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On the stereoselectivities of some hindered Diels–Alder reactions

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ABSTRACT

The *cis*-fused lactones were the major products isolated from Diels–Alder reactions of (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienyl methyl fumarate and maleate and from the cyclisation of the all (*E*)-2,4,6,8-tetramethyldeca-2,4,6,8-tetraenyl methyl fumarate in contrast to the Diels–Alder reactions of analogous substrates that lack the dienyl 2-methyl group. All of these Diels–Alder reactions led to the introduction of a methyl bearing quaternary centre. An intramolecular Diels–Alder reaction of a 3-(5,7-dimethylnona-5,7-dienoyl)pyrrolinone also gave mainly the *endo*-product, in this case with two adjacent quaternary centres.

1. Introduction

The Diels–Alder reaction is one of the most widely used reactions in organic synthesis because of the exquisite stereocontrol it can provide with the introduction of up to four stereocentres in the one reaction.[1] A classic example is the reaction between sorbyl alcohol **1** and maleic anhydride **2** that gives the *endo*-*cis*-fused lactone **3** as the dominant product, endo:exo=96:4.[2,3] Two processes were considered for this reaction, namely an intermolecular Diels–Alder reaction followed by anhydride ring-opening to give the lactone, or anhydride opening to give a maleate half ester, which then reacts via an intramolecular Diels–Alder reaction. A thorough investigation of this and related reactions concluded that the former process was taking place since the intramolecular Diels–Alder reactions of the maleate half ester **7** and the maleate bis-ester **8** both gave mainly the *exo*-*trans*-fused lactones **5** and **6** rather than the *endo*-*cis*-fused isomers **3** and **4**.[2,4,5] The *exo*-*trans*-fused lactone **11** was also the major product from the fumarate diester **9** albeit with slightly reduced stereoselectivity. It would appear that the *endo*-*cis*-fused lactones are formed by the *inter*molecular Diels–Alder reactions of dienyl alcohols and maleic anhydride, and that the *exo*-*trans*-fused lactones are the major products from *intra*molecular Diels–Alder reactions of both maleate and fumarate diesters.[6] This stereoselectivity has been observed for a variety of substrates and under microwave conditions,[7] and has been usefully employed in synthesis.[8]

An exception to this guideline would appear to be the Diels–Alder reaction of the pentadienyl methyl fumarate **12** that gave. the *cis*-fused, *endo*-isomer **13** as the exclusive product.[9] However as significantly more vigorous conditions were employed for this cyclisation, it may be that this *cis*-fused product **13** is a consequence of thermodynamic rather than kinetic control.

We here report Diels–Alder reactions of substrates related to the dienyl fumarate **12** that were carried out to study further the influence of a 2-methyl substituent on the diene on the viability and stereoselectivity of these reactions.

2. Results and discussion

(2*E*,4*E*)-2,4-Dimethylhexa-2,4-dien-1-ol **14**[10] and maleic anhydride **2** were heated under reflux in benzene for 42 h. On cooling the reaction mixture, the acid **15** crystallised out (34%). The ester **16** was obtained by esterification of the isolated acid **15**, and from a reaction in toluene heated under reflux that was treated with trimethylsilyldiazomethane on work-up (53%), see Scheme 1. The structure shown was initially assigned to the ester **16** on the basis of NOE studies that showed a significant enhancement of the 6-methyl group, 2-H and 3-H on irradiation of 1-H, and vice versa in all cases. This structure was confirmed by X-ray crystallography. Fig 1 shows a projection of the ester **16** that established the *cis*-fused, *endo*-stereochemistry.

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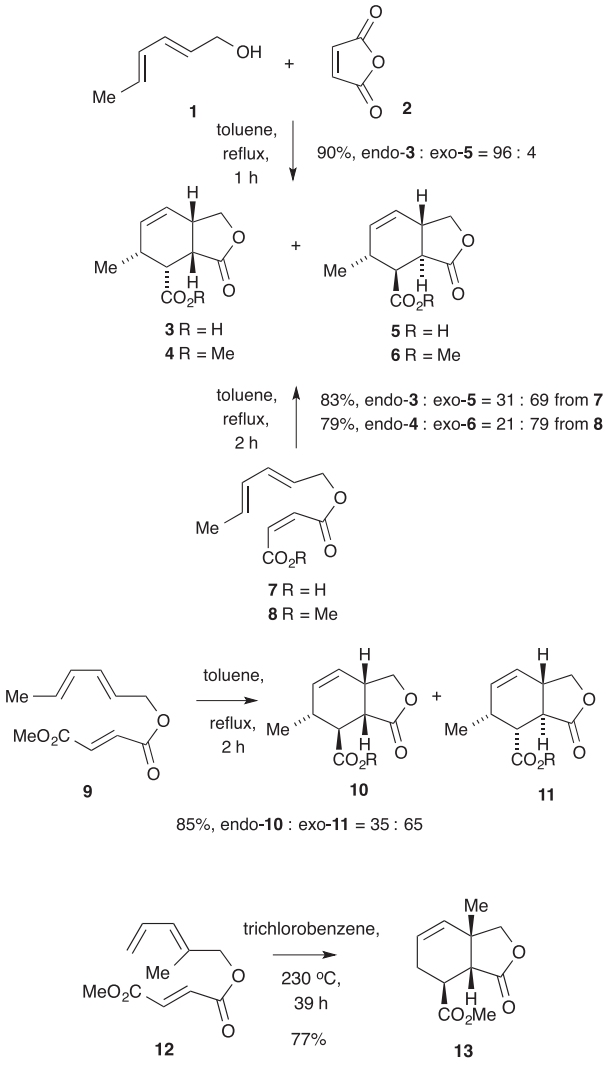

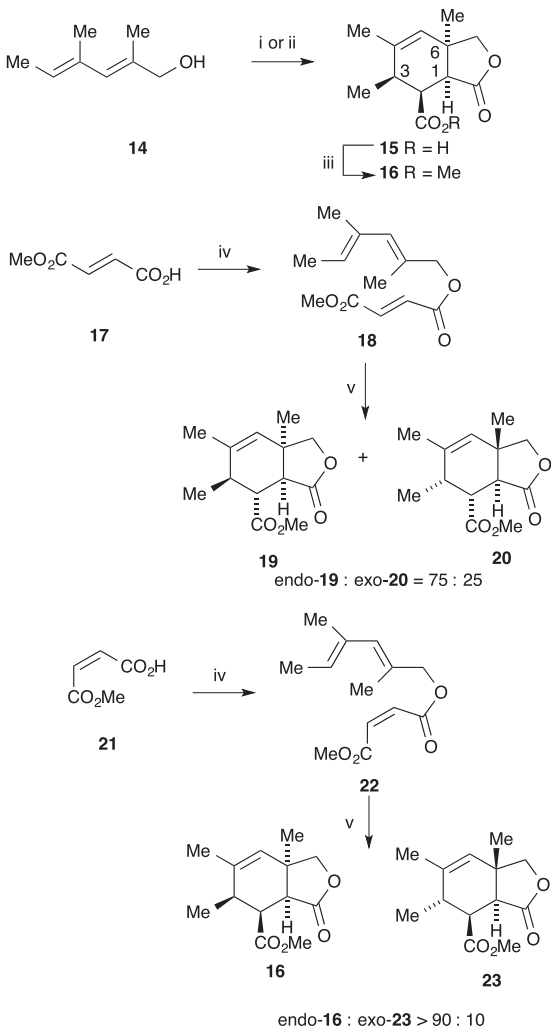

Scheme 1. Diels–Alder reactions of the 2,4-dimethylhex-2,4-dienol **14** and derivatives Reagents and conditions i, **2**, hydroquinone (trace), benzene, reflux, 42 h (**15**, 34%); ii, **2**, hydroquinone (trace), toluene, reflux, 20 h, then methanol, $TMSCHN_2$, rt, 1 h (**16**, 53%); iii, $TMSCHN_2$, toluene, methanol, rt 1 h (94%); iv **14**, EDCI, DMAP, DCM, 0 °C, 2 h (**18**, 85% from **17**; **22**, 21% and **18**, 10%, from **21**); v, dichlorobenzene, microwave, 230 °C, 30 min (**19**:**20**=75:25, 80% from **18**; **16**:**23**=90:10, 54% from **22**).

The formation of the *cis*-fused lactones **15** and **16** from these reactions is consistent with the studies using less hindered hexadienyl alcohols, e.g. sorbyl alcohol **1**, and can be explained by an *endo*-selective, intermolecular Diels–Alder reaction followed by lactonisation.

To check the viability and stereoselectivity of analogous intramolecular Diels–Alder reactions, the fumarate ester **18** was prepared by esterification of monomethyl fumarate **17** using the alcohol **14**. Heating this ester in toluene under reflux gave rise to a mixture of two products identified as the *endo-cis*-fused lactone **19** and its *exo*-isomer **20** in a 3:1 ratio. However, the reaction was slow and only a 15% yield was obtained after 5 days. Better conversion was obtained when the fumarate diester was heated in dichlorobenzene at 230 °C in a microwave oven for 30 min. The two products **19** and **20** were obtained, still in a 3:1 ratio, but in an improved yield of 80%. Reactions were also carried out in dimethyl sulfoxide in a microwave oven at 230 °C and under reflux at 110 °C. In these cases, lower yields, 43% and 23%, were obtained but the ratio of the products was unchanged, Scheme 1.

The *endo-cis*-structure **19** was assigned to the major product on the basis of NOE studies. This was confirmed by X-ray diffraction, see Fig 2. The minor product was therefore the *exo-trans*-isomer **20**.

The maleate diester **22** was prepared by esterification of monomethyl maleate using the dienol **14**. In this case the yield of the diester **22** was rather low and a small amount, ca. 10%, of the

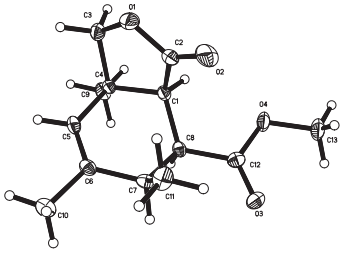

Fig. 1. The structure of the lactone **16** as established by X-ray crystallography.

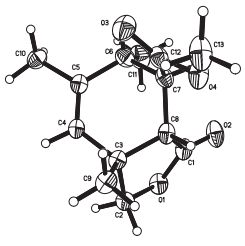

Fig. 2. The structure of the lactone **19** as established by X-ray crystallography.