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Intramolecular Diels–Alder Reactions of Carbon Acetal-tethered Trienes

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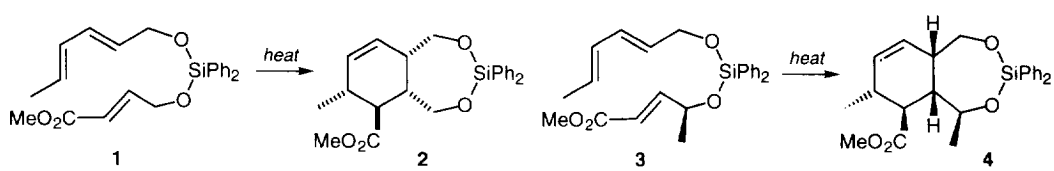
Abstract: The intramolecular Diels–Alder reactions of carbon acetal-tethered trienes **7**, **10**, **11** and **12** are described. The selectivities are rationalised in terms of the preferred "inside–outside" orientation of respectively the diene and dienophile tethering oxygen atoms. Copyright © 1996 Elsevier Science Ltd

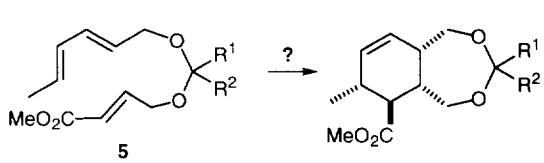
INTRODUCTION

We have demonstrated that silyl acetals,[1] tertiary and benzylic ethers[2] and dicarboxylic esters[3] may be deployed as tethers for intramolecular Diels–Alder (IMDA) reactions.[4] Temporary connection of dienes to dienophiles via these linking groups generates triene substrates whose [4+2] cycloaddition reactions exhibit greatly enhanced regio-and stereoselectivities with respect to the analogous intermolecular processes. In particular, silyl acetal-tethered triene **1** showed complete selectivity for the cis-fused product **2**, and incorporation of a stereocentre as in triene **3** resulted in a faster but equally selective reaction to give a single cis-fused isomer **4** (Scheme 1). These findings were interpreted in terms of the favoured "inside" conformation of the diene in the IMDA transition-states.[1]



Scheme 1

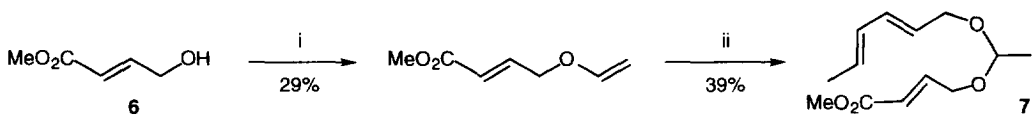
We were keen to study the effect on IMDA reactivity and stereoselectivity of changing the constitution of the tether, and particularly the reactions of triene substrates of the type **5** in which the reacting π-systems are connected via a carbon acetal (Scheme 2).[5] We report herein the results of these investigations.



Scheme 2

RESULTS AND DISCUSSION

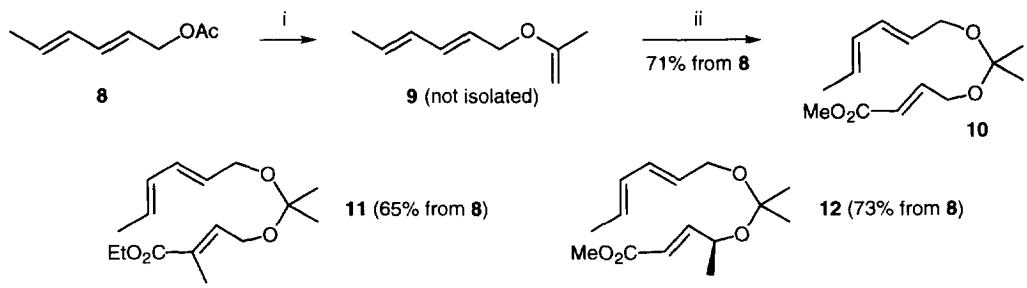
Several factors determined our choice of IMDA substrates. It was felt that comparison of the IMDA reactions of tethered trienes **7** and **10** would offer insights into the effect on reactivity of the level of substitution in the linking chain. Also, compound **7** contains a stereocentre within the tether, and we were keen to gauge the extent of asymmetric induction to newly-formed centres positioned three atoms away in the product. Triene **7** was prepared in low overall yield by Hg(II)-catalysed vinyl ether formation from ethoxyethene and the unsaturated alcohol **6**,[1] followed by acid-catalysed addition of (*E*,*E*)-2,4-hexadienol.(Scheme 3).



Reagents and conditions: (i) $Hg(OAc)_2$ (0.1 eq), ethoxyethene (0.65M), reflux, 24 h; (ii) (*E*,*E*)-2,4-hexadienol (1 eq), pTSA (0.1 eq), PhMe, rt, 3 h.

Scheme 3

In an alternative approach, IMDA substrate **10** was made by Tebbe methylenation[6] of (*E*,*E*)-2,4-hexadienyl acetate **8**, followed by Pd(II)-catalysed addition[7] of **6**. The use of pTSA instead of the palladium reagent in this reaction gave only low yields of **10**. The analogous isomeric trienes **11** and **12** were similarly prepared in good yields from respectively ethyl (*E*)-4-hydroxy-2-methyl-2-butenoate[8] and (+)-[4*S*]-methyl (*E*)-4-hydroxy-2-pentenoate[1] (Scheme 4).

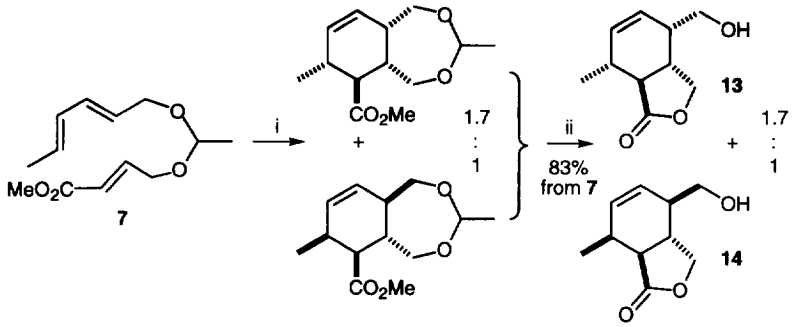


Reagents and conditions: (i) Tebbe reagent (1.1 eq), PhMe–THF, -40°C→rt, NaOH work-up; (ii) **6** (0.83 eq), $Pd(COD)Cl_2$ (0.2 eq), PhMe, rt, 24 h.

Scheme 4

As with our previous studies,[1-3] IMDA reaction temperatures and times were determined on small-scale reactions on deuteriotoluene solutions in base-washed nmr tubes prior to carrying out the preparative experiments in similarly treated resealable glass vessels. Thermolysis of **7** gave in high yield a 1.7:1 mixture of two cycloadducts, as evidenced by distinctive acetal proton signals at 4.74 and 4.64 ppm in the ^1H nmr spectrum. Cleavage of the spacer groups with methanolic HCl gave in good yield a 1.7:1 mixture of two hydroxylactones, the major component of which was identical with the unique product **13** obtained in the silyl acetal studies.[1] X-Ray crystallographic analysis showed the minor product to be **14** (Scheme 5, Figure).

Several features of the IMDA reaction of **7** are noteworthy. Firstly, triene **7** was substantially more reactive than the silyl acetal analogue **1**. This may be a consequence of the shorter tether C–O bonds in **7** compared with the Si–O linkages in **1**, which are such as to increase the effective concentration of the reacting π-systems. Secondly, the poor cis:trans selectivity contrasts sharply with the almost complete cis-selectivity observed in the reaction of **1**. These characteristics may be rationalised in terms of steric interactions between the exo-diene and the diene methylene unit, which are increased relative to those in the silyl acetal substrate because of the shorter bond lengths and a correspondingly more compact transition-state. Finally, the cis- and



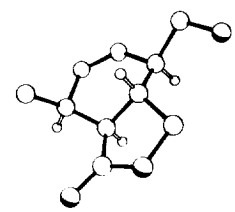


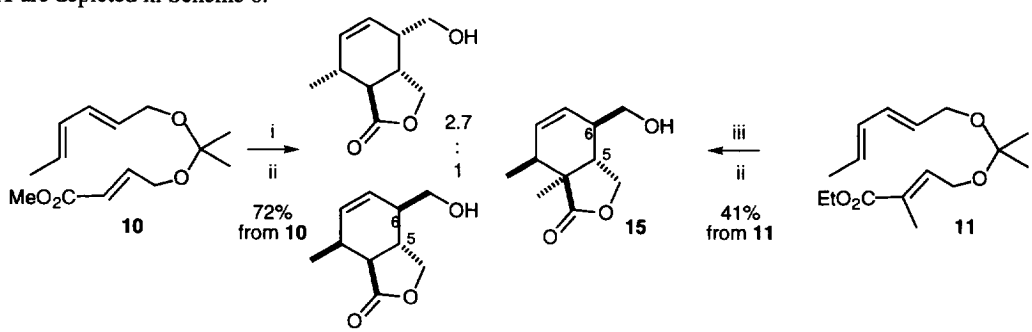
Figure
X-ray structure of **14**

Reagents and conditions: (i) PhMe, 165°C, 27 h; (ii) conc. HCl, MeOH, rt, 2 h.

Scheme 5

trans-fused cycloadducts implied by the subsequent generation of **13** and **14** were formed as single diastereomers, indicating a pronounced conformational bias in the transition-states.

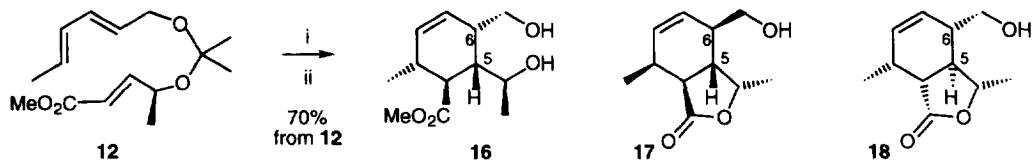
The IMDA reaction of the gem-dimethylated trienes **10** and **11** were examined next. Thermolysis of **10** followed by HCl–MeOH treatment gave in 72% overall yield a 2.7:1 mixture of lactones **13** and **14**. The striking increase in reactivity caused by the greater degree of substitution in the spacer unit may be attributed to a lowering of the population of unreactive, distal conformers which suffer repulsive non-bonded interactions between the diene and/or dienophile and the extra methyl group. In the IMDA reaction of **11**, incorporation of a methyl substituent α- to the dienophile ester group caused a lowering of reactivity in comparison to the α-unsubstituted analogue **10** to the extent that decomposition became a significantly competitive process, although the reaction did reach completion more rapidly than that of the monomethylated analogue **7**. On treatment with HCl–MeOH a single, oily hydroxylactone **15** was isolated in 41% yield based on the triene starting material. The assignment of the trans-ring junction stereochemistry followed from the appearance in the ^{1}H nmr spectrum of a signal corresponding to H-5 which exhibited inter alia two large coupling constants, strongly indicative of a trans-diaxial relationship with H-6. Although the low yield of **15** obtained from the sequence might be a consequence of selective decomposition of the cis-fused cycloadduct, the apparent trans-selectivity of the cycloaddition reaction is remarkable, and may be because the exo- transition-state leading to the cis-fused product is disfavoured by α-methyl–diene steric interactions. The IMDA and derivatisation reactions of **10** and **11** are depicted in Scheme 6.



Reagents and conditions: (i) PhMe, 165°C, 2.5 h; (ii) conc. HCl, MeOH, rt, 2 h; (iii) PhMe, 165°C, 4 h.

Scheme 6

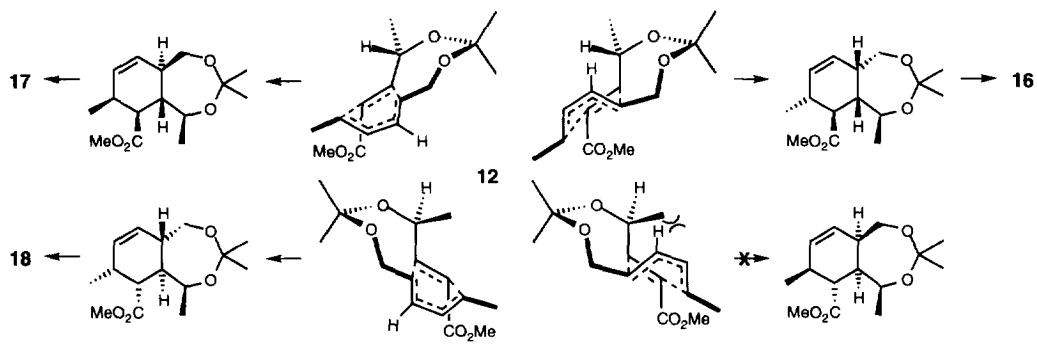
Finally, substrate **12** was subjected to IMDA reaction. This was the most reactive of the four trienes studied, and gave after thermolysis and brief exposure to the standard tether-cleavage reaction conditions a mixture of alcohols **16**, **17** and **18** in a 8:2:1 ratio in 70% overall yield (Scheme 7). The structure of **16** followed from the identity of its nmr characteristics with those of material derived from our previously-reported



Reagents and conditions: (i) PhMe, 165°C, 1.5 h; (ii) conc. HCl, MeOH, rt, 2 h. **16**:**17**:**18** = 8:2:1

Scheme 7

silyl acetal-tethered IMDA reaction.[1] That the second most abundant compound in the mixture was trans-fused was again indicated by the coupling constants of 14, 11 and 8 Hz observed for the H-5 signal; the latter value of 8 Hz strongly suggests that H-4 is oriented syn with respect to H-5, enabling the assignment of structure **17**. The implied directing effect of the methyl group is in the same sense as that observed in the silyl acetal-tethered substrates.[1] The two large coupling constants observed for the H-5 resonance in the minor component indicated it to be a second trans-fused compound, formulated as **18**. These assignments indicate that whereas the allylic methyl substituent completely controls the formation of cis-fused cycloadduct, the trans-products are formed almost non-selectively. This may be explained in terms of the lesser mutual proximity of the diene and the allylic stereocentre in the $endo_{ester}$ transition states leading to the trans-fused compounds (Scheme 8).



Scheme 8

CONCLUSIONS

In summary, we have demonstrated that carbon acetal-tethered trienes are readily available, highly reactive IMDA substrates which give the products of overall regiospecific and stereoselective intermolecular [4+2] cycloaddition upon facile cleavage of the tether. Incorporation in the dienophile part of the triene substrate of a stereocentre of defined absolute configuration enables the selective synthesis of highly oxygenated carbocycles with the generation of four new contiguous stereocentres.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

General procedures

^{1}H nmr spectra were recorded in $CDCl_3$ on a Jeol GX-270Q spectrometer, using residual isotopic solvent ($CHCl_3$, δ_H 7.26 ppm; $PhCD_2H$, δ_H 2.03 ppm) as internal reference. Infrared spectra were recorded on Perkin-Elmer 881 or Mattson 5000 FTIR spectrophotometers. Mass spectra were obtained using Jeol SX-102, VG-7070B, VG 12-253, VG ZAB-E and VG Autospec Q instruments. Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Optical rotation measurements were carried out using an Optical Activity AA-100 polarimeter. Air- and moisture-sensitive reagents were transferred via syringe or cannula, and reactions involving these materials were carried out in oven-dried flasks under a positive pressure of nitrogen. Liquid reagents were transferred via syringe. Chromatography refers to column chromatography on Merck Kieselgel 60 (230-400 mesh) or Matrex Silica 60 (35-70 micron) under pressure unless otherwise stated. Tlc refers to analytical thin-layer chromatography performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised with ultraviolet light, iodine and acidic ammonium molybdate(IV), vanillin or potassium permanganate solutions as appropriate. Petrol refers to redistilled 40°–60° petroleum ether, and ether to diethyl ether. Ether was distilled from sodium–benzophenone ketyl, dichloromethane from phosphorus pentoxide, and toluene from sodium. Other solvents and reagents were purified according to standard procedures.[9]

Preparation of methyl (*E*)-4-ethenyloxy-2-butenoate

A mixture of methyl (*E*)-4-hydroxy-2-butenoate **6** (1.24 g, 10.7 mmol, 1 eq) and $Hg(OAc)_2$ (340 mg, 1.07 mmol, 0.1 eq) in ethoxyethene (15 ml) was heated under reflux for 24 h. The mixture was allowed to cool and then concentrated under reduced pressure to give a pale yellow oil. This was purified by bulb-to-bulb distillation to give the desired *vinyl ether* (440 mg, 29%) as a colourless oil, $bp_{0.2}$ 125°C; ν_{max} (film) 2952, 1726, 1666, 1639, 1619, 1439, 1373, 1311, 1278, 1198, 1174, 1039, 1022, 964, 836 cm^{-1}; δ_H (270 MHz) 6.99 (1H, dt, J 16.0, 4.0 Hz, H-3), 6.47 (1H, dd, J 14.5, 6.5 Hz, OC*H*CH_2), 6.10 (1H, dt, J 16.0, 2.0 Hz, H-2), 4.40 (2H, dd, J 4.0, 2.0 Hz, H-4), 4.23 (1H, dd, J 14.5, 2.5 Hz, OCH:CH_{2trans}), 4.09 (1H, dd, J 6.5, 2.5 Hz, OCH:CH_{2cis}), 3.75 (3H, s, OCH_3); *m/z* (CI) 160 $[M+NH_4]^+$, 143 $[M+H]^+$, 134 $[M+NH_4-C_2H_2]^+$, 117 $[MH-C_2H_2]^+$, 102, 99, 73, 61, 55, 44 (Found: $[M+NH_4]^+$, 160.0974. $C_7H_{10}O_3$ requires $[M+NH_4]^+$, 160.0974).

Preparation of methyl (*E,E,E*)-6-methyl-5,7-dioxa-2,9,11-tridecatrienoate (7).

To a solution of methyl (*E*)-4-ethenyloxy-2-butenoate (150 mg, 1.07 mmol, 1.2 eq) in PhMe (1.0 ml) was added a solution of (*E,E*)-2,4-hexadienol (88 mg, 0.89 mmol, 1 eq) in PhMe (1.0 ml) containing pTSA (16 mg, 0.09 mmol, 0.1 eq). The mixture was stirred for 3 h and then diluted with ether, filtered through alumina and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (20% ether–petrol) gave the desired *triene* **7** (112 mg, 71%) as a colourless oil; ν_{max} (film) 2951, 2933, 2916, 1726, 1664, 1437, 1304, 1273, 1194, 1171, 1134, 1101, 1020, 991, 968 cm^{-1}; δ_H (270 MHz) 6.98 (1H, dt, J 15.5, 4.0 Hz, H-3), 6.16 (1H, dd, J 15.0, 10.5 Hz, H-10), 6.11 (1H, dt, J 15.5, 2.0 Hz, H-2), 6.12-5.99 (1H, m, H-11), 5.77-5.54 (2H, m, H-9 and H-12), 4.82 (1H, q, J 5.5 Hz, H-6), 4.26 (1H, ddd, J 16.0, 4.0, 2.0 Hz, H-4), 4.15 (1H, ddd, J 16.0, 4.0, 2.0 Hz, H-4), 4.10 (1H, dd, J 16.0, 6.5 Hz, H-8), 3.99 (1H, dd, J 16.0, 6.5 Hz, H-8), 3.74 (3H, s, OCH_3), 1.75 (3H, d, J 7.0 Hz, H-13), 1.34 (3H, d, J 5.0 Hz, C-6 CH_3); *m/z* (CI) 258 $[M+NH_4]^+$, 240 $[M]^+$, 205, 179, 161, 143, 124 $[M-MeO_2CC_3H_4O]^+$, 99 $[C_6H_{11}O]^+$, 81 $[C_6H_9]^+$ (Found: $[M+NH_4]^+$, 258.1716. $C_{13}H_{20}O_4$ requires $[M+NH_4]^+$, 258.1705).

IMDA Reaction of triene (7).

An ether solution of the triene **7** (98 mg, 0.41 mmol) was filtered through an alumina column, followed by azeotropic drying with toluene (3 x 10 ml). The triene was dissolved in dry toluene (15 ml) and the solution was degassed using the freeze-pump-thaw technique. The solution was then heated at 165°C for 27 h, whereupon the toluene was removed by evaporation under reduced pressure to give a pale yellow oil (86 mg, 87% mass recovery). This was shown by ^{1}H nmr analysis to consist of two diastereomeric cycloadducts in a 1.7:1 ratio; δ_H (270 MHz, PhMe-d_8) 5.37-5.27 (2H, m, H-9 or H-8 major and minor), 5.21-5.11 (2H, m, H-8 or H-9 major and minor), 4.73 (1H, q, J 5.0 Hz, H-4 major), 4.64 (1H, q, J 5.0 Hz, H-4 minor), [3.80-3.36 (6H, m), 3.26-2.96 (2H, m) all for H-2 and H-6 major and minor], 3.34 (3H, s, OCH_3 minor), 3.32 (3H, s, OCH_3 major), [2.47-2.05 (6H, m), 1.92-1.82 (2H, m) all for H-1, H-7, H-10 and H-11 major and minor], 1.09 (3H, d, J 5.0 Hz, C-4 CH_3 minor), 1.06 (3H, d, J 5.0 Hz, C-4 CH_3 major), 0.87 (3H, d, J 6.5 Hz, C-10 CH_3 major), 0.85 (3H, d, J 6.5 Hz, C-10 CH_3 minor). The crude oil (86 mg) was dissolved in methanol (10 ml) and conc. HCl (2 drops) was added. The solution was stirred for 2 h, whereupon solid $NaHCO_3$ was added carefully until effervescence ceased. The solid was filtered washed with CH_2Cl_2 and the filtrate concentrated under reduced pressure to give a pale brown oil, this was purified by chromatography (15% EtOAc–petrol) to give, in order of elution, the hydroxylactones **13** (15 mg, 24%), and **14** (9 mg, 15%), together with a mixed fraction (37 mg, overall yield 83%); **13**: colourless crystalline solid, mp 77-78°C (EtOAc–petrol); ν_{max} ($CHCl_3$) 3424, 2959, 2920, 2877, 1776, 1184, 1090, 1058, 1031, 994, 804, 777, 740, 721, 714 cm^{-1}; δ_H (270 MHz) 5.67 (1H, dt, J 10.0, 1.5 Hz, H-8), 5.57 (1H, ddd, J 10.0, 4.5, 2.5 Hz, H-7), 4.41 (1H, dd, J 9.0, 7.0 Hz, H-4), 4.32 (1H, dd, J 12.5, 9.0 Hz, H-4), 3.72 (1H, dd, J 11.0, 3.5 Hz, C-6 CH_2OH) 3.63 (1H, dd, J. 11.0, 7.5 Hz, C-6 CH_2OH), 2.61-2.56 (1H, m, H-6), 2.54-2.46 (1H, m, H-5), 2.42-2.32 (1H, m, H-9), 2.10 (1H, dd, J 14.0, 10.0 Hz, H-10), 1.67 (1H, br s, C-6 CH_2OH), 1.26 (3H, d, J 7.0 Hz, C-9 CH_3); *m/z* (CI) 200 [M+NH_4]$^+$, 183 [M+H]$^+$, 164 [M-H_2O]$^+$, 151 (M$^+$-CH_2OH), 137, 119, 107, 91, 79, in excellent agreement with previously published data;[1] **14**: colourless crystalline solid, mp 84-85°C (EtOAc–petrol); ν_{max} ($CHCl_3$) 3403, 2918, 1777, 1184, 1132, 1115, 1091, 1058, 1031, 994, 804, 779, 768, 741, 707 cm^{-1}; δ_H (270 MHz) 5.86 (1H, ddd, J 10.0, 6.0, 2.5 Hz, H-8 or H-7), 5.43 (1H, dt, J 10.0, 1.5 Hz, H-7 or H-8), 4.66 (1H, dd, J 9.0, 7.0 Hz, H-4), 4.01 (1H, dd, J 10.5, 9.0 Hz, H-4), 3.77 (1H, dd, J 10.0, 4.5 Hz, C-6 CH_2OH), 3.50 (1H, t, J 10.0 Hz, C-6 CH_2OH), 2.78-2.69 (1H, m, H-9), 2.52-2.25 (3H, m, H-1, H-5, H-6), 1.56 (1H, br s, C-6 CH_2OH), 1.06 (3H, d, J 7.0 Hz, C-9 CH_3); *m/z* (CI) 200 [M+NH_4]$^+$, 183 [M+H]$^+$, 164 [M-H_2O]$^+$, 151 151 [M-CH_2OH]$^+$, 137, 119, 107, 91 (Found: [M+NH_4]$^+$, 200.1283. $C_{10}H_{14}O_3$ requires [M+NH_4]$^+$, 200.1287).

Preparation of methyl (*E,E,E*)-6,6-dimethyl-5,7-dioxa-2,9,11-tridecatrienoate (10).

To a solution of (*E,E*)-2,4-hexadienyl acetate **8** (87 mg, 0.62 mmol, 1 eq) in PhMe (0.93 ml) and THF (0.31 ml) containing pyridine (10 µl) at -40°C was added Tebbe's reagent (1.35 ml of a 0.5M solution in PhMe, 1.1 eq) dropwise over 5 min. The mixture was stirred for 15 min at -40°C and then allowed to warm to rt over 2 h; the mixture was stirred for a further 2 h at rt. The reaction was cooled to -10°C and NaOH (0.19 ml of a 15% aqueous solution) added cautiously. The mixture was allowed to warm to rt and stirred until effervescence ceased, giving a green/blue solution. The mixture was diluted with ether (8 ml), dried (Na_2SO_4) and filtered through Celite®. The ether was removed under reduced pressure with cooling to give an orange liquid, which was diluted with pentane (30 ml) and filtered through Celite®. The pentane was removed under reduced pressure with cooling to give an approximately 0.3M PhMe solution of vinylic ether *1-(2-propenyloxy)-2,4-hexadiene* **9** as a yellow liquid; δ_H (270 MHz) 6.25 (1H, dd, J 15.0, 10.5 Hz, H-3), 6.12-5.92 (1H, m, H-4), 5.79-5.64 (2H, m, H-2 and H-5), 4.21 (2H, d, 6.0 Hz, H-1), 3.87 (1H, d, J 1.0 Hz, OC(CH_3)CH_2), 3.84 (1H, d, J 1.0 Hz, OC(CH_3)CH_2), 1.83 (3H, s, OC(CH_3)CH_2), 1.76 (3H, d, J 7.0 Hz, H-6). To this solution was added alcohol **6** (60 mg, 0.52 mmol, 0.83 eq) as a solution in PhMe (1.0 ml) followed by Pd(COD)Cl_2 (35 mg, 0.12 mmol, 0.2 eq), and the mixture stirred for 24 h. Pyridine (20 µl) was added, and the mixture was diluted with ether, filtered through Celite® and concentrated under reduced pressure to give a yellow oil. Purification by

chromatography (20% ether–petrol) yielded the desired *triene* **10** (112 mg, 71%) as a colourless oil; ν_{max} (film) 2993, 2949, 2927, 1726, 1383, 1304, 1271, 1209, 1169, 1155, 1107, 1036, 1022, 989, 968 cm^{-1}; δ_H (270 MHz) 7.00 (1H, dt, J 15.5, 4.0 Hz, H-3), 6.18 (1H, dd, J 15.0, 10.5 Hz, H-10), 6.12 (1H, dt, J 15.5, 2.0 Hz, H-2), 6.12-5.92 (1H, m, H-11), 5.79-5.64 (2H, m, H-9 and H-12), 4.14 (2H, dd, J 4.0, 2.0 Hz, H-4), 3.95 (2H, d, J 6.0 Hz, H-8), 3.75 (3H, s, OCH_3), 1.74 (3H, d, J 7.0 Hz, H-13), 1.40 (6H, s, C-6 CH_3); *m/z* (CI) 272 $[M+NH_4]^+$, 254 $[M]^+$, 236 $[M-H_2O]^+$, 214, 197, 174, 157 $[M-C_6H_9O]^+$, 134, 98 $[C_6H_9OH]^+$, 81 $[C_6H_9]^+$ (Found: $[M+NH_4]^+$, 272.1872. $C_{14}H_{22}O_4$ requires $[M+NH_4]^+$, 272.1862).

IMDA Reaction of triene (10).

An ether solution of triene **10** (100 mg, 0.39 mmol) was filtered through an alumina column, azeotropically dried with toluene (3 x 10 ml), and dissolved in further dry toluene (15 ml). The solution was then degassed using the freeze-pump-thaw technique. The solution was heated at 165°C for 2.5 h, and the toluene removed by evaporation under reduced pressure to give a pale yellow oil (94 mg, 94% mass recovery). This was shown by ^1H nmr analysis to consist of two diastereomers in a 2.7:1 ratio; δ_H (270 MHz, PhMe-d_8) 5.14-5.07 (2H, m, H-8 or H-9 major and minor), 5.06-4.94 (2H, m, H-9 or H-8 major and minor), 4.00 (1H, dd, J 12.0, 2.5 Hz, H-2 or H-6 minor), 3.80-3.83 (2H, m, H-2 or H-6 minor), 3.67 (1H, dd, J 12.5, 2.0 Hz, H-2 or H-6 major), 3.43 (1H, dd, J 2.5, 2.0 Hz, H-2 or H-6 major), 3.41-3.36 (2H, m, H-2 or H-6 major), 3.33 (3H, s, OCH_3 major), 3.26 (3H, s, OCH_3 minor), 3.25-3.19 (1H, m, H-2 or H-6 minor), [2.53-2.32 (2H, m), 2.17-2.10 (1H, m), 1.94-1.81 (2H, m) 1.59-1.45 (1H, m) all for H-1, H-7, H-10 and H-11 major and minor], 1.25 (3H, s, C-4 CH_3 minor), 1.23 (3H, s, C-4 CH_3 minor), 1.17 (3H, s, C-4 CH_3 major), 1.16 (3H, s, C-4 CH_3 major), 0.88 (3H, d, J 7.0 Hz, C-10 CH_3 major), 0.79 (3H, d, J 7.0 Hz, C-10 CH_3 major). The crude oil (94 mg) was dissolved in methanol (10 ml) and conc. HCl (2 drops) was added. The solution was stirred for 2 h, whereupon solid $NaHCO_3$ was added carefully until effervescence ceased. The solid was filtered and the residue washed with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure to give a pale brown oil which was purified by chromatography (15% EtOAc–petrol) to give, in order of elution, the hydroxylactone **13** (17 mg, 22%) and the hydroxylactone **14** (6 mg, 8%), together with a mixed fraction (53 mg, overall yield 72%); spectroscopic data were in agreement with those listed above.

Preparation of ethyl (*E*,*E*,*E*)-2,6,6-trimethyl-5,7-dioxa-2,9,11-tridecatrienoate (11).

An approximately 0.3M PhMe solution of vinylic ether **9** was prepared as described above, starting from (*E*,*E*)-2,4-hexadienyl acetate **8** (95 mg, 0.68 mmol). To this was added a solution of ethyl (*E*)-4-hydroxy-2-methyl-2-butenoate[8] (81 mg, 0.52 mmol, 0.83 eq) in PhMe (1.0 ml) followed by $Pd(COD)Cl_2$ (39 mg, 0.12 mmol, 0.2 eq), and the mixture was stirred for 24 h. Pyridine (20 µl) was added and the mixture diluted with ether, filtered through Celite® and concentrated under reduced pressure to give a yellow oil. The mixture was purified by chromatography (20% ether–petrol) to yield the desired *triene* **11** (124 mg, 65%) as a colourless oil; ν_{max} (film) 2991, 2937, 2916, 1712, 1464, 1381, 1367, 1250, 1209, 1155, 1134, 1103, 1057, 1026, 989 cm^{-1}; δ_H (270 MHz) 6.79 (1H, tq, J 6.0, 1.5 Hz, H-3), 6.19 (1H, dd, J 15.0, 10.5 Hz, H-10), 6.09-5.99 (1H, m, H-11), 5.75-5.55 (2H, m, H-9 and H-12), 4.19 (2H, q, J 7.0 Hz, OCH_2CH_3), 4.15 (2H, dq, J 6.0, 1.0 Hz, H-4), 3.98 (2H, d, J 6.0 Hz, H-8), 1.83 (3H, br s, C-2 CH_3), 1.74 (3H, d, J 7.0 Hz, H-13), 1.40 (6H, s, C-6 CH_3), 1.30 (3H, t, J 7.0 Hz, OCH_2CH_3); *m/z* (CI) 300 $[M+NH_4]^+$, 283 $[M+H]^+$, 242, 202 $[MH-C_6H_9]^+$, 185 $[M-C_6H_9O]^+$, 162, 144, 127, 98 $[C_6H_9OH]^+$, 81 $[C_6H_9]^+$ (Found: $[M+NH_4]^+$, 300.2160. $C_{16}H_{26}O_4$ requires $[M+NH_4]^+$, 300.2175).

IMDA Reaction of triene (11).

An ether solution of triene **11** (115 mg, 0.41 mmol) was filtered through an alumina column, azeotropically dried with toluene (3 x 10 ml), and dissolved in further dry toluene (15ml). The solution was degassed using the freeze-pump-thaw technique. The solution was then heated at 165°C for 2.5 h, and the

toluene removed by evaporation under reduced pressure to give a brown oil (67 mg, 58% mass recovery). ^{1}H Nmr analysis showed the presence of a complex mixture. The crude oil (67 mg) was dissolved in methanol (10 ml) and conc HCl (2 drops) was added. The solution was stirred for 2 h, when solid $NaHCO_3$ was added carefully until effervescence ceased. The solid was filtered, washing the residue with CH_2Cl_2 and the filtrate concentrated under reduced pressure to give a pale brown oil. Purification by chromatography (15% EtOAc–petrol) gave the *hydroxylactone* **15** (33 mg, 41%) as a colourless oil; ν_{max} (film) 3325, 2965, 2925, 2874, 2853, 1772, 1454, 1384, 1353, 1215, 1086, 1064, 1035, 1008, 986 cm^{-1}; δ_H (270 MHz) 5.64 (1H, ddd, J 10.0, 4.0, 3.0 Hz, H-7 or H-8), 5.44 (1H, dt, J 10.0, 2.0 Hz, H-8 or H-7), 4.48 (1H, dd, J 11.5, 9.0 Hz, H-4), 4.43 (1H, dd, J 9.0, 7.0 Hz, H-4), 3.77 (1H, dd, J 10.5, 9.0 Hz, C-6 C*H*$_2$OH), 3.73 (1H, dd, J 10.5, 6.0 Hz, C-6 C*H*$_2$OH), 2.69-2.62 (1H, m, H-6), 2.59-2.49 (2H, m, H-5 and H-9), 1.22 (3H, d, J 7.0 Hz, C-9 C*H*$_3$), 1.07 (3H, s, C-1 C*H*$_3$); *m/z* (CI) 214 $[M+NH_4]^+$, 197 $[M+H]^+$, 167 $[MH-2Me]^+$, 151, 121, 107, 91, 82 (Found: $[M+NH_4]^+$, 214.1439. $C_{11}H_{16}O_3$ requires $[M+NH_4]^+$, 214.1443).

Preparation of (-)-[4*S*]-methyl (*E*,*E*,*E*)-4,6,6-trimethyl-5,7-dioxa-2,9,11-tridecatrienoate (12).

An approximately 0.3M PhMe solution of vinylic ether **9** was prepared as described above, starting from (*E*,*E*)-2,4-hexadienyl acetate **8** (100 mg, 0.71 mmol, 1 eq). To this was added a solution of (+)-[4*S*]-methyl (*E*)-4-hydroxy-2-pentenoate[1] (77 mg, 0.59 mmol, 0.83 eq) in PhMe (1.0 ml) followed by $Pd(COD)Cl_2$ (40 mg, 0.14 mmol, 0.2 eq), and the mixture stirred for 24 h. Pyridine (20 µl) was added and the mixture diluted with ether, filtered through Celite® and concentrated under reduced pressure to give a yellow oil. This was purified by chromatography (20% ether–petrol) to yield the desired *triene* **12** (139 mg, 73%) as a colourless oil; $[\alpha]_D^{20}$ -22.6 (*c* 1.08, $CHCl_3$); ν_{max} (film) 3022, 2993, 2949, 2937, 2916, 1726, 1383, 1296, 1273, 1203, 1161, 1130, 1053, 1032, 987 cm^{-1}; δ_H (270 MHz) 6.94 (1H, dd, J 15.5, 5.5 Hz, H-3), 6.18 (1H, dd, J 15.0, 10.5 Hz, H-10), 6.09-6.00 (1H, m, H-11), 5.96 (1H, dd, J, 15.5, 1.5 Hz, H-2), 5.75-5.55 (2H, m, H-9 and H-12), 4.58-4.49 (1H, m, H-4), 4.02 (1H, dd, J 12.0, 6.0 Hz, H-8), 3.96 (1H, dd, J 12.0, 6.0 Hz, H-8), 3.74 (3H, s, OC*H*$_3$), 1.75 (3H, d, J 7.0 Hz, H-13), 1.40 (3H, s, C-6 (C*H*$_3$)$_2$), 1.33 (3H, s, C-6 (C*H*$_3$)$_2$), 1.24 (3H, d, J 6.5 Hz, C-4 C*H*$_3$); *m/z* (CI) 286 $[M+NH_4]^+$, 268 $[M]^+$, 228, 211, 178, 171 $[M-C_6H_9O]^+$, 113, 98 $[C_6H_9OH]^+$, 81 $[C_6H_9]^+$ (Found: $[M+NH_4]^+$, 286.2015. $C_{15}H_{24}O_4$ requires $[M+NH_4]^+$, 286.2018).

IMDA Reaction of triene (12).

An ether solution of triene **12** (120 mg, 0.45 mmol) was filtered through an alumina column, azeotropically dried with toluene (3 x 10 ml), and dissolved in further dry toluene (15 ml). The solution was degassed using the freeze-pump-thaw technique. The solution was then heated at 165°C for 1.5 h and the toluene removed by evaporation under reduced pressure to give a pale yellow oil (104 mg, 87% mass recovery). This was shown by ^{1}H nmr to consist of two stereoisomers in a 4:1 ratio together with a third cycloadduct; the appearance of the spectrum was complicated by the presence of some decomposition material. The crude oil (104 mg) was dissolved in methanol (10 ml) and conc. HCl (2 drops) was added. The solution was stirred for 2 h, whereupon solid $NaHCO_3$ was added carefully until effervescence ceased. The solid was filtered, washing the residue with CH_2Cl_2 and the filtrate concentrated under reduced pressure to give a pale brown oil. The oil was purified by chromatography (15% EtOAc–petrol) to give, in order of elution, the *hydroxylactone* **17** (12 mg, 14%) as an oily solid, and an 8:1 mixture of the dihydroxyester **16** and the presumed hydroxylactone **18** (58 mg, 56%) as an oil; **17**: $[\alpha]_D^{20}$ -22.6 (*c* 1.08, $CHCl_3$); ν_{max} (film) 3472, 3423, 2955, 2925, 2871, 2855, 1773, 1460, 1394, 1377, 1173, 1079, 1048, 739, 692 cm^{-1}; δ_H (270 MHz) 5.67 (1H, dt, J 10.0, 1.5 Hz, H-8 or H-7), 5.57 (1H, ddd, J 10.0, 4.5, 2.5 Hz, H-7 or H-8), 4.63 (1H, dq, J 10.5, 6.0 Hz, H-4), 3.75-3.62 (2H, m, C-6 C*H*$_2$OH), 2.61-2.56 (1H, m, H-6), 2.40-2.36 (1H, m, H-9), 2.20 (1H, dd, J 14.0, 10.0 Hz, H-1), 2.01 (1H, ddd, J 14.0, 10.5, 8.0 Hz, H-5), 1.46 (3H, d, J 6.0 Hz, C-4 C*H*$_3$), 1.26 (3H, d, J 6.5 Hz, C-9 C*H*$_3$); *m/z* (CI) 214 $[M+NH_4]^+$, 197 $[M+H]^+$, 178 $[MH-H_2O]^+$, 152, 121, 95, 81 (Found: $[M+NH_4]^+$,

197.1190. $C_{11}H_{17}O_3$ requires $[M+NH_4]^+$, 197.1178). Data for the major component of the more polar, 8:1 mixture of **16** and **18**: υ_{max} ($CHCl_3$) 3304, 2956, 2927, 2874, 1729, 1457, 1436, 1374, 1296, 1244, 1195, 1175, 1045, 1030, 746 cm^{-1}; δ_H (270 MHz) (**16** only) 5.57 (1H, ddd, J 10.0, 5.5, 2.5 Hz, H-4), 5.52 (1H, dt, J 10.0, 1.5 Hz, H-4), 3.86 (1H, dq, J 6.5, 2.5 Hz, C-2 C*H*(CH_3)OH), 3.78 (3H, s, OCH_3), 3.53 (2H, d, J 5.5 Hz, C-3 CH_2OH), 2.71 (1H, br quintet, J 5.5 Hz, H-3), 2.64-2.58 (1H, m, H-6), 2.53 (1H, dd, J 11.5, 10.5 Hz, H-1), 1.97 (1H, ddd, J 11.5, 4.0, 2.5 Hz, H-2), 1.35 (3H, d, J 6.5 Hz, C-2 CH(CH_3)OH), 0.97 (3H, d, J 7.0 Hz, C-6 CH_3); in agreement with previously published data;[1] *m/z* (CI) 246 $[M+NH_4]^+$, 229 $[M+H]^+$, 211 $[MH-H_2O]^+$, 180 $[MH-OMe-H_2O]^+$, 151, 133, 121, 107, 91.

X-Ray crystal data[10]

Data were corrected for Lorentz and polarisation factors; the non-hydrogen atoms were refined anisotropically. The positions of all the hydrogen atoms were determined from a ΔF map. The hydroxy hydrogen atom was refined isotropically subject to an O–H distance constraint. The positions of the remaining hydrogen atoms were idealised, assigned isotropic thermal parameters, $U(H) = 1.2U_{eq}(C)$, and allowed to ride on their parent carbon atoms. The methyl group was refined as a rigid body. All computations were carried out using the SHELXTL programme system.[11]

Compound **14**: data were measured using a Siemens P4/PC diffractometer, using Mo-K_α radiation (λ = 0.71073 Å, graphite monochromator), using ω-scans, with $7° \leq 2\theta \leq 45°$. $C_{10}H_{14}O_3$, M = 182.2, monoclinic, a = 12.707(2), b = 5.648(2), c = 14.105(2) Å, β = 106.17(2)°, V = 972 $Å^3$, space group $P2_1/n$, Z = 4, D_c = 1.25 g cm^{-3}, μ(Mo-K_α) = 0.91 cm^{-1}, $F(000)$ = 392. 1259 Independent reflections were measured of which 666 had $|F_o| > 4\sigma(|F_o|)$, and were considered to be observed. Refinement was by full-matrix least-squares based on F to give R = 0.043, R_w = 0.044 [$w^{-1} = \sigma^2(F) + 0.0007F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.12 and -0.13 $eÅ^{-3}$ respectively. The maximum and mean shift/error ratios in the final refinement cycle were 0.000 and 0.000 respectively.

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