pared to the reactant.[13] In this connection we note that, although enzymic participation should not be discounted, the results in the table *can* be rationalized without invoking any special enzymic function in directing either the rearrangement or the elimination which terminates it. Focusing attention on only those axial nonbonding interactions (CH_3–CH_3 or H–CH_3) which appear or disappear as the rearrangement of VI occurs, we see in the first three cases that the efficiency as a substrate falls off as the *change* in number of interactions decreases.[14] This trend may be due to removal of an essential part of the driving force for this rearrangement (*i.e.*, relative stabilization of tetracyclic C-20 carbonium ion), thus making the rearrangement step, *at least for the mononor cases*, less facile. The fact that the bisnor compound cyclized efficiently but did not rearrange suggests that the recognition or cyclization steps, *per se*, are not much affected by removal of methyl substituents.[15]

Another important stereochemical change during the rearrangement is that of the B-ring geometry. Evidently, in the absence of both 10′ and 15′ methyls, the strain of the *trans,syn,trans,trans*-ring system alone (as indicated by the bisnor case) does not contribute enough to the driving force to initiate the rearrangement. However, it seems that, with the 10′ and/or 15′ methyls intact, the B boat of the proto system could fortify the driving force, ensuring *continuation to term* ($\Delta^{8(9)}$) of the rearrangement. We wish to emphasize that specifically in the 10′- and 15′-nor cases, no annular double bond isomers were formed by premature elimination. In no case is a Δ^7 isomer found; although concerted loss of a 7β (axial) proton is possible, such elimination would leave a 9β proton, with ring C locked in a boat form. Thus, there is no need to assume that a specific function of the enzyme is removal of the 9β proton; although there may be a specific proton-accepting site in the enzyme, the product is the one which would be formed solely under thermodynamic control.

The above arguments should not be taken to imply that the only function of the cyclizing enzyme is one of protecting reactive intermediates from attack by solvent or bases during the reaction. From our various studies of the nonenzymic-catalyzed cyclization of squalene oxide and other terpenoid epoxides it is obvious that a critical role of the enzyme is specifying a unique chain folding which allows the annelation steps to proceed down *only* one path—a path which is *not* favored thermodynamically.

Acknowledgment. The authors are grateful to the National Institutes of Health (Grant No. GM 10421), the American Heart Association (grant-in-aid to R. B. Clayton), and to NASA (NGL 05-003-003 and NAS9-7889 to A. L. B.) for financial support. Also, thanks are due Miss Martha Petrie, University of California (Berkeley), for technical assistance in obtaining mass spectra.

(13) P. de Mayo in "Molecular Rearrangements, Part II," P. de Mayo, Ed., Wiley-Interscience, New York, N. Y., 1964, p 821; R. M. Coates, *Tetrahedron Lett.*, 4136 (1967); H. W. Whitlock and M. C. Smith, *ibid.*, 821 (1968); S. C. Pakraski and T. B. Samanto, *ibid.*, 3679 (1967).

(14) Under standard conditions, the yield of product reflects the rate of the overall bimolecular (enzyme + substrate) reaction. This rate in turn is composed of the rates of a number of sequential substeps: (1) formation of E–S complex, (2) tetracyclization, (3) rearrangement to lanostane, and (4) elimination of 9 proton (and separation of enzyme and product molecules at some point).

(15) Linking the C-20 charge center to a conjugated system may also provide stabilization comparable to the removal of both migrating methyls. See E. J. Corey, K. Lin, and H. Yamamoto, *J. Amer. Chem. Soc.*, **91**, 2132 (1969).

(16) National Science Foundation Predoctoral Fellow, 1966–present.

E. E. van Tamelen, R. P. Hanzlik[16]
Department of Chemistry, Stanford University
Stanford, California 94305

R. B. Clayton
Department of Psychiatry, Stanford University
Stanford, California 94305

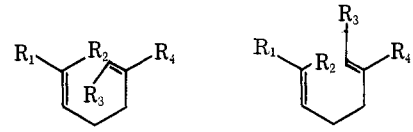
A. L. Burlingame
Space Sciences Laboratory, University of California
Berkeley, California 94720

Received December 8, 1969

A General 1,5-Diene Synthesis Involving Overall Allyl Alcohol Coupling with Geometrical and Positional Control

Sir:

The general utility and importance of 1,5-dienes with double bonds in specific geometrical arrangements (*e.g.*, juvenile hormones and sterol and cyclic terpene precursors) has made the practical synthesis of pure substances of, for example, types I and II the object of extensive investigation, resulting in the invention or novel development of useful coupling processes.[1–4] However, at the time we initiated this project, there did not exist a general method for performing this operation with the maintenance of the stereochemical and structural integrity of allylic systems essential to a truly catholic procedure. The need for such geometrically pure 1,5-dienes has climaxed in the development of a method for symmetric or asymmetric overall coupling of allyl alcohols which proceeds in good yield with essentially complete preservation of the position and geometry of the olefinic bonds.



I II

R_1, R_2, R_3, R_4 = H or alkyl

In its final form the synthetic sequence involves (1) conversion of the allyl alcohols to allyl bromides by means of carbon tetrabromide and triphenylphosphine, (2) quaternization of tributylphosphine with one of the allyl bromides,[5] (3) C-allylation of the derived ylide with

(1) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, **87**, 3277 (1965); K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, *ibid.*, **90**, 209 (1968).

(2) E. J. Corey and M. F. Semmelhack, *ibid.*, **89**, 2755 (1967), and references cited therein.

(3) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969). The example cited does not allow one to differentiate between coupling at the two possible reactive sites in an allylic Grignard reagent.

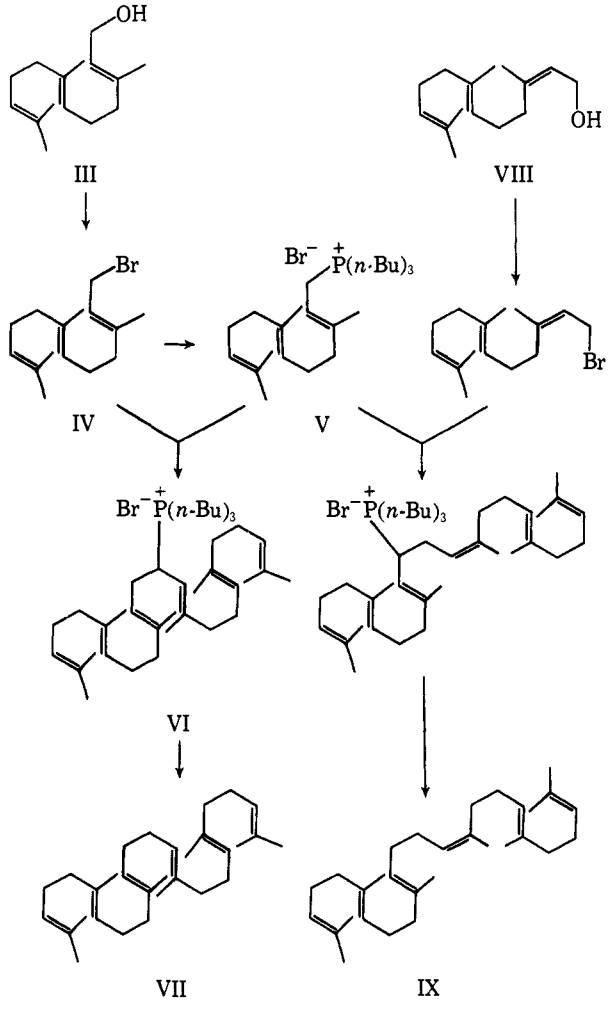
(4) J. F. Biellman and J. B. Ducep, *ibid.*, 3707 (1969), describe a sulfur-based coupling procedure terminating with lithium–ethylamine reduction.

(5) It was known[6] that the reaction of triphenylphosphine with primary allylic halides prepared by one of two known stereospecific methods[7,8] yielded primary phosphonium salts with retention of geometrical configuration.

the other bromide, and (4) reductive cleavage of the new phosphonium salt, carried out by means of lithium in ethylamine. The entire process, executed without deliberate purification of intermediates, can be carried out expeditiously in as high as 65% yield (based on starting phosphonium salt) and with less than 1% isomerization, either *cis–trans* or positional.

For instance (Scheme I), treatment of *trans,trans*-farnesol (III) in acetonitrile at 25° with a 10% molar excess of carbon tetrabromide and triphenylphosphine afforded after 3 hr pure[9] *trans,trans*-farnesyl bromide (IV, 90%), the triphenylphosphine oxide produced being removed by precipitation from pentane. Treatment of

Scheme I

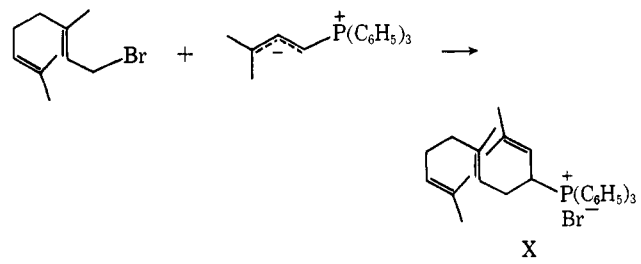


the bromide with tributylphosphine in benzene at ambient temperature gave, on evaporation and filtration chromatography through silica gel, *trans,trans*-farnesyltributylphosphonium bromide (V, 90%),[10] uncontaminated by starting material. Generation of ylide from V in tetrahydrofuran at −76° with phenyllithium and addition of 1 equiv of *trans,trans*-farnesyl bromide (IV) gave, after stirring for 3 hr and gradual warming to room temperature, coupled phosphonium salt IV (85%).[10,11] The new phosphonium salt was separated from less polar impurities by silica gel filtration chromatography and reduced at −76° with lithium in ethylamine under an argon atmosphere. After stirring for 3 hr the reaction mixture was worked up in the standard manner and the products were chromatographed on silica gel to yield pure (all-*trans*) squalene (VII, 65% based on V) identical with an authentic sample by ir, nmr (ratio of *cis*:*trans* allylic methyl groups 3.0:1.0), and glpc.

Because the reaction of allylidenephosphoranes at both α and γ sites has been reported,[12] it was important for the success of this synthesis to determine the extent and consequences of such behavior in the case at hand. Nmr analysis of the coupled phosphonium salts and the reduced products in every case (*vide infra*) revealed lack of aliphatic methyl resonance, a necessary result of coupling at the γ position. However geometrical isomerization during reaction could best be rigorously ruled out by coupling of both *cis*- and *trans*-allyl isomers and glpc comparison of the respective products. Coupling of *trans,trans*-farnesol (III) with *cis,trans*-farnesol (VIII) as described gave *trans,trans,cis,trans*-squalene (IX, 58% based on V),[10,13] nmr ratio of *cis*:*trans* allylic methyls 5.0:3.0. Squalene (VII) and the mono-*cis* isomer are easily separable by glpc, and the products of the above couplings showed less than 1% mutual contamination. However, it is important to note that when the couplings were carried out with the allyl chlorides instead of the allyl bromides, significant (5–15%) geometrical isomerism was observed, presumably due to the higher temperatures and longer reaction times required for the chloride reaction (3 hr at −76° *vs.* 5 hr at 65°). In every case where asymmetric coupling was involved, each allyl building block was used both as the phosphonium ylide and the alkylating bromide in order to have an absolute check on the purity of products and the generality of the sequence.

Although a variety of procedures for the final carbon–phosphorus cleavage were known, the development of this step proved to be a major hurdle. Fenton and Ingold[14] have reported that quaternary phosphonium halides are decomposed by hydroxide to hydrocarbon and phosphine oxide with cleavage of the most electronegative group. In order to investigate this reaction we prepared triphenylphosphonium salt X as shown in Scheme II. Cleavage of X with either aqueous hy-

Scheme II



X

(6) (a) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966; (b) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965; (c) A. Maercker, *Org. Reactions*, 14, 270 (1965); (d) "Newer Methods of Preparative Organic Chemistry," Vol. V, A. E. Foerst, Ed., Academic Press, New York, N. Y., 1968, pp 1–60.

(7) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969).

(8) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, 44, 1331 (1966).

(9) The ratio of *cis*:*trans* allylic methyl groups at δ 1.57 and 1.66 was 3.0:1.0 as anticipated for pure *trans,trans* compound.

(10) Satisfactory nmr, tlc, glpc, and analytical data were obtained for all new compounds.

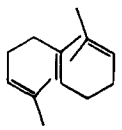
(11) Nmr ($CDCl_3$) δ 5.0–5.3 (6, broad), 1.9–2.2 (20, broad), 1.64 (6, s), 1.59 (18, s).

(12) H. Bestmann and H. Schulz, *Ann.*, 674, 11 (1964).

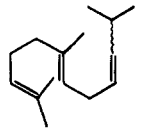
(13) Nmr (CCl_4) δ 5.0–5.3 (6, broad), 1.9–2.2 (20, broad), 1.64 (9, s), 1.59 (15, s), compared with a sample prepared independently.

(14) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 2342 (1929).

droxide or *t*-butoxide–*t*-butyl alcohol involved a significant degree of competition between phenyl and allyl as leaving groups. Most important, however, the hydrocarbon which did result from the desired phosphorus–allyl cleavage proved to be a 3:1 isomeric mixture of XI and XII, thus making this procedure unattractive from a synthetic standpoint. The carbon–



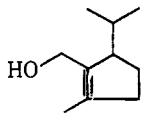
XI



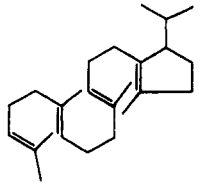
XII

phosphorus bond can also be cleaved reductively by $LiAlH_4$,[15] electrolysis,[16] zinc–acid, and lithium–amine.[17] However, treatment of X with $LiAlH_4$ led exclusively to SN2′ product XII. The method which demonstrated the greatest promise was the reported reduction with lithium in ethylamine at −76°, giving a 43% yield of the desired hydrocarbon XI. Since the low yield could be ascribed to competitive cleavage of phenyl and allyl (as observed for the hydroxide–water cleavages), or phenyl reduction by lithium–ethylamine, we used the tri-*n*-butylphosphonium salts, for which no such ambiguity should exist, in order to reach a successful conclusion (*vide supra*).

More highly hindered allylic systems such as the cyclopentenyl alcohol XIII[18] may also be coupled with, for example, *trans*-farnesol (III) to give XIV (63%).[19]

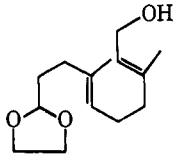


XIII

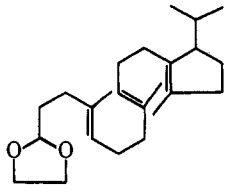


XIV

Coupling of XIII with the functionalized *trans*-farnesol trisnor acetal XV[10] to give acetal XVI[20] is further indi-



XV



XVI

cation of the general applicability of this sequence, as is the alkylation of the intermediate ylides by alkyl iodides and bromides. The generality of this method for the preparation of pure 1,5-dienes and the preparation of 1,4-dienes by lithium aluminum hydride reduction of substituted allyl phosphonium salts portend some breadth of synthetic utility.

Acknowledgments. The authors are grateful to the National Science Foundation (Grant No. GP 7187) and the National Institutes of Health (Grant No. GM 10421) for financial aid.

(21) National Institutes of Health Postdoctoral Fellow, 1969–present.

E. H. Axelrod, G. M. Milne,[21] E. E. van Tamelen
Stanford University, Department of Chemistry
Stanford, California 94305
Received November 29, 1969

Barriers in Ethyl Cations[1]

Sir:

Because of geometrical restrictions, many carbonium ions cannot achieve the preferred planar structure.[2,3] Bridgehead cations are examples of such nonplanar carbonium ions.[4] While it would be desirable to perform rigorous and reliable molecular orbital calculations on these ions, such calculations are impossible at present because of the large size of such systems. For finding the energies associated with nonplanarity and with torsional interactions in nonplanar ions, the ethyl cation, the simplest ion for which torsional barriers are possible, is an obvious model. In addition, it is the simplest ion in which classical and bridged structures may be compared.

Several calculations, at various levels of sophistication, have been reported for the ethyl cation.[3,5–8] However, the effects of extensive variation of geometry have not generally been considered, especially by the most refined methods. In this communication, we wish to report the results of two sets of *ab initio* calculations on ethyl cations which are relevant to both the rotational barrier in classical structures (planar and tetrahedral CH_2^+) and the bridge barrier for the interconversion by 1,2-hydride shift of equivalent classical structures.

The first set of calculations used the same basis set as ref 3, with two scaled s-type groups of gaussian orbitals on each hydrogen. In general, threefold rotational barriers computed by this method are accurate to within ±0.4 kcal/mol.[9] Five geometries were considered, and the energies are presented in Table I. For each calculation the methyl group was tetrahedral, with a CH bond length assumed to be 1.096 Å. The CH bond length in the trigonal CH_2^+ group was kept at

(1) Molecular Orbital Calculations on Carbonium Ions. III.[2,3]
(2) Part I: J. E. Williams, Jr., R. Sustmann, L. C. Allen, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 1037 (1969).
(3) Part II: R. Sustmann, J. E. Williams, M. J. S. Dewar, L. C. Allen, and P. v. R. Schleyer, *ibid.*, **91**, 5350 (1969).
(4) R. C. Fort and P. v. R. Schleyer, *Advan. Alicyclic Chem.*, 1, 283 (1966); G. J. Gleicher and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967).
(5) R. Hoffmann, *J. Chem. Phys.*, **40**, 2480 (1964); R. E. Davis and A. S. N. Murthy, *Tetrahedron*, **24**, 4595 (1968).
(6) T. Yonezawa, H. Nakatsuji, and H. Kato, *J. Amer. Chem. Soc.*, **90**, 1239 (1968); M. S. Isaacs, *Tetrahedron*, **25**, 3555 (1969); J. J. Dannenberg and T. D. Berke, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, No. PHYS 163.
(7) F. Fratev, R. Janoschek, and H. Preuss, "Arbeitsbericht der Gruppen Quantenchemie," Max-Planck Institut fur Physik und Astrophysik, No. 10, 1968, p 140; *Int. J. Quantum Chem.*, **3**, 893 (1969).
(8) During the course of this work we became aware of a similar *ab initio* study on the ethyl cation: G. V. Pfeiffer and J. G. Jewett, *J. Amer. Chem. Soc.*, **92**, 2143 (1970).
(9) L. C. Allen, *Chem. Phys. Lett.*, **2**, 597 (1968); W. H. Fink and L. C. Allen, *J. Chem. Phys.*, **46**, 2261 (1967).

(15) W. Bailey and S. Buckler, *J. Amer. Chem. Soc.*, **79**, 3567 (1957).
(16) L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, and P. Beck, *Tetrahedron Lett.*, 161 (1961).
(17) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Amer. Chem. Soc.*, 77, 3230 (1955).
(18) The synthesis and reactions of XIII were originally pursued by R. Anderson of these laboratories and will be reported elsewhere.
(19) Nmr (CCl_4) δ 5.0–5.3 (4, broad), 2.4–2.6 (1, broad), 1.8–2.4 (14, broad), 1.65 (3, s), 1.57 (12, broad s), 1.0–1.5 (3, broad m), 0.92 (3, d, J = 7 Hz), 0.64 (3, d, J = 7 Hz).
(20) Identical with an authentic sample prepared independently. Nmr (CCl_4) δ 5.0–5.3 (3, broad), 4.75 (1, t, J = 6 Hz), 3.78–3.95 (4, m), 2.4–2.6 (1, broad), 1.8–2.4 (14, broad), 1.56 (9, broad s), 0.92 (3, d, J = 7 Hz), 0.66 (3, d, J = 7 Hz).