results. While no definite statement can be made about this, we are presently making a more complete study of the hydrolyses of I, III, and other 2,5-diketopiperazinediones in order to clarify further the hydrolysis mechanism.

Registry No.—I, 17393-47-4; II, 15996-22-2; III, 17393-48-5; IX, 17393-49-6; L-seryl-L-serine hydrochloride, 17393-50-9.

Acknowledgments.—Supported in part by grants (AI-04615 and AI-05539) from the National Institute of Allergy and Infectious Diseases by a Public Health Service training grant (5TI-GM-626), by a grant (GM-10006) from the Division of General Medical Science, and by a National Institutes of Health Biomedical Grant from the University of Georgia. We thank Dr. James A. Marshall for discussions and suggestions and Dr. Wallace F. Runge for generous gifts of D-cycloserine.

Studies Relating to the Synthesis of (+)-Valeranone

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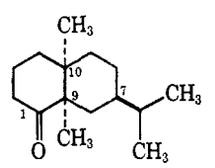
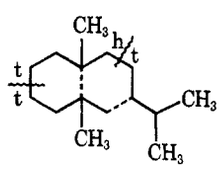
Several synthetic schemes leading from ketol **9**, the condensation product of (−)-dihydrocarvone (**8**) and methyl vinyl ketone, to (+)-valeranone (**19**) are described. The first of these employs norvaleranone (**18**), prepared from ketol **9** by sequential reduction (H_2/Pt, then $LiAlH_4$), acetylation, hydrogenolysis (Li, $EtNH_2$), hydroboration, and oxidation ($NaOH$–H_2O_2, then CrO_3). Angular methylation of norvaleranone was effected *via* the *n*-butylthiomethylene derivative **22**. A second route to valeranone involved conversion of ketol **9** into 2-oxovalerane (**39**). This conversion involved reduction (H_2/Pt, then $LiAlH_4$), selective mesylation, fragmentation (KO-*t*-Bu), addition of methyllithium, cation-initiated olefin cyclization (HCO_2H), saponification of the resulting formate, and oxidation (CrO_3) of the alcohol thus obtained. Transposition of the ketone grouping to the adjacent C-1 position completed the synthesis. Two methods are described for effecting this transposition. Both employ the 1-acetoxy derivative **50**, obtained from ketone **39** by bromination, dehydrobromination [$CH_3CON(CH_3)_2$, $CaCO_3$], acetoxylation [$Pb(OAc)_4$, BF_3], and hydrogenation. Conversion of ketone **50** into the thioketal derivative **51** followed by removal of the acetyl grouping ($LiAlH_4$) and desulfurization (Raney nickel) afforded alcohol **53** which yielded (+)-valeranone (**19**) upon oxidation (CrO_3). Alternatively, reduction ($NaBH_4$) of keto acetate **50** followed by mesylation and base treatment yielded the 1β,2β-oxide **56** which was converted into (+)-valeranone through reduction ($LiAlH_4$) followed by oxidation (CrO_3).

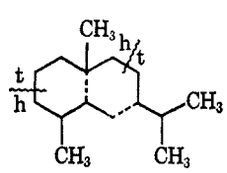
Valeranone, a naturally occurring sesquiterpene ketone first isolated by Stoll and coworkers[2] in 1957, was identified as 9α,10α-dimethyl-7β-isopropyl-1-decalone (**1**)[3] after extensive chemical investigation[4] and an initial erroneous structure proposal. Subsequently, several other natural products[5] were related to valeranone, and together these compounds comprise the valerane (**2**) family of sesquiterpenes. The valeranes are unusual among sesquiterpenes in two respects. Their carbon skeleton, although formally divisible into isoprene units (*cf.* **2**), cannot be derived from farnesol since two of the isoprene units must be linked in a tail to tail arrangement. Thus the valeranes differ from their more commonly found hydronaphthalene relatives, the eudesmanes (**3**) and the cadinanes (**4**) which may be formulated as head to tail linked isoprenoids.[6]



1



2



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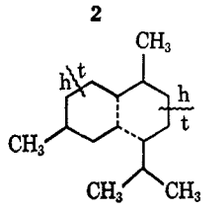


4

A second distinctive feature of the valeranes is their C-10 absolute configuration which is opposite that of most eudesmanes.[7] However, both families have the same isopropyl side-chain orientation. A biogenetic scheme which accomodates these points has been presented.[8]

The unusual structural features that confounded the structure elucidation of valeranone make this substance an interesting target for synthetic studies. An attractive starting point for such studies was suggested by the work of Howe and McQuillin[9] who found that (+)-dihydrocarvone (**5**) underwent annelation with ethyl vinyl ketone to give an 85:15 mixture of epi-α-cyperone (**6**) and α-cyperone (**7**) in about 60% yield. This sequence offers a direct route to bicyclic materials with the correct C-10 to C-7 stereochemical relationship of valeranone. Moreover, intermediates of known

(1) (a) Fellow of the Alfred P. Sloan Foundation, 1966–1968; (b) National Institutes of Health Predoctoral Fellow, 1965–1967.

(2) A. Stoll, E. Seebeck, and D. Stauffacher, *Helv. Chim. Acta*, **40**, 1205 (1957).

(3) Decalin numbering system. See formula **1**.

(4) J. Křepinský, M. Romaňuk, V. Herout, and F. Šorm, *Tetrahedron Lett.*, **5**, 169 (1962), and previous papers; E. Hõhne, *Collect. Czech. Chem. Commun.*, **28**, 3128 (1963); T. R. Govindachari, B. R. Pai, K. K. Purushothaman, and S. Rajadurai, *Tetrahedron*, **12**, 105 (1961); C. Djerassi, *Tetrahedron Lett.*, **6**, 226 (1961); H. Hikino, T. Hikino, Y. Takeshita, K. Meguro, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **11**, 1207 (1963); W. Klyne, S. C. Bhattacharyya, S. K. Paknikar, C. S. Narayanan, K. S. Kulkarni, J. Křepinský, M. Romaňuk, V. Herout, and F. Šorm, *Tetrahedron Lett.*, 1443 (1964); K. S. Kulkarni, S. K. Paknikar, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 1289 (1964).

(5) K. S. Kulkarni, S. K. Paknikar, and S. C. Bhattacharyya, *ibid.*, **20**, 1289 (1964). H. Hikino, Y. Hikino, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **11**, 1210 (1963); **13**, 1417 (1965). H. Hikino, Y. Takeshita, Y. Hikino, and T. Takemoto, *ibid.*, **13**, 631 (1965).

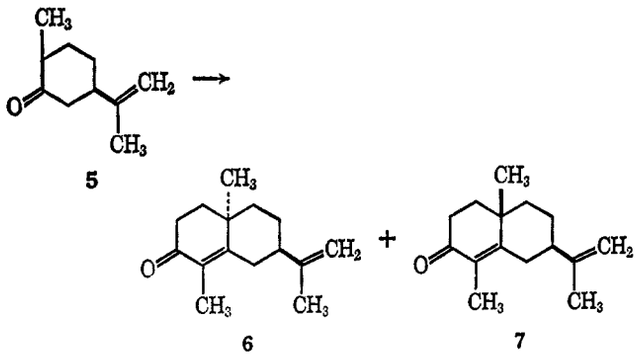
(6) *Cf.* L. Ruzicka, *Proc. Chem. Soc.*, 341 (1959).

(7) *Cf.* W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

(8) W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev.* (London), **21**, 331 (1967). Refer to pp 347–348.

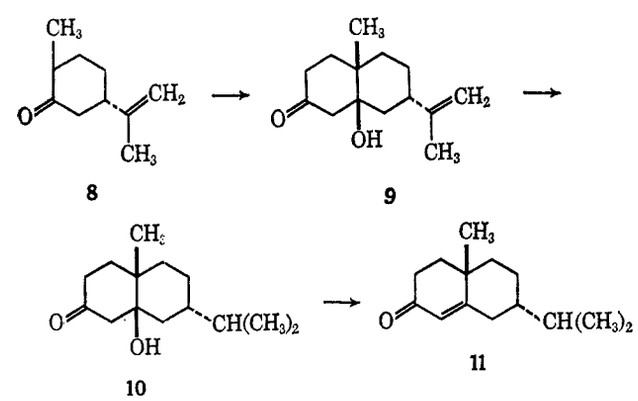
(9) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2423 (1955), and references to earlier work.

absolute stereochemistry should thus be available starting from optically active carvone of known configuration[10] thereby permitting the absolute, as well as the relative, stereochemical assignments of valeranone to be independently tested through synthesis.



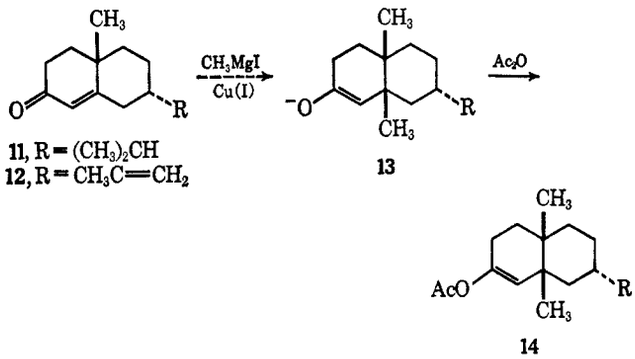
5 6 7

We decided to direct our synthetic efforts at (+)-valeranone, the antipode of the natural product (1), and therefore chose (−)-dihydrocarvone (8)[9,11] as our starting material. Annelation with methyl vinyl ketone under mild conditions[12] afforded the crystalline ketol **9** in 40% yield. The stereochemistry of this intermediate rested initially on analogy with related condensation reactions[12] and was later confirmed by the optical rotatory dispersion curve of ketol **9** and subsequent transformation products.[11,13] Hydrogenation of ketol **9** afforded the dihydro derivative **10**. Attempts to prepare ketol **10** directly *via* annelation of tetrahydrocarvone met with limited success, possibly because this ketol is lower melting and less crystallizable than ketol **9**, thereby rendering its separation from the complex mixture of annelation by-products more difficult.



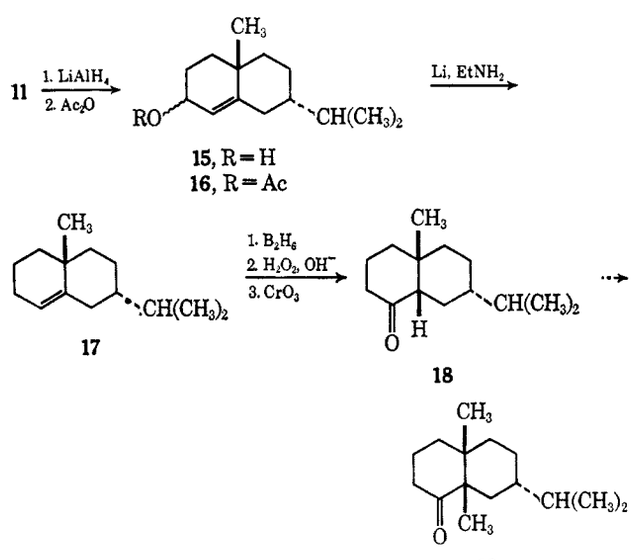
8 9 10 11

Our initial plan called for dehydration of ketol **10** and direct introduction of the second angular methyl group *via* copper-catalyzed conjugate addition of methylmagnesium iodide[14] to octalone **11**. We hoped to trap the initially formed enolate **13** as the enol acetate **14**,[15] thereby setting the stage for subsequent ketone transposition to C-1. This plan had to be abandoned, however, as we were unable to effect the conjugate methylation of octalone **11** or its unsaturated counterpart **12**.[11] Recently we have found that lithium dimethylcopper[16] adds to octalone **11** affording the *cis*-fused 1,4 adduct in 10% yield.[17] The aforementioned plan could thus still be considered potentially fruitful.



11, R = $(CH_3)_2CH$
12, R = $CH_3C{=}CH_2$
13 14

The ready availability of ketol **10** prompted us to seek alternative methods for converting this substance into valeranone. To that end, we next examined an approach based on the angular methylation of decalone **18**. Reduction of octalone **11** with lithium aluminum hydride afforded the alcohol **15**, a mixture of epimers, which was converted directly into olefin **17** by acetylation followed by reduction with lithium in ethylamine.[18] Hydroboration of olefin **17** followed by oxidation, first with alkaline hydrogen peroxide and then with chromic acid, gave the desired decalone **18**.[19]



15, R = H
16, R = Ac
17 18 19

The successful conversion of decalone **18** into (+)-valeranone (**19**) depends upon two essential points: (1) selective formation of the angular enolate and (2) stereoselective methylation of this enolate to give the *cis*-fused product. As for the first requirement, Cook and Lawrence[20] demonstrated some time ago that 1-decalone yields predominantly 2-methyldecalone, and

(10) A. J. Birch, *Ann. Rept. Progr. Chem.*, **47**, 192 (1951).

(11) J. A. Marshall, W. I. Fanta, and H. Roebke, *J. Org. Chem.*, **31**, 1016 (1966). Through an unfortunate oversight, we consistently refer to (−)-dihydrocarvone as (+) in this paper. We wish to correct this error and record our thanks to Professor A. R. Pinder for bringing it to our attention.

(12) J. A. Marshall and W. I. Fanta, *ibid.*, **29**, 2501 (1964).

(13) D. W. Theobald, *Tetrahedron*, **22**, 2869 (1966).

(14) *Cf.* A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962), and references therein.

(15) *Cf.* H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

(16) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966).

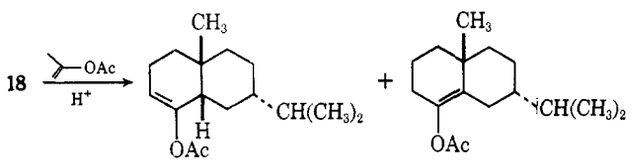
(17) H. Roebke, unpublished observations.

(18) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(19) A synthesis of decalone **18** along essentially the same lines has been independently carried out by Theobald[13] who has discussed the relevant stereochemical points.

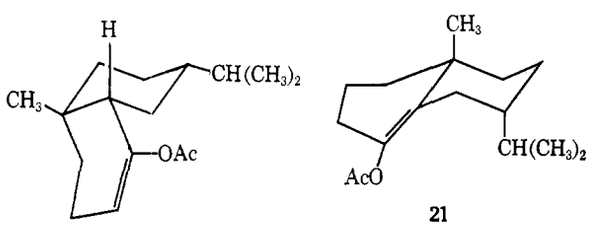
(20) J. W. Cook and C. A. Lawrence, *ibid.*, 817 (1937).

not the angularly substituted 9-methyl isomer, upon direct methylation. These findings encouraged the development of various methods for blocking the α-methylene position of 1-decalones, thereby forcing enolate formation and subsequent methylation at the angular position.[21] Recently, House and Trost[15] have shown that upon treatment with methyllithium, enol acetates afford the corresponding lithium enolates which can be alkylated with alkyl halides. Since the more substituted enol acetate can normally be prepared quite efficiently from ketones such as 1-decalone[15] this method offers a potentially general approach to angular methylation. However, it could not be applied to the valeranone problem since decalone **18** afforded an 85:15 equilibrium mixture of enol acetates **20** and **21**.



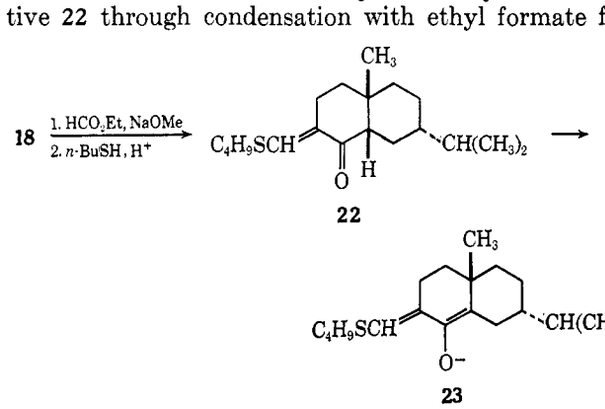
20 (85%) **21** (15%)

In this case, the intrinsically greater stability of the more substituted olefin isomer is apparently offset by unfavorable steric factors. Thus, the less substituted enol acetate isomer **20** can adopt an all-chair conformation wherein the isopropyl group assumes the equatorial orientation. In contrast, the more substituted enol acetate isomer requires an axially oriented isopropyl group in the all-chair conformation. The *trans* epimer of enol acetate **20** would likewise suffer from an axially oriented isopropyl group.



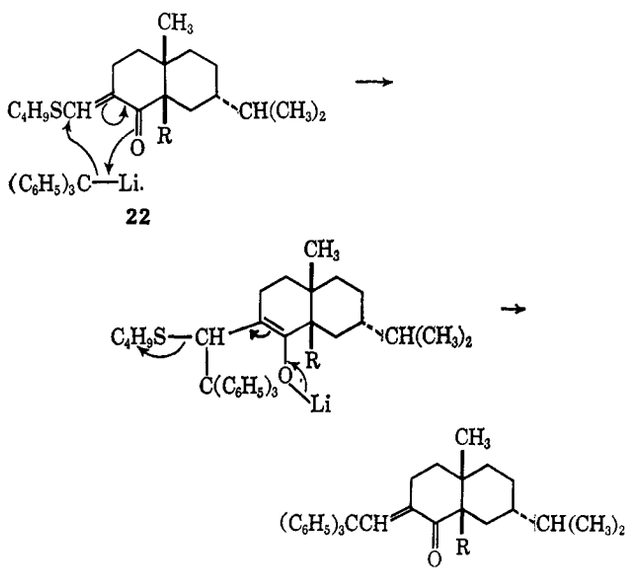
20 **21**

In view of the unfavorable distribution of enol acetate isomers **20** and **21**, we abandoned this approach and turned our attention to the blocking group method of angular methylation. For these studies ketone **18** was converted into the *n*-butylthiomethylene derivative **22** through condensation with ethyl formate fol-



lowed by acid-catalyzed addition of butanethiol to the resulting hydroxymethylene derivative.[22] Attempts to methylate this substance under the usual conditions using potassium *t*-butoxide as the base[22] failed completely. Only unchanged starting material could be isolated. At this point we suspected that the steric factors which had adversely influenced the formation of enol acetate **21** likewise destabilized enolate **23** thereby effectively raising the pK_a of ketone **22**.

We therefore turned to the stronger base triphenylmethyllithium[23] in 1,2-dimethoxyethane hoping to render enolate formation irreversible, or nearly so. To our surprise, the ir spectrum of the resulting product indicated that a triphenylmethyl moiety had displaced the thiobutyl grouping of ketone **22**. The nmr spectrum confirmed this indication and in addition showed that the desired angular methyl group had been introduced. These features point to **24** (R = CH_3) as the structure of the product in hand. One possible genesis of this product involves conjugate addition of triphenylmethyllithium to the butylthiomethylene ketone **22** followed by ketonization of the resulting enolate with expulsion of the butanethiol conjugate base. Alternatively, triphenylmethyllithium could transfer an electron to **22** affording a radical anion whose reaction with a triphenylmethyl radical leads to the aforementioned enolate.[24] In either case, the important question concerns the *timing* of the addition–elimination process. If this reaction precedes methylation the result will be of limited use to our synthetic objective as the conversion of ketone **24** (R = CH_3) into valeranone (**19**), while potentially feasible,[21] would undoubtedly be more troublesome than removal of the butylthiomethylene grouping.[22] On the other hand, if enolate **23** is formed initially then methylation must precede the unwanted addition reaction, and the desired ketone **26** could presumably be isolated after short reaction times. To test this possibility we treated the butylthiomethylene ketone **22** as before with triphenylmethyllithium in 1,2-dimethoxyethane, but omitted the methyl iodide. Unfortunately, the triphenyl ethylidene ketone **24** (R = H) was obtained in 99%



(21) *Cf.* W. S. Johnson, *J. Amer. Chem. Soc.*, **65**, 1317 (1943).

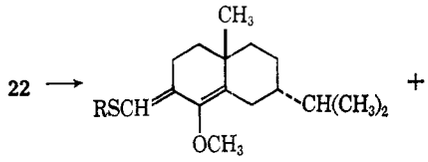
(22) *Cf.* R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).

(23) *Cf.* H. O. House and V. Kramar, *ibid.*, **28**, 3362 (1963). See p 3376, experiment E.

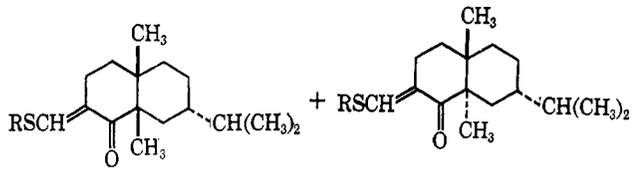
(24) *Cf.* G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964). We are indebted to Professor Russell for pointing out this possibility.

yield. Therefore, enolate **23** cannot be the initial product since this enolate would not participate in either 1,4 addition or electron transfer but would regenerate the starting ketone upon acidification.

We next examined sodium hydride in dimethyl sulfoxide[25] as a base solvent system for the angular methylation of ketone **22**. This modification afforded the enol ether **25** in 97% yield. Even though we could detect but a trace of the desired C-methylation product **26**, this result was nonetheless encouraging because it showed that enolate **23** could be efficiently generated under these conditions. When the methylation was conducted in 1,2-dimethoxyethane, an 85:15 mixture of the O- and C-methylated products could be isolated in 60% yield. In benzene as the solvent a 75:25 mixture of enol ether **25** and methylated ketones **26** and **27** (see below) was obtained in 75% yield.



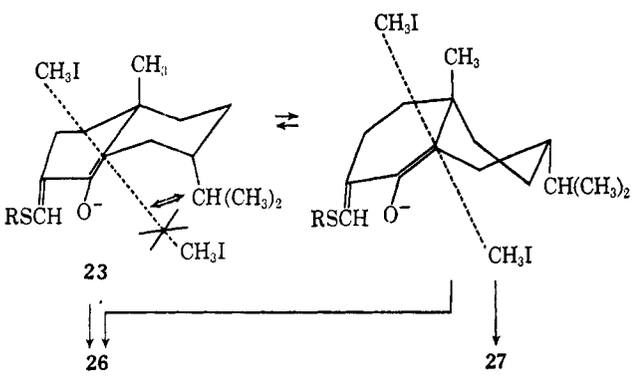
22 → **25**, R = *n*-Bu + RSCH, $CH(CH_3)_2$, OCH_3, CH_3



26 + **27**

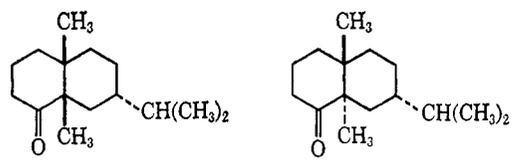
The observed trend toward higher ratios of C to O alkylation with decreasing solvent polarity was expected on the basis of previous work.[26] Although large amounts of O-alkylation products are usually not observed with simple ketones, steric factors undoubtedly play an important part in the present case. The cation may also be an important factor here as no product of O alkylation was found in methylations using triphenylmethyllithium as the base. However, in that case a different blocking group was involved, and this too may influence the extent of O alkylation.

We expected a predominance of the *cis*-fused C-methylation product **26** since models show the top face of enolate **23** to be more accessible than the bottom face. Approach from below invokes interactions with the concave face of the bicyclic ring system[27] which are particularly serious in the present case owing to the axial isopropyl group. Conceivably, the steric influence of this group could be largely alleviated through inversion to a boat conformer thereby allowing for the formation of the *trans* isomer **27**. Even so, the higher energy associated with reactions proceding through boat conformations should still favor a predominance of the *cis* isomer. In fact, the ratio of *cis* to *trans* products actually observed was approximately 92:8, as indicated by conversion of the C-methylated material into valeranone and what appeared to be an isomer thereof.



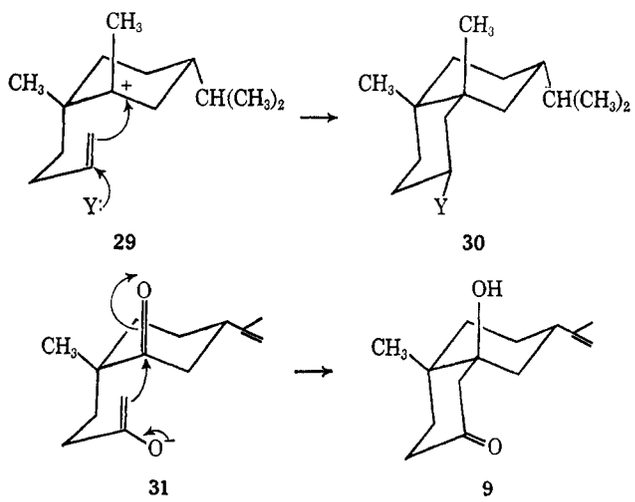
23 → **26** + **27**

The mixture of O- and C-methylated products was readily separated by chromatography on silica gel. The enol ether **25** yielded the starting ketone **22** upon mild acid hydrolysis, and the C-methylated material was converted into a mixture of (+)-valeranone (**19**) and a minor ketonic component, presumably the *trans* isomer **28**, upon vigorous basic hydrolysis.[22] The ir and nmr spectra of the synthetic ketone closely matched those of natural (−)-valeranone (**1**)[2,4] and the optical rotary dispersion curves of the two were enantiomeric.[28] Thus the structure of valeranone is completely confirmed by synthesis.[29]



19 **28**

Since the direct methylation of ketone **18** and its derivatives seemed beset with difficulties, we decided to explore alternative methods for introducing the elusive second angular methyl group which is characteristic of valeranone and its relatives.[30] As we noted earlier, annelation of dihydrocarvone (**8**) with methyl vinyl ketone stereoselectively afforded the *cis*-fused ketol **9**. These findings suggested that the cation **29**,[31] which is formally analogous to the precursor **31** of ketol **9**,



29 → **30**

31 → **9**

(25) *Cf.* E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

(26) C. L. Graham and F. J. McQuillin, *J. Chem. Soc.*, 4634 (1963); G. Brieger and W. M. Pelletier, *Tetrahedron Lett.*, 3555 (1965).

(27) W. S. Johnson, D. S. Allen, Jr., R. R. Hindersinn, G. N. Sausen, and R. Pappo, *J. Amer. Chem. Soc.*, **84**, 2181 (1962).

(28) We are grateful to Professor Bhattacharyya for the infrared comparison and to Professor Klyne for the dispersion curve.

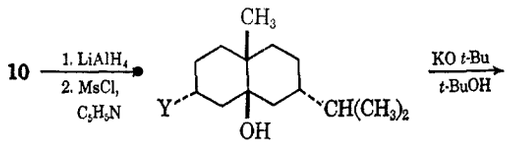
(29) A preliminary account of this work has appeared; see J. A. Marshall, W. I. Fanta, and G. L. Bundy, *Tetrahedron Lett.*, 4807 (1965).

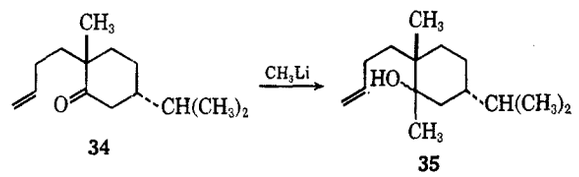
(30) Recently two highly imaginative methods for solving this problem have appeared: E. Wenkert and D. Berges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967); D. J. Dawson and R. E. Ireland, *Tetrahedron Lett.*, 1899 (1968).

(31) *Cf.* W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968), and references cited therein.

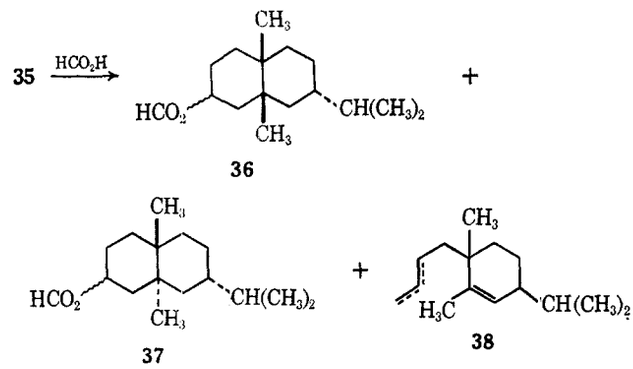
might display a similar stereochemical preference and lead to the *cis*-9,10-dimethyldecalin derivative **30**. Thus the problems of introducing the second angular methyl group and constructing the *cis*-fused decalin system might be solved simultaneously.

The butenylcyclohexanol **35**, a likely precursor of cation **29**, was synthesized from ketol **9** along the lines reported by Henbest and coworkers[32] for a similar conversion in a steroidal system. Reduction of ketol **9** with lithium aluminum hydride gave diol **32**. This diol was converted into the monomethanesulfonate derivative **33** which underwent fragmentation to the butenylcyclohexanone **34** upon treatment with potassium *t*-butoxide in *t*-butyl alcohol. Addition of methyllithium to this ketone afforded the desired tertiary alcohol **35** as a mixture of epimers.

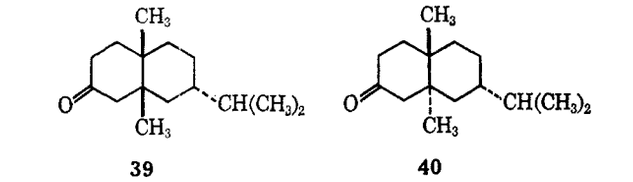




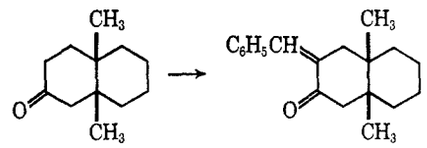
Alcohol **35** was converted into a mixture of isomeric formates **36** and **37** in 40–50% yield upon treatment with formic acid at room temperature. The remaining material appeared to be a mixture of isomeric dienes (**38**) according to infrared and gas chromatographic analysis. This mixture was unaffected by formic acid at room temperature, but at reflux, a 30% yield of formates **36** and **37** was obtained after 3 hr. Prolonged heating did not improve this yield.



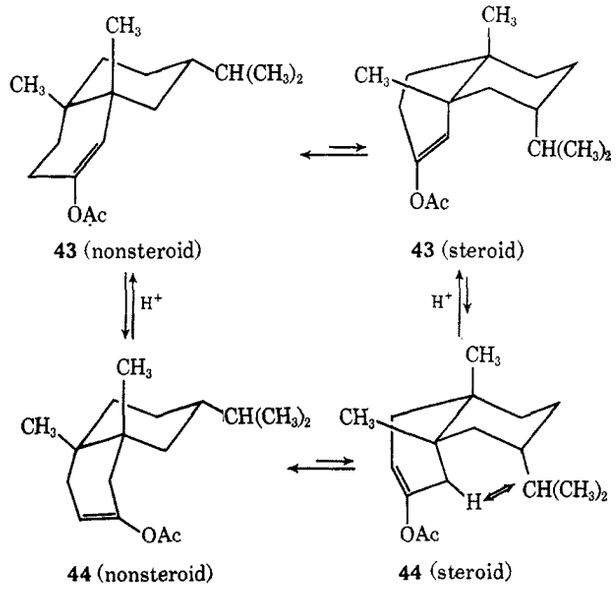
Saponification of the formate mixture followed by oxidation gave an 87:13 mixture of ketones **39** and, presumably, **40** which could be separated by chromatography on silica gel. The ir spectrum of the major component exactly matched that of the enantiomeric compound prepared from natural (−)-valeranone by Bhattacharyya.[33] The minor product was presumed to be the *trans*-fused decalone **40** on the basis of spectral data and its mode of formation.



Having found an efficient route to ketone **39**, an intermediate with the essential skeletal and stereochemical features of the valerane sesquiterpenes, we next turned our attention to methods for transposing the carbonyl function of ketone **39** to complete the synthesis. With ketone **39** this conversion is complicated by the fact that the transposition must be directed to the more hindered methylene position. Thus methods involving condensation reactions appeared unpromising owing to the congestion of transition states leading to C-1 derivatives. In this connection, *cis*-9,10-dimethyl-2-decalone (**41**), a prototype of decalone **39**, affords the 3-benzylidene derivative **42** in high yield upon condensation with benzaldehyde.[11]



Ketone transposition methods based on selective enolization[34] likewise appeared unpromising as decalone **39** afforded a 1:1 mixture of isomeric enol acetates **43** and **44** under conditions where 3-keto *cis* A/B steroids predominantly yield the 3-enol acetate isomer.[35] This contrasting behavior can be attributed to the isopropyl group of decalone **39** which, by virtue of its preference for the equatorial conformation, forces enol acetates **43** and **44** to adopt nonsteroid conformations where energy differences between the two isomers should be minimal.



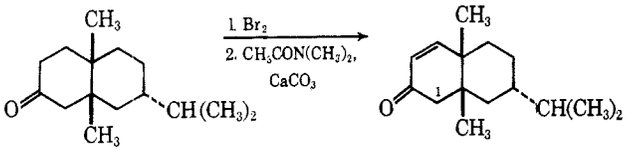
(32) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957).

(33) We are indebted to Dr. Bhattacharyya for providing a spectrum of this ketone.

(34) For example, epoxidation of the enol acetate followed by thermal rearrangement. *Cf.* K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

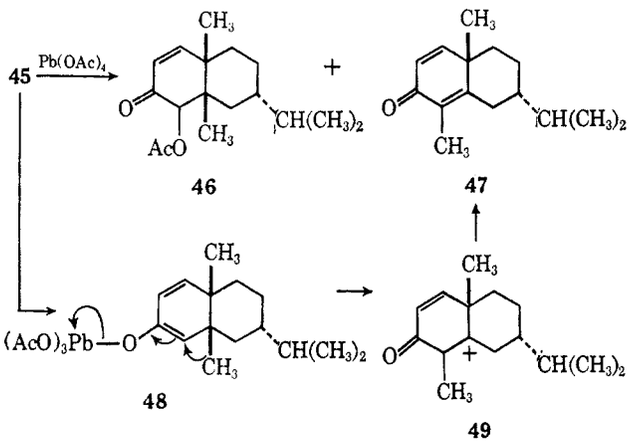
(35) B. E. Edwards and P. N. Rao, *ibid.*, **31**, 324 (1966).

In view of the foregoing considerations, we decided to block the more accessible α position of decalone **39** by introducing a double bond at the 3,4 position. The requisite intermediate, octalone **45**, could be obtained in 85% yield by bromination of decalone **39** followed by dehydrobromination of the crude α-bromo ketone mixture. The high yield of octalone **45** thereby obtained in no way indicates a like predominance of the 3-bromo ketone since the 1-bromo isomer could lead directly to **45** *via* 1,4 elimination of HBr through the 2-enol.[36] These findings are thus compatible with the enol acetylation experiments with decalone **39** described above.



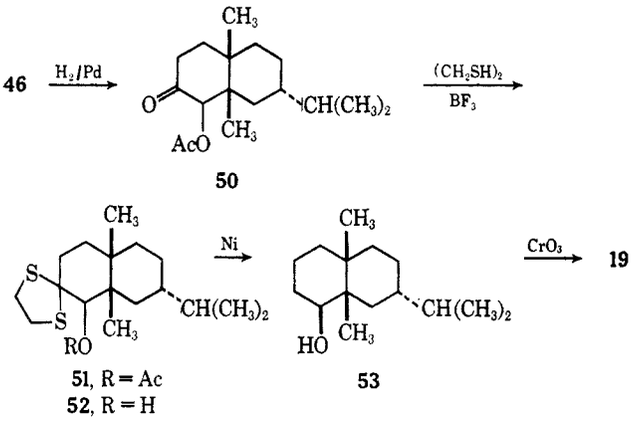
39 **45**

Since enolization of octalone **45** is restricted to C-1 we can now consider methods for carbonyl transposition involving enolic forms. Direct acetoxylation of this position seemed to offer a particularly efficient means of achieving our goal. We therefore examined the reaction of ketone **45** with lead tetraacetate.[37] After a number of unpromising experiments, we eventually obtained a 7:1 mixture of the acetoxy ketone **46** and dienone **47** in about 30% yield together with about 35% of the starting octalone **45**. Dienone **47** presumably arises by isomerization of the intermediate enol lead ester **48** followed by proton loss from the resulting cation **49**.[38]

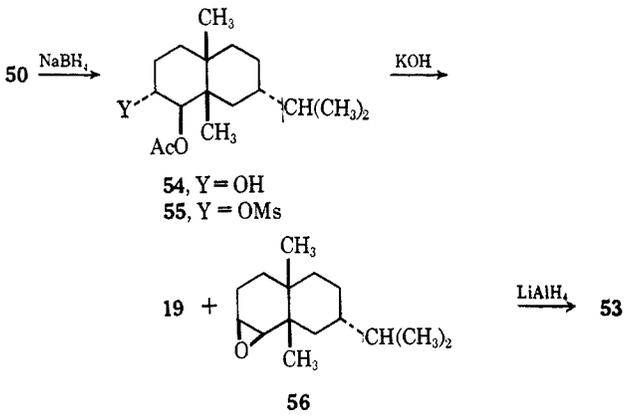


46 **47** **48** **49**

Hydrogenation of the unsaturated keto acetate **46** afforded the dihydro derivative **50**. Direct removal of the ketone grouping through desulfurization of the thioketal acetate **51** was not attempted because the desisopropyl analog of **51** gave a considerable amount of an elimination product when this reaction was carried out.[39] Since less elimination was observed with the corresponding alcohol, acetate **51** was first converted into the alcohol **52** with lithium aluminum hydride, and this material was desulfurized with Raney nickel in ethanol. Oxidation of the resulting alcohol **53** afforded (+)-valeranone (**19**), identical with the previously prepared sample.



An alternative more efficient conversion of acetoxy ketone **50** into valeranone (**19**) was achieved through reduction with sodium borohydride and subsequent conversion of the hydroxy acetate **54** into the acetoxy mesylate **55**. This material yielded a mixture of (+)-valeranone (16%) and oxide **56** (84%) upon treatment with base. Reduction of the oxide with lithium aluminum hydride led to the 1-decalol **53** in quantitative yield. The nmr spectrum of this material agreed with that reported by Hikino, *et al.*,[40] for the enantiomeric alcohol prepared from natural valeranone. Thus keto acetate **50** must be the 1β isomer and must afford mainly the *trans*-hydroxy acetate **54** upon reduction with sodium borohydride.[41]



56

Experimental Section[42]

10β-Methyl-7α-isopropyl-1(9)-octal-2β-ol (15).—A stirred solution of 9.88 g (48 mmol) of octalone **11**[11] in 300 ml of anhydrous ether was treated portionwise with 2.04 g (54 mmol) of lithium aluminum hydride. After 4 hr, 4 ml of water and 3.2 ml of 10% aqueous sodium hydroxide were cautiously added dropwise. The mixture was stirred for several hours to granulate the salts and was filtered. Removal of the solvent from the filtrate

(36) *Cf.* M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).
(37) *Cf.* H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.*, 4472 (1961).
(38) J. A. Marshall and G. L. Bundy, *Chem. Commun.*, 500 (1966).
(39) A. R. Hochstetler, unpublished results.
(40) H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1408 (1965).
(41) A preliminary account of this work has appeared: J. A. Marshall and G. L. Bundy, *Tetrahedron Lett.*, 3359 (1966).
(42) (a) The isolation procedure consisted of diluting the reaction mixture with water or saturated brine, thoroughly extracting with the specified solvent, washing the combined extracts with saturated brine, and drying the organic phase over anhydrous magnesium sulfate. Mixtures containing pyridine were thoroughly washed with 2% aqueous sulfuric acid, saturated brine, and saturated aqueous sodium bicarbonate. The solvent was removed on a rotary evaporator. (b) Gas chromatography was performed on an F & M Model 700 or 720 instrument using helium as the carrier gas. (c) Microanalyses were performed by Micro-Tech Laboratories, Inc. Skokie, Ill.

under reduced pressure afforded 10.1 g of a viscous oil which crystallized on standing. Recrystallization from pentane at −10° gave 6.73 g (67%) of alcohol **15**: mp 84–85°; $\lambda_{max}^{CCl_4}$ 2.79, 3.02 (OH), 6.02 (C=C), 9.69, 11.71 μ. A second crop of 0.6 g (6%), mp 82–84°, was collected. The analytical sample, mp 85–85.5°, was obtained by recrystallization.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.45; H, 11.6.

10β-Methyl-7α-isopropyl-1(9)-octal-2β-yl Acetate (16).—A solution of 1.0 g (4.8 mmol) of alcohol **15**, 0.2 g of sodium acetate, and 25 ml of acetic anhydride was heated at reflux under nitrogen for 1 hr. The cooled solution was poured into saturated brine, and the product was isolated with ether and toluene[42a] affording 1.18 g of yellow oil which crystallized. Recrystallization from pentane at −10° afforded 0.5 g (42%) of acetate **16**: mp 53–54.5°; $\lambda_{max}^{CCl_4}$ 5.78 (ester CO), 6.02 (C=C), 7.30, 8.06, 9.76, and 10.20 μ.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.9; H, 10.4.

10β-Methyl-7α-isopropyl-1(9)-octalin (17).—The procedure of Hallsworth, *et al.*,[18] was employed. To a solution of 2.04 g (8.2 mmol) of acetate **16** in 70 ml of distilled ethylamine was added 0.86 mg (120 mg-atom) of lithium wire cut into small pieces. The deep blue solution was efficiently stirred for 30 min, and aqueous ammonium chloride was cautiously added to discharge the color. The product was isolated with ether[42a] and chromatographed on 150 ml of Florisil. The olefin was eluted with 250 ml of hexane which was removed by careful fractionation at atmospheric pressure. Distillation of the residue afforded 1.26 g (80%) of colorless olefin **17**: bp 105° (0.2 mm); λ_{max}^{film} 6.02 (C=C), 9.86, 10.05, 12.35, and 12.48 μ; $\delta_{TMS}^{CCl_4}$ 5.17–5.37 (H-1), 1.09 (C-10 CH_3), and 0.86 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{14}H_{24}$: C, 87.47; H, 12.53. Found: C, 87.4; H, 12.4.

Elution of the aforementioned chromatographic column with 50% ether in benzene gave 300 mg (15%) of allylic alcohol **15**, identified by comparison of the ir spectrum with that of an authentic sample.

Olefin **17** was more efficiently prepared without purification of the intermediate alcohol **15** and acetate **16**. In this way the conversion of octalone **11** into olefin **17** was consistently effected in 70–75% over-all yield.

10β-Methyl-7α-isopropyl-*cis*-1-decalone (18).—To a solution of 1.92 g (10 mmol) of olefin **17** in 40 ml of dry tetrahydrofuran at 0° was added dropwise with stirring, 42 ml of 0.5 *M* diborane[43] in tetrahydrofuran. After 4 hr at room temperature, the mixture was cooled to 0° and treated cautiously with 2 ml of water followed by 60 ml of 10% aqueous sodium hydroxide and 60 ml of 20% aqueous hydrogen peroxide. After 1 hr at 0° and 1 hr at room temperature, the product was isolated with ether[42a] affording 2.19 g of crude decalol which crystallized on standing.

The crude decalol was dissolved in 50 ml of acetone, the solution was cooled to 0°, and 3 ml of Jones reagent[44] was added dropwise with stirring over 15 min. After an additional 10 min, isopropyl alcohol was added and the product was isolated with ether[42a] affording 1.86 g (90%) of decalone **18**: bp 70° (bath temperature) at 0.2 mm; λ_{max}^{film} 5.86 (CO), 7.21, 7.64, 8.11, 8.64, and 10.35 μ; $\delta_{TMS}^{CCl_4}$ 0.87 (C-10 CH_3) and 0.87 ppm (CH_3 doublet, J = 6 Hz).

The dinitrophenylhydrazone derivative, mp 169–171° (lit.[13] mp 172–173°), was prepared in 72% yield.

Anal. Calcd for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27; N, 14.42. Found: C, 62.1; H, 7.2; N, 14.3.

Conversion of Decalone 18 into the Enol Acetates 20 and 21.—The procedure of Moffett and Anderson[45] was employed. A solution of 3.04 g (14.6 mmol) of decalone **18** and 260 mg of sulfosalicylic acid in 16.5 ml of acetic anhydride and 55 ml of toluene was heated at 130° for 3.5 hr with slow distillation of the toluene–acetic acid azeotrope (head temperature 108°). The reaction mixture was cooled, and the product was isolated with ether[42a] and distilled giving 3.34 g (91%) of enol acetate: bp 85° (bath temperature) at 0.1 mm; λ_{max}^{film} 5.68 (CO), 8.20, 8.41, and 9.11 μ; $\delta_{TMS}^{CCl_4}$ 5.25 (C-2 triplet, J = 4 Hz), 2.04 (acetyl CH_3), 1.00 (C-10 CH_3), and 0.87 ppm (CH_3 doublet, J = 6 Hz). Gas chromatography[46] showed that this was an 85:15 mixture of isomers, and the integrated nmr spectrum indicated that the trisubstituted isomer **20** was the predominant component. A 110-mg sample of the 85:15 mixture of enol acetates **20** and **21** in 0.15 ml of acetic anhydride and 18 mg of methanesulfonic acid was allowed to stand for 120 hr. The product isolated in 65% yield was shown to be an 80:20 mixture of **20** and **21** by gas chromatography.[46]

10β-Methyl-7α-isopropyl-2-*n*-butylthiomethylene-*cis*-1-decalone (22).—A mixture of 0.54 g (10 mmol) of sodium methoxide, 0.74 g (10 mmol) of ethyl formate, and 0.54 g (2.6 mmol) of decalone **18** in 30 ml of benzene initially at 0° was allowed to reach room temperature and stand for 24 hr. Ice water was added, and the benzene phase was extracted with cold 5% aqueous sodium hydroxide. The combined aqueous extracts were acidified with cold aqueous hydrochloric acid and thoroughly extracted with benzene. The benzene solution was dried over anhydrous magnesium sulfate and concentrated to a volume of 50 ml under reduced pressure.

To the above benzene solution was added 75 mg of *p*-toluenesulfonic acid monohydrate and 0.27 g (3 mmol) of *n*-butanethiol. The mixture was heated at reflux under nitrogen with continuous removal of water *via* a Dean–Stark trap for 6 hr. The cooled solution was washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled affording 0.63 g (79%) of thiomethylene ketone **22**: bp 125° (bath temperature) at 0.3 mm; λ_{max}^{film} 6.01 (C=C), 6.50 (CO), 7.70, 7.82, 8.30, 11.11, 11.50, and 11.69 μ; $\delta_{TMS}^{CCl_4}$ 7.47 (vinylic H), 2.88 (–SCH_2– triplet, J = 7 Hz), 0.94 (C-10 CH_3), and 0.89 ppm (CH_3 doublet, J = 7 Hz).

Attempted Methylation of the *n*-Butylthiomethylene Ketone 22. A. Using Potassium *t*-Butoxide as the Base.—A solution of 216 mg (0.7 mmol) of decalone **22** in 2 ml of *t*-butyl alcohol was added under nitrogen to a solution of potassium *t*-butoxide. After 5 min, the solution was cooled to 0° and 456 mg (3.2 mmol) of methyl iodide was added. The solution was allowed to stand at room temperature for 20 hr and was heated at reflux for 1.5 hr. The product was isolated with ether[42a] affording 206 mg (96%) of recovered starting material identified by ir and nmr spectral comparison.

B. Using Triphenylmethyllithium as the Base.—To 10.5 ml of 1.3 *M* triphenylmethyllithium[23] in 1,2-dimethoxyethane (DME) was added a solution of 92 mg (0.30 mmol) of decalone **22** in 4 ml of DME under nitrogen. After 30 min, 0.06 ml (0.9 mmol) of methyl iodide was added. After 3 hr, the product was isolated with ether[42a] and chromatographed on alumina. Elution with hexane afforded 315 mg (80% recovery) of triphenylmethane, mp and mmp 92–93°. Elution with benzene afforded 129 mg (93%) of crystalline triphenyl ethylidene ketone **24** (R = CH_3): mp 179–181°; λ_{max}^{KBr} 3.29 (aromatic C—H), 5.95 (CO), 6.19 (C=C), 6.24 (aromatic C=C), 6.70, 6.91, 7.21, 7.28, 7.90, 8.37, 9.62, 10.30, 10.90, 13.01, 13.17, and 14.17 μ; $\delta_{TMS}^{CCl_4}$ 7.34 (phenyl H, singlet 15 H), 1.11 (angular CH_3, 3 H), 0.94 (CH_3 doublet J = 4 Hz, 6 H), and 0.84 ppm (angular CH_3, 3 H).

When this experiment was repeated and the methyl iodide was omitted, the triphenyl ethylidene ketone **24** (R = H), mp 164–166°, was obtained in 99% yield: λ_{max}^{KBr} 3.29 (aromatic C—H), 5.95 (CO), 6.20 (C=C), 6.24 (aromatic C=C), 6.70, 7.91, 8.39, 9.63, 12.87, 13.01, 13.18, 13.35, and 14.19 μ; $\delta_{TMS}^{C_6D_6}$ 7.34 (phenyl H, singlet, 15 H), 0.82 (CH_3 doublet, J = 4 Hz, 6 H), and 0.79 ppm (angular CH_3, 3 H). The mass spectrum showed a molecular ion peak at m/e 462 (calcd for $C_{34}H_{38}O$, m/e 462). The analytical sample, mp 167–168, was obtained by sublimation at 150° (0.08 mm).

Anal. Calcd for $C_{34}H_{38}O$: C, 88.26; H, 8.28. Found: C, 88.1; H, 8.1.

C. Using Sodium Hydride in Dimethyl Sulfoxide as the Base.—The mineral oil was removed from 60 mg (1.2 mmol) of 50% sodium hydride dispersion by successive washing with benzene and dimethyl sulfoxide. The washed sodium hydride was suspended in 2 ml of dimethyl sulfoxide, and a solution of 66 mg (0.21 mmol) of decalone **22** in 4 ml of dimethyl sulfoxide was added under nitrogen. The mixture was stirred at room temperature for 6 hr, and 0.1 ml of methyl iodide was added. An exothermic reaction took place, and the dark brown solution rapidly turned light yellow. After 6 hr, the product was isolated

(43) H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4233 (1960).

(44) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(45) R. B. Moffett and H. V. Anderson, *J. Amer. Chem. Soc.*, **76**, 747 (1954).

(46) A 13-ft by 1/4-in. column of 16% Carbowax 20M on 60–80 mesh Diatoport S was used for this analysis.

with ether[42a] and distilled affording 67 mg (97%) of enol ether **25**: bp 120° (bath temperature) at 0.05 mm; λ_{max}^{film} 5.91 (C=C), 7.22, 7.30, 8.30, 9.18, 9.42, and 9.69 μ; $\delta_{TMS}^{CCl_4}$ 5.91 (vinylic H), 3.39 (OCH_3), 1.08 (C-10 CH_3), and 0.82 ppm (CH_3 doublet, J = 6 Hz); λ_{max}^{EtOH} 281, 292 mμ. The ir spectrum showed that a small amount of ketonic product was present.

The enol ether was hydrolyzed in 90% yield by the procedure of Levine[47] using a mixture of diethyl ether (8 ml) and 70% perchloric acid (5 drops) at reflux for 3.5 hr. The product was identified as decalone **22** by comparison of the ir spectrum.

(+)-Valeranone (19).—A suspension of sodium hydride in dimethyl sulfoxide (35 ml) was prepared from 1.10 g of 50% dispersion, as outlined above in C, and 1.02 g (3.31 mmol) of decalone **22** was added. After 6 hr, the dimethyl sulfoxide was removed by distillation (45° at 0.5 mm), and the residual solid was suspended in 150 ml of dry benzene and treated with 10 ml of methyl iodide. The mixture was stirred under nitrogen for 6 hr; an additional 5 ml of methyl iodide was added; and the mixture was heated at reflux for 1 hr. The product was isolated with ether[42a] and chromatographed on 250 ml of silica gel. Elution with 25% benzene in hexane yielded 0.37 g (46%) of enol ether **25** identified by ir spectra comparison.

Elution with 75% benzene in hexane gave 0.23 g (29%) of methylated decalones **26** and **27**: λ_{max}^{film} 6.02 (C=C), 6.49 (CO), 7.22, 7.29, 7.69, 7.84, 8.32, 8.51, 8.67, 9.55, 10.09, 11.08, and 12.38 μ.

When the methylation of decalone **22** was carried out as described above but using 1,2-dimethoxyethane as the solvent, an 85:15 mixture of O- and C-methylated products was secured in 60% yield.

The *n*-butylthiomethylene blocking group was removed according to the procedure of Ireland and Marshall.[22] A 0.28-g (0.89 mmol) sample of decalones **26** and **27** (~9:1, see below) in 10 ml of diethylene glycol was heated at reflux under nitrogen for 15 hr. The product was isolated with hexane[42a] affording 0.18 g (89%) of ketonic product: bp 80° (bath temperature) at 0.05 mm; λ_{max}^{film} 5.88 (CO), 7.60, 7.77, 7.88, 8.02, 8.63, 9.53, 10.64, and 12.05; $\delta_{TMS}^{C_6H_6}$ 1.08 (C-9 CH_3), 0.78 (CH_3 doublet, J = 5 Hz), and 0.67 ppm (C-10 CH_3); $n^{30}D$ 1.492 (lit.[48] 1.488); ORD, a_{273}^{323} +120° [for (−)-valeranone, lit.[49] a_{273}^{323} −116°].

The ir and nmr spectra were identical with those of natural (−)-valeranone.[2,4] Gas chromatography[46] revealed the presence of 9% of an impurity with a retention time comparable to that of the major component, but different from that of the unmethylated decalone **18**. This impurity may therefore be the *trans* product **28**.

The semicarbazone derivative, mp 185–190° (for the semicarbazone of (−)-valeranone, lit.[48] mp 206–208°), was prepared in 80% yield. The analytical sample, mp 198–199°, was secured after three recrystallizations from aqueous ethanol.

Anal. Calcd for $C_{16}H_{29}N_3O$: C, 68.78; H, 10.46; N, 15.04. Found: C, 68.8; H, 10.4; N, 15.0.

The 2,4-dinitrophenylhydrazone derivative exhibited mp 104–105° (for the 2,4-dinitrophenylhydrazone of (−)-valeranone, lit.[48] mp 101°).

10β-Methyl-7α-isopropyl-2α-methanesulfonoxy-9β-decalol (33).—To a stirred solution of 47.5 g (0.21 mol) of ketol **9**[11] in 500 ml of dry ether was added portionwise 6.8 g (0.18 mol) of lithium aluminum hydride. The mixture was stirred for 2 hr and cautiously treated with 13.6 ml of water and 10.9 ml of 10% aqueous sodium hydroxide. After stirring overnight, the mixture was filtered, and the ether was removed from the filtrate at reduced pressure affording 47.8 g of diol **32**: λ_{max}^{film} 2.95 (OH), 7.21, 7.30, 9.81, 10.03, 10.62, and 11.12 μ.

The crude diol was dissolved in 200 ml of dry pyridine. The solution was chilled to 0°, treated dropwise with 17.2 ml (0.23 mol) of methanesulfonyl chloride, and allowed to stand for 3 hr at room temperature. The product was isolated with ether[42a] affording 64.6 g (100%) of crystalline mesylate **33**: mp 116–118°; λ_{max}^{KBr} 2.83 (OH), 7.28, 7.43, 7.74, 8.43, 8.60, 10.23, 10.50, 10.60, 11.58, 12.00, and 13.21 μ; $\delta_{TMS}^{CDCl_3}$ 5.0–4.5 (H-2), 3.00 (CH_3SO_3–), 1.87 (OH), 1.00 (C-10 CH_3), and 0.88 ppm (CH_3 doublet, J = 5 Hz), The analytical sample, mp 117–118°, was obtained by recrystallization from ethyl acetate–heptane.

Anal. Calcd for $C_{15}H_{28}O_4S$: C, 59.18; H, 9.27; S, 10.53. Found: C, 59.2; H, 9.4; S, 10.5.

(47) S. G. Levine, *J. Amer. Chem. Soc.*, **80**, 6150 (1958).

(48) T. R. Govindachari, S. Rajadurai, and B. R. Pai, *Chem. Ber.*, **91**, 908 (1958).

(49) D. W. Theobald, *Tetrahedron Lett.*, 969 (1966).

2β-Methyl-5α-isopropyl-2-(3-butenyl)cyclohexanone (34).—The procedure of Clayton, Henbest, and Smith[32] was employed. A solution of 1.74 g (5.72 mmol) of methanesulfonate **33** in 150 ml of dry *t*-butyl alcohol was treated with 15 ml of 3% potassium *t*-butoxide in *t*-butyl alcohol, and the solution was heated at reflux for 6 hr. The product was isolated with ether[42a] and chromatographed on silica gel. Elution with benzene gave 1.17 g (97%) of ketone **34**: bp 60° (bath temperature) at 0.2 mm; λ_{max}^{film} 5.86 (CO), 6.09 (C=C), 9.00, 10.02, and 10.98 μ; $\delta_{TMS}^{CCl_4}$ 6.1–4.8 (CH=CH_2), 0.94 (C-2 methyl), and 0.94 ppm (CH_3 doublet, J = 4 Hz). The gas chromatogram[50] showed a single peak.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.6; H, 11.55.

9β,10β-Dimethyl-7α-isopropyl-2-decalone (39) and 9α,10β-Dimethyl-7α-isopropyl-2-decalone (40).—A solution of 19.2 g (92 mmol) of cyclohexanone **34** in 50 ml of dry ether was added dropwise with stirring to 375 ml of 1.6 *M* methyllithium in ether at 0°. The mixture was stirred for 1.5 hr at room temperature and small chips of ice were cautiously added to decompose the excess methyllithium. The product was isolated with ether[42a] affording 20.4 g (99%) of alcohol **35**: λ_{max}^{film} 2.90 (OH), 3.26, 6.09 (C=CH_2), 8.96, 10.03, and 11.01 μ.

A 1.11-g (4.95 mmol) sample of the above alcohol was dissolved in 55 ml of 98% formic acid, and the mixture was stirred for 2 hr. The product was isolated with hexane[42a] and chromatographed on 100 ml of silica gel. Elution with hexane afforded 0.57 g of a mobile hydrocarbon: λ_{max}^{film} 6.08 (C=C), 10.05, and 11.00 μ. The gas chromatogram[46] showed two closely spaced peaks in the ratio 2:1, presumably the isomeric olefins **38**.

Elution with ether gave 0.59 g (48%) of formates **36** and **37**: λ_{max}^{film} 5.81 (CO), 8.44, 10.49, 10.72, and 10.90 μ. This material could be recovered unchanged in 98% yield from refluxing formic acid after 2 hr.

An 8.89-g (35 mmol) sample of a formate mixture comparable to the one described above was dissolved in 225 ml of 95% ethanol and treated with 44 ml of 10% aqueous sodium hydroxide. After 1.5 hr, the product was isolated with ether[42a] and distilled affording 7.80 g (98%) of an alcohol mixture: bp 80–85° (bath temperature) at 0.05 mm; λ_{max}^{film} 3.00 (OH), 9.41, and 9.66 μ.

A 7.70-g sample of the above alcohol in 600 ml of acetone was cooled to 0°, and 10 ml of Jones reagent[44] was added dropwise with stirring. Isopropyl alcohol was added to destroy the excess oxidizing agent and the product was isolated with ether[42a] affording 6.44 g (84%) of decalone, bp 80° (bath temperature) at 0.05 mm. The gas chromatogram[46] showed two closely spaced peaks in the ratio 87:13.

A 2.48-g portion of this material was chromatographed on 525 ml of silica gel. Elution with benzene afforded 0.24 g (10%) of the minor isomer, tentatively identified as the *trans*-decalone **40**: bp 60° (bath temperature) at 0.03 mm; λ_{max}^{film} 5.86 (CO), 7.59, 8.01, 8.63, 9.53, 10.64, and 12.05 μ; $\delta_{TMS}^{CCl_4}$ 1.03 (angular CH_3), 0.90 (CH_3 doublet, J = 6 Hz), and 0.82 ppm (angular CH_3).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.75; H, 11.7.

The dinitrophenylhydrazone derivative, mp 102–105°, was prepared in 80% yield. Two recrystallizations from 95% ethanol gave the analytical sample, mp 104–105°.

Anal. Calcd for $C_{21}H_{30}N_4O_4$: C, 62.67; H, 7.51; N, 13.92. Found: C, 62.3; H, 7.3; N, 14.1.

Elution of the above chromatogram with 1% ether in benzene afforded 2.01 g (81%) of the *cis*-decalone **39**: bp 84–85° (0.07 mm); λ_{max}^{film} 5.85 (CO), 7.60, 8.04, 8.50, 8.89, and 13.18 μ; $\delta_{TMS}^{CCl_4}$ 1.10 (angular CH_3), 0.95 (angular CH_3), and 0.85 ppm (CH_3 doublet, J = 5 Hz). The gas chromatogram[46] showed that this material contained over 95% of the major component present in the starting ketone mixture. The infrared spectrum was identical with a spectrum of the enantiomeric compound prepared by Bhattacharyya.[33]

The analytical sample was obtained by preparative gas chromatography[50] followed by short-path distillation.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.9; H, 11.7.

Cyclization of Diene 38.—A 500-mg sample of diene **38** in 15 ml of 98% formic acid was heated at reflux for 3 hr. The gas chromatogram[46] of the product, which was isolated with ether,[42a] showed it to contain about 30% formates **36** and **37**. The remaining material consisted of a mixture of hydrocarbons.

(50) A 10-ft by 1/2-in. column of 20% Carbowax 20M on 60–80 mesh Chromosorb W was employed.

No further change in composition was observed when the reflux time was extended for an additional 11 hr.

Conversion of Decalone 39 into the Enol Acetates 43 and 44.—The procedure of Edwards and Rao[35] was employed using their reagent A (15 ml) and 86 mg of decalone **39**. After 15 min, the mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure affording 94 mg (92%) of a pale yellow oil: λ_{max}^{film} 5.70 (CO), 7.31, 8.18, 8.97, 9.50, 9.88, 10.90, and 11.07 μ; $\delta_{TMS}^{CCl_4}$ 5.05 (H-3 of **44**, broad multiplet, 0.5 H), 4.85 (H-1 of **43**, singlet, 0.5 H), 1.96 (CH_3CO_2, 1 H), 0.86 (angular CH_3's, 6 H), and 0.85 ppm (CH_3 doublet, J = 8 Hz). Only a single peak was observed on the gas chromatogram,[46] but the integrated nmr spectrum indicated a 1:1 mixture of isomeric enol acetates **43** and **44**.

9β,10β-Dimethyl-7α-isopropyl-3-octal-2-one (45).—A solution of 1.01 g (4.55 mmol) of decalone **39** in 10 ml of glacial acetic acid was cooled to 10°, and 5.18 ml of 1.02 M bromine in acetic acid was added dropwise with stirring over 10 min. The product was isolated with hexane[42a] affording 1.38 g (100%) of bromo ketone: λ_{max}^{film} 5.80 (broad, CO), 12.64, and 13.10 μ; $\delta_{TMS}^{CCl_4}$ 5.1–4.6 (–CHBr broad multiplet), 1.21 (angular CH_3), 1.00 (angular CH_3), and 0.87 ppm (CH_3 doublet, J = 6 Hz).

The above bromo ketone in 30 ml of dimethylacetamide containing 1.5 g of calcium carbonate[51] was heated at reflux under nitrogen for 35 min. The cooled mixture was filtered, and the product was isolated with heptane[42a] affording 0.89 g (89%) of octalone **45**: bp 70° (bath temperature) at 0.03 mm; λ_{max}^{film} 5.95 (CO) 7.95, 11.30, 11.61, and 12.85 μ; $\delta_{TMS}^{CCl_4}$ 6.37 (H-3, H-4; AB quartet, $\Delta\nu_{AB}$ = 41 Hz, J = 10.5 Hz), 1.09 (angular CH_3's), and 0.85 ppm (CH_3 doublet, J = 6 Hz).

The 2,4-dinitrophenylhydrazone had mp 158–159° after four recrystallizations from ethanol.

Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 62.8; H, 7.0; N, 14.0.

9β,10β-Dimethyl-7α-isopropyl-1-acetoxy-3-octal-2-one (46).—A solution of 1.47 g (6.68 mmol) of octalone **45**, 10.2 g of lead tetraacetate, and 6.5 ml of boron trifluoride etherate in 160 ml of benzene was heated under nitrogen at 50° for 23 hr. The product was isolated with ether[42a] affording 1.42 g of a brown oil, λ_{max}^{film} 5.70 (ester CO), 5.95 (ketone CO), 8.16 and 9.68 μ. The gas chromatogram[52] showed five components, two of which predominated. The mixture was separated by preparative gas chromatography[52] affording 0.29 g (20%) of starting octalone **45**, 15 mg (1%) of dienone **47** (see below), and 0.12 g (8%) of acetoxy octalone **46**: λ_{max}^{film} 5.72 (ester CO), 5.94 (ketone CO), 6.17 (C=C), 7.29, 8.15, 9.63, 11.08, and 12.27 μ; $\delta_{TMS}^{CCl_4}$ 6.21 (H-3, H-4 AB quartet, $\Delta\nu_{AB}$ = 40 Hz, J_{AB} = 10.5 Hz), 2.05 (CH_3CO), 1.17 (angular CH_3), 1.00 (angular CH_3), and 0.83 ppm (CH_3 doublet, J = 5 Hz).

The approximate yields of products before preparative gas chromatography were estimated as octalone **45**, 35%; dienone **47**, 5%; and acetoxyoctalone **46**, 25%.

1,10β-Dimethyl-7α-isopropyl-1(9),3-hexal-2-one (47).—The procedure of Caine and Dawson[53] was employed. A solution of 1.39 g (6.32 mmol) of 1,10β-dimethyl-7α-isopropyl-1(9)-octal-2-one[9,12] (the enantiomer of **6**) and 1.59 g (7.0 mmol) of 2,3-dicyano-5,6-dichloro-1,4-benzoquinone in 66 ml of dry benzene containing 3.4 ml of acetic acid was heated at reflux under nitrogen for 34 hr. The mixture was cooled to 0° and filtered, and the solvent was distilled under reduced pressure. The residue was chromatographed on 50 g of Fisher alumina affording 1.09 g (79%) of hexalone **47** eluted with benzene. A purified sample, mp 57–58°, was obtained *via* preparative gas chromatography:[52] λ_{max}^{KBr} 6.02 (CO), 6.12, 6.21 (C=C), 7.11, 7.19, 7.29, 7.56, 8.55, 9.23, 9.72, 11.44, 11.71, 11.83, 12.64, and 13.68 μ; $\delta_{TMS}^{CCl_4}$ 6.35 (H-3, H-4 AB quartet, $\Delta\nu_{AB}$ = 35 Hz, J_{AB} = 10 Hz), 1.85 (C-1 CH_3 doublet, J = 1 Hz, 3 H), 1.26 (angular CH_3, 3 H), 0.95 (CH_3 doublet, J = 5 Hz, 3 H), and 0.82 ppm (CH_3 doublet, J = 5 Hz, 3 H).

The ir spectrum and gas chromatographic retention time (peak enhancement) of this material exactly matched those of the material isolated in 1% yield from the preceding experiment.

The analytical sample, mp 59–60°, was obtained after three recrystallizations from pentane at −78°.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.4; H, 10.3.

9β,10β-Dimethyl-7α-isopropyl-1-acetoxy-2-decalone (50).—A solution of 125 mg (0.45 mmol) of octalone **46** in 10 ml of absolute ethanol containing 50 mg of 5% palladium–carbon was stirred under an atmosphere of hydrogen for 8 hr. The mixture was filtered, and the filtrate was distilled affording 125 mg (100%) of decalone **50**: bp 85° (bath temperature) at 0.05 mm; λ_{max}^{film} 5.72 (ester CO), 5.80 (ketone CO), 8.16, and 9.65 μ; $\delta_{TMS}^{CCl_4}$ 4.56 (H-1), 2.05 (CH_3CO), 1.16 (angular CH_3), 0.92 (angular CH_3), and 0.85 (CH_3 doublet, J = 5 Hz).

Combustion analyses of redistilled samples gave analytical values which were 0.6% high for carbon. These values were not improved by additional redistillation.

9β,10β-Dimethyl-7α-isopropyl-1β-decalol (53). A. *Via* **Thioketal 52.**—A solution of 60 mg of keto acetate **50**, 0.06 ml of ethanedithiol, and 0.06 ml of boron trifluoride etherate in 1 ml of acetic acid was allowed to stand at room temperature for 3 hr. The product was isolated with ether[42a] affording 73 mg (96%) of thioketal **51**, a viscous, colorless oil: λ_{max}^{film} 5.72 (ester CO), 8.14, 8.91, and 9.76 μ; $\delta_{TMS}^{CCl_4}$ 4.80 (H-1), 3.5–2.9 (SCH_2CH_2S), 2.05 (CH_3CO), 1.00, 0.94, 0.87 ppm (angular CH_3's and isopropyl CH_3's).

The above thioketal in 5 ml of ether was treated with 50 mg of lithium aluminum hydride. After 1 hr, 0.2 ml of water was added; the mixture was poured into 10% aqueous potassium sodium tartrate; and the product was isolated with ether[42a] affording 64 mg (100%) of alcohol **52**: λ_{max}^{film} 2.91 (OH), 9.59 μ; $\delta_{TMS}^{CCl_4}$ 3.5–2.0 (SCH_2CH_2S and H-1), 1.04 (angular CH_3), 1.02 (angular CH_3), and 0.86 ppm (CH_3 doublet, J = 5 Hz).

The above sample of thioketal alcohol **52** was dissolved in 8 ml of ethanol and heated at reflux with 3 g of W-2 Raney nickel[54] for 3.5 hr under nitrogen. The mixture was filtered and the product was isolated from the filtrate with hexane[42a] affording 18 mg (40%) of decalol **53**: λ_{max}^{film} 2.90 (OH), 7.92, 9.45, and 9.70 μ. The gas chromatogram[55] indicated a purity of 70% for this material. The major component was shown to be decalol **53** by ir and chromatographic comparison with the sample prepared in **B** of this experiment.

B. *Via* **Acetoxy Methanesulfonate 55.**—A solution of 134 mg (0.45 mmol) of acetoxydecalone **50** in 3 ml of ethanol was cooled to 0°, and 6 mg (0.16 mmol) of sodium borohydride was added. After 1.5 hr, the product was isolated with ether[42a] affording 136 mg (100%) of hydroxy acetate **54**: λ_{max}^{film} 2.90 (OH), 5.79 (ester CO), 7.98, 9.70, 10.15, and 14.70 μ; $\delta_{TMS}^{CCl_4}$ 4.45 (H-1), 3.70 (H-2), 3.45 (OH), 2.00 (CH_3CO), 0.95 (angular CH_3), 0.84 (angular CH_3), and 0.83 ppm (CH_3 doublet, J = 5 Hz).

The above hydroxy acetate in 1.0 ml of dry pyridine was cooled to 0° and treated with 0.95 ml of methanesulfonyl chloride. After 12 hr at room temperature, the product was isolated with ether[42a] affording 170 mg (97%) of acetoxy mesylate **55**: λ_{max}^{film} 5.76 (ester CO), 7.30–7.40, 8.17, 8.47, 9.71, 10.21, 10.55, 10.64, 10.80, 11.45, and 11.88 μ; $\delta_{TMS}^{CCl_4}$ 4.52 (H-1 and H-2), 3.02 (CH_3SO_3), 2.04 (CH_3CO), 0.98 (angular CH_3), 0.89 (angular CH_3), and 0.85 ppm (CH_3 doublet, J = 5 Hz).

The above sample of acetoxy mesylate **55** was heated at reflux for 1 hr with 15 ml of isopropyl alcohol containing 1.5 g of potassium hydroxide. The product was isolated with ether[42a] affording 105 mg (100%) of colorless oil which was chromatographed on 20 ml of silica. Elution with 50% benzene in hexane afforded 74 mg (72%) of oxide **56**: λ_{max}^{film} 7.20, 7.28, 7.83, 9.72, 10.02, 10.61, 10.76, 10.98, 11.58, 11.91, and 13.32 μ; $\delta_{TMS}^{CCl_4}$ 3.03 (H-2 triplet, J = 4 Hz), 2.46 (H-1 doublet, J = 4 Hz), 1.12 (angular CH_3), 0.93 (angular CH_3), and 0.87 ppm (CH_3 doublet, J = 6 Hz).

Elution with benzene afforded 19 mg (18%) of (+)-valeranone (**19**) identified by comparison with the previously prepared sample.

A 68-mg sample of the oxide **56** in 5 ml of dry tetrahydrofuran was treated with 100 mg of lithium aluminum hydride. The mixture was heated at reflux for 2 hr, allowed to cool, treated with 0.5 ml of water, and poured into 10% aqueous potassium sodium tartrate solution. The product was isolated with ether[42a] affording 67 mg (98%) of solid decalol, a 97:3 mixture[56] of the

(51) G. Green and A. Long, *J. Chem. Soc.*, 2532 (1961).

(52) A 10.5-ft by 1/2-in. column of 15% LP-118 silicon gum rubber GE SE-30 on 60–80 mesh Chromosorb W was used.

(53) D. Caine and J. B. Dawson, *J. Org. Chem.*, **29**, 3108 (1964).

(54) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 181.

(55) A 19-ft by 1/4-in. column of 15% 1:4 potassium hydroxide–Carbowax 20M on 60–80 mesh Chromosorb W was used for this analysis.

(56) An 18-ft by 1/4-in. column of 12% Carbowax 20M on 60–80 mesh Chromosorb W was used for this analysis.

1β and, presumably, the 1α epimers. Sublimation at 35° (0.08 mm) afforded 55 mg (81%) of decalol **53**: mp 52–54°; λ_{max}^{film} 2.91 (OH), 7.19, 7.28, 7.94, 8.69, 8.98, 9.42, 9.74, 10.20, 10.34, 10.61, 10.73, and 14.57 μ; $\delta_{TMS}^{CCl_4}$ 3.25 (H-1), 1.73 (OH), 1.00 (angular CH_3), 0.98 (angular CH_3), and 0.84 ppm (CH_3 doublet, J = 5 Hz).

The analytical sample, mp 54–55° (for the enantiomer, lit.[40] mp 56–57°), was secured after an additional sublimation.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.5; H, 12.5.

Reduction of (+)-Valeranone (19).—A 15-mg sample of (+)-valeranone (**19**) in 5 ml of dry ether was stirred with 30 mg of lithium aluminum hydride for 3 hr at room temperature. The mixture was treated with 0.06 ml of water and 0.05 ml of 10% aqueous sodium hydroxide, stirred for several hours, and filtered. The solvent was removed from the filtrate under reduced pressure affording 14 mg (90%) of an alcohol mixture containing 63% 1β-decalol **53** and 37% 1α epimer identified by peak enhancement[56] with the previously prepared mixture.

(+)-Valeranone (19).—A solution of 20 mg of decalol **53** in 10 ml of acetone was cooled to 0° and treated dropwise with 0.3 ml of Jones reagent.[44] Isopropyl alcohol was added to destroy the excess reagent, and the product was isolated with ether[42a] affording 19 mg (95%) of (+)-valeranone (**19**) identified by comparison with the sample prepared previously *via* angular methylation.

Registry No.—**15,** 5090-56-2; **16,** 5195-62-0; **17,** 5195-63-1; **18,** 5195-64-2; (+)-valeranone (**19**), 17414-58-3; **20,** 17408-81-0; **21,** 17408-82-1; **22,** 5090-58-4; **24** (R = Me), 17408-83-2; **24** (R = H), 17408-77-4; **25,** 5195-65-3; **26,** 5090-59-5; **27,** 17414-60-7; **32,** 17408-61-6; **33,** 17448-31-6; **34,** 10208-75-0; **35,** 17408-63-8; **36,** 10208-77-2; **37,** 17414-62-9; **39,** 10208-73-8; **40,** 17408-64-9; **40** dinitrophenylhydrazone, 17408-65-0; **43,** 17378-42-6; **44,** 10253-25-5; **45,** 17408-66-1; **45** dinitrophenylhydrazone, 17408-67-2; **46,** 17408-68-3 **47,** 17408-69-4; **50,** 17408-70-7; **51,** 17408-71-8; **52,** 17408-72-9; **53,** 17408-73-0 **54,** 17408-74-1; **55,** 17408-75-2; **56,** 17408-76-3.

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Thiocyanate-Catalyzed *cis–trans* Isomerization of *cis*-β-Acetylacrylic Acid. A Model for Maleylacetoacetic Acid[1]

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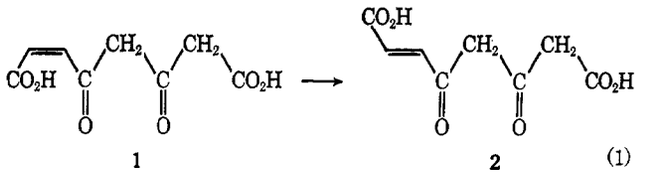
The kinetics of *cis–trans* isomerization of *cis*-β-acetylacrylic acid, a model for maleylacetoacetic acid, has been measured in the absence of any catalyst and in the presence of thiocyanate ion over five powers of ten in acid concentration. A kinetic scheme is proposed to account for the dependence of the rate on thiocyanate and hydronium ion concentrations. Rate constants have been obtained by fitting the data to the kinetic scheme. The similarities and differences of this system to the enzymatic system are discussed.

Homogentisic acid, an intermediate in the oxidation of aromatic amino acids such as tyrosine and phenylalanine, has been shown to undergo further oxidation to 4-maleylacetoacetic acid (4,6-dioxo-*cis*-2-octenedioic acid, **1**) in animal liver[2] and bacterial cells.[3] From these same extracts, an enzyme has been isolated which together with glutathione (GSH) catalyzes the *cis–trans* isomerization of 4-maleylacetoacetic acid to 4-fumarylacetoacetic acid (**2**, eq 1).[2,3] Also present is another enzymatic system which catalyzes the specific hydrolysis of **2** to fumaric and acetoacetic acids.



1 **2** (1)

Similar to the metabolism of aromatic amino acids is the bacterial oxidation of nicotinic acid. Soluble extracts of *Pseudomonas fluorescens* catalyze the oxidative conversion of nicotinic acid into N-formylmaleamic acid through the intermediacy of 2,5-dihydroxypyridine.[4] Here too, there is an enzyme present in these extracts which catalyzes the *cis–trans* isomerization of the maleic acid product to fumaric acid. It also appears that thiol groups are necessary for isomerase activity.[5]

As an extension of our earlier interest in the mechanism of the catalyzed *cis–trans* isomerization of maleic acid,[6] it was decided to investigate possible models for the enzyme–coenzyme-catalyzed isomerization of 4-maleylacetoacetic acid. 4-Maleylacetoacetic acid has not been synthesized or isolated in pure form.[2] Its high lability suggested the synthesis of a more stable model substrate, *cis*-β-acetylacrylic acid, **3**, possessing what appears to be the same functional groups necessary for facile isomerization. Its preparation is described elsewhere.[7] We report here the kinetics of the spontaneous and thiocyanate ion catalyzed isomerization of *cis*-β-acetylacrylic acid.

Results and Discussion

The uv and nmr spectra of *cis*- and *trans*-β-acetylacrylic acid have been reported.[7] Nmr spectra indicate that in neutral or basic media the *cis* acid exists as an open anion, **4**, but in acidic solution the acid has

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) For a review see W. E. Knox in "The Enzymes," Vol. 2, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1960, pp 282–289.

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