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Intramolecular Diels–Alder Reactions of Diester-tethered Trienes. Synthesis of Medium Ring-containing Carbocycles and Heterocycles

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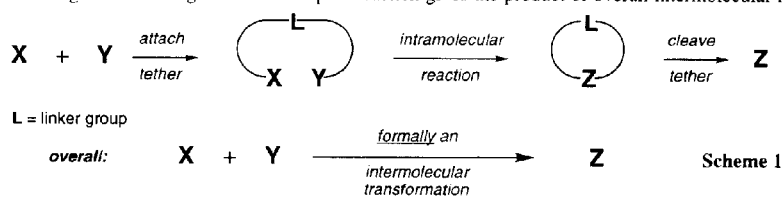
Abstract

Intramolecular Diels–Alder reactions of cyclohexane-1,2-dicarboxylic anhydride-derived diester-tethered trienes are described. The stereoselectivities of most of the cycloaddition processes studied may be rationalised in terms of an preferred 'inside'-oriented diene giving rise to an *endo*-transition state.

Keywords: Diels–Alder, stereoselective, macrolide, heterocycle

1. INTRODUCTION

Tethered reactions are commonly defined as those of substrates in which two mutually reactive functional groups enter into a reaction rendered unimolecular by the presence of a linker which temporarily joins them together. Cleavage of the tether post-reaction gives the product of overall intermolecular reaction



Scheme 1

(Scheme 1). Tethering confers significant advantages on processes compared with their intermolecular counterparts, in that unimolecular transformations often show enhanced rate, regioselectivity and

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stereoselectivity. The former effect derives from the less negative entropy of activation for the intramolecular process, whilst the latter benefits stem from the constraints imposed by the linking moiety upon the mutual approach of the reactive functional groups. The synthetic disadvantages associated with the necessity to add up to two extra steps to the synthetic sequence have been avoided in some cases by the design of systems which undergo spontaneous reaction on covalent attachment of the reactive functional groups; in these instances only the tether cleavage step is additional.[1] A large variety of organic chemical transformations of tethered substrates has been realised, and the use of silicon tethers has been particularly prominent.[2,3] For some time we and others[4] have been studying the [4+2] cycloaddition reactions of tethered substrates. We have deployed silaketals,[5] tertiary and benzylic ethers[6] and acetals[7] as removable tethering groups and have found that high stereoselectivity and complete regioselectivity often may be attained. Latterly we have sought to extend our investigations to more unusual, chiral tethering moieties with a view both to exploring the possibilities for medium-ring synthesis and to assessing the prospects for diastereoselective reactions in what would effectively be an auxiliary-based approach. We now report in full the results of these investigations.[8]

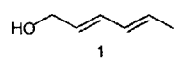
2. RESULTS AND DISCUSSION

From a synthetic perspective esters are attractive as tethering groups because of the ease with which they may be incorporated into the substrate and cleaved in the product. However, the presence of an ester within the tether often confers low reactivity on substrates because of its preferred *Z*-geometry,[9] which is such that the proximal conformations required for efficient unimolecular reaction are only sparsely populated. Prior to the start of our study the viability of intramolecular Diels–Alder (IMDA) reactions of trienes with ester groups within the chain linking the diene and dienophile had been amply demonstrated in a diverse range of examples.[10] Significantly however, in some cases substrates having esters in the tethers were less reactive than closely-related but non-ester-containing analogues. The magnitude of this effect was borne witness by the observation that competing diene isomerisation had taken place prior to cycloaddition.[11,12] We reasoned that in the formation of medium-ring lactones by intramolecular [4+2] cycloaddition reactions the increased tether length would be such that the favoured *Z*-ester geometry would now easily be accommodated within reactive, proximal conformations of the triene substrate. It was felt also that the presence of *two* trigonal planar ester groups would substantially attenuate the unfavourable transannular interactions normally associated with medium rings.

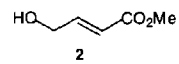
Synthesis of tethered IMDA substrates

One of our initial aims was to look at diastereoselectivity in IMDA reactions of substrates possessing chiral tethers in an auxiliary-type approach. A conformationally restricted tether was sought which would increase the population of reactive conformations, and which would have potential ultimately in the generation of enantiomerically pure cycloadducts and their derivatives. In order to simplify synthesis C_2-symmetry appeared attractive, and consequently the *trans*-cyclohexane-1,2-dicarboxy unit was chosen as the tether for the first target substrates. (*E,E*)-2,4-Hexadienol **1**[13] and (*E*)-methyl 4-hydroxybut-2-enoate **2**[14] were selected to provide the diene and dienophile cycloaddition partners to enable comparisons to be made with our earlier work on silaketal-tethered substrates.[5]

The syntheses of the first series of substrates began with (±)-*trans*-cyclohexane-1,2-dicarboxylic anhydride **3**, whose reaction with **1** in the presence of pyridine and DMAP gave the half-ester **4**. A wide variety of agents was assessed for the coupling of **2** with **4**. Reaction of **4** with oxalyl chloride–DMF gave the corresponding acid chloride; this reacted in crude form with **2** in the presence of pyridine, but yields of the desired triene **5** were disappointingly low. Attempted coupling of **2** and **4** using dicyclohexylcarbodiimide resulted always in the isolation of good yields of the adduct **6**, which did not enter into further reaction with **2**. Finally, it was established that formation of the mixed



1



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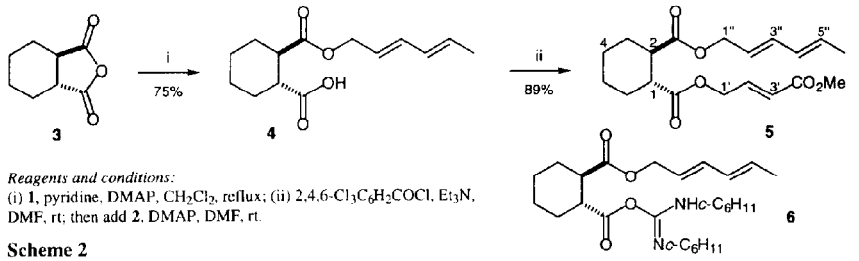
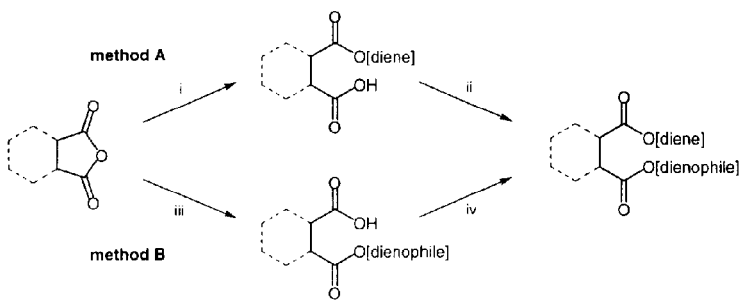


Reagents and conditions:
(i) **1**, pyridine, DMAP, CH_2Cl_2, reflux; (ii) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMF, rt; then add **2**, DMAP, DMF, rt.

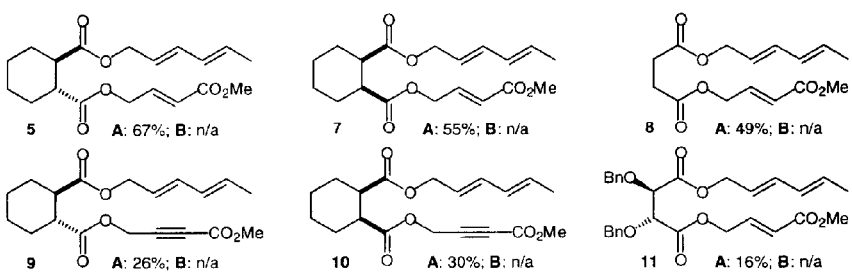
Scheme 2

anhydride of **4** and 2,4,6-trichlorobenzoic acid according to the Yamaguchi procedure[15] followed by reaction with **2** *in situ* reproducibly gave acceptable yields of **5** (Scheme 2). A similar procedure was carried out using the achiral spacer *cis*-cyclohexane-1,2-dicarboxylic anhydride, and with furfuryl alcohol and methyl 4-hydroxy-2-butynoate[16] as alternative diene- and dienophile-containing components. In addition, acyclic tethering units based on succinic anhydride and di-*O*-benzyltartaric anhydride[17] were used, since it was considered that IMDA reactions of the derived trienes would provide valuable information concerning the impact on [4+2] reactivity of conformational restriction of the tether. In the cases of furan-containing trienes/dienynes **12**-**15** the overall yields were improved when the dienophile was introduced prior to the diene. The syntheses of all of the IMDA substrates are summarised in Scheme 3.

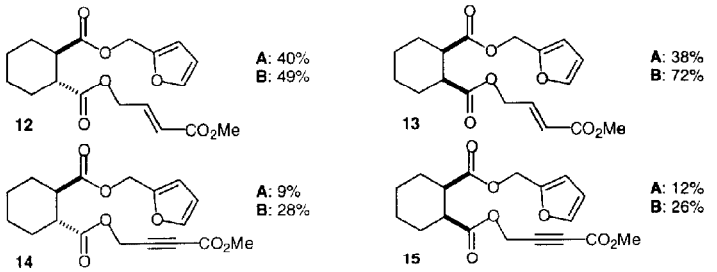


Reagents and conditions: (i) [diene]OH, pyridine, DMAP, CH_2Cl_2, reflux; (ii) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMF, rt, then add [dienophile]OH, DMAP, DMF, rt; (iii) [dienophile]OH, pyridine, DMAP, CH_2Cl_2, reflux; (iv) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMF, rt, then add [diene]OH, DMAP, DMF, rt

Scheme 3

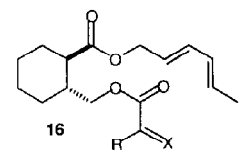


yields are for the two steps from the appropriate anhydride using either method A or B; n/a = not attempted

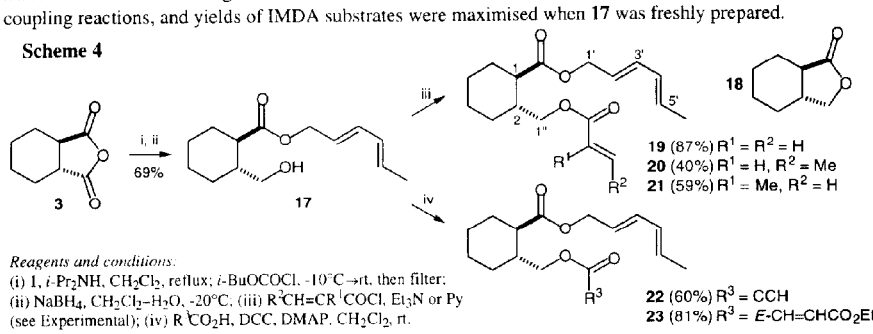


yields are for the two steps from the appropriate anhydride using either method A or B

We became interested also in the synthesis of a second series of IMDA substrates with generic structure **16**. It was considered that the cycloaddition behaviour of these 'reversed' trienes would provide insights concerning the importance of the position of the ester functional group within the tether. As before, the synthetic sequence began with *trans*-cyclohexane-1,2-dicarboxylic anhydride **3**, using an adaptation of the procedure of Zwanenberg.[18] Thus, nucleophilic ring-opening with **1** in the presence of diisopropylamine gave the half-ester **4** as its diisopropylammonium salt; reaction *in situ* with *i*-butyl chloroformate gave the mixed carboxylic–carbonic anhydride. This was separated from precipitated diisopropylammonium chloride by simple filtration, after which aqueous sodium borohydride treatment of the filtrate gave key intermediate **17**. Coupling of **17** with dienophile-containing acid chlorides in the presence of base, or with acids using DCC completed the assembly of the modified substrates (Scheme 4). Alcohol **17** was slowly converted into the *trans*-lactone **18**[19] on storage, with concomitant liberation of **1**; this occurred to varying extents during the coupling reactions, and yields of IMDA substrates were maximised when **17** was freshly prepared.



Scheme 4

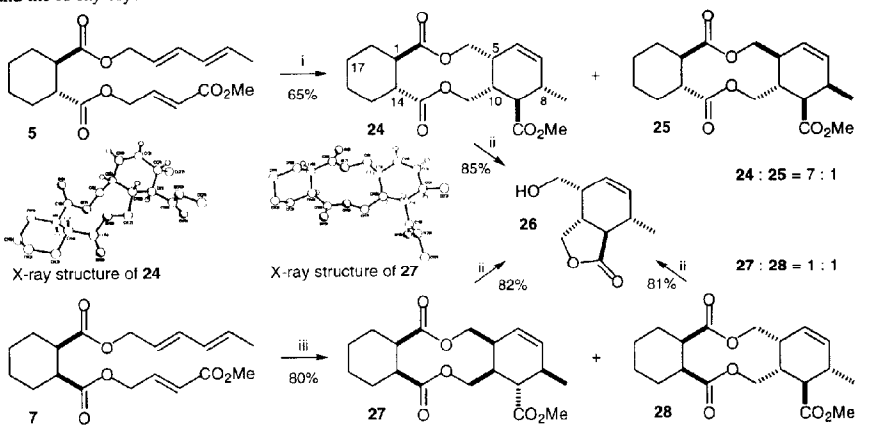


Reagents and conditions:
(i) 1, *i*-Pr_2NH, CH_2Cl_2, reflux; *i*-BuOCOCl, -10°C→rt, then filter;
(ii) $NaBH_4$, CH_2Cl_2–H_2O, -20°C; (iii) $R^2CH{=}CR^1COCl$, Et_3N or Py (see Experimental); (iv) R^3CO_2H, DCC, DMAP, CH_2Cl_2, rt.

Intramolecular homo-Diels–Alder reactions

Cycloaddition studies were carried out by the usual protocol[5-7] of running small-scale reactions in deuterated solvent in sealed nmr tubes prior to carrying out preparative-scale runs in resealable glass vessels. Triene–diester **5** reacted sluggishly to yield a *ca.* 7:1 mixture of cycloadducts in good yield. The structure of the major, crystalline diastereomer was shown to be **24** by single-crystal X-ray analysis. This confirmed the preliminary assignment made on the basis of the high-yielding conversion of **24** into the known[5] hydroxylactone **26** upon sequential LiOH-mediated saponification and acid-catalysed cyclisation. The minor product could not be obtained in a crystalline form suitable for X-ray analysis, but structure **25** was assigned, since this would arise from a diequatorial spacer conformation with an *endo*-oriented diene. Treatment of **25**

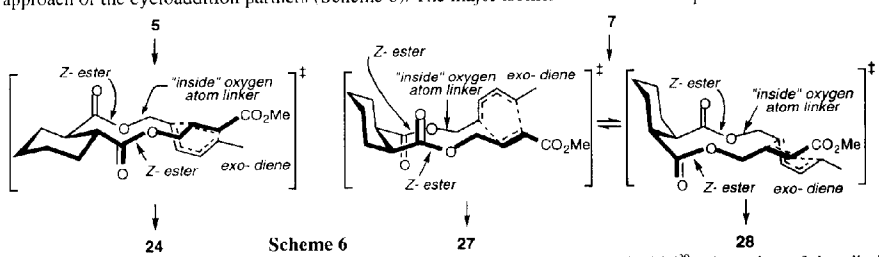
with LiOH followed by TFA as before gave a hydroxylactone which was different from **26**. Triene **7** was less reactive than the *trans*-isomer **5**, giving a 1:1 mixture of products. One of these was assigned structure **27** by X-ray analysis; the structure of the other isomer was conclusively established as being **28** by its conversion into **26** by the hydrolysis–cyclisation reaction sequence carried out on **24**. Cycloadduct **27** also gave **26** on LiOH treatment followed by acidolysis allowing also the recovery of *trans*-cyclohexane-1,2-dicarboxylic acid and subsequent recycling through conversion into **3** by simple dehydration. The IMDA reactions of **5** and **7** and the X-ray crystal structures of **24** and **27** are shown in Scheme 5.



Reagents and conditions: (i) PhMe, 180°C, 100 h; (ii) LiOH, THF–MeOH–H_2O, rt; TFA, CH_2Cl_2, rt; (iii) PhMe, 180°C, 200 h

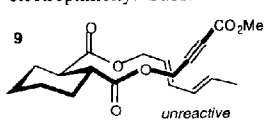
Scheme 5

The selectivities observed in the IMDA reactions of **5** and **7** were in line with our expectations. In **5** the *trans*-diequatorial nature of the diene- and dienophile-containing substituents on the cyclohexane spacer is such that only one cyclohexane conformation having both esters in the favourable *Z*-form allows close mutual approach of the cycloaddition partners (Scheme 6). The major isomer **24** arises from a putative transition-state

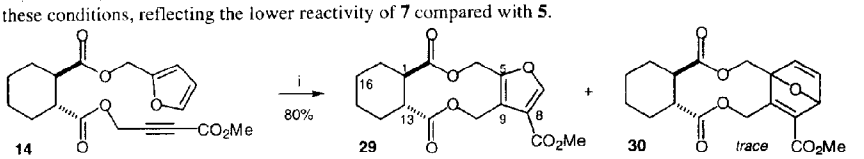


Scheme 6

in which the diene is *exo*-with respect to the dienophile ester group with an 'inside'[20] orientation of the alkyl C–O bond. This tendency was observed in our earlier studies of silaketal-tethered trienes,[5] and may be rationalised as combining optimum diene nucleophilicity with dienophile electrophilicity. Substrate **7** is conformationally more labile than **5**, and has available two conformations in which *exo*- approach of the 'inside'-oriented diene is possible, resulting in a reaction which gives *cis*-fused products but with zero selectivity. Neither of the two dienyne substrates **9** and **10** was reactive under thermal conditions analogous to those used in the reactions of **5** and **7**. This may be



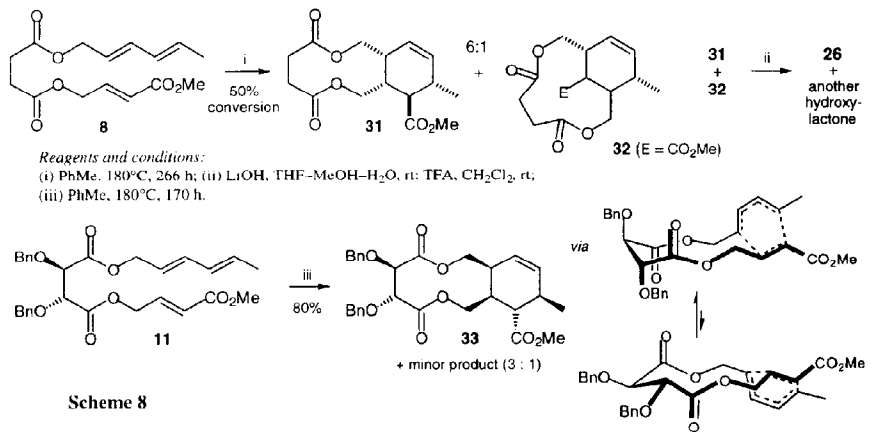
attributed to the predominant population of conformations which are unreactive on account of the non-accessibility of simultaneous alignment of the alkyne carbon atoms with the diene. Furan-containing substrates **12** and **13** were apparently unreactive also, although in these cases it is likely that the cycloaddition processes are reversible,[21] and that the equilibria favour the aromatic starting materials.[22] Interestingly, heating of the alkyne–furan substrate **14** under the standard conditions gave in high yield the product **29** of a cycloaddition–cycloelimination sequence, with only trace quantities of the initial cycloadduct **30** detectable by mass spectroscopy (Scheme 7). The generation of ethyne in the second stage of the tandem sequence was evidenced by a build-up of pressure in the reaction vessel. Isomer **15** having the *cis*- spacer was inert under these conditions, reflecting the lower reactivity of **7** compared with **5**.



Reagents and conditions: PhMe, 180°C, 133 h.

Scheme 7

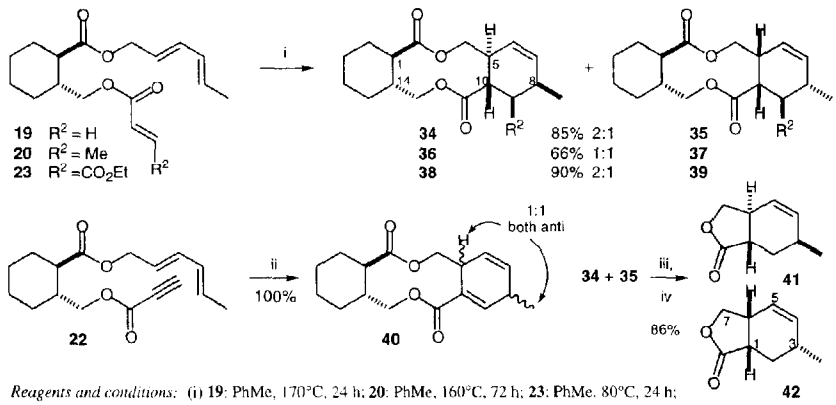
One of the goals of our programme was to assess the enhancement in IMDA reaction rate arising from conformational restriction by the cyclohexane spacer, and the study of substrates with acyclic spacer units provided an opportunity to evaluate the extent of such an effect. As expected, the succinate-containing substrate **8** was markedly less reactive than **5** and **7**, undergoing 50% conversion to a 6:1 mixture of two products after prolonged heating. The major isomer was assigned as **31** following its conversion into **26** upon base-catalysed hydrolysis and acid-mediated cyclisation as before. Subjection of the minor product to identical conditions gave a lactone whose ^{1}H nmr spectrum did not match that of the lactone derived from presumed cycloadduct **25**. We speculate that the minor cycloadduct is a regioisomer **32**; non-regioselective IMDA reactions have been reported in cases where the tether is sufficiently long and conformationally flexible.[23] IMDA Reaction of **11** was more rapid than that of **8**, giving rise to a 3:1 mixture of cycloadducts. Although neither of these was crystalline, structure **33** was assigned to the major isomer on the basis of previous experiments. The IMDA rate increase observed upon substitution of the succinate spacer with benzyloxy groups may be attributed to the increased population of reactive conformations, in which dipole–dipole repulsion between the alkoxy groups is minimised.[24] The reactions of **8** and **11** are depicted in Scheme 8.



Reagents and conditions:
(i) PhMe, 180°C, 266 h; (ii) LiOH, THF–MeOH–H_2O, rt; TFA, CH_2Cl_2, rt;
(iii) PhMe, 180°C, 170 h.

Scheme 8

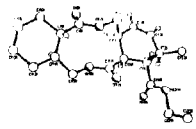
Attention was turned next to the IMDA reactions of 'reversed' ester-containing substrates **19-23**. Heating of a solution of the acryloyl triene **19** at 170°C overnight resulted in the formation in high yield of a 2:1 mixture of two inseparable cycloadducts. Treatment of this material with LiOH followed by acid gave two lactones **41** and **42** in addition to **18**; the major isomer **41** showed two large couplings to H-1, characteristic of the *trans*-ring junction, from which the major cycloadduct was assigned structure **34**. As expected, the analogous crotonyl triene **20** reacted more sluggishly, giving a 1:1 mixture of cycloadducts in 66% yield. By analogy, these were assigned as having structures **36** and **37**. The methacryloyl derivative **21** was inert under the more forcing conditions used for IMDA reaction of **20**. Substrate **23**, possessing the fumarate dienophile was the most reactive of those studied, undergoing complete cycloaddition after heating in toluene overnight at 80°C. Two major products **38** and **39** were formed in a 2:1 ratio. Structural assignments were made on the basis of the observation of a 2% n.O.e. between C-8 CH_3 group and H-10 in **38**, and from single-crystal X-ray analysis of **39**. The IMDA reaction of propiolate **22** gave the two possible cycloadducts **40** non-selectively; substrate **22** showed reactivity comparable to that of acrylate **19** (Scheme 9).



Reagents and conditions: (i) **19**: PhMe, 170°C, 24 h; **20**: PhMe, 160°C, 72 h; **23**: PhMe, 80°C, 24 h; (ii) PhMe, 150°C, 24 h; (iii) LiOH, THF–MeOH, rt; (iv) *p*-TSA, CH_2Cl_2, reflux.

Scheme 9

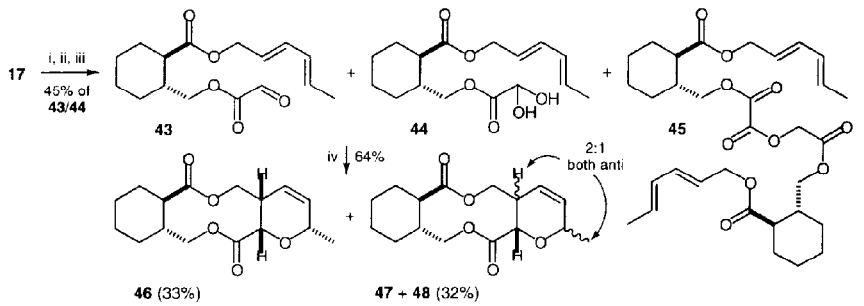
Two principal trends emerged from the IMDA reactions of 'reversed' ester-containing trienes depicted in Scheme 9. Firstly, these modified substrates are considerably more reactive than triene **5**. We speculate that this is because of the greater flexibility of the alkyl C–O bond in the tether compared to the acyl C–O linkage present in the dicarboxylate-tethered substrates, allowing closer mutual approach of the diene and dienophile. In this regard it is striking that propiolate **22** is reactive whereas the closely-related dienyne **9** is not, and this may be indicative of the greater conformational freedom allowed by the change in position of the tether ester. Secondly, where stereoselectivity is observed, the predominant cycloadducts are *trans*-fused; these arise from the preferred adoption of the previously less favoured 'outside' conformation of the diene. For substrates **19** and **23** this corresponds to *exo*-orientation of the diene with respect to the ester group within the tether; in the most reactive substrate **23** this diene approach is *endo*- to the ethyl ester group outside the tether. Despite these differences in the behaviour of the 'normal' and 'reversed' substrates, the topicity of reaction of the dienophile with respect to the tethering group in the major products is the same as that observed for **5**.



X-ray structure of **39**

Intramolecular hetero-Diels–Alder reactions

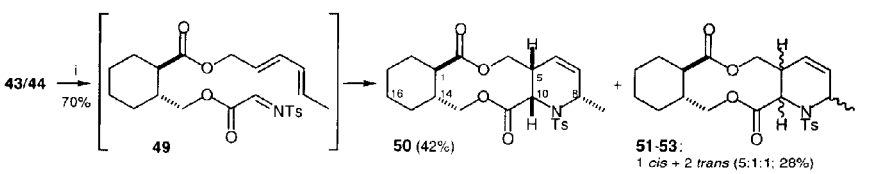
The final part of our study was devoted to an investigation of reactions of hetero-Diels–Alder substrates related to **19-23**. Heterodienophilic groups were sought in which the ester would activate the C=X bond towards cycloaddition, and would allow the synthesis of several heterotrienes from a common ester-containing precursor if it were introduced at a sufficiently early stage in the assembly sequence. In the event, esterification of alcohol **17** using TBDPS-protected glycolic acid[25] followed by desilylation and oxidation gave the aldehyde **43** which existed as an equilibrium mixture containing predominantly the hydrate **44**; the presence of **43** was confirmed by its conversion into **23** on Wittig reaction with ethoxycarbonylmethylene-triphenylphosphorane. The modest yield obtained in the final oxidation step was largely a result of competitive formation of the oxalate **45**, presumably through nucleophilic interception of **43** by unconsumed starting material, followed by oxidation. Thermolysis of the azeotropically-dried[26] glyoxalate **43/44** gave a 5:1 mixture of *cis*- and *trans*-fused cycloadducts **46/47** and **48** in good yield. Structural assignments followed from the H5–H10 J-values of 3 and 9.5 Hz respectively for the two *cis*- and single *trans*- isomer, and on the basis of the dienophile topicity observed in all previous cycloadditions of this type (Scheme 10).



Reagents and conditions: (i) $TBDPSOCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt; (ii) TBAF, THF, rt; (iii) Dess–Martin periodinane, CH_2Cl_2, reflux (68% **43/44** + 21% **45**); (iv) PhMe, 150°C, 24 h.

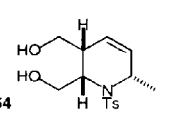
Scheme 10

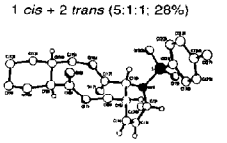
Finally, we looked at tethered hetero-IMDA reactions of activated imines. Heating of a mixture of **43/44** with tosyl isocyanate effected *in-situ* bimolecular [2+2] cycloaddition, extrusion of CO_2 to give **49** and intramolecular [4+2] cycloaddition,[27] giving the piperidine **50** as the major compound in 42% isolated yield. Again, ^1H nmr spectroscopy allowed its identification as a *cis*-fused compound, and the structure **50** was unambiguously assigned by X-ray crystallography. The remaining material comprised largely the other *cis*-



Reagents and conditions:
(i) TsNCO, PhMe, 125°C, 16 h;
(ii) $LiAlH_4$, THF, rt.

Scheme 11





X-ray structure of **50**

fused isomer **51**, with small amounts of the *trans*-fused compounds **52** and **53** formed also. Reduction of the mixture of cycloadducts using $LiAlH_4$ gave a mixture of diols, with **54** (arising from **50**) isolated in 65% yield. Thus, IMDA reaction of the *N*-tosylimine derivative **49** showed not only enhanced *cis*-selectivity (*ca.* 8:1) with respect to the parent oxygen analogue **43**, but a preference (2:1) for one of the *cis*-fused products over the other. The increased predominance for the *cis*-fused isomers may reflect the steric bulk of the tosyl substituent on the imine, which we presume to have *tr*

ans-geometry; steric interactions between this and the diene are such that the latter approaches the dienophile *endo*- with respect to the ester.[28] The generation and IMDA reaction of **49** are depicted in Scheme 11.

3. CONCLUSIONS

The results presented herein demonstrate that diester-tethered trienes and dienynes are readily-accessible substrates which in many cases undergo highly stereoselective intramolecular Diels–Alder reactions. For the most part, stereochemistry may be understood by a consideration of steric effects in reactive conformations possessing Z-configured ester-linkages. Synthetic manipulation of the cycloadducts allows recycling of the chiral *trans*-cyclohexane-1,2-dicarboxylate spacer. Although all of the substrates we have examined are racemic, the selectivities obtained are such that this approach would be viable for the synthesis of single enantiomers. To this end, we are exploring modifications of the sequence used to generate half-ester **4** and alcohol **17** by using enantiomerically pure secondary amine bases to effect resolution of the product of the initial ring-opening step. Also, we are seeking to extend the hetero-Diels–Alder chemistry to include substrates possessing acylnitroso and diazodicarboxylate functionality.[29] The results of these studies will be reported in due course.

4. EXPERIMENTAL

General Procedures

^1H Nmr and ^{13}C nmr spectra were recorded in $CDCl_3$ on either Jeol GX-270Q, Bruker DRX-300, Bruker DRX-400 or Bruker AM-500 spectrometers, using residual isotopic solvent ($CHCl_3$, δ_H = 7.26 ppm; $CDCl_3$, δ_C = 77.0 ppm) as internal reference. Infrared spectra were recorded on Perkin-Elmer 881 and Mattson 5000 FTIR spectrophotometers. Mass spectra were recorded using VG-7070B, VG707E, VG Autospec Q or Jeol SX-102 instruments. Elemental combustion analyses were performed in the microanalytical laboratories of Imperial College. Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) or Matrex Silica 60 (35-70 micron) under pressure. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised with ultraviolet light and iodine, acidic ammonium molybdate (IV), vanillin or potassium permanganate solutions as appropriate. Standard solvents were distilled under dried nitrogen; diethyl ether and tetrahydrofuran from sodium-benzophenone ketyl, CH_2Cl_2 from phosphorus pentoxide, acetonitrile from calcium hydride and toluene from sodium. Petrol refers to petroleum ether bp 40-60°C which was distilled prior to use. Solutions were concentrated under vacuum on a rotary evaporator at 25°C, except where otherwise stated. Azeotropically dried compounds were dissolved in dry toluene and concentrated at least three times. Molecular sieves were activated by heating over a flame under vacuum. Other solvents and reagents were purified before use according to standard procedures.[30]

Preparation of (±)-(*E*,*E*)-2,4-hexadienyl *trans*-cyclohexane-1,2-dicarboxylate (4).

To a stirred solution of **1** (100 mg, 1.02 mmol, 1.0 equiv), (±)-*trans*-cyclohexane-1,2-dicarboxylic anhydride (236 mg, 1.53 mmol, 1.5 equiv) and DMAP (23 mg, 0.10 mmol, 0.1 equiv) in CH_2Cl_2 (3 ml) was added pyridine (121 mg, 124 µl, 1.53 mmol, 1.5 equiv). The mixture was heated at 45°C for 16 h and then

partitioned between saturated aqueous NH_4Cl (10 ml) and ether (10 ml). The aqueous layer was extracted with ether (3 x 20 ml) and the combined organic layers dried ($MgSO_4$). The solution was filtered and the solvent removed by rotary evaporation to give a viscous pale yellow oil. Purification by chromatography (50% ether–petrol) afforded the carboxylic acid **4** (193 mg, 75%) as a clear, colourless oil; R_f 0.22 (50% ether–petrol); ν_{max} (film) 2937, 2859, 1736, 1448, 1383, 1314, 1251, 1176, 1113, 1035, 990, 922 cm^{-1}; δ_H (500 MHz) 6.23 (1H, dd, J 15, 11 Hz, H-3'), 6.03 (1H, ddd, J 15, 11, 1.5 Hz, H-4'), 5.73 (1H, dq, J 15, 6.5 Hz, H-5'), 5.59 (1H, dt, J 15, 6.5 Hz, H-2'), 4.59 (1H, dd, J 13, 7 Hz, H-1'), 4.55 (1H, dd, J 13, 7 Hz, H-1'), 2.64 (1H, dt, J 12, 3.5 Hz, H-1), 2.58 (1H, dt, J 12, 3.5 Hz, H-2), 2.13-2.07 (2H, m, H-3, H-6), 1.82-1.87 (2H, m, H-3, H-6), 1.76 (3H, d, J 6.5 Hz, CH_3), 1.42-1.25 (4H, m, H-4, H-5); *m/z* (EI) 252 $[M]^+$, 234, 206 $[MH\text{-}COOH]^+$, 155 $[M\text{-}CH_3CH{=}CH\text{-}CH{=}CHCH_2O]^+$, 127 $[M\text{-}CH_3CH{=}CH\text{-}CH{=}CHCH_2OCO]^+$, 109, 97, 81 $[CH_3CH{=}CH\text{-}CH{=}CHCH_2]^+$ (Found: C, 66.57; H, 8.09. $C_{14}H_{20}O_4$ requires C, 66.64; H, 7.99%).

Preparation of (±)-(*E,E,E*)-2,4-hexadienyl (3-methoxycarbonyl-2-propenyl) *trans*-cyclohexane-1,2-dicarboxylate (5).

To a stirred solution of azeotropically dried **4** (100 mg, 0.40 mmol, 1.0 equiv) in DMF (2.0 ml) under N_2 at rt was added 2,4,6-trichlorobenzoyl chloride (97 mg, 62 µl, 0.40 mmol, 1.0 equiv) and Et_3N (100 mg, 138 µl, 0.99 mmol, 2.5 equiv). The solution was stirred at rt for 1 h whereupon a solution of **2** (46 mg, 0.40 mmol, 1.01 equiv) and DMAP (2 mg, 0.02 mmol, 0.04 equiv) in DMF (2.0 ml) was added *via* cannula and the mixture stirred for a further 1 h. The solution was partitioned between ether (5 ml) and H_2O (5 ml) and the organic layer alternately extracted with H_2O (2 x 5 ml) and washed with brine (2 x 5 ml). The combined organic layers were dried ($MgSO_4$) and the solvents removed under reduced pressure to yield a brown oil. Purification by chromatography (40% ether–petrol) afforded the **5** (124 mg, 89%) as a clear, colourless oil; R_f 0.35 (50% ether–petrol); ν_{max} (film) 3443, 2937, 2860, 1727, 166, 1438, 1384, 1315, 1254, 1166, 1114, 1075, 1036, 992, 854 cm^{-1}; δ_H (500 MHz) 6.92 (1H, dt, J 16, 4.5 Hz, H-2'), 6.22 (1H, dd, J 15, 10.5 Hz, H-3"), 6.03 (1H, dd, J 15.5, 2.0 Hz, H-3'), 6.01 (1H, ddd, J 16, 5.5, 1.5 Hz, H-4'), 5.74 (1H, dq, J 15, 6.5 Hz, H-5'), 5.58 (1H, dt, J 15.5, 7 Hz, H-2'), 4.75 (1H, ddd, J 16.5, 4.5, 2 Hz, H-1'), 4.69 (1H, ddd, J 16, 4.5, 2 Hz, H-1'), 4.58 (1H, dd, J 13, 6.5 Hz, H-1"), 4.53 (1H, dd, J 13, 6.5 Hz, H-1"), 3.75 (3H, s, OCH_3), 2.68 (1H, dt, J 11, 3.5 Hz, H-1), 2.63 (1H, dt, J 11, 4 Hz, H-2), 2.12-2.09 (2H, m, H-3, H-6), 1.81-1.79 (2H, m, H-3, H-6), 1.75 (3H, d, J 6.5 Hz, H-6"), 1.43-1.21 (4H, m, H-4, H-5); *m/z* (EI) 253 $[M\text{-}OCH_2CH{=}CH\text{-}CH{=}CHCH_3]^+$, 109, 99, 81 $[CH_2CH{=}CH\text{-}CH{=}CHCH_3]^+$, 67 (Found: C, 65.02; H, 7.63. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%).

Preparation of (±)-(*E,E,E*)-2,4-hexadienyl (3-methoxycarbonyl-2-propenyl) *cis*-cyclohexane-1,2-dicarboxylate (7).

Prepared as for **5** starting from *cis*-cyclohexane-1,2-dicarboxylic anhydride, **1** and **2** on a 3 mmol scale to give **7** (55%) as a clear, colourless oil; R_f 0.36 (50% ether–petrol); ν_{max} (film) 3023, 2997, 2941, 2858, 1728, 1666, 1448, 1438, 1379, 1365, 1308, 1277, 1245, 1234, 1172, 1128, 1103, 1077, 1026, 991, 967 cm^{-1}; δ_H (300 MHz) 6.95 (1H, dt, J 16.5, 4.5 Hz, H-2'), 6.24 (1H, dd, J 16.5, 11 Hz, H-3"), 6.05 (2H, m, H-4", H-3'), 5.76 (1H, dq, J 16.5, 5.5 Hz, H-5"), 5.60 (1H, dt, J 15, 6.5 Hz, H-2'), 4.75 (2H, d, J 4.5 Hz, H-1'), 4.59 (2H, d, J 7.5 Hz, H-1"), 3.76 (3H, s, OCH_3), 2.90 (2H, m, H-1, H-2), 2.17-1.96 (2H, m, H-3, H-6), 1.90-1.80 (2H, m, H-3, H-6), 1.78 (3H, d, J 7.5 Hz, H-6"), 1.63-1.48 (4H, m, H-4, H-5); δ_C (75.4 MHz) [173.3, 173.1 (C=O)], 166.3 (CO_2Me), 141.7 (C-3'), [134.9, 131.2, 130.5, 123.6 (C-2", C-3", C-4", C-5")], 121.6 (C-1'), [65.0, 62.5 (C-1', C-1")], 51.7 (OCH_3), [42.7, 42.2 (C-1, C-2)], [26.4, 26.0 (C-3, C-6)], [23.9, 23.6 (C-4, C-5)], 18.1 (C-6"); *m/z* (EI) 253 $[M\text{-}OCH_2CH{=}CH\text{-}CH{=}CHCH_3]^+$, 207 $[M\text{-}CO_2CH_2CH{=}CH\text{-}CH{=}CHCH_3]^+$, 109, 99 $[CH_2CH{=}CHCO_2Me]^+$, 81 $[CH_2CH{=}CH\text{-}CH{=}CHCH_3]^+$, 68, 55 (Found: C, 64.94; H, 6.91. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%).

Preparation of (*E,E,E*)-2,4-hexadienyl (3-methoxycarbonyl-2-propenyl) 1,4-butanedioate (8).

Prepared as for **5** starting from succinic anhydride, **1** and **2** on a 2.52 mmol scale to give **8** (49%) as a clear, colourless oil; R_f 0.31 (50% ether–petrol); ν_{max} (film) 3022, 2993, 2952, 2884, 2855, 1728, 1666, 1437, 1385, 1352, 1312, 1275, 1194, 1157, 1109, 1078, 1039, 1018, 992 cm^{-1}; δ_H (300 MHz) 6.96 (1H, dt, J 16, 4.5 Hz, H-2'), 6.25 (1H, dd, J 13.5, 10.5 Hz, H-3"), 6.10 (1H, m, H-4"), 6.05 (1H, dt, J 16, 1 Hz, H-3'), 5.75 (1H, dq, J 15, 6.5 Hz, H-5"), 5.62 (1H, dt, J 15, 6.5 Hz, H-2"), 4.78 (2H, dd, J 6.5, 3.5 Hz, H-1'), 4.60 (2H, d, J 6.5 Hz, H-1"), 3.76 (3H, s, OCH_3), 2.69 (4H, m, H-2, H-3), 1.79 (3H, d, J 6.5 Hz, H-6"); δ_C (75.4 MHz) [171.9, 171.6 (C=O)], 166.2 (CO_2Me), 141.3 (C-3'), [135.2, 131.5, 130.4, 123.4 (C-2", C-3", C-4", C-5")], 121.9 (C-2'), 65.4 (C-1"), 62.8 (C-1'), 51.8 (OCH_3), [29.1, 29.0 (C-2, C-3)], 18.2 (C-6"); *m/z* (EI) 296 $[M]^+$, 199, 99 $[CH_3CH{=}CHCO_2Me]^+$, 81 $[CH_2CH{=}CH{-}CH{=}CHCH_3]^+$, 68, 55 (Found: C, 60.70; H, 6.79. $C_{15}H_{20}O_6$ requires C, 60.80; H, 6.83%).

Preparation of (±)-(*E,E*)-2,4-hexadienyl (3-methoxycarbonyl-2-propynyl) *trans*-cyclohexane-1,2-dicarboxylate (9).

Prepared as for **5** starting from **3**, **1** and methyl 3-hydroxy-2-butynoate on a 0.37 mmol scale to give **9** (26%) as a clear, colourless oil; R_f 0.50 (90% ether–petrol); ν_{max} (film) 3023, 3004, 2860, 2248, 1724, 1379, 1361, 1317, 1161, 1112, 1082, 1037, 992, 962 cm^{-1}; δ_H (270 MHz) 6.24 (1H, dd, J 16, 11 Hz, H-3"), 6.03 (1H, ddd, J 16, 11, 1 Hz, H-4"), 5.76 (1H, dq, J 16, 7.5 Hz, H-5"), 5.60 (1H, dt, J 16, 6.5 Hz, H-2"), 4.82 (1H, d, J 16 Hz, H-1'), 4.72 (1H, d, J 18 Hz, H-1'), 4.59 (2H, dd, J 7, 1.5 Hz, H-1"), 3.78 (3H, s, OCH_3), 2.63 (2H, m, H-1, H-2), 2.50-2.04 (2H, m, H-3, H-6), 1.86-1.78 (2H, m, H-3, H-6), 1.77 (3H, d, 7 Hz, H-6"), 1.49-1.25 (4H, m, H-4, H-5); δ_C (75.4 MHz) [174.4, 174.0 (C=O)], 153.3 (CO_2Me), [134.9, 131.2, 130.4, 123.6 (C-2", C-3", C-4", C-5")], [81.3, 77.7 (C-2', C-3')], 65.1 (C-1"), [52.8, 51.4 (C-1', OCH_3)], [44.7, 44.6 (C-1, C-2)], [28.77, 28.75, 44.73, 44.59 (C-3, C-4, C-5, C-6)], 18.1 (C-6"); *m/z* (CI) 366 $[M{+}NH_4]^+$, 286, 190, 98, 81 (Found: $[M{+}NH_4]^+$, 366.1936. $C_{19}H_{24}O_6$ requires $[M{+}NH_4]^+$, 366.1917).

Preparation of (±)-(*E,E*)-2,4-hexadienyl (3-methoxycarbonyl-2-propynyl) *cis*-cyclohexane-1,2-dicarboxylate (10).

Prepared as for **5** starting from *cis*-cyclohexane-1,2-dicarboxylic anhydride, **1** and methyl 3-hydroxy-2-butynoate on a 0.37 mmol scale to give **10** (30%) as a clear, colourless oil; R_f 0.28 (90% ether–petrol); ν_{max} (film) 3023, 3003, 2940, 2859, 2247, 1724, 1436, 1377, 1364, 1338, 1301, 1261, 1218, 1182, 1164, 1127, 1102, 1080, 1030, 990, 960, 750 cm^{-1}; δ_H (300 MHz) 6.18 (1H, dd, J 14.5, 9.5 Hz, H-3"), 5.98 (1H, dd, J 14.5, 9.5 Hz, H-4"), 5.70 (1H, dq, J 16, 6.5 Hz, H-5"), 5.55 (1H, dt, J 13.5, 5.5 Hz, H-2"), 4.77 (1H, d, J 14.5 Hz, H-1'), 4.68 (1H, d, J 14.5 Hz, H-1'), 4.50 (2H, d, J 6.5 Hz, H-1"), 3.72 (3H, s, OCH_3), 2.85 (1H, m, H-1), 2.78 (1H, m, H-2), 2.08-1.83 (2H, m, H-3, H-6), 1.81-1.60 (2H, m, H-3, H-6), 1.74 (3H, s, H-6"), 1.55-1.20 (4H, m, H-4, H-5); δ_C (75.4 MHz) [173.1, 172.6 (C=O)], 153.3 (CO_2Me), [134.8, 131.2, 130.4, 132.6 (C-2", C-3", C-4", C-5")], [81.5, 77.7 (C-2', C-3')], 65.0 (C-1"), [52.8, 51.4 (C-1', OCH_3)], [42.6, 42.4 (C-1, C-2)], [26.3, 25.8 (C-3, C-6)], [23.7, 23.5 (C-4, C-5)], 18.1 (C-6"); *m/z* (EI) 348 $[M]^+$, 251 $[M{-}OCH_2CH{=}CH{-}CH{=}CHCH_3]^+$, 191, 109, 97 $[OCH_2CH{=}CH{-}CH{=}CHCH_3]^+$, 81 $[CH_2CH{=}CH{-}CH{=}CHCH_3]^+$ (Found: $[M]^+$, 348.1565. $C_{19}H_{24}O_6$ requires $[M]^+$, 348.1573).

Preparation of (11).

Prepared as for **5** starting from (2*R*,3*R*)-2,3-bis(benzyloxy)-1,4-butanedioic anhydride,[17] **1** and **2** on a 0.24 mmol scale to give **11** (16%) as a colourless solid; R_f 0.34 (90% ether–petrol); mp 67-68°C; ν_{max} (CH_2Cl_2) 3027, 3008, 2952, 2933, 2915, 2890, 2869, 2852, 1725, 1660, 1455, 1434, 1340, 1320, 1284, 1259, 1197, 1164, 1139, 987, 644 cm^{-1}; δ_H (300 MHz) 7.35-7.30 (10H, m, phenyl), 6.91 (1H, dt, J 15.5, 4.5 Hz, H-2'), 6.26 (1H, dd, J 15, 10.5 Hz, H-3"), 6.05 (1H, d, J 15.5 Hz, H-3'), 6.04 (1H, dd, J 15, 10.5 Hz, H-4"), 5.57 (1H, dq, J 15, 7 Hz, H-5"), 5.59 (1H, dt, J 15, 7.5 Hz, H-2"), 4.83-4.76 (4H, m, H-1", C-2 PhCH_2O, C-3 PhCH_2O), 4.69-

4.62 (2H, m, H-1'), 4.61 (1H, d, J 12 Hz, C-2 PhCH_2O or C-3 PhCH_2O), 4.60 (1H, d, J 12 Hz, C-3 PhCH_2O or C-2 PhCH_2O), 4.45 (1H, d, J 4.5 Hz, H-2 or H-3), 4.40 (1H, d, J 4.5 Hz, H-3 or H-2), 3.76 (3H, s, OCH_3), 1.79 (3H, d, J 6.5 Hz, H-6"); δ_C (75.4 MHz) [168.9, 168.6 (C=O)], 166.1 (CO_2Me), [140.6, 122.1 (C-2', C-3')], [135.3, 131.7, 130.3, 122.9 (C-2", C-3", C-4", C-5")], [128.4, 128.3, 128.1, 128.0, 127.96, 127.94 (phenyl)], [78.7, 78.6 (C-2, C-3)], [73.1, 73.0 (PhCH_2O)], [65.9, 63.2 (C-1', C-1")], 51.7 (OCH_3), 18.2 (C-6"); *m/z* (CI) 526 $[M+NH_4]^+$, 446, 266, 198, 108 (Found: $[M+NH_4]^+$, 526.2429. $C_{29}H_{32}O_8$ requires $[M+NH_4]^+$, 526.2441).

Preparation of (±)-2-furylmethyl (*E*)-3-methoxycarbonyl-2-propenyl *trans*-cyclohexane-1,2-dicarboxylate (12) *Method B.*

Prepared as for **5** starting from **3**, **2** and furfuryl alcohol on a 0.37 mmol scale to give **12** (49%) as a clear, colourless oil; R_f 0.62 (90% ether–petrol); ν_{max} (film) 2940, 2860, 1727, 1667, 1503, 1438, 1380, 1251, 1278, 1229, 1167, 1114, 1036, 997, 967 cm^{-1}; δ_H (300 MHz) 7.41 (1H, br s, H-5"), 6.92 (1H, dt, J 16, 4.5 Hz, H-2'), 6.39 (1H, d, J 3 Hz, H-3"), 6.36 (1H, dd, J 9, 3 Hz, H-4"), 6.04 (1H, dt, J 16, 2 Hz, H-3'), 5.11 (1H, d, J 13 Hz, H-1"), 5.01 (1H, d, J 13 Hz, H-1"), 4.70 (2H, m, H-1'), 3.76 (3H, s, OCH_3), 2.69 (2H, m, H-1, H-2), 2.12-2.09 (2H, m, H-3, H-6), 1.82-1.68 (2H, m, H-3, H-6), 1.40-1.21 (4H, m, H-4, H-5); δ_C (75.4 MHz) [174.4, 174.1 (C=O)], 166.2 (CO_2Me), 149.4 (C-2"), 143.1 (C-5"), 141.4 (C-3'), 121.6 (C-2'), [110.5, 110.4 (C-3", C-4")], 62.5 (C-1'), 58.2 (C-1"), 51.6 (OCH_3), [44.74, 44.71 (C-1, C-2)], [28.9, 28.8 (C-3, C-6)], [25.1, 25.1 (C-4, C-5)]; *m/z* (CI) 368 $[M+NH_4]^+$, 350 $[M]^+$, 241, 161, 154, 99, 81 (Found: $[M+NH_4]^+$, 368.1711. $C_{18}H_{22}O_7$ requires $[M+NH_4]^+$, 368.1710) (Found: C, 61.82; H, 6.06. $C_{18}H_{22}O_7$ requires C, 61.70; H, 6.33%).

Preparation of (±)-2-furylmethyl (*E*)-3-methoxycarbonyl-2-propenyl *cis*-cyclohexane-1,2-dicarboxylate (13) *Method B.*

Prepared as for **5** starting from *cis*-cyclohexane-1,2-dicarboxylic anhydride, **2** and furfuryl alcohol on a 0.37 mmol scale to give **13** (72%) as a clear, colourless oil; R_f 0.54 (90% ether–petrol); ν_{max} (film) 2945, 2859, 1727, 1667, 1503, 1438, 1378, 1363, 1355, 1309, 1279, 1245, 1230, 1173, 1127, 1102, 1078, 1026, 991, 967, 921 cm^{-1}; δ_H (300 MHz) 7.41 (1H, d, J 1.1 Hz, H-5"), 6.92 (1H, dt, J 16, 4.5 Hz, H-2'), 6.39 (1H, d, J 3 Hz, H-3"), 6.35 (1H, dd, J 3, 2 Hz, H-4"), 6.02 (1H, dt, J 16, 2 Hz, H-3'), 5.10 (1H, d, J 13 Hz, H-1"), 5.04 (1H, d, J 13 Hz, H-1"), 4.69 (2H, d, J 4.5 Hz, H-1'), 3.76 (3H, s, OCH_3), 2.94-2.85 (2H, m, H-1, H-2), 2.06-1.99 (2H, m, H-3, H_e-6), 1.85-1.71 (2H, m, H-3, H-6), 1.56-1.38 (4H, m, H-4, H-5); δ_C (75.4 MHz) [173.0, 172.9 (C=O)], 166.4 (CO_2Me), 149.5 (C-2"), 143.1 (C-5"), 141.5 (C-3'), 121.6 (C-2'), [110.5, 110.4 (C-3", C-4")], 62.5 (C-1'), 58.03 (C-1"), 51.6 (OCH_3), [42.6, 42.5 (C-1, C-2)], [26.3, 26.0 (C-3, C-6)], [23.7, 23.4 (C-4, C-5)]; *m/z* (CI) 368 $[M+NH_4]^+$, 351 $[M+H]^+$, 241, 161, 99, 81 (Found: $[M+NH_4]^+$, 368.1712; $C_{18}H_{22}O_7$ requires $[M+NH_4]^+$, 368.1709) (Found: C, 61.12; H, 5.97. $C_{18}H_{22}O_7$ requires C, 61.70; H, 6.33%).

Preparation of (±)-2-furylmethyl 3-methoxycarbonyl-2-propynyl *trans*-cyclohexane-1,2-dicarboxylate (14) *Method B.*

Prepared as for **5** starting from **3**, methyl 3-hydroxy-2-butynoate and furfuryl alcohol on a 0.75 mmol scale to give **14** (28%) as a clear, colourless oil; R_f 0.61 (90% ether–petrol); ν_{max} (film) 3150, 3124, 2940, 2861, 2248, 1726, 1503, 1436, 1373, 1318, 1253, 1162, 1113, 1080, 1066, 1038, 1015, 996 cm^{-1}; δ_H (270 MHz) 7.41 (1H, d, J 1.5 Hz, H-5"), 6.39 (1H, d, J 3 Hz, H-3'), 6.36 (1H, dd, J 9, 3 Hz, H-4'), 5.11 (1H, d, 13 Hz, H-1'), 5.01 (1H, d, J 13 Hz, H-1'), 4.80 (1H, d, J 16.5 Hz, H-1'), 4.67 (1H, d, J 16.5 Hz, H-1'), 3.78 (3H, s, OCH_3), 2.71-2.58 (2H, m, H-1, H-2), 2.15-2.06 (2H, m, H-3, H-6), 1.84-1.73 (2H, m, H-3, H-6), 1.45-1.20 (4H, m, H-4, H-5); δ_C (75.4 MHz) [174.1, 173.8 (C=O)], 153.3 (CO_2Me), 149.4 (C-2"), 143.2 (C-5"), [110.5, 110.3 (C-3", C-4")], [81.2, 77.7 (C-2', C-3')], 58.2 (C-1"), [52.8, 51.4 (C-1', OCH_3)], [44.6, 44.5 (C-1, C-2)], [28.7, 28.6 (C-3, C-6)], [25.0, 24.9 (C-4, C-5)]; *m/z* (CI) 366 $[M+NH_4]^+$, 348 $[M]^+$, 241, 195, 161, 98, 81 (Found: $[M+NH_4]^+$, 366.1575. $C_{18}H_{20}O_7$ requires $[M+NH_4]^+$, 366.1553) (Found: C, 62.10; H, 5.79. $C_{18}H_{20}O_7$ requires C, 61.88; H, 5.79%).

Preparation of (±)-2-furylmethyl 3-methoxycarbonyl-2-propynyl-*cis*-cyclohexane-1,2-dicarboxylate (15)
Method B.

Prepared as for **5** starting from *cis*-cyclohexane-1,2-dicarboxylic anhydride, methyl 3-hydroxy-2-butynoate and furfuryl alcohol on a 0.75 mmol scale to give **15** (26%) as a clear, colourless oil; R_f 0.61 (90% ether–petrol); ν_{max} (film) 2943, 2859, 2249, 1722, 1449, 1436, 1371, 1339, 1263, 1163, 1129, 1101, 1079, 1031, 992 cm^{-1}; δ_H (300 MHz) 7.43 (1H, s, H-5''), 6.42 (1H, d, J 3 Hz, H-3''), 6.37 (1H, dd, J 3.5, 2 Hz, H-4''), 5.09 (2H, d, J 4 Hz, H-1''), 4.78 (1H, d, J 16.5 Hz, H-1'), 4.69 (1H, d, J 16.5 Hz, H-1'), 3.80 (3H, s, OCH_3), 2.95-2.84 (2H, m, H-1, H-2), 2.16-1.94 (2H, m, H-3,H-6), 1.83-1.77 (2H, m, H-3, H-6), 1.52-1.49 (4H, H-4, H-5); δ_C (75.4 MHz) [172.9, 172.6 (C=O)], 153.3 (CO_2Me), 149.5 (C-2''), 143.2 (C-5''), [110.5, 110.4 (C-3'', C-4'')], [81.5, 77.6 (C-2', C-3')], 58.2 (OCH_3), [52.9, 51.4 (C-1', C-1'')], [42.5, 42.4 (C-1, C-2)], [26.2, 25.9 (C-3, C-6)], [23.7, 23.4 (C-4, C-5)]; *m/z* (CI) 366 $[M+NH_4]^+$, 349 $[M+H]^+$, 300, 270, 195, 98, 81 (Found: $[M+NH_4]^+$, 366.1573; $C_{18}H_{20}O_7$ requires $[M+NH_4]^+$, 366.1553) (Found: C, 62.55: H, 5.77. $C_{18}H_{20}O_7$ requires C, 61.88; H, 6.06%).

Preparation of (17).

A solution of **1** (640 mg, 6.52 mmol), **3** (1 g, 6.52 mmol) and diisopropylamine (0.92 ml, 7.1 mmol) in CH_2Cl_2 (10 ml) was heated under reflux for 2 h. The solution was cooled to -10°C and isobutyl chloroformate (0.94 ml, 7.2 mmol) was added. The solution was allowed to warm to rt over a period of 1 h. The ammonium salt was removed by filtration, rinsing with tetrahydrofuran. The filtrate was cooled to -20°C and sodium borohydride (360 mg, 9 mmol) in water (1 ml) was added dropwise to the vigorously stirred solution. The reaction was warmed to rt over 1 h and was then stirred for a further 1 h. The mixture was filtered through $MgSO_4$, rinsing with ether and the combined filtrate and washings concentrated under reduced pressure. Chromatography of the residue (16% EtOAc–hexane) gave **17** (1.066 g, 69%) as a colourless oil; ν_{max} (film) 3485, 1730 cm-1; δ_H (300 MHz, $CDCl_3$) 6.26 (1H, dd, J 15, 10.5 Hz, H-3'), 6.05 (1H, dd, J 15, 10.5 Hz, H-4'), 5.75 (1H, m, H-5'), 5.65 (1H, dt, J 15, 6.5 Hz, H-2'), 4.58 (2H, d, J 6.5 Hz, 2 x H-1'), 3.50 (2H, m, CH_2OH), 1.77 (3H, d, J 6.5 Hz, 6'-Me); δ_C (75.4 MHz) 176.1 (CO_2R), 135.0 (C-3'), 131.3 (C-5'), 130.4 (C-4'), 123.6 (C-2'), 66.7 (CH_2OH), 64.8 (C-1''), 46.5 (C-1), 39.5 (C-2), 32.0 (C-6), 29.7 (C-3), 25.3 (C-4), 25.2 (C-5), 18.1 (C-6') (Found: $[M+NH_4]^+$, 256.1913. $C_{14}H_{22}O_4$ requires $[M+NH_4]^+$, 256.1902).

Preparation of (19).

To a solution of **17** (204 mg, 0.86 mmol) in CH_2Cl_2 (2 ml) was added acryloyl chloride (0.9 ml, 1.1 mmol) and triethylamine (0.12 ml, 0.86 mmol) and the mixture stirred at 20°C for 0.5 h. The mixture was filtered, rinsing with ether and the combined filtrate and washings concentrated under reduced pressure. Chromatography of the residue (9% ether–petrol) gave **19** (185 mg, 87%) as an oil; ν_{max} (film) 1728 cm^{-1}; δ_H (400 MHz) 6.38 (1H, dd, J 17.5 and 1.5 Hz, H-3''), 6.22 (1H, dd, J 15, 10.5 Hz, H-3'), 6.10 (1H, dd, J 17.5, 10.5 Hz, H-2''), 6.04 (1H, ddd, J 15, 10.5, 1.5 Hz, H-4'), 5.80 (1H, dd, J 10.5, 1.5 Hz, H-3''), 5.75 (1H, m, H-5'), 5.65 (1H, td, J 15, 6.5 Hz, H-2'), 4.56 (2H, m, H-1'), 4.05 (1H, dd, J 11, 5.5 Hz, H-1''), 4.02 (1H, dd, J 11, 5 Hz, H-1''), 2.20 (1H, td, J 11.5, 3.5 Hz, 1-H), 1.77 (3H, d, J 7 Hz, H-6'); δ_C (100.6 MHz) 175.2 (C=O), 166.1 (C=O), 134.8 ($CH=CH_2$), 131.2 ($CH=CH_2$), 130.7 (C-3'), 130.4 (C-4'), 128.4 (C-2'), 123.6 (C-5'), 67.6 (CH_2O), 64.8 (CH_2O), 46.4 (C-1), 38.3 (C-2), 29.8 (C-6), 28.5 (C-3), 25.2 (C-4), 25.0 (C-5), 18.1 (C-6') (Found: $[M+NH_4]^+$, 310.2175. $C_{17}H_{24}O_4$ requires $[M+NH_4]^+$, 310.2167).

Preparation of (20).

Prepared as for **19** starting from **17** and *trans*-crotonyl chloride on a 0.42 mmol scale to give **20** (40%) as a colourless oil; ν_{max} (film) 1730 cm^{-1}; δ_H (400 MHz) 6.95 (1H, dq, J 15.5, 7 Hz, H-5''), 6.22 (1H, dd, J 15, 10.5 Hz, H-3'), 6.03 (1H, ddd, J 15, 10.5, 1.5 Hz, H-4'), 5.82 (1H, dq, J 15.5, 1.5 Hz, H-4''), 5.74 (1H, m, H-5'), 5.57 (1H, td, J 15, 6.5 Hz, H-2'), 4.55 (2H, m, H-1'), 4.02 (1H, dd, J 11, 6 Hz, H-1''), 3.98 (1H, dd, J 11, 5

Hz, H-1"), 2.20 (1H, td, J 11.5, 3.5 Hz, H-1), 1.10 (1H, qd, J 11, 3.5 Hz, H-3), 1.85 (3H, dd, J 7, 1.5 Hz, H-6"), 1.77 (3H, d, J 6.5 Hz, H-6'), 1.45 (1H, qd, J 11, 3.5 Hz, H-6); δ_C (100.6 MHz) 175.2 (C=O), 166.4 (C=O), 144.7 (COCH=*C*H), 134.8 (C-3'), 131.1 (C-4'), 130.4 (C-2'), 123.6 (C-5'), 122.5 (CO*C*H=CH), 67.2 (C-1"), 64.8 (C-1'), 46.4 (C-1), 38.4 (C-2), 29.8 (C-3), 28.5 (C-6), 25.2 (C-4), 25.0 (C-5), 18.1 (dienophile CH_3), 18.0 (diene CH_3) (Found: $[M+NH_4]^+$, 324.2166. $C_{18}H_{26}O_4$ requires $[M+NH_4]^+$, 324.2174).

Preparation of (21).

Prepared as for **19** starting from **17** and methacryloyl chloride on a 0.42 mmol scale to give **21** (59%); ν_{max} (film) 1729 cm^{-1}; δ_H (400 MHz) 6.26 (1H, dq, J 2.5, 1 Hz, H-5"), 6.24 (1H, dd, J 15, 10.5 Hz, H-3'), 6.05 (1H, ddd, J 15, 10.5, 1.5 Hz, H-4'), 5.82 (1H, dq, J 2.5, 1.5 Hz, H-5"), 5.72 (1H, m, H-5'), 5.60 (1H, td, J 15, 6.5 Hz, H-2'), 4.56 (2H, m, H-1'), 4.02 (2H, d, J 5.5 Hz, H-1"), 2.22 (1H, td, J 11.5, 3.5 Hz, H-1), 1.93 (3H, t, J 1.5 Hz, H-5"), 1.77 (3H, d, J 6.5 Hz, H-6'), 1.12 (1H, qd, J 11, 3.5 Hz, H-3), 1.50 (1H, qd, J 11, 3.5 Hz, H-6); δ_C (100.6 MHz) 175.2 (C=O), 163.0 (C=O), 134.8 (C-5"), 131.1 (C-4"), 130.4 (C-3'), [129.0, 125.5 (C-4' and C-2')], 123.6 (C-5'), 67.7 (C-1"), 64.8 (C-1'), 46.4 (C-1), 38.4 (C-2), 29.8 (C-3), 28.7 (C-6), 25.9 (C-4), 25.2 (C-5), 18.3 (COCH*Me*), 18.1 (C-6'); *m/z* (CI) 324 $[M+NH_4]^+$.

Preparation of (22).

To a solution of the alcohol **17** (130 mg, 0.54 mmol) in CH_2Cl_2 (2 ml) under nitrogen was added DCC (150 mg, 0.73 mmol) and DMAP (10 mg, 0.05 mmol). Propiolic acid (0.05 ml, 0.59 mmol) was added dropwise and the solution was stirred for 1 h. The mixture was filtered, rinsing with ether and the combined filtrate and washings concentrated under reduced pressure. Chromatography of the residue (5% EtOAc–petrol) gave **22** (97 mg, 60%); ν_{max} (film) 1719 cm^{-1}; δ_H (270 MHz) 6.25 (1H, dd, J 15, 10.5 Hz, H-3'), 6.04 (1H, ddd, J 15, 10.5, 1.5 Hz, H-4'), 5.74 (1H, m, H-5'), 5.62 (1H, td, J 15, 6.5 Hz, H-2'), 4.59 (2H, d, J 6.7 Hz, H-1'), 4.10 (1H, dd, J 11, 5.5 Hz, H-1"), 4.01 (1H, dd, J 11, 5 Hz, H-1"), 2.87 (1H, s, COCCH), 2.20 (1H, td, J 11.5, 3.5 Hz, H-1), 1.77 (3H, d, J 7 Hz, H-6'); δ_C (100.6 MHz) 174.9 (C=O), 152.6 (C=O), 135.0 (C-3'), 131.1 (C-4'), 130.5 (C-2'), 123.7 (C-5'), [74.6, 74.7 (C-4" and C-5")], 69.2 (C-1"), 65.0 (C-1'), 46.2 (C-1), 38.2 (C-2), 29.7 (C-6), 28.4 (C-3), 25.2 (C-4), 25.0 (C-5), 18.0 (C-6') (Found: $[M+NH_4]^+$, 308.1857. $C_{17}H_{22}O_4$ requires $[M+NH_4]^+$, 308.1861).

Preparation of (23).

Prepared as for **22** starting from **17** and ethyl fumarate on a 1.9 mmol scale to give **23** (81%) as a colourless oil; ν_{max} (film) 1719 cm^{-1}; δ_H (500 MHz) 6.82 (2H, s, *COCHCH*), 6.23 (1H, dd, J 15, 10.5 Hz, H-3'), 6.03 (1H, ddd, J 15, 10.5 and 1.5 Hz, H-4'), 5.75 (1H, m, H-5'), 5.58 (1H, td, J 15, 6.5 Hz, H-2'), 4.60 (2H, m, H-1'), 4.25 (2H, q, J 7 Hz, OCH_2CH_3), 4.10 (1H, dd, J 11, 5.5 Hz, H-1"), 4.05 (1H, dd, J 11, 5 Hz, H-1"), 2.21 (1H, td, J 11.5, 3.5 Hz, H-1), 2.01 (1H, m, 2-H), 1.95 (1H, m, H-6), 1.83 (3H, m, H-4 and H-3), 1.75 (3H, d, J 6.5 Hz, H-6'), 1.50 (1H, qd, J 11, 3.5 Hz, H-6), 1.32 (3H, t, J 7.0 Hz, OCH_2CH_3), 1.30 (2H, m, H-5), 1.13 (1H, qd, J 11, 3.5 Hz, H-3); δ_C (100.6 MHz) 175.2 (C=O), 165.0 (C=O), 164.8 (C=O), [135.0 and 133.8 (C-4" and C-5")], and 133.3 (C-3'), 131.2 (C-4'), 130.5 (C-2'), 123.6 (C-5'), 68.3 (OCH_2CH_3), 64.9 (C-1'), 61.3 (C-1"), 46.2 (C-1), 38.3 (C-2), 29.8 (C-6), 28.6 (C-3), 25.2 (C-4), 25.1 (C-5), 18.1 (=CH*C*H$_3$), 14.1 (OCH_2CH_3) (Found: $[M+NH_4]^+$, 382.2226. $C_{20}H_{28}O_6$ requires $[M+NH_4]^+$, 382.2230).

IMDA Reaction of (5).

A solution of **5** (880 mg, 2.51 mmol) in toluene (75 ml) was degassed by passing nitrogen through for 5 min followed by sonication for 5 min. The process was repeated 3 times. The solution was transferred to an autoclave and heated at 180°C for 100 h. Removal of the solvent under reduced pressure and purification of the residue by chromatography (50% ether–petrol) afforded a mixture of **24** and **25** (7:1 by ^1H nmr; 572 mg, 65%). Recrystallization (ether–petrol) afforded a pure sample of **24**; R_f 0.40 (50% ether–petrol); mp 123-

124°C; ν_{max} (CH_2Cl_2) 2940, 2863, 1735, 1448, 1359, 1326, 1297, 1250, 1203, 1182, 1118, 1013, 917, 735 cm^{-1}; δ_H (500 MHz) 5.63 (1H, d, J 11 Hz, H-6), 5.59 (1H, ddd, J 11, 5, 2.5 Hz, H-7), 4.42 (1H, dd, J 12, 1.5 Hz, H-11), 4.16 (1H, dd, J 13, 10.5 Hz, H-4), 3.84 (1H, dd, J 12, 5 Hz, H-11), 3.74 (3H, s, OCH_3), 3.54 (1H, dd, J 13, 11 Hz, H-4), 3.15-3.09 (1H, m, H-5), 2.57-2.47 (2H, m, H-8, H-10), 2.40 (1H, dt, J 12.5, 4 Hz, H-1), 2.29 (1H, dt, J 12.5, 4 Hz, H-14), 2.00 (1H, dd, J 12.5, 9 Hz, H-9), 1.92-1.85 (2H, m, H-15, H-18), 1.83-1.76 (2H, m, H-15, H-18), 1.74-1.59 (2H, m, H-16, H-17), 1.30-1.22 (2H, m, H-16, H-17), 0.96 (3H, d, J 7 Hz, C-8 CH_3); ***m/z*** (CI) 368 $[M+NH_4]^+$, 351 $[M+H]^+$, 119, 107, 91, 81 (Found: C, 64.47; H, 8.63. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%).

Hydrolysis–lactonisation of cycloadduct (24).

To a solution of $LiOH{\cdot}H_2O$ (90 mg, 2.14 mmol, 15 equiv) in H_2O (290 µl) was added cycloadduct **24** (50 mg, 0.14 mmol, 1.0 equiv) in MeOH (860 µl) and THF (290 µl) *via* cannula. The solution was stirred at rt for 1 h, acidified with 1M HCl and partitioned between ether (2 ml) and brine (2 ml). The aqueous layer was extracted with ether (5 x 2 ml), the combined organic layers dried ($MgSO_4$) and the solvents removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.5 ml) and TFA (*ca.* 10 µl) was added. The solution was stirred at rt for 1 h and then partitioned between ether (2 ml) and H_2O (2 ml). The aqueous layer was extracted with ether (3 x 2 ml) and the combined organic fractions dried ($MgSO_4$). The solution was filtered and the solvents removed under reduced pressure. Purification by chromatography (90% ether–petrol) afforded the hydroxylactone **26** (22 mg, 85%) as a colourless crystalline solid, mp 77-78°C (lit.[5] mp 78-81°C; all other data were in accord with published data.[5]

IMDA Reaction of (7).

A solution of **7** (938 mg, 2.68 mmol) in toluene (75 ml) degassed as described above was heated at 180°C for 200 h. The solvent was removed under reduced pressure and the residue purified by chromatography (25% ether–petrol) to give a mixture **27** and **28** (1:1 by ^1H nmr; 751 mg, 80%). Further chromatography effected separation of the two cycloadducts; **27**: R_f 0.41 (50% ether–petrol); mp 127-128°C; ν_{max} (CH_2Cl_2) 2953, 2934, 1733, 1448, 1282, 1261, 1228, 1191, 1167, 1130, 1024, 1007 cm^{-1}; δ_H (500 MHz) 5.62 (1H, d, J 9 Hz, H-6), 5.58 (1H, ddd, J 9, 5, 2 Hz, H-7), 4.33-4.25 (1H, br m, H-4), 4.01-3.95 (2H, m, H-11), 3.72 (3H, s, OCH_3), 3.66-3.60 (1H, m, H-4), 3.13-3.06 (1H, m, H-5), 2.97-2.93 (1H, m, H-14), 2.70-2.64 (1H, m, H-1), 2.56-2.43 (2H, br m, H-8, H-10), 2.16-2.04 (2H, br m, H-9, H-15), 1.97-1.91 (1H, br m, H-18), 1.85-1.79 (1H, br m, H-15), 1.70-1.62 (3H, br m, H-16, H-17, H-18), 1.51-1.42 (2H, br m, H-16, H-17), 0.97 (3H, d, J 7.5 Hz, C-8 CH_3); *m/z* (CI) 368 $[M+NH_4]^+$, 351 $[M+H]^+$, 197, 178, 119, 81 (Found: $[M+NH_4]^+$, 368.4319. $C_{19}H_{26}O_6$ requires $[M+NH_4]^+$, 368.4323) (Found: C, 65.42; H, 7.43. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%); **28**: R_f 0.35 (50% ether–petrol); mp 154°C; ν_{max} (CH_2Cl_2) 3021, 2949, 2870, 1737, 1728, 1653, 1448, 1389, 1374, 1341, 1280, 1264, 1231, 1192, 1165, 1129, 1090, 1060, 1026, 999 cm^{-1}; δ_H (500 MHz) 5.63 (1H, dd, J 9.5, 1.5 Hz, H-6), 5.60 (1H, ddd, J 9.5, 5, 2 Hz, H-7), 4.46-4.38 (1H, m, H-4), 4.22 (1H, dd, J 13, 11.5 Hz, H-11), 3.85 (1H, dd, J 11.5, 5 Hz, H-11), 3.74 (3H, s, OCH_3), 3.60-3.50 (1H, br m, H-4), 2.97-2.90 (2H, br m, H-5, H-14), 2.70 (1H, br m, H-1), 2.61-2.48 (2H, br m, H-8, H-10), 2.08-1.97 (3H, m, H-9, H-15, H-18), 1.85-1.73 (2H, H-15, H-18), 1.66-1.42 (4H, m, H-16, H-17), 0.97 (3H, d, J 7.5 Hz, C-8 CH_3); *m/z* (CI) 368 $[M+NH_4]^+$, 351 $[M+H]^+$, 280, 244, 210, 182, 165 (Found: $[M+H]^+$, 351.4243. $C_{19}H_{26}O_6$ requires $[M+H]^+$, 351.4231) (Found: C, 65.29; H, 7.28. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%).

IMDA Reaction of (14).

A solution of dienyne **14** (5 mg, 0.01 mmol) in d_8-toluene (0.72 ml) degassed as described above was transferred to a silylated nmr tube and the tube sealed by flame. The tube was heated at 180°C for 133 h. The tube was found to be under a slight positive pressure when the it was opened. The solvent was removed under reduced pressure to yield a pale yellow oil (4.5 mg). Purification of this residue by chromatography (20%

ether–petrol) afforded the cycloadduct **29** (3.61 mg, 80%) as a clear, colourless oil, and a trace amount of the cycloadduct **30**; **29**: R_f 0.50 (50% ether–petrol); δ_H (300 MHz) 7.92 (1H, s, H-7), 5.97 (1H, d, J 14.5 Hz, H-4), 5.66 (1H, d, J 14 Hz, H-10), 4.94 (1H, d, J 14.5 Hz, H-4), 4.73 (1H, d, J 14 Hz, H-10), 3.84 (3H, s, OCH_3), 2.43-2.39 (2H, m, H-1, H-13), 1.97-1.92 (2H, m, H-14, H-17), 1.84-1.82 (2H, m, H-14, H-17), 1.32-1.23 (4H, m, H-15, H-16); *m/z* (CI) 340 $[M+NH_4]^+$, 323 $[M+H]^+$, 186, 168, 153, 81; **30**: *m/z* (CI) (Found: $[M+NH_4]^+$, 366.1590; $C_{18}H_{21}O_7$ requires $[M+NH_4]^+$, 366.1553).

IMDA Reaction of (8) and hydrolysis–cyclisation of the cycloadducts.

A solution of **8** (15 mg, 0.05 mmol) in d_8-toluene (2 ml) degassed as described above was heated in a silylated, flame-sealed nmr tube at 180°C for 266 h. The toluene was removed under reduced pressure to yield a pale yellow oil (14 mg). This was shown by ^{1}H nmr to contain **8, 31** and a small quantity of a second cycloadduct; **31**: R_f 0.59 (90% ether–petrol); δ_H (300 MHz) 5.57-5.48 (2H, m, H-6, H-7), 4.58 (1H, dd, J 13.5, 2.0 Hz, H-11), 4.04 (1H, t, J 12.5 Hz, H-4), 3.90 (1H, dd, J 12.5, 6.0 Hz, H-4), 3.68 (3H, s, OCH_3), 3.57 (1H, t, J 12.5 Hz, H-11), 2.98-2.89 (1H, m, H-5), 2.68-2.40 (6H, m, H-1, H-8, H-10, H-14), 2.00 (1H, dd, J 13.5, 12.0 Hz, H-9), 0.90 (3H, d, J 7.5 Hz, C-8 CH_3). To a solution of $LiOH{\cdot}H_2O$ (29 mg, 0.70 mmol, 15 equiv) in H_2O (94 µl) was added the crude IMDA reaction product (14 mg, 0.05 mmol, 1.0 equiv) in MeOH (282 µl) and THF (94 µl) *via* syringe. The solution was stirred at rt for 1 h, acidified with 1M HCl and then partitioned between ether (1 ml) and brine (1 ml). The aqueous layer was extracted with ether (5 x 1 ml) and the combined organic fractions were dried ($MgSO_4$). The solution was filtered and the solvents removed under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (470 µl) and TFA (*ca.* 10 µl) was added. The solution was stirred for 1 h at rt and partitioned between ether (1 ml) and H_2O (1 ml). The aqueous layer was extracted with ether (3 x 1 ml) and the combined ethereal fractions dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography (90% ether–petrol) afforded a mixture (*ca.* 6:1 by ^{1}H nmr) of hydroxylactone **26** and a second hydroxylactone, as a colourless crystalline solid. The second hydroxylactone had the following physical and spectroscopic characteristics: R_f (0.13) (90% ether–petrol); δ_H (500 MHz) 5.83 (1H, ddd, J 9.5, 5, 3 Hz), 5.47 (1H, dt, J 9.5, 2 Hz), 4.46 (1H, dd, J 9, 7 Hz), 4.17 (1H, dd, J 11.5, 9 Hz), 3.88-3.82 (1H, m), 3.69-3.63 (1H, m), 2.64-2.59 (1H, m), 2.55-2.50 (1H, m, H-4), 2.42-2.36 (1H, m, H-5), 2.33 (1H, dd, J 13.5, 9.5 Hz), 1.41 (1H, br s), 1.01 (3H, d, J 7 Hz).

IMDA Reaction of (11).

A solution of **11** (5 mg, 0.010 mmol) in d_8-toluene (0.5 ml) degassed as described above was heated in a silylated, flame-sealed nmr tube at 180°C for170 h. The toluene was removed under reduced pressure to yield a pale yellow oil (4.8 mg). Analysis of the crude product by ^{1}H nmr indicated the presence of a mixture of two cycloadducts (3:1): the major product was assigned structure **33**: R_f 0.26 (50% ether–petrol); δ_H (500 MHz) 7.47-7.28 (10H, m, Ar), 5.64 (1H, dd, J 10, 2.5 Hz, H-7), 5.55 (1h, ddd, J 10, 5, 2.5 Hz, H-6), 4.79-4.73 (4H, m, H-4, H-11, 2 x PhCH_2), [4.58 (1H, d, J 11 Hz), 4.46 (1H, d, J 11 Hz) (H-1 and H-8)], [4.34, 4.30 (both 1H, d, J 3 Hz, H-1 and H-14)], 4.33-4.28 (2H, m, 2 x PhCH_2), 3.99 (1H, dd, J 10.5, 10 Hz, H-9), 3.73 (3H, s, CO_2CH_3), 3.05-2.95 (1H, m, H-5), [2.58-2.52 (1H, m), 2.49-2.43 (1H, m) (H-8 and H-10), 1.02 (3H, d, J 7 Hz, C-8 CH_3). Data for the minor product: δ_H (500 MHz) *inter alia* 3.74 (3H, s, CO_2CH_3), 1.00 (3H, d, J 7 Hz, C-8 CH_3).

IMDA Reaction of (19) and hydrolysis–cyclisation of the cycloadducts.

A solution of **19** (150 mg, 0.5 mmol) in toluene (5 ml) degassed as described above was heated at 170°C for 24 h in a resealable glass tube. The solvent was removed under reduced pressure and the residue chromatographed (23% ether–petrol) to yield an inseparable mixture of cycloadducts **34** and **35** (2:1 by ^{1}H nmr; 130 mg, 87%). The crude product was dissolved in a mixture of methanol (3.2 ml) and THF (2 ml) and a solution of $LiOH{\cdot}H_2O$ (280 mg, 7 mmol) in water (2.8 ml) was added. The solution was stirred at 20°C for 1 h

and acidified with HCl (2M). The mixture was partitioned between brine (10 ml) and ether (10 ml) and the aqueous phase extracted with ether. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 ml), *p*-toluenesulfonic acid (70 mg, 0.26 mmol) added, and the mixture heated under reflux for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (23% ether–petrol) to give firstly **41** (30 mg, 43%) as a colourless solid, mp 66-68°C (hexane); ν_{max} (film) 1778 cm^{-1}; δ_H (500 MHz) 5.75 (1H, dt, J 10, 1.5 Hz, H-5), 5.68 (1H, dt, J 10, 2.5 Hz, H-4), 4.46 (1H, dd, J 11.5, 7 Hz, H-7), 3.87 (1H, dd, J 11.5, 8 Hz, H-7), 2.75 (1H, m, H-1), 2.56 (1H, m, H-6), 2.23 (1H, td, J 12.5, 3 Hz, H-3), 1.95 (1H, td, J 12.5, 3 Hz, H-2), 1.83 (1H, dd, J 13, 3 Hz, H-2), 1.08 (3H, d, J 7.5 Hz, Me) (Found: $[M+NH_4]^+$, 170.1185. $C_9H_{12}O_2$ requires $[M+NH_4]^+$, 170.1181) (Found: C, 71.1; H, 7.5. $C_9H_{12}O_2$ requires C, 71.0; H, 7.8%); this was followed by **18** and **42** (2:1 ratio by ^1H nmr); data for the mixture: ν_{max} (film) 1779 cm^{-1}; **42**: δ_H (500 MHz) 5.75 (1H, m, J 10 Hz, H-5), 5.56 (1H, ddd, J 10, 4 , 2.5 Hz, H-4), 4.46 (1H, t, J 8.5 Hz, H-7), 3.87 (1H, t, J 8.5 Hz, H-7), 2.68 (1H, m, H-1), 2.56 (1H, m, H-6), 2.25 (1H, m, H-3), 1.95 (2H, m, H-2), 1.08 (3H, d, J 7.5 Hz, Me).

IMDA Reaction of (20).

A solution of **20** (30 mg, 0.1 mmol) in d_8-toluene (1 ml) degassed as described above was heated in a silylated, flame-sealed nmr tube at 160°C for 72 h. The solvent was removed under reduced pressure and the residue chromatographed (23% ether–petrol) to give a mixture of two cycloadducts (1:1 by ^1H nmr; 20 mg); data for the mixture: ν_{max} (film) 1730 cm^{-1}; *m/z* (CI) 324 $[M+NH_4]^+$; **36**: δ_H (400 MHz) *inter alia* 5.65 (1H, br d, J 10 Hz, CH=C*H*), 5.55 (1H, ddd, J 10, 5, 2.5 Hz, C*H*=CH), 4.25-3.95 (4H, m, 2 x CH_2O), 3.20 (1H, m, H-5), 1.12 (3H, d, J 7 Hz, Me), 1.10 (3H, d, J 6.5 Hz, Me); **37**: δ_H (400 MHz) *inter alia* 5.82 (1H, ddd, J 10, 5, 2.5 Hz, H-7), 5.26 (1H, dq, J 10, 2.5 Hz, H-6), 4.53 (1H, t, J 11 Hz, CH_2O), 4.43 (1H, dd, J 11.5, 4 Hz, CH_2O), 3.82 (1H, dd, J 11 and 4 Hz, CH_2O), 3.63 (1H, t, J 11 Hz, CH_2O), 2.90 (1H, m, H-5), 2.20 (1H, m, H-8), 2.05 (1H, dd, J 11, 6 Hz, H-10), 2.03 (1H, m, H-9), 0.92 (3H, d, J 7 Hz, Me), 0.90 (3H, d, J 7 Hz, Me).

IMDA Reaction of (22).

A solution of **22** (61 mg, 0.2 mmol) in toluene (2 ml) degassed as described above was heated at 150°C for 24 h. The solution was cooled and the solvent removed under reduced pressure to yield an inseparable mixture of cycloadducts (1:1 by ^1H nmr; 61 mg, 100%); ν_{max} (film) 1722 cm^{-1}; δ_H (270 MHz) *inter alia* 6.95 (1H, dd, J 4.5, 1.5 Hz, H-9 isomer A), 6.90 (1H, dd, J 4.5, 1.5 Hz, H-9 isomer B), 5.60-6.00 (4H, m, H-6, H-7 both isomers), 3.80-3.70 (2H, m, H-8 both isomers), 3.00-2.70 (2H, m, H-5 both isomers), 0.86 (3H, d, J 6.5 Hz, Me one isomer); *m/z* (CI) 308 ($[M+NH_4]^+$.

IMDA Reaction of (23).

A solution of **23** (560 mg, 1.5 mmol) in toluene (2 ml) degassed as described above was heated at 80°C for 24 h. The solution was cooled and the solvent removed was under reduced pressure to yield a mixture of **38** and **39** (2:1 by ^1H nmr; 520 mg, 90%). A portion was subjected to chromatography (16% ether–hexane) followed by HPLC (Vydac C_{18} 25 cm x 20 mm column, UV detection @ 230 nm, mobile phase: 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B); gradient elution, using 77% solvent B→pure solvent B; flow rate 5 ml min^{-1}) to give **38** (60%) and **39** (27%); **38**: ν_{max} (film) 1735 cm^{-1}; δ_H (400 MHz) *inter alia* 5.61 (1H, dt, J 10, 1.5 Hz, H-6), 5.56 (1H, ddd, J 10, 5, 2.5 Hz, H-7), 4.46 (1H, dd, J 11, 3.5 Hz, H-4), 4.42 (1H, dd, J 11, 3.5 Hz, H-13), 4.26-4.16 (2H, m, CH_2CH_3), 3.54 (1H, t, J 11.5 Hz, H-4), 3.42 (1H, m, H-5), 3.05 (1H, dd, J 12, 5 Hz, H-9), 2.45 (1H, dd, J 12, 10.5 Hz, H-10), 2.42 (1H, m, $CHCH_3$), 2.05 (1H, td, J 11, 3.5 Hz, H-1), 1.30 (3H, t, J 7 Hz, CH_2CH_3), 1.10 (3H, d, J 6.5 Hz, $CHCH_3$); δ_C (100.6 MHz) [176.1, 175.5, 173.0 (C=O)], 135.0 (CH=*C*H), 123.2 (*C*H=CH), 69.8 (OCH_2CH), 63.8 (OCH_2CH), 60.6 (CH_2CH_3), 49.7 (C-1), 44.3 (C-9), 43.2 (C-10), 35.7 (C-14), 35.3 (C-8), 33.7 (C-5), [29.9, 27.2, 25.5, 24.8 (cyclohexane CH_2)], 19.6 ($CHCH_3$), 14.2 (CH_2CH_3) (Found: $[M+NH_4]^+$, 382.2212; $C_{20}H_{32}O_6$ requires $[M+NH_4]^+$, 382.2203) (Found:

C, 65.81; H, 7.8. $C_{20}H_{28}O_6$ requires C, 65.9; H, 7.7%): **39**: mp 118-120°C (CH_2Cl_2–ether); ν_{max} (film) 1736 cm^{-1}; δ_H (500 MHz) *inter alia* 5.60 (1H, dt, J 10, 1.5 Hz, H-7), 5.56 (1H, ddd, J 10, 5 , 2.5 Hz, H-6), 4.67 (1H, t, J 11 Hz, H-13), 4.38 (1H, dd, J 11, 3 Hz, H-4), 4.06-4.17 (2H, m, CH_2CH_3), 3.60 (1H, dd, J 11, 3 Hz, H-13), 3.55 (1H, t, J 11 Hz, H-4), 3.45 (1H, m, H-5), 3.00 (1H, dd, J 12, 5 Hz, H-10), 2.50 (1H, dd, J 12, 11.5 Hz, H-9), 2.38 (1H, m, $CHCH_3$), 1.28 (3H, t, J 7 Hz, CH_2CH_3), 1.08 (3H, d, J 6.5 Hz, $CHCH_3$); δ_C (100.6 MHz) [175.9, 175.5, 173.0 (C=O)], 135.0 (CH=CH), 123.2 (CH=CH), 67.9 (OCH_2CH), 63.7 (OCH_2CH), 60.6 (CH_2CH_3), 47.7 (C-1), 44.3 (C-9), 43.4 (C-10), 39.8 (C-14), 35.2 (C-8), 33.7 (C-5), [29.7, 28.3, 24.8, 24.6 (cyclohexane CH_2)], 19.6 ($CHCH_3$), 14.2 (CH_2CH_3), (Found: $[M+H]^+$, 365.1964. $C_{20}H_{28}O_6$ requires $[M+H]^+$, 365.1953).

Preparation of *t*-butyldiphenylsilyloxyacetic acid (42).

To a solution of glycolic acid (500 mg, 6.7 mmol) in CH_2Cl_2 (3 ml), was added *t*-butylchlorodiphenylsilane (1.8 mmol, 17 mmol), triethylamine (0.94 ml, 17 mmol) and DMAP (60 mg, 0.3 mmol). The solution was stirred at rt for 1 h and the solvent removed under reduced pressure. The residue was filtered, rinsing with ether and the filtrate concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 ml) and water (15 ml) and potassium carbonate (2 g, 62 mmol) added. The homogenous solution was stirred at rt for 1 h. The THF was removed under reduced pressure and the resulting aqueous solution was cooled to 0°C and the pH adjusted to 4 using 1M HCl. The aqueous phase was extracted with ether and the combined organic phases were washed with brine. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield an oily residue (2.4 g). Chromatography (50% ether–petrol) yielded the silyl ether **42** (1.76 g, 85%). Mass spectrometry results and ^1H nmr parameters were identical to those reported in the literature.[25]

Preparation of (43/44).

To a solution of the alcohol **17** (200 mg, 0.84 mmol) in dry CH_2Cl_2 (2 ml) was added *t*-butyldiphenylsilyloxyacetic acid (300 mg, 0.95 mmol), DCC (210 mg, 1.0 mmol) and DMAP (20 mg, 0.1 mmol). The mixture was stirred at rt for 2 h and filtered, washing the filter cake repeatedly with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure and the residue purified by chromatography (50% ether–petrol) to yield the expected ester (386 mg, 83%). A similarly-prepared sample of this ester (1.6 g, 3 mmol) was dissolved in THF (25 ml) and the solution cooled to 0°C. TBAF (1.0 ml of a 95% THF solution, 3.5 mmol) was added and the solution allowed to warm to rt. After 30 min, the reaction was quenched with brine and the mixture extracted with ether. The combined organic layers were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue (23% ether–petrol) yielded alcohol (710 mg, 80%). A solution of the alcohol so prepared (570 mg, 1.97 mmol) in CH_2Cl_2 (1 ml) was added to periodinane (2 g, 4.8 mmol in CH_2Cl_2 5 ml) and the resulting heterogenous mixture was heated under reflux for 16 h. The reaction was cooled and diluted with ether before pouring into a solution of saturated aqueous $NaHCO_3$ containing $Na_2S_2O_3$ with stirring. The organic phase was washed with saturated aqueous $NaHCO_3$, water, brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue (60% ether–petrol) gave oxalate **45** (120 mg, 21%); ν_{max} (film) 1778, 1749, 1731 cm^{-1}; δ_H (270 MHz) 6.25 (2H, m, 2 x H-3'), 6.05 (2H, ddd, J 15, 10.5, 1.5 Hz, 2 x H-4'), 5.72 (2H, m, 2 x H-5'), 5.60 (2H, m, 2 x H-2'), 4.75 (2H, s, OCH_2CO), 4.60 (4H, m, 2 x H-1'), 4.20 (2H, m, 2 x H-1''), 4.00 (2H, m, 2 x H-1''), 2.20 (2H, td, J 11, 3.5 Hz, 2 x H-1), 1.77 (6H, d, J 6.5 Hz, CH_3); *m/z* (CI) 606 $[M+NH_4]^+$, followed by an equilibrium mixture of aldehyde **43** and hydrate **44** (390 mg, 68%); data for the mixture: ν_{max} (film) 3465, 1732 cm^{-1}; δ_H (400 MHz) *inter alia* 9.35 (1H, s, CHO, **43**), 6.24 (1H, dd, J 15, 10.5 Hz, H-3'), 6.05 (1H, ddd, J 15, 10.5, 1.5 Hz, H-4'), 5.76 (1H, m, H-5'), 5.60 (1H, td, J 15, 6.5 Hz, H-2'), 5.20 (1H, s, $CH(OH)_2$, **44**), 4.60 (2H, m, H-1'), 4.20-4.00 (2H, m, H-1''), 2.20 (1H, td, J 11, 3.5 Hz, H-1), 1.77 (3H, d, J 6.5 Hz, CH_3), (Found: $[M+NH_4]^+$, 312.1830. $C_{16}H_{22}O_5$ requires $[M+NH_4]^+$, 312.1837).

Generation and *in-situ* hetero-IMDA reaction of (43).

A solution of **43/44** (200 mg, *ca.* 0.64 mmol) in toluene (3 ml) degassed as described above was heated to 150°C for 24 h. The solvent was removed under reduced pressure and the residue purified by chromatography (50% ether–petrol) to afford a mixture of cycloadducts (120 mg, 64%). This mixture was subjected to reverse-phase HPLC (Vydac C_{18} 25 cm x 20 mm column; UV detection @ 230 nm; mobile phase: 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B); gradient elution, using 23% solvent B→pure solvent B; flow rate 5 ml min^{-1}) to give firstly **46** (50% by peak integration); ν_{max} (film) 1732 cm^{-1}; δ_H (400 MHz) 5.75 (2H, m, H-6, H-7), 4.58 (1H, dd, J 11.5, 3.5 Hz, H-13), 4.40 (1H, ddd, J 11.5, 3.5, 1 Hz, H-4), 4.34 (1H, m, H-8), 4.22 (1H, d, J 3 Hz, H-10), 3.84 (1H, t, 11.5 Hz, H-4), 3.50 (1H, t, J 11.5 Hz, H-13), 3.20 (1H, m, H-5), 2.45 (1H, tq, J 11.5, 3.5 Hz, H-14), 2.00 (1H, td, J 11, 3.5 Hz, H-1), 1.35 (3H, d, J 6.5 Hz, C-8 CH_3), 0.80 (1H, qd, J 11, 3.5 Hz, H-15); δ_C (100.6 MHz) 176.2 (C=O), 172.9 (C=O), 134.4 (C-7), 122.7 (C-6), 72.9 (C-10), 69.8 (C-13), 62.6 (C-4), 50.1 (C-1), 36.0 (C-5), 34.5 (C-14), 29.9 (C-8), [29.7, 27.3, 25.6, 24.9 (cyclohexane CH_2)], 21.2 (CH_3), (Found $[M+NH_4]^+$, 312.1181. $C_{16}H_{22}O_5$ requires $[M+NH_4]^+$, 312.1181), followed by an inseparable mixture of **47** (*cis*-fused) and **48** (*trans*-fused) (2:1 by ^1H nmr); data for the mixture; ν_{max} (film) 1736 cm^{-1}; *m/z* (CI) 312 $[M+NH_4]^+$; **47**: δ_H (300 MHz) *inter alia* 5.75 (2H, m, H-6 and H-7), [4.85, 4.38 (2H, m, H-4 and H-13)], 4.20 (1H, d, J 3 Hz, H-10), [3.85, 3.60 (2H, m, H-4 and H-13)], 3.20 (1H, m, H-5), 1.27 (3H, d, J 7 Hz, CH_3); **48**: δ_H (300 MHz) *inter alia* 5.45 (1H, dt, J 10, 1 Hz, H-6), 5.90 (1H, dt, J 10, 2.5 Hz, H-7), [4.75, 4.50 (2H, m, H-4 and H-13)], 3.95 (1H, d, J 9.5 Hz, H-10), [3.80, 3.76 (2H, m, H-4 and H-13)], 1.30 (3H, d, J 6.5 Hz, CH_3).

Generation and *in-situ* hetero-IMDA reaction of (49).

To a solution of **43/44** (130 mg, 0.41 mmol) in toluene (2 ml) degassed as described above was added *p*-toluenesulfonylisocyanate (200 mg, 1 mmol). The mixture was heated at 120°C for 16 h and concentrated under reduced pressure. The residue was chromatographed (50% ether–petrol) to effect partial separation of **50** (42 mg, 23%); ν_{max} (film) 1736 cm^{-1}; δ_H (500 MHz) *inter alia* 7.68 (2H, d, J 8.5 Hz, *ortho*-Ts), 7.29 (2H, d, J 8.5 Hz, *meta*-Ts), 5.76 (1H, dt, J 10.5, 2.5 Hz, H-7), 5.70 (1H, dt, J 10, 2.5 Hz, H-6), 4.97 (1H, dd, J 12, 3 Hz, H-4), 4.58 (1H, d, J 5.5 Hz, H-10), 4.52 (1H, t, J 11.5 Hz, H-13), 4.44 (1H, m, H-8), 3.85 (1H, dd, J 12, 2.5 Hz, H-4), 3.60 (1H, dd, J 11.5, 4.5 Hz, H-13), 2.40 (3H, s, TsMe), 2.25 (1H, m, H-5), 2.10 (1H, m, H-14), 2.00 (1H, td, J 11, 3.5 Hz, H-1), 1.60 (3H, d, J 6.5 Hz, $CHCH_3$); δ_C (100.6 MHz) 179.2 (C=O), 173.0 (C=O), 143.7 (*ipso*-Ts), 131.5 (C-7), 129.8 (*ortho*-Ts), 127.0 (*para*-Ts), 122.5 (C-6), 117.0 (*meta*-Ts), 68.0 (C-13), 63.4 (C-4), 54.4 (C-10), 50.2 (C-1), 46.5 (C-5), 39.7 (C-14), 37.4 (C-8), [28.5, 27.9, 24.8 (cyclohexane CH_2)], 22.4 (Ts*Me*), 21.6 (*CHCH*$_3$); *m/z* (CI) (Found: $[M+NH_4]^+$, 465.2059. $C_{23}H_{29}NO_9S$ requires $[M+NH_4]^+$, 465.2059). The remaining mixture (87 mg, 47%) was subjected to reverse-phase HPLC (Vydac C_{18} 25 cm x 20 mm column, UV detection @ 230 nm, mobile phase: 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B); gradient elution, using 23% solvent B→pure solvent B; flow rate 5 ml min^{-1}) to give further **50** (40% by peak integration; 42% combined yield of **50**). This was followed by an inseparable mixture of three cycloadducts (60% by peak integration; 5:1:1 by ^1H nmr; 28% yield) which were characterised as a mixture; ν_{max} (film) 1722 cm^{-1}; δ_H (400 MHz) **51**: *inter alia* 7.70-7.20 (4H, m, Ts), 5.70-5.90 (2H, m, H-6 and H-7), 4.93 (1H, dd, J 12, 5 Hz, H-4), 4.62 (1H, d, J 5.5 Hz, H-10), 4.42 (1H, m, H-8), 4.37 (1H, dd, J 11.5, 2.5 Hz, H-13), 3.82 (1H, dd, J 12, 2.5 Hz, H-4), 3.45 (1H, t, J 11.5 Hz, H-13), 2.50 (3H, s, TsMe), 1.65 (3H, d, J 6.5 Hz, $CHCH_3$), **52**: *inter alia* 7.70-7.20 (4H, m, Ts), 5.70-5.80 (2H, m,H-6 and H-7), 5.20 (1H, t, J 11.5 Hz, H-13), 3.86 (1H, d, J 10.5 Hz, H-10), 2.40 (3H, s, TsMe), 1.32 (3H, d, J 7 Hz, $CHCH_3$), **53**: *inter alia* 7.70-7.20 (4H, m, Ts), 5.70-5.90 (2H, m, H-6, H-7), 5.20 (1H, t, J 11.5 Hz, H-13), 3.90 (1H, d, J 10.5 Hz, H-10), 2.50 (3H, s, TsMe), 1.36 (3H, d, J 6.5 Hz, $CHCH_3$); *m/z* (CI) 465 $[M+NH_4]^+$.

Reduction of cycloadduct mixture (50)-(53).

To a solution of the cycloadducts **50-53** (20 mg, 0.045 mmol) in tetrahydrofuran (1 ml) was added lithium aluminium hydride (150 µl of a 1M solution in THF, 0.15 mmol) and the reaction was stirred for 1 h. Ethyl acetate was added and the mixture poured into saturated aqueous $NaHCO_3$. The aqueous phase was extracted with chloroform. The combined organic layers were washed sequentially with 1M HCl, water and brine. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue (70% EtOAc–petrol) afforded **54** (8.5 mg, 60%) as a colourless oil; ν_{max} (film) 3477 cm^{-1}; δ_H (400 MHz) 7.70 (2H, d, J 8.5 Hz, *ortho*-Ts), 7.27 (2H, d, J 8.5 Hz, *meta*-Ts), 5.65 (1H, dt, J 10.5, 3 Hz, H-3), 5.40 (1H, br d, J 10.5 Hz, H-4), 4.40 (1H, m, H-2), 4.20 (1H, q, J 7 Hz, H-6), 3.55-3.65 (4H, m, CH_2OH), 3.80 (1H, m, H-5), 2.40 (3H, s, TsMe), 1.38 (3H, d, J 7.0 Hz, H-2) (Found: $[M+H]^+$, 312.1295. $C_{15}H_{21}NO_4S$ requires $[M+H]^+$, 312.1294).

X-Ray crystal data.

Crystal data for **24**: $C_{19}H_{26}O_6$, M = 350.4, triclinic, space group $P\bar{1}$ (no. 2), a = 7.279(2), b = 10.891(4), c = 12.807(4) Å, α = 65.67(3), β = 83.64(3), γ = 77.29(3)°, V = 902.2(5) Å^3, Z = 2, D_c = 1.290 g cm^{-3}, μ(Mo-Kα) = 0.95 cm^{-1}, F(000) = 376, T = 293 K; clear plates, 0.62 x 0.34 x 0.08 mm, Siemens R3m/V diffractometer, ω-scans, 2358 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give R_1 = 0.031, wR_2 = 0.079 for 2090 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \le 45°$] and 227 parameters.

Crystal data for **27**: $C_{19}H_{26}O_6$, M = 350.4, monoclinic, space group $P2/n$ (no. 13), a = 19.043(9), b = 5.419(2), c = 19.561(7) Å, β = 115.82(3)°, V = 1817(1) Å^3, Z = 4, D_c = 1.281 g cm^{-3}, μ(Cu-Kα) = 7.81 cm^{-1}, F(000) = 752, T = 293 K; clear blocks, 0.30 x 0.20 x 0.20 mm, Siemens P4/PC diffractometer, ω-scans, 2910 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give R_1 = 0.055, wR_2 = 0.148 for 2651 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \le 125°$] and 227 parameters.

Crystal data for **39**: $C_{20}H_{28}O_6$, M = 364.4, orthorhombic, space group $Pbca$ (no. 61), a = 14.572(2), b = 10.825(2), c = 24.135(2) Å, V = 3806.9(9) Å^3, Z = 8, D_c = 1.272 g cm^{-3}, μ(Mo-Kα) = 0.93 cm^{-1}, F(000) = 1568, T = 203 K; clear blocky prisms, 0.73 x 0.40 x 0.23 mm, Siemens P4/PC diffractometer, ω-scans, 3089 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give R_1 = 0.050, wR_2 = 0.111 for 2108 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \le 50°$] and 236 parameters.

Crystal data for **50**: $C_{23}H_{29}NO_5S$, M = 447.5, monoclinic, space group $P2_1/c$ (no. 14), a = 6.931(1), b = 14.125(3), c = 23.181(2) Å, β = 94.31(1)°, V = 2263.1(6) Å^3, Z = 4, D_c = 1.314 g cm^{-3}, μ(Cu-Kα) = 16.0 cm^{-1}, F(000) = 952, T = 293 K; clear platy needles, 0.60 x 0.10 x 0.03 mm, Siemens P4/PC diffractometer, ω-scans, 3359 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give R_1 = 0.053, wR_2 = 0.119 for 2336 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \le 120°$] and 281 parameters.

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6. REFERENCES AND NOTES

1. For a recent example of IMDA reaction of a substrate possessing a N–Si–C tether generated *in situ*, see: Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.
2. Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.
3. Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813.
4. Carbon acetal-tethered trienes: Boeckmann, Jr., R. J.; Flann, C. J. *Tetrahedron Lett.* **1983**, *24*, 1655; Boeckmann, Jr., R. J.; Estep, K. G.; Nelson, S. G.; Walters, M. A. *Tetrahedron Lett.* **1991**, *32*, 4095. Silaketal-tethered trienes: Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885; Gillard, J. W.; Fortin. R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. M. *Tetrahedron Lett.* **1991**, *32*, 1145; Shea, K. J.; Staab, A. J.; Zandi, K. S. *Tetrahedron Lett.* **1991**, *32*, 2715; Shea, K. J.; Gauthier, D. R. *Tetrahedron Lett.* **1994**, *35*, 7311. Silyl-ether-based tethers: Sieburth, S. McN.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279. Boron-based tethers: Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450;
5. Ainsworth, P. J.; Craig, D.; Reader, J. C.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 11601.
6. Ainsworth, P. J.; Craig, D.; Reader, J. C.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1996**, *52*, 695.
7. Ainsworth, P. J.; Craig, D.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1996**, *52*, 8937.
8. Preliminary communications: Craig, D.; Ford, M. J.; Stones, J. A. *Tetrahedron Lett.* **1996**, *37*, 535; Craig, D.; Gordon, R. S. *Tetrahedron Lett.* **1998**, *39*, 8337.
9. Simonetta, M.; Carra, S. *General and Theoretical Aspects of the –COOH and –COOR Groups* In *The Chemistry of Carboxylic Acids and Esters*, Patai, S., Ed.; Wiley: New York, 1969, p 13.
10. For reviews of the IMDA reaction, see: Carlson, R. G. *Ann. Rep. Med. Chem.* **1974**, *9*, 270; Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10; Oppolzer, W. *Synthesis* **1978**, 793; Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63; Funk, R.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41; Ciganek, E. *Org. React.* **1984**, *32*, 1; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183; Taber, D. F. *Intramolecular Diels–Alder Reactions and Alder Ene Reactions*; Springer: Berlin, 1984; Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187; Roush, W. R. In *Advances in Cycloaddition*, Curran, D. P., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, p 91; Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 513.
11. Boeckman, R. K. jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789.
12. Substrates whose IMDA reactions give rise to γ-lactones often suffer from especially low reactivity. For an example, see: White, J. D.; Nolen, E. G. jr.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150.
13. Available from Aldrich Chemical Co., or by $LiAlH_4$ reduction of methyl sorbate.
14. Prepared by Wittig reaction of glycolaldehyde dimer (Aldrich) with methoxycarbonylmethylenetriphenylphosphorane; see ref. 5.
15. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
16. Prepared by reaction of the lithio-anion (LDA) of methyl propiolate (Aldrich) with paraformaldehyde.
17. Ohwada, J.; Inouye, Y.; Kimura, M.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 287.
18. Nefkens, G. H. L.; Thuring, J. W. J. F.; Zwanenburg, B. *Synthesis* **1997**, 290.
19. Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J. M.; Buendia, J. *Tetrahedron Lett.* **1992**, *33*, 4889; Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905.
20. Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187; Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257.
21. Smith, M. B. *Organic Synthesis*, McGraw–Hill: New York, 1994, p 1143.
22. For recent examples of the use of IMDAF reactions in synthesis, and leading references, see: Brickwood, A. C.; Drew, M. G. B.; Harwood, L. M.; Ishikawa, T.; Marais, P.; Morisson, V. *J. Chem.*

Soc., Perkin Trans. 1 **1999**, 913; Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617.

23. Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, 2537.
24. Saito, S.; Morikawa, Y.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5424; *Synlett* **1990**, 523.
25. Roth, G. A.; McClymont, E. L. *Synth. Commun.* **1992**, *22*, 411.
26. Typically, samples of **43/44** were dried by repeated evaporation of anhydrous toluene solutions.
27. Hamley, P.; Homes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Synlett* **1991**, 29.
28. Craig, D.; Fischer, D. A.; Kemal, Ö.; Marsh, A.; Plessner, T.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1991**, *47*, 3095; Clasby, M. C.; Craig, D.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 1509.
29. For examples of the use of acylnitroso dienophiles in hetero-IMDA chemistry, see: Narusc, M.; Aoyagi, S., Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213; Davies, G.; Russell, A. T.; Sanderson, A. J.; Simpson, S. J. *Tetrahedron Lett.* **1999**, *40*, 4391.
30. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd edn.; Pergamon: Oxford, 1988.