

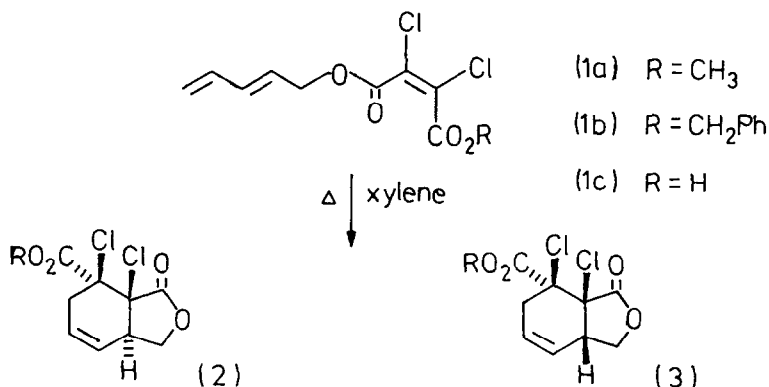
THE USE OF ESTERS OF DICHLOROMALEIC ACID
IN INTRAMOLECULAR DIELS ALDER REACTIONS

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Abstract: Intramolecular cyclisation of acyclic triene esters derived from dichloromaleic anhydride affords bicyclic lactones, which by dechlorodecarboxylation, dechlorination or dehydrochlorination are readily elaborated to give novel unsaturated lactones.

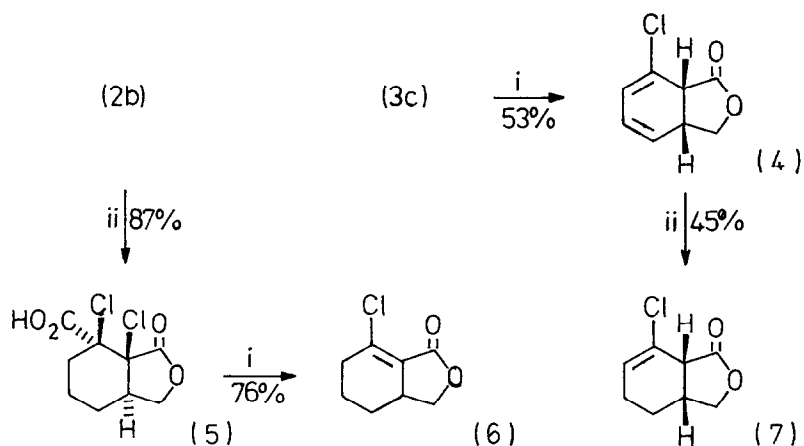
The synthetic potential¹ of the intramolecular Diels Alder reaction of triene esters incorporating a dienophilic unit derived from an acrylate or a maleate ester is well established. However, in a further elaboration of the adducts introduction of further functionality is often needed and can be difficult. One solution to this problem is to introduce directly the extra functionality in the diene unit. Examples of this strategy are known *e.g.* in the recent use² of 1-acyloxy-1,3-pentadien-5-ols, which are readily prepared from pyridines. An alternative strategy is the use of a dienophilic unit incorporating additional functionality. Although such a strategy has been successfully used in the total synthesis³ of gibberellic acid, using a β -chloroacrylate ester, there are few examples of the intramolecular Diels Alder reaction involving a dienophilic ester unit incorporating the additional functionality. In this paper we describe the novel use of dichloromaleic anhydride, which permits both the introduction of extra functionality into the dienophilic unit, and the subsequent elaboration of Diels Alder adducts to give further functionalised bicyclic lactones.



R = CH₃ 68% yield (2a) : (3a) = 100:0
R = CH₂Ph 40% yield (2b) : (3b) = 9:1
R = H 20% yield (2c) : (3c) = 0:100

Scheme 1

Although there is no report of the use of derivatives of the readily available dichloromaleic anhydride in the intramolecular Diels Alder reaction, we find that by cyclisation of either a half acid or a diester of dichloromaleic acid bicyclic lactones are obtained (Scheme 1). Thus cyclisation of the diester (1a), obtained by treatment of dichloromaleic anhydride with methanol and subsequent esterification with 2,4-pentadien-1-ol gave stereospecifically the *trans*-lactone (2a).⁴ Similarly, but in poorer yield, the diester (1b) gave preferentially the *trans*-lactone (2b). In contrast the half acid (1c), obtained by direct reaction of dichloromaleic anhydride with 2,4-pentadien-1-ol gave only the *cis*-lactone (3c). Assignment of structures is easily made by analysis of coupling constants in compounds (2a) (2b) and (3c) and from their respective i.r. data [(2a) ν_{\max} 1805 cm^{-1} ; (2b) ν_{\max} 1805 cm^{-1} ; and (3c) ν_{\max} 1790 cm^{-1}]. The contrasting outcome of the cyclisation of the esters (1a) and (1b) from the cyclisation of the acid (1c) has good precedent. White and Sheldon⁵ first noted the differing stereochemical outcome of cyclisation of a triene ester and a triene acid. A further example² of cyclisation of an acid derived from maleic anhydride to give a bicyclic *cis*-lactone has been reported more recently. White and Sheldon⁵ suggest that in such cyclisations to give a *cis*-lactone reactions proceed by thermodynamic control. Internal protonation of the lactone carbonyl in the case of the acids might facilitate the reverse Diels Alder reaction and hence lead to the more thermodynamically stable *cis*-lactones. Alternatively, the differing stereochemical outcome may reflect a kinetic control. The esters (2a) and (2b) are formed *via* an *endo* transition state and the acid (3c) *via* an *exo* transition state. In view of recent results,⁶ which show that apparently minor factors markedly influence the relative importance of the *endo*- and *exo*-modes of cyclisation in the intramolecular Diels Alder reaction, it is premature to conclude that thermodynamic factors control either earlier^{2,4} or the present cyclisation of acids to give *cis*-lactones.

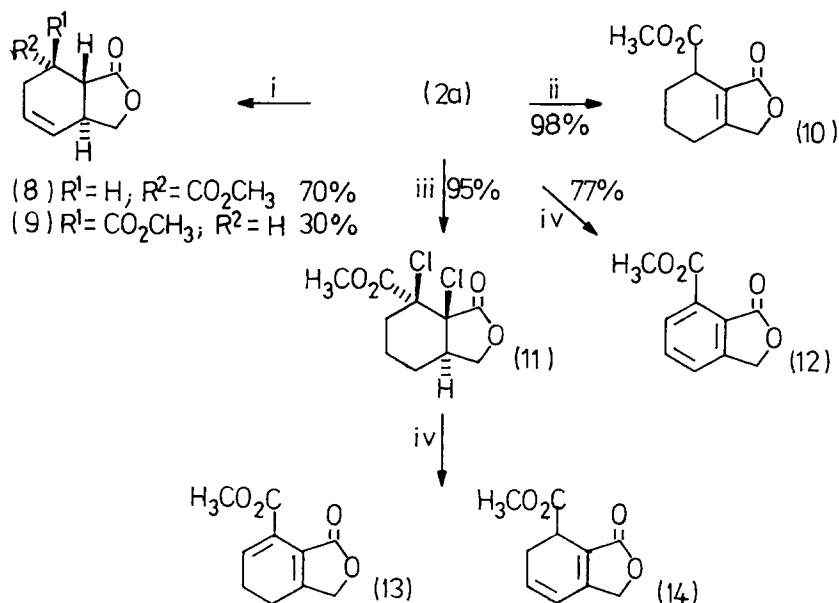


Reagents: i) Et_3N , THF, Δ ; ii) $\text{H}_2/\text{Pd/C}$, EtOAc.

Scheme 2

In both the acid (3c) and the esters (2a) and (2b) there is a *trans*-relationship between a vicinal chlorine substituent and the respective acid or ester functionality. Dechlorodecarboxylation of such a chloroacid by *trans* antiperiplanar elimination should occur easily. We find that treatment of the acid (3c) with triethylamine in tetrahydrofuran under reflux affords the chlorodiene (4) in 53% yield. In a second dechlorodecarboxylation the acid (5), available by reductive cleavage of the benzyl ester (2b), gives under similar conditions the lactone (6) in 76% yield. The isomeric lactone (7) is available by selective reduction of the chlorodiene (4) (Scheme 2).

A second approach to elaboration of the adducts is by reductive dechlorination of the vicinal substituents. Using zinc in acetic acid reduction of (2a) leads quantitatively to a mixture (7:3) of the esters (8) and (9). Alternatively, reduction of (2a) with hydrogen over palladium on charcoal in ethyl acetate gives the unsaturated lactone (10) in 98% yield. The course of this transformation contrasts with reduction of (2a) over platinum in methanol which gives the dichlorolactone (11) in 95% yield. Under controlled reductive conditions (2a) can hence be elaborated to three different types of bicyclic lactone *via* dechlorination (Scheme 3).



Reagents: i) Zn, AcOH; ii) H₂, Pd/C, EtOAc; iii) H₂, PtO₂;

iv) Et₃N, THF, Δ.

Scheme 3

A further elaboration is possible *via* dehydrochlorination. Direct dehydrochlorination of (2a) affords the known⁷ aromatic lactone (12) in 77% yield. Dehydrochlorination of the saturated lactone (11) gives a mixture of the unsaturated lactones (13) (35%) and (14) (28%).

These results show that both acids and esters derived from intramolecular Diels Alder reaction of esters of dichloromaleic acid can readily be used to give a wide variety of functionalized lactones. The use of dichloromaleic anhydride in combination with other functionalized dienes should permit the development of new synthetic strategies based on the dechlorodecarboxylations, dechlorinations and dehydrochlorinations described in this paper.

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