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CYCLIC ORTHOESTERS AS REAGENTS FOR CLAISEN REARRANGEMENTS

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A recent[1] synthesis of des-AB-cholestane-8β,9α-diol made use in the opening step of a Claisen rearrangement between the allyl alcohol (5)† and methyl (R)-orthodihydrocitronellate. It seemed at first sight that a similar approach, using the alcohol (5) and the orthoester (13), might be suitable for a synthesis of the ketone (14), an important degradation product[2] of vitamin D_2. However, the use of an orthoester as complex as (13) presents problems. First, the considerable difficulty of its preparation is aggravated by the need to use it in excess in the reaction. Secondly, it contains a reactive function (the double bond) the presence of which would complicate later stages of the synthesis. When a Claisen rearrangement is attended by circumstances of this kind, it may be preferable to use for it a simpler orthoester, containing a masked reactive function which, at a convenient later stage, can be used for structural elaboration. The present communication draws attention to

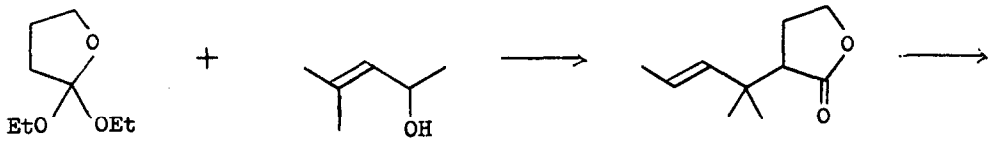
†The structures in this communication represent absolute configurations. Racemates are denoted by the prefix rac.

the value for this and related purposes of cyclic orthoesters such as (1) and (6). They can be prepared easily and in good yield from γ- or δ-lactones by Meerwein's[3] method.

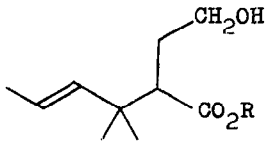
Reaction of the alcohol rac-(2) with the cyclic orthoester (1) (3 mols) under the usual[1] conditions gave the γ-lactone rac-(3) (65%), which was characterised as the p-bromophenacyl ester rac-(4; R=CO·C_6H_4·Br) m.p. 78-79°. The formation of an ester such as rac-(4; R=Et) releases a hydroxy-group which can be used, via a halide or aldehyde, for chain extension. Alternatively, the hydroxy-group could be replaced by hydrogen; in this particular example the product so obtained would be more easily obtained directly by reaction of rac-(2) with ethyl orthobutyrate; however, the indirect method will be worth while in some cases because of its stereochemical consequences (v. inf.).

In reaction with rac-(5) the orthoester (1) gave (65%) the homogeneous γ-lactone rac-(7) m.p. 109-111°. Six-membered cyclic orthoesters gave significantly higher yields than their five-membered counterparts; thus (6; R=H) reacted with rac-(5) to give the δ-lactone rac-(8; R=H) m.p. 130-132° in ca. 80% yield. With the same alcohol, rac-(6; R=Me) gave, as expected, approximately equal amounts of two δ-lactones, epimeric at the position bearing the lactonic oxygen atom; i.e. rac-(8; R=Me) and its epimer. The more strongly adsorbed epimer (Kieselgel; benzene-ethyl acetate) had m.p. 110-112°; the less, m.p. 117-119°.

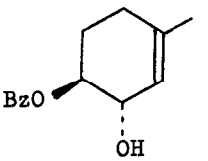
With alcohols such as rac-(5), containing two different groups at the allyl terminus, the cyclic orthoester reaction creates two new adjacent chiral centres, apparently with complete, certainly with very high, stereoselectivity. Their relative configurations are imposed by the geometry of the transition state (c.f. 9). Extensions of the related Meerwein-Eschenmoser[4] reaction can also create two new adjacent chiral centres[5]; with 1,1-dimethoxy-1-dimethylaminopropane the product from



(1) (2) (3)



(4)



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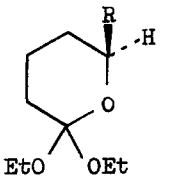
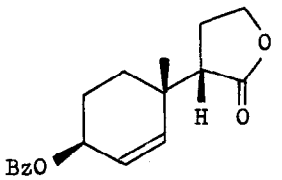


(6)



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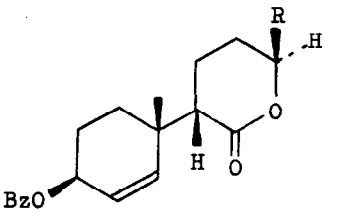

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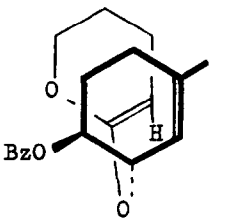

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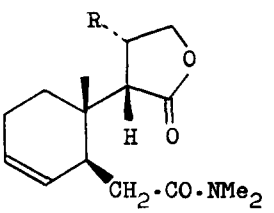

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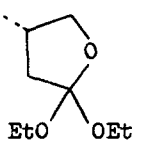

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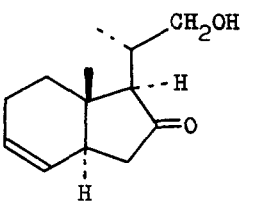

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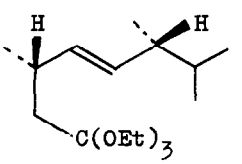

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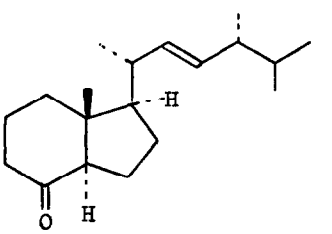

(14)

trans-crotyl alcohol is predominantly (85%) an erythro-dimethylamide, whereas cis-crotyl alcohol gives predominantly (90%) the threo isomer. The relative configurations obtained in the cyclic orthoester reaction are the reverse of those which result from the extended Meerwein-Eschenmoser reaction. Moreover, in products from the cyclic orthoester reaction two of the groups attached to one chiral centre can readily be further elaborated, and this should make the reaction of considerable value in the construction of compounds (e.g. terpenes) which contain adjacent tertiary or quaternary chiral centres.

The special stereochemical attributes of the cyclic orthoester reaction are not involved in a projected synthesis of the ketone (14). Debenzoylation of rac-(7) with methanolic sodium methoxide, and reaction of the product with 1,1-dimethoxy-1-dimethylaminoethane gave the dimethylamide rac-(10; R=H). Similar methods, starting with the optically active compounds (5) and (11) should give the dimethylamide (10; R=Me), which contains structural features necessary for the formation of the hydrindenone (12). From this, the ketone (14) should be accessible by standard methods.

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