The labeling of alternate aromatic carbons would be in accord with a phloroglucinol pathway, but this was eliminated in earlier studies.[4] This labeling would also be in accord with a shikimate-type pathway provided, at some stage in the biosynthesis, a symmetrical intermediate is produced. Thus, C-1 of shikimate or a related precursor would become C-6a and C-7a of a nybomycin precursor such as **5** (cf. Figure 1). Furthermore, since C-6 of glucose is distributed between C-2 and C-6 of shikimate in about equal amounts,[12] enrichments at C-7, C-11a, and C-12a of nybomycin should be in the approximate ratio 2:1:1; this is roughly observed (3:1:1) in the enrichment factors ($I_e/I_u - 1$) from peak intensity data (Table I). Since determination of carbon peak intensities is less than quantitative[13] the data at least qualitatively support the proposed route.

Additional evidence for a shikimate-type biosynthetic pathway was obtained by administering sodium [2-^{13}C]pyruvate (90 atom %, 1.0 g in 900 ml)[14] to producing cultures of *Streptomyces sp.* D-57. The nybomycin butyrate derived from this feeding was highly labeled (Table II); the ^{13}C NMR spectrum indicated very high enrichment (>5 times natural abundance) in eight carbon atoms (Table I).[15] Only two of the central aromatic carbons of **3**, C-6a and C-7a, were highly enriched and in about equal amounts. As a consequence of the high enrichment levels, resonances at C-6a and C-7a were each split into a doublet of triplets ($^1J_{CC}$ = 54 Hz, $^3J_{CC}$ = 4 Hz) by virtue of direct coupling ($^1J_{CC}$) to C-6 and C-8, respectively, and long range coupling ($^3J_{CC}$) to two other highly enriched centers (C-4 and C-8 for C-6a; C-6 and C-10 for C-7a). Magnitudes of J_{CC} and coupling patterns observed ($^3J_{CC} > {}^2J_{CC}$) are in accord with established couplings for related aromatic systems.[16]

The above labeling pattern is completely consistent with the proposed biosynthetic scheme (Figure 1). The high level of incorporation at C-6a and C-7a follows directly from conversion of C-2 of pyruvate via phosphoenolpyruvate to the carboxyl bearing carbon (C-1) of shikimate[12] or a related, possibly symmetrical, precursor **4**.[17] Although labeling patterns from both feeding experiments support the intermediacy of a symmetrical intermediate in nybomycin biosynthesis they do not establish at what stage the proposed intermediate becomes symmetrical, i.e., whether the symmetrical intermediate is monocyclic (**4**) or tricyclic (e.g., **5**). Experiments to characterize intermediates are in progress.

Finally, labeling of carbons outside the central ring in both precursor feeding experiments may be rationalized via known biochemical pathways existing in most microorganisms[20] and from results of previous biosynthetic studies on nybomycin. Thus, D-[6-^{13}C]glucose and sodium [2-^{13}C]pyruvate are metabolized to acetate (labeled at C-2 and C-1, respectively), which supplies the outer carbons of each pyridone ring. Both precursors label the anticipated carbons (Table II). Enhancements at C-2 and C-11′ arise from channeling the appropriate labeled carbons of glucose and pyruvate into the "one carbon" metabolic pool, which is readily accomplished through serine metabolism.[21]

Acknowledgment. This work was supported by Public Health Service Grants AI 01278 and AI 04769 from the National Institute of Allergy and Infectious Diseases. The ^{13}C Fourier transform NMR spectra and mass spectra were obtained on instruments purchased, in part, with grants from the National Science Foundation, the National Cancer Institute (CA 11388), and the National Institute of General Medical Sciences (GM 16864). We thank Mr. Stephen Silber for the ^{13}C NMR spectra, Mr. Joseph Wrona for the isotope ratio mass spectra, The Upjohn Company for a soil stock of *Streptomyces sp.* D-57 and a sample of nybomycin, and Dr. Masao Taniguchi for a sample of D-[6-^{13}C]glucose.

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2,6-Substituted Homotropilidenes. Influence of Substituents on Valence Topomerization

Sir:

The Cope rearrangement which involves a bond breaking of one σ bond and the formation of another is one of the best studied reactions.[1] Nevertheless, different opinions exist about

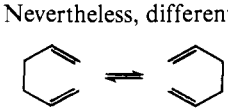


Table I. Kinetic Data of Valence Isomerization in Bridged and Nonbridged Homotropilidenes

R	$\Delta H_{298}^{\ddagger}$ (kcal/mol)	$\Delta S_{298}^{\ddagger}$ (eu)	$\Delta G_{298}^{\ddagger}$ (kcal/mol)	$\Delta G_T^{\ddagger}$	k (s^{-1})	Ref
1 (a) H	12.3 ± 0.3	−5.9 ± 0.5	14.1 ± 0.1	14.45[a]	8 394[a]	7
(b) *m*-$CF_3C_6H_4$	14.7 ± 0.4	−5.9 ± 0.6	16.5 ± 0.1	16.8[a]	640[a]	This work
(c) C_6H_5	14.5 ± 0.3	−6.8 ± 0.5	16.5 ± 0.1	16.9[a]	550[a]	This work
(d) *p*-$N(CH_3)_2C_6H_4$	17.9 ± 0.5	2.1 ± 1.0	17.3 ± 0.1	17.2[a]	350[a]	This work
(e) CH_3	18.2 ± 0.5	0.7 ± 0.8	18.0 ± 0.1	18.0[a]	130[a]	This work
2 (a) H	8.0 ± 0.2	1.6 ± 1.0	7.6 ± 0.1	7.8[b]	20 000[b]	8
(b) C_6H_5	6.8 ± 0.3	−8.3 ± 1.2	9.3 ± 0.1	8.3[b]	7 000[b]	This work
(c) CH_3[c]			9.5 ± 0.5	8.8[b]	1 800[b]	This work
3 CH_3			13.8 ± 0.2[d]			8, 9
			14.9 ± 0.2[d]			
4 CH_3			13.6			11

[a] At 353 K. [b] At 206 K. [c] Preliminary results of **2c** in a mixture of undesired synthetic side products. [d] The methyl group prefers the 3-positon by 1.1 kcal/mol.

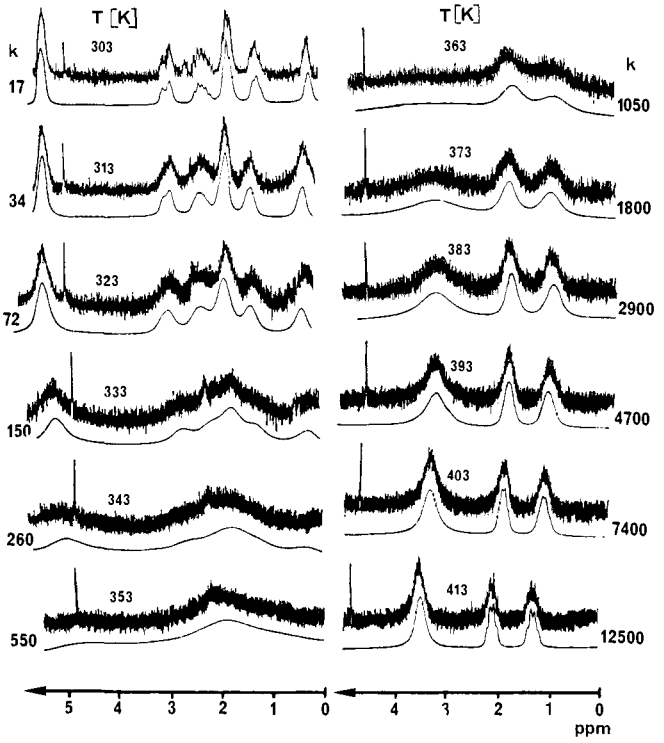


Figure 1. Observed and calculated line shapes of **1c** in $C_2D_2Cl_4$.

the temporal succession of bond breaking and bond formation. Three extreme cases (A–C) of transition states which differ

initial step: bond breaking "synchronous" bond formation
A B C

in the initial step are possible. It is reasonable to assume that the transition state depends on the structure and substitution of the hexadiene system. Whereas the rearrangement of that system was considered as the classical example for a synchronous reaction, recent studies of the influence of phenyl groups on the barriers of rearrangement have shown[2] that the transition state of 1,5-hexadiene is very similar to C. In contrast homotropilidene should represent the extreme case for a rearrangement involving a transition state like A because (a) bond breaking as the initial step parallels with the relief of strain of the cyclopropane ring (transition state D or E), and (b) bond formation leads to a second strained three-membered ring (transition state F).

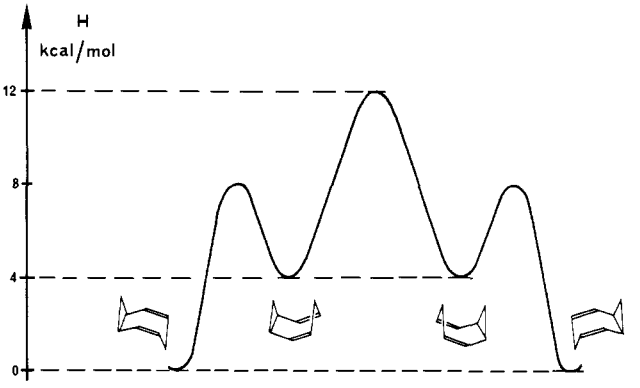
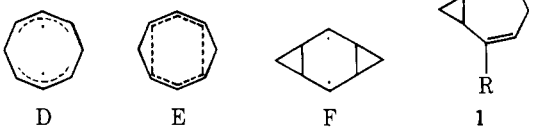


Figure 2. Energy profile of valence isomerization of homotropilidenes.



D E F **1**

To support this assumption we synthesized 2,6-disubstituted homotropilidenes **1**[3,4] and studied their rearrangements by ^1H NMR spectroscopy. The complete line shape analysis of the $ABC_2 \rightleftarrows DEF_2$ exchange was performed by Binsch's DNMR 3 program.[5,6] An example is shown in Figure 1. The evaluation of the kinetic data using the Eyring equation led to the data of Table I.

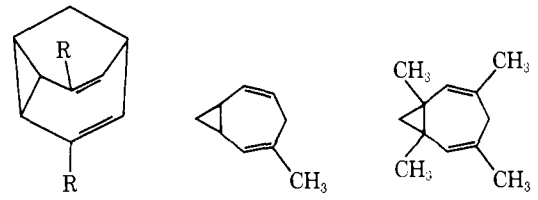
The values of $\Delta S^{\ddagger}$ are about −5 to −7 eu in cases of best accuracy. The line shape analysis of **1d** and **1e** was complicated by the superposition of the nonexchanging signals of the methyl groups with the exchange broadened signals. Therefore we think that these values are less certain although the regression analysis gives satisfying results. Consequently we prefer to discuss the relative rates at one temperature of a certain class of compounds (see table).

The results show that substitution in the 2,6 position by methyl or aryl decreases the rates of rearrangement. The interpretation of the barrier is complicated by the fact that the valence isomerization of homotropilidene occurs through the "boat"-conformation[10] (Figure 2). This is also proved in the 2,6-disubstituted compounds **1b–e** by the exchange scheme.

The increase in the barrier could be interpreted as an effect of electron donating groups (such as methyl[12] or phenyl) on the basis of the increase in electron density in the transition state (calculated by MINDO/2 for barbaralane[13]). The small, but in our opinion significant, rate decrease from **1b** to **1d**

(decrease of the Hammett σ-constants) tends in the same direction. Nevertheless, the steric effect of substituents in 2,6-position destabilizes the homotropilidene-"boat" conformation which would result in the same substituent effect. Indeed force field calculations show that the energy of the "boat"-conformation of a **1a** (R = H) is about 4 ± 2 kcal/mol higher in energy than the "chair"-conformation, but this difference increases to about 8 ± 2 kcal/mol in **1c** (R = C_6H_5) and **1e** (R = CH_3).[14] The boat-like conformation of the transition state should cause a similar increase in energy comparing **1a, 1c,** and **1e.**

To prove this, we have prepared[15] the phenyl-substituted barbaralane **2b** starting from triasteranedione[16] and analyzed the rearrangement by means of ^1H NMR spectroscopy.[17]



2 3 4

Phenyl groups in the 2,6-position of **2** destabilize the transition state (Table I), but the effect is smaller compared to the couple **1a/1c.** This difference could be interpreted as the steric destabilization effect on the transition state of **1,** but generally the retarding effect of 2,6-substitution in **1** and **2** is quite different from the observation of Dewar et al. in substituted 1,5-hexadienes[2] and provides evidence that in (bridged) homotropilidenes the transition state is like D or E.

In this connection it is interesting to compare the barriers of **3** and **4** with **1a.** The steric destabilization should operate in **3** and **4** in the same manner like in **1e.** Consequently the net effect of zero in influencing the transition state should be a result of an electronic stabilization effect in the 1,3,5,7 position. This gives evidence that the character of the transition state is more allylic (D) than synchronous (E). Thus the investigation of (bridged) homotropilidenes opens the opportunity to study the substituent effect on the initial bond breaking type of the Cope rearrangement.

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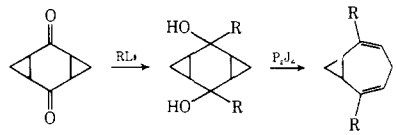

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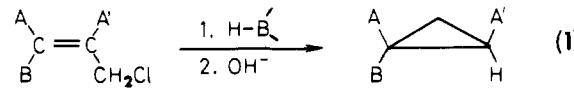
On the Stereochemistry of Conversion of Allylic Halides to Cyclopropanes via γ-Haloalkylboranes

Sir:

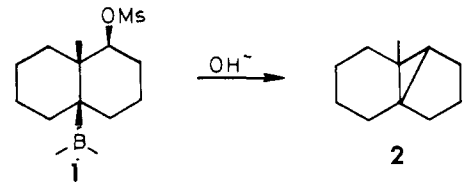
We wish to report that conversion of allylic halides to cyclopropanes by hydroboration followed by base-promoted cyclization[1-4] (1,3-elimination) of the intermediate γ-chloroborane is stereospecific. The relative locations of substituents in reactant and product are illustrated by eq 1.



(1)

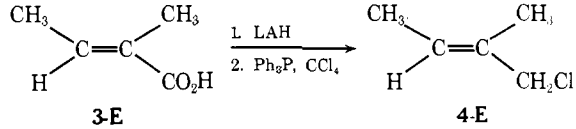
This two-step transformation was first reported by Hawthorne and Dupont[1] and has been the subject of several subsequent investigations.[1-4] A major improvement involves hydroboration with 9-borabicyclo[3.2.1]nonane (**9-BBN**).[3] This leads to increased regioselectivity in the desired direction and formation of a γ-chloroborane structurally predisposed to undergo base-promoted cyclization.[3,4]

In an earlier stereochemical investigation Marshall and Bundy[5] observed that the bicycloborane methane sulfonate (**1**) undergoes cyclization to give the tricyclic hydrocarbon (**2**) and noted that the 1,3-elimination involves inversion of both reaction centers. However, this is a biased system; cyclization with retention of configuration at either center leads to a highly strained product and is thus precluded from the outset.



1 2

In this study we have converted the isomeric 1-chloro-2-methyl-2-butenes (**4**) to 1,2-dimethylcyclopropane. (*E*)-1-Chloro-2-methyl-2-butene (**4-*E***)[6] was derived from (*E*)-2-methyl-2-butanoic (tiglic) acid (**3-*E***) (Aldrich Chemical), or tiglaldehyde (Eastman Organic Chemicals) by reduction to (*E*)-2-methyl-2-buten-1-ol[6] with lithium aluminum hydride followed by conversion to **4-*E*** with triphenylphosphine and carbon tetrachloride.[7] Both configuration and location of the double bond were fully preserved, e.g., **3-*E*** (>99.9% *E* isomer)[8,9] gave **4-*E*** without detectable[9] intercontamination by either the geometric or allylic isomer.



3-E 4-E