CATIONIC CYCLIZATION INVOLVING A REMOTE ALLENE FUNCTION IN THE TRIFLUOROETHANOLYSIS OF 5,6-HEPTADIEN-1-YL p-TOLUENESULFONATE

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ABSTRACT

In order to determine whether a remote allene function would undergo intramolecular nucleophilic substitution, 5,6-heptadien-1-yl p-toluenesulfonate (14) was synthesized and solvolyzed. The major products of the trifluoroethanolysis of 14 were the cyclic trifluoroethyl ethers of 2-methylenecyclohexanol (24) and 1-cyclohexenemethanol (25). The minor product was the direct displacement product, 5,6-heptadien-1-yl 2,2,2-trifluoroethyl ether (23). The cyclic triflurorethyl ethers were also obtained from the solvolysis of two arenesulfonate esters of 24 and 25, the alcohols having been synthesized by an independent route. Kinetic data showed a rate enhancement for 14 relative to its saturated analog.

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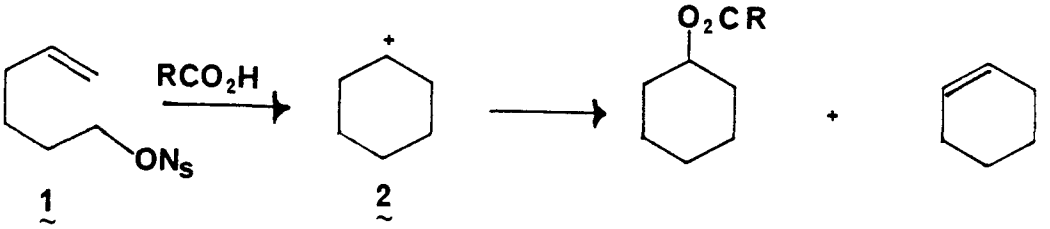
INTRODUCTION

The phenomenon of neighboring group participation in carbonium ion chemistry has been extensively investigated.[1] The extent of interaction of an intramolecular nucleophile with a cationic center is judged mainly on the basis of structural and kinetic evidence. Specifically, in a solvolysis reaction participation is demonstrated by the appearance of cyclized or rearranged products and by rate acceleration relative to appropriate model compounds.[2] These criteria are met in most reactions in which the neighboring group is a carbon-carbon π bond. Olefinic, acetylenic and allenic bonds have all been found to undergo cationic cyclization. Of particular relevance to this study are those systems in which the nucleophile is separated from the ionizing center by several carbons.

The double bond was the first of the π moieties to be investigated as an internal nucleophile. Although most of the emphasis has been directed toward elucidation of homoallyl participation,[3] there are many examples in which the double bond is further removed from the cationic carbon.[4] A classic study of the latter case is the solvolysis of 5-hexenyl arenesulfonate esters. In both the acetolysis[5] and formolysis[6] of p-nitrobenzenesulfonate 1 significant amounts of the products were cyclic (16% and 55% respectively),

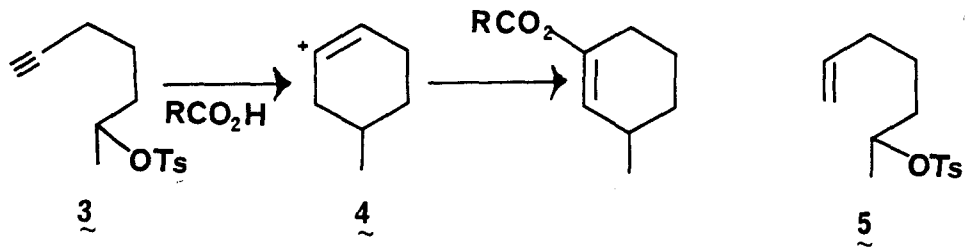


1 2

their immediate precursor the cyclohexyl cation 2. There was minor rate enhancement in each case, the rate observed approximately twice that for the solvolysis of n-hexyl nosylate. Cationic cyclizations of this type are also well knwon in natural products chemistry as they provide the basis

for transformations leading to the biosynthesis of sterols.[7] The synthetic utility of these reactions has been shown as polyolefinic compounds will undergo biomimetic cyclization to form multicyclic products.[8] Cyclic products are also formed when a double bond reacts with a vinyl cation center.[9]

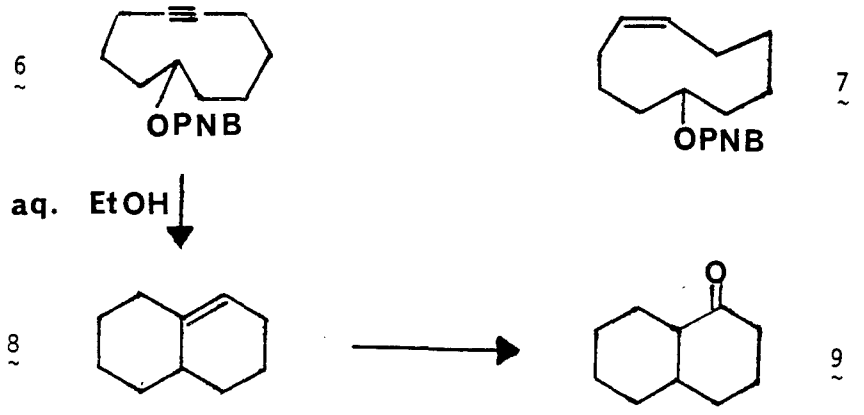
Although not as common as olefinic participation, anchimeric assistance by acetylenic bonds in solvolysis is well documented. The reactions of homopropargyl derivatives were investigated[10,11] before those of compounds with the triple bond more distant from the ionizing center. The results in the latter case are analogous to those seen for olefinic substrates. In the acetolysis, formolysis and trifluoroacetolysis of p-toluenesulfonate 3 Peterson and Kamat found products from cyclic cation 4 in addition to acyclic substitution products.[12]



3 4 5

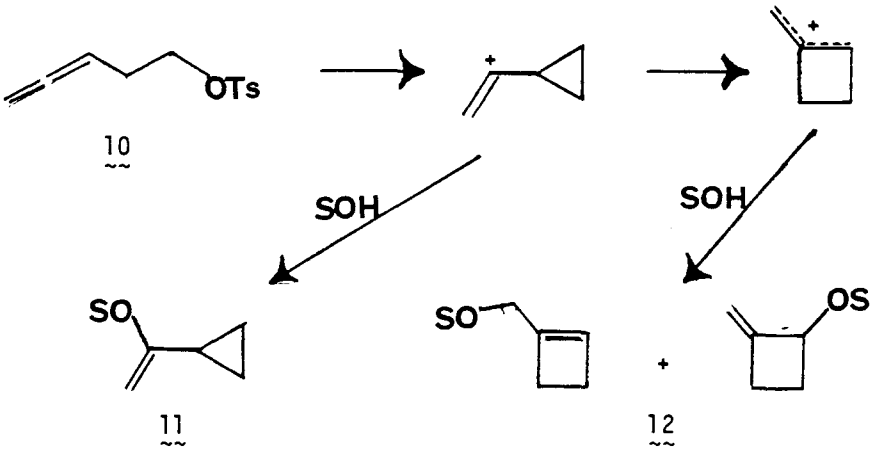
The rate accelerations were modest with the ratio of the rate constant for participation (k_Δ) to that for unassisted solvolysis (k_s) calculated to be 6.5 for the trifluoroacetolysis. Taking into account rate retardation from the inductive effect of the double bond the conclusion was that the triple bond in 3 tended to participate more than the double bond in 5.

A more marked rate acceleration was seen in the solvolysis of cyclodecynyl p-nitrobenzoate 6 in aqueous ethanol, the acetylenic compound reacting twenty times faster than olefinic compound 7.[13] The transannular cyclization to give vinyl cation 8 was the only pathway in evidence. No unrearranged



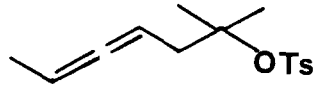
products were formed as 6 yielded decalone 9 exclusively. Acetylenic participation has also been successfully applied to biogenetic polyolefinic cyclizations.[8b,14]

The remaining π moiety to consider as a neighboring group is the allene. In the solvolysis of homoallenyl compounds (e.g., 10) the cyclic products formed are either cyclopropyl (11) or cyclobutyl (12) derivatives.[10,15]



The distribution of products (cyclic as well as acyclic) is largely dependent on the degree of substitution[16] as is the magnitude of rate acceleration.[17]

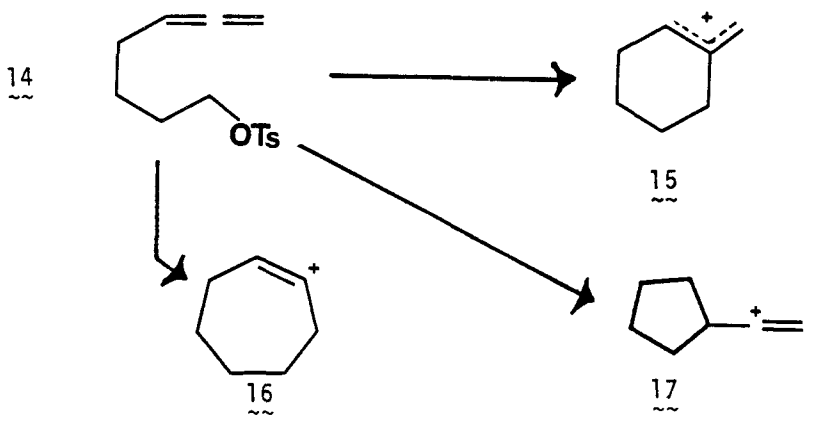
For example, 10 yields cyclopropyl derivatives and has a k_Δ/k_s ratio of 0.9 while tosylate 13 gives only rearranged acyclic products and has

13 

k_Δ/k_s = 5150.[18] Another indication of the effectiveness of the allene function as a nucleophile comes from the comparative rate studies of homoallyl and homoallenyl systems. The finding was that the extent of participation was considerably greater in homoallenyl substrates.[19]

Having seen that olefins and acetylenes participate readily in solvolysis and can generate cyclic products even when the site of unsaturation is far from the incipient cationic carbon, the expectation is that an allene function should exhibit analogous behavior. This expectation is based on the consideration that allenes are reactive generally toward intermolecular electrophiles[20] in addition to being so specifically in homoallenyl systems. The absence of any reports of long range allenyl participation prior to 1972[21] (when the present research was initiated) prompted this investigation of whether cyclization will occur in an appropriate allenic system.

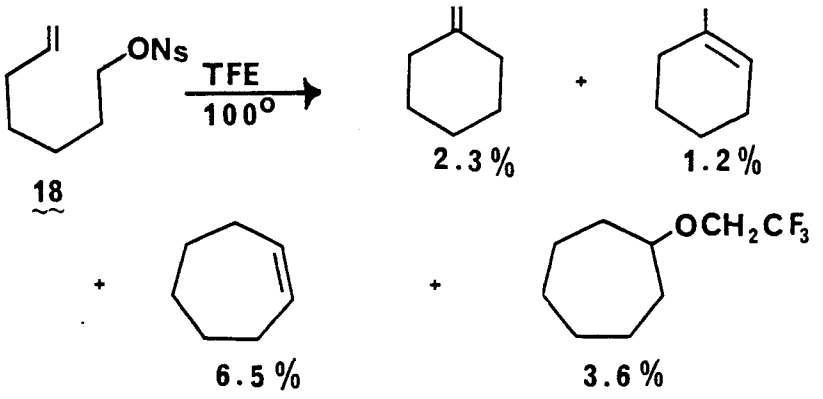
The compound selected for study is heptadienyl tosylate 14 whose structure permits the central carbon of the allene to be in a configuration to assist ionization. Cyclization by this path leads to 15, a relatively strain-free and resonance stabilized cation. Other configurations of the molecule bring the terminal allene carbons in proximity to the ionizing carbon and reaction at these sites generates cations 16[22] and 17. These ions are less likely to be intermediates in the reaction due to the additional strain encountered in forming five- and seven-membered rings.



Trying to invoke the patterns exhibited by allenes in electrophilic addition as a guide to determining the favored cyclization mechanism provides no certain answers because of the complexities of those additions. Allene itself and monosubstituted allenes protonate only at the terminal carbon[23] but react with halogens in the opposite manner.[24] Increasing alkyl substitution generally produces more attack on the central carbon yet substituents that can stabilize an intermediate vinyl cation will favor terminal attack.[25]

Having decided upon a compound that can undergo cyclization it was also necessary to find an appropriate solvent to promote that reaction. The basic requirements are that the solvent be sufficiently polar to facilitate ionization yet weakly nucleophilic so that external nucleophile attack is minimized. In the reactions discussed above there is a strong correlation between increasing amounts of cyclic products and decreasing solvent nucleophilicity. An illustration of this trend is found in thesolvolyses of 3. In the acetolysis of 3, 27% of the products are cyclic while in the tri-

fluoroacetolysis the percentage rises to 91%.[12] Similar findings have been reported in homopropargyl,[11,26] homoallenic,[27] and olefinic[28] systems. It was in the 5-hexenyl system that the efficacy of 2,2,2-trifluoroethanol (TFE) in augmenting cyclizations was first demonstrated. Trifluoroethanolysis of 1 yielded more cyclic material (78%)[29] than had been obtained previously (vide supra). Additionally, cyclization was observed in a reaction where virtually none had been seen before-- the solvolysis of 6-heptenyl nosylate (18).[5,6] The cyclic products formed in the trifluoroethyanolysis of 18



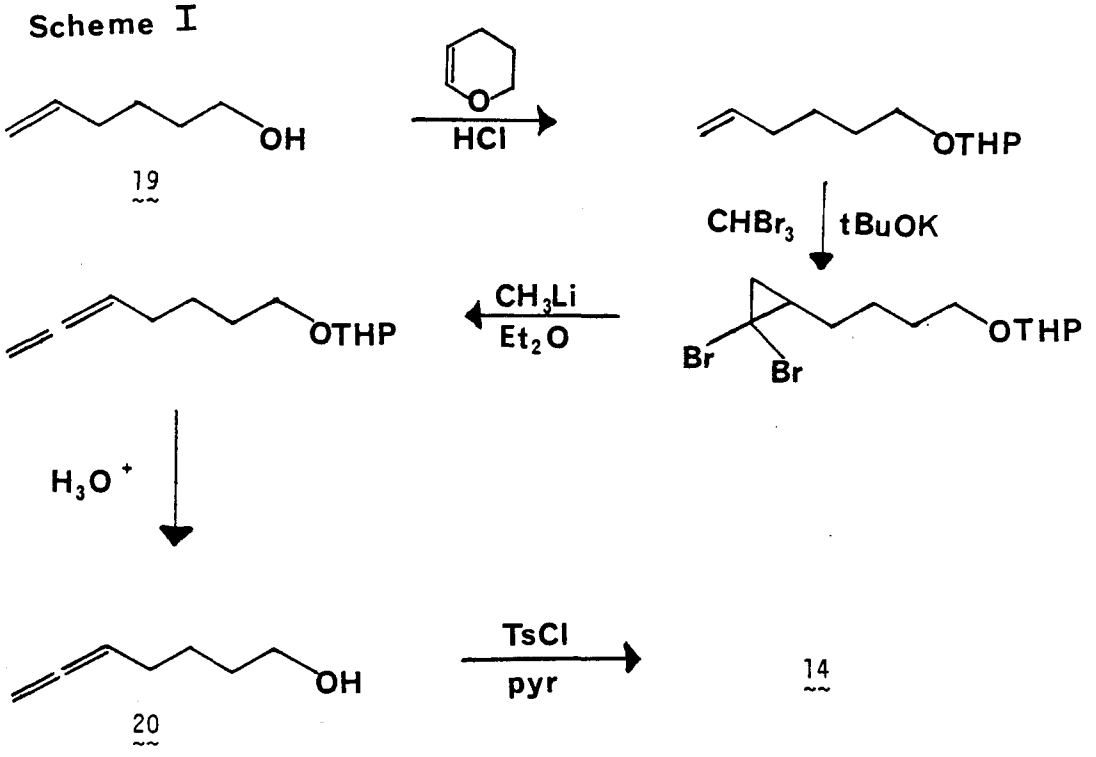
contained both six- and seven-membered rings. Subsequent investigations substantiated the low nucleophilicity of TFE.[30] Another attribute of TFE is that is is not as acidic as other solvents of similar nucleophilicity (e.g., formic acid, trifluoroacetic acid) and the problem of undesirable side reactions is avoided.

The results of the trifluoroethanolysis of 5,6-heptadien-1-yl p-toluenesulfonate are presented in the following sections.

SYNTHESES AND SOLVOLYSES

The synthesis of 5,6-heptadien-1-ol (20) from 5-hexen-1-ol (19) is outlined in Scheme I. The principal transformation was the conversion of the olefin function to an allene by the standard method of dibromocarbene addition followed by alkyllithium reduction.[31] To avoid any complications from the strongly basic conditions that these reactions require it was decided to protect the hydroxyl group of 19. Protection as a tetrahydropy-

Scheme I

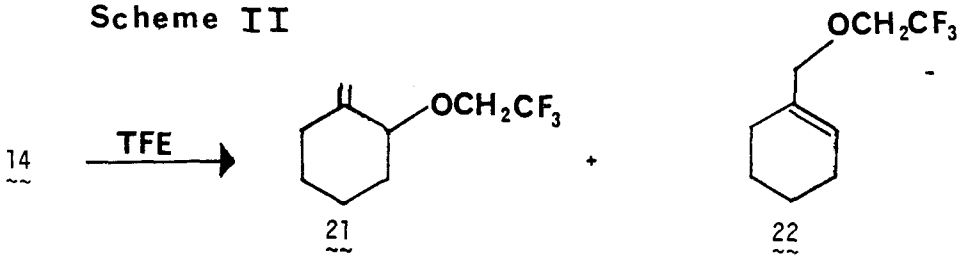


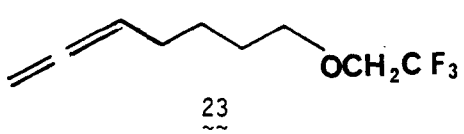
ranyl ether was the choice since these ethers are known to be stable to strong base.[32] The synthetic steps were straightforward and 20 was obtained in 48% yield overall based on 19. A similar procedure has been reported as a general method of synthesizing allenic alcohols.[33] Alcohol 20 was convert-

ed to 14 by conventional means.

Solvolysis of 14 in anhydrous TFE buffered with 2,6-lutidine gave rise to the products shown in Scheme II. At both 60° and 100° the major components were the cyclized trifluoroethyl ethers 21 and 22 and a minor component the allenic ether 23. The product distributions are given in Table I and it is evident that there was no significant difference in product ratios

Scheme II





23

at the two temperatures. The proportions of ethers was also invariant during the course of the reaction as can be seen from the data in Table II. Another minor component found was tentatively identified as an olefin on the basis of vpc retention time and infrared spectrum. It constituted 4.7% of the mixture at 60° and was subsequently shown by others to be the acyclic elimination product 1,2,6-heptatriene.[34]

Trifluoroethyl ethers 21 and 22 were identified by their infrared and NMR spectra. Each had a band in the infrared (1650 and 1665 cm^{-1}, respectively) characteristic of a C=C stretch and absorptions (δ 4.83 and 5.65) in the vinyl region of the NMR. Even though all the resonances were

TABLE I Trifluoroethyl Ether Products Formed in the Trifluoroethanolysis[a] of 5,6-heptadien-1-yl Tosylate (14) at 60° and 100°

Temp.	Reaction time, hr	Products, % 21	22	23	Yield[b]
60°	424	49.0	45.8	5.2	66%
100°	9	47.4	46.8	5.8	59%

[a]Solvolyses buffered with 2 equivalents of 2,6-lutidine. Substrate concentration 0.1M. [b]Determined by vpc using internal standard.

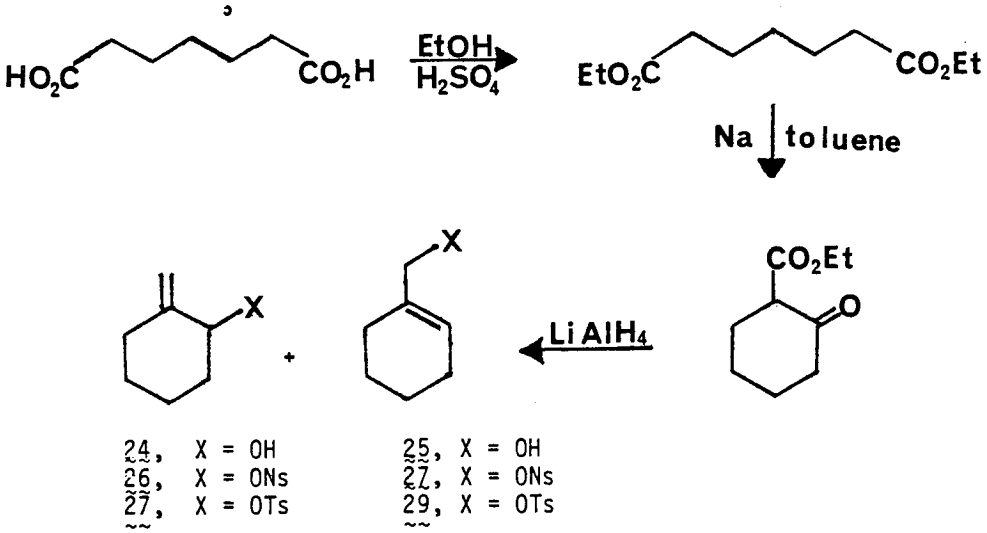
TABLE II Distribution of Trifluoroethyl Ether Products from the Trifluoroethanolysis of 14 at 100° as a Function of Time.

Reaction time, hr	Products, % 21	22	23
1	48.1	47.7	4.2
2	48.1	47.2	4.7
7	47.7	47.0	5.3
24	47.5	46.2	6.3
69	48.7	45.6	5.7

consistent for 21 and 22, confirmation of the structures was sought by and independent synthesis (vide infra). Allenic ether 23 was identified by comparison with the product obtained from the reaction of 14 with sodium trifluoroethoxide. Vpc retention times confirmed that the two compounds were identical.

The preparation of the parent alcohols of 21 and 22 is outlined in Scheme III; the overall yield was 63% based on pimelic acid. The NMR spectra of 2-methylenecyclohexanol (24) and 1-cyclohexenemethanol (25) correspond closely to their respective trifluoroethyl ethers except for the vinyl

Scheme III



24, X = OH
26, X = ONs
27, X = OTs

25, X = OH
27, X = ONs
29, X = OTs

proton resonances in 21 and 24. In alcohol 24 these signals are two singlets (separated by 11 Hz) while in ether 21 only a broad singlet (1/2 band width = 3.5 Hz) is seen. To obtain a derivative that would serve as a better model compound for 21, 24 was acetylated. The NMR spectrum of 2-methylenecyclohexyl acetate has only one resonance for the olefinic protons, a broad singlet with 1/2 band width = 7 Hz.

The nosylates (26,27) and tosylates (28,29) of 24 and 25 were prepared. Trifluoroethanolysis of these esters yielded 21 and 22, the product percentages given in Table III. A previously reported solvolysis in this system

$$26 + 27 \xrightarrow{TFE} 21 + 22 \xleftarrow{TFE} 28 + 29$$

was the hydrolysis of 2-methylenecyclohexyl brosylate is aqueous acetone. In that reaction 24 and 25 were formed in a 42:58 ratio.[35]

In order to determine any accelerative effects in solvolysis by the allene function a comparison was sought from the trifluoroethanolysis of the corresponding saturated compound. Solvolysis of n-heptyl tosylate (30) in TFE gave n-heptyl trifluoroethyl ether (31) as the major product (43% yield).

30 31

At 60° and 100° the rate of this reaction was observed to be slower than that of the reaction of 14. The quantitiative assessment of the difference in rates was obtained from the calculation of rate constants using vpc data for the appearance of ether 22. These rate constants are shown in Table IV and compare favorably with those subsequenly obtained by B.-A. Weissman. The latter constants were measured titrimetrically and found to have values of 8.15×10^{-7} sec^{-1} for 14 and 4.0×10^{-7} sec^{-1} for 30.[36]

TABLE III - Distribution of Cyclic Trifluoroethyl Ethers 21 and 22 Formed in the Trifluoroethanolysis of the Nosylates (26, 27) and Tosylates (28,29) of 2-Methylenecyclohexanol and 1-Cyclohexenemethanol.

Substrate	Products, %	
	21	22
26 + 27	62	38
28 + 29	53	47

TABLE IV - Rate Constants[a] for the Trifluoroethanolysis of 5,6-Heptadien-1-yl Tosylate (14) and n-Heptyl Tosylate (30) at 60° and 100°.

Substrate	Rate Constant, sec^{-1}	
	k(60°)	k(100°)
14	1.8×10^{-6}	7.1×10^{-5}
30	7.2×10^{-7}	7.5×10^{-6}

[a]Determined from vpc data for the appearance of 1-cyclohexenemethyl 2,2,2-trifluoroethyl ether (22).

DISCUSSION

The cationic cyclization observed in the solvolysis of 14 indicates that long range allenic participation is entirely analogous to that seen in olefinic and acetylenic systems. Consider some of the characteristics of this cyclization reaction that correspond to those of the other π systems.

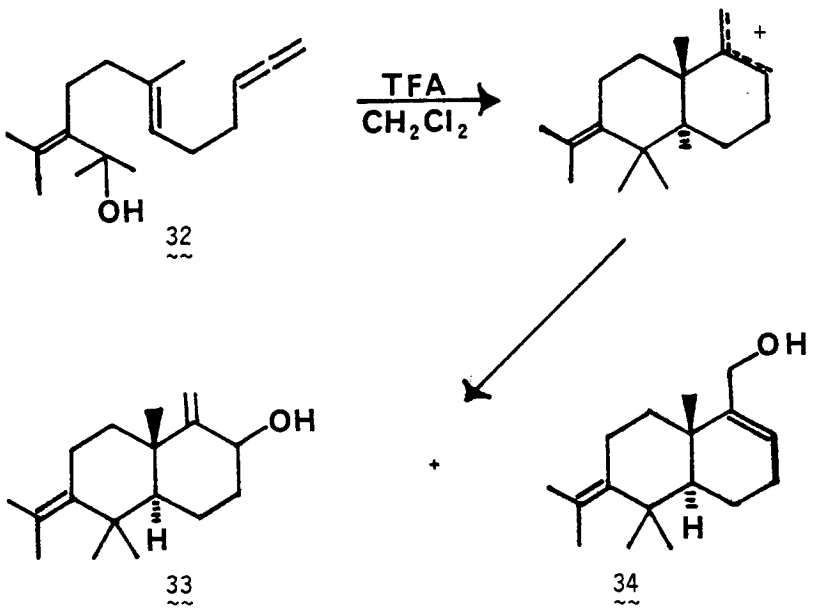
The products formed are to a very large extent cyclic and the degree of cyclization is dependent upon the non-nucleophilicity of the solvent. Participation by the allene function represents the major pathway in the trifluoroethanolysis of 14 as ethers 21 and 22 constitute 90% of the products. The remaining products are the result of direct displacement (23) or elimination. No participation is evident in the acetolysis of 14: the only product is 5,6-heptadien-1-yl acetate.[36]

The two-fold increase in rate of 14 relative to 30 is in the range of rate accelerations observed for olefinic and acetylenic systems. In regard to an allenyl system the rate enhancement is comparable to that found for homoallenyl tosylate 10 which solvolyzes 1.9 times as fast as its model compound.[18] As previously noted k_Δ/k_s for 10 was 0.90. Utilizing the same assumptions made in that case (i.e., $k_\Delta = k_{allene} - k_{model}$) and also the titrimetric rate constants to ensure a valid comparison, k_Δ/k_s of 14 can be calculated. The value of 1.04 obtained is very similar to that of 10 but is significantly larger than that of the closely related compound, tosylate 38. (The γ-allenyl systems are discussed in more detail below.) For 38 k_Δ/k_s was 0.26 and the rate retarding inductive effect of the allene group[18,19] was apparent as 38 solvolyzed only 0.45 as fast as its saturated analog.[37]

The cyclized products and kinetic data show that there is a significant amount of assistance in the ionization of 14 yet the magnitude of rate

acceleration is not sufficient to invoke full-fledged participation, including the formation of a bridged ion in the rate-determining step. More likely the trifluoroethanolysis of 14 can be considered borderline participation, similar to that seen in the other systems with remote π bonds. In the transition state most of the positive charge is still localized on the ionizing carbon as it begins to interact with the allene π bond. It has been suggested that in the cyclization of 3 the transition state for solvolysis bore almost no resemblance to cation 4 from which products were generated.[12]

The expectation that allenes could be useful synthetically, in a biomimetic cyclization for example, has been fulfilled. The reaction of alcohol 32 with trifluoroacetic acid in dichloromethane was investigated by Hall and



32 33 34

Johnson concurrently with the present research. The products isolated after

hydrolysis were the bicyclic alcohols 33 and 34.[38] These findings are completely analogous to the results of this study.

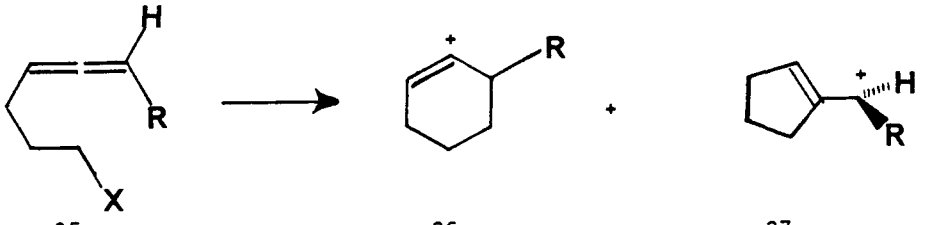
The formation of only six-membered ring compounds from the solvolysis of 14 can be attributed to steric factors rather than to electronic factors governing additions to allenes or the difference in stability of the possible intermediate ions (15 versus 16 or 17). Of the likely interactions between the two allene π bonds and the ionizing center (C-1) the more favorable is that with the nearer C-5,C-6 π bond. This overlap is basically the same found in the 5-hexenyl system that leads to six-membered rings. Reaction with the C-6,C-7 bond is feasible as cyclizations to form seven-membered rings are known.[29] However, molecular models indicate that the geometry of the allene prevents this π bond from attaining a configuration in which effective overlap can be achieved.

The other factors that could decide which cyclization path is followed are less important. Based on the results of electrophilic addition to monosubstituted allenes, the terminal allene carbons of 14 should react with C-1 to form 16 or 17. Since the cyclization proceeds solely via 15 this consideration is not relevant. Although 15 is allylic and therefore inherently more stable than the vinyl cation alternatives little of the resonance stabilization is available in the transition state. Initial attack upon the central allene carbon leaves the resulting empty p orbital orthogonal to the remaining system.[23] A rotation of approximately 90° is required before the stabilization can be fully realized.

Therefore in order to decide which cation should be favored on the basis of greater stability it is more appropriate to compare 16 and 17 to the cation formed before the rotation takes place. This ion is actually a cyclohexyl

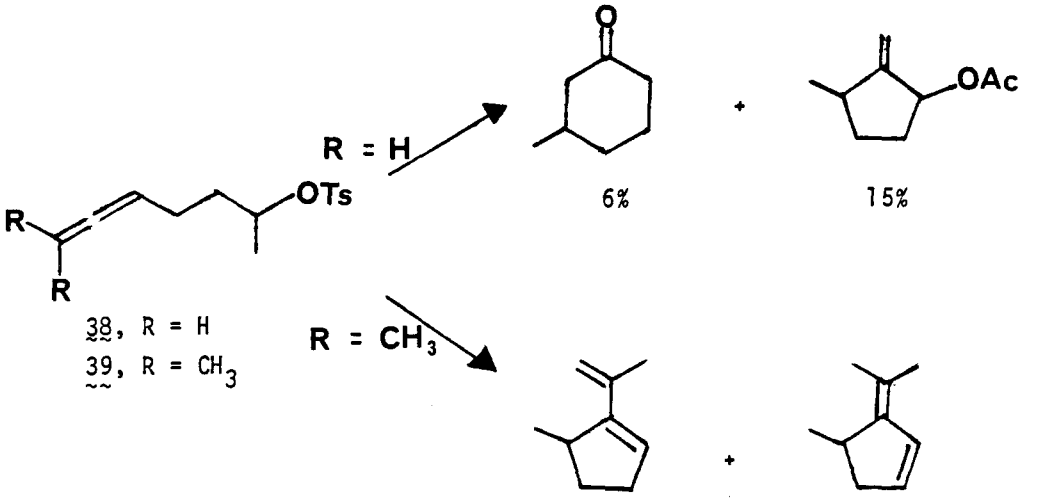
cation (15 with the charge localized at C-1) and should be preferred since it is a secondary carbonium ion. It is not clear however that the extent to which the cyclohexyl cation is more stable than the vinyl cations is what determines the course of the cyclization. More significant is the ability of 14 to attain, with a minimum of strain, a configuration is which C-1 and C-6 can easily interact. This circumstance is the principal factor influencing the formation of six-membered rings.

Subsequent investigations have provided more information regarding the balance of steric and electronic factors affecting allenic cyclizations. In the homologous γ-allenyl system (35) it is the terminal π bond of the allene that can readily react with the ionizing carbon and generate either a cyclohexenyl cation[39] (36) or what is initially a cyclopentenecarbinyl cation (37). Both five- and six-membered ring products have been observed

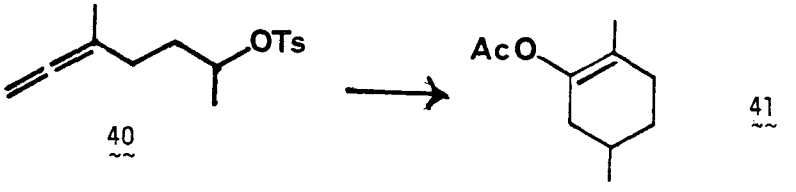


35 36 37

in the reactions of 35 with the distribution of products highly dependent on the substitution pattern in the allene group. Although the acetolysis of the parent γ-allenyl compound (35, X = OTS, R = H) did not yield any cyclic products, small amounts of products from both ions were observed in the solvolysis of tosylate 38.[37] When Ragonnet, Santelli and Bertrand acetolyzed the dimethyl compound 39 more cyclization occurred (80%) but only cyclopentene



derivatives were formed. The only cyclic product observed in the acetolysis of 40 was cyclohexenyl acetate 41. Since tosylates 38 and 40 were optically

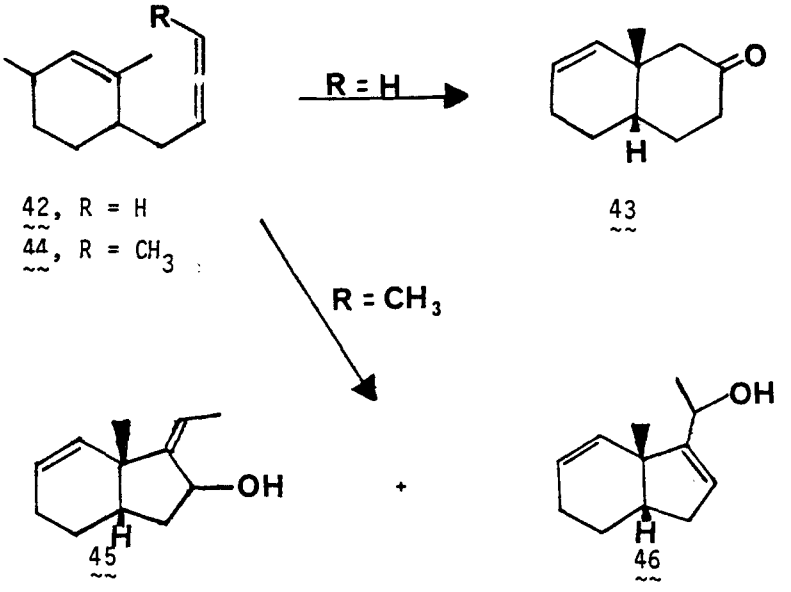


40 41

active it was possible to determine that the reactions proceeded with an inversion of configuration at the cationic carbon and that there was retention of optical activity during the cyclization. The orientation of reacting groups in these instances was interpreted as being primarily influenced by steric considerations, electronic factors assuming a minor role.

In the other γ-allenyl system studied there was a clear differentiation between the two cyclization pathways. Formolysis of alcohol 42 yielded only

one product which was then hydrolyzed to ketone 43. The substitution of a methyl group on the allene caused the cyclization to take place by the other



route. Subjecting alcohol 44 to the same reaction conditions as 42 produced allylic alcohols 45 and 46.[40] Harding, Puckett and Cooper attributed this reversal of behavior to a change in the relative stability of the intermediates. If 42 reacted in the same manner as 14 electrophilic attack would occur at the central carbon to generate a cation analogous to 37 (R = H). However as this ion is primary the alternative cyclohexenyl cation 36 is favored and six-membered ring formation is observed. With the addition of a methyl group to the allene (44) the cyclopentenecarbinyl cation (37, R = CH_3) becomes a secondary ion. It is thus more stable than the vinyl cation and only five-membered ring products are formed. The exclusivity of pathway exhibited in 42 and 44 compared to the acyclic compounds (38-40) is a

consequence of the constraints of molecular motion imposed by the ring system of 42 and 44 which limits the potential overlap between the π bond and the cationic carbon.

The effectiveness of the allene function as a remote intramolecular nucleophile has been demonstrated in this study. Although the basic elements of the cyclization of a δ-allenyl substrate have been established here, other aspects of the reaction require elucidation. A comparison with the findings in the γ-allenyl system provides an indication of what remains to be determined. In the γ-allenyl system the cyclization pathway is sensitive to changes in substitution on the allene. Increasing the alkyl substitution on the allene produces large rate accelerations relative to model compounds,[37] a phenomenon also noted in homoallenic solvolyses.[18] From the retention of optical activity in the reaction of 38 and 40 it appears that the allene function assisted in solvolysis to the extent that it could control the configuration at the ionizing carbon. Whether similar effects will be observed in the δ-allenyl system warrants further investigation.

EXPERIMENTAL

General

Infrared (IR) spectra were recorded in carbon tetrachloride solution on a Perkin Elmer IR 257 grating spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were obtained on a Varian Associates A60-A spectrometer with carbon tetrachloride as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethylsilane followed by the multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, m = multiplet), splitting, integration, and assignment. Qualitative and preparative vapor phase chromatography (vpc) analyses were carried out on a Varian Aerograph 90-P3 instrument with thermal conductivity detector and helium carrier gas flow of 60 ml/min (unless otherwise noted). Analytical vpc was performed on a Hewlett Packard 5750 chromatograph equipped with a flame ionization detector and Hewlett Packard 3370A digital intetrator. The following columns were employed and will be referred to by the indicated letters: column A, 10 ft x 1/4 in 8% TCEP on 60/80 Chromosorb P-NAW, aluminum; column B, 5 ft x 1/4 in 5% DEGS on 60/80 Chromosorb P-NAW, stainless steel; column C, 10 ft x 1/4 in 10% DEGS on 60/80 Chromosorb P-NAW, stainless steel; column D, 15 ft x 1/8 in 10% DEGS on 100/120 Chromosorb P-NAW, stainless steel; column E, 10 ft x 1/4 in 5% Carbowax 20M on 60/80 Chromosorb p-NAW, aluminum. Boiling points are uncorrected.

5-Hexen-1-yl tetrahydropyranyl ether was prepared by a combination of the methods of Parham and Anderson[41] and Robertson.[42] To a 100 ml 3-neck flask equipped with reflux condenser, addition funnel and thermometer was added 17.6g (0.21 mole) of 2,3-dihydropyran (freshly distilled from

NaOH-Na_2CO_3) and 5 drops of concentrated HCl. The solution was stirred magnetically as 20.0g (0.20 mole) of 5-hexen-1-ol (Peninsular Chemical Research) was added dropwise over 0.5 hr with the reaction temperature kept below 50°. After stirring overnight, Na_2CO_3 was added and the solution filtered following dilution with ether. Removal of solvent and excess dihydropyran and distillation of the residue gave 36.0g (97%) of tetrahydropyranyl ether, bp 55°/0.6mm; IR 3075, 2930, 2870, 1640 (C=C), 1455, 1443, 1354, 1324, 1285, 1260, 1200, 1140, 1120, 1080, 1035, 990, 914, 870 cm^{-1}; NMR δ 1.22-1.70 (m, 10H, $-CH_2-$), 2.08 (broad q, J ~ 6 Hz, 2H, $-CH_2C=C$), 3.13-3.90 (m, 4H, $-CH_2O$), 4.52 (broad s, 1H, -OCHO-), 4.83 and 5.06 (broad s and d, 2H, $CH_2=C$), 5.47-6.03 (complex m, 1H, -CH=C).

5,6-Heptadien-1-yl Tetrahydropyranyl Ether. To a 300ml 3-neck flask containing 100ml dry pentane and fitted with flexible Teflon tube and thermometer was added 12.9g (0.070 mole) of 5-hexen-1-yl tetrahydropyranyl ether and 37.8g (0.15 mole) of bromoform. The solution was stirred magnetically under N_2, cooled to -25°, and 22.4g (0.20 mole) of potassium t-butoxide (Alfa Inorganics) added through the Teflon tube over 4 hr. The stirring was continued 4 additional hours at -25°, then overnight at ambient temperature. After quenching with 100ml water the reaction mixture was filtered and the layers separated. The aqueous phase was extracted three times with pentane and the combined washes dried over Na_2SO_4-Na_2CO_3. Following removal of the solvent the residue was heated to 65° at 0.05mm to distil away other impurities. In this way a brown oil of 18.4g (74%) was obtained with spectral properties of the dibromocyclopropane ether; IR 2940, 2860, 1453, 1440, 1352, 1284, 1258, 1200, 1134, 1119, 1077, 1035, 906, 867, 678 cm^{-1}; NMR δ 1.18 (m, 1H, -CH-), 1.63 (broad s, 14H, $-CH_2-$),

3.13-4.00 (m, 4H, $-CH_2O-$), 4.53 (broad s, 1H, $-O\overset{|}{C}HO-$).

The above crude ether (16.2g, 45 mmoles) was dissolved in 80ml dry (LAH) ether under N_2 in a 300ml 3-neck flask with addition funnel, thermometer and stir bar. The stirred solution was cooled to -30° and 25ml 2M methyllithium in ether (50mmoles) added slowly over 1.5 hr. Additional stirring for 1.5 hr while the solution was warming to -10° was followed by quenching with 100ml water, added dropwise initially. The ether layer was separated, the aqueous washed three times with ether, and the combined extract solution dried over Na_2CO_3. Removing the ether and vacuum distilling the residue yielded 8.2g (93%) of allenic ether, bp 46-50°/0.03 mm; IR 2920, 2860, 1950 (C=C=C), 1455, 1443, 1355, 1285, 1260, 1201, 1140, 1120, 1080, 1037, 909, 870, 845 cm^{-1}; NMR δ 1.58 (broad s, 10H, $-CH_2-$), 2.00 (m, J = 2 Hz, 2H, $-CH_2C=C=C$), 3.12-3.95 (m, 4H, $-CH_2O-$), 4.52 (broad s, 1H, $-O\overset{|}{C}HO-$), 4.60 (overlapping d of t, J = 6.5 and 3 Hz, 2H, $CH_2=C=C$), 5.07 (skewed p, J = 6.5 Hz, 1H, $-CH=C=C$).

5,6-Heptadien-1-ol (20). To a 200ml flask with reflux condenser containing 40ml acetone and 80ml water was added 7.9g (40 mmoles) of 5,6-heptadien-1-yl tetrahydropyranyl ether. After adding 0.2g p-toluenesulfonic acid the solution was stirred under nitrogen and heated at 80° for 10 hr. Dilution with 50ml water was followed by neutralization with $NaHCO_3$. After having added 5g $Na_2S_2O_5$ and enough NaCl to saturate the solution, the solution was washed with pentane once and ether three times. Solvent was removed from the Na_2SO_4-Na_2CO_3 dried extracts and the residue distilled. The main fraction had a bp of 65-7°/2mm but vpc analysis (column A, 120°) indicated 15% residual tetrahydropyranyl ether; thus, of 4.77g of material collected, 3.22g (72%) was 5,6-heptadien-1-ol; IR 3600, ~3300 (OH), 2920, 2860, 1951

(C=C=C), 1440, 1250, 1060, 1035, 865, 846 cm^{-1}; NMR δ 1.50 (m, 4H, $-CH_2-$), 2.00 (m, J = 3 Hz, 2H, $-CH_2C=C=C$), 3.53 (t, J = 6 Hz, 2H, $-CH_2O-$), 3.73 (s, 1H, -OH), 4.60 (overlapping d of t, J = 6.5 and 3 Hz, 2H, $CH_2=C=C$), 5.07 (skewed p, J = 6.5 Hz, 1H, -CH=C=C).

5,6-Heptadien-1-yl Tosylate (14). To an ice cold solution of 1.35g (12 mmoles) 5,6-heptadien-1-ol in 25ml of dry pyridine was added 4.75g (25 mmoles) of recrystallized p-toluenesulfonyl chloride with stirring. The solution was then allowed to stand in a refrigerator for 24 hr. The resulting solution containing pyridine hydrochloride crystals was poured into 50g of ice water, stirred 15 min and the pink oil taken up in ether. The aqueous layer was washed twice more with ether and the combined extracts washed twice with cold 3N HCl and once with water before drying over Na_2SO_4. Removal of the ether left a yellow oil which was dissolved in pentane. Attempts to crystallize the tosylate by cooling to -78° were unsuccessful. However, purification was effected by decanting the pentane from the solidified tosylate, redissolving in pentane, refreezing the tosylate and repeating the process twice. The slightly yellow oil obtained was dried in vacuo, yielding 2.76g (86%); IR 2930, 2860, 1952 (C=C=C), 1498, 1445, 1370, 1190, 847, 662 cm^{-1}; NMR δ 1.55 (m, 4H, $-CH_2-$), 1.88 (m, 2H, $-CH_2C=C=C$), 2.42 (s, 3H, $-CH_3$), 3.97 (t, J = 6 Hz, 2H, $-CH_2O-$), 4.58 (overlapping d of t, J = 6.5 and 3 Hz, 2H, $CH_2=C=C$), 4.98 (skewed p, J = 6.5 Hz, 1H, -CH=C=C), 7.28 and 7.70 (AB q, J = 8 Hz, 4H, aryl H).

n-Heptyl Tosylate (30) was prepared from 1-heptanol (Matheson Coleman Bell) in the same manner as its unsaturated analog; IR 2920, 2860, 1600, 1500, 1470, 1370, 1190, 1180, 1100, 660 cm^{-1}; NMR δ 0.85 (skewed t, J = 5 Hz, 3H, alkyl CH_3), 1.03-1.73 (m, 10H, $-CH_2-$), 2.43 (s, 3H,

aryl CH_3), 3.95 (t, J = 6 Hz, 2H, $-CH_2O-$), 7.28 and 7.72 (AB q, J = 8 HZ, 4H, aryl H). The nmr data were in accord with those previously reported.[18]

n-Heptyl Acetate was prepared from 1-heptanol with acetyl chloride and pyridine in ether solution by the method of Sarel and Newman[43] in 91% yield; IR 2920, 2860, 1739 (C=O), 1471, 1390, 1370, 1240, 1040 cm^{-1}; NMR δ 0.88 (skewed t, J = 5 Hz, 3H, $-CH_3$), 1.33 (broad s, 10H, $-CH_2-$), 1.95 (s, 3H, CH_3CO_2-), 3.98 (t, J = 6 Hz, 2H, $-CH_2O-$).

Solvolysis of 5,6-Heptadien-1-yl Tosylate. A solution of 2ml 2,2,2-trifluoroethanol (Aldrich, 99+%, distilled from molecular sieves), 50$\mu\ell$ 2,6-lutidine (0.43 mmole) and 8$\mu\ell$ n-heptyl acetate (internal standard) was stirred magnetically in a 5ml vial. 5,6-Heptadien-1-yl tosylate (55mg, 0.2 mmole) was added and the vial sealed with two serum caps before placing in an oil bath at 60±3°. The reaction was followed by vpc by injecting 5$\mu\ell$ aliquots of the solution directly onto column B at 100° and comparing product peak areas to that of the acetate.

After 424 hours the vial was removed from the bath and the contents transferred to a centrifuge tube containing 2ml pentane and 5ml water. The aqueous layer was extracted twice more with pentane and the yellowish organic fractions combined. This solution was dried over Na_2SO_4-$MgSO_4$ and filtered through $CaSO_4$ before removing the pentane by rotary evaporation.

Analysis of this mixture on column C at 125° showed products with retention times of 1.2, 2.4, 4.8 and 5.6 minutes. The first three products were isolated by preparative vpc and spectral data obtained. The IR spectrum of the product at 1.2 min exhibited a band at 1650cm^{-1}. This characteristic C=C stretch and the short retention time (solvent trifluoroethanol was at 1.4 min.) indicated an olefin. However, lack of material prevented further attempts at structure elucidation. The next two products were identified

as 21 and 22. Eluted first was 2-methyl enecyclohexyl 2,2,2-trifluorethyl ether (21): IR 3075, 2950, 2870, 1650 (C=C), 1450, 1440, 1430, 1280, 1155, 1120, 1090, 989, 975, 917, 902, 888, 678 cm^{-1}; NMR δ 1.70 (m, 6H, $-CH_2-$), 2.12 (m, 2H, $-CH_2C=C$), 3.68 (q, J ~ 9 Hz, 2H, $-OCH_2CF_3$), 3.88 (m, 1H, -CHO-), 4.83 (broad s, 2H, $CH_2=C$). Second was 1-cyclohexenemethyl 2,2,2-trifluoroethyl ether (22): IR 2930, 2860, 2840, 1665 (C=C), 1450, 1440, 1430, 1360, 1305, 1280, 1160, 1138, 1105, 1008, 970, 922, 847, 830 cm^{-1}; NMR δ 1.65 (m, 4H, $-CH_2CH_2-$), 2.00 (m, 4H, $-CH_2C=C$), 3.67 (q, J = 8.5 Hz, 2H, $-OCH_2CF_3$), 3.92 (broad s, 2H, $-CH_2O-$), 5.65 (m, 1H, -CH=C). The last product was subsequently determined to be 23 by comparison of retention time with that of the ether prepared directly from the tosylate.

For the solvolysis at 100° the solution was mixed as above and 50μℓ aliquots sealed in 4 inch sections of 4mm Pyrex tubing at -78° at reduced pressure. The sealed tubes were placed in an oil bath at 100±3°, removed at appropriate intervals, opened and analyzed.

Product distributions at 60° and 100° were determined using analytical vpc column D (120°, flow rate = 0.7). The retention times in minutes for the ethers were 8.0, 13.1 and 15.0 (n-heptyl acetate 20.7) with the order of elution the same as above. The unidentified olefin had a retention time of 4.7 min.

Solvoysis of n-heptyl tosylate was carried out using the procedures described above for the allenic tosylate.

The reaction mixture that had been stirred at 60° for 665 hours was worked up and the major product collected by preparative vpc (column B, 95°). Spectral data were consistent for n-heptyl 2,2,2-trifluoroethyl ether (31): IR 2920, 2850, 1465, 1440, 1415, 1378, 1310, 1280, 1150, 1005, 970, 862, 825, 662 cm^{-1}; NMR δ 0.90 (skewed t, J = 5 Hz, 3H, CH_3-),

1.32 (broad s, 10H, $-CH_2$), 3.55 (t, J = 6 Hz, 2H, $-CH_2O-$), 3.72 (q, J = 8.5 Hz, 2H, $-OCH_2CF_3$). No attempt was made to identify the minor products which had retention times on column D (120°) of 3.3 and 4.5 min. compared to the ether at 9.4 min. and acetate at 21.2 min.

5,6-Heptadien-1-yl 2,2,2-Trifluoroethyl Ether (23). To a 25ml 3-neck flask under N_2 containing 5ml 2,2,2-trifluoroethanol and a stir bar was added 0.25g (11 mmole) sodium. After the sodium had reacted completely the solution was cooled to 0° and 1.1g (4 mmole) 5,6-heptadien-1-yl tosylate added. Stirring was continued for 3.5 hr at 0° and the mixture placed in a freezer overnight. Following additional stirring at room temperature for 0.5 hr, 5ml ether was added to the mixture and then 10ml water. The yellow ether layer was separated and extracted with water. The combined aqueous layers were extracted with pentane. The ether and pentane solutions were combined, dried over Na_2SO_4 and filtered through $CaSO_4$ before concentrating by rotary evaporation.

Vpc analysis (column C, 110°, 100ml/min) showed one product with a retention time identical to that of the last product of the allenic tosylate solvolysis. Spiking that solvolysis mixture with the above ether and using column D showed precise correspondence to the third product ether of the solvolysis.

Diethyl Pimelate was prepared from pimelic acid (Matheson Coleman Bell) by the procedure used for dimethyl hendecanedioate.[44] The diester was obtained in 88% yield, b.p. 75°/0.04 mm (lit.[45] 149°/14 mm); IR 2970, 2930, 2860, 1735 (C=O), 1465, 1445, 1420, 1372, 1180, 1095, 1032, 860 cm^{-1}; NMR δ 1.22 (t, J = 7 Hz, 6H, $-CH_3$), 1.10-1.83 (m, 6H, $-CH_2-$), 2.22 (unsymmetrical t, J = 6 Hz, 4H, $-CH_2CO_2-$), 4.05 (q, J = 7 Hz, 4H, $-CH_2O-$).

2-Carbethoxycyclohexanone was prepared from diethyl pimelate using

the method for the Dieckmann condensation of diethyl adipate.[46] The yield was 81%, b.p. ~50°/0.1mm; IR ~3000 (OH), 2930, 2850, 1740 (ester C=O), 1718 (ketone C=O), 1656 (enol C=O), 1615 (enol C=C), 1465, 1447, 1422, 1400, 1360, 1297, 1215, 1176, 1082, 1060, 1015, 965, 913, 874, 695 cm^{-1}; NMR δ 1.28 (t, J = 7 Hz, 3H, $-CH_3$), 1.63 (m, 4H, $-CH_2CH_2-$), 2.20 (m, 4H, $-CH_2C=C$), 3.2 (m, ~0.2H, $-COCHCO_2-$), 4.17 (q, J = 7 Hz, $-CH_2O-$), 12.08 (s, 0.85H, enol -OH). The spectra exhibit resonances for both the keto and enol forms of the compound.[47]

Reduction of 2-Carbethoxycyclohexanone. The ketoester was reduced with lithium aluminum hydride in ether using the procedure of Dreiding and Hartman.[48] The major components of the alcohols obtained in 88% yield were 2-methylenecychexanol (24) and 1-cyclohexenemethanol (25) (73:27 respectively) and the minor component was 2-hydroxymethylcyclohexanol. In order to obtain spectral data of the allylic alcohols, amounts of each were collected by preparative vpc (column E, 150°, 100ml/min). No other attempt to separate the isomers was made; the mixture was used in subsequent reactions.
2-Methylenecyclohexanol (24): IR 3600, ~3350 (OH), 3070, 2920, 2860, 1650 (C=C), 1450, 1080, 1030, 995, 947, 900, 860 cm^{-1}, NMR δ 1.10-2.60 (envelope, 8H, $-CH_2-$), 3.40 (s, 1H, -OH), 3.98 (m, 1H, -CHO-), 4.65 (s, 1H, C=CH- anti to -OH), 4.83 (s, 1H, C=CH- syn to -OH).
1-Cyclohexenemethanol (25): IR 3600, ~3320 (OH), 2920, 2860, 1670 (weak C=C), 1450, 1440, 1380, 1270, 1170, 1140, 1085, 1055, 1015, 960, 920, 905, 860, 835 cm^{-1}; NMR δ 1.63 (m, 4H, $-CH_2CH_2-$), 1.98 (m, 4H, $-CH_2C=C$), 2.83 (s, 1H, -OH), 3.85 (s, 2H, $-CH_2O-$), 5.58 (m, 1H, C=CH-).

2-Methylenecyclohexyl Acetate and its allylic isomer were prepared from the corresponding alcohols by acetylation with acetic anhydride in pyridine. Following workup and solvent removal the major isomer was isolated

by vpc (column B, 95°): IR 3080, 2940, 2860, 1740 (C=O), 1658 (C=C), 1450, 1370, 1240, 1150, 1060, 1050, 1000, 950, 915, 900 cm^{-1}; NMR δ 1.67 (m, 6H, $-CH_2-$), 2.02 (s, 3H, CH_3-), 2.22 (m, 2H, $-CH_2C=C$), 4.75 (broad s, 2H, $CH_2=C$), 5.13 (m, 1H, $-\dot{C}HO-$).

Preparation and Solvolysis of Tosylates 28 and 29. Alcohols 24 and 25 were reacted with tosyl chloride in pyridine at -25° and under N_2 to keep the solution dry. The work-up procedure was the same as described earlier for the allenic tosylate with the additional precaution taken to keep all solutions ice cold. The slightly yellow oil obtained became a mixture of yellow and white solid when cooled to -78° in pentane; it would decompose overnight at room temperature and after two weeks in the freezer. Spectral data were consistent for 2-methylenecyclohexyl tosylate (28) and its allylic isomer (29): IR 2930, 2860, 1650, 1595, 1490, 1445, 1365, 1186, 1176, 1115, 1095, 1005, 982, 945, 903, 884, 665 cm^{-1}; NMR δ 1.1-2.2 (broad m, $-CH_2-$), 2.40 (s, $-CH_3$), 3.68-4.12 (broad m, $-CH_2O-$ and $-\dot{C}HO-$), ~4.75 (m, -CH=C and $CH_2=C$), 7.27 and 7.67 (AB q, J = 8 Hz, aryl H). However the sample was not pure as the NMR integration indicated a 50% excess of aryl protons. No attempt was made to assign the resonances for each isomer.

Solvolysis of the tosylates was done in the same manner as the acyclic tosylates with the reaction mixture stirred several days at room temperature. Vpc analysis (column D, 120°) showed two products with retention times identical to those of 21 and 22.

Preparation and Solvolysis of Nosylates 26 and 27. A modification of the method of Streitweiser and Schaeffer[49] was used in preparing the nosylates. To a stirred solution of 1.1g (10 mmole) 24 and 25 in 12ml pyridine under N_2 was added 2.0g (13 mmole) recyrstallized p-nitrobenzenesulfonyl chloride.

Stirring was continued for 1 1/4 hr and the reaction mixture poured into 12ml concentrated hydrochloric acid in 60 ml ice water. The resulting oil was taken up in ether, the layers separated, and the aqueous extracted twice more with ether. All solutions were kept ice cold during work-up. The combined ether solution was washed twice with 6N HCl and once with cold water before drying over Na_2SO_4. Filtration through $CaSO_4$ and removal of solvent left a residue that was a yellow and white semisolid at 0°. The IR and NMR spectra were consistent for the nosylates (26, 27); IR 2920, 2860, 1650, 1605, 1535, 1475, 1450, 1360, 1195, 1175, 1080, 1015, 855 cm^{-1}; NMR δ 1.1-2.3 (broad m, $-CH_2-$), 3.7-4.0 (broad m, $-CH_2O-$ and -CHO-), 4.8 (m, -CH=C and CH_2=C), 8.18 and 8.42 (AB q, J = 9 Hz, aryl H). The presence of the starting alcohols was noted in the spectra and also by their distinctive odor.

Due to the tendency of the nosylates to decompose no effort was made to purify them. The above mixture was solvolyzed at room temperature for 5 days. Following work-up vpc analysis (column C, 110°, 100ml/min) showed ether products with retention times corresponding to the cyclized ethers of the allenic tosylate solvolysis. Spiking that mixtrue confirmed the identification of the products as 21 and 22.

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