1.8276 g, 7.1276 mmol, 1.0 equiv.) in dry diethyl ether (3 mL) was added to a stirred solution of DIBAL-H (1.5 M in toluene, 10.454 mL, 15.681 mmol, 2.2 equiv.) at −78 °C. After 30 min, methanol (1.0 mL) was added cautiously to destroy excess hydride. The resulting solution was slowly poured into ice-cold 2 M HCl (16 mL) with stirring. Ice and concentrated HCl were added as needed to keep the solution cool and acidic. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 × 10 mL). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give compound **9** (1.4394 g, 6.3090 mmol, 89%) as a colourless viscous oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.28 (d, *J* = 16.1 Hz, 1 H), 5.80 (ddd, *J* = 16.1, 5.9, 5.9 Hz, 1 H), 5.31 (m, 1 H), 5.11 (m, 1 H), 4.32 (m, 2 H), 4.19 (dd, *J* = 5.9, 1.0 Hz, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1 (C), 130.9 (CH), 127.6 (CH), 114.9 (CH_2), 63.8 (CH_2), 62.9 (CH_2), 26.0 (CH_3), 18.5 (C), −5.3 (CH_3) ppm. IR (neat): ṽ = 3332 (OH), 2955, 2925, 2884, 2857 (C−H), 1612 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 227 (0.5) $[M - H]^+$, 213 (1) $[M - CH_3]^+$, 211 (3) $[M - OH]^+$, 171 (20) $[M - C_4H_9]^+$, 153 (10) $[M - C_4H_{11}O]^+$, 75 (100). HRMS: calcd. $C_{11}H_{21}O_2Si$ $[M - CH_3]^+$: 213.1311; found 213.1313.

Methyl (2*E*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]penta-2,4-dien-1-yl Maleate (10): The dienol **9** (119 mg, 0.520 mmol) was converted into the maleate **10** (114 mg, 0.333 mmol, 64%) using the procedure described above for the maleate **12**. The maleate **10** was obtained as a colourless viscous oil. R_f = 0.46 (20% ethyl acetate/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.32 (d, *J* = 16.1 Hz, 1 H), 6.23 (s, 2 H), 5.73 (ddd, *J* = 16.1, 6.4, 6.4 Hz, 1 H), 5.34 (m, 1 H), 5.13 (m, 1 H), 4.70 (d, *J* = 6.9 Hz, 2 H), 4.29 (m, 2 H), 3.75 (s, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6 (C), 164.9 (C), 143.7 (C), 134.4 (CH), 129.9 (CH), 129.7 (CH), 121.6 (CH), 116.0 (CH_2), 65.9 (CH_2), 62.6 (CH_2), 52.1 (CH_3), 25.9 (CH_3), 18.3 (C), −5.4 (CH_3) ppm. IR (neat): ṽ = 2954, 2885, 2856 (C−H), 1732 (C=O), 1648, 1614 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 325 (5) $[M - CH_3]^+$, 309 (10) $[M - CH_3O]^+$, 10], 283 (100) $[M - C_4H_9]^+$. HRMS: calcd. $C_{16}H_{25}O_5Si$ 325.1471; found 325.1471.

Methyl (2*E*)-4-Hydroxymethylpenta-2,4-dien-1-yl Maleate (1): Acetic acid (431.0 mg, 7.178 mmol, 10.0 equiv.) and TBAF (1.0 M in THF, 1.436 mL, 1.436 mmol, 2.0 equiv.) were added to a solution of the maleate **10** (244.4 mg, 0.7178 mmol, 1.0 equiv.) in THF (2 mL) stirred at room temp. After 3 h, the reaction mixture was diluted with diethyl ether (20 mL) and washed with satd. aq. $NaHCO_3$ (20 mL), brine (20 mL), dried ($NaSO_4$), filtered and concentrated in vacuo. The crude mixture was subjected to column chromatography on silica (60% ethyl acetate/hexanes) to give compound **1** (138.2 mg, 0.8510 mmol, 85%) as a colourless oil. R_f = 0.32 (60% ethyl acetate/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.30 (d, *J* = 16.4 Hz, 1 H), 6.22 (m, 2 H), 5.79 (ddd, *J* = 15.9, 6.3, 6.3 Hz, 1 H), 5.27 (m, 1 H), 5.13 (m, 1 H), 4.68 (dd, *J* = 6.5, 1.1 Hz, 2 H), 4.25 (s, 2 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7 (C), 165.0 (C), 144.0 (C), 134.1 (CH), 129.9 (CH), 129.6 (CH), 122.5 (CH), 116.9 (CH_2), 65.8 (CH_2), 62.5 (CH_2), 52.2 (CH_3) ppm. IR (neat): ṽ = 3502 (OH), 3053, 3000, 2953, 2928, 2855 (C−H), 1730 (C=O), 1645, 1614 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 226 (5) $[M]^+$, 208 (3) $[M - H_2O]^+$, 195 (10) $[M - CH_3O]^+$, 166 (30) $[M - C_2H_4O_2]^+$, 113 (100) $[M - C_5H_5O_3]^+$. HRMS: calcd. $C_{11}H_{14}O_5$ 226.0841; found 226.0840.

Methyl (2*E*)-Penta-2,4-dien-1-yl Fumarate (13):[21] To a stirred solution of dienol **16**[16] (664.0 mg, 7.839 mmol, 1.0 equiv.) in dichloromethane (16 mL) at 0 °C was added triethylamine (1.996 g, 19.73 mmol, 2.5 equiv.) and methyl (*E*)-4-chloro-4-oxo-2-butenoate[22] (1.407 g, 9.472 mmol, 1.2 equiv.). The mixture was stirred at 0 °C for 10 min and then warmed to room temperature. The mixture was diluted with diethyl ether (50 mL) and washed with 2 M HCl (35 mL), satd. aq. $NaHCO_3$ (35 mL), water (35 mL) and brine (35 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was subjected to column chromatography on silica (10% ethyl acetate/hexanes) to give maleate **13** (586.0 mg, 2.987 mmol, 38%) as a colourless oil. The physical data confirmed **13** to be consistent with that reported in the literature.[21]

Methyl (2*E*)-4-Ethylpenta-2,4-dien-1-yl Fumarate (15): (2*E*)-4-Ethyl-2,4-dien-1-ol (**17**)[17] (273.1 mg, 2.435 mmol, 1.0 equiv.) and (*E*)-$HO_2CHC{=}CHCO_2Me$ (380.1 mg, 2.922 mmol, 1.2 equiv.) were stirred in diethyl ether (4 mL) under Ar at 0 °C. A solution of DCC (602.9 mg, 2.922 mmol, 1.2 equiv.) and DMAP (119.0 mg, 0.974 mmol, 0.4 equiv.) in diethyl ether (12 mL) was added dropwise. The mixture was warmed to room temp. and stirred for 2 h. The mixture was then filtered, washing with diethyl ether (20 mL), and the filtrate washed with 2 M HCl (20 mL), satd. aq. $NaHCO_3$ (20 mL), brine (20 mL), dried ($NaSO_4$), filtered and concentrated in vacuo. The crude material was subjected to column chromatography on silica (10−30% ethyl acetate/hexanes) to give the fumarate **15** (314.7 mg, 1.403 mmol, 69% based on recovered SM) as a colourless oil followed by (2*E*)-4-ethyl-2,4-dien-1-ol (**17**) (43.5 mg, 0.388 mmol, 16% recovery) as a yellow oil. Physical data for **15**: R_f = 0.38 (10% ethyl acetate/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.82 (m, 2 H), 6.31 (d, *J* = 15.9 Hz, 1 H), 5.74 (ddd, *J* = 15.9, 6.6, 6.6 Hz, 1 H), 4.99 (m, 2 H), 4.70 (d, *J* = 6.7 Hz, 2 H), 3.75 (s, 3 H), 2.16 (q, *J* = 7.5 Hz, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2 (C), 164.5 (C), 146.5 (C), 137.1 (CH), 133.6 (CH), 133.4 (CH), 121.4 (CH), 115.9 (CH_2), 65.9 (CH_2), 52.2 (CH_3), 24.4 (CH_2), 12.3 (CH_3) ppm. IR (neat): ṽ = 3081, 3036, 2969, 2880 (C−H), 1726 (C=O), 1647, 1610 cm^{-1} (C=C). EIMS (70 eV): *m*/*z* (%) = 224 (10) $[M]^+$, 195 (5) $[M - C_2H_5]^+$, 165 (5) $[M - C_2H_3O_2]^+$, 113 (100) $[M - C_7H_{11}O]^+$. HRMS: calcd. $C_{12}H_{16}O_4$: 224.1049; found 224.1042.

Methyl (2*E*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]penta-2,4-dien-1-yl Fumarate (11): The dienol **9** (958 mg, 4.19 mmol) was converted into fumarate **11** (1.16 mg, 3.42 mmol, 81%) using the procedure described above for fumarate **15**. Fumarate **11** was obtained as a colourless oil. R_f = 0.37 (10% ethyl acetate/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.86 (s, 2 H), 6.34 (d, *J* = 16.1 Hz, 1 H), 5.74 (ddd, *J* = 16.1, 6.5, 6.5 Hz, 1 H), 5.35 (m, 1 H), 5.14 (m, 1 H), 4.72 (dd, *J* = 6.5, 1.1 Hz, 2 H), 4.30 (m, 2 H), 3.79 (s, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =

165.4 (C), 164.7 (C), 143.7 (C), 134.5 (CH), 133.5 (CH), 133.5 (CH), 121.7 (CH), 116.3 (CH_2), 66.0 (CH_2), 62.7 (CH_2), 52.4 (CH_3), 25.9 (CH_3), 18.4 (C), −5.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2956, 2931, 2857 (C−H), 1727 (C=O), 1646, 1614 cm^{-1} (C=C). EIMS (70 eV): *m/z* (%) = 339 (30) $[M - H]^+$, 309 (20) $[M - CH_3O]^+$, 283 (100) $([M - C_4H_9]^+$. HRMS: calcd. $C_{17}H_{27}O_5Si$: 339.1628; found 339.1628.

Methyl (2*E*)-4-(Hydroxymethyl)penta-2,4-dien-1-yl Fumarate (4): The fumarate **11** (26.9 mg, 0.079 mmol) was converted into the fumarate **4** (14.7 mg, 0.065 mmol, 82%) using the procedure described above for the maleate **1**. The fumarate **4** was obtained as a colourless oil. R_f = 0.39 (50% ethyl acetate/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.83 (s, 2 H), 6.32 (d, *J* = 16.2 Hz, 1 H), 5.80 (dt, *J* = 16.1, 6.3 Hz, 1 H), 5.30 (s, 1 H), 5.15 (s, 1 H), 4.70 (dd, 2 H, *J* = 6.4 Hz), 4.27 (m, 2 H), 3.76 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4 (C), 164.6 (C), 143.9 (C), 134.1 (CH), 133.5 (CH), 133.5 (CH), 122.5 (CH), 117.0 (CH_2), 65.8 (CH_2), 62.6 (CH_2), 52.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3517 (OH), 3081, 3036, 3001, 2957, 2927 (C−H), 1723 (C=O), 1645, 1614 cm^{-1} (C=C). EIMS (70 eV): *m/z* (%) = 226 (4) $[M]^+$, 208 (4) $[M - H_2O]^+$, 113 (100) $[M - C_5H_5O_3]^+$. HRMS: calcd. $C_{11}H_{14}O_5$: 226.0841; found 226.0835.

IMDA Reactions of the Triene Substrates

IMDA Reaction of the Maleate 12: The maleate **12** (435.0 mg, 2.217 mmol, 1.0 equiv.) and BHT (butylated hydroxy toluene; 2,6-di-*tert*-butyl-4-methylphenol) (48.5 mg, 0.222 mmol, 0.1 equiv.) in toluene (222 mL, 10 mM) were stirred at 110 °C for 4 h. The reaction mixture was concentrated in vacuo, a portion of the residue dissolved in $CDCl_3$ and ^1H NMR analysis carried out. The residue contained *trans*:*cis* bicycles (**18/19**) (83:17, confirmed by GC analysis of the crude reaction mixture). The residues chromatographed on silica (30% ethyl acetate/hexanes) to give the bicycle **18** (293.8 mg, 1.497 mmol, 80%) followed by the bicycle **19** (63.7 mg, 0.325 mmol, 17%).

(±)-Methyl (3a*S*,7*S*,7a*R*)-1-Oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (18): Colourless crystalline solid, recrystallised from 20% ethyl acetate/hexanes. R_f = 0.20 (30% ethyl acetate/hexanes). M.p. 93−94 °C. ^1H NMR (400 MHz, CD_3Cl): δ = 5.78 (m, 1 H), 5.73−5.67 (m, 1 H), 4.47 (dd, *J* = 8.2, 8.2 Hz, 1 H), 3.83 (dd, *J* = 11.4, 8.0 Hz, 1 H), 3.66 (s, 3 H), 3.30 (dd, *J* = 8.1, 3.1 Hz, 1 H), 3.17 (m, 1 H), 2.73−2.68 (m, 1 H), 2.56−2.45 (m, 1 H), 2.36 (dd, *J* = 13.4, 3.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.3 (Q), 172.4 (Q), 128.4 (CH), 123.9 (CH), 70.6 (CH_2), 52.0 (CH_3), 44.0 (CH), 36.0 (CH), 35.4 (CH), 28.7 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3030, 2953, 2901, 2848 (C−H), 1780, 1727 (C=O), 1633 cm^{-1} (C=C). EIMS (70 eV): *m/z* (%) = 196 (25) $[M]^+$, 165 (20) $[M - CH_3O]^+$, 150 (45) $[M - CH_2O_2]^+$, 136 (30) $[M - C_2H_4O_2]^+$, 91 (100) $[M - C_3H_5O_4]^+$, 79 (45) $[M - C_3H_5O_4]^+$. $C_{10}H_{12}O_4$: calcd. C 61.22, H 6.16; found C 61.36, H 6.39.

(±)-Methyl (3a*S*,7*R*,7a*S*)-1-Oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (19): Colourless crystalline solid, recrystallised from 30% ethyl acetate/hexanes. R_f = 0.15 (30% ethyl acetate/hexanes). M.p. 113−115 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.84 (m, 1 H), 5.55 (m, 1 H), 4.31 (dd, *J* = 9.0, 6.1 Hz, 1 H), 4.02 (d, *J* = 9.0 Hz, 1 H), 3.69 (s, 3 H), 3.46 (dd, *J* = 7.4, 3.9 Hz, 1 H), 3.14 (m, 1 H), 2.73 (ddd, *J* = 11.0, 6.3, 3.9 Hz, 1 H), 2.34−2.18 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.0 (C), 172.5 (C), 128.9 (CH), 125.6 (CH), 71.8 (CH_2), 51.9 (CH_3), 40.0 (CH), 36.7 (CH), 36.4 (CH), 22.5 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3022, 3003, 2953, 2923, 2894, 2844 (C−H), 1776, 1729 cm^{-1} (C=O). EIMS (70 eV): *m/z* (%) = 196 (5) $[M]^+$, 164 (45) $[M - CH_4O]^+$, 136 (90) $[M - C_2H_4O]^+$, 92 (100) $[M - C_3H_4O_4]^+$, 79 (85) $[M - C_3H_5O_4]^+$. $C_{10}H_{12}O_4$: calcd. C 61.22, H 6.16; found C 61.02, H 6.43.

IMDA Reaction of Maleate 14: The maleate **14** (134 mg, 0.599 mmol) was thermolysed, using the procedure described above for the maleate **12**, giving the bicycle **20** (89.0 mg, 0.397 mmol, 66%) and the bicycle **21** (31.1 mg, 0.139 mmol, 23%).

(±)-Methyl (3a*S*,7*S*,7a*R*)-5-Ethyl-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (20): Colourless oil. R_f = 0.27 (30% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.46 (m, 1 H), 4.44 (dd, *J* = 7.4, 7.4 Hz, 1 H), 3.79 (dd, *J* = 11.4, 7.8 Hz, 1 H), 3.64 (s, 3 H), 3.28 (dd, *J* = 7.9, 3.6 Hz, 1 H), 3.11 (m, 1 H), 2.58 (d, *J* = 18.4 Hz, 1 H), 2.42 (m, 1 H), 2.32 (dd, *J* = 13.6, 3.6 Hz, 1 H), 1.95 (q, *J* = 7.5 Hz, 2 H), 0.96 (t, *J* = 7.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5 (C), 172.5 (C), 141.9 (C), 116.6 (CH), 71.0 (CH_2), 52.1 (CH_3), 44.5 (CH), 41.5 (CH), 36.6 (CH), 35.6 (CH), 32.1 (CH_2), 29.3 (CH_2), 11.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2965, 2898, 2849 (C−H), 1781, 1734 (C=O), 1649 cm^{-1} (C=C). EIMS (70 eV): *m/z* (%) = 225 (15) $[M + H]^+$, 193 (20) $[M - CH_3O]^+$, 180 (30) $[M - CO_2]^+$, 178 (30) $[M - CH_2O_2]^+$, 164 (25) $[M - C_2H_4O_2]^+$, 121 (100) $[M - C_3H_3O_4]^+$,. HRMS: calcd. $C_{12}H_{16}O_4$: 224.1049; found 224.1050.

(±)-Methyl (3a*S*,7*R*,7a*S*)-5-Ethyl-1-oxo-1,3,3a,6,7,7a−hexahydroisobenzofuran-7-carboxylate (21): Colourless crystalline solid, recrystallised from 20% ethyl acetate/hexanes. R_f = 0.22 (30% ethyl acetate/hexanes). M.p. 89−91 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.29 (m, 1 H), 4.36 (dd, *J* = 8.7, 5.8 Hz, 1 H), 4.08 (d, *J* = 9.1 Hz, 1 H), 3.77 (s, 3 H), 3.47 (dd, *J* = 7.5, 4.1 Hz, 1 H), 3.17 (m, 1 H), 2.79 (ddd, *J* = 10.5, 6.3, 4.1 Hz, 1 H), 2.34−2.22 (m, 2 H), 2.02 (2 H, C, *J* = 7.2 Hz), 1.00 (t, *J* = 7.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2 (C), 172.9 (C), 142.6 (C), 118.2 (CH), 72.6 (CH_2), 52.2 (CH_3), 40.1 (CH), 37.4 (CH), 37.0 (CH), 30.5 (CH_2), 26.1 (CH_2), 12.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2965, 2918, 2852 (C−H), 1771, 1735 (C=O), 1669 cm^{-1} (C=C). EIMS (70 eV): *m/z* (%) = 224 (100) $[M]^+$, 193 (30) $[M - CH_3O]^+$, 164 (70) $[M - C_2H_4O_2]^+$. HRMS: calcd. $C_{12}H_{16}O_4$: 224.1049; found 224.1039.

IMDA Reaction of the Maleate 10: The maleate **10** (43.2 mg, 0.127 mmol) was thermolysed, using the procedure described above for maleate **12**, giving a mixture of the bicycles **22** and **23** [39.7 mg, 0.117 mmol, 92%; **22**:**23** (73:27)].

To confirm the stereochemical outcome of the IMDA reaction of **10**, the mixture of the bicycles **22** and **23** was transformed to the bicycles **2** and **3** using Roush's mild deprotection procedure.[23] TAS-F [tris(dimethylamino)sulfonium difluorotrimethylsilicate] (1.0 M in DMF, 338 μL, 0.338 mmol, 5.0 equiv.) was added to the mixture of **22** and **23** (39.7 mg, 0.117 mmol, 1.0 equiv.) in DMF (300 μL) stirred at 0 °C. The reaction was stirred at 0 °C for 30 min, then at room temp. for 12 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (8 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases dried ($NaSO_4$), filtered and concentrated in vacuo. A portion of the residue was dissolved in $CDCl_3$ and ^1H NMR analysis carried out. The residue contained *trans*:*cis* bicycles (**2/3**) (73:27). The residues were passed through a short silica plug (ethyl acetate) to give a mixture of bicycles **2** and **3** [23.6 mg, 0.104 mmol, 82% over two steps from the maleate **10**; **2/3** (73:27)] as a colourless oil.

IMDA Reaction of the Maleate 1: The maleate **1** (105 mg, 0.462 mmol) was thermolysed using the procedure described above for maleate **12**. The reaction mixture was purified by recrystallisation and HPLC to give the bicycle **2** (45.4 mg, 0.201 mmol, 45%) and the bicycle **3** (49.2 mg, 0.217 mmol, 49%).

(±)-Methyl (3a*S*,7*S*,7a*R*)-5-Hydroxymethyl-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (2): Colourless oil. HPLC: R_t = 17.77 min [Zorbax sil, 60% THF/hexanes, 9.0 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.84 (m, 1 H), 4.52 (dd, *J* = 7.7, 6.8 Hz, 1 H), 4.06 (m, 2 H), 3.87 (dd, *J* = 11.8, 8.3 Hz, 1 H), 3.70 (s, 3 H), 3.39 (dd, *J* = 7.9, 3.4 Hz, 1 H), 3.21 (m, 1 H), 2.70 (br. d, *J* = 18.7 Hz, 1 H), 2.53 (m, 1 H), 2.40 (dd, *J* = 13.7, 3.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2 (C), 172.5 (C), 140.0 (C), 119.0 (CH), 70.8 (CH_2), 65.9 (CH_2), 52.4 (CH_3), 44.7 (CH), 36.5 (CH), 35.4 (CH), 29.5 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3468 (OH), 3002, 2954, 2905 (C−H), 1780, 1730 cm^{-1} (C=O). EIMS (70 eV): *m*/*z* (%) = 226 (15) $[M]^+$, 208 (30) $[M - H_2O]^+$, 195 (30) $[M - CH_3O]^+$, 180 (60) $[M - CH_2O_2]^+$, 166 (40) $[M - C_2H_4O_2]^+$, 121 (100) $[M - C_3H_5O_4]^+$. HRMS: calcd. $C_{11}H_{14}O_5$: 226.0841; found 226.0838.

(±)-Methyl (3a*S*,7*R*,7a*S*)-5-Hydroxymethyl-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (3): Colourless crystalline solid, recrystallised from 70% ethyl acetate/hexanes. M.p. 141−142 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 5.66 (m, 1 H), 4.45 (dd, *J* = 8.8, 5.9 Hz, 1 H), 4.12 (d, *J* = 8.9 Hz, 1 H), 3.97 (m, 2 H), 3.75 (s, 3 H), 3.61 (dd, *J* = 7.6, 3.9 Hz, 1 H), 3.26 (m, 1 H), 2.93 (ddd, *J* = 11.8, 5.6, 4.1 Hz, 1 H), 2.33 (dd, *J* = 17.9, 5.5 Hz, 1 H), 2.21−2.13 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 178.8 (C), 174.7 (C), 141.1 (C), 121.6 (CH), 73.7 (CH_2), 66.3 (CH_2), 52.5 (CH_3), 41.5 (CH), 38.2 (CH), 38.1 (CH), 24.3 (CH_2) IR (KBr): $\tilde{\nu}$ = 3326 (OH), 2947, 2909, 2868 (C−H), 1772, 1754, 1734 cm^{-1} (C=O). EIMS (70 eV): *m*/*z* (%) = 226 (35) $[M]^+$, 195 (45) $[M - CH_3O]^+$, 166 (100) $[M - C_2H_4O_2]^+$. HRMS: calcd. $C_{11}H_{14}O_5$: 226.0841; found 226.0843.

IMDA Reaction of the Fumarate 13:[21] The fumarate **13** (574 mg, 2.93 mmol) was thermolysed, using the procedure described above for the maleate **12**, giving the bicycle **25** (189 mg, 0.964 mmol, 35%) and the bicycle **24** (229 mg, 1.17 mmol, 42%). Physical data for **24** and **25** were consistent with the literature.[21]

IMDA Reaction of the Fumarate 15: The fumarate **15** (36 mg, 0.160 mmol) was thermolysed, using the procedure described above for the maleate **12**, giving the bicycle **26** (16.6 mg, 0.074 mmol, 46%) and the bicycle **27** (9.8 mg, 0.044 mmol, 27%).

(±)-Methyl (3a*S*,7*R*,7a*R*)-5-Ethyl-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (26): Colourless crystalline solid, recrystallised from 10% ethyl acetate/hexanes. R_f = 0.25 (20% ethyl acetate/hexanes). M.p. 75−77 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 5.61 (m, 1 H), 4.48 (dd, *J* = 8.1, 6.9 Hz, 1 H), 3.94 (dd, *J* = 11.6, 8.2 Hz, 1 H), 3.75 (s, 3 H), 2.91 (m, 1 H), 2.85 (ddd, *J* = 11.7, 10.4, 6.9 Hz, 1 H), 2.60 (dd, *J* = 13.4, 11.4 Hz, 1 H), 2.51 (m, 1 H), 2.29 (m, 1 H), 2.03 (q, *J* = 7.7 Hz, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 176.9 (Q), 176.0 (Q), 143.4 (Q), 117.8 (CH), 72.7 (CH_2), 52.6 (CH_3), 46.1 (CH), 41.9 (CH), 40.9 (CH), 34.8 (CH), 30.2 (CH_2), 12.5 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2965, 2899, 2848 (C−H), 1791, 1738 cm^{-1} (C=O). EIMS (70 eV): *m*/*z* (%) = 224 (90) $[M]^+$, 193 (25) $[M - CH_3O]^+$, 164 (90) $[M - C_2H_4O_2]^+$, 135 (40) $[M - C_3H_5O_3]^+$, 105 (100) $[M - C_5H_{11}O_3]^+$, 91 (100) $[M - C_5H_9O_4]^+$. HRMS: calcd. $C_{12}H_{16}O_4$: 224.1049; found 224.1047.

(±)-Methyl (3a*S*,7*S*,7a*S*)-5-Ethyl-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (27): Colourless oil. R_f = 0.22 (20% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, C_6D_6): δ = 4.85 (s, 1 H), 3.54 (dd, *J* = 8.8, 6.4 Hz, 1 H), 3.41 (dd, *J* = 8.9, 1.2 Hz, 1 H), 3.24 (s, 3 H), 3.16 (m, 1 H), 2.89 (dd, *J* = 7.8, 3.3 Hz, 1 H), 2.61 (m, 1 H), 2.24 (d, *J* = 17.5 Hz, 1 H), 2.14 (m, 1 H), 1.68 (q, *J* = 7.5 Hz, 2 H), 0.76 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 176.6 (Q), 173.4 (Q), 141.0 (Q), 118.7 (CH), 72.1 (CH_2), 51.6 (CH_3), 39.7 (CH), 37.8 (CH), 34.4 (CH), 30.6 (CH_2), 26.5 (CH_2), 11.7 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2965, 2915, 2853 (C−H), 1771, 1734 cm^{-1} (C=O). EIMS (70 eV): *m*/*z* (%) = 224 (45) $[M]^+$, 192 (100) $[M - CH_4O]^+$, 178 (35) $[M - CH_2O_2]^+$, 164 (50) $[M - C_2H_4O_2]^+$, 105 (80) $[M - C_5H_{11}O_3]^+$. HRMS: calcd. $C_{12}H_{16}O_4$: 224.1049; found 224.1044.

IMDA Reaction of the Fumarate 11: The fumarate **11** (37.7 mg, 0.111 mmol) was thermolysed, using the procedure described above for the maleate **12**, giving the bicycle **28** (19.7 mg, 0.058 mmol, 52%) and the bicycle **29** (9.3 mg, 0.027 mmol, 25%).

(±)-Methyl (3a*S*,7*R*,7a*R*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (28): Colourless oil. R_f = 0.19 (20% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 4.47 (dd, *J* = 7.9, 6.8 Hz, 1 H), 4.01 (m, 2 H), 3.91 (dd, *J* = 11.7, 8.3 Hz, 1 H), 3.77 (s, 3 H), 2.87 (m, 1 H), 2.82 (ddd, *J* = 11.8, 10.3, 6.8 Hz, 1 H), 2.59 (dd, *J* = 13.7, 11.7 Hz, 1 H), 2.49 (dd, *J* = 17.6, 7.0 Hz, 1 H), 2.29 (dd, *J* = 17.7, 10.2 Hz, 1 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.05 (3 H, 0.05) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 174.1 (C), 173.9 (C), 140.4 (C), 117.2 (CH), 70.9 (CH_2), 65.6 (CH_2), 52.3 (CH_3), 45.0 (CH), 40.5 (CH), 39.2 (CH), 30.9 (CH_2), 25.9 (CH_3), 18.4 (C), −5.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2954, 2930, 2897, 2857 (C−H), 1792, 1740 cm^{-1} (C=O). EIMS (70 eV): *m*/*z* (%) = 340 (1) $[M]^+$, 325 (15) $[M - CH_3]^+$, 309 (10) $[M - CH_3O]^+$, 283 (100) $[M - C_4H_9]^+$, 251 (15) $[M - C_3H_5O_3]^+$, 223 (15) $[M - C_4H_5O_4]^+$. HRMS: calcd. $C_{17}H_{28}O_5Si$: 340.1706; found 340.1701.

(±)-Methyl (3a*S*,7*S*,7a*S*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (29): Colourless oil. R_f = 0.22 (20% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.58 (m, 1 H), 4.42 (dd, *J* = 8.9, 6.0 Hz, 1 H), 4.12 (dd, *J* = 8.9, 0.9 Hz, 1 H), 3.99 (m, 2 H), 3.70 (s, 3 H), 3.31 (dd, *J* = 7.4, 2.5 Hz, 1 H), 3.27 (ddd, *J* = 6.3, 2.3, 2.3 Hz, 1 H), 3.25 (m, 1 H), 2.42 (d, *J* = 18.0 Hz, 1 H), 2.17 (m, 1 H), 0.90 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4 (C), 173.6 (C), 138.8 (C), 118.7 (CH), 72.6 (CH_2), 66.0 (CH_2), 52.4 (CH_3), 40.0 (CH), 37.1 (CH), 34.0 (CH), 25.9 (CH_3), 18.4 (C), −5.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2954, 2929, 2856 (C−H), 1773, 1737 cm^{-1} (C=O). EIMS (70 eV): *m*/*z* (%) = 340 (1) $[M]^+$, 325 (10) $[M - CH_3]^+$, 309 (15) $[M - CH_3O]^+$, 283 (100) $[M - C_4H_9]^+$, 251 (25) $[M - C_3H_5O_3]^+$, 223 (15) $[M - C_4H_5O_4]^+$. HRMS: calcd. $C_{17}H_{28}O_5Si$: 340.1706; found 340.1690.

IMDA Reaction of the Fumarate 4: The fumarate **4** (28.9 mg, 0.128 mmol) was thermolysed, using the procedure described above for the maleate **12**, giving a mixture of the bicycles **5** and **6** [23.0 mg, 0.012 mmol, 83%; **5**/**6** (91:9)].

To confirm the stereochemical outcome of the IMDA reaction of **4**, the mixture of the bicycles **5** and **6** was transformed to the bicycles **28** and **29** as follows. 2,6-Lutidine (43.8 mg, 0.408 mmol, 4.0 equiv.) was added to a solution of the bicycles **5** and **6** (23.0 mg, 0.102 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (1.0 mL) stirred at room temp. The solution was cooled to 0 °C and TBS-triflate (80.8 mg, 0.306 mmol, 3.0 equiv.) added dropwise. The reaction was warmed to room temp. and stirred for 20 min. Ethyl acetate (15 mL) and water (15 mL) were added to the reaction. The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic phases were combined and washed with 0.3 M $NaHSO_4$ (30 mL), brine (30 mL), dried ($NaSO_4$), filtered and concentrated in vacuo. The crude material was subjected to column chromatography on silica (20% ethyl acetate/hexanes) to give a mix-

ture of the bicycles **28** and **29** [29.3 mg, 0.0861 mmol, 71% over two steps from SM **4**; **28**/**29** (91:9)] as a colourless oil.

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