Stereochemical Aspects of Some Claisen Rearrangements with Cyclic Orthoesters

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For some representative reactant pairs, chemical determinations have been made of the relative stereochemistry at the two new asymmetric centres which are set up when an allylic alcohol reacts with a cyclic orthoester. The results give directly the fractions of the total reaction which proceed through chair- and boat-type transition states; interpretations are provided in terms of steric interactions in these states. For some of the reactions there is evidence that the transition state (chair or boat) is not a symmetrical cyclohexane-like entity, the incipient new C–C bond being considerably longer than the C–O bond which is undergoing cleavage.

THE preceding paper [1] described rearrangement reactions between the cyclic allylic alcohol *rac*-(1) † and some cyclic orthoesters, and noted their remarkable stereoselectivity. In the reaction between *rac*-(1) and 2,2-diethoxytetrahydropyran (3),† for example, two new asymmetric centres are created at the termini of the new C–C bond; the configuration at the terminus in the cyclohexene ring is controlled directly by the configuration at the original allylic hydroxy-centre, whereas that at the new centre in the lactone ring is controlled by the geometry (chair-like or boat-like) of the transition state. In principle, two products, *rac*-(6) and *rac*-(4), can therefore be formed; only one product was obtained in practice. We attributed this initially [2] to the well known preference of Claisen rearrangements for a chair-like transition state.[3] Later, as a result of experiments with a wider range of orthoesters, we were led to revise this view,[4] and to make direct experimental determinations of the configurations present in representative reaction products. The present paper describes these determinations, and discusses the results in relation to the transition states of the reactions.

METHODS AND RESULTS

We show first that the product from *rac*-(1) and the orthoester (3) has the configuration *rac*-(4), and not *rac*-(6). It appeared possible to degrade compounds corresponding to these two structures by a route which would maintain their stereochemistry, and would give respectively the *threo*- and *erythro*-diols, *rac*-(9) and *rac*-(10). As a preliminary, therefore, authentic samples of these two diols were prepared from the Diels–Alder reaction pro-

† All the structures in this paper represent absolute configurations. Racemates are denoted by the prefix *rac*-, and enantiomers by the prefix *ent*-; thus *rac*-(1) means the racemate corresponding to the optically active compound (1), and *ent*-(1) means the enantiomer of compound (1).

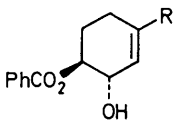
[1] C. B. Chapleo, P. Hallett, B. Lythgoe, I. Waterhouse, and P. W. Wright, preceding paper.

[2] C. B. Chapleo, P. Hallett, B. Lythgoe, and P. W. Wright, *Tetrahedron Letters*, 1974, 847.

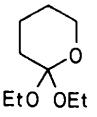
[3] P. Vittorelli, T. Winkler, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 1457; P. Vittorelli, H. J. Hansen, and H. Schmid, *ibid.*, 1975, **58**, 1293.

[4] B. Lythgoe and D. A. Metcalfe, *Tetrahedron Letters*, 1975, 2447.

ducts,[5] *rac*-(8) and *rac*-(7), respectively. The route used, which was the same in each case, is outlined in Scheme 1. The diols *rac*-(9) and *rac*-(10) so obtained proved



(1) R = Me
(2) R = H



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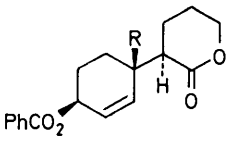
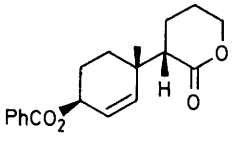


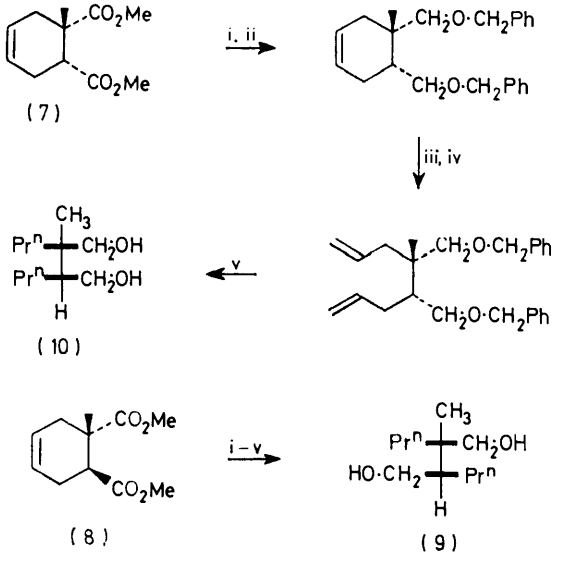
(4) R = Me
(5) R = H



(6)

easily distinguishable by their n.m.r. spectra, and by the properties of their bis-*p*-nitrobenzoates, m.p. **39** and 101°, respectively.

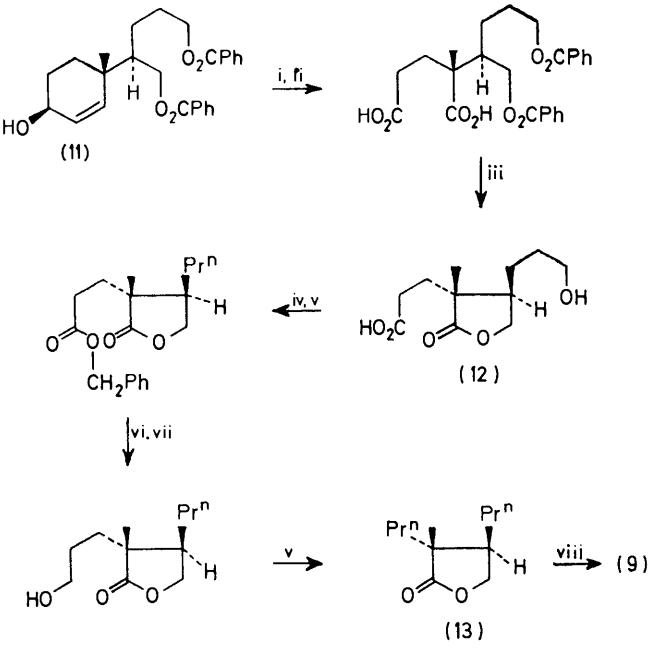
The cyclic orthoester reaction product *rac*-(4) was then reduced with lithium aluminium hydride to give a diprimary secondary triol which, by reaction with a restricted amount of benzoyl chloride, was converted into the diprimary dibenzoate *rac*-(11). This was then degraded, as shown in Scheme 2, to give the γ-butyrolactone *rac*-(13). None of the intermediates in this sequence, except the lactonic hydroxy-acid *rac*-(12), was crystalline, but they showed no sign of stereochemical heterogeneity;



SCHEME 1 Reagents: i, $LiAlH_4$; ii, $PhCH_2Cl$–KOH; iii, OsO_4–$NaIO_4$; iv, $CH_2{:}PPh_3$; v, H_2–Pd

they were routinely purified by p.l.c. Reaction of the lactone *rac*-(13) with lithium aluminium hydride gave a product which was identified by its n.m.r. spectrum and by the properties of its bis-*p*-nitrobenzoate, m.p. 39°, as *threo*-diol, *rac*-(9). This showed that the Claisen orthoester reaction product was the isomer *rac*-(4); it owes its formation to a boat-shaped transition state. We had, in fact, already reached this conclusion tentatively from the observation (see later) that reaction between *rac*-(1) and the orthoester *rac*-(19) gives *two* products; this could be rationalised if the reaction between *rac*-(1) and the parent orthoester (3) proceeded through a boat-shaped transition state, but not otherwise.

The available evidence suggests that the following products of reactions which are closely analogous to that leading to *rac*-(4) have analogous configurations, and are



SCHEME 2 Reagents: i, MnO_2; ii, RuO_4–$NaIO_4$;* iii, OH^-; H^+; iv, $PhCHN_2$; v, $(PhO)_3PMeI$; $NaBH_3CN$;† vi, H_2–Pd; vii, B_2H_6; viii, $LiAlH_4$

* D. M. Piatak, H. B. Bhat, and E. Caspi, *J. Org. Chem.*, 1969, **34**, 112.
† R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *Chem. Comm.*, 1971, 1097.

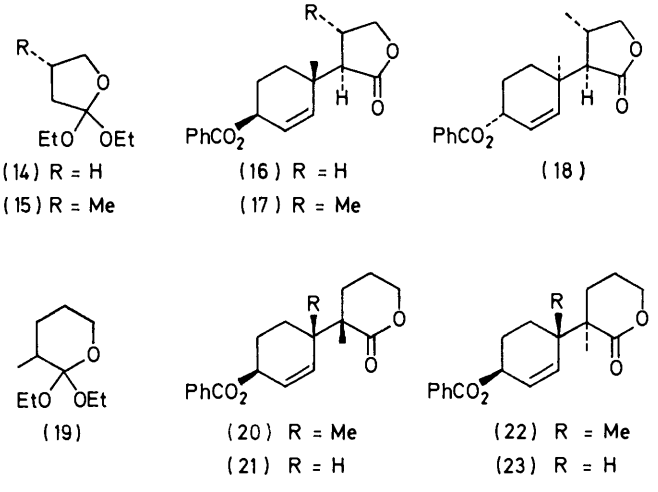
formed through boat-like transition states: (*a*) the δ-lactone *rac*-(5), sole product from the cyclohexenol *rac*-(2) and the orthoester (3); (*b*) the γ-lactone *rac*-(16), sole product [1] from *rac*-(1) and the orthoester (14); (*c*) the γ-lactone (17), sole product [1] from the optically active reaction partners (1) and (15). In this last case, confirmatory evidence is provided by the conversion [1] of (17), without change of configuration at the two relevant centres, into a perhydroindane derivative with the same stereochemistry as des-AB-cholestane.

Although only one product (17) is formed from the

[5] I. N. Nazarov and V. F. Kucherov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1954, 73; J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, 1967, **32**, 3919.

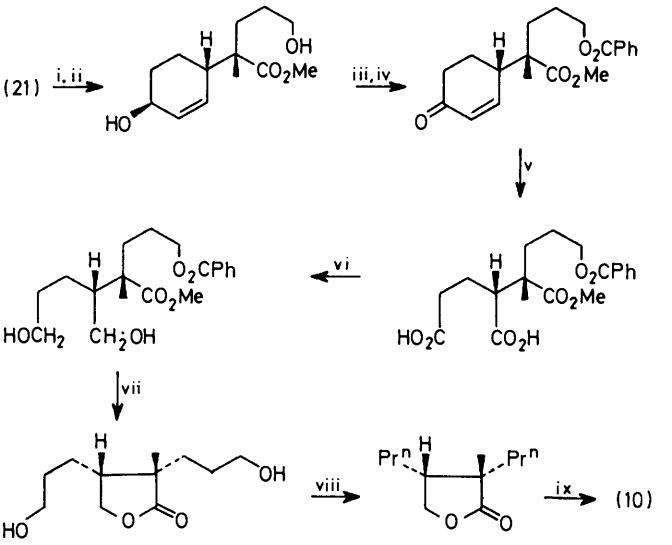
cyclohexenol (1) and the orthoester (15), reaction of *ent*-(1) with the same orthoester gave both possible diastereoisomers in the ratio *ca.* 70 : 30 (n.m.r.). The major (70%) isomer, obtained by crystallisation of the mixture, was shown to have the configuration (18) by hydrogenating it over palladium, so abolishing the asymmetry in the cyclohexane ring. The resulting dihydro-compound was identical with that obtained by similar hydrogenation of the γ-lactone (17). Thus the major product (18) arises by way of a chair-shaped transition state. This is tantamount to saying that reaction of (1) with *ent*-(15) must proceed similarly to give, as the major product, *ent*-(18).

Next we studied the effect of a methyl substituent at position 3 in the 2,2-diethoxytetrahydropyran ring. Reaction of the cyclohexanol *rac*-(1) and the cyclic orthoester *rac*-(19) gave two products (*ca.* 65 : 35); they were separated by chromatography, were shown not to be interconvertible under the conditions of the reaction, and were found to give a common dihydro-compound on hydrogenation over palladium. Evidently they were the pair of diastereoisomers *rac*-(20) and *rac*-(22) (not necessarily respectively). A similar mixture (*ca.* 65 : 35) of diastereoisomers *rac*-(21) and *rac*-(23) (not necessarily respectively) was obtained by interaction of the cyclohexenol *rac*-(2) and the orthoester *rac*-(19); these diastereoisomers were separated by chromatography. Two analogous products (*ca.* 65 : 35) were also formed when the cyclohexenol *rac*-(1) reacted with 2,2-diethoxy-3-methyltetrahydrofuran, but in this case, although their



presence was apparent from the n.m.r. spectra, the two components of the mixture could not easily be separated by chromatography.

It was of interest to determine the configuration of the major isomer of the pair *rac*-(21) and *rac*-(23), and we show that this isomer is in fact *rac*-(21), which is formed through a chair-shaped transition state. This identification follows from its degradation, as outlined in Scheme 3, to the *erythro*-diol *rac*-(10) (see Scheme 1). The diol was identified by its n.m.r. spectrum, and by conversion into its bis-*p*-nitrobenzoate, m.p. 101°. The close analogy between the results of the reactions between the cyclohexenols *rac*-(1) and -(2) and the orthoester (3) on the one hand, and between the same two cyclohexenols



SCHEME 3 Reagents: i, OH^-; H^+; ii, CH_2N_2; iii, MnO_2; iv, PhCOCL–pyridine; v, RuO_4–$NaIO_4$; vi, B_2H_6; vii, NaOMe–MeOH: viii, $(PhO)_3PMeI$; $NaBH_3CN$; ix, $LiAlH_4$

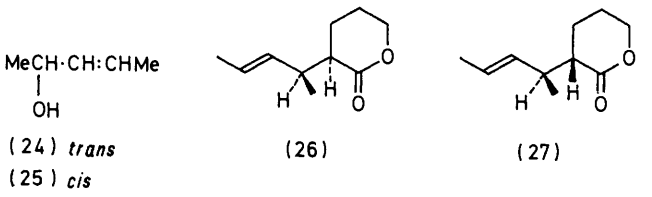
and the orthoester *rac*-(19) on the other, leads us to conclude that the major (65%) isomer from the reaction between *rac*-(1) and *rac*-(19) also arises through a chair-shaped transition state, and has the configuration *rac*-(20).

Since the foregoing results all related to the use of cyclic allylic alcohols, it seemed desirable to extend them by the examination of the behaviour of representative acyclic allylic alcohols, and the simplest compounds which show the stereochemical effects which are our present concern are the geometrically isomeric alcohols *rac*-(24) [6] and *rac*-(25).[7] The products expected from reaction of these isomers with the orthoester (3) were the diastereoisomers *rac*-(26) and *rac*-(27), in both of which the double bond has the *trans*-geometry; in the event, this expectation was fulfilled.

We proposed to identify the isomers *rac*-(26) and *rac*-(27) by converting them into the diastereoisomeric primary alcohols *rac*-(31) and *rac*-(30), and a preliminary preparation of authentic samples of these two alcohols was therefore undertaken. As before, configurational options were obtained by reliance on products of Diels–Alder reactions. The commercially available mixture (*ca.* 4 : 1) of the *trans*- and *cis*-forms of 2-methyl-1,2,3,6-tetrahydrobenzaldehyde provided, after reduction with lithium aluminium hydride, and crystallisation of the *p*-nitrobenzoates of the resulting alcohol mixture, the pure *trans*-derivative, m.p. 42—44°, which, on hydrolysis,

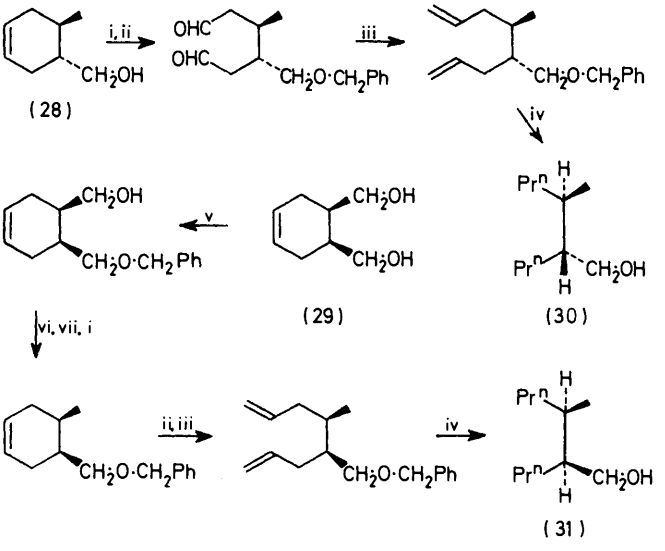
[6] E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 1953, 3144.
[7] R. Heilmann, G. de Gaudemaris, and P. Arnaud, *Bull. Soc. chim. France*, 1957, 119.

gave the pure alcohol [8] *rac*-(28). This was transformed as shown in Scheme 4 into the *threo*-alcohol *rac*-(30). As



starting material for the preparation of the corresponding *erythro*-alcohol *rac*-(31) we used *cis*-1,2-bis(hydroxymethyl)cyclohex-4-ene (29); its transformation into the desired alcohol is outlined in Scheme 4. The alcohols *rac*-(30) and *rac*-(31) were readily distinguished by conversion into their 3,5-dinitrobenzoates, m.p. 43 and 29°, respectively.

The *trans*-allylic alcohol *rac*-(24) was prepared by treatment of crotonaldehyde with methylmagnesium iodide. It reacted in boiling benzene with 2,2-diethoxytetrahydropyran (3) to give in *ca.* 50% yield a mixture (*ca.* 88 : 12 by g.l.c.) of two δ-lactones. The major product, which had the longer retention time, was also distinguishable from the minor by the position of its CH*Me* n.m.r. signal. When a portion of the mixture was hydrogenated over palladium, g.l.c. of the saturated

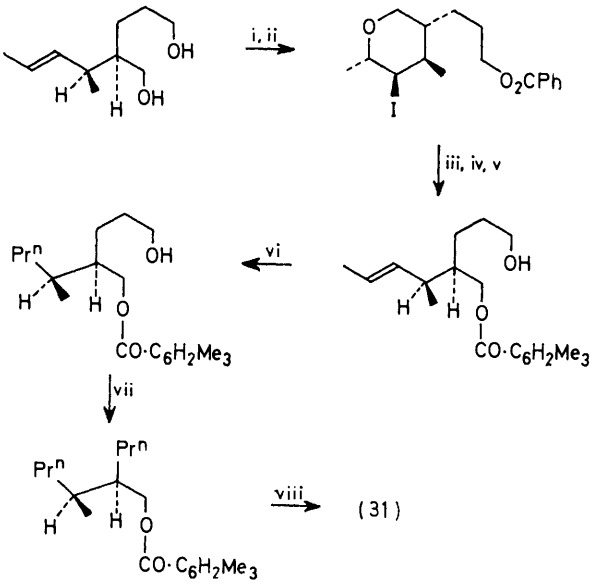


SCHEME 4 Reagents: i, NaH–Me_2N·CHO; $PhCH_2Br$;* ii, OsO_4–$NaIO_4$; iii, CH_2:PPh_3; iv, H_2–Pd; v, PhCOCl–pyridine; vi, $(PhO)_3PMeI$; $NaBH_3CN$; vii, OH^-

* J. S. Brimacombe, D. Portsmouth, and M. Stacey, *J. Chem. Soc.*, 1964, 5614.

material showed the presence of two products in the same ratio as their unsaturated precursors. The latter are not, therefore, *cis,trans*-isomers at the double bond; they are the diastereoisomers *rac*-(26) and *rac*-(27) which contain ($\nu_{max.}$ 970 cm^{-1}) a *trans*-double bond.

The mixture of δ-lactones (88 : 12) from the orthoester reaction was reduced with lithium aluminium hydride to give isomeric diprimary diols, which were then transformed by the reaction sequence shown in Scheme 5. The formulae correspond to the products derived from the major δ-lactone, now shown to be *rac*-(26). During



SCHEME 5 Reagents: i, aq. KI_3;* ii, PhCOCl–pyridine; iii, Zn–AcOH; iv, 2,4,6-$Me_3C_6H_2$·CO_2H–$(CF_3CO)_2O$; v, OH^-; vi, H_2–Pd; vii, $(PhO)_3PMeI$; $NaBH_3CN$; viii, $LiAlH_4$

* K. Bowden, B. Lythgoe, and D. J. S. Marsden, *J. Chem. Soc.*, 1959, 1662.

this sequence, the intermediates, which were non-crystalline, were treated so as to avoid removing one of the two stereoisomers present. The final product of the reaction sequence, a mixture of alcohols, was converted into the 3,5-dinitrobenzoates; crystallisation gave the homogeneous derivative, m.p. 28—29°, of the *erythro*-alcohol *rac*-(31) in *ca.* 64% yield from the alcohol mixture. The major (88%) product of the orthoester reaction with *rac*-(24) was therefore the δ-lactone *rac*-(26), which is formed by way of a chair-shaped transition state. The minor product, *rac*-(27), is formed by way of a boat-shaped transition state.

The *cis*-allylic alcohol [7] *rac*-(25) was prepared from pent-3-yn-2-ol by hydrogenation over Lindlar catalyst. *cis*-Pent-3-en-2-ol *rac*-(25) and 2,2-diethoxytetrahydropyran (3) reacted in boiling benzene to give a mixture (*ca.* 70 : 30) of the same two lactones (g.l.c.; n.m.r.) as resulted from the *trans*-alcohol *rac*-(24). In the present case, however, the major isomer was *rac*-(27) and the minor *rac*-(26). Thus, here again, the major isomer (*ca.* 70%) arises by way of a chair-shaped transition state.

[8] H. E. French and D. M. Gallagher, *J. Amer. Chem. Soc.*, 1942, **64**, 1497.

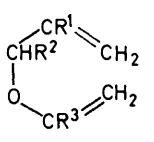
The above results are summarised, for convenience, in the Table.

Reaction	Allylic alcohol	Orthoester	Major or exclusive product	Transition state
A	*rac*-(24)	(3)	*rac*-(26)	88% Chair
B	*rac*-(25)	(3)	*rac*-(27)	70% Chair
C	*rac*-(1)	(3)	*rac*-(4)	100% Boat
D	*rac*-(2)	(3)	*rac*-(5)	100% Boat
E	*rac*-(1)	(14)	*rac*-(16)	100% Boat
F	(1)	(15)	(17)	100% Boat
G	(1)	*ent*-(15)	*ent*-(18)	70% Chair
H	*rac*-(1)	*rac*-(19)	*rac*-(20)	65% Chair
J	*rac*-(2)	*rac*-(19)	*rac*-(21)	65% Chair

DISCUSSION

In some forms [9] of the Claisen rearrangement the interpretation of product stereochemistry is complicated by uncertainties as to the geometry of the vinyl (as opposed to the allyl) double bond. In the present reactions no such uncertainty exists, and the geometry of the transition state can be deduced directly from the nature of the product. The results shown in the Table offer a striking illustration of the way in which reactant structure can control the reaction pathway; it was therefore of interest to attempt to interpret the results in terms of currently held views on the nature of the transition states.

For the related Cope rearrangement, Doering [10] in 1971 stated that ' the geometry to be assigned to the converted transition state has remained undecided between the familiar 4-centred π complex ' (pictured, for example, by Doering and Roth [11]) ' and the cyclohexane-2,5-diyl diradical . . .' (chair and boat forms of the latter were depicted in 1974 by Dewar).[12] In 1973, Faulkner and



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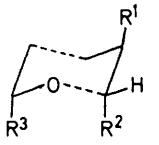

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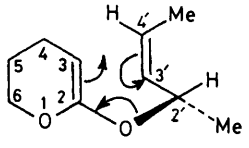

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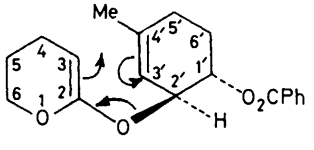

(35)

Petersen [13] showed that, in its application to the Claisen rearrangement, the π-complex model failed to account for the effect of substituents on the experimentally determined ratio of *trans*- to *cis*-olefin formed in the reaction. They therefore proposed instead ' a cyclohexane-like transition state, with all six centres tetrahedral, in which the residues R^1 and R^3 ' [see (32)] ' occupy axial conformations '. The influence of the nature of large groups R^2 and R^3 in decreasing the amount of *cis*-olefinic product was then apparent from the conformation (33) which leads to *cis*-isomer. Although it was not so described, Faulkner's chair-shaped transition state is clearly the cyclohexane-2,5-diyl diradical of Doering. It is in terms of this and the corresponding boat form that we shall discuss our results. We mention also at this stage a further aspect of the transition states which has already been pointed out by Hansen and Schmid.[14] In a typical Cope rearrangement, the transition state should

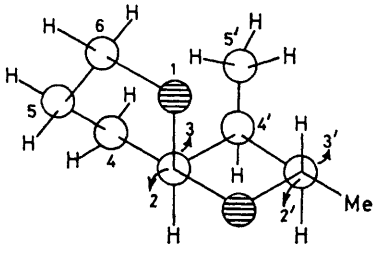

FIGURE 1 Idealised chair-form of cyclohexanediyl diradical transition state for the reaction between (*Z*)-pent-3-en-2-ol and 2,2-diethoxytetrahydropyran [Newman projection along the 2,3- and 2′,3′-bonds; shaded circles are oxygen and open circles carbon atoms; *cf.* structure (34)]

lie about half-way along the reaction co-ordinate between reactants and products; in the Claisen rearrangement, which is irreversible, the transition state is expected to lie closer to the reactants. It will be seen below that our results illustrate the importance of this consideration.

Figures 1 and 2 illustrate idealised chair and boat forms respectively of the transition state for reaction B between (*Z*)-pent-3-en-2-ol and 2,2-diethoxytetrahydropyran; whereas the boat diagram is sufficiently clear as a perspective, the corresponding perspective for the chair form seems confusing and uninformative, and we therefore use a diagram based on a Newman projection of the transition state ring, viewed along the C(2)–C(3) orthoester bond and along the C(2′)–C(3′) bond of the allylic alcohol. In the chair (Figure 1) the orthoester ring is represented as a boat; this form obviates some unfavourable interactions which are present if it is a chair. We have no evidence on the nature of the orthoester ring in the boat transition state (Figure 2); there are no important unfavourable interactions if it is a chair, and we have therefore used that form.

We consider first reaction A (see Table). Diagrams for the chair and boat forms of its transition state can be constructed from Figures 1 and 2, respectively, simply

[9] W. Sucrow and W. Richter, *Chem. Ber.*, 1971, **104**, 3679; W. Sucrow, B. Schubert, W. Richter, and M. Slopianka, *ibid.*,' p. 3689; W. Sucrow, M. Slopianka, and P. P. Caldeira, *ibid.*, 1975, **108**, 1103; R. E. Ireland and A. K. Willard, *Tetrahedron Letters*, 1975, 3975.

[10] W. E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, 1971, **27**, 5299.

[11] W. E. Doering and W. R. Roth, *Tetrahedron*, 1962, **18**, 67.

[12] M. J. S. Dewar, S. Kirschner, H. W. Kollmar, and L. E. Wade, *J. Amer. Chem. Soc.*, 1974, **96**, 5242.

[13] D. J. Faulkner and M. R. Petersen, *J. Amer. Chem. Soc.*, 1973, **95**, 553.

[14] H. J. Hansen and H. Schmid, *Tetrahedron*, 1974, **30**, 1959.

by interchanging the positions of the H and the Me at C-4′. It is then clear that in neither the chair nor the boat model are there any very serious steric interactions;

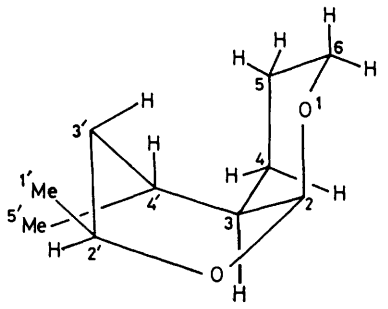

FIGURE 2 Idealised boat-form of cyclohexanediyl diradical transition state (perspective) for the reaction between (*Z*)-pent-3-en-2-ol and 2,2-diethoxytetrahydropyran; *cf.* structure (34)

it is therefore not surprising that, experimentally, the chair-type reaction is preferred.

If we compare reaction B with reaction A, it is apparent that in the chair form of the transition state for reaction B an additional 1,3-diaxial interaction, between the OCH_2 group at C-2, and the Me at C-4′, is present. In the boat-diagram for reaction B, an eclipsing butane interaction which is present in reaction A between the C-5′ Me and the C-4 CH_2 groups, has been relieved. Both these effects, of which the first is expected to be the more important, favour an increase in the proportion of boat-type reaction in reaction B as compared with reaction A. It is interesting to note the modest scale of the shift (18%) thus caused.

We next compare reaction C with reaction B. The idealised chair and boat forms of the transition state for reaction C are represented in Figures 3 and 4. In both,

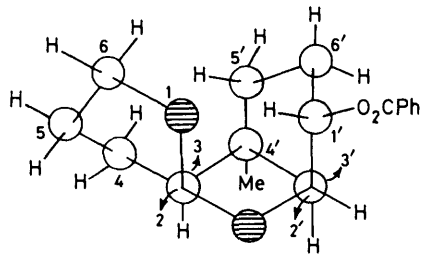

FIGURE 3 Idealised chair-form of cyclohexanediyl diradical transition state for the reaction between the allylic alcohol (1) and 2,2-diethoxytetrahydropyran [Newman projection along the 2,3- and 2′,3′-bonds; shaded circles are oxygen, open circles carbon atoms; *cf.* structure (35)]

the cyclohexene ring is portrayed as a boat; models suggest that in reactions with cyclohexenols the double bond termini cannot approach close enough to initiate rearrangement unless the ring is boat-shaped; this form then persists along the reaction co-ordinate. Comparing the chair models (Figures 3 and 1), the principal new effect is the introduction of an extra 1,3-diaxial interaction, between the OCH_2 group at C-2 and the C-1′ group CHOBz attached to C-2′. In the boat model for reaction C an additional eclipsed butane interaction is present between the methyl at C-4′ and the C-4 methylene group at C-3; the magnitude of this effect is unlikely to approach that of the new 1,3-diaxial interaction in the chair form, and it was therefore to be expected that in reaction C a further increase in boat form reaction would be observed. What is surprising, at first sight at least, is the magnitude of the shift; one might have expected a shift of 20%, comparable to that in passing from reaction A to reaction B; in fact, all chair form reaction is extinguished. This dramatic disparity is interpreted as meaning that the chair-type transition state is here not symmetrical, as we are accustomed to draw chair forms in cyclohexane compounds; the C(2)–C(4′) distance must be considerably greater than the C(2)–C(2′) distance. Such a lack of symmetry is in fact inherent in a reaction in which the transition state is closer to reactants than to products;

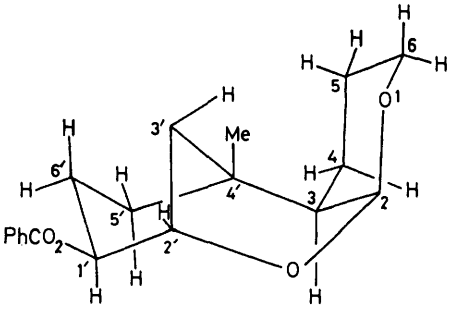

FIGURE 4 Idealised boat-form of cyclohexanediyl diradical transition state (perspective) for the reaction between the allylic alcohol (1) and 2,2-diethoxytetrahydropyran; *cf.* structure (35)

the O–C(2′) distance remains short, but the C(3)–C(4′) distance has not yet contracted to the normal single bond distance. In this cyclic modification, as in the ordinary Claisen orthoester [15] reaction, the dominant interaction in the chair transition state is not that between the axial groups at C-2 and C-4′, but between those at C-2 and C-2′, the power of which is apparent from the small amounts of *cis*-olefin to which the reaction normally gives rise.[13]

Models of the chair transition state for reaction E show little essential difference from the situation depicted in Figure 3, apart from the five-membered nature of the heterocycle; the same is also true of the boat transition state in relation to Figure 4. It is therefore understandable that the preference for boat-type reaction found in reaction C should also prevail in reaction E. When, as in reaction F, an (*S*)-methyl group is introduced onto C-4 of the heterocyclic ring, no new interactions are introduced into the boat-form transition state. In the chair-form transition state however, there is then a significant

[15] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, 1970, **92**, 741.

interaction between the new methyl group, and the C-4′-attached methyl group. It is therefore to be expected that reaction F, like reaction E, will follow an exclusive boat-course; and this accords with the experimental findings. In reaction G, however, the new (*R*)-methyl group in the orthoester ring shows no unfavourable interactions in the chair transition state, but in the boat transition state it shows a very strong unfavourable interaction with the methyl group at C-4′. It is no doubt this interaction which is responsible, in reaction G as compared with reaction F, for the dramatic change from 100% boat- to 70% chair-type reaction.

Finally, we compare the outcome of reaction H with that of reaction C. The new methyl group introduced into the orthoester component at C-3 (see Figure 3; H at C-3 replaced by Me) mainly affects the chair transition state by introducing a new 1,3-diaxial H–Me interaction, and a new gauche Me–Me interaction. It affects the boat transition state (see Figure 4; H at C-3 replaced by Me) mainly by introducing a new eclipsed butane interaction between the new methyl and the C-5′ methylene groups. The effect of the latter might be thought to be about the same as that of the existing eclipsed interaction between the methyl group at C-4′ and the C-4 methylene group. The comparative outcome of the reactions C and D, and H and J, suggests that the magnitude of this effect, in relation to others now considered, is not large. The models of the transition states based on Figures 3 and 4 do not therefore provide a reason for the dramatic change in reaction mode caused by the introduction of the new methyl group. However, if conformations are considered which are closer to reactants along the reaction co-ordinate, no strong interactions are apparent on the chair pathway, but on the boat pathway the new methyl group causes a very strong interaction with the methylene group at C-5′. In the course of traversing the reaction co-ordinate to the idealised symmetrical representation (Figure 4) of the boat transition state, this unfavourable interaction is first maximised, and then relieved. In result, the effective energy maximum lies at a point considerably closer to the initial state than that represented by the symmetrical model of Figure 4. At this point, the adverse interaction is potent, and its effect is to divert the reaction decisively in the direction of the chair form.

In summary then, we conclude that our present experimental findings can be satisfactorily accounted for if, but only if, proper allowance is made for factors which can distort the idealised symmetrical transition state to which reference is usually made, by influencing the position along the reaction co-ordinate at which the energy maximum actually occurs.

EXPERIMENTAL

Unless otherwise specified, ^{1}H n.m.r. data refer to solutions in deuteriochloroform, and light petroleum refers to the fraction b.p. 60—80 °C. T.l.c. and p.l.c. were carried out with Kieselgel GF_{254}. $[\alpha]_D$ Data refer to solutions in chloroform.

(±)-erythro-3-*Hydroxymethyl*-3-*methyl*-2-*propylhexan*-1-*ol*, rac-(10).—(±)-1-Methylcyclohex-4-ene-1,*cis*-2-dimethanol [16] (2 g), powdered potassium hydroxide (14.5 g), and benzyl chloride (25 cm^3) were stirred vigorously together under reflux for 8 h in boiling xylene (40 cm^3), water formed being removed azeotropically. Water was added to the cooled mixture, and steam-volatile materials were removed in steam. The product was then isolated with chloroform; evaporation of the solvent, followed by removal of dibenzyl ether at 120 °C and 0.5 mmHg gave the bis(benzyl ether) of the starting diol (78%) still containing a little dibenzyl ether. It had $\nu_{max.}$ ($CHCl_3$) 1 095s, 695m, and 655w cm^{-1}, τ 2.70 (10 H, s, ArH), 4.42 (2 H, s, =CH), 5.58 (4 H, s, $PhCH_2O$), and 8.90 (3 H, s, CH_3) (Found: M^+, 336.208 721. $C_{23}H_{28}O_2$ requires M, 336.208 919).

The above bis(benzyl ether) (2 g) in ether (40 cm^3) and water (40 cm^3) was stirred vigorously under nitrogen, and osmium tetraoxide (0.05 mol) was added. After 15 min freshly powdered sodium periodate (2.1 mol) was added in portions during 1 h, and the mixture was stirred overnight. The mixture was then examined (t.l.c.) for the presence of starting material, and if any was present, more periodate was added, and the reaction continued for up to 3 days if necessary. Water was added, the ether layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with aqueous sodium sulphite, aqueous sodium carbonate, and brine, and then dried and evaporated. The crude dialdehyde thus obtained (yield *ca.* 50% by n.m.r.) showed $\nu_{max.}$ ($CHCl_3$) 2 730w, 1 720s, 1 600w, 1 585w, 1 090s, and 695s cm^{-1}, τ 0.15 (1 H, t, *J* 3 Hz, $CH_2{\cdot}CHO$), 0.31 (1 H, t, *J* 2 Hz, $CH_2{\cdot}CHO$), 5.57 (4 H, s, 2 × $O{\cdot}CH_2Ph$), and 9.03 (3 H, s, CH_3).

To a stirred solution of methylenetriphenylphosphorane (2.4 mol) in dry tetrahydrofuran under nitrogen the above dialdehyde (1 mol), dissolved in dry tetrahydrofuran, was added slowly. Stirring was continued at room temperature for 4 h, and the suspension was then heated for 15 h under reflux. To the cooled mixture, water (1 cm^3) was added, followed by ether, and the solution was washed with 2N-hydrochloric acid and then with brine, and then dried and evaporated. Chromatography on Kieselgel (benzene–light petroleum, 1 : 1) removed triphenylphosphine oxide, and gave the crude diene (37%) as an oil, $\nu_{max.}$ 1 640w, 1 600w, 1 585w, 1 090s, 995m, 915m, and 695s cm^{-1}, τ 3.8—4.43 (2 H, m, 2 × =CHR), 4.74—5.20 (4 H, m, 2 × CH_2=CHR), 5.54 (4 H, s, 2 × $O{\cdot}CH_2Ph$), 6.42br (2 H, d, $CH{\cdot}CH_2{\cdot}O{\cdot}CH_2Ph$), 6.71 (2 H, s, $CH_2{\cdot}O{\cdot}CH_2Ph$), and 9.11 (3 H, s, CH_3).

Hydrogenation (5% Pd–C in ethanol) of the above material, and work-up in the usual way, gave the crude (±)-*erythro*-diol (10) as an oil [*ca.* 12% overall from the ester *rac*-(7)], $\nu_{max.}$ ($CHCl_3$) 3 620w, 3 340m, 1 045m, and 1 020m cm^{-1}, τ 6.36br (2 H, s, $W_{\frac{1}{2}}$ 5 Hz, $CH_2{\cdot}OH$), and 9.02 (3 H, s, CH_3).

The *bis*-p-*nitrobenzoate* formed crystals, m.p. 100—101° (from chloroform–light petroleum), τ 8.87 (3 H, s, CH_3) (Found: C, 61.9; H, 6.0; N, 5.65. $C_{25}H_{30}N_2O_8$ requires C, 61.7; H, 6.2; N, 5.8%).

(±)-threo-3-*Hydroxymethyl*-3-*methyl*-2-*propylhexan*-1-*ol*, rac-(9).—The starting material, dimethyl 1-methylcyclohex-4-ene-1,*trans*-2-dicarboxylate, *rac*-(8), was converted by reduction with lithium aluminium hydride into the corresponding diol, and then by reaction with benzyl chloride and potassium hydroxide into the bis(benzyl ether), τ 4.40br (2

[16] B. W. Langley, B. Lythgoe, B. Scales, R. M. Scrowston, S. Trippett, and D. Wray, *J. Chem. Soc.*, 1962, 2972.

H, s, =CH), 5.56 (4 H, s, 2 × PhCH_2·O), and 9.13 (3 H, s, CH_3) (Found: M^+, 336.208 385. $C_{23}H_{28}O_2$ requires M, 336.208 385). This was converted, as described for the *cis*-isomer, into the *threo*-dialdehyde, τ 0.07 (1 H, t, J 2.5 Hz, CH_2·C*H*O), 0.18 (1 H, t, J 1.5 Hz, CH_2·C*H*O), 5.54 (4 H, s, 2 × O·CH_2Ph), and 8.98 (3 H, s, CH_3). Reaction with methylenetriphenylphosphorane, as described for the *erythro*-isomer, gave the *threo*-diene, τ 3.9—4.5 (2 H, m, 2 × =C*H*R), 4.8—5.2 (4 H, m, 2 × CH_2=CHR), 5.57 (4 H, s, 2 × O·CH_2Ph), 6.46br (2 H, d, CH·CH_2·O·CH_2Ph), 6.68 (2 H, s, CH_2·O·CH_2Ph), and 9.08 (3 H, s, CH_3).

Hydrogenation gave the crude *threo*-diol (9), τ 6.36br (2 H, s, $W_{\frac{1}{2}}$ 5 Hz, CH_2·OH) and 9.23 (3 H, s, CH_3). The *bis*-p-*nitrobenzoate* formed needles, m.p. 37—39° (from chloroform–light petroleum), τ 8.90 (3 H, s, CH_3) (Found: C, 61.65; H, 6.2; N, 5.7. $C_{25}H_{30}N_2O_8$ requires C, 61.7; H, 6.2; N, 5.8%).

Degradation of the Benzoate Lactone (4) *to the Lactonic Acid* (12).—The benzoate lactone (4) was reduced with lithium aluminium hydride in ether to give a mixture of benzyl alcohol and the desired triol; this mixture was dissolved in water and washed with benzene, so removing most of the benzyl alcohol. The triol, isolated by continuous extraction with ether, formed a gum. A portion (3.118 g), dissolved in dry pyridine (10 g) was stirred at 0 °C during dropwise addition (3 h) of benzoyl chloride (4.2 g) in chloroform (170 cm³). Stirring was continued while the mixture was allowed to reach room temperature, and for a further 16 h; water (0.1 cm³) was then added, and stirring was continued for 1 h. The solution was diluted with much ether, and was washed thoroughly with water; the washings were retained for recovery of unchanged triol. The organic phase was washed with dilute hydrochloric acid, aqueous sodium carbonate, and brine, and was dried and evaporated. Chromatography on neutral alumina (grade III) with benzene gave the tribenzoate of the triol (2 g); elution with 5% ethyl acetate in benzene gave a dibenzoate fraction (3 g) containing the dibenzoate (11). A portion (270 mg) in acetone (30 cm³) was stirred with active manganese dioxide for 5 h at 25 °C; the solution was filtered, the residue was washed with boiling acetone, and the filtrate and washings were evaporated under reduced pressure. P.l.c. (10% ethyl acetate–benzene) gave as the less polar fraction the αβ-unsaturated ketone dibenzoate (180 mg), $\lambda_{max.}$ (EtOH) 280 nm (ε 34,400), $\nu_{max.}$ ($CHCl_3$) 1 715s, 1 675s, 1 600w, 1 585w, 1 275s, and 710m cm^{-1}, τ 3.2 (1 H, d, J 10.5 Hz, β =CH of enone), 4.06 (1 H, d, J 10.5 Hz, α =CH of enone), 5.4—5.8 (4 H, m, 2 × CH_2·O·CO), 7.51 (2 H, distorted t, J *ca.* 5 Hz, CH_2·CO), and 8.69 (3 H, s, CH_3).

To finely powdered ruthenium dioxide (30 mg), suspended in acetone (15 cm³), was added sodium periodate (120 mg) in the minimum amount of water; the mixture was stirred for 30 min, and stirring was continued while a solution of the above oxo-dibenzoate (236 mg) in acetone (15 cm³) was added dropwise; at the same time more periodate (900 mg) in acetone (4.5 cm³) and water (4.5 cm³) was added. Stirring was continued for a further 16 h, and t.l.c. then showed the absence of starting material; propan-2-ol (4 cm³) was added to destroy the oxidant. The mixture was filtered, the residue was washed with boiling acetone, and the filtrate and washings were evaporated under reduced pressure. The residue was dissolved in ethyl acetate–ether and the gummy acidic material (212 mg) was isolated by extraction with aqueous sodium hydrogen carbonate. It was kept at room temperature overnight with a solution of sodium hydroxide (110 mg) in water (5 cm³), and the mixture was then treated with N-hydrochloric acid (2.8 cm³). The white precipitate of benzoic acid was removed by extraction four times with light petroleum; continuous extraction of the aqueous phase with chloroform then gave the *hydroxylactonic acid* rac-(12), which separated from chloroform–light petroleum as needles (80 mg), m.p. 121—122.5°, $\nu_{max.}$ (Nujol) 3 440m, 1 760s, and 1 715s cm^{-1}, τ [$(CD_3)_2CO$] 5.57 (1 H, t, J 9 Hz), 6.10 (1 H, t, J 9 Hz, CO·O·CH_2), 6.40 (2 H, distorted t, J *ca.* 6 Hz, CH_2·OH), and 8.90 (3 H, s, CH_3) (Found: C, 57.2; H, 7.75. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%).

Conversion of the Lactonic Acid rac-(12) *into the* threo-*Diol* rac-(9).—The lactonic acid (12) (500 mg) was kept overnight in tetrahydrofuran (5 cm³) with an excess of ethereal α-diazotoluene and the excess of reagent was then destroyed with ethereal acetic acid. The solution was evaporated under reduced pressure, and the residue was chromatographed on silica, impurities being removed with 2% ethyl acetate–benzene, and with ether. Elution with ethyl acetate then gave a hydroxy-benzyl ester lactone as an oil (627 mg), $\nu_{max.}$ ($CHCl_3$) 3 620w, 3 500w, 1 765s, 1 730s, and 1 015m cm^{-1}, τ 8.90 (3 H, s, CH_3), *m/e* 320 (M^+) and 91 (base peak, $PhCH_2$). The hydroxy-ester (627 mg) in dry hexamethylphosphoramide (10 cm³) and triphenyl phosphite methiodide (1.8 g) were stirred together under nitrogen at room temperature for 30 min. The mixture was then warmed to 70 °C, sodium cyanoborohydride (488 mg) was added, and stirring was continued at the same temperature for 2.5 h. The mixture was then poured into aqueous 5% sodium chloride (100 cm³) and the product, isolated from the aqueous solution with ether, was subjected to p.l.c. to give the benzyl ester lactone (354 mg), $\nu_{max.}$ ($CHCl_3$) 1 765s, 1 730s, 1 610w, 1 500w, 1 265s, 1 015m, and 695m cm^{-1}, τ 2.68 (5 H, s, ArH), 4.91 (2 H, s, O·CH_2Ph), 5.78 and 6.24 (2 H, 2 dd, J 8 and 9, and 9 and 9 Hz, OCH_2 of lactone), and 8.96 (3 H, s, CH_3) (Found: M^+, 304.165 61. Calc. for $C_{18}H_{24}O_4$: M, 304.167 45). Hydrogenation in ethanol over 5% palladised charcoal gave the lactonic acid (225 mg) as an oil, $\nu_{max.}$ ($CHCl_3$) 1 765s, 1 715s, and 1 015m cm^{-1}, τ 8.88 (3 H, s, CH_3) (Found: M^+, 214.121 01. $C_{11}H_{18}O_4$ requires M, 214.120 50).

The lactonic acid (200 mg) in dry tetrahydrofuran was stirred and cooled (−5 to 0 °C) under nitrogen during dropwise addition of a solution of diborane in tetrahydrofuran (0.55 cm³ of a solution 1.71M in BH_3). The mixture was stirred overnight at room temperature, and then cooled to 0 °C and treated with water (1 cm³). After 30 min, aqueous sodium hydrogen carbonate (5 cm³) was added, and ether, and the organic phase was separated, washed, dried, and evaporated, giving the lactonic alcohol as a gum, $\nu_{max.}$ (film) 3 620w, 3 480w, 1 765s, and 1 015m cm^{-1}, τ 8.90 (3 H, s, CH_3) (Found: M^+, 200.141 62. Calc. for $C_{11}H_{20}O_3$: M, 200.141 24).

Deoxygenation of this alcohol (160 mg) with triphenyl phosphite methiodide, followed by sodium cyanoborohydride, was effected in the way already described, and the product was purified by p.l.c. to give the lactone *rac*-(13) (112 mg) as a liquid, $\nu_{max.}$ ($CHCl_3$) 1 765s and 1 015m cm^{-1}, τ 8.93 (3 H, s, CH_3). The lactone (112 mg) was reduced in the usual way with lithium aluminium hydride (23 mg) in ether (3 cm³); this gave the *threo*-diol (9) as a viscous oil (110 mg) with R_F (25% ethyl acetate–benzene), i.r., and n.m.r. data identical with those of authentic material (described above). A sample (108 mg) was converted into

the bis-*p*-nitrobenzoate; it formed needles (180 mg), m.p. 37—39°, identical (mixed m.p. and i.r. and n.m.r. spectra) with authentic material.

The Benzoate Lactone rac-(5).—Interaction of a 1 : 1 mixture of the isomeric monobenzoates [17] of (±)-cyclohex-3-ene-1,*trans*-2-diol with 2,2-diethoxytetrahydropyran, as described [1] for the preparation of *rac*-(4), and chromatography of the crude product on silica gel (5% EtOAc in C_6H_6) gave (2RS)-2-[(4SR)-4-*benzoyloxycyclohex*-2-*enyl*]*pentan*-5-*olide*, rac-(5) (80%). It formed plates (from chloroform–ether–light petroleum), m.p. 108.5—109°, $\nu_{max.}$ ($CHCl_3$) 1 715s, 1 600w, 1 585w, 1 275s, and 710m cm^{-1}, τ 4.14br (2 H, s, =CH), 4.39br (1 H, distorted t, *J ca.* 9 Hz, C*H*·OBz), 5.69 (2 H, distorted t, *J* 6 Hz, CO·O·CH_2 of lactone), and 6.99 (1 H, m, CH·CO of lactone) (Found: C, 72.2; H, 6.65. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%).

Interaction of the Allylic Alcohol ent-(1) *with the Orthoester* (15).—The alcohol *ent*-(1) (154 mg) and the orthoester (15) (347 mg) were brought into reaction at 140 °C in xylene (10 cm^3) in the presence of propionic acid for 23 h. The crude product, purified by p.l.c. (5% EtOAc–C_6H_6) gave the alcohol *ent*-(1) (58 mg) and a mixture (95 mg) of benzoate lactones, not resolved by t.l.c. It showed tertiary methyl n.m.r. signals at τ 8.64(s) and (major isomer) 8.76(s). Crystallisation from chloroform–light petroleum gave (2R,3R)-2-[(1R,4R)-4-*benzoyloxy*-1-*methylcyclohex*-2-*enyl*]-3-*methylbutan*-4-*olide* (18) as prisms (38 mg), m.p. 136—138°, $[\alpha]_D^{24}$ + 112° (*c* 0.98), $\nu_{max.}$ ($CHCl_3$) 1 760s, 1 712s, 1 270s, and 708s cm^{-1}, τ 1.95 (2 H, m, ArH), 2.53 (3 H, m, ArH), 4.12 (1 H, dd, *J* 10 and 3 Hz, =CH), 4.31 (1 H, d, *J* 10 Hz, =CH), 4.49 (1 H, m, C*H*·OBz), 5.64 (1 H, dd, J_{gem} 9, J_{vic} 6 Hz, CH·O), 6.22 (1 H, dd, J_{gem} 9, J_{vic} 6 Hz, CH·O), 8.76 (3 H, s, CH_3), and 8.79 (3 H, d, *J* 7 Hz, CH*Me*) (Found: C, 72.7; H, 7.1. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%).

Hydrogenation.—The above benzoate lactone (44 mg) was hydrogenated in ethanol (5 cm^3) over 5% palladised charcoal (30 mg). Normal work-up and crystallisation from chloroform–light petroleum gave the dihydro-compound, (2R,3R)-2-[4-*benzoyloxy*-1-*methylcyclohexyl*]-3-*methylbutan*-4-*olide* as needles (30 mg), m.p. 100—101°, $[\alpha]_D^{20}$ −22.5° (*c* 0.6), $\nu_{max.}$ ($CHCl_3$) 1 763s, 1 715s, 1 280s, and 710s cm^{-1}, τ 1.95 (2H, m, ArH), 2.53 (3 H, m, ArH), 5.02 (1 H, m, C*H*·OBz), 5.65 (1 H, apparent t, *J* 9 Hz, CH·O), 6.23 (1 H, dd, $J_{g\cdot m}$ 9, J_{vic} 6 Hz, CH·O), 8.78 (3 H, d, *J* 7 Hz, CH*Me*), and 8.89 (3 H, s, Me) (Found: C, 72.35; H, 7.45. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65%).

Hydrogenation of the benzoate lactone (17) under the same conditions gave a saturated benzoate lactone, m.p. 100—101°, not depressed on admixture with the material described above. The $[\alpha]_D$, i.r., and n.m.r. characteristics were also identical.

Reaction of the Allylic Alcohol rac-(1) *with the Orthoester* rac-(17).—(±)-2,2-Diethoxy-3-methyltetrahydropyran, *rac*-(19), prepared from 2-methylpentan-5-olide by Meerwein's [18] method, had b.p. 68—69° at 9 mmHg, $\nu_{max.}$ ($CHCl_3$) 2 980s, 2 940s, 1 465m, 1 450m, 1 240s, 1 190s, 1 125s, 1 000s, and 975s cm^{-1}, τ 6.15—6.52 (6 H, m, CH_2·O), 7.82—8.60 (5 H, m, CH_2 and C*H*Me), 8.80 (6 H, t, *J* 7 Hz, CH_2*Me*), and 9.03 (3 H, d, *J* 6.5 Hz, CH*Me*). The reaction of this orthoester with *rac*-(1) (1.0 g) was conducted in the usual way, and gave a crude product (1.86 g) which was chromatographed on silica gel, and then on Kieselgel (with 5% EtOAc–C_6H_6) to give unchanged *rac*-(1) (294 mg), a less polar isomer *rac*-(22) (268 mg), and a more polar isomer *rac*-(20) (505 mg). The major isomer, (2SR)-2-[(1SR,4SR)-4-*benzoyloxy*-1-*methylcyclohex*-2-*enyl*]-2-*methylpentan*-5-*olide*, rac-(20), formed plates (from chloroform–light petroleum), m.p. 155.5—157°, $\nu_{max.}$ ($CHCl_3$) 1 715s, 1 600w, 1 585w, 1 270s, and 710m cm^{-1}, τ 1.83—2.03 (2 H, m, ArH), 2.40—2.73 (3 H, m, ArH), 4.28 (2 H, d, *J* 3.5 Hz, =CH), 4.52br (1 H, s, CH·OBz), 5.70 (2 H, m, CO·O·CH_2 of lactone), 8.70 (3 H, s, CH_3), and 8.76 (3 H, s, CH_3) (Found: C, 73.3; H, 7.25. $C_{20}H_{24}O_4$ requires C, 73.1; H, 7.4%).

The minor isomer, (2RS)-2-[(1SR,4SR)-4-*benzoyloxy*-1-*methylcyclohex*-2-*enyl*]-2-*methylpentan*-5-*olide*, rac-(22), formed prisms (from chloroform–light petroleum), m.p. 148.5—150.5°, $\nu_{max.}$ ($CHCl_3$) 1 715s, 1 600w, 1 585w, 1 270s, and 710m cm^{-1}, τ (ArH as for the major isomer) 3.93br (1 H, d, J_{vic} 10.5 Hz, =CH), 4.28 (1 H, dt, J_{vic} 10.5, $J_{allylic}$ 1.5 Hz, =CH), 4.52br (1 H, C*H*·OBz), 5.70 (2 H, m, CO·O·CH_2 of lactone), 8.70 (3 H, s, Me), and 8.72 (3 H, s, Me) (Found: C, 73.25; H, 7.05%).

Reaction of the Allylic Alcohol rac-(2) *with the Orthoester* rac-(19).—Carried out in the same way as the foregoing reaction, this gave in 75% yield a mixture (63 : 37) of two isomeric products which was separated by chromatography and crystallisation. The major isomer, (2SR)-2-[(1SR,4SR)-4-*benzoyloxycyclohex*-2-*enyl*]-2-*methylpentan*-5-*olide*, rac-(21), formed needles (from chloroform–light petroleum), m.p. 94.5—96.5°, $\nu_{max.}$ ($CHCl_3$) 1 713s, 1 600w, 1 585w, 1 270s, 1 022m, and 710m cm^{-1}, τ 4.08br (1 H, d, *J* 12 Hz, =CH), 4.33br (1 H, s, =CH), 4.52 (1 H, m, C*H*·OBz), 5.75 (2 H, m, CO·O·CH_2), 7.04 (1 H, m, allylic H), and 8.69 (3 H, s, Me) (Found: C, 72.9; H, 7.3. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%).

The minor isomer, (2RS)-2-[(1SR,4SR)-4-*benzoyloxycyclohex*-2-*enyl*]-2-*methylpentan*-5-*olide*, rac-(23), formed needles (from chloroform–light petroleum), m.p. 134.5—136°, $\nu_{max.}$ ($CHCl_3$) 1 713s, 1 600w, 1 585w, 1 270s, 1 022m, 1 013m, and 710m cm^{-1}, τ 4.13 (2 H, s, =CH), 4.48 (1 H, m, C*H*O·Bz), 5.70 (2 H, m, CO·O·CH_2 of lactone), 7.30 (1 H, m, allylic H), and 8.60 (3 H, s, Me) (Found: C, 72.7; H, 7.0%).

Hydrogenation of the Isomeric Benzoate Lactones rac-(20) *and* rac-(22).—Hydrogenation of the isomer *rac*-(20) over palladised charcoal in ethanol in the usual way, and crystallisation of the product from chloroform–light petroleum, gave (±)-(4-*benzoyloxy*-1-*methylcyclohexyl*)-2-*methylpentan*-5-*olide* as needles, m.p. 176—178°, $\nu_{max.}$ ($CHCl_3$), 1 712, 1 600w, 1 585w, 1 280s, and 710m cm^{-1}, τ 5.14 (1 H, m, C*H*·OBz), 5.57 (2 H, m, CO·O·CH_2 of lactone), 8.72 (3 H, s, Me), and 8.88 (3 H, s, Me) (Found: C, 73.05; H, 7.95. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%).

Hydrogenation of the isomer *rac*-(22) gave the same product (m.p. and mixed m.p., i.r., and n.m.r.).

Degradation of the Benzoate-lactone rac-(21) *to the* erythro-*Diol* rac-(10).—The benzoate-lactone (1 g) in ethanol (10 cm^3) was kept overnight at room temperature with N-sodium hydroxide (3 mol. equiv.); the ethanol was removed under reduced pressure, N-hydrochloric acid (3.15 mol) was added, and the benzoic acid so formed was removed by extraction with light petroleum. The dihydroxy-acid was then isolated by continuous extraction with chloroform; treatment of a solution in methanol with ethereal diazomethane gave the dihydroxy-acid methyl ester. It was oxidised with active

[17] I. J. Bolton, R. G. Harrison, and B. Lythgoe, *J. Chem. Soc.* (*C*), 1971, 2950.

[18] H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Chem. Ber.*, 1956, **89**, 2060.

manganese dioxide in acetone, as described for the preparation of *rac*-(12), giving the hydroxy-methyl ester of the cyclohexenone as an oil which was homogeneous to t.l.c. It had $\lambda_{max.}$ (EtOH) 228.5 nm (ε 9 000), $\nu_{max.}$ ($CHCl_3$) 3 670w, 3 620w, 3 470m, 1 725s, 1 680s, 855w, 830w, and 820w cm^{-1}, τ 8.83 (2 H, s, CH_3). The benzoate, prepared in the usual way, had $\nu_{max.}$ ($CHCl_3$) 1 720s, 1 680s, 1 600w, 1 585w, 1 275s, 1 110s, 905m, and 710m cm^{-1}, τ 3.07 (1 H, d, *J* 10.5 Hz, =CH), 3.95 (1 H, dd, *J* 10.5 and 3 Hz, =CH), 5.70br (2 H, $W_{\frac{1}{2}}$ 8 Hz, CH_2·OBz), 6.28 (3 H, s, OMe), and 8.72 (3 H, s, CH_3).

Cleavage with ruthenium tetraoxide and sodium periodate, as described for the preparation of *rac*-(12), converted the above benzoate (760 mg) into the benzoate methyl ester dicarboxylic acid (805 mg), τ 8.9 (3 H, s, CH_3). This was reduced in the usual way with diborane to give the diol methyl ester benzoate (532 mg), which formed a waxy solid, τ 8.73 (3 H, s, CH_3). It was kept for 40 h at room temperature with sodium methoxide [from sodium (69 mg)] in dry methanol (12 cm^3), and then acetic acid (2 cm^3) was added, and solvents were removed under reduced pressure. The residue, dissolved in water (10 cm^3), was extracted with light petroleum to remove methyl benzoate, and then, after the addition of solid sodium hydrogen carbonate and sodium chloride, was extracted continuously with ether, which gave the lactonic diol (130 mg) as an oil, $\nu_{max.}$ ($CHCl_3$) 3 680w, 3 620w, 3 420m, and 1 760s cm^{-1}, τ 8.77 (3 H, s, CH_3). Its solution in hexamethylphosphoramide (6 cm^3) was treated in the usual way with methyltriphenoxyphosphonium iodide (1.08 g), followed by sodium cyanoborohydride (302 mg). After purification of the product by p.l.c., 2-methyl-2,3-dipropylbutan-4-olide (60 mg) was obtained as a liquid, $\nu_{max.}$ ($CHCl_3$) 1 770s cm^{-1}, τ 5.68 (1 H, dd, *J* 9 and 9.5 Hz, lactonic O·CH), 6.17 (1 H, dd, *J* 10 and 9.5 Hz, lactonic O·CH), 7.80 (1 H, m, Pr*C*H·CH_2·O), 8.79 (3 H, s, tert. Me), and 9.05 (6 H, m, 2 × CH_3·CH_2). It was apparent from this that the isomer present was not identical with *rac*-(13).

Reduction of the above lactone (60 mg) with lithium alumium hydride in ether in the usual way gave the *erythro*-diol *rac*-(10) (56 mg); its R_F value and i.r. and n.m.r. spectra were identical with those of authentic material. The bis-*p*-nitrobenzoate had m.p. 100—101°, not depressed on admixture with authentic material, and its i.r. and n.m.r. spectra were likewise identical.

(±)-threo-3-*Methyl*-2-*propylhexan*-1-*ol*, rac-(30).—The mixture *ca.* (3.6 : 1) of *trans*- and *cis*-2-hydroxymethyl-1-methylcyclohex-4-enes (obtained from the commercial aldehyde mixture) was converted into the *p*-nitrobenzoates in the usual way; crystallisation from light petroleum (b.p. 30—40 °C) at −10 °C gave the p-*nitrobenzoate* of the *trans*-isomer as needles, m.p. 42—44° (Found: C, 65.7; H, 6.4; N, 5.25. $C_{17}H_{25}NO_4$ requires C, 65.4; H, 6.2; N, 5.1%). Hydrolysis with aqueous ethanolic potassium hydroxide gave the corresponding alcohol. A portion was converted into the phenylcarbamate, m.p. 81.5—82.5° (lit.,[8] 82—83°). The alcohol (1.1 g) in dry dimethylformamide (90 cm^3) was converted with sodium hydride (0.99 g) into the sodio-derivative, which was then kept for 20 h with benzyl bromide (4.28 g). The mixture was then stirred with methanol (10 cm^3) for 2 h, solvents were removed under reduced pressure, and the residue was treated with ether and water. The ether phase was washed, dried, and evaporated. Chromatography on silica and elution with benzene gave a mixture of the benzyl ether of *trans*-2-hydroxymethyl-1-methylcyclohex-4-ene (1.32 g) and dibenzyl ether (1.21 g). It showed τ 9.05 (3 H, d, *J* 6.5 Hz, CH*Me*). Oxidation with osmium tetraoxide (85 mg) and sodium periodate (3 g) gave a mixture of dibenzyl ether (1.2 g) and the dialdehyde (1.17 g); the latter had $\nu_{max.}$ (film) 2 720m and 1 720s cm^{-1}, τ 0.28 (2 H, m, CHO) and 9.1 (3 H, m, CH*Me*).

The above mixture, dissolved in tetrahydrofuran (8 cm^3) was added under nitrogen to a stirred solution of methylenetriphenylphosphorane [from methyltriphenylphosphonium bromide (4 g)] in tetrahydrofuran (90 cm^3); the mixture was then heated under reflux for 20 h. It was then worked up in the usual way to give a crude product which was triturated with light petroleum (b.p. 40—60 °C) to leave undissolved triphenylphosphine oxide; chromatography on silica (benzene) gave a product containing the required diene benzyl ether (0.74 g) (contaminated with much dibenzyl ether); it had $\nu_{max.}$ (film) 1 640m and 1 090s cm^{-1}, τ 4.9 (4 H, m, $=CH_2$), 5.1 (2 H, m, =CH), and 9.1 (3 H, d, *J* 5 Hz, CH*Me*).

Hydrogenation of a portion of the above mixture (containing 0.57 g of diene) in ethanol (30 cm^3) containing concentrated hydrochloric acid (30 mg) over 10% palladised charcoal gave the *threo*-alcohol *rac*-(30) (0.37 g). The 3,5-*dinitrobenzoate* separated from ethanol as needles, m.p. 42—43°, $\nu_{max.}$ ($CHCl_3$) 1 730s, 1 550s, and 1 350s cm^{-1}, τ 0.82 (3 H, m, ArH) 5.60 (2 H, dd, *J* 6 and 4 Hz, CH_2·O), and 8.9—9.2 (9 H, m, Me) (Found: C, 57.95; H, 7.05; N, 7.95. $C_{17}H_{24}N_2O_6$ requires C, 57.9; H, 6.9; N, 7.95%).

(±)-erythro-3-*Methyl*-2-*propylhexan*-1-*ol*, rac-(31).—*cis*-1,2-Bis(hydroxymethyl)cyclohex-4-ene (10 g) in dry pyridine (100 cm^3) was stirred at 0 °C during dropwise addition of benzoyl chloride (10.44 g), and then kept at room temperature for 20 h. The mixture was then diluted with ether, and washed with dilute hydrochloric acid, and water, and was dried and evaporated. Chromatography on alumina (grade III) with benzene and then with 2% ethyl acetate–benzene gave the hydroxy-monobenzoate as an oil (8.39 g).

A portion of the above compound (5 g) was treated in hexamethylphosphoramide (100 cm^3), as described for the preparation of the diol *rac*-(9), with methyltriphenoxyphosphonium iodide (18.6 g) and then with sodium cyanoborohydride (5.1 g), to give a mono-ol monobenzoate which, on alkaline hydrolysis in the usual way, provided *cis*-2-hydroxymethyl-1-methylcyclohex-4-ene as an oil (1.3 g), $\nu_{max.}$ (film) 3 320s and 1 650w cm^{-1}, τ 4.38 (2 H, m, =CH), 6.40 (2 H, m, CH_2·O), and 9.15 (3 H, d, *J* 6 Hz, CH*Me*). The p-*nitrobenzoate* formed needles [from light petroleum (b.p. 40—60 °C)], m.p. 47.5—48.5°, $\nu_{max.}$ ($CHCl_3$) 1 720s, 1 530s, and 1 350m cm^{-1}, τ 1.7 (4 H, s, ArH), 4.3 (2 H, m, =CH), 5.6 (2 H, m, CH_2·O), and 9.0 (3 H, d, *J* 5 Hz, CH*Me*) (Found: C, 65.3; H, 6.3; N, 5.3. $C_{15}H_{17}NO_4$ requires C, 65.4; H, 6.2; N, 5.1%).

cis-2-Hydroxymethyl-1-methylcyclohex-4-ene was transformed, by methods essentially identical with those used with the *trans*-isomer, into (±)-*erythro*-3-methyl-2-propylhexan-1-ol, *rac*-(31). The 3,5-*dinitrobenzoate* formed needles [from ether–light petroleum (b.p. 30—40 °C) at −40 °C], m.p. 28—29°, $\nu_{max.}$ ($CHCl_3$) 1 730s, 1 550s, and 1 350s cm^{-1}, τ 0.82 (3 H, m, ArH), 5.6 (2 H, d, *J* 6 Hz, CH_2·O), and 8.9—9.2 (9 H, m, Me) (Found: C, 58.2; H, 6.7; N, 8.3. $C_{17}H_{24}N_2O_6$ requires C, 57.9; H, 6.9; N, 7.95%).

Reaction of (±)-(E)-*Pent*-3-*en*-2-*ol*, rac-(24), *with* 2,2-*Diethoxytetrahydropyran*.—The alcohol *rac*-(24), prepared by reaction of crotonaldehyde with methylmagnesium iodide, was homogeneous to g.l.c.; the α-naphthylcarbamate had m.p. 108—110° (lit.,[6] 110—111°). The alcohol (3.5 g), the orthoester (6.75 g) and propionic acid (30 mg) were heated

together under reflux in benzene (50 cm³) for 2 h with azeotropic removal of ethanol. After 4 h, more propionic acid (30 mg) was added, and the reaction was continued under reflux for 24 h. Distillation gave a product, b.p. 147° at 14 mmHg, as an oil (3.143 g) which did not separate on t.l.c.; it had $\nu_{max.}$ (film) 1 735s, 1 670w, and 970s cm^{-1}, τ 4.52 (2H, m, =CH), 5.72 (2 H, m, CH_2·O), 8.32 (3 H, d, *J* 5 Hz, =CMe), and 8.91 (minor isomer) and 8.94 (major isomer) (3 H, doublets, *J* 7 Hz, CH*Me*). G.l.c. on a 35 m WCOT dilauryl phthalate column at 120 °C showed 12% with retention time 34 min, and 88% with retention time 36.25 min.

Hydrogenation in ethyl acetate (10% Pd–C) gave a mixture, $\nu_{max.}$ (film) 1 735s cm^{-1}, τ 5.7 (2 H, m, CH_2·O) and 9.08 (minor isomer) and 9.11 (major isomer) (3 H, doublets, *J* 7 Hz, CH*Me*); g.l.c. on a 5 ft column of 5% Carbowax 20M at 151 °C showed 12% with 17 min and 88% with 18.5 min retention time.

Reaction of (±)-(Z)-*Pent-3-en-2-ol*, rac-(25), *with* 2,2-*Diethoxytetrahydropyran*.—The alcohol, prepared by hydrogenation [7] of pent-3-yn-2-ol over Lindlar catalyst, was homogeneous to g.l.c.; the *p*-nitrobenzoate had m.p. 77—78° (lit.,[19] 77.5—78°).

The reaction, carried out in the way described for the (*E*)-alcohol, gave a lactone mixture with similar i.r. and n.m.r. characteristics, but in this case the isomer having τ 8.91 was the major, and that having τ 8.94 the minor isomer. G.l.c. as before showed the two isomers were present in the ratio 70 (faster-moving) to 30 (slower-moving).

Conversion of the δ-*Lactone* rac-(26) *into the* erythro-*Alcohol* rac-(31).—The mixture of *rac*-(26) (88%) and *rac*-(27) (12%), obtained from the (*E*)-alcohol *rac*-(24), was reduced with lithium aluminium hydride in ether. The resulting diol (305 mg) in ethanol (2 cm³) was treated with aqueous 0.1N-potassium tri-iodide (8.82 cm³) at room temperature, and then kept at 0 °C for 1 h; the excess of iodine was then removed with 0.1N-sodium thiosulphate. After saturation of the solution with salt, isolation with ether gave the iodo-ether (495 mg), homogeneous to t.l.c. (ethyl acetate) (Found: M^+, 298.043 02. Calc. for $C_{10}H_{19}IO_2$: *M*, 298.043 16); τ 8.0 (3 H, d, *J* 7 Hz, MeC·O) and 9.0 (3 H, d, *J* 7 Hz, MeC·CI).

The iodo-ether was converted in the usual way into the benzoyl derivative (0.62 g), $\nu_{max.}$ 1 710s cm^{-1}, which was stirred with activated zinc dust (6.08 g) in refluxing acetic acid (7.4 cm³) for 1 h. Addition of chloroform (20 cm³) and filtration, followed by washing of the filtrate with aqueous 2N-sodium carbonate and then with water, and evaporation, gave the hydroxy-monobenzoate as an oil (410 mg), $\nu_{max.}$ (film) 3 420m, 1 715s, and 970m cm^{-1}, τ 8.35 (3H, d, *J* 5 Hz, MeC=), and 9.0 and 9.02 (3 H, doublets, *J* 7 Hz, MeCH). A portion (200 mg) was brought into reaction [20] with a mixture of mesitoic acid (130 mg) and trifluoroacetic anhydride (170 mg) in benzene (4 cm³) to give the mesitoate benzoate as an oil (230 mg), τ 7.72 (9 H, s, Ar*Me*). It was kept at room temperature for 24 h with potassium hydroxide (50 mg) in ethanol (10 cm³); the ethanol was then removed under reduced pressure, and the residue was dissolved in water and extracted with ether. Evaporation of the washed and dried ethereal solution gave the diol monomesitoate as an oil (162 mg), $\nu_{max.}$ ($CHCl_3$) 3 420m, 1 710s, and 970m cm^{-1}, τ 7.72 (9 H, s, Ar*Me*), 8.35 (3 H, d, *J* 5 Hz, =CHMe), and 9.0 and 9.02 (3 H, doublets, *J* 7 Hz, CH*Me*). Hydrogenation in ethyl acetate over palladised charcoal gave the saturated hydroxy-mesitoates (160 mg), τ 7.72 (9 H, s, Ar*Me*) and 9.1 (6 H, m, CH*Me*). This material was treated in hexamethylphosphoramide with methyl triphenoxyphosphonium iodide (452 mg) and then with sodium cyanoborohydride (126 mg), in order to deoxygenate the free alcohol group; chromatography on silica with light petroleum (b.p. 40—60 °C) gave the mesitoate (97 mg), $\nu_{max.}$ (film) 1 730 cm^{-1}. It was reduced with lithium aluminium hydride in ether to give the free alcohol (35 mg), $\nu_{max.}$ (film) 3 350m cm^{-1}. This was converted into the 3,5-dinitrobenzoate, which formed needles (55 mg) [from light petroleum (b.p. 30—40 °C) at −40 °C], m.p. 28—29°; the i.r. and ^{1}H n.m.r. spectra were identical with those of the 3,5-dinitrobenzoate of the *erythro*-alcohol *rac*-(31).

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[19] A. N. Nesmayanow, A. E. Borisov, and N. V. Novikova, *Doklady Akad. Nauk S.S.S.R.*, 1958, **119**, 712.
[20] R. C. Parish and L. M. Stock, *J. Org. Chem.*, 1965, **30**, 927.