TILDEN LECTURE*

Concerning Stereochemical Choice in Enzymic Reactions

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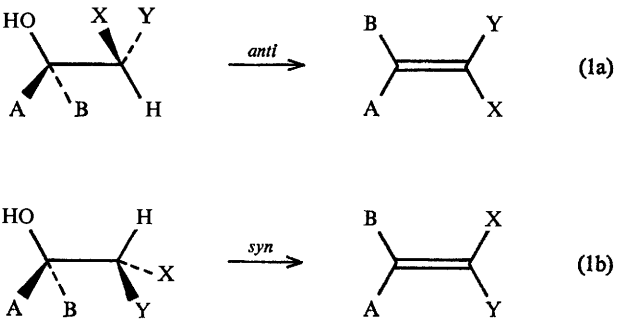
1 Introduction

I shall attempt in this lecture to explore the question: 'What determines stereochemical choice in enzymic reactions?' The general problem has recently been raised and discussed at length in a number of stimulating review articles by Irwin Rose and Kenneth Hanson.[1–5] I propose here to focus on a few selected issues that seem to me to be ripe for discussion.

I can best illustrate the kind of stereochemical choice I want to discuss with a simple, hypothetical example. In principle, an aliphatic alcohol (1) can dehydrate by either an *anti* (1a) or a *syn* (1b) mechanism (Scheme 1). If (i) A, B, X, and Y



Scheme 1

are different, then the product alkenes formed in the two cases will be geometrical isomers. If, however, (ii) X and Y (say) are identical, the product alkenes will be identical, regardless of whether they are formed by *anti* or *syn* elimination.

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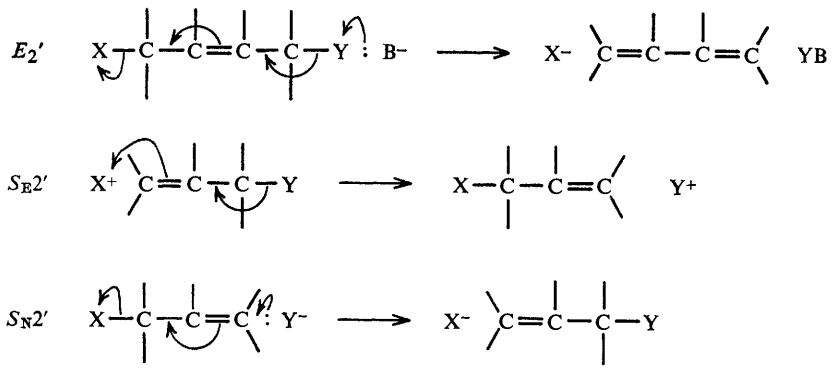
[1] I. A. Rose in 'The Enzymes', 3rd Edn., Vol. 2, ed. P. D. Boyer, Academic Press, New York, 1970, p. 281.
[2] I. A. Rose, *Critical Revs. in Biochem.*, 1972, **1**, 33.
[3] K. R. Hanson, *Ann. Revs. Plant Physiol.*, 1972, **23**, 335.
[4] K. R. Hanson and I. A. Rose, *Accounts Chem. Res.*, 1975, **8**, 1.
[5] I. A. Rose and K. R. Hanson in 'Applications of Biochemical Systems in Organic Chemistry', Part II, ed. J. B. Jones, C. J. Sih, and D. Perlman, Wiley-Interscience, New York, 1976, p. 507.

In a biological context, the stereochemical course of the elimination is not then dictated by the necessity to produce a particular metabolite (the *E* or *Z* alkene). Yet every relevant case so far investigated has turned out to be completely stereospecific *for a particular enzyme*. This prompts the question: 'What determines the enzyme's choice between two alternative stereochemical modes?' The short answer must be 'the enzyme's structure and the consequent geometry of the transition state for the reaction'. But this merely invites the more interesting questions: (i) has evolution perhaps followed a stereo-electronically preferred pathway? (ii) do different enzymes always manifest the same stereospecificity for the same reaction type? and (iii) if so, do non-enzymic models exhibit the same preference?

I have selected as probes in this exploration a group of related reaction types that are all concerned with events at allylic carbon: the *E*2′, S_E2', and S_N2' reactions (Scheme 2). My reason for selecting them is that each presents a simple



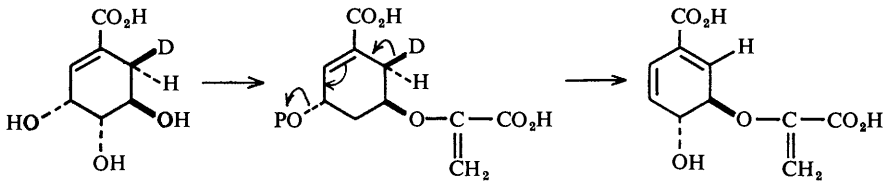
Scheme 2

stereochemical choice (*syn versus anti*) and that the associated problems have had, for quite distinct reasons, a good deal of attention from organic and bio-organic chemists; the recent spate of publications, even since I first gave this lecture in London, bears this out. I hope that what I have to say may appeal similarly to an audience with mixed interests. However, the point must be firmly made at the outset that until the enzymology of the biological reactions is firmly established, any parallel between them and their non-enzymic counterparts must remain speculative and, at best, a stimulus to further constructive thinking.

2 The *E*2′ Reaction

Probably the best-known example of a formal *E*2′ reaction in a biological system is the conversion of shikimate (2) into chorismate (4), a key step on the pathway from sugars to phenylalanine, tyrosine and tryptophan, and a multitude of

phenylpropanoids found in animals, higher plants, and micro-organisms.[6,7] The reaction is known[8,9] to go through the enol-pyruvyl-5-phosphate (3) and is formally a conjugate 1,4-elimination of the elements of phosphoric acid (Scheme 3; arrows).



(2) (3) (4)

Scheme 3

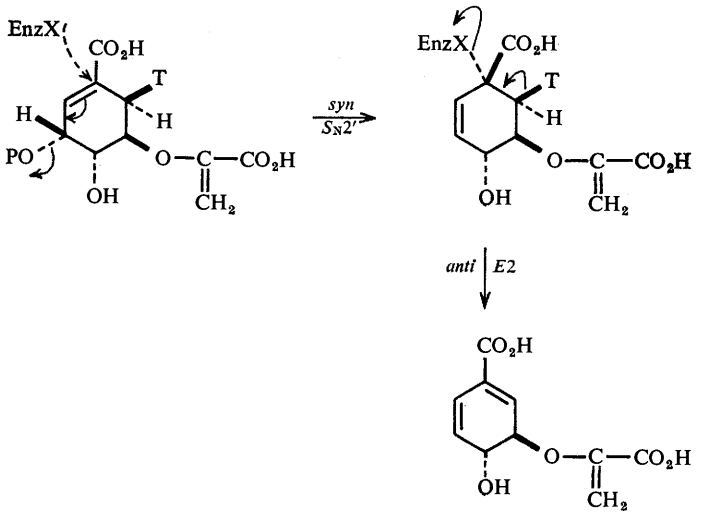
This elimination was shown independently by Hill[10] and Floss[11] to proceed with *anti*-stereochemistry. Hill and Newkome[10] prepared specimens of shikimic acid stereospecifically deuteriated in either the (6*R*) or (6*S*) positions. When these were converted into phenylalanine and tyrosine *via* chorismate by a blocked mutant of *Escherichia coli*, the (6*R*) deuterium label was lost, the (6*S*) label retained (Scheme 3). Onderka and Floss[11] obtained analogous results when the C-6 tritiated shikimates, prepared enzymically, were converted into chorismate by an *Aerobacter aerogenes* mutant. The observed *anti*-stereochemistry is contrary to both simple intuition* and such theoretical predictions as have been published,[12–14] and this caused Floss to suggest[11] a two-step process for the enzymic reaction (Scheme 4). It is analogous to Cornforth's X-group mechanism for the prenyl coupling reaction (see p. 456).

Note, however, that it will account for the observed stereochemistry only on the assumption that the S_N2' step is a *syn* process (see p. 462); the second *anti-E*2 step is of course unexceptionable.

The earliest relevant model systems for 1,4-conjugate elimination (or the reverse 1,4-conjugate addition to 1,3-dienes) were examined by Cristol and his

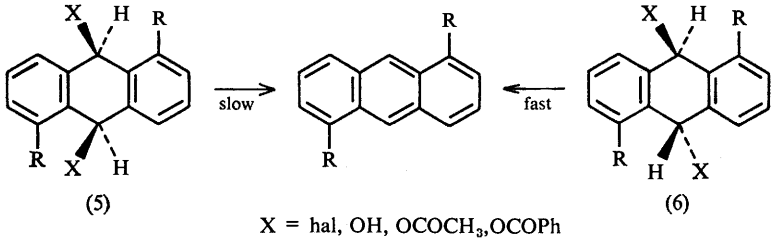
*For reasons similar to those opposing *syn* stereochemistry in the S_E2' reaction (see p. 456). *anti-E2'* stereochemistry would amount to nucleophilic substitution with retention at the carbon bearing the departing anion.

[6] T. A. Geissman and D. H. G. Crout, 'Organic Chemistry of Secondary Plant Metabolism', Freeman, Cooper and Co., San Francisco, 1969, p. 137.
[7] E. Haslam in 'Comprehensive Organic Chemistry', Volume 5, ed. D. H. R. Barton and W. D. Ollis, Pergamon Press, London, 1979, p. 1167.
[8] J. G. Levin and D. B. Sprinson, *J. Biol. Chem.*, 1963, **239**, 1142.
[9] H. Morell, M. J. Clark, P. F. Knowles, and D. B. Sprinson, *J. Biol. Chem.*, 1967, **242**, 82.
[10] R. K. Hill and G. R. Newkome, *J. Amer. Chem. Soc.*, 1969, **91**, 5893.
[11] D. K. Onderka and H. G. Floss, *J. Amer. Chem. Soc.*, 1969, **91**, 5894; H. G. Floss, D. K. Onderka, and M. Carroll, *J. Biol. Chem.*, 1972, **247**, 736.
[12] K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, 1966, **39**, 2116; K. Fukui, *Tetrahedron Letters*, 1965, 2427.
[13] N. T. Anh, *Chem. Comm.*, 1968, 1089.
[14] O. S. Tee, J. A. Altmann, and K. Yates, *J. Amer. Chem. Soc.*, 1974, **96**, 3141.



Scheme 4

colleagues.[15]* They found that base-catalysed 1,4-elimination from the *trans* (6) compounds (Scheme 5) was up to 1200 times faster than for the *cis* (5) compounds.



(5) (6)

X = hal, OH, $OCOCH_3$,OCOPh

Scheme 5

Rate differences were greatest with large *peri*-substituents (R = CH_3, Cl). However, the conclusions from these experiments are suspect. A reappraisal[17] suggests that the base-catalysed reactions were non-concerted, proceeding by an *ElcB* mechanism. Such a process may, nevertheless, show a steric preference. Hill and Bock have recently examined[18] a model reaction much closer struc-

*The apparent *syn*-1,4-addition of DBr to cyclohexa-1,3-diene[16] is almost certainly not a simple concerted process.

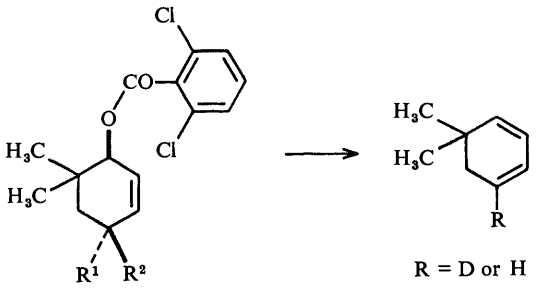
[15] S. J. Cristol, W. Barasch, and C. H. Tieman, *J. Amer. Chem. Soc.*, 1955, **77**, 583; see also P. B. de la Mare, R. Koenigsberger, and J. S. Lomas, *J. Chem. Soc.* (*B*), 1966, 834.

[16] G. S. Hammond and J. Warkentin, *J. Amer. Chem. Soc.*, 1961, **83**, 2554.

[17] S. J. Cristol, *Accounts Chem. Res.*, 1971, **4**, 393.

[18] R. K. Hill and M. G. Bock, *J. Amer. Chem. Soc.*, 1978, **100**, 637

turally to the shikimate system and carried out under conditions that are likely to favour concerted reaction. They caused the cyclohexenyl 2,6-dichlorobenzoates (7) and (8) to undergo 1,4-elimination by treating them with potassium t-butoxide in *m*-xylene in presence of 18-crown-6-ether at 100 °C (Scheme 6).



(7) $R^1 = D$; $R^2 = H$
(8) $R^1 = H$; $R^2 = D$

Scheme 6

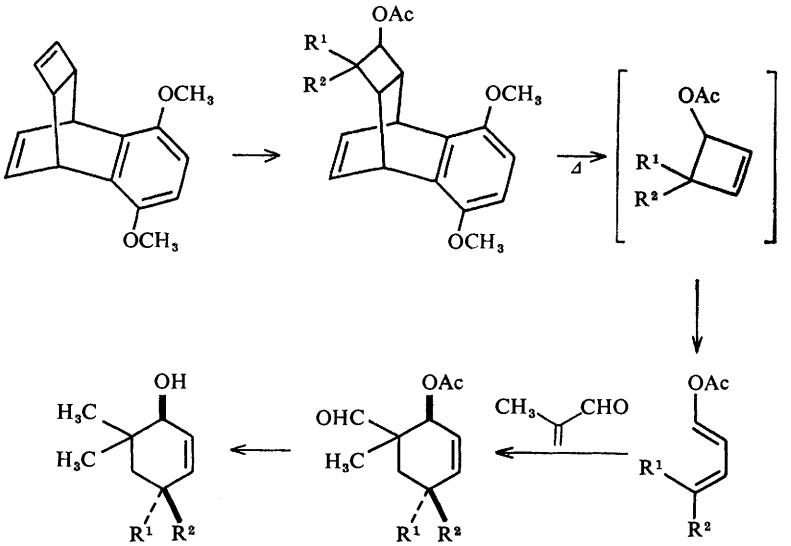
1,2-Elimination to give the conjugated cyclohexadiene was avoided by *gem*-dimethylation of position 6 and deuterium exchange did not occur with the non-polar medium. Under these conditions the 1,3-diene was produced from (7) and (8) with retention of 90 ± 2 and 15 ± 5% deuterium, respectively, showing this base-catalysed 1,4-elimination reaction to be predominantly, if not exclusively, *syn*.

The real challenge of this work was in the preparation of the stereospecifically labelled esters (7) and (8) and this was neatly accomplished by successive thermal pericyclic reactions of predictable stereochemistry (Scheme 7).

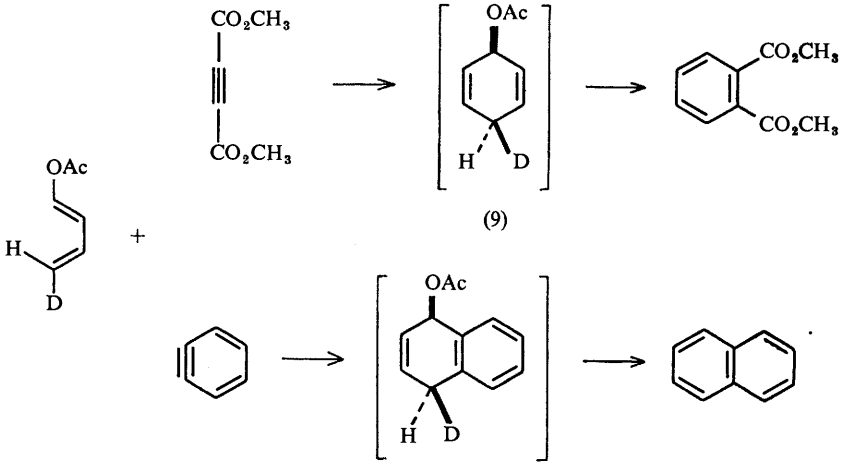
Using the specifically deuteriated acetoxy-butadienes, Hill and Bock have concurrently produced good evidence that the thermal 1,4-conjugate cyclo-elimination of 1,4-dihydrobenzenes (9) and (10) to benzenes proceeds, almost exculsively, as expected, with *syn* geometry (Scheme 8). A similarly high degree of stereoselectivity had previously been demonstrated[19] by Fleming and Wildsmith, using *trans*-3,6-dideuteriocyclohexa-1,4-diene. However, such presumably intramolecular pericyclic processes must necessarily proceed in a *syn* manner.

Hill and Bock's model is an excellent analogue for the shikimate–chorismate conversion and to the extent that its stereochemistry is plainly opposite to that of the enzymic reaction, a concerted one-step mechanism for the latter becomes less likely. However, it is a less good model for the more general *E*2′ reaction. In particular, 1,4-disubstituted cyclohexadienes are necessarily *cis*, and not *trans*, but-2-enes and their products of elimination must be s-*cis*-butadienes. It is clearly desirable to remove from the model these as well as other conformational

[19] I. Fleming and E. Wildsmith, *Chem. Comm.*, 1970, 223.



Scheme 7



(9)

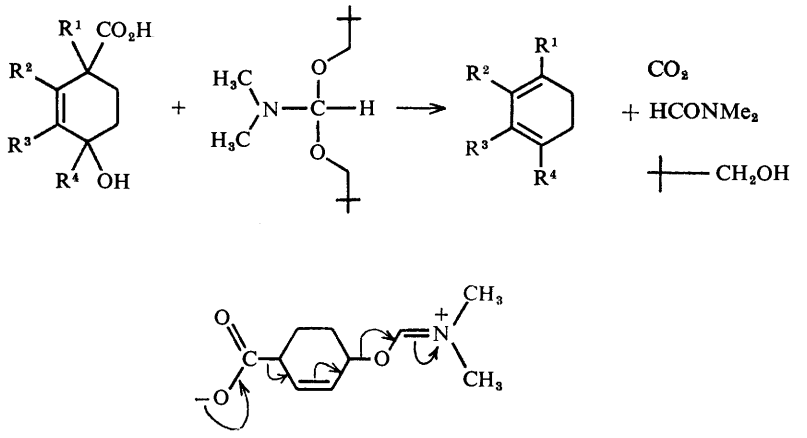
(10)

Scheme 8

constraints inherent in cyclohexenyl systems. With this in mind, Eschenmoser and his colleagues have recently addressed themselves to the challenge of studying concerted 1,4-elimination in acyclic systems.[20] The reaction chosen for study

[20] C. Moody, E. Vogel, and A. Eschenmoser; personal communication from Prof. Eschenmoser, ETH, Zürich.

had previously been examined[21] in a cyclohexenyl system (Scheme 9). The two leaving groups, $-CO_2H$ and $-OH$, are made to undergo conjugate decarboxylation and dehydration under exceedingly mild conditions.



Scheme 9

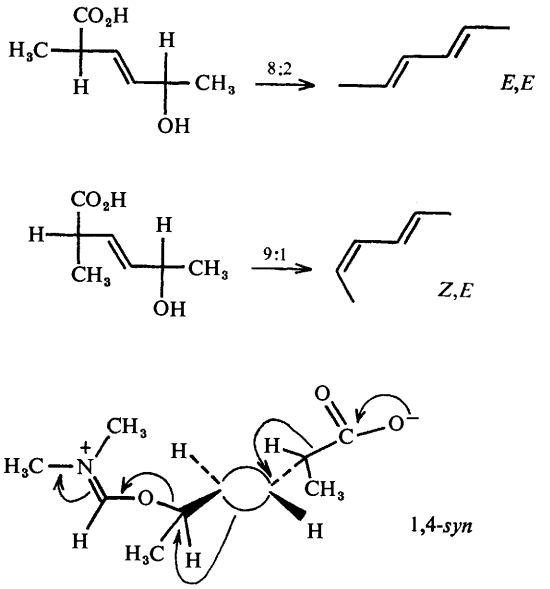
By simply stirring the hydroxycyclohexene-carboxylic acid with *NN*-dimethylformamide–dineopentyl acetal in a non-polar solvent, cyclohexa-1,3-dienes are formed regiospecifically under non-isomerising conditions. The remarkable ease of reaction probably depends on activation of both functions to be eliminated by the DMF-acetal:deprotonation of carboxyl and conversion of $-OH$ into a highly effective leaving group, as in Scheme 9 (arrows).

When the reaction was applied to the diastereomeric acyclic substrates in Scheme 10, *syn*-1,4-elimination was by far the preferred pathway in both cases.

3 The S_E2' and S_E' Reactions

We were drawn to this area of chemistry through our interest in terpenoid structure and biosynthesis. The fundamental process in terpenoid biosynthesis is the assembly of acyclic polyisoprenoids by the joining together of C_5 fragments in characteristic head-to-tail fashion. The process is employed twice in succession in the formation of farnesol, and the same enzyme, prenyl transferase (EC 2.5.1.1), mediates both additions of isopentenyl pyrophosphate, first to dimethylallyl pyrophosphate and then to geranyl pyrophosphate. This is certainly the best-studied example, at a biochemical level, of the isoprene coupling reaction, and prenyl transferase has now been obtained crystalline and homogeneous from several sources.[22,23]

[21] A. Ruttimann, A. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, 1975, **58**, 1450.
[22] N. L. Eberhart and H. C. Rilling, *J. Biol. Chem.*, 1975, **250**, 863.
[23] B. C. Reed and H. C. Rilling, *Biochemistry*, 1975, **14**, 50.

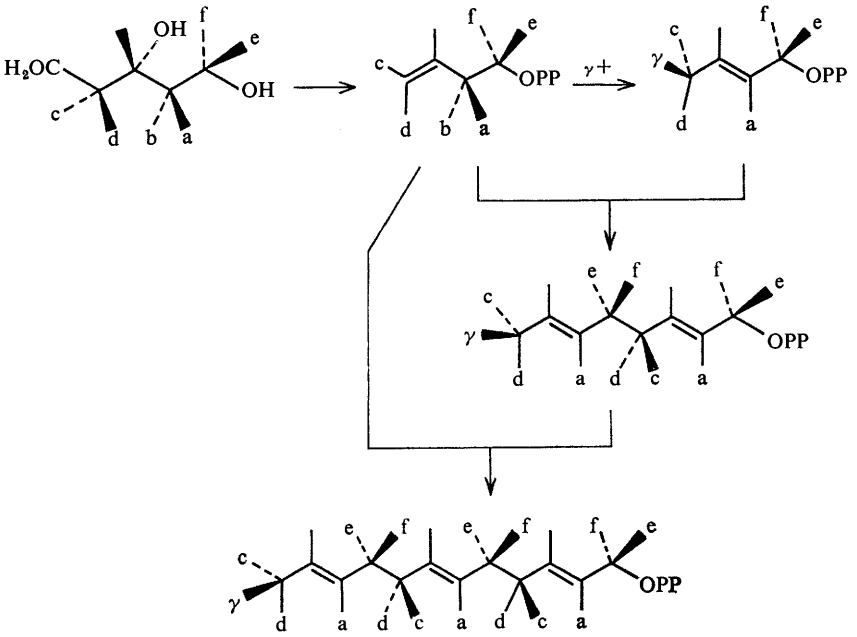


Scheme 10

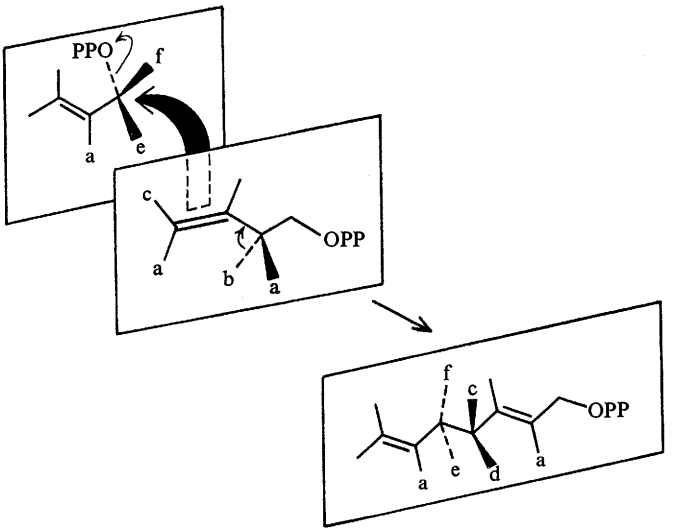
The stereochemical details of the chain-forming process become evident only when one uses isotopic labels. This was done some fifteen years ago by Cornforth and Popjak and their colleagues[24–26] and for the formation of farnesol in rat livers the results are as shown in Scheme 11.

Scheme 12 attempts a three-dimensional representation of the first condensation. Here the stereochemical situation is clearly established by experiment: the new C–C bond formed between the condensing C_5 units, and the allylic CH_b bond of isopentenyl pyrophosphate cleaved in the condensation reaction, are *syn* (behind the plane containing isopentenyl pyrophosphate, as drawn) and this allows one to speculate about the mechanism, formally S_E2', of the prenyl transferase reaction. Two alternatives have been considered. One depicts the reaction as the result of a continuous electron flow, so that the departure of OPP^-, C–C bond formation, and allylic H loss are more or less concerted (Scheme 12, arrows). The relative timing of these steps is not defined. Much recent effort by Rilling and Poulter[27–29] seems to support the intermediacy of an allylic cation formed from dimethylallyl pyrophosphate. The salient feature of the

[24] J. W. Cornforth, R. H. Cornforth, C. Donninger, and G. Popjak, *Proc. Roy. Soc. B*, 1966, **163**, 492.
[25] J. W. Cornforth, R. H. Cornforth, G. Popjak, and L. Yengoyan, *J. Biol. Chem.*, 1966, **241**, 3970.
[26] J. W. Cornforth, *Tetrahedron*, 1974, **30**, 1515.
[27] C. D. Poulter, D. M. Satterwhite, and H. C. Rilling, *J. Amer. Chem. Soc.*, 1976, **98**, 3376.
[28] C. D. Poulter, J. C. Argyle, and E. A. Marsh, *J. Amer. Chem. Soc.*, 1977, **99**, 957.
[29] D. N. Brems and H. C. Rilling, *J. Amer. Chem. Soc.*, 1977, **99**, 8352.

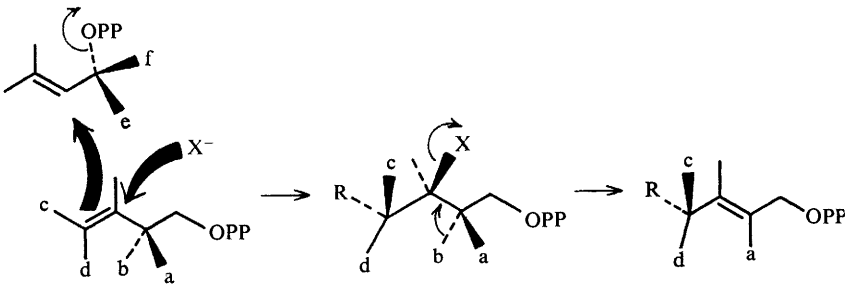


Scheme 11



Scheme 12

first mechanism is that catalytic sites on the enzyme become involved only at the extremes of the substrate system, *i.e.*, they catalyse loss of OPP^- at one end and of H^+ at the other. Here, as in the chorismate–shikimate conversion (see p. 449), the observed (*syn*) stereochemistry runs counter to chemical intuition. In Cornforth's words[30] 'C-3 of isopentenyl pyrophosphate is having electrons supplied to it (to form the new double bond) and withdrawn from it (to form the C–C bond) on the same side; effectively a nucleophilic substitution with retention of configuration. This seems energetically far less favourable than a concerted mechanism in which electrons are supplied to, and withdrawn from, opposite sides of C-3.' This led him to suggest a two-step mechanism (Scheme 13): the first step is *anti*-addition of a nucleophilic group X^- (part of the enzyme



Scheme 13

or, conceivably, an enzyme-bound water molecule) and the allylic cation R^+ (from dimethylallyl pyrophosphate) across the double bond of isopentenyl pyrophosphate. The second is *anti*-elimination of X^- and H_b^+ from the intermediate to generate the new double bond. It is the distinctive feature of this second mechanism that it involves an additional nucleophile X^-, if only as a partner in a close ion pair with C-3 of isopentenyl pyrophosphate. This is stereoelectronically attractive and also has the merit that it does not demand major conformational changes in either substrates or enzyme. In evolutionary terms it is, of course, less economical. Poulter and Rilling have more recently suggested[31] that the departing OPP^- ion may assist removal of the allylic hydrogen, thus causing the loss of H_b rather than H_a (see Scheme 12).

So much for *E*-prenyl transferases that combine $(C_5)_n + C_5$ coupling with the simultaneous formation of a *trans*-double bond. It has to be said that only the enzyme from rat liver has been properly studied in stereochemical detail, though it would be surprising if the other transferases that make geraniol and farnesol turned out to differ in their stereochemistry. What of *Z*-transferases that presumably combine isoprenoid coupling with formation of *cis*-double bonds? Such enzymes must be involved in the formation of natural rubber and leaf

[30] J. W. Cornforth, *Angew. Chem. Internat. Edn.*, 1968, **7**, 903.
[31] C. D. Poulter and H. C. Rilling, *Biochemistry*, 1976, **15**, 1079.

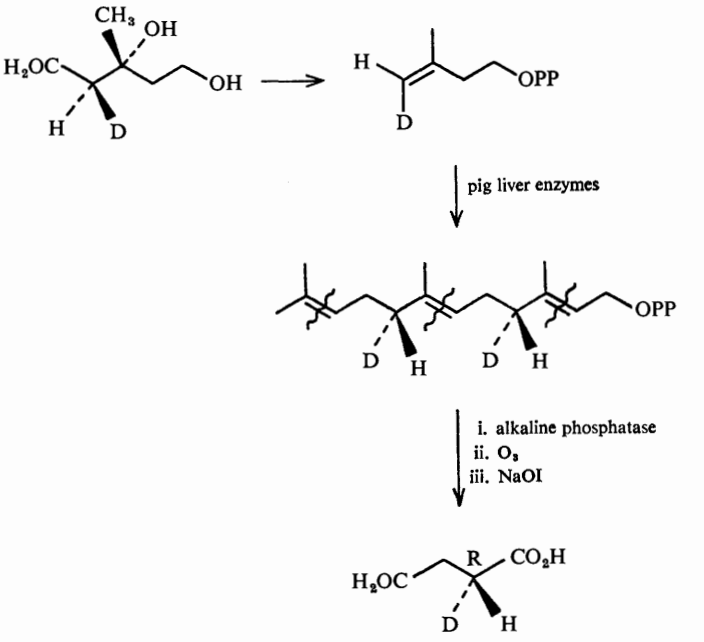
polyprenols. But the stereochemistry attending the formation of these substances is not so clear.

In 1966 Cornforth and his colleagues from Shell Sittingbourne and the Natural Rubber Producers' Research Association at Welwyn Garden City found[32] that, when poly-*cis*-rubber is biosynthesised from mevalonic acid by natural rubber latex (from *Hevea brasiliensis*), ^3H of [4*S*,4$^3H_1$]mevalonate is retained and ^3H from [4*R*,4$^3H_1$]mevalonate is lost. The situation was reversed in farnesol obtained simultaneously from the same source (as is the case with farnesol from other sources). Cornforth and his colleagues concluded that in rubber biosynthesis *cis*-double bonds must be formed directly, not *via trans*-double bonds. This gave rise to the notion that isoprene residues that incorporate ^3H from [4*R*,4$^3H_1$]mevalonate are biogenetically *trans*, while those that incorporate ^3H from [4*S*,4$^3H_1$]mevalonate are biogenetically *cis*. Hemming and his colleagues were later able to correlate the *cis*:*trans*-double bond ratio in leaf polyprenols with the ratio of (4*R*)/(4*S*)-^3H loss from mevalonate.[33–35]

But the experiment with rubber, and also those with leaf polyprenols, provides only half the answer to the question: 'Does the formal S_E2' condensation of C_5 units here proceed, as in farnesol formation, with *syn* stereochemistry or is it, on the contrary, an *anti* process?' For farnesol Cornforth and his colleagues had clearly demonstrated[25] that the two new C–C bonds were both formed by addition of the allylic group to that side of the double bond of isopentenyl pyrophosphate on which the groups $-CH_2CH_2OPP$, $-CH_3$, –H, and –H appear in clockwise order (Scheme 12). This was done by incorporating [2*R*,2$^2H_1$]mevalonate into farnesol and showing by polarimetry that [2*R*,2$^2H_1$]succinic acid was formed by successive ozonolysis and hypoiodite oxidation, as in Scheme 14. Taken together with the already established *anti*-loss of $-CO_2H$ and –OH from mevalonic acid, this defined the C–C bond formation as indicated in Schemes 11 and 12.

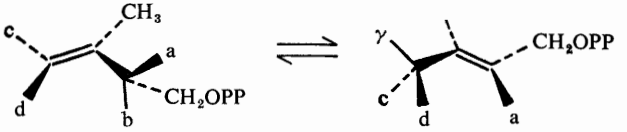
I know of no corresponding experiment for the *Z*-prenyl transferase of rubber latex or the mixed *Z*- and *E*-transferases active in leaf polyprenol biosynthesis. Thus there is, on present evidence, an even chance that the *Z*-prenyl transferase reaction proceeds with *anti* stereochemistry. There is, however, another step in terpenoid biosynthesis, formally also S_E2', whose stereochemistry is firmly established as *anti*. This is the isomerisation of isopentenyl to dimethylallyl pyrophosphate, mediated by isopentenylpyrophosphate isomerase (EC 5.3.3.2). It must, of course, precede the first $C_5 + C_5$ condensation for which both substrates of the isomerase are required. Indeed, *Hevea* latex, which lacks the isomerase, requires added dimethylallyl pyrophosphate to initiate rubber bio-

[32] B. L. Archer, D. Barnard, E. G. Cockbain, J. W. Cornforth, R. H. Cornforth, and G. Popjak, *Proc. Roy. Soc. B*, 1966, **163**, 519.
[33] D. P. Gough and F. W. Hemming, *Biochem. J.*, 1967, **106**, 100.
[34] K. J. Stone and F. W. Hemming, *Biochem. J.*, 1967, **104**, 43.
[35] F. W. Hemming in 'Natural Substances Formed Biologically from Mevalonic Acid', ed. T. W. Goodwin. Academic Press, London, 1970, p. 105.



Scheme 14

synthesis.[36] Cornforth and his colleagues have beautifully established[37] the stereochemistry of the isomerisation in the sense depicted in Scheme 15. The solution to this most subtle problem called for the differentiation of antipodal methyl groups ($-C^1H^2H^3H$), then recently perfected jointly by Cornforth and Eggerer[38] and independently by Arigoni.[39]

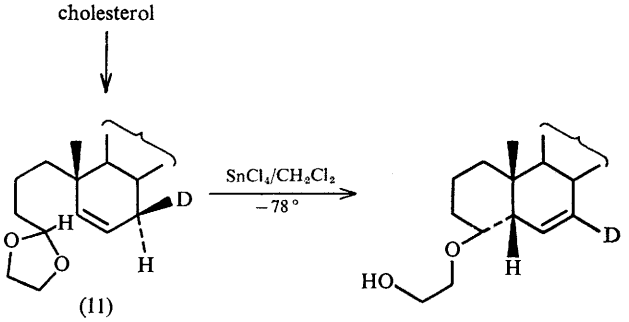


Scheme 15

In spite of Cornforth's very persuasive intuitive preference for *anti*-S_E2' stereochemistry, we felt the need to demonstrate stereochemical preference in an

[36] B. W. Agranoff, H. Eggerer, U. Henning, and F. Lynen, *J. Amer. Chem. Soc.*, 1959, **81**, 1254.
[37] J. W. Cornforth, K. Clifford, R. Mallaby, and G. T. Phillips, *Chem. Comm.*, 1971, 1599; *Proc. Roy. Soc. B*, 1972, **182**, 277.
[38] J. W. Cornforth, J. W. Redmond, H. Eggerer, W. Buckel, and C. Gutschow, *Nature (London)*, 1969, **221**, 1212; *Europ. J. Biochem.*, 1970, **14**, 1.
[39] D. Arigoni, J. Luthy, and J. Retey, *Nature (London)*, 1969, **221**, 1213.

appropriate laboratory model system. There were, to be sure, computational predictions, based on MO theory, which favoured *anti* stereochemistry.[12,13] But the state of the art was not then (and is not now) such as to remove the need for experiment. In any case, I think we were provoked by the existence in the literature of Stork and White's classic experiment[40] on S_N2' stereochemistry (see p. 462) which had no parallel for the somewhat analogous S_E2' reaction. Our first model,[41] utilising *intramolecular* electrophilic substitution at allylic carbon (S_E'), was based on the ring-A-seco-cholestenal [see (11), Scheme 16] and clearly

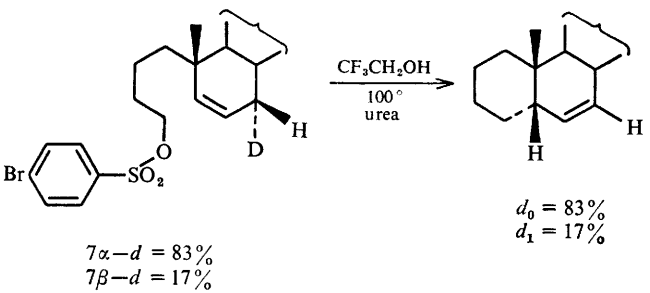


(11)

7β–d = ≮ 95% d_1 = ≮ 95%

Scheme 16

owes its design to W. S. Johnson's sterling work on polyene cyclisations in steroid synthesis.[42,43] Schemes 16 and 17 show the stereochemical outcome of cyclisation in two key experiments. It corresponds cleanly to a *syn* S_E' process in all three cases (the second experiment with a 7α/7β-D mixture effectively



7α–d = 83%
7β–d = 17%

d_0 = 83%
d_1 = 17%

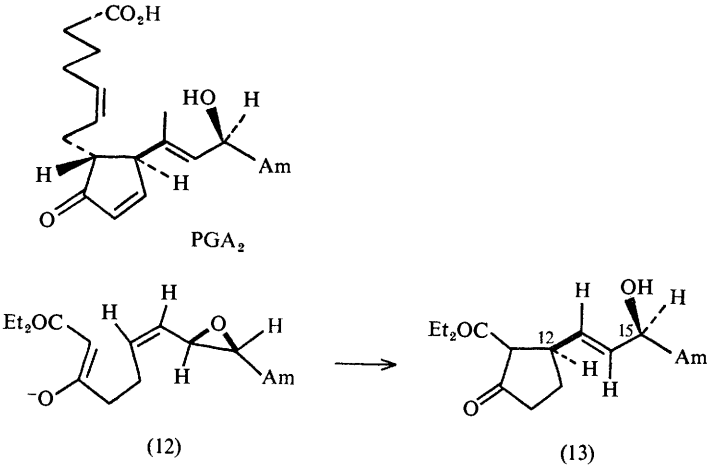
Scheme 17

[40] G. Stork and W. N. White, *J. Amer. Chem. Soc.*, 1956, **78**, 4609.
[41] I. M. Cunningham and K. H. Overton, *J.C.S Perkin I*, 1975, 2140.
[42] W. S. Johnson, *Accounts Chem. Res.*, 1968, **1**, 1.
[43] W. S. Johnson, L. R. Hughes, and J. L. Carlson, *J. Amer. Chem. Soc.*, 1979, **101**, 1281.

combines two experiments in one). However, the allylic *syn*-hydrogen (or deuterium) lost in each case is *quasi*-axial in a cyclohexenyl system and thus intrinsically labile.[44] The result obtained, clean as it is, may thus simply reflect this enhanced lability. Indeed, it is conceivable that S_E' reactions might proceed in either *syn* or *anti* fashion, provided that the allylic CH bond can be aligned with the adjacent π-orbital. The outcome of attempts in our laboratory to put this notion to the test in an acyclic model currently awaits incorporation of the necessary isotopic labels.

4 The S_N2' and $S_{N'}$ Reactions

The concept of the S_N2' reaction has, since it was first put forward independently by Hughes[45] and Winstein[46] in 1938, had a far greater impact on the thinking of organic chemists than either of the other reactions I have discussed. In part this must be the result of the practical appeal and potential that nucleophilic displacement at allylic carbon has in classical organic synthesis, but I suspect that a much-quoted paper[40] on the stereochemistry of the S_N2' reaction, published by Stork and White in 1956, and the general acceptance of its conclusions into chemical thinking have played an important part. The conclusions were that a *syn* relationship exists between the entering and departing groups in the S_N2' reaction. This has been widely accepted and used to rationalise observed stereochemistry but occasionally also to plan stereo-controlled synthesis. A felicitous example features in an early synthesis of the prostaglandin[47] (*RS*)-PGA_2 by the Roussel–Uclaf group in 1972 (Scheme 18).



Scheme 18

[44] H. L. Goering and R. R. Josephson, *J. Amer. Chem. Soc.*, 1962, **84**, 2779.
[45] E. D. Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185.
[46] S. Winstein, Ph.D. Dissertation, Calif. Inst. Technol., 1938.
[47] J. Martel, E. Toromanoff, J. Mathieu, and G. Nomine, *Tetrahedron Letters*, 1972, 1491; J. Martel, A. Blade-Font, C. Marie, M. Vivat, E. Toromanoff, and J. Buendia, *Bull. Soc. Chim. France, Partie II*, 1978, 131.

They planned to establish the chiral centres at C-12 and C-15 in the prostaglandin intermediate (13) in the correct configurations on the assumption that the precursor (12) would undergo epoxide opening by a *syn*-S_N' mechanism In practice, reaction of the pyrrolidine enamine of the β-keto-ester (12) with sodium amide in tetrahydrofuran did indeed lead to a single diastereomeric racemate that was converted into (*RS*)-PGA_2.

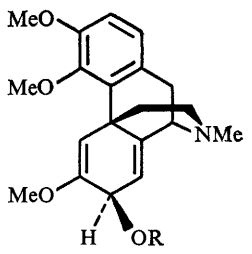
It may be as well at this point to comment briefly on the current status of the S_N2' reaction in physical-organic chemistry. Its very existence was called in question[48] by Bordwell in a review article with the arresting title 'Are Nucleophilic Bimolecular Concerted Reactions Involving Four or More Bonds a Myth?' Some of the specific criticisms made there were countered in a subsequent spirited paper by de la Mare and Vernon.[49] In a more general sense one should note that the objections raised by Bordwell are really concerned with the extent of bond making and bond breaking that has taken place at the transition state and that they in no way invalidate the possibility of stereochemical preference. This point is reinforced by Epiotis in a recent theoretical analysis of the S_N2' reaction.[50] He additionally predicts *syn* preference with uncharged nucleophiles (NR_3), *anti* preference with charged nucleophiles (OH^-), while being careful to point out that steric and solvent effects may reverse these predictions. Earlier qualitative theoretical treatments had all predicted *syn* preference.[12,13,51–56] As we shall see, the experimental evidence now available is not nearly so clearcut and in any case one must allow for the fact that very few of the laboratory reactions that have been designated "S_N2'" have been thus characterised by the appropriate criteria of physical-organic chemistry. In the case of the biological examples, the designation is even more notional.

Two examples, taken from natural product chemistry, will further illustrate how firmly the idea of *syn* preference expressed in Stork's 1956 paper had become part of the grammar of organic chemistry.

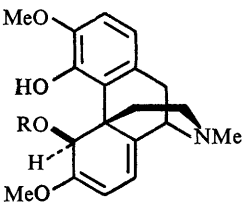
Salutaridinol-I (14), but not its epimer, is the natural precursor of thebaine in the opium poppy. Since direct allylic displacement of –OR by the phenolic hydroxyl would amount to *anti*-S_N' displacement, Barton and Kirby invoked[57] allylic rearrangement with retention, followed by internal nucleophilic displacement with inversion, to account for the established configurational relationship between thebaine and its precursor (Scheme 19).

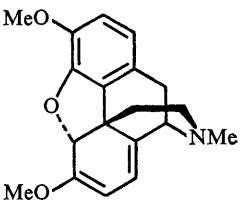
I have previously (see p. 449) made reference to Floss's proposal to rationalise by a two-step sequence the unexpected net *anti*-1,4-elimination in the biological

[48] F. G. Bordwell, *Accounts Chem. Res.*, 1970, **3**, 281.
[49] P. B. de la Mare and C. A. Vernon, *J. Chem. Soc.* (*B*), 1971, 1700.
[50] R. L. Yates, N. D. Epiotis, and F. Bernardi, *J. Amer. Chem. Soc.*, 1975, **97**, 6615.
[51] K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, 1967, **40**, 2018.
[52] W. Drenth, *Rec. Trav. Chim. Pays-Bas*, 1967, **86**, 318.
[53] J. Mathieu, *Bull. Soc. chim. France*, 1973, 807.
[54] J. Mathieu and A. Rassat, *Tetrahedron*, 1974, **30**, 1753.
[55] C. L. Liotta, *Tetrahedron Letters*, 1975, 523; 1660.
[56] M. E. Toromanoff, *Compt. rend.*, 1977, **284**, *C*, 113.
[57] D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1967, 128.



(14)
Salutaridinol-I



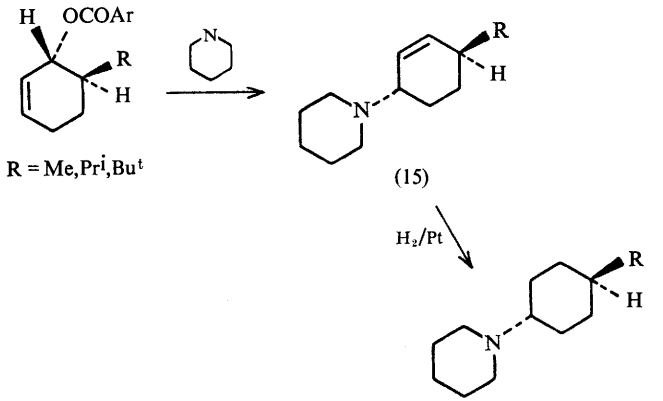


thebaine

Scheme 19

conversion of shikimate into chorismate. This depends on the assumption of *syn*-S_N2' displacement in the first step.

What, then, is the present experimental evidence for S_N2' stereochemistry? The essentials of Stork and White's paper[40] which held the stage for over twenty years, can be briefly summarised as in Scheme 20: piperidinolysis of

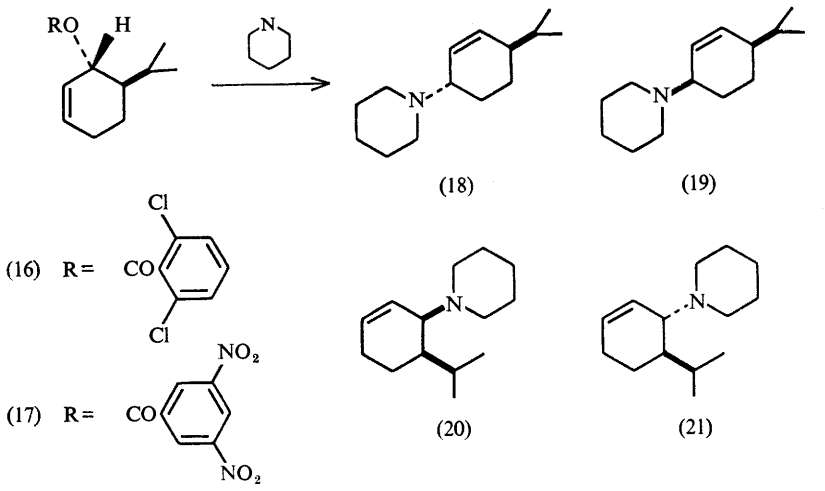


Scheme 20

trans-6-alkyl-cyclohex-2-enyl 2,6-dichlorobenzoates leads exclusively to those S_N2' products (15) resulting from entry of the attacking nucleophile *syn* to the departing benzoate anion. The identity and homogeneity of the products were established by hydrogenation and melting-point comparison of the reduced picrates, picrolonates, and methiodides with authentic specimens. Second-order kinetics were established for the reaction in solvent xylene. In view of the importance of these conclusions and some misgivings about the experimental evidence that supported them, we decided to re-investigate the reaction with the

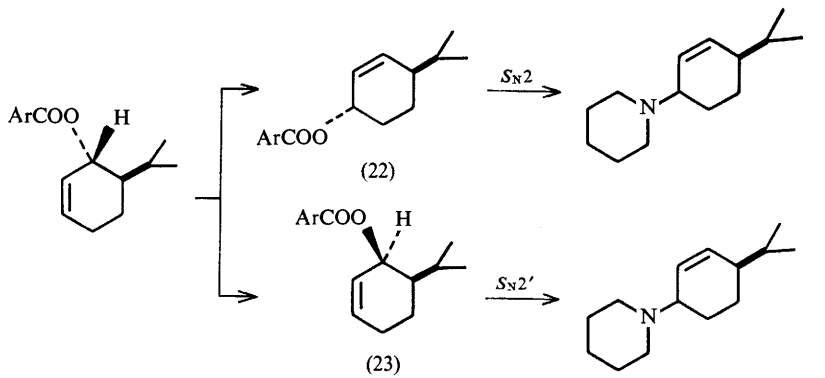
benefit of g.l.c. analysis and also to include the epimeric *cis*-esters in our study.[58]

Like Stork's 2,6-dichlorobenzoate (16), the *trans*-3,5-dinitrobenzoate (17) afforded on piperidinolysis the four isomeric amines (18)—(21), which were separable by g.l.c. (Scheme 21).



Scheme 21

The ratio of apparent *anti*-S_N2' product (19) to *syn*-S_N2' product (18) increased with time, making it clear that these could not both be formed from the same ester. Kinetic experiments confirmed that the apparent *anti* product was in fact formed *via* the allylically rearranged ester (22) and probably to some extent *via* the epimeric ester (23), shown to be formed during the reaction (Scheme 22).

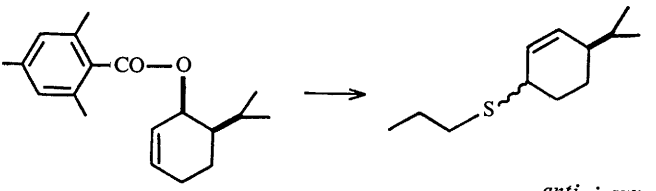


Scheme 22

[58] A. A. Dobbie and K. H. Overton, *J.C.S. Chem. Comm.*, 1977, 722.

The *cis*-ester behaved similarly. Thus, although the course of the reaction is more complex than was revealed by Stork and White's original analysis, our results supported their conclusion that in the cyclohex-2-enyl esters under study, the S_N2' reaction proceeds predominantly, and perhaps exclusively, with *syn* stereochemistry.

Stork has himself recently returned to a study of the S_N2' reaction[59] with *trans*- and *cis*-6-isopropylcyclohex-2-enyl esters. With piperidine as nucleophile, the results of this work are in essential agreement with ours, *i.e.*, predominant or exclusive *syn* displacement. However, when piperidine was replaced with the charged nucleophile propanethiolate, the results differed dramatically: the *trans*-ester afforded substantial proportions of *anti*-product; with the *cis*-ester the *anti* product even predominated (with sodium but not with lithium thiolate) (Scheme 23).



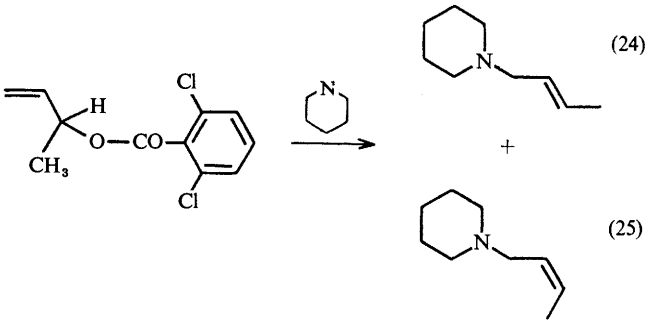
	anti	: *syn*
C_3H_7SNa	65	35
C_3H_7SLi	50	50

Scheme 23

While our results with cyclohexenyl esters and piperidine were unambiguous, their significance was limited by the steric constraints and conformational bias existing in cyclohexenyl systems, to which I have already referred (see pp. 451 and 459). We therefore turned to the study of an acyclic model.

Stork and White had previously reported[40] that α-methylallyl esters apparently afforded the geometrically isomeric S_N2' products (24) and (25) with piperidine (Scheme 24). In our hands, repetition of this experiment afforded as major products the *trans*-olefin (24) and the S_N2' product, but only minor amounts of the *cis*-olefin (25). Nevertheless, formation of the *trans*-olefin (24) was clearly amenable to stereochemical analysis by introduction of a deuterium label, as in Scheme 25. The (*S*)-ester must form *trans*-olefin *via* the conformation shown (C–O bond coplanar with adjacent π-orbital) and piperidine can enter *anti* (a) or *syn* (b) to the departing group, leading, respectively, to the (*R*) and (*S*) configurations at the new chiral centre. Experimentally the analysis requires (a) synthesis of optically active ester of known configuration having deuterium located in one terminal position and (b) a method for determining the (*R*)/(*S*)

[59] G. Stork and I. Kreft, *J. Amer. Chem. Soc.*, 1977, **99**, 3850; 8373.



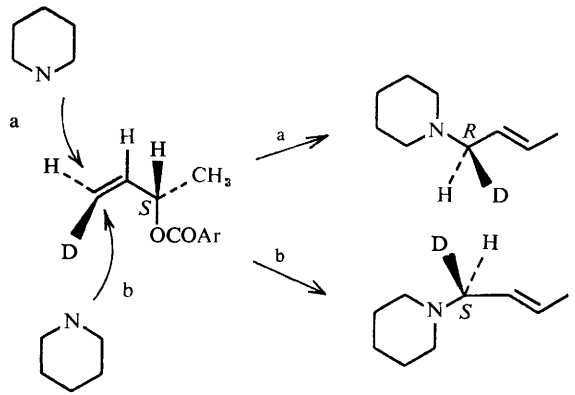
(24)

(25)

Scheme 24

ratio at the new chiral centre and hence the *anti/syn* ratio in the S_N2' displacement.

Experimental distinction between the (*R*) and (*S*) configurations proved troublesome, but was eventually possible in the following way:[60] when piperidine was replaced by (+)- or (−)-α-phenylethylamine, the aminolysis proceeded analogously (*cf.* Scheme 25) and now the diastereotopic hydrogens at the new



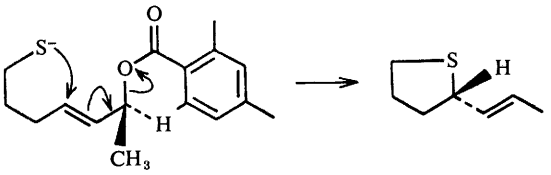
Scheme 25

D-bearing chiral centre of the product were well separated in the Eu(dpm)$_3$-shifted n.m.r. spectrum. This soon revealed that in the aminolysis both (*R*) and (*S*) configurations were formed *and in unequal amounts*, corresponding to both *syn* and *anti* S_N2' reaction. Control experiments had established that this did not result from any of the possible rearrangements or equilibrations of starting ester or product amine. *syn* Entry predominated over *anti* by a factor of *ca.*

[60] T. Oritani and K. H. Overton, *J.C.S. Chem. Comm.*, 1978, 454.

1.4—1.8 over a series of aminolyses in which the chirality of ester and base and the nature of the alkyl substituent were varied.[60]

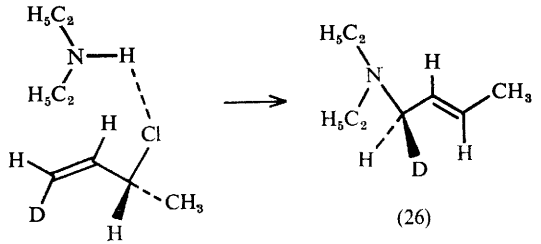
Two further interesting examples of the S_N' reaction with acyclic substrates, both based on the α-alkyl-allyl system, have been reported recently. In an intramolecular variant (S_N'),[61] Stork and Kreft have attached the nucleophile, again propanethiolate, to the α-methylallyl system in such a way as to favour allylic displacement concomitant with 5-*exo-trig* ring closure[62] (Scheme 26).



Scheme 26

Molecular models indicate no clear steric bias that would favour *syn* or *anti* displacement, yet the reaction appears to be, probably exlusively, *anti* with an *E*:*Z* ratio of 93:7.

In a closely related study,[63] displacement of the deuteriated α-methylallyl chloride with diethylamine and with piperidine resulted in probably exclusive *syn* reaction. The chirality of (26) was conveniently established by polarimetry: the di-imide reduction product of (26) had the unexpectedly high $[\alpha]_{365}$ of +19° (ether) (Scheme 27). The ratio of S_N2' to S_N' product was 99:1, that of *E*:*Z* S_N2'



(26)

Scheme 27

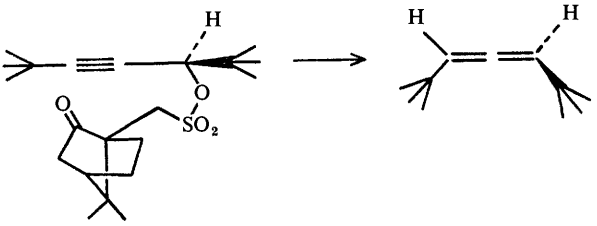
product 95:5. The clean *syn*-S_N2' reaction observed here may well reflect the more effective hydrogen bonding between the amine and allyl chloride, resulting

[61] G. Stork and A. F. Kreft, *J. Amer. Chem. Soc.*, 1977, **99**, 3851.
[62] J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.
[63] R. M. Magid and O. S. Fruchey, *J. Amer. Chem. Soc.*, 1977, **99**, 8368; 1979, **101**, 2107.

in the appropriate orientation for *syn* attack, as suggested long ago by Winstein and Young.[64]

Thus of the small number of examples of the acyclic S_N2' reaction at present on record, one proceeds with *syn*, one with *anti*, and a third with slight predominance of *syn* over *anti* stereochemistry. It becomes apparent that, contrary to the long-held view that S_N' reactions proceed with *syn* stereochemistry, the whole spectrum spanned by the *syn* and *anti* extremes is to be expected, depending in any particular case on the nature of the displacing and displaced groups, counter ions, and solvent.

The allylic displacement of optically active propargylic esters, chlorides, and ammonium salts with nucleophiles is, from a synthetic point of view, an interesting extension of the S_N2' reaction, since it offers access to optically active allenes. There is the additional attraction that a highly stereoselective displacement could lead to allenic hydrocarbons (which cannot be conveniently resolved) of high optical purity. In 1969 Borden and Corey[65] converted the propargyl camphor sulphonate (27) and its diasteromer into the 1,3-di-t-butylallenes with lithium aluminium hydride (Scheme 28). Allene of highest optical purity was



(27)

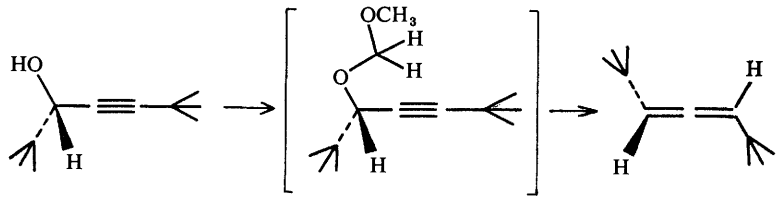
Scheme 28

obtained with the tosylate and $LiAlH(OCH_3)_2H_2$. The S_N2' mechanism for these reactions, rather than trapping of propargyl cation by hydride ion, was supported by failure of $LiAl(OBu^t)_3H$ to displace the camphor sulphonate (27). From the configurations of the propargyl alcohols and of the derived allenes, both deduced by the Lowe–Brewster rules, Corey inferred favoured *anti* stereochemistry for the displacement. The optical purity of the allene and hence the *degree* of preference for *anti*-displacement were not available from this work. By chemical correlation of the alcohol with the allene (Scheme 29), *via* sigmatropic rearrangement of the ketal (28), Arigoni has recently confirmed[66] the *anti*

[64] W. G. Young, D. Webb, and H. L. Goering, *J. Amer. Chem. Soc.*, 1951, **73**, 1074; see also R. H. de Wolfe and W. G. Young in 'The Chemistry of the Alkenes', ed. S. Patai, Interscience, London, 1964, pp. 691—694; C. K. Ingold 'Structure and Mechanism in Organic Chemistry', Cornell U.P., Ithaca, 1969, pp. 853—861.

[65] W. T. Borden and E. J. Corey, *Tetrahedron Letters*, 1969, 313.

[66] D. Arigoni, Euchem. Conference on Structure, Synthesis and Biosynthesis of Mono- and Sesquiterpenoids, Varenna, 1977.

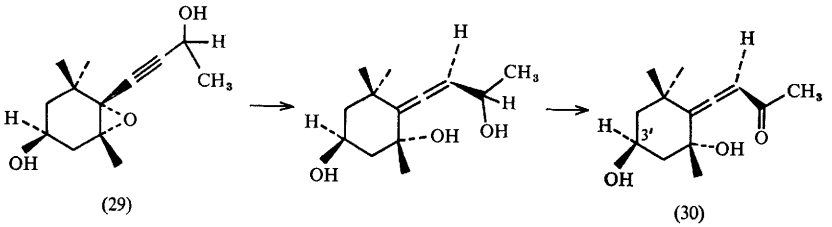


(28)

Scheme 29

mode for the displacement and also shown that under optimal conditions it can be highly stereoselective.

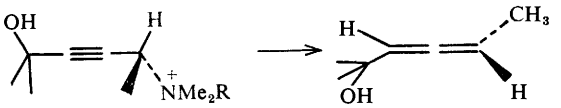
Two related allene-forming hydride displacements of propargyl derivatives apparently proceed preferentially by the *syn* mode. Weedon and his colleagues synthesised the allenic grasshopper ketone (30)[67] *via* hydride opening of the acetylenic epoxide (29) and established that this had proceeded in *syn* fashion by *X*-ray analysis of the 3′-*p*-bromobenzoate of (30) (Scheme 30).



(29) (30)

Scheme 30

Claesson and Mosher have based syntheses of α- and β-allenic alcohols on the hydride displacement of α- and β-acetylenic quaternary ammonium salts.[68] They infer from indirect evidence that this reaction shows a preference for *syn* stereochemistry (Scheme 31).



Scheme 31

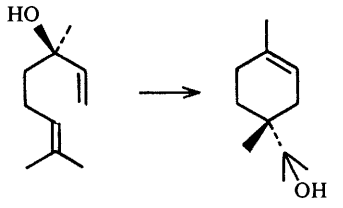
[67] S. W. Russell and B. C. L. Weedon, *Chem. Comm.*, 1969, 85; T. E de Ville, M. B. Hursthouse, S. W. Russell, and B. C. L. Weedon, *J.C.S. Perkin I*, 1974, 848.

[68] A. Claesson, L.-I. Olsson, G. R. Sullivan, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1975, **97**, 2919.

Stereoselectivity has also been observed in the preparatively useful reactions of α-propargylic acetates,[69] chlorides,[70] and carbamates[71] with organo-cuprates. Although formally related to the preceding examples, these reactions are certainly mechanistically distinct from normal nucleophilic substitutions and therefore not relevant to this discussion.

I turn finally to some formal examples of the S_N' reaction in terpenoid biosynthesis. Each involves formation of a carbocyclic ring by nucleophilic allylic displacement of an ester, the intramolecular nucleophile being a suitably situated olefinic double bond. The first example provides a laboratory model for what is surely a key step in the biosynthesis of a number of mono- and sesquiterpenoids.

It has been known for some time[72,73] that (*R*)-linalool can be converted either with aqueous acid or by solvolysis of its esters, into (*R*)-α-terpineol with remarkably high retention of enantiomeric purity (Scheme 32). There is really no



(*R*)-linalool (*R*)-α-terpineol

Scheme 32

compelling reason for expecting *syn* rather than *anti* cyclisation, although both Rittersdorf[72] and Winstein[73] did so, largely on the basis of Stork and White's experiments.[40] Recently Arigoni and his colleagues have established[74] that, on the contrary, cyclisation proceeds predominantly in the *anti* mode.

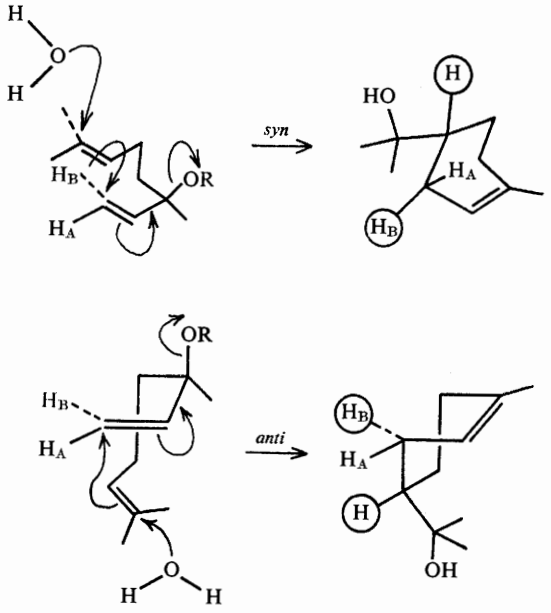
In order to distinguish the *syn* and *anti* modes, it is necessary to identify H_A or H_B in the cyclisation product (Scheme 33).

(*RS*)*-Linalool, doubly deuteriated as in (31) (Scheme 34), was prepared from dehydrolinalool and cyclised to α-terpineol (32) by solvolysis of the *p*-nitrobenzoate. The ^1H n.m.r. spectrum of the dihydrocineole (33), obtained *via* the *trans*-epoxide, showed that H_B and the adjacent tertiary hydrogen were ($\lesssim 85\%$) *syn* and therefore cyclisation had proceeded predominantly *anti*.

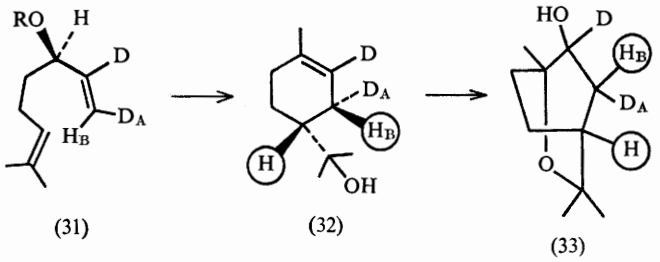
The same conclusion emerges from the first investigation[75] of an analogous

*The use of *rac*-linalool in this experiment is, of course. perfectly in order, since only the relative configurations of H and H_A (or H_B) in the product (32) are at issue.

[69] J. L. Luche, E. Barreiro, J. M. Dollat, and P. Crabbé, *Tetrahedron Letters*, 1975, 4615.
[70] O. J. Muscio, Y. M. Yun, and J. B. Phillip, *Tetrahedron Letters*, 1978, 2379.
[71] W. H. Pirkle and C. W. Boeder, *J. Org. Chem.*, 1978, **43**, 1950; 2091.
[72] W. Rittersdorf and F. Cramer, *Tetrahedron*, 1968, **24**, 43.
[73] S. Winstein, G. Valkanas, and C. F. Wilcox, *J. Amer. Chem. Soc.*, 1972, **94**, 2286.
[74] S. Godtfredsen, J. P. Obrecht, and D. Arigoni, *Chimia* (*Switz.*), 1977, **31**, 62.
[75] D. E. Cane and P. P. N. Murthy, *J. Amer. Chem. Soc.*, 1977, **99**, 8327.



Scheme 33



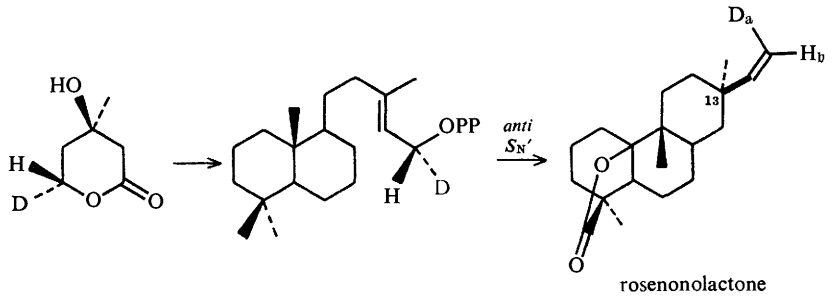
(31) (32) (33)

Scheme 34

in vivo cyclisation, that leading to the formation of ring C in rosenonolactone biosynthesis in cultures of *Trichothecium roseum* (Scheme 35).*

Since the deuterium label from (5*R*)-[5^{2}H$_1$]mevalonate appears at position *a* rather than *b* (a parallel experiment with (5*S*)-[5^{2}H$_1$]mevalonate gave the complementary result), and the configuration at C-13 in rosenonolactone is as shown, the formation of ring C must take place by *anti* displacement. This conclusion could be extracted from the ^{2}H n.m.r. spectra of rosenonolactone biosynthesised from [5-^{2}H$_2$], (5*R*)-, and (5*S*)-[5^{2}H$_1$]mevalonates. This fruitful application of ^{2}H

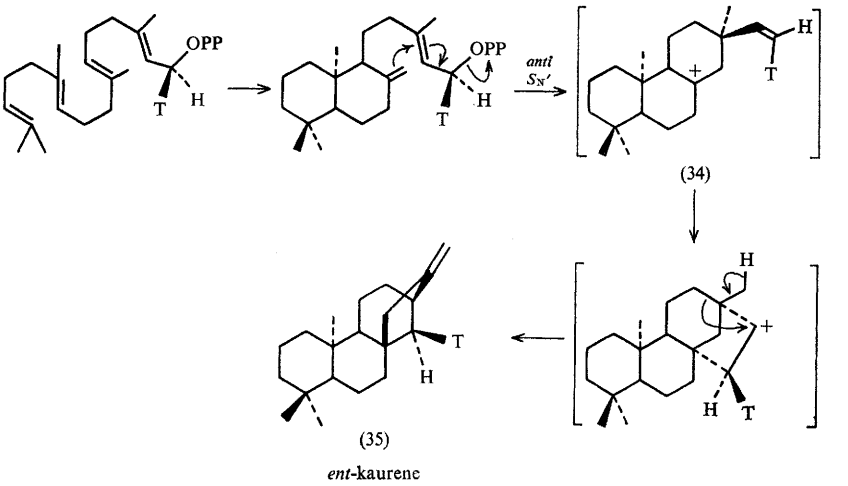
*Only the relevant labels are shown in Schemes 35, 37, and 38.



Scheme 35

magnetic resonance to the solution of a biosynthetic problem brings out both the advantages and the difficulties of the method.

The analogous formation of ring C in the *ent*-pimarenyl cation (34) on the pathway to *ent*-kaurene (35) in *Marah macrocarpus* (Scheme 36)[76] and on to

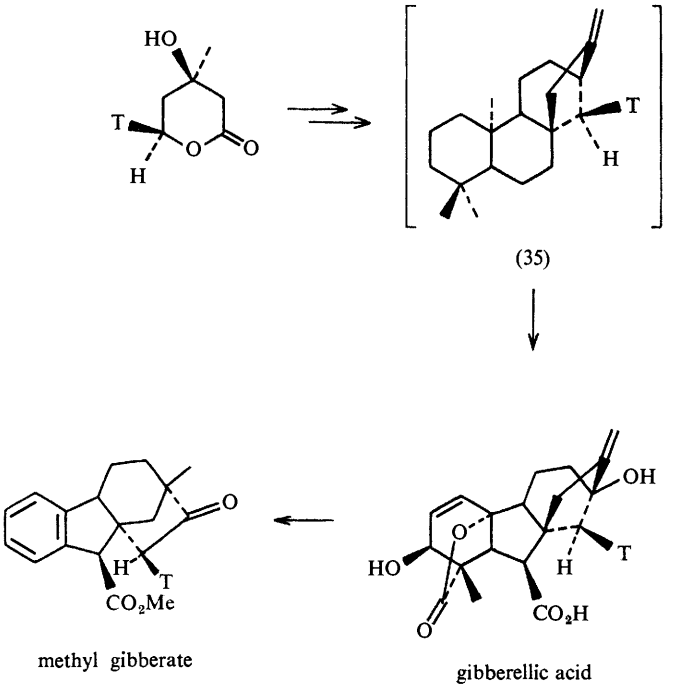


Scheme 36

gibberellic acid in *Gibberella fujikuroi* (Scheme 37)[77] may similarly proceed by *anti*-cyclisation. This inference depends on certain assumptions about the conformational behaviour of intermediates.

One final example concerns formation of the eight-membered ring in the

[76] P. L. Cavender and R. M. Coates; personal communications from Prof. Coates, Illinois.
[77] R. Evans, J. R. Hanson, and L. J. Mulheirn, *J.C.S. Perkin I*, 1973, 753; I am indebted to Profs. Cane and Coates for drawing my attention to this paper.



methyl gibberate

gibberellic acid

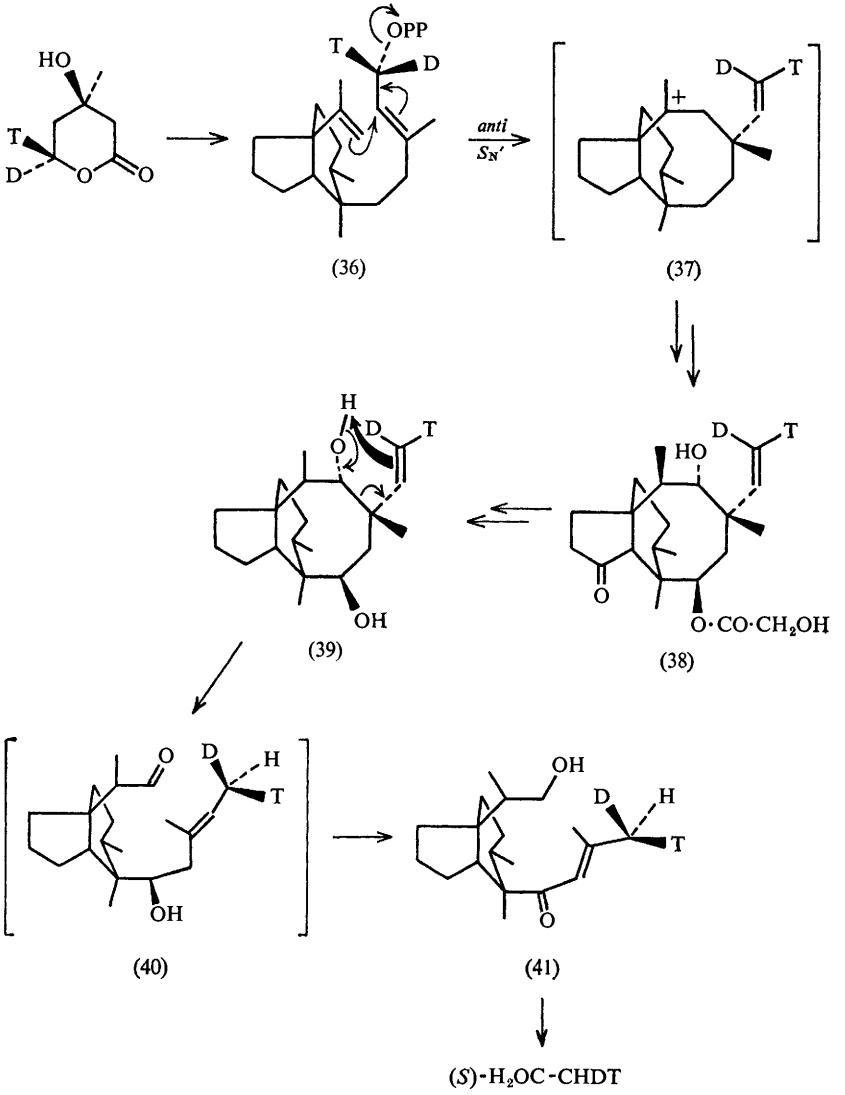
Scheme 37

biosynthesis of pleuromutilin (38) by the fungus *Pleurotus mutilus*. The ingenious solution of this stereochemical problem depends on chiral acetic acid (Scheme 38).[78]

There is a clear parallel, in the cyclisation, with rosenonolactone biosynthesis. In the bicyclic intermediate (36) a methylene double bond interacts with a tertiary cation, generated by loss of OPP^- and double-bond shift. Again the configuration of the newly created quaternary methyl group is established and one has to determine whether the pyrophosphate departs *syn* or *anti* to the direction in which the new bond is made. This was done by again taking advantage of isotopic substitution at C-5 of mevalonic acid. This time a double label (D and T) at C-5 of mevalonate will lead to isotopic labels in the intermediate (36) as shown. Cyclisation [(36) →(37)] *with anti-*S_N' *stereochemistry* would result in the labelling pattern in (37). That this was indeed the pattern obtained was ingeniously established by taking advantage of an electrocyclic transfer of ^1H from the hydroxyl group of pleuromutilin (38). Thus pyrolysis of the derivative (39)* gave, presumably *via* the initial fragmentation product (40), the enone (41).

*H-transfer must be to the *re*-face of the double bond in (39).

[78] H. Hasler, Ph.D. Thesis, ETH, Zürich, 1979.



Scheme 38

The terminal methyl group was shown to have the (*S*)-configuration by Kuhn–Roth oxidation and enzymatic assay of the acetic acid formed.[38,39] *anti*-Stereochemistry is thereby established for the cyclisation of (36) to (37),* as in the analogous cyclisation in rosenonolactone biosynthesis.

Acknowledgment—I am greatly indebted to Professors Arigoni, Coates, and Eschenmoser for permission to refer to their unpublished work.

*Interestingly, this result is independent of the absolute configuration of pleuromutilin since with either enantiomer the chirality of the methyl group of (41) is the result of a net inversion of C-5 in mevalonic acid.