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Formation of Medium-ring Diolides via Intramolecular Diels–Alder Reactions of Dicarboxylic Ester-tethered Trienes

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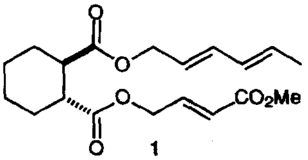
Abstract: The synthesis and IMDA reactions of diester-tethered trienes **1**, **2** and **3** are described.

Intramolecular Diels–Alder (IMDA) reactions of tethered trienes followed by tether cleavage give the products of highly selective overall intermolecular [4+2] cycloaddition. In this context, we[1] and others[2] have developed reaction sequences which deliver polysubstituted cyclohexenes with excellent levels of regiochemical and stereochemical control. Specifically, we have demonstrated that silyl acetals[1(i)-(iii)] and benzylic or tertiary ether linkages[1(iv)] may readily be incorporated into triene substrates, and that the trienes undergo efficient, selective IMDA reactions. The tethers may easily be removed in good yields to give monocyclic products. In a search for novel tethering groups, ester linkages did not augur well because of the unfavourable dipole orientation and the loss of favourable $n_{\text{alkyl oxygen}}$–$\sigma^*_{\text{C=O}}$ overlap in the ester *E*-conformation required for IMDA reaction to take place.[3] It occurred to us that a tether containing a *diester* group would not prevent the diene and dienophile attaining the requisite close mutual proximity if the incipient heterocycle was sufficiently large[4] to accommodate two *Z*-ester linkages. It was felt that the medium-ring ester-containing products would not suffer from prohibitively destabilising transannular interactions, and additionally that incorporation of a *conformationally restricted* diester spacer would offset the anticipated decrease in reactivity arising from the more negative entropy of activation usually associated with formation of a larger ring. We describe in this Letter the synthesis and thermal IMDA reactions of the dicarboxylic ester-tethered trienes **1**, **2** and **3**, and demonstrate that the diester linkage may effectively be deployed as a stereocontrol element in reactions of this type.



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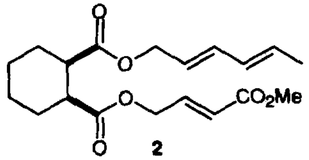

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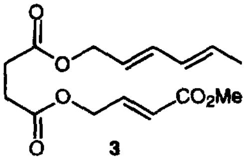

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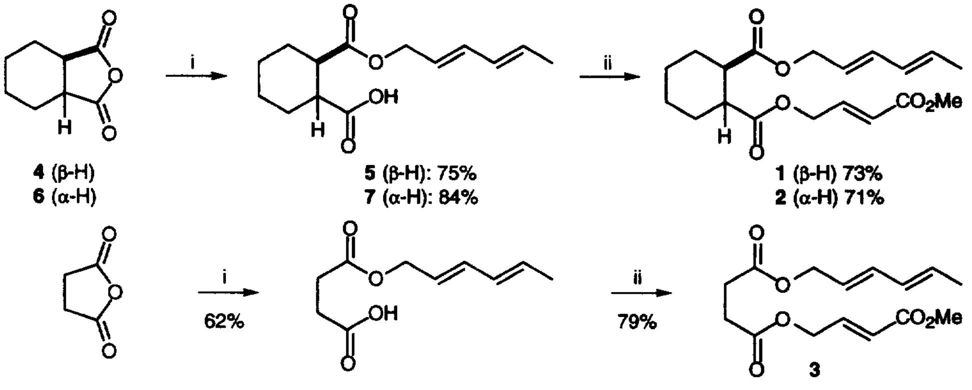
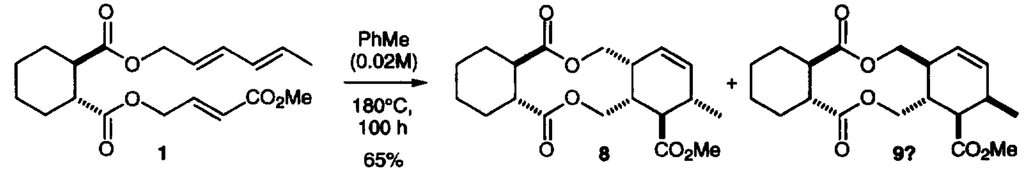
Trienes **1** and **2** were simply and efficiently prepared from respectively racemic *trans*-cyclohexane-1,2-dicarboxylic anhydride **4**[5] and its *cis* isomer **6**,[5] (*E*,*E*)-2,4-hexadienol[6] and methyl (*E*)-4-hydroxy-2-butenoate.[7] Thus, reaction of **4** with the dienol in the presence of pyridine and *N*,*N*-dimethyl-4-aminopyridine (DMAP) gave the half-ester **5**, which was coupled with the dienophile alcohol via the intermediate 2,4,6-trichlorobenzoyl chloride-derived mixed anhydride to give triene **1**. An analogous sequence of reactions starting from **6** provided the cis-analogue **2** via half-ester **7**, and substitution of cyclohexane-1,2-dicarboxylic anhydride with succinic anhydride led to the acyclic triene **3**. The syntheses of the three trienes are summarised in Scheme 1.[8]

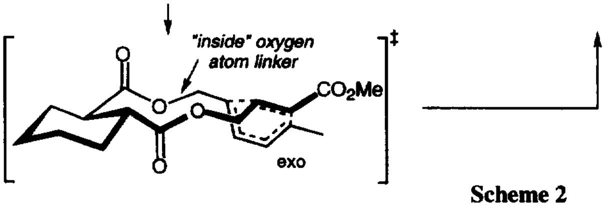


(i) (*E*,*E*)-2,4-hexadienol (1 eq), pyridine (1.5 eq), DMAP (0.04 eq), CH_2Cl_2 (0.3M), reflux, 18 h; (ii) 2,4,6-$Cl_3C_6H_2COCl$ (1 eq), Et_3N (2.5 eq), DMF (0.2M), rt, 1-3 h, then add methyl (*E*)-4-hydroxy-2-butenoate (1.01 eq), DMAP (0.04 eq), DMF (0.1M), rt.

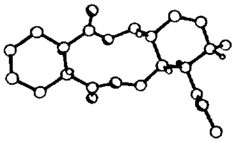
Scheme 1

Thermolysis of **1** as described previously[1] gave in good yield a 7:1 mixture of two cycloadducts. On the basis of the expected trans-diequatorial disposition of the ester linking groups with respect to the cyclohexane ring, and the pronounced preference for an "inside"-oriented diene oxygen atom link observed previously with the silyl acetal-tethered IMDA reactions,[1(i)-(iii)] we assigned the trans,cis-fused structure **8** to the major product, arising via an exo-transition-state (Scheme 2). Confirmation of the identity of **8**[9] was provided by X-ray analysis (Figure 1),[10] in line with our working model for the preferred transition-state conformation. Independent assignment of the stereochemistry of the cyclohexene portion of **8** was provided by chemical correlation of a derivative with the de-tethered product of a silyl acetal reaction. Thus, hydrolysis of **8** followed by acid-catalysed cyclisation gave hydroxylactone **12** (Scheme 4), identical in all respects to material described previously.[1(i)] We have not been able to characterise fully the analogous lactone derivative of **9**, but we assign the endo-derived structure shown since this too would arise from the diequatorial conformer of diester **1**.





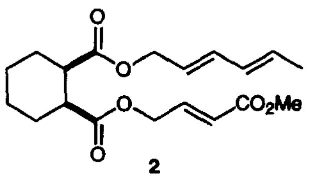
Scheme 2

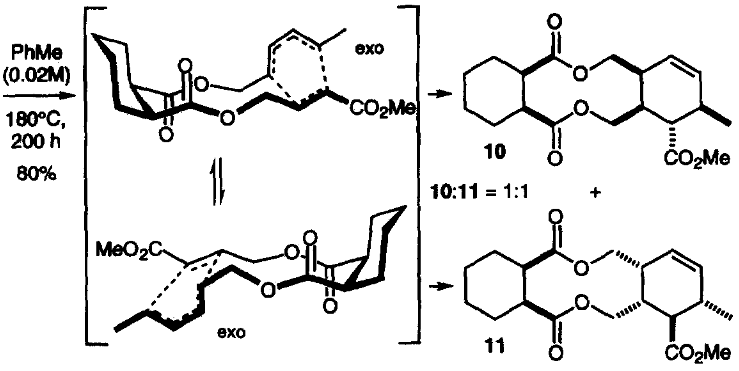


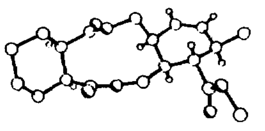
X-ray structure of 8

Figure 1

The thermal cyclisation behaviour of the cis-diester-tethered triene **2** differed from that of **1** in two respects. Firstly, the IMDA reaction was significantly slower, and secondly, two products were formed in a 1:1





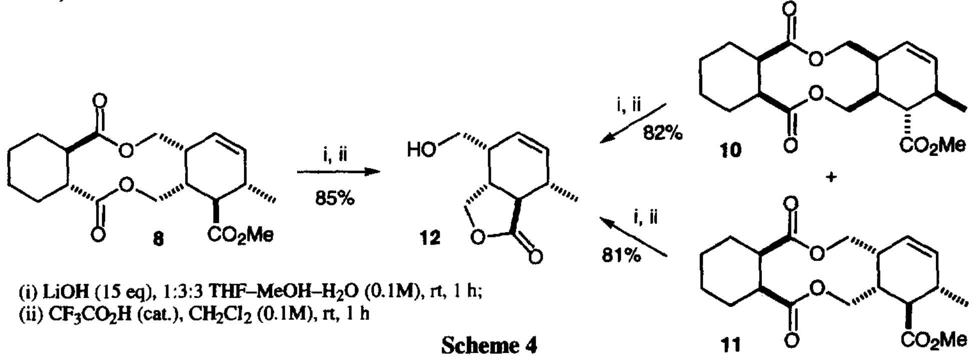


X-ray structure of **10**

Figure 2

Scheme 3

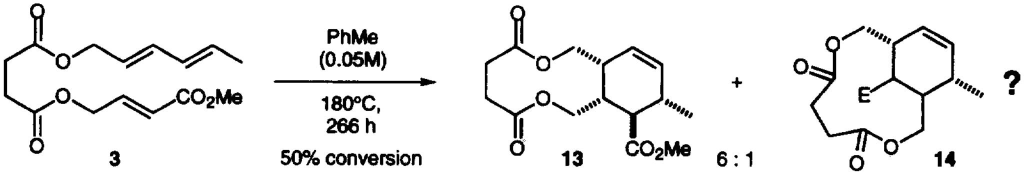
ratio. The cis-orientation of the ester groups on the cyclohexane ring is such that there are two putative low-energy reactive conformations for triene **2** which possess "inside"-oriented diene oxygen tethers. Cyclisation via these conformations gives the diastereomeric cis,cis-fused products **10** and **11** (Scheme 3). The structure of **10**[11] was assigned unambiguously by X-ray analysis (Figure 2). Both **10** and **11** gave only **12** upon hydrolysis followed by acid-catalysed lactonisation as before, confirming the cis,cis-fused nature of **11**[12] (Scheme 4).



(i) LiOH (15 eq), 1:3:3 THF–MeOH–H_2O (0.1M), rt, 1 h;
(ii) CF_3CO_2H (cat.), CH_2Cl_2 (0.1M), rt, 1 h

Scheme 4

The foregoing results demonstrate clearly that trans-tethered triene **1** undergoes selective IMDA reaction on account of both the inherent cis-bias of the diene–dienophile pairing,[1(i)-(iii)] and the conformational bias of the diester-containing chain linking the diene and dienophile. The conformational flexibility of the cis-1,2-disubstituted cyclohexane spacer in **2** is such that both possible cis,cis-fused diastereomers are formed in the IMDA reaction; it is noteworthy that no products are formed which arise via an endo transition-state. We presume that the enforced axial orientation of one ester group causes conformational changes which render the endo-conformation even less reactive. In both **1** and **2** it seems likely that the 1,2-disubstituted cyclohexane spacer discourages rotation of the diene/dienophile π-systems into distal, unreactive conformations, and that this results in a rate increase for IMDA reaction relative to conformationally more labile substrates. In order to gauge the magnitude of any such effect the IMDA reaction of **3** was investigated. Thermolysis of **3** as before was extremely sluggish, and after prolonged reaction times resulted in partial conversion to a ca. 6:1 mixture of two new compounds. Transformation of the major isomer into lactone **12** was effected by the standard hydrolysis–cyclisation sequence, enabling its assignment as **13**. Subjection of the minor product to identical derivatisation conditions gave a lactone whose ^{1}H nmr spectrum did not match that of the lactone derived from presumed cycloadduct **9**. We speculate that the minor cycloadduct is a regioisomer **14** (Scheme 5); non-regioselective IMDA reactions have been reported in cases where the tether is sufficiently long and conformationally flexible.[13]



Scheme 5

In summary, we have demonstrated that conformationally restricted diester-tethered trienes undergo stereoselective IMDA reactions. In the case of **2**, where increased conformational flexibility in the spacer group results in loss of stereoselectivity, the reaction nevertheless gives only exo-products arising from the "inside"-oriented linking oxygen atom α- to the diene. Conformational lability in the diester-linked triene **3** caused a decrease in reactivity and regioselectivity. We are currently looking at non-covalent ways to limit mobility in the spacer, including dipole–dipole and steric repulsion effects.[14] The results of these studies will be reported in due course.

ACKNOWLEDGEMENTS

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2. See refs 2 and 4 in ref 1(iii). For a recent application of C_2-symmetric tethers in type 2 IMDA processes, see: Shea, K. J.; Gauthier, R. J., Jr. *Tetrahedron Lett.* **1994**, *35*, 7311.
3. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983, chapter 3.
4. For an account of the use of the IMDA reaction for the synthesis of members of the cytochalasan family of macrolactones, see: Thomas, E. J. *Acc. Chem. Res.* **1991**, *24*, 229.
5. Aldrich Chemical Company.
6. Used as supplied by Aldrich, or prepared by $LiAlH_4$ reduction of the corresponding acid.
7. Prepared directly by reaction of methoxycarbonylmethylenetriphenylphosphorane with glycolaldehyde dimer (slow addition of phosphorane to a suspension/solution of dimer in benzene, reflux; 91%), or by sequential monoprotection of 1,2-ethanediol (TBDMSCl (1.1 eq), NaH (1 eq), THF; 80%), oxidation (py·SO_3, Et_3N, DMSO) and olefination with methoxycarbonyl-methylenetriphenylphosphorane in situ (62% for the two-step, one-pot sequence) followed by desilylation (HCl, MeOH; 89%).
8. Yields cited herein are for pure materials, characterised by nmr, ir, low-resolution ms, and either high-resolution ms or elemental combustion analysis.
9. Compound **8**: mp 123-124°C.
10. We thank Dr D. J. Williams and Mr A. J. P. White of this Department for the X-ray structure determinations described herein.
11. Compound **10**: mp 127-128°C.
12. Compound **11**: mp 154°C.
13. Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, 2537.
14. For example, we are looking at the synthesis and asymmetric IMDA reactions of trienes possessing bis(TBDPS)tartrate spacers as conformational control elements.

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