Complete Determination of the Stereochemistry of a 3,5-Dialkylpyrazoline Thermal Decomposition. Synthesis, Absolute Configuration, and Pyrolysis of (+)-(3*R*,5*R*)- and (+)-(3*R*,5*S*)-3-Ethyl-5-methyl-1-pyrazolines[1a]

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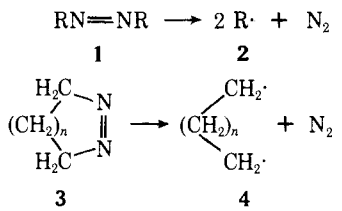
Abstract: (+)-(3*R*,5*R*)-3-Ethyl-5-methyl-1-pyrazoline (**15t**) and (+)-(3*R*,5*S*)-3-ethyl-5-methyl-1-pyrazoline (**15c**) have been prepared in optically active form and their absolute stereochemistries determined by chemical correlation with (−)-(3*R*)-3-hexanol and (−)-(2*R*)-2-bromohexane. Pyrolysis at 292 °C in the gas phase (atmospheric pressure, He) gave optically active *cis*- and *trans*-1-ethyl-2-methylcyclopropanes (**16c** and **16t**), whose absolute stereochemistries have been determined previously. This study has allowed elucidation of the complete stereochemistry of the pyrazoline → cyclopropane reaction in this case, and the results are: **15t** gives **16c** in nearly racemic form but with slight preference for single inversion (rotation of methyl-bearing carbon); **15t** gives **16t** with double inversion; **15c** gives **16t** with single inversion, but predominant rotation of the ethyl-bearing carbon, and **15c** gives **16c** with excess double retention of configuration. A mechanism is proposed which rationalizes the highly divergent stereochemical behavior of the two isomeric pyrazolines.

Introduction

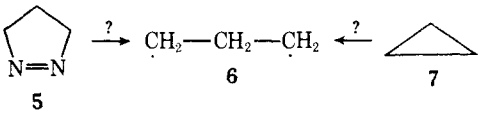
The thermal and photochemical decomposition of azo compounds (**1**) is a clean and general method of producing[2] a wide variety of organic free radicals (**2**). Analogously, many cyclic azo compounds (**3**) have now been prepared and their



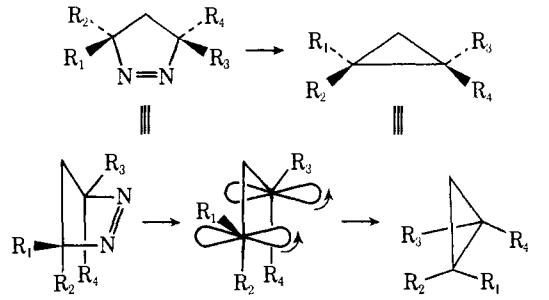
decompositions extensively investigated[3] as a means of generating various types of biradicals (**4**). Two questions central to studies of the mechanisms of the **3** → **4** reaction have been: (1) do the two C–N bonds in the azo compound break sequentially or simultaneously, and (2) is the intermediate so generated identical with that formed upon cleavage of a carbon–carbon bond in a carbocyclic ring of appropriate size?

For cases in which $n > 2$, the mechanism of decomposition is reasonably well understood and appears to parallel those of acyclic systems—i.e., the simultaneity of C–N bond cleavage depends to some extent upon the level of substitution at the α-carbon atoms, and the intermediate ultimately generated exhibits the sort of chemical behavior one expects of a methylene chain having classical free radical character at each terminus.[4] The $n = 2$ case has presented something of a problem due to the propensity of six-membered azo compounds to rearrange to hydrazones by catalyzed hydrogen transfer; however, it has recently been demonstrated that the chemistry of these systems is well accounted for by assuming that they decompose partly by a concerted mechanism and partly to an intermediate which is identical with that produced on thermolysis of the corresponding cyclobutanes.[5]

In contrast to the progress made during the past few years in understanding the decomposition of acyclic and large-ring cyclic azo compounds, the situation with regard to five-membered azo compounds (pyrazolines, **5**) has remained seriously confused. This is an important system, because its decomposition in principle provides a means of independently generating trimethylene (**6**), which has long been considered as an intermediate[6] in the much-studied decomposition of cyclopropane (**7**). The complexity of the present situation is perhaps best illustrated by considering the stereochemistry of decomposition of 3,5-disubstituted pyrazolines. A set of early experiments at first seemed to indicate that pyrazoline decomposition stereochemistry would not be unusual,[7a,b] but as additional experiments were carried out[7c] this picture changed dramatically. The most extensive and elegant studies on pyrazoline decomposition were carried out by Crawford's group,[8] and it is probably fair to say that their single most perplexing result was obtained in a study of the stereochemistry of the thermal conversion of 3,5-dimethylpyrazolines **8c** and **8t** to cyclopropanes **9** (summarized in Scheme I). Whereas the diradical



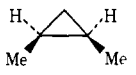
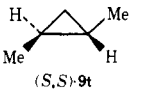
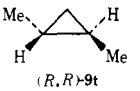
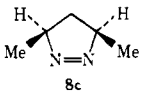
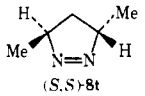
Scheme I



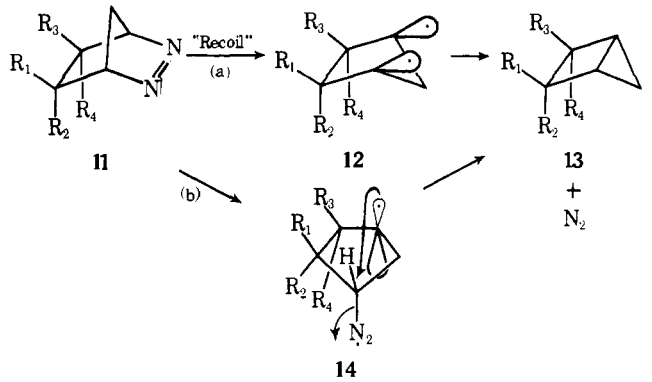
8c, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
8t, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
10
9c, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
9t, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$

hypothesis would predict either complete stereochemical scrambling or some excess retention of stereochemical configuration upon decomposition, Crawford's reactions clearly proceeded with excess overall *inversion* at one reacting center.[8b,c] To make matters worse, Allred[9] and Roth[10] and their co-workers then reported decompositions of somewhat related, but more rigid, pyrazolines of general structure **11** in which predominant *double* inversion of configuration (i.e., inversion

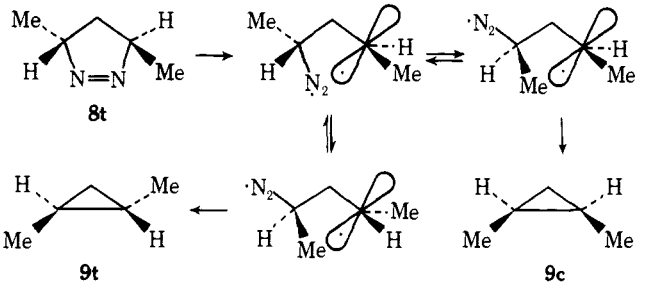
Table I. Stereochemical Information Available in the 3,5-Dimethylpyrazoline Thermolysis (calculated using the data of ref 8c and 8h)

Starting material	Products, %			
	 9c	 9c	 (S,S)-9t	 (R,R)-9t
 8c	33		66	
 (S,S)-8t	73		10	16

Scheme II



Scheme III



at both centers) was involved (cf. Scheme II). In later experiments using optically active **8t,** Crawford found that some double inversion in the monocyclic system could be observed as well.[8h]

In order to explain these results, some of the most provocative mechanistic ideas of the past few years were conceived. Crawford attributed the single inversion process observed in **8** to a two-step mechanism in which the so-called "envelope" conformation of the pyrazoline (cf. Scheme I) directly generated a planar "π-cyclopropane" diradical (**10**) which was required to undergo *conrotatory* closure to cyclopropane **9**.[8c] This conrotatory-closure postulate received almost immediate theoretical support from some early calculations on **10** (rechristened the "0,0 diradical") carried out by Hoffmann. These indicated that the two "radical" orbitals in **10** interacted primarily by coupling through a "pseudo-p" orbital made up by combining the two central methylene C–H bonds.[11] Allred accounted for his observation by postulating (path a, Scheme II) that the α-carbon atoms in **11** are forced to "recoil" into inverted configuration **12** by the departing nitrogen atoms[9] (interestingly, this is perhaps the first suggestion that a dynamic effect might be necessary to explain these decompositions; this sort of argument was later put into somewhat more sophisticated language by Freeman, Pucci, and Binsch).[12] Roth and Martin suggested a more conventional mechanism,[10] involving initial cleavage of only one C–N bond to give **14,** followed by backside attack of the radical center at the remaining nitrogen-bound carbon (path b, Scheme II).

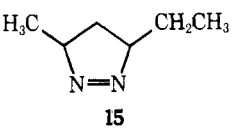
Of all these explanations, only the Roth-Martin single C–N cleavage pathway[10] is capable of accounting for stereochemistry of *both* mono- and bicyclic pyrazoline decompositions. Its application to the bicyclic system has been summarized above; in this case it is the rigidity of the system which dictates which lobe of the carbon p-orbital in the intermediate diazenyl diradical **14** will be used to form the new bond. In the monocyclic case, there is no such restriction on this orbital (cf. Scheme III), and rotation about the C–C bonds in the diazenyl intermediates allows reaction to take place with both single and double inversion, as is observed.[13] This mechanism is not a panacea, however; it depends critically on the assumption of sequential C–N bond cleavage, and much evidence has accumulated against application of this postulate to pyrazolines, especially in symmetrical systems such as the ones under consideration here.[8g,k] In addition, the mechanism outlined in Scheme III does not provide a very good explanation for the relatively large amount of **9c,** relative to all other stereoisomers, formed in the decomposition of **8t;** one would expect the barrier to rotation about the radical C–C bond to be by far the lowest in the molecule.

Statement of Problem

The project described in this paper was designed to (a) provide the remaining information about the stereochemistry of 3,5-dialkylpyrazoline decomposition, and (b) test the single C–N bond cleavage hypothesis.

(a) **Complete Stereochemistry of 3,5-Dialkylpyrazoline Decomposition.** Table I summarizes the stereochemical information available from Crawford's studies on **8c** and racemic and optically active **8t.** It is immediately obvious that the meso character of **8c** and **9c** prevents determination of a significant amount of stereochemical information in the decomposition or formation of cis isomers in this series—i.e., one cannot tell which carbon is inverted in the conversion of **8t** to **9c** or **8c** to **9t,** and one cannot tell whether the conversion of **8c** to **9c** occurs with net double retention, or double inversion as in the **8t** to **9t** conversion.

This information would be available, however, from the decomposition of unsymmetrically substituted pyrazolines, where both the cis and trans isomers are capable of optical resolution. We therefore decided to examine the total decomposition stereochemistry of such an unsymmetrical system. Because we had determined the absolute configurations and optical purities of the *cis*- and *trans*-1-ethyl-2-methylcyclopropanes (**16**) in the course of an earlier study,[14] decomposition of the corresponding *cis*- and *trans*-3-ethyl-5-methylpyrazolines (**15**) seemed like an ideal choice. We therefore set out to



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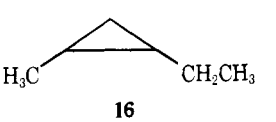

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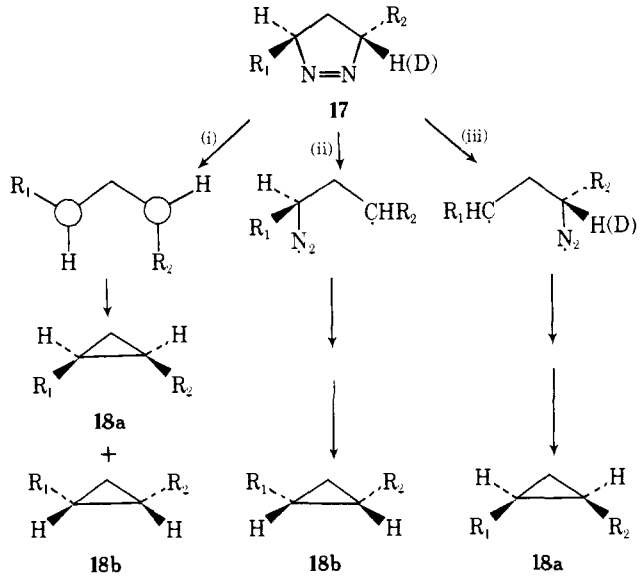
prepare these materials using a route that would provide them in optically active form and would allow us to determine their absolute stereochemistries.

(b) **An Approach to the Resolution of the Sequential or Simultaneous C–N Bond Cleavage Question.** The ability of the experiment described above to reveal the stereochemistry of the "cis" side of the pyrazoline reaction mechanism also suggested a means of using a combination of stereochemical and isotope effect techniques to examine the C–N bond cleavage question. The proposition is essentially that outlined for a generalized *trans*-pyrazoline substrate (**17**) in Scheme IV.

Scheme IV

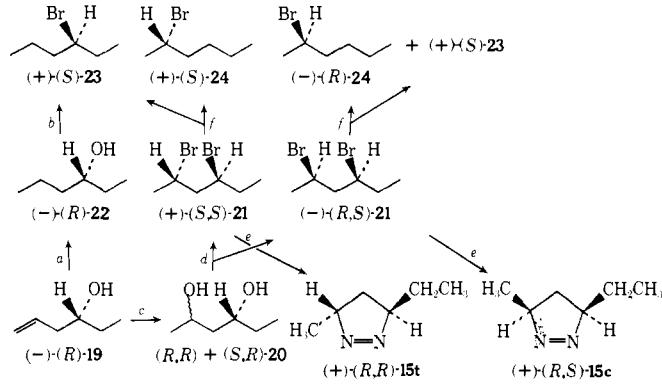


If decomposition occurs by sequential C–N cleavage, there are two possible pathways for this process, as shown by paths ii and iii in Scheme IV. The initial expected result of this is that a small difference between R_1 and R_2 should give rise to low optical activity in the cis product **18**. In addition, however, it is now well known that there is an appreciable secondary deuterium isotope effect observed on the C–N bond-breaking process,[8g] and substitution of D for H at the indicated carbon in **17** should therefore *slow* k_{ii} relative to k_{iii}. The result of this would be to change the optical rotation of the *cis*-cyclopropane **18** obtained; i.e., the ratio of **18a** to **18b** should increase upon deuteration. If, on the other hand, **17** decomposes directly to a 0,0 diradical by simultaneous C–N bond cleavage (path i), a point of symmetry is reached on the reaction coordinate. Compound **18** should now be obtained in optically inactive form, and there is no way that deuteration can modify the optical result in this mechanism. Part of this project, therefore, was aimed at the additional goal of obtaining optically active pyrazolines **15** having specific monodeuteration at either the methyl- or ethyl-substituted carbon.

Results

A. Synthesis, Optical Resolution, and Correlations. Scheme V summarizes the pathways used to synthesize racemic and optically active pyrazolines **15c** and **15t**, as well as the chemical correlations employed to determine and then confirm the structures, absolute configurations, and optical purities of the compounds shown in the scheme. The pyrazoline synthesis was based on the method Crawford, Mishra, and Dummel[8j] used to prepare the corresponding 3,5-dimethyl derivatives. Optical activity was introduced into our system by crystallization of the brucine salt of the half acid phthalate of 1-hexen-4-ol (**19**), which was in turn prepared by addition of allylmagnesium bromide to propionaldehyde. The absolute configuration and optical purity of this partially resolved alcohol were determined

Scheme V



[a] H_2–Pt–EtOAc. [b] 1. TsCl–pyridine; 2. LiBr–acetone (1 h, 25 °C). [c] 1. $Hg(OAc)_2$–THF, H_2O; 2. $NaBH_4$, OH^-. [d] Ph_3PBr_2–CH_3CN; dibromides separated by preparative VPC. [e] 1. NH_2NH_2–EtOH; 2. HgO–pentane. [f] $(n\text{-Bu})_3SnH$–2,6,10,14-tetramethylpentadecane.

by hydrogenation to 3-hexanol (**22**) of known stereochemistry,[15] and confirmed by NMR analysis of the MTPA derivative[16] of the unsaturated alcohol. Because we were unable to separate **15c** and **15t** by gas chromatography (despite a number of attempts to do so), separation of diastereomers was carried out at the dibromide (**21**) stage. In order to assign the stereochemistry of each dibromide (as well as determine that no optical purity had been lost in the conversion of diols **20** to dibromides **21**), each pure optically active dibromide was reduced to a mixture of monobromides **23** and **24** with Bu_3SnH and the optical purities of each monobromide determined by a combination of polarimetric and GC analysis. This showed that the **20** → **21** conversion had been carried out with negligible loss of optical activity.

Assuming that conversion of dibromides **21** to pyrazolines **15** proceeds with complete inversion of stereochemistry,[8h,j] the specification of the configuration of one dibromide as *S,S* (via the reduction described above) requires that it be the precursor of **15t**; thus (*R,S*)-**21** leads to **15c**. The pyrazoline stereochemical assignments made in this way were confirmed by NMR using the procedure described by Crawford, Mishra, and Dummel,[8j] and NMR also served to assure us that each pyrazoline showed no detectable contamination by its opposite diastereomer.

For the isotope effect study referred to in the previous section, we prepared **15c** and **15t** containing deuterium at the ethyl-bearing carbon atom. The precursor of these substances was 1-hexen-4-ol-*4-d*, which was in turn obtained by oxidation of racemic protio-**19** followed by reduction with $LiAlD_4$. The deuterated material was then resolved and converted to pyrazolines using the route outlined above for the protiated series.

B. Product Distributions. In order to legitimately compare our results with those obtained by Crawford and Mishra in the dimethyl series, it is important to determine that the structural modification involved in changing a methyl to an ethyl group does not have a significant effect upon the reaction mechanism. Evidence for this point of view is provided by a comparison of the products formed on thermal decomposition of **15c** and **15t** (Table II) with those formed on decomposition of the dimethylpyrazolines **8c** and **8t** (Table I). The cis/trans ratios of cyclopropane products **16c** and **16t** very closely resemble the ratios obtained[8c] by Crawford and Mishra for the *cis*- and *trans*-dimethyl systems **8c** and **8t**. An even closer evaluation is possible by comparing the stereochemistry of formation of *trans*-cyclopropane product from optically active **15t** with that[8h] from optically active **8t** (Table I); in this comparison, the amounts of each comparable *trans*-cyclopropane enantiomer formed from the two *trans*-pyrazolines are very similar

Table II. Products Formed on Thermal Decomposition of 3-Ethyl-5-methyl-1-pyrazolines in the Gas Phase at Atmospheric Pressure

Starting material	Temp, °C	Products, % 16t	16c	Olefins	Ratio, 16c/16t
15t	261	25.4	74.5	0.1	2.9
	306	26.8	71.3	2.0	2.7
	352	27.9	69.2	3.0	2.5
15t-d_1	260	26.2	71.2	2.6	2.7
	292	27.9	69.5	2.6	2.5
	314	28.6	68.6	2.8	2.4
	350	29.4	67.2	3.5	2.3
15c	260	67.6	31.1	1.2	0.46
	314	65.7	32.1	1.8	0.49
	350	64.7	33.2	1.9	0.51
15c-d_1	260	67.7	31.2	1.3	0.46
	300	67.6	31.1	1.3	0.46
	350	65.7	32.1	2.4	0.49

Table III. Percent Yields and Absolute Stereochemistry of Cyclopropane Products Formed on Thermal Decomposition of (+)-(3*R*,5*R*)- and (+)-(3*R*,5*S*)-3-Ethyl-5-methyl-1-pyrazolines at 292 °C (gas phase, He flow system, atmospheric pressure)

		Products: (+)-16t			(+)-16c		
Starting material		% yield	Predominant stereochemistry	% optical purity maintained	% yield	Predominant stereochemistry	% optical purity maintained
(+)-15c	R = H	65.7	Ethyl	14.2 ± 0.4	32.1	Double	36.5 ± 2.9
	R = D	67.6	rotation	16.9 ± 0.6	31.1	retention	29.9 ± 1.5
(+)-15t	R = H	27.1	Double	22.5 ± 0.5	70.6	Methyl	0.8 ± 0.2
	R = D	28.6	inversion	23.8 ± 1.2	68.6	rotation	0.8 ± 0.4

(see following section). Consequently, we are confident that the general decomposition mode for 3,5-dimethyl-1-pyrazolines is not altered in our unsymmetrical ethyl-methyl system. The data in Table II also demonstrate the operation of a small temperature effect which (as expected)[8] tends to decrease the selectivity of the reaction as the temperature is raised. The results also show a slight decrease in the cis/trans product ratio for the deuterated cases, but the effect is essentially within experimental error, especially for **15c**. Product distributions were the same within experimental error when carried out on either racemic or optically active samples of **15c** and **15t**.

C. **Stereochemistry**. Preparative flow pyrolyses of optically active pyrazolines **15c** and **15t** were carried out on ca. 100-mg samples at 292 °C at atmospheric pressure and a helium carrier gas flow of 60 mL/min. VPC analysis showed no unreacted pyrazoline; the product distributions were monitored by VPC and shown to be in good agreement with those carried out on smaller samples and reported in Table II. The cyclopropanes **16c** and **16t** were separated and purified by preparative VPC; they were then dissolved in 1 mL of spectral grade *n*-hexane and their optical rotations were measured on a Perkin-Elmer 141 digital-readout polarimeter. The stereochemistry of each reaction was calculated using the maximum rotations and absolute configurations of the pyrazolines determined in this work and similar stereochemical information determined earlier for the cyclopropanes.[14] Table III shows the percent yield and predominant enantiomer of each cyclopropane formed from each pyrazoline of a given absolute configuration, the percent optical purity maintained in the transformation, and the predominant overall structural change which must occur to produce that stereochemistry.

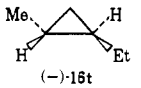
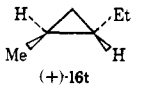
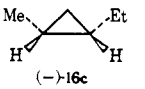
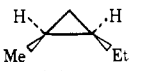
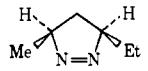
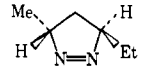
Discussion

The most important results of this study are summarized in Table III. If we look first at the decomposition of optically active *trans*-pyrazoline (+)-**15t**, we find that the results are clearly those expected on the basis of Crawford's earlier work.[8h] *trans*-Cyclopropane **16t** is produced with some excess inversion at both the carbon carrying the methyl and that carrying the ethyl group (here referred to as "double inversion"), and the percent enantiomer in excess is almost exactly that observed by Crawford in the dimethyl series. This supports the idea that the mechanisms are the same for the dimethyl and methylethyl pyrazolines, and provides supportive evidence that the configurational determinations made for the compounds used in this work are correct in both sign and magnitude. Furthermore, as Crawford and Mishra surmised, the *cis*-cyclopropane **16c** produced from **15t** is in fact very nearly racemic. Thus Crawford's estimate[8h] of the percent of the reaction which is required to proceed via achiral intermediates—in the trans case, at least—is essentially correct.

The stereochemistry of decomposition of isotopically labeled **15t** is very nearly the same as that for the unlabeled compound; the two results are essentially within experimental error of being identical. As outlined in the Introduction, we had intended to use the pathway outlined in Scheme IV to interpret these results. However, it became clear upon examining the stereochemical data obtained in the decomposition of (+)-**15c** (discussed below) that the true mechanism was much too complicated to allow making such a judgment.

Having the results of the trans decomposition in hand, the data obtained from (+)-**15c** were quite startling. Examination

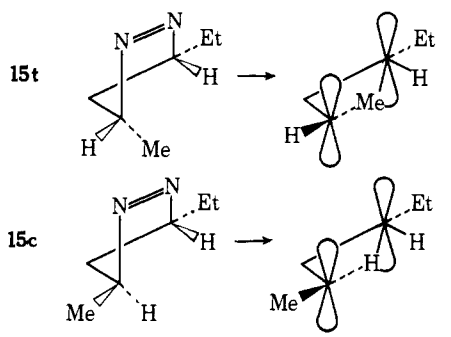
Table IV. Yield of Each Cyclopropane Enantiomer Formed from Pure (+)-(3*R*,5*R*)- and (+)-(3*R*,5*S*)-3-Ethyl-5-methylpyrazolines at 292 °C

Starting material	Products, %			
	 (−)-15t	 (+)-16t	 (−)-16c	 (+)-16c
 (+)-15c	28	38	10	22
 (+)-15t	10	17	35	36

of Table III shows that **15c** decomposes in a manner which (a) gives a larger overall percentage of optically active product than **15t** (and thus less of the total product is allowed to be formed from an achiral intermediate such as the 0,0 diradical), and (b) *gives both cis- and trans-cyclopropane products by overall stereochemical changes opposite to those observed for the trans isomer* ***15t.*** Whereas **15t** is converted to the corresponding *trans*-cyclopropane with excess double inversion of configuration, **15c** is converted to *cis*-cyclopropane with *excess double retention.* In addition, where **15t** gives *cis*-cyclopropane with a small amount of excess rotation of the ring C–C bond bearing the methyl group ("methyl rotation"), **15c** is converted to *trans*-cyclopropane **16t** by overall rotation of the C–C bond which bears an ethyl group ("ethyl rotation").

In order to most easily visualize the stereochemical changes which take place in these transformations, it is useful to examine Table IV. Here the absolute percentage of each cyclopropane enantiomer formed from each pure pyrazoline enantiomer is directly given. Before we consider specific mechanisms which might be able to account for these data, let us deal with the possible intervention of 0,0 diradicals in these reactions. First, while it is clear that one may state (as Crawford does) that the data *require* only 6% of the products from **15t** to be formed from chiral intermediates, *at least 20% of the products must arise by a chiral pathway* in the case of **15c** (and, therefore, presumably in the case of **8c** as well). One may then ask whether it is reasonable to construct a mechanism which utilizes the achiral 0,0 diradical as a precursor to the racemic part of the products and a different, chiral path for the remainder. We believe that such a mechanism would not be reasonable, because it is difficult to understand why the *cis*-pyrazoline should not give the larger proportion of racemic products. If (as has been postulated[8]) the 0,0 diradical is formed from the "envelope" configuration of the pyrazoline, this conformation has both alkyl groups in sterically favorable pseudo-equatorial positions in **15c** (cf. Scheme VI) and presumably leads to a transition state which is sterically uncrowded. The *trans*-pyrazoline, on the other hand, must always generate an N_2-extrusion transition state having one alkyl group in an axial position. Making the reasonable assumption that the ground-state energies of **15c** and **15t** do not differ by a large amount, **15t** should be expected to give *less* (rather than more) 0,0 diradical (i.e., achiral) products than **15c**. Therefore, while it is still possible that the 0,0 intermediate may account for some fraction of the achiral product mixture, we believe it would be rather artificial to contend that it is an intermediate of major importance.

Scheme VI



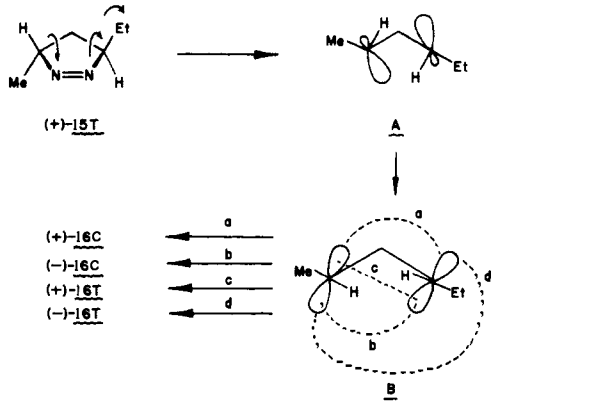
Similarly, both the "recoil" [9] and single C–N bond cleavage mechanisms,[10] at least in their simplest incarnations, also do not account well for our data. The recoil mechanism fits the data for **15c,** where single inversion and double retention now make up a majority of the reaction pathway, especially poorly. Using the single C–N cleavage mechanism it is difficult to provide a satisfying rationale for the relative amounts of all the products observed, and it is especially difficult to account for the change from double inversion to double retention in **15t** relative to **15c**.

In short, any mechanism suggested must explain the following critical observations: (1) a large fraction of chiral products; (2) single inversion as the major (but not exclusive) pathway from both pyrazolines **15c** and **15t;** (3) predominant ethyl rotation in the **15c** → **16t** conversion and predominant methyl rotation in the **15t** → **16c** conversion; (4) predominant double inversion in the conversions **15t** → **16t** and **8t** → **9t,** but double retention for **15c** → **16c;** (5) probable simultaneous C–N bond rupture[8g,k] in the initial step of the reaction.

It is obviously very difficult to devise a mechanism which uses the same basic principles to account for strikingly different behavior from such very similar molecules **15c** and **15t**. We have been able to devise only one which accounts even moderately well for our observations, and it is outlined in detail below. However, these reactions are clearly much more complicated than was previously believed, and it is clear that they will not be understood until much more study, or perhaps a dramatic new insight, has been applied to them. The following mechanistic discussion should therefore be considered as a working hypothesis rather than a definitive solution to this problem.

We employ the following postulates, some of which have been suggested by recent theoretical studies, in explaining our results. First, we hypothesize, in agreement with the suggestion of Fukui,[17] that in the initial phases of decomposition azo compound **15t** travels along a reaction coordinate which "feels like" a $[\sigma 2_s + \sigma 2_a]$ pathway. That is, as shown in Scheme VII nitrogen is extruded in a "nonlinear" fashion, and this causes a pseudo-conrotation of the ring bonds. The "clockwise" conrotation shown in Scheme VII should be much more favorable than the opposite "counterclockwise" conrotation, because the latter would compress both alkyl substituents toward the inside of the carbon framework. This motion leads to transient A (we deliberately avoid using the term "intermediate"; the two C–N bonds may not yet be completely

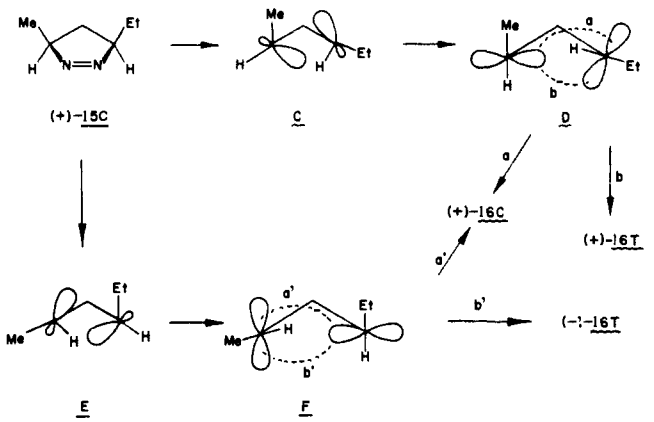
Scheme VII



broken in A if it is a transition state) having instantaneously pyramidal radical centers. Now, if we consider how these pyramidal centers become planar, center-of-mass arguments require that planarization take place almost exclusively *by motion of the hydrogen atom* attached to the radical carbon, with almost no motion of the alkyl ligands. This will serve to effectively "invert" the radical carbon atoms, leading to transient B (the N_2 molecule at this point is presumably completely separated from the organic fragment). "Least motion" considerations now serve to account for the relative amounts of products—pathways a and b lead to cis product and are chemically equivalent, thus accounting for the formation of nearly racemic **16c**. Paths c and d lead to trans product, but c is clearly more favorable than d, and thus **16t** is formed with double inversion of configuration.

The cis decomposition (Scheme VIII) is a bit more com-

Scheme VIII



plicated, since in this case the two possible nonlinear N_2 extrusions are energetically similar and should be competitive in rate. Each is also sterically more demanding than in the "clockwise" trans case, since in both instances one of the alkyl groups tends to be forced into a pseudo-axial position. We assume that the response to this steric compression is that somewhat less rotation takes place on the side of the molecule which experiences the axial interaction. This leads in one instance to a transient of structure C (once again, the C–N bonds may not be completely broken here), and in the other rotational direction to structure E. In C, planarization again occurs by hydrogen motion, now generating D. Closest-approach ring-closure pathways are represented by paths a (giving doubly retained cis product) and b (leading to singly inverted, ethyl-rotated product). Rehybridization in E leads to F, which may now close by path a′, leading once again to doubly retained cis product, or b′, leading to methyl-rotated trans product. (−)-**16c**, the product observed in smallest amount, can only be formed through utilization of the most "remote" p-orbital lobe in D and F (this path not shown explicitly in Scheme VIII). A satisfactory account of the product distribution may be obtained if one makes the reasonable assumption that the methyl compression rotational pathway leading to C is somewhat favored over the ethyl compression pathway leading to E.

Conclusion

It is very difficult to devise a unified diradical mechanism of the conventional type (i.e., one involving relatively long-lived, easily described intermediates which undergo a series of product-forming steps in competition with various conformational changes) to account for the observations described in this paper. One is therefore faced with the alternatives of (a) simply presenting the data and suggesting a pathway which accounts for only part of it, (b) suggesting that the data may be rationalized only by a fortuitous combination of different mechanisms, without trying to specify the factors that control which path is followed in a given case, or (c) trying to construct an hypothesis which will account for all the observations (at least in the systems studied here) with a minimum of ad hoc assumptions. We have chosen the last of these alternatives, and we once again emphasize that the mechanism outlined in Schemes VII and VIII must be treated as a working hypothesis. It is also meant to apply only to monocyclic 3,5-dialkylpyrazolines; clearly when the pyrazoline structure is changed drastically (e.g., as in compound **11**), other factors intervene to change the mechanism also.

One interesting aspect of the mechanism outlined in Schemes VII and VIII is that the "transients" discussed there must be very short-lived. One can therefore think of this mechanism as being "quasi-concerted" in conventional terms; however, it is interesting that reaction courses similar to these have recently been employed to verbalize the results of ab initio theoretical calculations on potential energy surfaces for organic thermal reactions[18] and analyses of the dynamics of molecules moving across such surfaces.[19] These energy surfaces have often been very flat in the region of the transition state, with few deep potential wells representing stable, long-lived intermediates. Discussions of reactions proceeding over such surfaces have involved the presentation of "snapshots" of points along particular reaction coordinates.[18,19] These points are very often not more than short-lived "stages" through which reacting molecules pass in times no longer (and possibly much shorter) than those associated with molecular vibrations.

Normally one would be unable to obtain from stereochemical data a picture of a reaction mechanism nearly as detailed as the series of "snapshots" obtainable from a quantum mechanical or trajectory calculation. Often thermal reactions take place in such a way as to present data which is consistent with either conventional or "snapshot" mechanistic analysis; because conventional mechanisms are much simpler, chemists naturally have chosen to use them as a way of understanding and explaining how reactions take place. The pyrazoline decomposition is unusual in that it has resisted a completely satisfying conventional analysis for several years, and the present work serves to reinforce the premise that conventional mechanistic analysis will never be able to provide a satisfactory understanding of this reaction. Even if the picture outlined in the previous section is incorrect in detail, it seems inescapable that mechanistic language similar to that used to describe recent theoretical and dynamical calculations[18,19] will be required to provide an understanding of pyrazoline thermolysis. We believe that questions such as "is this reaction stepwise or concerted?" and "is this species an intermediate or transition state?" are already losing their meaning for reactions of this type, and we have therefore deliberately avoided attempting to raise such questions in describing the transients postulated in Schemes VII and VIII.

Theorists are now able to provide extremely detailed descriptions of small portions of chemical reaction potential en-

ergy surfaces. Unfortunately, for the extremely large multidimensional surfaces involved in organic reactions, one never knows whether the part of the surface investigated theoretically is in fact the one utilized by the reaction. Ironically, experimentalists are *forced* to investigate the true potential surfaces of complex reactions, but at present their ability to examine the detailed behavior of large organic molecules passing over those surfaces is very poor. Clearly new techniques need to be developed which will provide a much more detailed picture of the mechanisms of the chemical reactions of complex molecules; only in that way will we be able to truly test the sort of hypotheses set out in this paper.

Experimental Section

General. Proton NMR spectra were obtained on either an A-60-A or T-60 Varian Associates NMR spectrometer. ^{19}F NMR spectra were obtained on an XL-100 Varian Associates analytical NMR spectrometer. Carbon tetrachloride or deuteriochloroform were used as solvents with tetramethylsilane as an internal standard for all proton spectra. All ^{19}F NMR spectra were run using deuteriochloroform as solvent with trifluoroacetic acid as an external standard.

Infrared spectra were obtained on a Perkin-Elmer 257 grating infrared spectrophotometer using carbon tetrachloride as solvent. Optical rotations were obtained on a Perkin-Elmer 141 digital readout polarimeter, using a 1-mL microcell with a 10-cm path length. Concentrations are reported in grams per milliliter.

All analytical vapor phase chromatography was performed on a Hewlett-Packard 5750 research chromatograph equipped with either a Hewlett-Packard 3370A integrator or an Autolabs Systems I computing integrator. The chromatograph was equipped with a flame ionization detector; maximum sensitivity was maintained at the following gas pressures (lb/in.^{2}): He, 40; H_2, 14; air, 30. Stainless steel columns (⅛ in.) were utilized for all analytical work. Preparative vapor phase chromatography was performed on a Varian Aerograph 90-P3 chromatograph equipped with a thermal conductivity detector. The following columns were employed, and will be referred to using the indicated letters: Column A, 10 ft × ¼ in., 10% DEGS on 60/80 Chromosorb P-NAW, stainless steel; column B, 5 ft × ¼ in., 5% DEGS on 60/80 Chromosorb P-NAW, stainless steel; column C, 10 ft × ¼ in., 8% TCEP on 60/80 Chromosorb P-NAW aluminum; column D, 5 ft × ¼ in., 3% SE30 on 100/120 Varaport 30, stainless steel; column E, 10 ft × ¼ in., 5% Carbowax on 60/80 Chromosorb P-NAW, aluminum; column F, 10 ft × ¼ in., 10% UCC-W98 on 60/80 Chromosorb W-AW DMCS, glass; column G, 20 ft × ¼ in., 20% Carbowax on 60/80 Chromosorb P-NAW, aluminum; column H, 25 ft × ⅛ in., 25% $\beta\beta$-ODNP on 100/120 Chromosorb W-AW DMCS, stainless steel; column I, 10 ft × ¼ in., 10% Carbowax 1500 on 60/80 Chromosorb P-NAW, stainless steel; column J, 10 ft × ¼ in., 12% UCC-W98 on 60/80 Chromosorb P-NAW, stainless steel; column K, 12 ft × ¼ in., 10% DEGS on 60/80 Chromosorb P-NAW, stainless steel; column L, 10 ft × ¼ in., 10% DEGS on 60/80 Chromosorb W-AW DMCS, glass; column M, 10 ft × ¼ in., 30% SE-30 on 60/80 Chromosorb W-AW DMCS, glass; column N, 12 ft × ⅜ in., 10% UCW-98 on 60/80 Chromosorb W-AW, glass; column O, 10 ft × ¼ in., 20% Carbowax 20M on 60/80 Chromosorb P-NAW, glass; column P, 20 ft × ⅛ in., 25% STAP on 100/120 Chromosorb W-AW DMCS, stainless steel; column Q, 25 ft × ⅛ in., 25% $\beta\beta$-ODNP on 100/120 Chromosorb W-AW DMCS, stainless steel.

Mass spectral analyses were performed on a duPont high resolution mass spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Boiling points are uncorrected.

Syntheses. I. Racemic Undeuterated Series. (±)-1-Hexen-4-ol (19) was prepared by a procedure similar to that of Hwa and Sims[20] for reaction of allylmagnesium bromide with acrolein. Into a 5-L three-necked flask fitted with mechanical stirrer, reflux condenser, and addition funnel was placed 153.0 g (6.28 g-atoms) of Mg turnings. The flask was then flamed out under N_2, after which 360 mL of anhydrous ether and three iodine crystals were added. Several milliliters of a solution of 351 g (2.90 mol) of allyl bromide in 2.6 L of anhydrous ether were then added, at which point spontaneous reflux began. The rest of the allyl bromide solution was then added slowly over 6.5 h at a rate sufficient to maintain a gentle reflux. Upon completion of the addition, the dark brown solution was stirred for 2 h at room temperature. Then 108 g (1.86 mol) of propionaldehyde was added over 3 h again at a rate sufficient to promote a mild reflux. The reaction was then stirred 1 h at room temperature and left overnight under N_2.

The reaction mixture was decanted slowly off of the excess Mg turnings into 2 L of an ice–water mixture. The remaining Mg turnings were rinsed with ether which was also added to the ice water. To this mixture was then added slowly a solution of 120 mL of concentrated H_2SO_4 in 400 mL of H_2O. The aqueous layer of the resulting mixture was washed with ether, after which the combined ether layers were dried over $MgSO_4$.

The ether was slowly distilled off through a 24-in. tantalum wire column. The product was distilled at reduced pressure through a 6-in. Vigreux column to give 161.6 g of the alcohol (86.6% yield; bp 63–65 °C (50 mm)): IR 3570, 3400 (br), 3075, 2960, 2920, 2880, 1640, 1440, 1000, 995, and 920 cm^{-1}; NMR (CCl_4) δ 0.93 (t, J = 6.5 Hz, 3 H, $-CH_2CH_3$), 1.38 (q, 2 H, $-CHOHCH_2CH_3$), 1.73 (s, 1 H, OH), 2.0–2.3 (m, 2 H, $=CHCH_2-$), 3.48 (quintuplet, 1 H, $-CHOH$), 4.8–5.2 (m, 2 H, vinyl CH_2), 5.4–6.2 (m, 1 H, vinyl CH). Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.01; H, 12.11.

(±)-2,4-Hexanediol (20). The procedure used was based on that of Brown and Geoghegan.[21] Into a 3-L three-necked flask fitted with mechanical stirrer, addition funnel, and room temperature water bath were placed 159.5 g (0.5 mol) of mercuric acetate in 500 mL of H_2O. THF (500 mL) was added to give a yellow suspension, to which was added 50 g (0.5 mol) of **19** over a period of 8 min. During this time the yellow color disappeared. The reaction was allowed to stir for 17 min, after which 500 mL of a 3 N aqueous NaOH solution was added. A 500-mL solution 0.5 M in $NaBH_4$ and 3 N in NaOH was then added slowly (25 min) to give a black suspension.

After 15 min of stirring, the solution was saturated with NaCl, and the two resulting layers separated. The aqueous layer was extracted with THF and the combined organic layers were then washed with saturated aqueous NaCl and dried over K_2CO_3.

After removal of solvent by distillation through a Vigreux column, the product was distilled at reduced pressure (bp 73–74 °C (1.2 mm)) to give 51.5 g of **20** as a viscous colorless liquid (87.3% yield). VPC analysis of this compound could only be performed well on column E (150 °C, 100 mL/min), since it either did not come off at all or tailed unacceptably under all other conditions tried. No conditions were ever found under which the diol diastereomers separated: IR 3650–3040 (v br), 2980, 2960, 2940, 1465, 1380, 1330, 1150, 1115, 1080, 1060, 1040, 1010, 965, 930, 900, 855, and 830 cm^{-1}; NMR ($CDCl_3$) δ 0.75–2.7, overlapping m, 10 H, containing 0.94 (perturbed t, J = 6.5 Hz, 3 H, $-CH_2CH_3$), and a pair of doublets (J = 6.0 Hz) at 1.20 and 1.23 ($CHOHCH_3$ of each of diastereomeric diols), 2.86 (s, 2 H, -OH), 3.6–4.4 (m, 2 H, $-CHOH-$).

(±)-2,4-Dibromohexane (21). Bromination was accomplished by a modification of the procedure of Schaefer et al.[22] Into a flamed 1-L three-necked flask fitted with mechanical stirrer, reflux condenser, addition funnel, and N_2 inlet was placed 205.3 g (0.778 mol) of triphenylphosphine in 340 mL of acetonitrile (distilled from P_2O_5). With the reaction flask cooled to 0 °C, 121.5 g (0.76 mol) of bromine was added dropwise with stirring. The reaction was then returned to room temperature and 45.0 g of the diastereomeric diol mixture **20** in 47.5 mL of acetonitrile was added over 10 min, during which time the reaction warmed to 50–60 °C and all solids dissolved. The reaction was cooled to room temperature and stirred for ¾ h.

Most of the CH_3CN was removed at aspirator pressure. (The solvent was collected and redistilled through a Vigreux column at atmospheric pressure to recover dibromide contained in it.) As the reaction flask was then heated to 120–140 °C at 0.5 mm, the dibromide product distilled off leaving behind a white solid Ph_3PO residue. (Liquid nitrogen traps must be used in this procedure to protect the vacuum pump from the large quantities of HBr evolved.) The crude product was dissolved in 120 mL of ether, washed in succession with saturated aqueous sodium bicarbonate and sodium chloride solutions, and dried over $MgSO_4$.

The ether was distilled off at atmospheric pressure, after which the mixture of dibromide diastereomers was distilled quickly at reduced pressure (bp 43–45 °C (1 mm)) to give 64.9 g of product (69.7% yield). Extensive heating was avoided, since this is known to cause diastereomeric interconversion, which would lead to racemization in the active series.

The two diastereomeric dibromides were found to separate cleanly on several VPC columns: e.g., column E (160 °C, 100 ml/min); col-

umn A (140 °C, 100 ml/min). Later column K (150 °C, 100 ml/min) was found to give the best separation. The two diastereomers, which were formed in a (2*R*,4*R*)/(2*R*,4*S*) ratio of 2.8:1, were separated by preparative VPC, and the following spectra were obtained: IR of (±)-(2*R*,4*R*) 3000, 2940, 1467, 1459, 1419, 1384, 1298, 1240, 1213, 1168, 1135, 1176, 982, 974, and 889 cm^{-1}; NMR of (±)-(2*R*,4*R*) δ 1.08 (perturbed t, *J* = 7.0 Hz, 3 H, $-CH_2CH_3$), 1.6–2.24 (m, 4 H, $-CH_2-$), 1.78 (d, *J* = 7.0 Hz, 3 H, $-CHBrCH_3$), 3.90–4.56 (m 2 H, $-CHBr-$); IR of (±)-(2*R*,4*S*) 3000, 2960, 2940, 1467, 1459, 1384, 1294, 1270, 1242, 1208, 1179, 1132, 1009 (w), 999 (w), 987 (w), 907, and 871 cm^{-1}; NMR of (±)-(2*R*,4*S*) δ 1.07 (perturbed t, *J* = 7.0 Hz, 3 H, $-CH_2CH_3$), 1.53–2.05 (m, 2 H, $-CH_2-$), 1.72 (d, *J* = 7.0 Hz, 3 H, $-CH_3$), 2.05–2.76 (m, 2 H, $-CH_2-$), 3.8–4.4 (m, 2 H, $-CHBr-$).

(±)-*trans*-3-Ethyl-5-methylpyrazolidine. Into a 10-mL round-bottomed flask fitted with two rubber serum caps and magnetic spin bar and flushed with Ar were placed 1.64 mL of 98% aqueous ethanol and 0.5 mL (15.8 mmol) of 97+% anhydrous hydrazine. The reaction flask was cooled in an ice bath and 1.02 g (4.18 mmol) of VPC purified (±)-(2*R*,4*R*)-**21** was slowly added using a syringe, with stirring. The reaction was then heated to 60 °C with continued rapid stirring and checked by VPC (column F, 100 °C, 100 ml/min) at regular intervals. After 5 days, the reaction was essentially complete, although a small amount of starting material was still visible in a VPC trace. During the course of the reaction, an oily lower layer was observed to separate out ($N_2H_4 \cdot HBr$); the reaction flask was cooled to 0 °C and stirring continued until this oily lower layer crystallized.

The reaction mixture was filtered and the residual solid washed twice with small portions of ethanol. The combined ethanol solutions were placed over 0.5 g of crushed KOH in the refrigerator for 2–3 h during which time a KBr precipitate formed and settled. The solution was again filtered and the solid washed with small portions of ethanol.

Most of the ethanol was distilled off at 40-mm pressure and the remaining solution was vacuum transferred to leave behind a white solid residue. The pyrazolidine was isolated from the solution by preparative VPC (column F, 100 °C, 100 ml/min); 158 mg (33.5% yield) of product was collected: IR 3660, 3300 (v br), 2970, 2930, 2890, 1620 (w), 1455, 1440, 1410, 1380, 1320, 1065, 1025, and 805 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (t, 3 H, ethyl CH_3), 1.67 (five-line pattern, 2 H, ethyl $-CH_2-$), 1.08–1.67 (m, 5 H, $-CH_2-$, $-CH_3$), 3.19 (seven-line pattern, 2 H, $-CH-$), 3.93 (s, 2 H, $-NH$).

(±)-*trans*-3-Ethyl-5-methyl-1-pyrazoline (15t). It was observed that the bubbling of oxygen through the NMR solution of pyrazolidine caused gradual oxidation to the corresponding pyrazoline, **15t**. This procedure was used for a small scale preparation of the *trans*-pyrazoline. (For a procedure more suitable in larger scale reactions, see the preparation of (+)-**15t** below.) The NMR solution was thus left stirring overnight in a stoppered container under O_2 atmosphere. The product ((±)-**15t**) was then isolated by preparative VPC (column F, 100 °C, 100 ml/min): IR 2970, 2950, 2890, 1710, 1460, 1385, 1380, 1315, 1190, 1140, 1130, 970, and 895 cm^{-1}; NMR ($CDCl_3$) δ 1.01–2.2 (m, 4 H, $-CH_2-$), 1.01 (t, *J* = 7.0 Hz, 3 H, ethyl CH_3), 1.34 (d, *J* = 7.0 Hz, 3 H, CH_3), 4.52 (seven-line pattern, 2 H, $-CH-$). The NMR showed no detectable amount of the *cis*-pyrazoline (**15c**) described below.

(±)-*cis*-3-Ethyl-5-methylpyrazolidine. The *cis*-pyrazolidine was prepared from (±)-(2*R*,4*S*)-**21** using the same procedure as in the trans case. Into a dry, Ar flushed, 10-mL round-bottomed flask fitted with two rubber serum caps and a magnetic spin bar were placed 0.9 mL of 98% aqueous ethanol and 0.275 mL (8.18 mmol) of 97+% anhydrous hydrazine. The reaction flask was cooled to 0 °C and 0.553 g (2.27 mmol) of (±)-(2*R*,4*S*)-**21** was added with a syringe. The reaction was stirred at 60 °C for 4 days, by which time it was essentially complete, although small amounts of starting material could still be seen in the VPC trace.

Workup was accomplished as in the trans case and preparative VPC (column F, 105 °C, 100 ml/min) afforded a sample of pure *cis*-pyrazolidine: IR 3400 (v br), 2960, 2920, 2870, 1630 (w), 1450, 1375, 1330, 1235, 1220, 970, and 900 cm^{-1}; NMR ($CDCl_3$) δ 0.7–3.4 (series of highly split m, 12 H), 3.7 (s, 2 H, $-NH$).

(±)-*cis*-3-Ethyl-5-methyl-1-pyrazoline (15c). The *cis*-pyrazolidine proved less amenable to the oxygen oxidation used in the trans case. In this case, $Cu(OAc)_2$ was added a few milligrams at a time to the stirred NMR solution until VPC analysis (column F, 100 °C, 100 ml/min) showed reaction to be essentially complete. Product pyrazoline was vacuum transferred from the solid residue and (±)-**15c** isolated from the resulting solution by preparative VPC (column F, 105 °C, 100 ml/min). (This procedure was not very satisfactory; for a better procedure more applicable to larger scale reactions, see the preparation of (+)-**15t** below.) NMR ($CDCl_3$) δ 0.37–0.87 (d of t, *J* = 12.5 and 9.0 Hz, 1 H, 1 C(4)H), 1.07 (t, *J* = 7.0 Hz, 3 H, ethyl CH_3), 1.53 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.65–2.30 (m, 3 H, ethyl CH_2 and 1 H from C(4)), 4.12 (seven-line pattern, 2 H, $-CH$). The NMR showed no detectable amount of the *trans*-pyrazoline described above.

II. Optically Active Undeuterated Pyrazoline Synthesis. (−)-(*R*)-1-Hexen-4-ol (19). A. 1-Hexen-4-yl Phthalate. The procedure followed was essentially that described by Ingersoll[23] with some modifications. Into a 500-mL round-bottomed flask fitted with reflux condenser, large magnetic stirring bar, and a nitrogen inlet were placed 82.2 g (0.83 mol) of racemic **19** and 120 g of phthalic anhydride. The reaction was heated for 18 h at 105–110 °C to give a viscous yellow oil, the NMR of which indicated the presence of unreacted starting material. Phthalic anhydride (5 g more) was added, and the reaction was stirred for an additional 8 h.

The crude phthalate half ester was then added to a solution of 122 g (1.135 mol) of sodium carbonate in 2.5 L of water and stirred without warming until the oil had dissolved. This slightly cloudy solution was extracted in succession with benzene and hexane to remove any unreacted starting materials. Concentrated HCl (200 mL, 2.32 mol) was added slowly with stirring, causing the phthalate half ester to precipitate as a light yellow oil.

The oil was then taken up in chloroform, washed with saturated aqueous NaCl solution, and dried over Na_2SO_4. The chloroform was then stripped off on a rotovap and the resulting pale yellow oil pumped on at 2 mm for 45 min. In this and other preliminary runs, no successful way of inducing this oil to crystallize was ever found: NMR (CCl_4) δ 0.97 (t, *J* = 6.5 Hz, 3 H), 1.66 (q, *J* = 6.5 Hz, 2 H), 2.44 (t, *J* = 6.0 Hz, 2 H), 4.8–5.3 (m, 3 H), 5.4–6.2 (m, 1 H), 7.3–7.9 (m, 4 H), 11.76 (s, 1 H).

B. Brucine Salt Formation and Recrystallization. The above oil (111.8 g, 0.45 mol) was dissolved in 200 mL of warm ethyl acetate. To this was slowly added a slurry of 177.2 g of brucine (0.45 mol) in 400 mL of hot ethyl acetate. The resulting mixture was placed on a steam bath and ethyl acetate was added until all solids had dissolved. The solution was allowed to cool gradually to room temperature, during which time light tan mushroom-shaped crystal formations were observed to form. After several hours at room temperature, the solution was placed in the refrigerator overnight. The crystals were filtered, crushed, and washed quickly with cold ethyl acetate. This recrystallization was repeated 12 more times to give 139.8 g of brucine salt (0.218 mol).

C. Decomposition of Brucine Salt. The brucine salt was dissolved in the minimum amount of hot ethanol and added to 698 mL of 0.725 N HCl (0.505 mol). The phthalate ester separated from the solution as a pale yellow oil, which again resisted all attempts at crystallization. The aqueous solution was extracted with ether, which was added to the original oil, causing brucine dissolved in the oil to precipitate. Sufficient 1 N HCl was added to dissolve the brucine, after which this aqueous solution was itself extracted with ether. The combined organic layers were washed in succession with 1 N HCl and saturated aqueous NaCl solution and dried over Na_2SO_4. The ether was removed under aspirator pressure, and the resulting oil was pumped on for 1 h at 10 mm and 0.5 h at 2 mm.

The active phthalate half ester was placed in a 500-mL three-necked flask to which was added a solution of 21.76 g (0.544 mol) of sodium hydroxide in 65.3 mL of water. The solution was placed in an oil bath preheated to 95–100 °C and steam was introduced to effect the steam distillation. A lighter organic layer was soon observed to form. The distillation was continued until no organic layer remained in the reaction flask and the distillate in the condenser had lost its characteristic milky appearance. The lower layer of the distillate was saturated with NaCl; the organic layer was then separated and dried over K_2CO_3 to give 19.46 g (0.195 mol) of alcohol **19** >99% pure by VPC (column A, 105 °C, 100 mL/min). The following rotations were obtained: $[\alpha]^{25}_D$ −0.188°; $[\alpha]^{25}_{436}$ −0.873°; $[\alpha]^{25}_{365}$ −2.11° (neat); $[\alpha]^{25}_D$ +1.57 (*c* 0.084 in $CHCl_3$).

Hydrogenation to optically active 3-hexanol (vide infra) shows that this sample of **19** is 38.4% optically pure and has the *R* configuration.

(−)-(*R*)-3-Hexanol (22). (−)-(*R*)-**19** was subjected to atmospheric

pressure hydrogenation to give 3-hexanol, whose absolute configuration and maximum rotation (recorded on neat samples) are known.[15] In a 10-mL flask were placed 0.2225 g (2.225 mmol) of (−)-**19** ($[\alpha]^{25}_D$ −0.188, neat) and 48 mg of PtO_2 in 3 mL of ethyl acetate. The reaction was stirred at room temperature until hydrogen uptake ceased (70 min), at which point VPC analysis (column A, 80 °C, 60 mL/min) showed the reaction to be complete. The product 3-hexanol was purified by preparative VPC (column A) to give 0.1695 g of optically active product.

This material was placed in a 1-mL volumetric flask and sufficient racemic 3-hexanol was added to total 1.00 mL (0.621 g of racemic 3-hexanol). The following optical rotations were obtained for this material: $[\alpha]^{25}_D$ −0.588°; $[\alpha]^{25}_{436}$ −1.114°; $[\alpha]^{25}_{365}$ −1.666°. When these values are then corrected for the dilution with racemic 3-hexanol, the following values are obtained for the original active sample derived from the (−)-**19**: $[\alpha]^{25}_D$ −2.74°; $[\alpha]^{25}_{436}$ −5.20°; $[\alpha]^{25}_{365}$ −7.76°. Based on $[\alpha]^{18}_D$ max −7.13° for (*R*)-3-hexanol,[15] this sample of (−)-**22**, and thus the (−)-**19** produced above, must have optical purities of 38.4% and must have the *R* configuration.

(+)-(*S*)-1-hexen-4-ol (19). The ethyl acetate was stripped off the mother liquor from the above brucine salt recrystallizations to give approximately 120 g (0.187 mol) of brucine salt. This salt was decomposed to the phthalate half ester, which was in turn subjected to saponification and steam distillation as described above to give 14.92 g of (+)-**19**. Subsequent hydrogenation to (+)-(*S*)-3-hexanol showed this material to be 35.8% optically pure.

Optically Active 2,4-Hexanediol (20). A diastereomeric mixture of the optically active 2,4-hexanediols having the *R* configuration at the C(4) position was produced by the oxymercuration–hydroboration procedure described above for the racemic series. Since no simple means was ever found for separation of the diastereomers, no rotations were obtained for the individual diastereomers.

(+)-(2*S*,4*S*)-2,4-Dibromohexane and (−)-(2*R*,4*S*)-2,4-Dibromohexane (21). The above mixture of optically active diol diastereomers was converted to the corresponding mixture of dibromide diastereomers by the procedure described above in the racemic series. The dibromide diastereomers were separated by careful preparative VPC (column A). About 3 g of the 2*S*,4*S* and 1 g of the 2*R*,4*S* isomer were collected, providing a sufficient amount of 2*S*,4*S* to carry on the reaction sequence. VPC analysis showed the 2*S*,4*S* to be free of any 2*R*,4*S* contamination, while the 2*R*,4*S* sample contained several percent 2*S*,4*S*. The following rotations were obtained: 2*S*,4*S*, $[\alpha]^{25}_D$ +27.7° (neat); 2*R*,4*S*, $[\alpha]^{25}_D$ −0.632° (*c* 0.0372 in $CHCl_3$).

(+)-(3*R*,5*R*)-*trans*-3-Ethyl-5-methyl-1-pyrazoline (15t). The 3.2 g of VPC pure (+)-(2*S*,4*S*)-**21** was then converted to (3*R*,5*R*)-*trans*-3-ethyl-5-methylpyrazolidine by the procedure described above in the racemic series, except that in this case the reaction was allowed to proceed for 9 days 18 h to ensure complete reaction. The workup was also carried out as described above up to the distillation of the final work-up solution. Here the pressure was reduced to the point where the boiling point of ethanol was roughly 30 °C; ethanol was distilled off under these conditions until VPC analysis (column F, 100 °C, 75 ml/min) showed the solution remaining in the pot to be roughly 30% pyrazolidine and 70% ethanol. This mixture was then vacuum transferred at 0.02 mm and the resulting solution used directly in the oxidation step.

A 100-mL flask was next fitted with a magnetic stirring bar and an addition funnel protected with a drying tube. The flask was charged with 5.97 g (2.75 mmol) of red mercuric oxide and 3.9 g of anhydrous Na_2SO_4 (2.74 mmol) in 27 mL of reagent grade pentane. The flask was cooled to 0 °C and, with rapid stirring, the above pyrazolidine–ethanol solution (theoretically 1.31 mmol of pyrazolidine) was added dropwise over 5 min. The mercuric oxide quickly blackened as the pyrazolidine was added. The reaction was allowed to stir for an additional 30 min at 0 °C.

The reaction mixture was then filtered and the solid residue triturated twice with pentane. Most of the pentane was then distilled off at atmosphere pressure through a 20-cm Vigreux column, and the pure pyrazoline was isolated from the remaining solution by preparative VPC (column F, 100 °C, 75 mL/min) in an overall yield of 31.9% based on **21**. The following optical rotations were obtained for this material (*c* 0.019 in *n*-heptane): $[\alpha]^{25}_D$ +140.5°, $[\alpha]^{25}_{436}$ +331°; $[\alpha]^{25}_{365}$ +763°. Based on the 38.4% optical purity of (−)-(*R*)-**19**, this suggests that for (+)-(3*R*,5*R*)-**15t**, $[\alpha]^{25}_D$ max +366°. NMR analysis showed no detectable contamination of this material with the *cis*-pyrazoline isomer.

(+)-(3*R*,5*S*)-*cis*-3-Ethyl-5-methyl-1-pyrazoline (15c). The synthetic and work-up procedures used were the same as for **15t**. however, 1.83 g (7.5 mmol) of the dibromide diastereomer (−)-(2*R*,4*S*)-**21**, 97.9% VPC pure, was available. (−)-(2*R*,4*S*)-**21** was contaminated with 2.1% of the 2*S*,4*S* dibromide diastereomer. In this case the reaction was allowed to proceed for 8 days and 13 h.

After oxidation, 120 mg of the pyrazoline (97.9% cis, 2.1% trans) was isolated by preparative VPC, column C (100 °C, 75 ml/min). Spectra correlate with those of racemic **15c**: IR 3010, 2970, 2920, 1520, 1470, 1375, 1285, 1210, 1150, 1043, 960, and 923 cm^{-1}; NMR (CCl_4) δ 0.30–0.85 (d of t, *J* = 12.5 and 9.0 Hz, 1 H, 1 C(4)H), 1.07 (t, *J* = 7.0 Hz, 3 H, $-CH_2CH_3$), 1.53 (d, *J* = 7.0 Hz, 3 H, $-CH_3$), 1.65–2.30 (m, 3 H, $-CH_2CH_3$, 1 C(4)H), 4.12 (seven-line pattern, 2 H, >CH–); optical rotations (*c* 0.0098 g in 1 mL of *n*-heptane) $[\alpha]^{25}_{589}$ +3.4°, $[\alpha]^{25}_{578}$ +4.4°, $[\alpha]^{25}_{546}$ +5.3°, $[\alpha]^{25}_{436}$ +22°, $[\alpha]^{25}_{365}$ +106°. Anal. Calcd for $C_6H_{12}N_2$: C, 64.29; H, 10.71; N, 25.00. Found: C, 64.09; H, 10.84; N, 24.51.

III. Synthesis of Optically Active Deuterated Pyrazoline. 1-Hexen-4-one. Jones reagent was prepared by mixing 150 g of CrO_3 with 200 mL of water at 0 °C in a 500-mL Erlenmeyer flask. Then 131 mL of concentrated H_2SO_4 was slowly added, followed by addition of 400 mL of water; this solution was maintained at 5 °C. Into a 2-L, three-necked flask equipped with magnetic stirrer, thermometer, 500-mL addition funnel, and 0 °C cooling bath was placed 120 g (1.20 mol) of **19** in 600 mL of acetone. The precooled Jones reagent was added dropwise at such a rate as to maintain the reaction temperature at less than 20 °C. The reaction was stirred for 4 h at 5 °C after addition was complete.

After warming to room temperature, the reaction mixture was decanted from the chromium salts and diluted with 1 L of saturated aqueous NaCl solution. The aqueous phase was separated and washed four times with a total of 850 mL of pentane, which was combined with the organic phase. The organic phase was washed with cold, saturated aqueous $NaHCO_3$, which in turn was extracted with pentane. The combined organics were washed quickly with a saturated NaCl solution and dried over Na_2SO_4.

Most of the pentane was distilled off through a Vigreux column with the pot maintained at 45 °C. The product was distilled at 48–50 °C (30 mm) to yield 48 g of ketone (40.0% yield): IR 3090, 2990, 2920, 2890, 1720, 1640, 1475, 1430, 1415, 1385, 1355, 1145, 1110, 1050, 1030, 995, and 925 cm^{-1}; NMR (CCl_4) δ 1.01 (t, 3 H, *J* = 7.5 Hz, $-CH_2CH_3$), 2.36 (q, *J* ≃ 7.5 Hz, 2 H, $-CH_2CH_3$), 3.06 (d, *J* = 7.0 Hz, 2 H, CH_2=CHCH_2–), 4.8–5.25 (m, 2 H, CH_2=C–), 5.6–6.25 (m, 1 H, CH_2=CH–).

1-Hexen-4-ol-*4-d* (19-d_1). Into a 1-L, three-necked flask fitted with a mechanical stirrer, 500-mL addition funnel, water condenser, and N_2 inlet were placed 5.0 g (0.119 mol) of lithium aluminum tetradeuteride (Stohler Isotope Chemicals 99% D) and 250 mL of anhydrous ethyl ether. The flask was cooled to −20 °C and 37 g (0.37 mol) of 1-hexen-4-one in 300 mL of anhydrous diethyl ether was added dropwise with stirring. After the addition was complete, the reaction was stirred at −20 °C for 1 h and then warmed to 0 °C. An additional 100 mL of diethyl ether was added, followed by the cautious, dropwise addition of 5 mL of water over the course of 1 h. Then 5 mL of a 15% NaOH–water solution was added, followed by the dropwise addition of 15 mL of water.

The fine, white aluminum salts were filtered off, washed with ethyl ether, and the combined organic phase was dried over $MgSO_4$. The ether was slowly distilled off through a 12-in. Vigreux column. The product was fractionated through a 6-cm Vigreux, yielding 32 g of **19-d_1** (85.0% yield, bp 62 °C (50 mm)): mass spectral analysis showed the alcohol to be 87.3% deuterated; IR 3570, 3400 (br), 2960, 2920, 2880, 2100, 1665, 1640, 1460, 1440, 1000, and 920 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, *J* = 6.5 Hz, 3 H, $-CH_2CH_3$), 1.43 (t, 2 H, CH_2CH_3), 1.90 (s, 1 H, –O*H*), 1.97–2.36 (m, 2 H, allylic CH_2), 5.4–6.2 (m, 1 H, vinyl CH).

Resolution and Recovery of 1-Hexen-4-ol-*4-d*. The procedure used was the same as that described above for resolution and recovery of unlabeled 4-hexen-1-ol (**19**).

A. 1-Hexen-4-yl Phthalate Half Ester. Racemic alcohol (32 g, 0.32 mol) and 46.7 g (0.32 mol) of phthalic anhydride gave 59 g (0.24 mol) of phthalate. Despite various attempts, the oily material could not be induced to crystallize: NMR ($CDCl_3$) δ 0.97 (t, *J* = 6.5 Hz, 3 H), 1.72 (q, *J* = 6.5 Hz, 2 H), 2.45 (d, *J* = 6.0 Hz, 2 H), 4.90–5.40 (m, 2 H), 5.40–6.40 (m, 1 H), 7.30–8.05 (m, 4 H), 11.70 (s, 1 H).

B. Brucine Salt Formation and Recrystallization. Brucine (93.5 g,

Table V. Specific Rotations at Two Wavelengths of 1-Ethyl-2-methylcyclopropane Pyrolysis Products

Precursor	λ, nm	**16t**, g/mL, *n*-hexane	$[\alpha]^{25}_{\lambda}$, deg	**16c**, g/mL, *n*-heptane	$[\alpha]^{25}_{\lambda}$, deg
(+)-**15t**	589	0.061	+3.2	0.184	+0.06
	365		+9.29		+0.18
(+)-**15c**	589	0.0136	+2.0	0.0056	+2.9
	365		+5.7		+7.9
(+)-**15c-*d*$_1$**	589	0.0159	+2.6	0.0133	+2.3
	365		+7.1		+6.6
(+)-**15t-*d*$_1$**	589	0.0035	+2.8	0.0155	+0.2
	365		+10.0		+0.2

0.24 mol) was reacted with 59 g (0.24 mol) of phthalate. Recrystallizations (11) of the resulting salt from ethyl acetate accomplished the desired resolution.

C. Brucine salt decomposition was performed on 64 g of the brucine salt by reaction with concentrated hydrogen chloride, recovering 25.0 g (0.10 mol) of the half ester.

D. Saponification was accomplished with aqueous sodium hydroxide. After steam distillation and drying, 7.5 g (0.075 mol) of active labeled alcohol was isolated. The following observed rotations were obtained on the neat alcohol: α_{589} −0.166°; α_{546} −0.213°; α_{436} − 0.728°; α_{365} −1.840°. Comparing these values with those obtained on the nondeuterated alcohol, the material is 39.5% optically pure. The polarimetric determination was checked by making the esters of **19** and **19-*d*$_1$** with α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl)[16] and integration of the NMR absorbances of the diastereomeric CF_3 groups. This technique showed **19-*d*$_1$** to be 40 ± 1% optically pure. Comparison of the ^{19}F NMR and polarimetric results confirms that α_{max} for **19** and **19-*d*$_1$** are virtually identical.

MTPA Ester Formation. The procedure of Mosher[16] was followed. In a typical procedure, 4 drops of alcohol, 6 drops of MTPA-Cl, 10 drops of CCl_4, and 10 drops of pyridine were stirred for 12 h in a 5-mL, single-necked flask equipped with a drying tube. Water (1 mL) was added to the reaction mixture and the solution was extracted with diethyl ether, washed with aqueous 0.1 N HCl, 1 N NaOH, and saturated Na_2CO_3 solutions, and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the ester was dissolved in $CDCl_3$ for the NMR spectra.

(+)-(3*R*,5*R*)-*trans*-3-Ethyl-5-methyl-1-pyrazoline-*3-d* (15t-*d*$_1$). The procedure described above for racemic, unlabeled material was used to convert a sample of 3.15 g (0.013 mol) of >99.99% VPC pure, C(3)-deuterated (+)-(2*S*,4*S*)-**21** to pyrazolidine. Then, into a 100-mL single-necked flask, equipped with magnetic stirrer and addition funnel with drying tube, was placed 5.97 g (0.028 mol) of red mercuric oxide, 3.9 g (0.028 mol) of anhydrous sodium sulfate powder, and 27 mL of olefin-free, P_2O_5-distilled pentane. The flask was cooled to 0 °C and the pyrazolidine solution was added dropwise over the course of 5 min. The solution immediately turned black (elemental mercury is formed). The reaction was stirred for an additional 1 h at 0 °C.

After warming to room temperature, the pentane was decanted off and the residue was thoroughly washed with pentane. The pentane solutions were combined and most of the solvent was distilled off through a 20-cm Vigreux column, keeping the pot temperature at <45 °C.

The pure pyrazoline (180 mg) was isolated by preparative VPC, column N (100 °C, 75 ml/min): IR 2970, 2940, 2870, 1710, 1545, 1460, 1375, 1285, 1250, 1210, 1150, 1130, 1055, 1000, 970, and 895 cm^{-1}; NMR (CCl_4) δ 0.85–2.20 (m, 4 H), 1.01 (t, *J* = 7.0 Hz, 3 H, $-CH_2CH_3$), 1.34 (d, *J* = 7.0 Hz, 3 H, $-CH_3$), 4.52 (six-line pattern, 1 H, >C*H*–); optical rotations (*c* 0.0125 g in *n*-heptane) $[\alpha]^{25}_{D}$ +145°, $[\alpha]^{25}_{578}$ +151°, $[\alpha]^{25}_{546}$ +175°, $[\alpha]^{25}_{436}$ +340°, $[\alpha]^{25}_{365}$ +787°; high resolution mass spectrum, calcd for P − 28 peak: 85.100173; obsd: 85.1004.

(+)-(3*R*,5*S*)-*cis*-3-Ethyl-5-methyl-1-pyrazoline-*3-d* ((+)-15c-*d*$_1$). The synthetic and work-up procedures used were the same as for **15t**. However, only 1.67 g (6.8 mmol) of (−)-(2*R*,4*S*)-**21**, 99.15% VPC pure, was available. The dibromide was contaminated with 0.85% of its opposite diastereomer. Here the reaction was allowed to proceed for 8 days and 21 h.

After oxidation, 125 mg of 1-pyrazoline (99.15% cis, 0.85% trans) was isolated by preparative VPC, column N (100 °C, 75 ml/min): IR 2965, 2915, 2870, 1558, 1458, 1372, 1326, 1247, 1200, 1100, 1055, 1000, 970, and 898 cm^{-1}; NMR (CCl_4) δ 0.37–0.87 (br d of d, *J* = 12.5 and 9.0 Hz, 1 H, 1 C(4)H), 1.08 (t, *J* = 7.0 Hz, 3 H, $-CH_2CH_3$), 1.53 (d, *J* = 7.0 Hz, 3 H, $-CH_3$), 1.62–2.30 (m, 3 H, $-CH_2CH_3$ and C(4)H), 4.12 (six-line pattern, 1 H, >C*H*–); optical rotations (*c* 0.0060 g in 1 mL of *n*-heptane) $[\alpha]^{25}_{589}$ +3.6°, $[\alpha]^{25}_{578}$ +4.5°, $[\alpha]^{25}_{546}$ +5.6°, $[\alpha]^{25}_{436}$ +25°, $[\alpha]^{25}_{365}$ +108°; high resolution mass spectrum, calcd on P − 28 peak: 85.100173; obsd: 85.1005.

(+)-(3*S*)-3-Bromohexane (23). To 200 mg (2 mmol) of 8.2% optically pure (−)-(3*R*)-3-hexanol (**22**) and 5 mL of pyridine in a 10-mL Erlenmeyer flask was added 420 mg (2.2 mmol) of *p*-toluenesulfonyl chloride (recrystallized from diethyl ether) at 0 °C. The flask was placed in a refrigerator; after 2 days needle-like white crystals of pyridine hydrochloride had come out of solution, and the reaction mixture developed a slight yellow tinge.

The solution was poured into 30 mL of an ice–water mixture and was stirred for 15 min. A white oil settled out of solution and was taken up in 100 mL of diethyl ether. The ether layer was washed with aqueous HCl, followed by water, and was dried over Na_2SO_4. The ether was removed by rotary evaporation and 100 mg of the white oily tosylate was recovered.

The tosylate (0.4 mmol) was taken up in 100 mg of spectroquality acetone in a screw-cap vial. LiBr (42 mg, 0.5 mmol) in 300 mg of acetone was added. After 30 min lithium tosylate precipitated from solution. After 1 h total reaction time, 18.6 mg of 3-bromohexane was preparatively separated from the reaction mixture by VPC, column M (90 °C, flow 80 ml/min): NMR δ 0.85–1.25 (overlapping t, 6 H, $-CH_2CH_3$), 1.30–2.20 (m, 6 H, CH_2–), 3.90 (pentet, *J* = 6.5 Hz, 1 H, BrC*H*<); optical rotations (*c* 0.0186 g in $CHCl_3$) $[\alpha]^{25}_{589}$ +1.1°, $[\alpha]^{25}_{436}$ +1.5°, $[\alpha]^{25}_{365}$ +2.4°.

Partial Reduction of (+)-(2*S*,4*S*)-2,4-Dibromohexanes (21). To 100 mg (0.41 mmol) of optically active (+)-(2*S*,4*S*)-**21**, VPC pure, and 1 mL of 2,6,10,14-tetramethylpentadecane in a 5-mL, single-necked flask at 0 °C was added dropwise 500 mg (2.8 mmol) of tri-*n*-butyltin hydride. The addition was monitored by VPC and terminated when the monobromide attained a maximum value relative to unreduced **21** and completely reduced hexane.

The bromide mixture was vacuum transferred at 0.02 mm and purified by preparative VPC, column M (100 °C, 75 ml/min). The composition of the monobromohexane mixture (**23** + **24**) was determined to be 58% 3-bromohexane, 42% 2-bromohexane by analytical VPC, column P (65 °C, 30 ml/min). Relative FID sensitivities of 2-bromohexane–3-bromohexane = 1.44/1.00 were determined by integration of authenic samples using the same VPC conditions: observed optical rotations (0.0123 g in 1 mL of $CHCl_3$) $[\alpha]^{25}_{589}$ +0.110°, $[\alpha]^{25}_{578}$ +0.113°, $[\alpha]^{25}_{546}$ +0.133°, $[\alpha]^{25}_{436}$ +0.226°, $[\alpha]^{25}_{365}$ +0.354°.

Partial Reduction of (−)-(2*R*,4*S*)-2,4-Dibromohexane. (−)-(2*R*,4*S*)-2,4-Dibromohexane was partially reduced by the same procedure as for the (+)-(2*S*,4*S*) diastereomer. The monobromohexane mixture was purified and determined to contain 58% 3-bromohexane and 42% 2-bromohexane in the same manner as for the (+)-(2*S*,4*S*) diastereomer: optical rotations (0.0149 g in 1 mL of $CHCl_3$) $[\alpha]^{25}_{589}$ −0.060°, $[\alpha]^{25}_{578}$ −0.069°, $[\alpha]^{25}_{546}$ −0.081°, $[\alpha]^{25}_{436}$ −0.131°, $[\alpha]^{25}_{365}$ −0.215°.

Pyrolyses. Injection Port Pyrolyses. Pyrazoline pyrolyses used to determine product distributions were carried out in the injection port (glass-lined) of a Hewlett-Packard 5750 research vapor-phase chromatograph equipped with a flame ionization detector and a Spectra Physics, Autolabs System I computing integrator. The injection block was packed outside the glass liner with glass wool to maintain temperature stability. Product analyses were performed on column Q (25

°C, 10 ml/min). Satisfactory peak separation was attained with the exception of the separation of *cis*-3-hexene from the *cis*-cyclopropane. However, since the hexene accounts for less than 1% of the products, negligible error was introduced by this problem.

Injection of authentic samples of the reaction products demonstrated that no product interconversion occurred on the column or injection port. The pyrazolines were injected as 10% solutions in *n*-octane. Injection of the pyrazoline at an inlet port temperature of 100 °C showed that no pyrazoline decomposition to reaction products occurred by catalytic process on the VPC column. Pyrolyses were performed at least three times at a given temperature with reproducibility within 1%.

Flow Pyrolyses. Preparative scale flow pyrolyses were carried out utilizing a quartz tube flow system contained in a Hoskins tube furnace. Auxiliary heating wires, wrapped with asbestos tape, prevented sample condensation in the flow system at both the inlet and outlet sides. The pyrolysis products were collected in a double U-tube trap filled with Pyrex helices. The first trap was maintained at −78 °C and the second trap was maintained at −196 °C. Drying towers attached to the traps prevented any condensation of moisture in the traps. The temperature of the quartz tube was monitored by an iron-constantan thermocouple. The neat pyrazoline was introduced into the pyrolysis zone by a flow of helium (60 ml/min).

In a typical pyrolysis, ~100 mg of VPC purified pyrazoline was carried through the reaction zone over the course of 3 h. The pyrolysis products were vacuum transferred from the collection traps. VPC analysis on column N (100 °C, 75 ml/min) showed no unreacted pyrazoline. The *cis*- and *trans*-methylethylcyclopropanes were separated and purified by preparative VPC using column Q (60 °C, 65 ml/min). Specific rotations of these cyclopropanes, obtained from pyrazolines having optical purity levels described above, are given in Table V.

Acknowledgment. We are grateful to the National Science Foundation (Grant No. CHE-74-14711-A02), Chevron Research Corporation, Alfred P. Sloan Foundation, and Camille and Henry Dreyfus Foundation for financial support of this work, and to Professor Peter B. Dervan for helpful discussions.

References and Notes

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