FLUXIONAL NORBORNYL CATIONS SYNTHETIC APPROACHES TO TRICYCLO [6, 2, 1, $0^{1,6}$] UNDECA - 2, 4 - DIENYL CATIONS AND 3, 3 - DIMETHYLTRICYCLO [4, 2, 1, $0^{1,4}$] NONAN - 2 - ONE

Dissertation for the Degree of Ph. D.

MICHIGAN STATE UNIVERSITY

SAMRAN BHU - ANANTANONDH

1975

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ABSTRACT

FLUXIONAL NORBORNYL CATIONS

SYNTHETIC APPROACHES TO TRICYCLO[6,2,1,$0^{1,6}$]

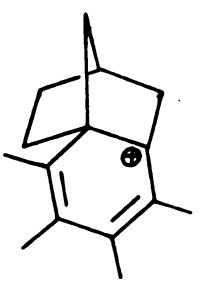
UNDECA-2,4-DIENYL CATIONS AND 3,3-DIMETHYLTRICYCLO

[4,2,1,$0^{1,4}$]NONAN-2-ONE

By

Samran Bhu-anantanondh

Synthetic approaches to 2,3,4,5-tetramethyltricyclo-[6,2,1,$0^{1,6}$]undeca-2,4-dienyl cation 26, tricyclo-[6,2,1,$0^{1,6}$]undeca-2,4-dienyl cation 27 and 3,3-dimethyl-tricyclo[4,2,1,$0^{1,4}$]nonan-2-one 31 were investigated.



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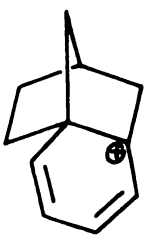

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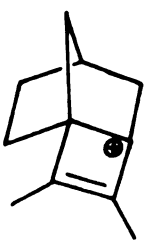

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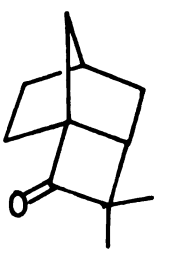

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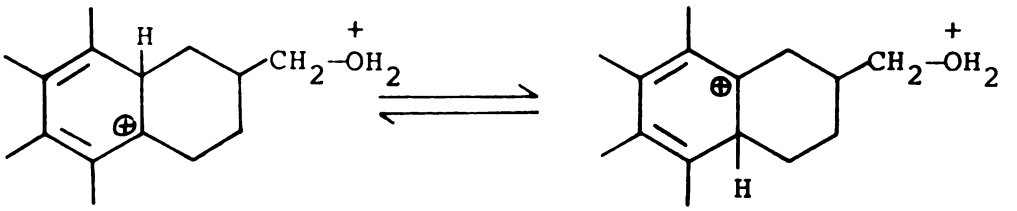
The cations 26 and 27 were predicted to undergo thermally allowed-suprafacial [1,6] sigmatropic migration with retention of configuration of the shifting centers. Due to the accelerating effect of the norbornyl skeleton, it was

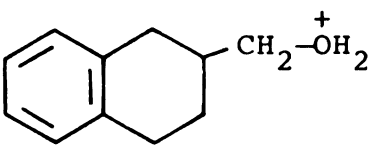
expected that the cation 28 might exhibit the thermally forbidden [1,4] sigmatropic migration with retention.

The synthetic pathways to the compounds 29 and 30 which were proposed to form the cations 26 and 27 in strong acid media are outlined below. The alcohol 29 reacted with fluorosulfonic acid to form a protonated ion



51a 51 51b

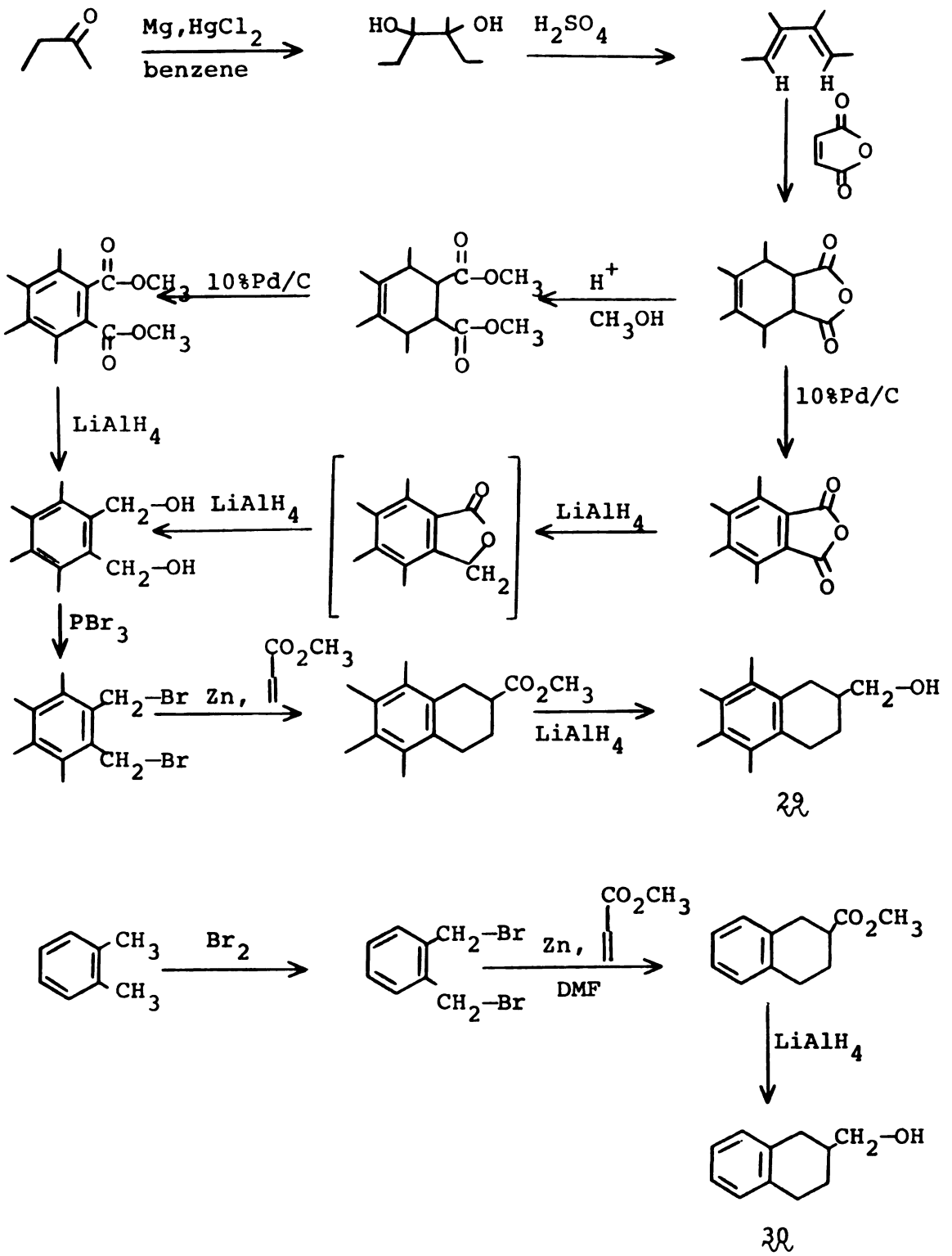
51a or 51b at -60°, and consisted of a rapidly equilibrating pair ions at -40° to -20°. The alcohol 30 reacted with fluorosulfonic acid to form the ion 47. (The solutions were observed by both C-13 and proton nmr spectroscopy.)



47

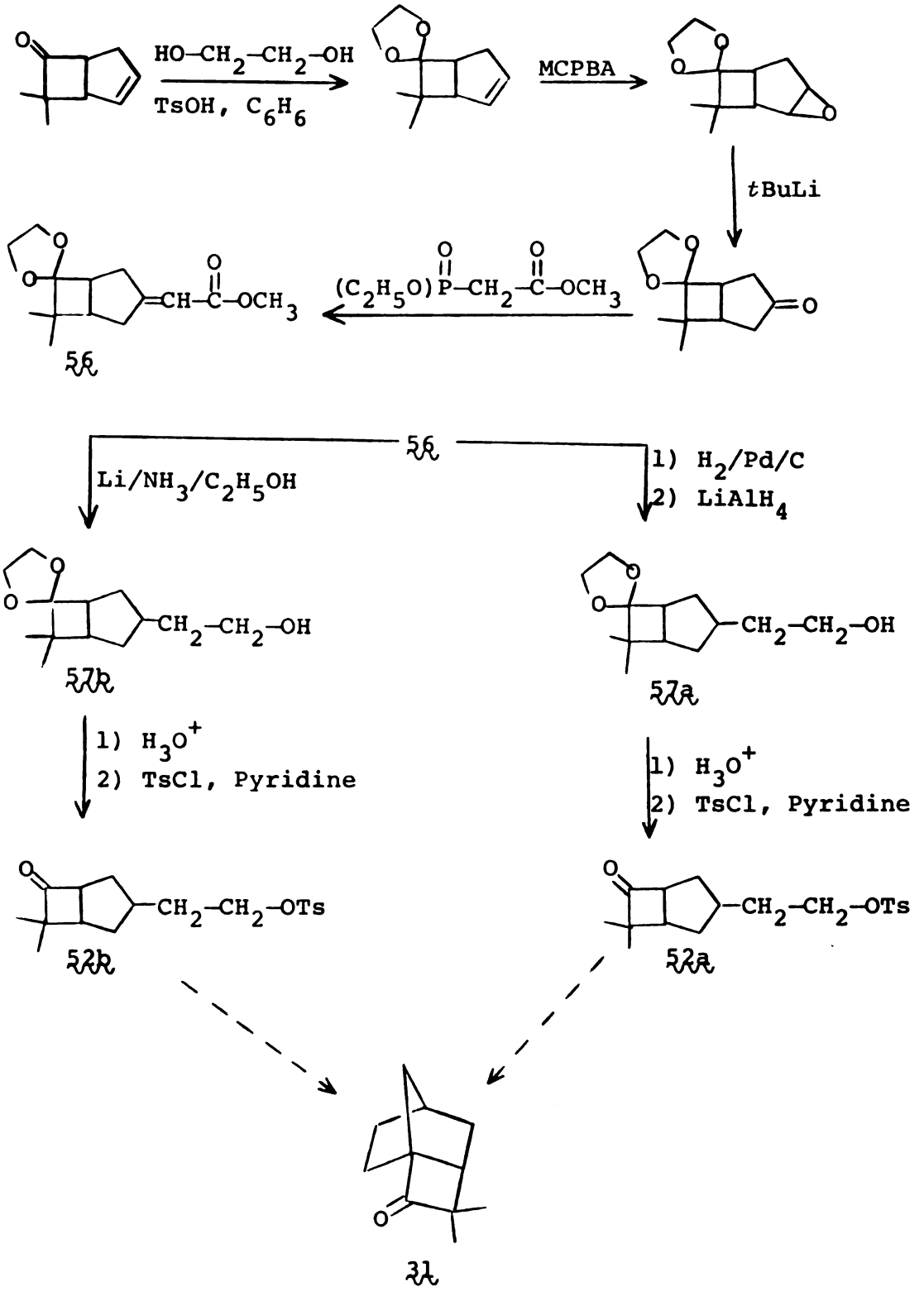
The synthetic approach to the ketone 31 (proposed precursor for the cation 28) is shown. Attempts to cyclize the keto tosylate 52 with various bases under various conditions were unsuccessful.

Besides the intermediates shown, a variety of compounds containing the bicyclo [3,2,0] skeleton were prepared.


Mg,HgCl2
benzene
H2SO4
10%Pd/C
H+
CH3OH
10%Pd/C
LiAlH4
LiAlH4
LiAlH4
PBr3
Zn,
LiAlH4
Br2
Zn,
DMF
LiAlH4

29

30


HO–CH2–CH2–OH
TsOH, C6H6
MCPBA
tBuLi
(C2H5O)P–CH2–C–OCH3
CH–C–OCH3
56
Li/NH3/C2H5OH
1) H2/Pd/C
2) LiAlH4
CH2–CH2–OH
57b
57a
1) H3O+
2) TsCl, Pyridine
CH2–CH2–OTs
52b
52a
31

FLUXIONAL NORBORNYL CATIONS

SYNTHETIC APPROACHES TO TRICYCLO[6,2,1,$0^{1,6}$]UNDECA-2,4-DIENYL CATIONS

AND

3,3-DIMETHYLTRICYCLO[4,2,1,$0^{1,4}$]NONAN-2-ONE

By

Samran Bhu-anantanondh

A DISSERTATION

Submitted to

Michigan State University

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for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1975

To my parents, sister, brother and Sirina Phisanbut

for

their encouragement

ACKNOWLEDGEMENTS

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Thanks to the Royal Thai Government for financial support and also to the Department of Chemistry for partial support during the time in the United States.

Thanks also go to the Farnum group: Botto, Chambers, Duhl, Geraci, Hagadorn, Lindsey, Mader, Raghu, Reitz and Wolf whose friendship made the life bearable while away from home.

Finally, thanks to Miss Mallika Thammakosala and Mrs. Carol Smith for their help in typing this dissertation.

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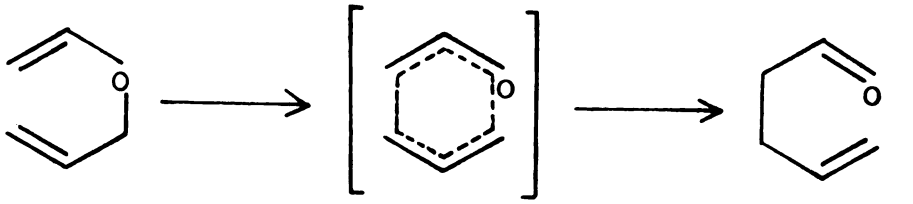
INTRODUCTION

The uncatalyzed thermal intramolecular rearrangement was first detected by Claisen[1] in 1912. The required structural feature of the Claisen rearrangement is a vinyl (or phenyl) allyl ether which rearranges to the isomeric γ,δ-unsaturated carbonyl system according to equation 1. The gross mechanistic picture was described by Claisen[2] as a cyclic process involving simultaneous bond-breaking and -forming, accompanied by relocation of

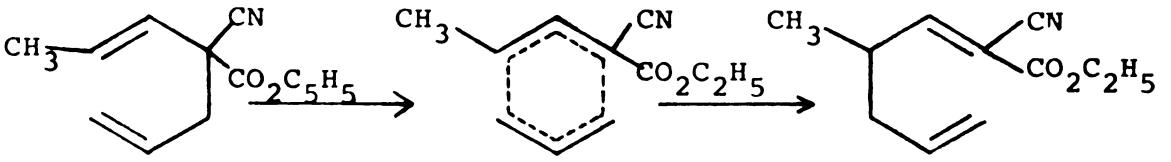


(1)

the double bond in the allylic system. Since then, the details of this mechanistic pathway have been studied. A great deal of evidence collected, such as the absence of mixed products in crossing experiments,[3,4] the first-order kinetics, and the negative entropy of activation[5] support the proposed mechanism as a concerted one-step reaction.

The all-carbon analog of the Claisen rearrangement was first discovered by Cope and Hardy.[6] They found that

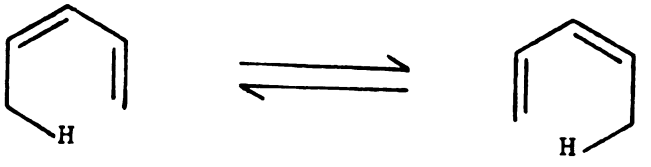
when the ester 1 was heated at 150-160° for four hours, it completely rearranged into ester 2 which is formed by migration of an allyl group as shown in equation 2.



1 2 (2)

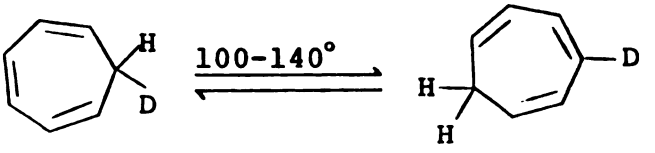
Cope-type rearrangements have been extensively studied to date.[7] The absence of "cross over" products, the first-order kinetics, and the negative entropy of activation again were interpreted as evidence that the reaction proceeds through a concerted process with a cyclic transition state as proposed by Cope.

Another thermal isomerization involving [1,5]hydrogen transfer with migration of both carbon-carbon double bonds as described in equation 3 has been observed.[8] Borg[9] had shown that rearrangement of deuterated cycloheptatriene 3



(3)

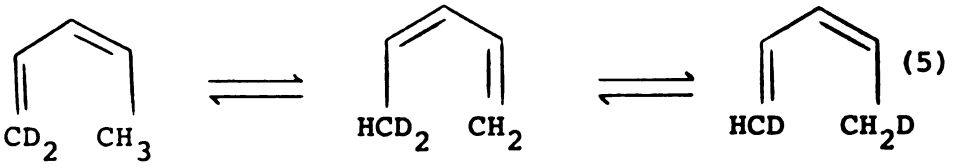
to 4 upon heating occurred through [1,5]hydrogen migration. Roth[10] also studied the [1,5] shift in 1,3-pentadiene.



(4)

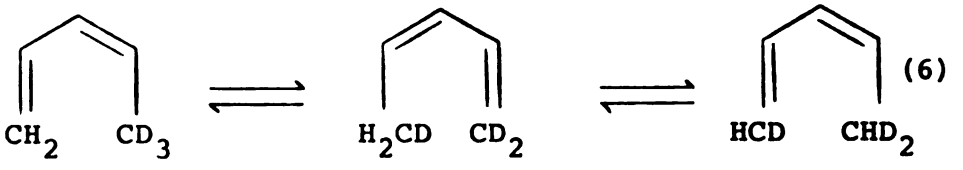
3 4

He found that when deuterated compounds 5 and 6 were heated at 200°, they isomerized to 5a, 5b and 6a, 6b respectively. A more beautiful example by the same author[11]



(5)

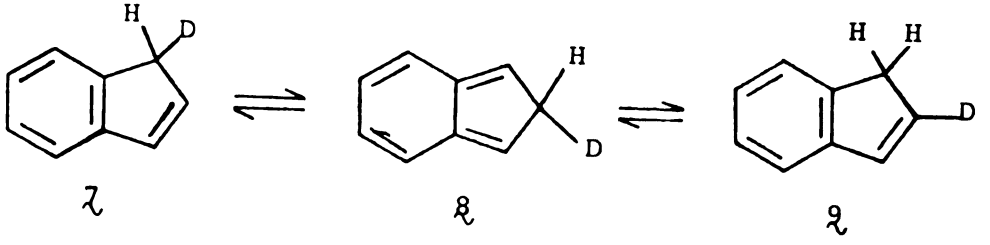
5 5a 5b



(6)

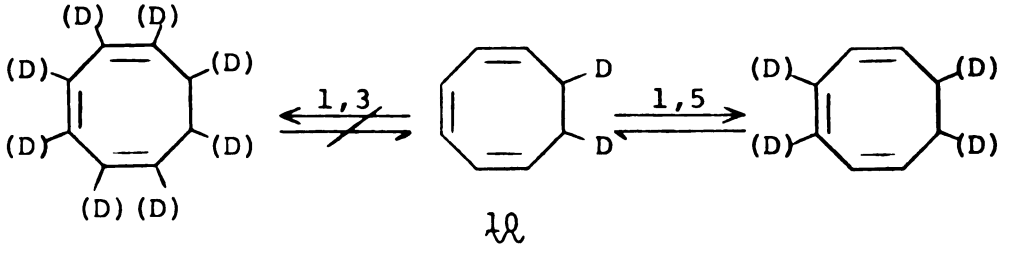
6 6a 6b

demonstrated the preference for a [1,5] shift over a [1,3] shift under thermal conditions. Thus, heating compound 7 scrambled deuterium over all nonaromatic positions through [1,5] shifts even though they have to proceed through the unfavorably nonaromatic isoindene 8. Also, on heating



7 8 9 (7)

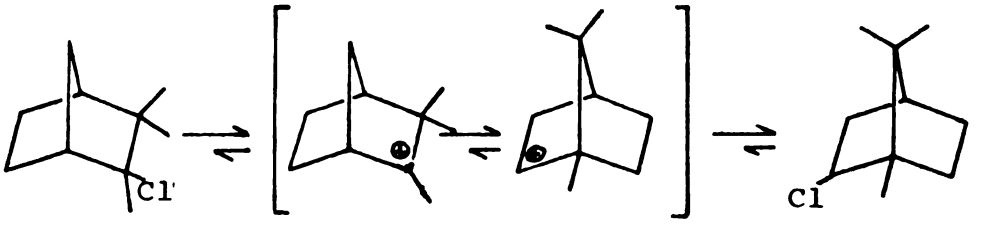
7,8-dideutero cycloocta-1,3,5-triene 10, deuterium scrambling was found only in positions 3, 4, 7 and 8.



10

This proves that migration through a sequence of [1,5] shifts is preferred over [1,3] shifts under thermal conditions.

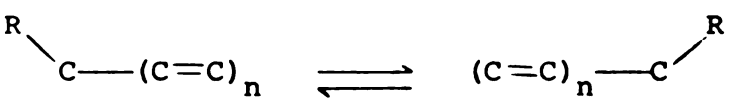
Alkyl migration in a charged species has also been known for a long time. Meerwein[13] demonstrated that cationic carbon intermediates were involved in the camphene hydrochloride-isobonyl chloride (11 ⇌ 12) isomerization. This simple [1,2] alkyl shift is commonly known as the Wagner-Meerwein rearrangement.



11 12

It was not until 1965 that concerted reactions in organic chemistry become understood through the application of molecular orbital theory. By using the concepts of symmetry, overlap, bonding and the nodal structure, Woodward and Hoffmann[14] were able to rationalize the chemical behavior of three classes of concerted reactions: electrocyclic, cycloaddition and sigmatropic reactions. Because of this theory, namely "the conservation of orbital symmetry," photochemical and thermal transformations of polyene compounds as well as the stereochemical results of these transformations become clearly understood. Furthermore, this theory makes possible the prediction of a number of thermal or photochemical reactions as well as their stereochemistry.

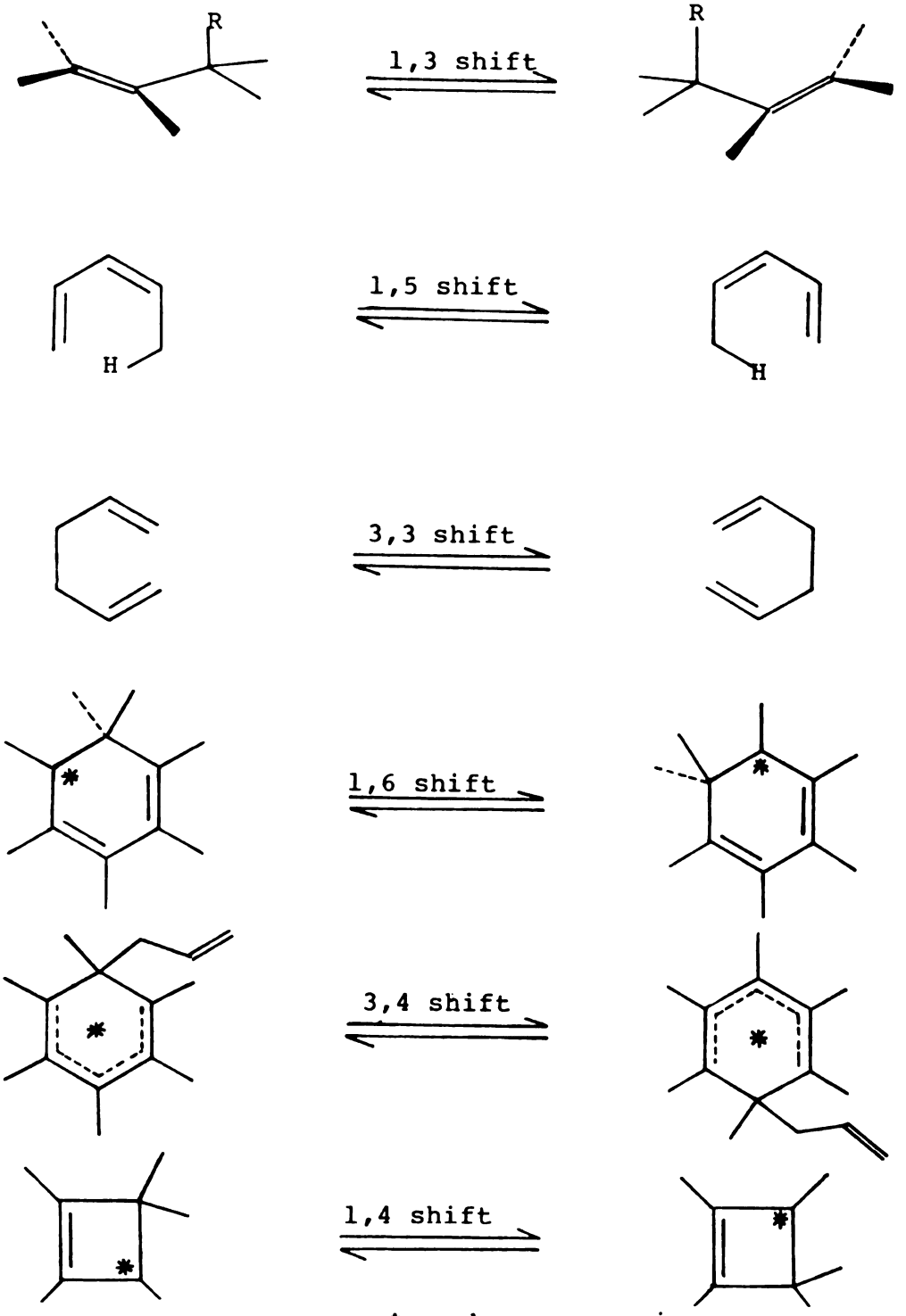
A sigmatropic reaction is defined as an intramolecular rearrangement where a σ-bond migrates from one end of an allylic (n = 1) or polyenylic (n = 2,3 etc.) chain to the other.[15] The reaction is named an [i,j] sigmatropic



shift when the bond migrates from position [1,1] to position [i,j] as shown in Figure 1.

Figure 1

Classification of i,j sigmatropic shifts



Dependent on the steroechemical results, there are two different types of sigmatropic rearrangements: suprafacial shifts and antarafacial shifts. A suprafacial shift is one where a group migrates on the same face of the pi-system. An antarafacial shift is one where the migrating group flips from one face to the opposite face of the conjugated system. If a migrating group can undergo inversion of configuration, suprafacial and antarafacial additions to a sigma bond can be defined in terms of retaining or inverting configuration of the atoms that form the migrating bond. A suprafacial addition arises when both atoms retain or invert configuration. An antarafacial addition arises when one atom retains and the other inverts configuration, as shown in Figure 2.

For sigmatropic changes of order [i,j] in which both i and j are greater than 1 and migration occurs with retention of configuration at the shifting site, the orbital symmetry rules for the neutral, cationic and anionic species are summarized in Figure 3. However if migration proceeds with inversion of configuration at the shifting center, the selection rules are precisely reversed.

The Woodward-Hoffman rules make unambiguous predictions in pericyclic reactions. The experimental results are all in accord with prediction: rapid methyl or hydrogen migration found in benzenonium ion[16,17] and

Figure 2

Suprafacial and antarafacial migration on π and σ systems

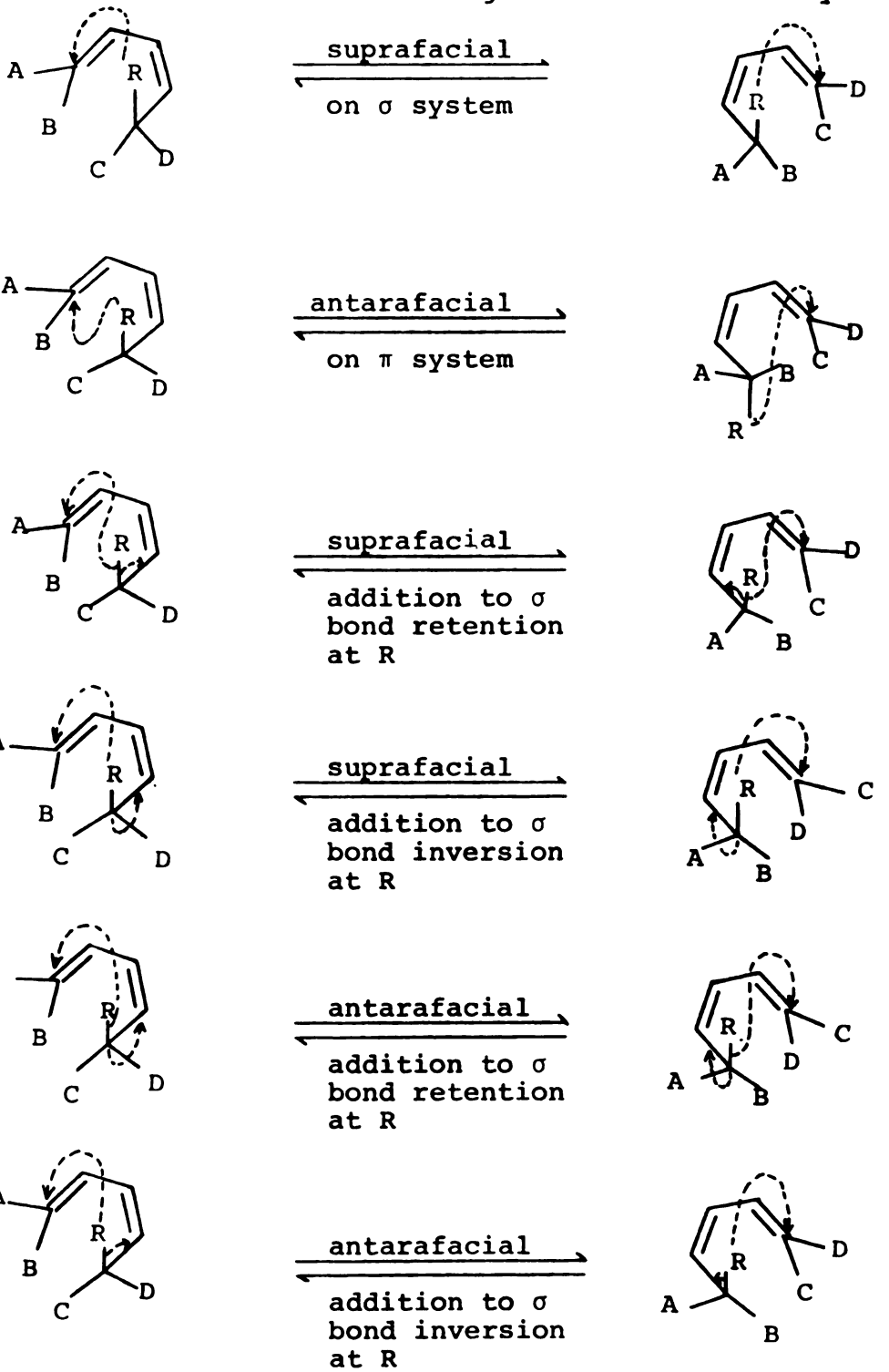


Figure 3

Selection rules for sigmatropic reactions of order [i,j] with i and j >1 and migration occurs with retention; q is an integer.

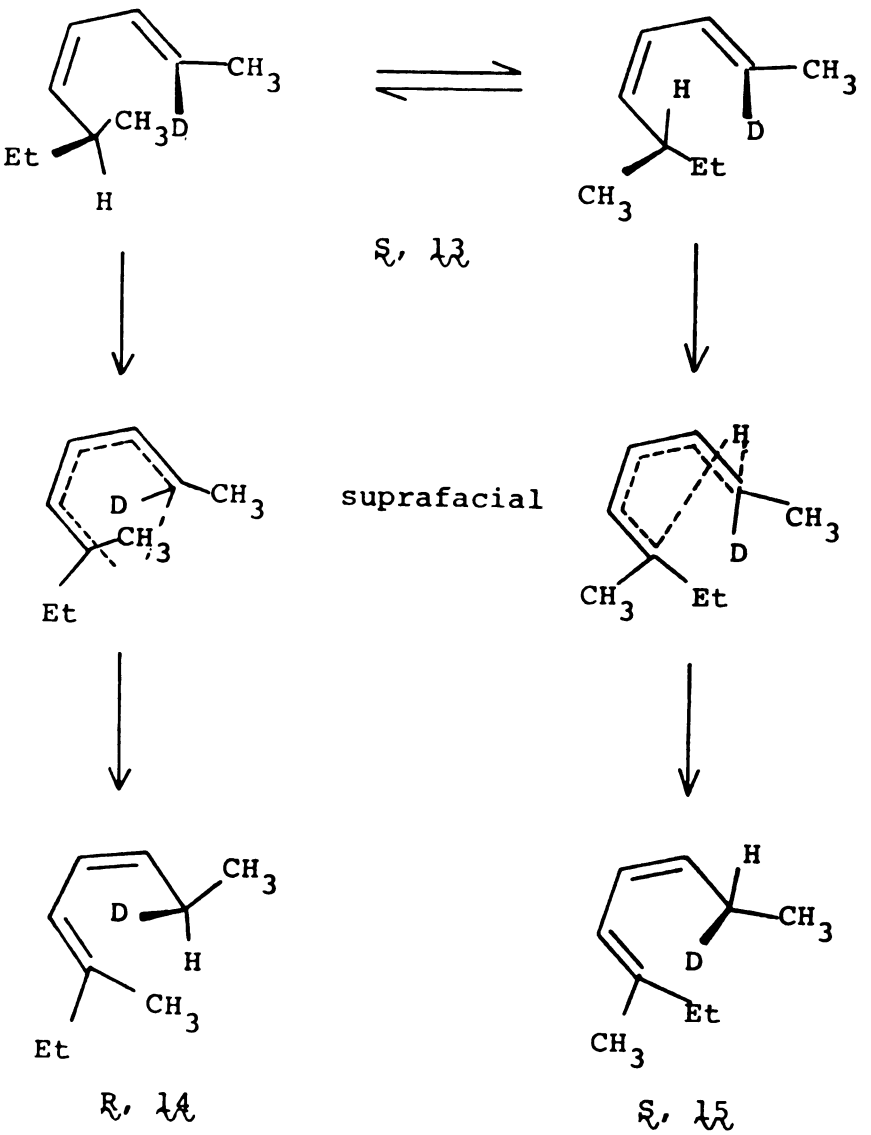
i+j			ground state	excited state
neutral	cation	anion		
4q	4q+1	4q+3	antara-supra	supra-supra
			supra-antara	antara-antara
4q+2	4q+3	4q+1	supra-supra	antara-supra
			antara-antara	supra-antara

very slow methyl or hydrogen migration, if any, found in cyclobutenium ion[18] agree with thermally allowed [1,6] sigmatropic shift and thermally forbidden [1,4] sigmatropic shift in cationic species respectively. In addition, a number of cases which were not known before, particularly concerning the stereochemistry of sigmatropic shifts, have been tested and seem to support the predictive value of orbital symmetry rules. In his study of the stereochemistry of thermal rearrangements, Roth[19] showed that at 250°, diene 13 proceeded by way of [1,5] suprafacial sigmatropic hydrogen shift to a mixture of 14 and 15 as predicted. Berson[15] also demonstrated that bicyclic

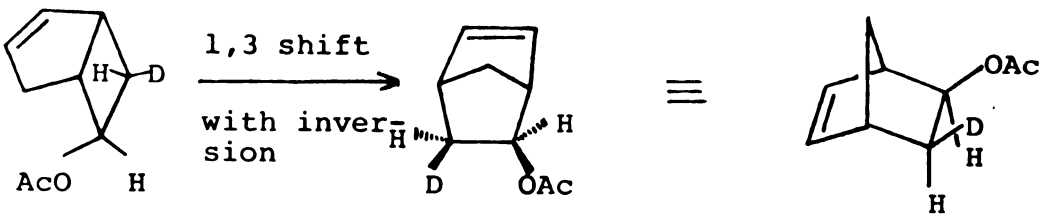
Figure 4

Thermal Rearrangement of (S)-*Cis,Trans*-

3-methyl-7-deuteroocta-4,6-diene



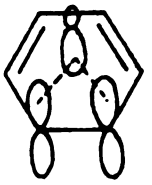
compound 16 underwent [1,3] thermal sigmatropic shift to 17 with inversion of configuration of the migrating group, which is completely consistent with the orbital symmetry rules.



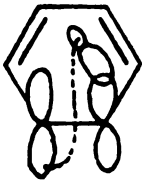
16 17

It would be worthwhile to discuss the geometric and steric requirements of the transition state of sigmatropic shifts. For example, in [1,6] migration of heptamethylbenzenonium ion, suprafacial migration with retention of configuration of the shifting carbon would allow maximum bonding overlap throughout the transition with little adjustment. However, the transition state for antarafacial shift with inversion of the migrating center would be unfavorably distorted in order to assure optimum overlap. Thus this would require higher activation energy. As predicted, suprafacial [1,6] migrations in benzenonium ions were rapid but antarafacial migration did not occur. In contrast to the benzenonium ions, the symmetry rules predict thermally allowed-antarafacial [1,4] sigmatropic shift with retention of configuration of the migrating center and allowed-suprafacial [1,4] shift with inversion of configuration of the migrating center in

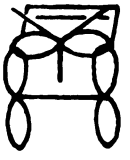
pentamethylcyclobutenyl cation. Antarafacial migration in such a small ring would result in a severe distortion in the transition state and highly strained product and will require a prohibitively high activation energy. Suprafacial migration with inversion of the shifting carbon also faces severe steric hindrance which still causes an energetic disadvantage in the transition state as shown in Figure 5. Thus the [1,4] sigmatropic shifts did not proceed in cyclobutenyl cations.



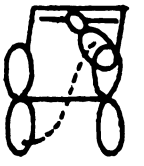
suprafacial-retention



antarafacial-inversion



suprafacial-inversion



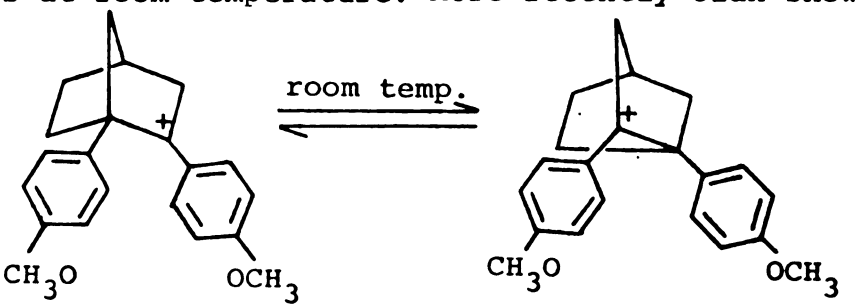
antarafacial-retention

Figure 5

Transition State for Thermally-Allowed Sigmatropic Shifts in Benzenonium and Cyclobutenium Ions.

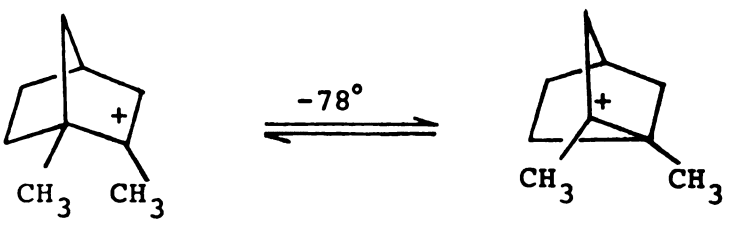
It is well known that [1,2] sigmatropic shifts or commonly called Wagner-Meerwein rearrangements in norbornyl cations are so facile that they require relatively

small activation energy.[19] Schleyer[20] showed that the 1,2-dianisyl-2-norbornyl cation 18 possessed a rapidly equilibrating ions at room temperature. More recently Olah showed

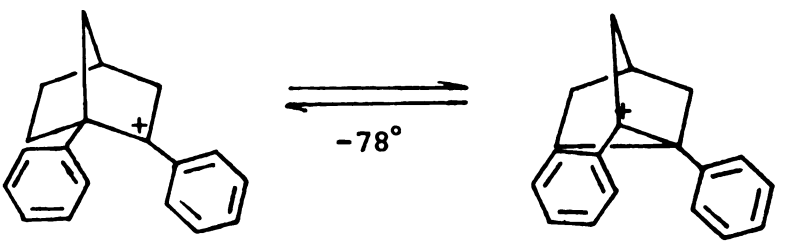


18 18a

that both 1,2-dimethyl-2-norbornyl cation[21] 19 and 1,2-diphenyl-2-norbornyl cation[22] 20 were rapidly equilibrating ions having low energy barriers for the 1,2-Wagner-Meerwein shifts.



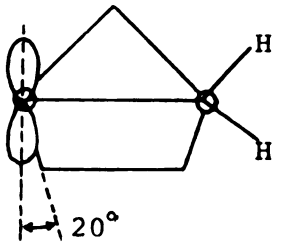
19 19a

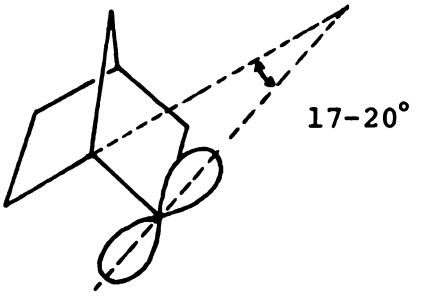


20 20a

In the crystal studies of some norbornyl derivatives, Macdonald and Trotter[23] found that there was a considerable

strain in norbornyl skeleton. The carbon-carbon single bonds are all of normal length with the average distance of 1.54 Å. However all the angles are less than tetrahedral value ranging from 101° to 108° except the bridge angle being 96-97°. Estimating from a molecular model of the rigid norbornyl system,[24] if sp^2 hybridization at C-2 is assumed, the deviation of the vacant p orbital from the C_6-C_1-C_2 plane is approximately 20°. Furthermore the C_6-C_1 bond is nearly parallel to the empty p-orbital, this deviation being approximately 17-21°. Such a suit-

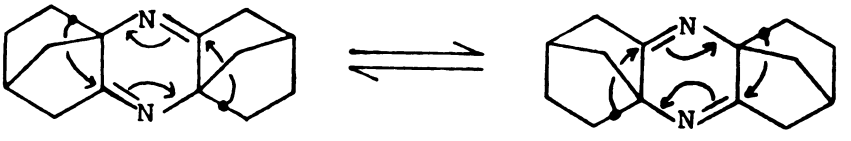




able stereo-electronic arrangement in the norbornyl skeleton allows maximum overlap in the transition state with little adjustment and thus helps accelerate the allowed process for sigmatropic rearrangements.

The accelerating effect of the norbornyl system was shown by Farnum and Carlson,[25] in their study of sigmatropic shifts in 1,2,3,4,4a,6,7,8,9,9a-decahydro-syn-2,4a,7,9a-dimethanophenazine 22, a compound which is predicted to undergo two simultaneous sigmatropic shifts photochemically. According to the orbital symmetry rules,

if the synchroneous rearrangement of 22 proceeds with retention of configuration at both migrating centers, then it will be a [$\sigma s^2 + \pi s^2 + \sigma a^2 + \pi a^2$] or entirely suprafacial or entirely antarafacial process. As expected, the optically active compound 22 did undergo



22 22a

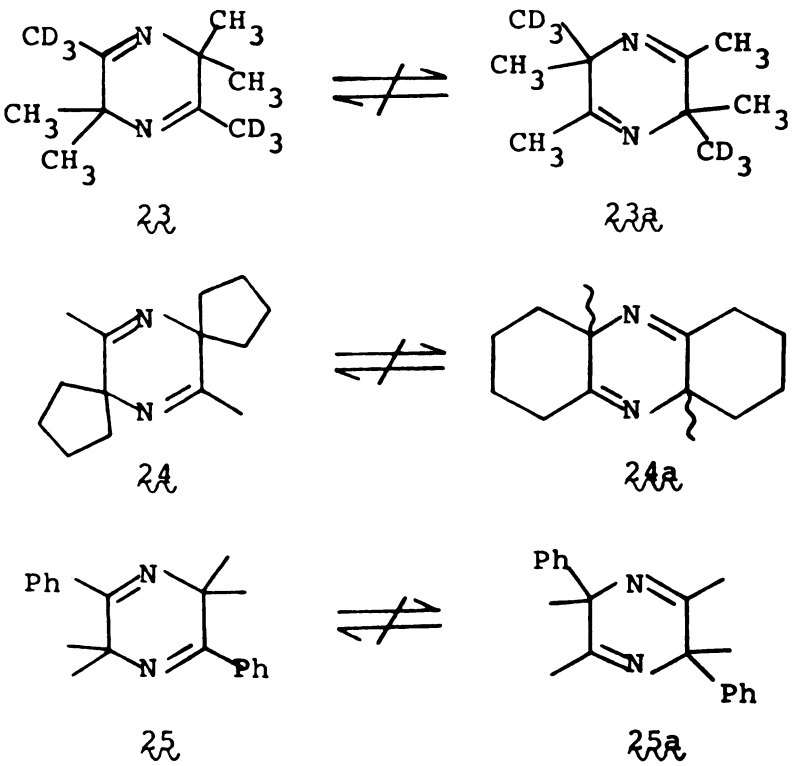
racemization upon irradiation. Under thermal condition 22 did not racemize.

The same study[26] was also carried out on dihydropyrazines 23, 24 and 25 listed in Figure 6, none of which showed such a rearrangement under photochemical or thermal conditions. It is very interesting that in the study of these synchroneous sigmatropic shifts, only the norbornyl system promoted the rearrangement.

The stereoelectronic factor that enhances or retards the rate of sigmatropic reaction is receiving increasing attention in the literature.[27,28] Berson and coworkers[29] showed that violation of conservation rules in a reaction could be permitted if the structural features of the substrates interfered with the concerted-allowed pathway. Thus rearrangements occurred through a concerted-forbidden process.

Figure 6

Dihydropyrazines subjected to study under photochemical or thermal conditions.



23 23a

24 24a

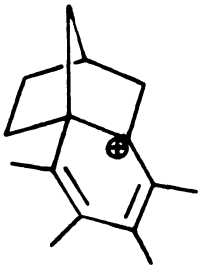
25 25a

It was our interest to design a system that provides a unique framework in such a way that maximum stereo-electronic efficiency could be obtained in order to super-accelerate an already facile sigmatropic process or perhaps to permit the concerted-forbidden reactions to occur. As described earlier, the norbornyl skeleton should be one that is well suited for rearrangement. Furthermore it has already been known to accelerate a

photochemically allowed process. Thus if the norbornyl skeleton could be fused into previously known systems where sigmatropic migrations are predicted to be allowed or forbidden processes, the resultant compounds should allow an excellent opportunity for the rate enhancement of sigmatropic shifts and the possible detection of rearrangement in a forbidden process.

A few examples of the designed-fused norbornyl systems[30] for neutral, carbonium ion and carbanion species as well as their thermal and photochemical orbital symmetry selection rules (assuming retention of configuration of migrating carbon) are summarized in Table 1. None of these has been explored to date, therefore it would be worthwhile to investigate this area of sigmatropic shifts.

The initial goal of this study was to synthesize the cations 26, 27 and 28. The cations 26 and 27 were predicted to show thermally allowed-suprafacial shifts with retention, and the rate of rearrangement was expected to



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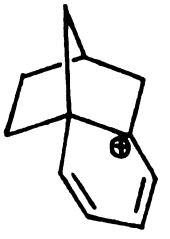

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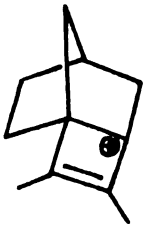
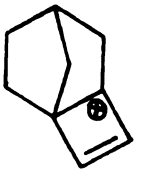
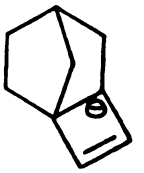
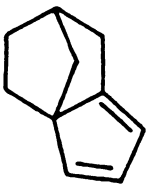
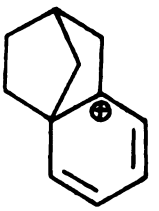
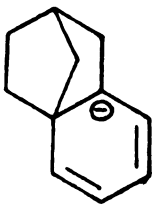
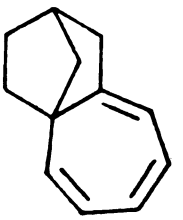


28

be faster than that of benzenonium ions. The cation 28

TABLE I

Selected Norbornyl-fused Cyclic Sigmatropic Systems.

Rearrangement type	Compound	Woodward-Hoffmann selection rules	
		Δ	hν
1,4 sigmatropic shift		forbidden	allowed
		allowed	forbidden
1,5 sigmatropic shift		allowed	forbidden
1,6-sigmatropic shift		allowed	forbidden
		forbidden	allowed
1,7 sigmatropic shift		forbidden	allowed

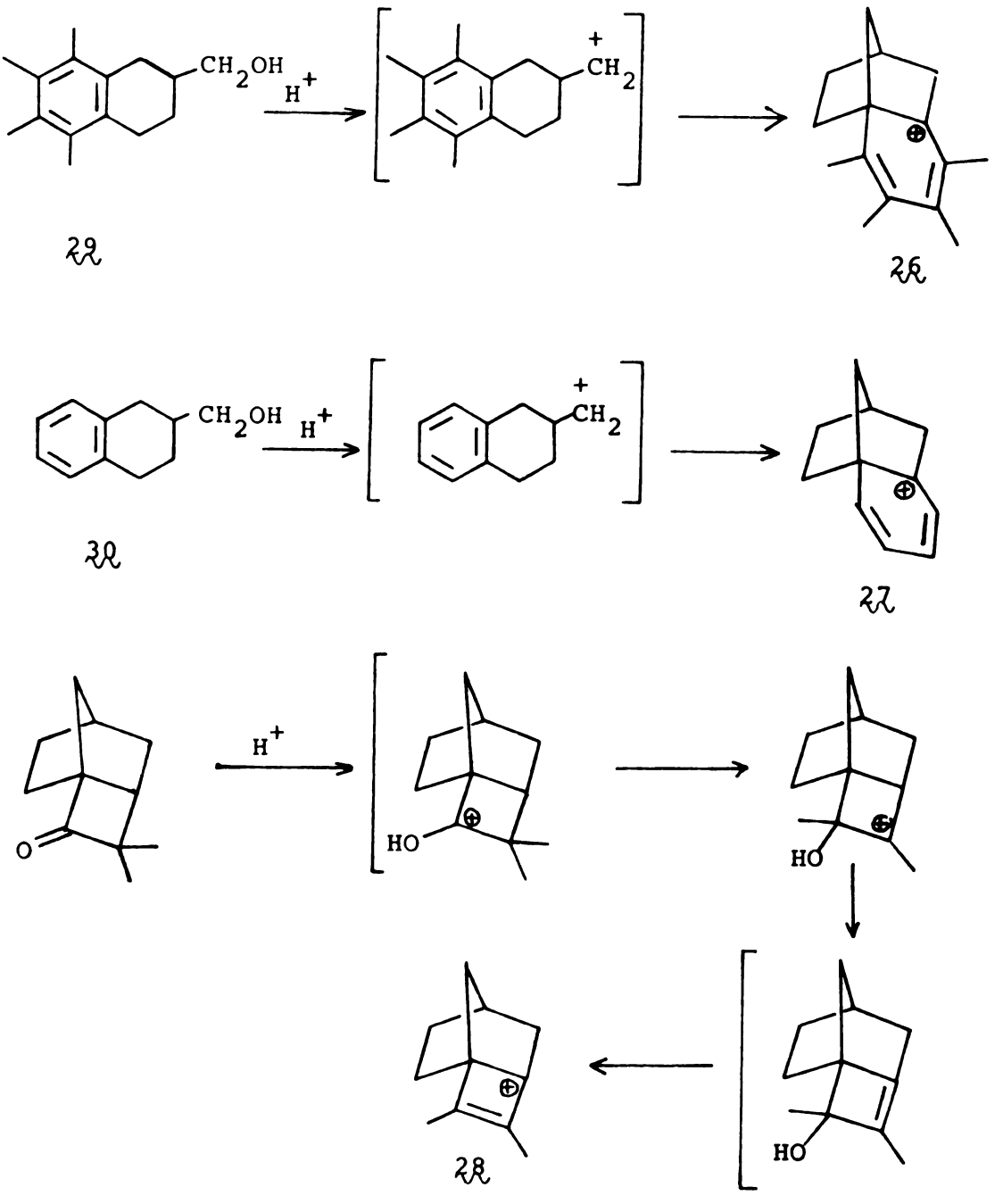
was predicted to show a thermally allowed-suprafacial shift with inversion. Since inversion would cause a severe strain in the transition state and because of the accelerating effect of the norbornyl skeleton, the reaction might proceed through a forbidden-suprafacial-retention pathway.

We proposed to make the cations 26, 27 and 28 from alcohols 29, 30 and ketone 31 as shown in Figure 7.

Thus the main part of this project was simply to synthesize the compounds 29, 30 and 31 and to investigate their chemical properties in strong acid media.

Figure 7

Pathways proposed to obtain ions 26, 27 and 28



RESULTS AND DISCUSSION A

Synthesis of 2-hydroxymethyl-1,2,3,4-tetrahydro-5,6,7,8-tetramethylnaphthalene 29 and 2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene 30 and their reactions with fluorosulfonic acid.

As mentioned previously, we proposed to make cations 26 and 27 from alcohols 29 and 30 respectively. Therefore our intention was to prepare compounds 29 and 30. The synthesis of the alcohol 29 was carried out as outlined in Figure 8. The first step was the formation of dimethylhexane diol 32. This compound was obtained according to Berkoff's procedure[31] by the coupling reaction of 2-butanone. The diol 32 showed diastereotopic ethyl groups in the nmr spectrum with centers at δ 1.41 and 0.90 for the methylene and methyl protons respectively.

Conversion of the diol 32 to the diene 33 was achieved in poor yield by distilling 32 with concentrated sulfuric acid. The nmr spectrum showed that the distillate contained another unidentified diene which is believed to be 41. The diene 33 could be purified by redistillation.

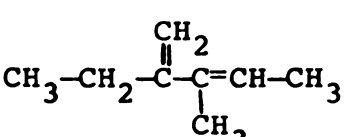


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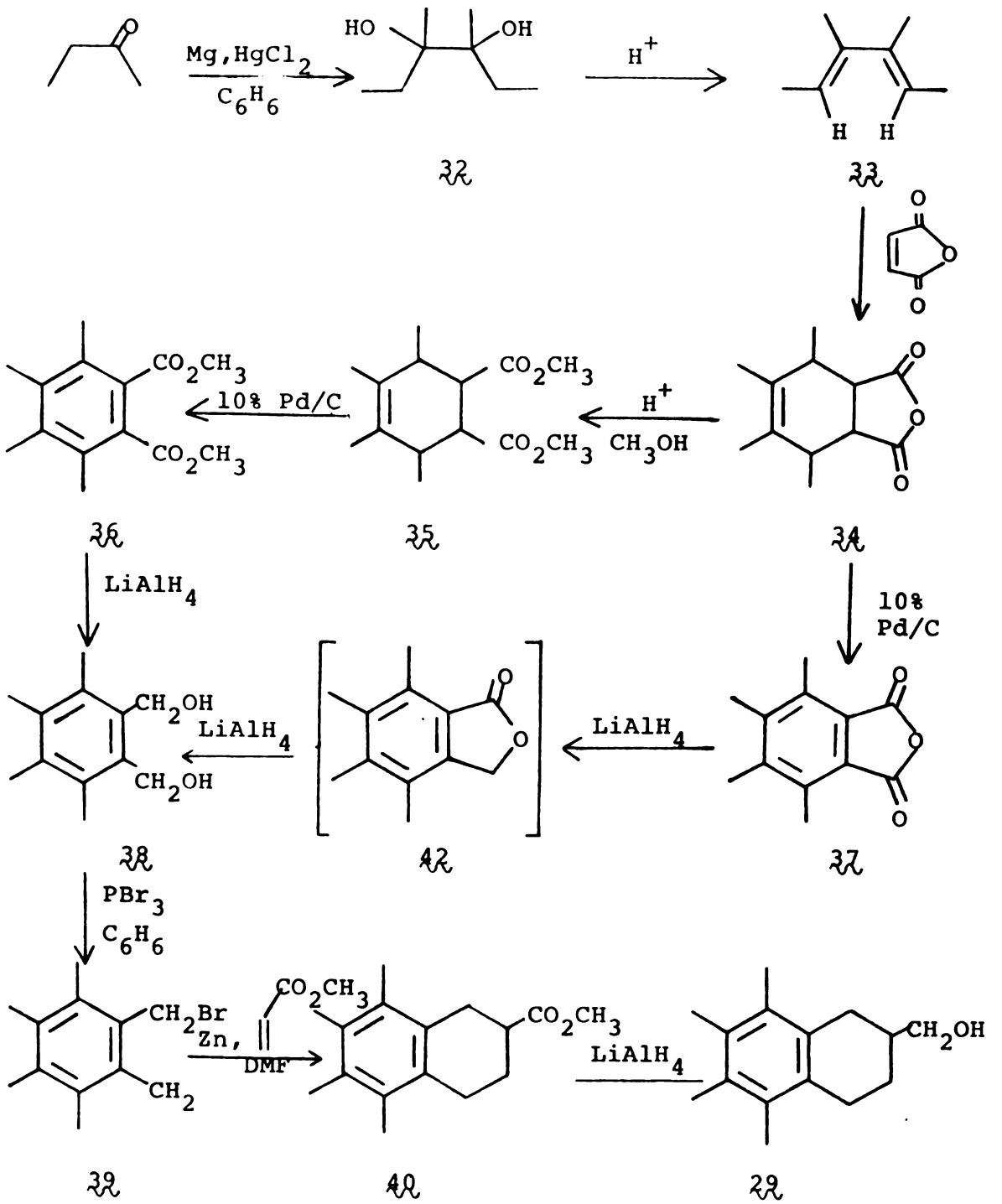
Figure 8

Synthetic Pathways to Alcohol 29



However, the impure diene 33 could be used without further purification. Treatment of the diene 33 with maleic anhydride formed the Diels-Alder adduct, tetrahydrophthallic anhydride 34 (m.p. 91.5-94°). The overall yield of 34 from the diol 32 was 23%. The spectral data were consistent with the assigned structure. The nmr spectrum showed two types of methyl proton absorptions at δ 1.42 (d, J = 7 Hz, 6H) and 1.67 (s, 6H).

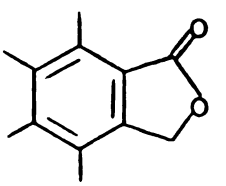
Esterification of 34 on refluxing with a catalytic amount of concentrated sulfuric acid in excess methanol gave the diester 35 in 74% yield, m.p. 50-52°. The singlet absorption of six protons at δ 3.63 in the nmr spectrum and the ir absorption at 1745 cm^{-1} supported the diester structure. Dehydrogenation of the tetrahydroester 35 was carried out on direct heating with 10% palladium-charcoal under a nitrogen atmosphere to afford the aromatic ester 36 in fair yield (60%). The two singlet signals with the same ratio of protons at δ 2.20 and 2.23 in the nmr spectrum gave evidence that four methyl groups are now attached to an aromatic ring. Other spectral properties were also in accord with the aromatic ester 36.

Treatment of the ester 36 with lithium aluminum hydride in refluxing ether produced a clean diol 38 in 90% yield. The ir spectrum of the purified alcohol 38

(m.p. 171.5-173°) showed the hydroxy absorption at 3330 cm^{-1}. The nmr spectrum exhibited the methylene proton signal at δ 4.70. The mass spectrum had the parent peak at m/e 194 (calc. mass of 38, 194).

The alcohol 38 could be obtained by an alternative pathway from the tetrahydrophthallic anhydride 34. Dehydrogenation of 34 upon heating with 10% palladium-charcoal afforded the desired phthallic anhydride 37 in 50% yield. Again, two singlet signals in the nmr spectrum at δ 2.33 and 2.63 were clearly evidence that the aromatic ring was formed. The ir spectrum showed absorptions at 1851 and 1785 cm^{-1} which were characteristic of an anhydride.

Attempts to reduce 37 to the alcohol 38 with lithium aluminum hydride in one step were unsuccessful. In all trials, the isolated material had the same relative intensity of signals in the nmr spectrum. This material was not identified and it was believed to be a mixture of two compounds. One of these was suggested to be the lactone 42. However, when this material was reacted with



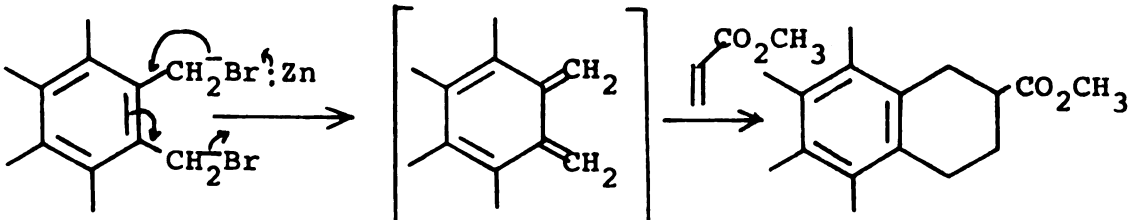
42

lithium aluminum hydride again, it proceeded smoothly and cleanly to the alcohol 38 in 95% yield from 37.

The dibromide 39 which served as a key intermediate for the synthesis of the alcohol 29, was obtained from the reaction of the diol 38 with phosphorus tribromide. The white, needle-like solid was obtained in greater than 80% yield, m.p. 163-164° after recrystallization from hexane. All spectral properties were in accord with the assigned structure.

Conversion of the dibromide 39 to the ester 40 was achieved in 72% yield by reaction with activated zinc and methyl acrylate in dimethylformamide. The spectral data of this solid ester, m.p. 91-92.5°, fully supported the proposed structure.

The course of this reaction probably involved debromination by zinc to form a 1,3-diene intermediate 43 followed by Diels-Alder reaction with methyl acrylate to the desired ester.



39 43 40

Finally, reduction of the ester 40 using lithium aluminum hydride provided the alcohol 29 in 95% yield (m.p. 101-102°). The mass spectrum showed the parent

peak at m/e 218 (calc. mass for alcohol 29, 218). Both ir and nmr spectra were consistent with the expected structure.

The synthesis of the alcohol 30 was carried out in a similar way to that of the alcohol 29 (Figure 9). Bromination of *o*-xylene 44 afforded the dibromo compound 45 in 48% yield. This lachrymal compound 45, m.p. 92-93°, was then converted to the bicyclic ester 46 in the same fashion as described for the preparation of the ester 40. Finally, treatment of the ester 46 with lithium aluminum hydride gave the desired alcohol 30 cleanly and smoothly. The spectral data of all compounds were in accord with assigned structures.

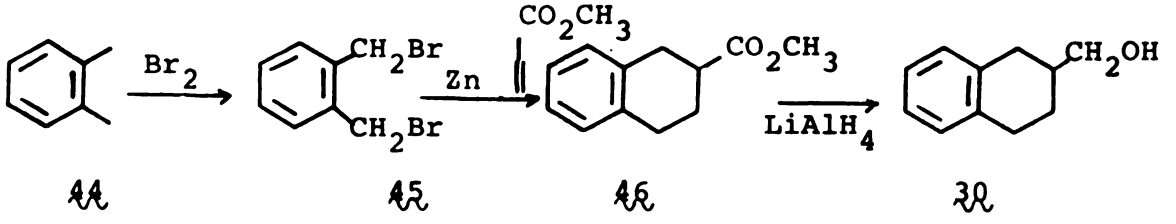
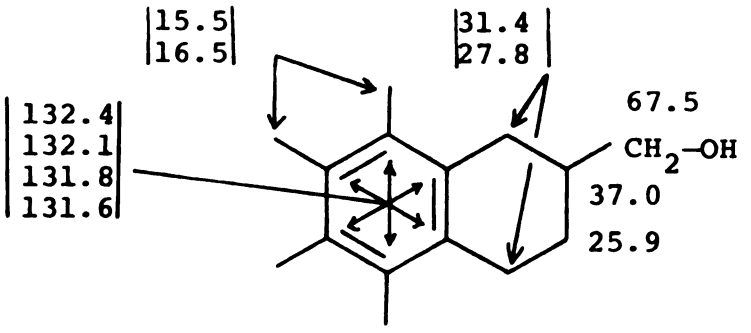


Figure 9

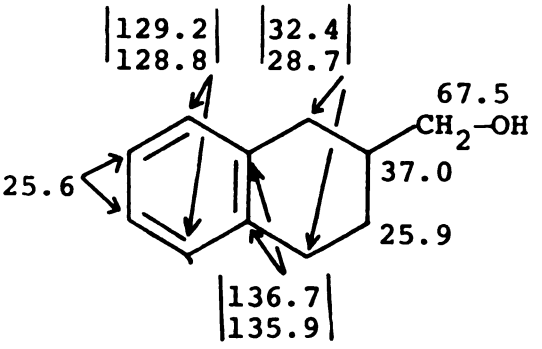
Synthetic Pathways to Alcohol 30

The C-13 nmr spectra showed that both alcohols 29 and 30 possess partially symmetrical structures. The alcohol 29 showed only four aromatic carbon signals at δ 132.4, 132.1, 132.8 and 131.6 and two signals for the methyl groups at 16.5 and 15.5. The alcohol 30 showed five

aromatic carbon signals at δ 136.7, 135.9, 129.2, 128.8 and 125.6. On the basis of some model compounds[32] and coupled spectra of both alcohols, the chemical shifts were assigned as shown in Figure 10.



29



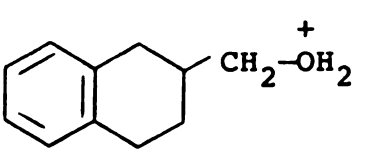
30

Figure 10

C-13 nmr Chemical Shift Assignment of 29 and 30

At this point, we had both alcohols 29 and 30 in hand. The next step was to look into their reactions in fluorosulfonic acid solution. These reactions were followed by both H-nmr and C-13 nmr spectroscopy.

The compound 30 was slowly added into a solution of fluorosulfonic acid and fluorosulfuryl chloride at -78°. The mixture was observed by C-13 nmr spectroscopy at various temperatures. The temperature-independent (-50° to -10°) spectrum consisted of aromatic absorptions at δ 136.6, 134.6, 130.1, 127.0 and 126.5 along with saturated carbon absorptions at 79.4, 34.4, 31.4, 29.0 and 25.0. All saturated carbon peaks were broad at -50° and only slightly sharpened up at -10°. When the solution of the ion was warmed to higher temperature, it slowly decomposed. The C-13 nmr data suggested the structure 47. The charge distribution in the ion remained about the same as

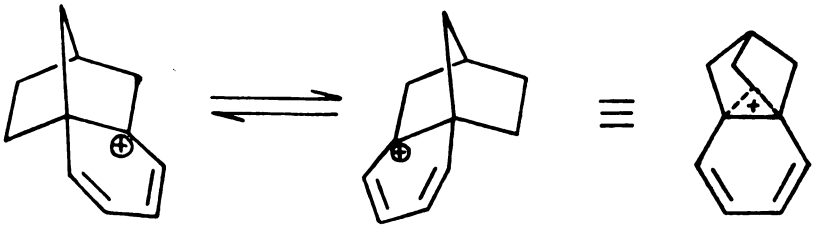


47

in the neutral compound except for the methylene carbon attached to the hydroxy group. The change in the chemical shift of this methylene carbon was likely to be expected for a protonated alcohol. The difference of 12 ppm (79.4

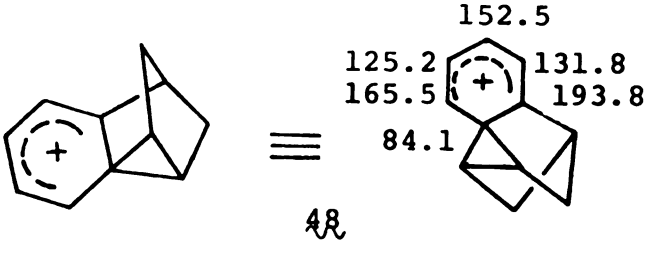
ppm in ion 47 and 67.5 ppm in 30) was comparable to that of 15 ppm between methanol and its protonated form (62.0 ppm in $CH_3\overset{+}{O}H_2$ and 47.4 ppm in CH_3OH).[33]

The nmr data rules out the desired static classical ion 27, since, for this, a cationic carbon peak in the nmr spectrum should be expected. Besides that, the posi-



27a 27 27b

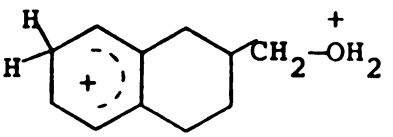
tive charge should be built up in the aromatic ring as in the case of ion 48.[34] Rapidly equilibrating pairs of classical ions (27a ⇌ 27b) were also rules out, because the C-13 nmr would exhibit a simpler spectrum.



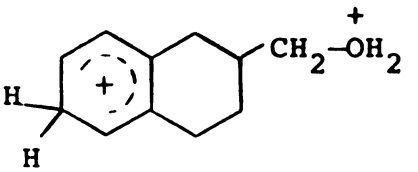
48

Charge Distribution in Cation 48

Protonation on the aromatic ring to form the classical ion 49 could be excluded since the nmr data did not show any significant positive-charge distribution which is a

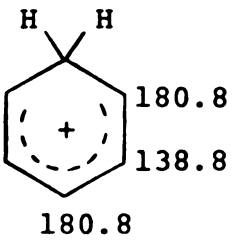


49a



49b

characteristic of a carbocation ion such as benzenium ion ion 54.[34]



50

C-13 Chemical Shift in Benzenium Ion

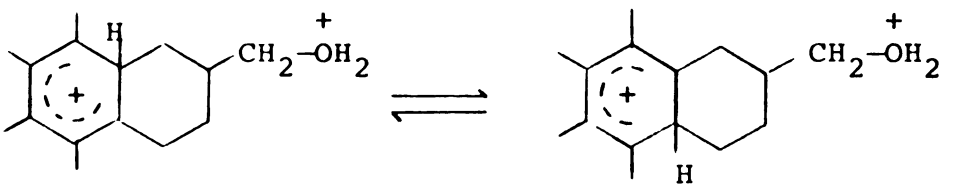
The HNMR spectra of 30 in FSO_3H–FSO_2Cl solution showed resonances at δ 7.5 (m), 4.6 (bs) and 1.43-3.56 (m). The broad signal at δ 4.6 was consistent with the chemical shift of methylene protons alpha to oxygen in a protonated alcohol.[35] The relative integral ratio of signals at δ 7.5 and 4.6 of 2 and no other signal at δ 4.0-6.0 as expected for the added proton ruled out ion 49. Thus both HNMR and CNMR spectra were in accord with the proposed ion 47.

When the alcohol 29 was dissolved in fluorosulfonic acid, a purple solution was formed. The CNMR spectrum, at -50°, showed a signal at δ 77.7 and two other broad

absorptions at δ 20-25 and 29-34. Aromatic carbon absorptions were not detected. The broad signals gradually sharpened as the solution was slowly warmed up to -20° to -15°. At -15°, the two broad signals resolved into several sharp peaks. Chemical shifts were recorded as followed: 77.7, 33.9, 31.9, 31.5, 23.7, 21.2, 20.7 and 20.2 ppm. The aromatic signals could not be obtained again, possibly due to relaxation time. However, the spectrum showed a very broad absorption at δ 140-170. When the solution was warmed above -10°, the spectrum began changing with the appearance of several saturated carbon signals, presumably from decomposition.

The HNMR spectra of the solution also showed broad signals at lower temperatures (-60° to -40°). At -60°, the spectrum possessed broad absorptions at δ 4.75, 4.21 and 3.48-1.39. When the solution was warmed up to -40°, the signal at δ 4.21 became broader while the other became sharper. However at -20°, methyl absorptions were resolved. The spectrum showed three singlet peaks at δ 2.46, 2.41 and 2.10 with relative area of 1:1:2. Other absorptions were at δ 4.73 (broad doublet), 4.31 (multiplet) and 3.38-1.40 (multiplet).

The HNMR spectrum at -60° indicated that either ion 51a or 51b was formed. At -40° to -20°, it indicated that rapid equilibration of ions (51a ⇌ 51b) occurred resulting



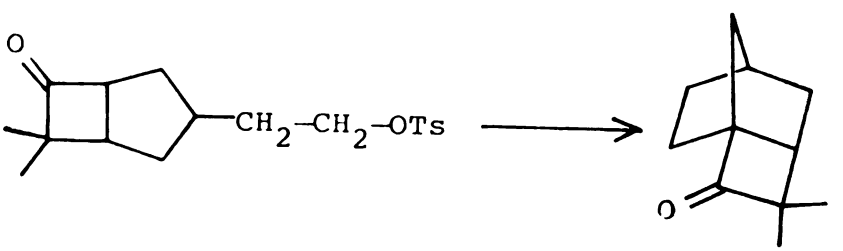
51a 51b

in broadening of the added proton at δ 4.21 due to coupling with more different protons. The C-13 chemical shift study indicated protonation of hydroxy group. However due to poor resolution of the aromatic signals, the CNMR could not confirm protonation on the aromatic ring as suggested by the HNMR spectrum.

RESULTS AND DISCUSSION B

Synthetic Approach to 3,3-Dimethyltricyclo[4,2,1,$0^{1,4}$] nonan-2-one 31

We proposed to achieve the synthesis of tricyclic ketone 31 by means of cyclization of the bicyclic keto tosylate 52. The total synthetic plan is outlined in

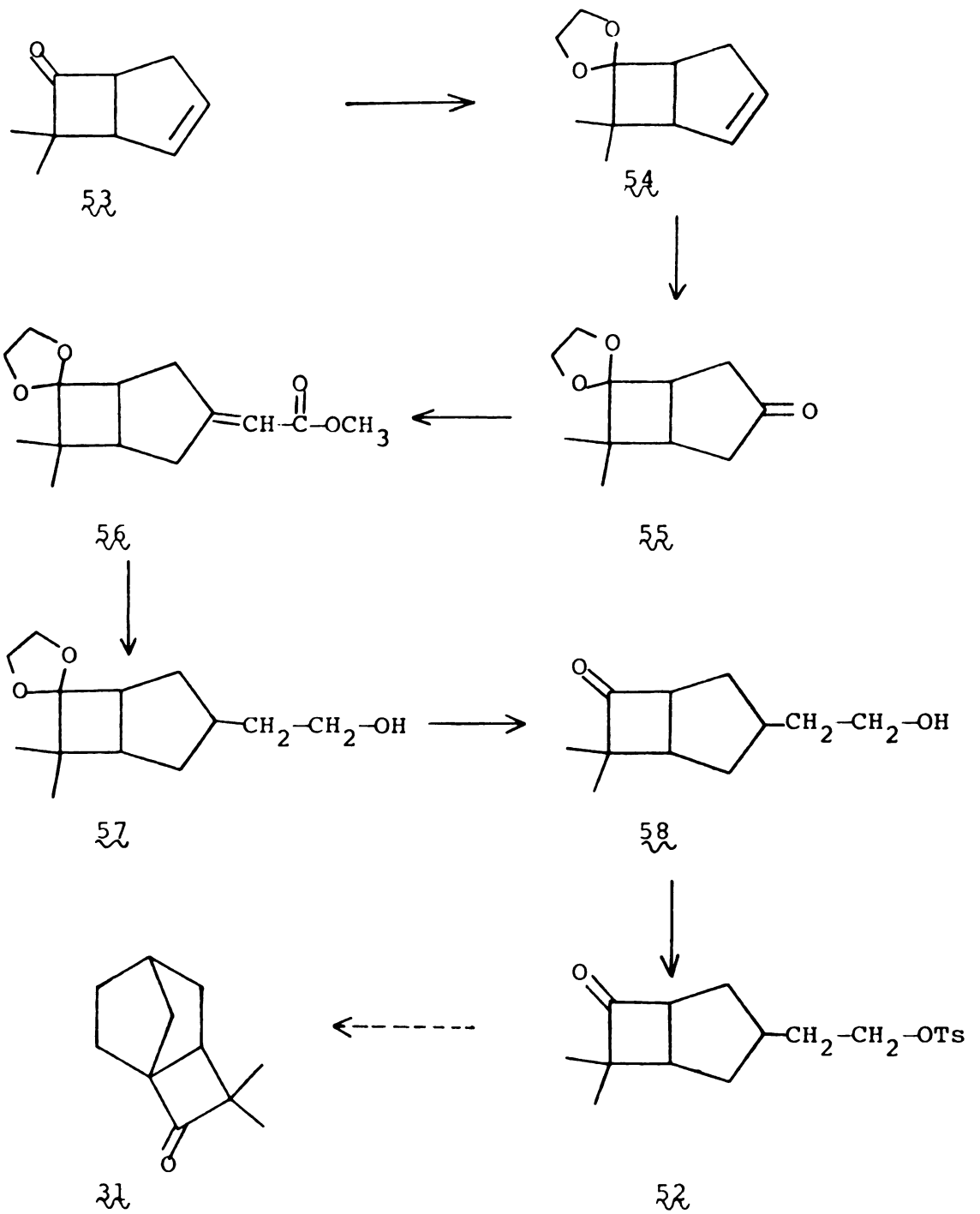


52 31

Figure 11. This route required 7,7-dimethylbicyclo[3,2,0] hept-2-ene-6-one 53 as a starting material. This compound is well suited as a starting material in many ways. First, it provides two functionalities, ketone and olefin, in which each function could be easily transformed to the desired structure. Second, it has been known in the literature[36] and can be synthesized without much difficulty. Finally, it is a very stable compound and can be kept under nitrogen atmosphere at room temperature for at least nine months.

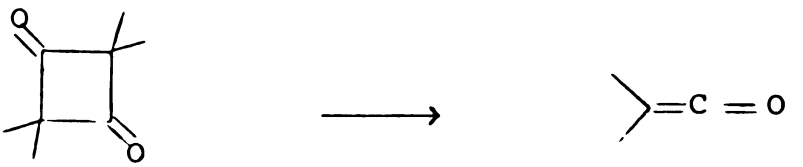
Figure 11

Proposed Synthetic Pathways to 31

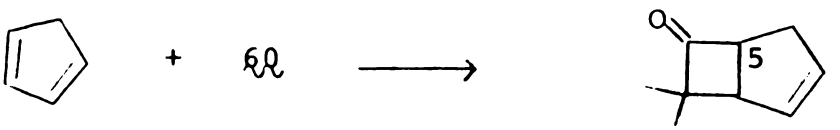


The synthesis of 7,7-dimethyl-6,6-ethylenedioxybicyclo-[3,2,0]heptan-3-one 55.

According to the literature, the ketone 53 was prepared by means of addition of dimethylketene generated by direct pyrolysis of 2,2,4,4-tetramethyl-1,3-dione 59[37] to cyclopentadiene. With some modification, we generated

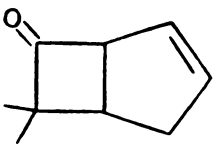


59 60



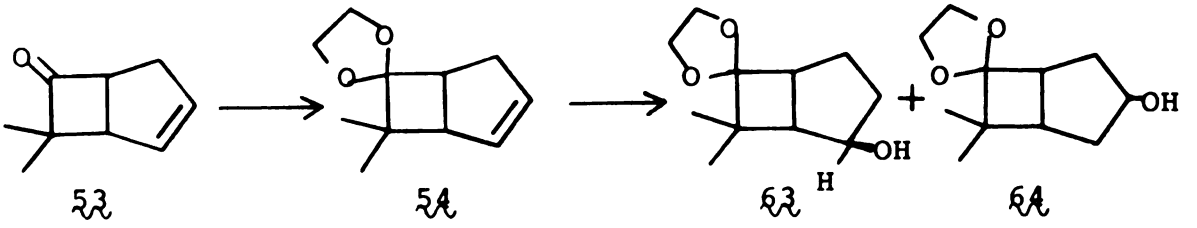
53

dimethylketene 60 by pyrolyzing its dimer 59 and passed it directly into a solution of cyclopentadiene in acetonitrile. This reaction afforded a 56% yield of 53. The nmr and ir spectra were consistent with those reported previously. The chemical shift of the methine proton (H-5) at δ 3.38 and its multiplicity (doublet of triplet, J = 7, 3 Hz) appear to distinguish the ketone 53 from its isomer 61 which has never been observed from such a reaction.

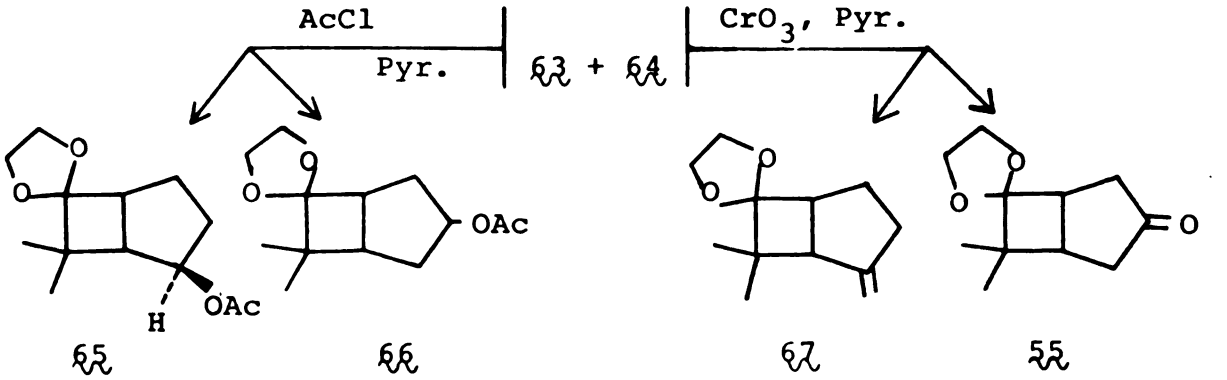


61

The next step of the synthesis requires protection of the carbonyl function in the compound 53 followed by transformation of the olefinic function to another. Hydroboration and oxidation appears to be a suitable pathway to convert an olefin to an alcohol.



53 54 63 64



65 66 67 55

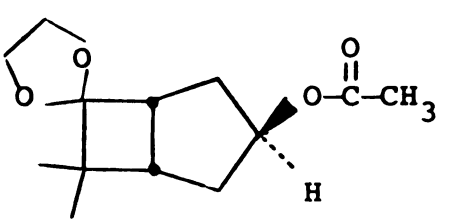
The ketone 53 was therefore protected as an ethylene ketal 54. This ketalization proceeded cleanly and in quantitative yield. The presence of the ketal function

moved chemical shifts of all protons to higher field as expected especially that of the methine proton (H-5), which moved from δ 3.83 in 53 to δ 2.96 in 54. Treatment of 54 with diborane in tetrahydrofuram followed by oxidation with hydrogen peroxide in basic solution afforded a mixture of alcohols in more than 95% yield. Gas chromatographic analysis showed that the mixture consisted of two alcohols with a ratio of 7:3. These two alcohols were presumed to be alcohols 63 and 64 respectively. The proof of this was given later. Attempts to separate these two isomers on column chromatography were unsuccessful. Separation by preparative vpc gave only pure 63 which is the major isomer. Reinjection of the other collected fraction still showed the presence of 63.

The proton magnetic resonance spectrum allowed a decision about the stereochemistry of 63. The spin-spin coupling of the proton (δ 3.96) alpha to the hydroxy group showed a broad doublet with a coupling constant of 4 Hz. This was consistent with that expected from the <u>exo</u> alcohol 63.

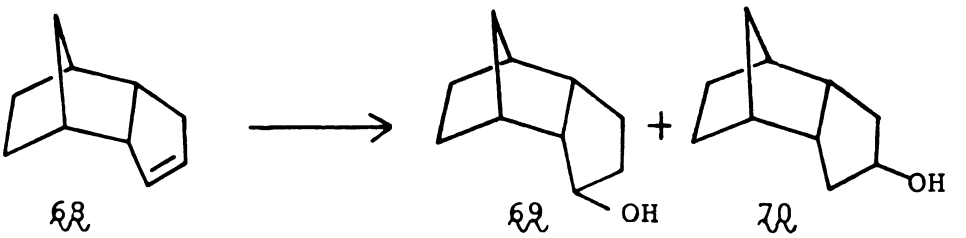
Although the ketal alcohol 64 could not be separated, it could be characterized as an acetate. Treatment of the mixture of alcohols 63 and 64 with excess acetyl chloride in pyridine afforded a mixture of acetates 65 and 66 in 92% yield and a ratio of 2:1 respectively as analyzed by

gas chromatography. Conversion of the ketal alcohol 64 to the acetate 66 was complete but 7.2% of the ketal alcohol 63 remained. Separation of acetate isomers was achieved by column chromatography. The spin-spin coupling of the proton alpha to the acetyl group in the nmr spectra permitted the isomeric acetates to be identified as 65 and 66 respectively. The broad doublet at δ 4.88 (J = 4 Hz) was consistent with the assigned structure 65 as well as its stereochemistry. A triplet at δ 5.17 (J = 7 Hz) was also in accord with the acetate 66. The stereochemistry of 66 could not be established from the nmr or ir spectra. However, the stereochemistry of this compound was suggested to be an *exo* acetate 66a on the basis of attack of borane on the less hindered side.



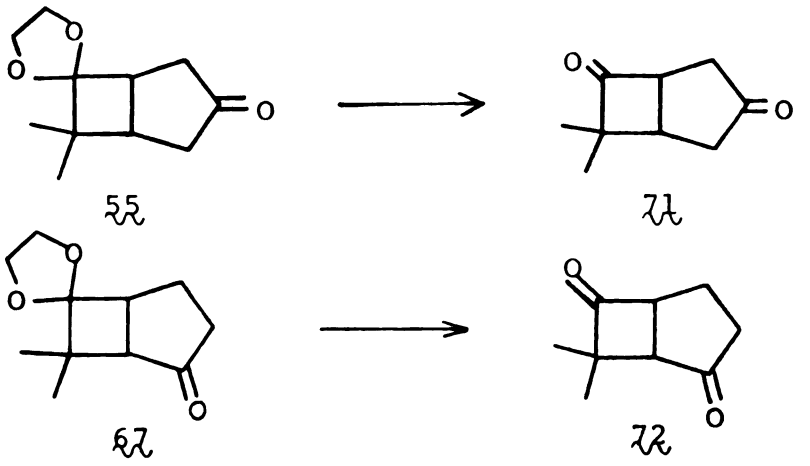
66a

It is very interesting that hydroboration of 54 gave 63 as a major product. Brown[38] also observed that hydroboration of 68 gave a mixture of alcohols 69 and 70 with a ratio of 6:4. The reason for this is not clear.

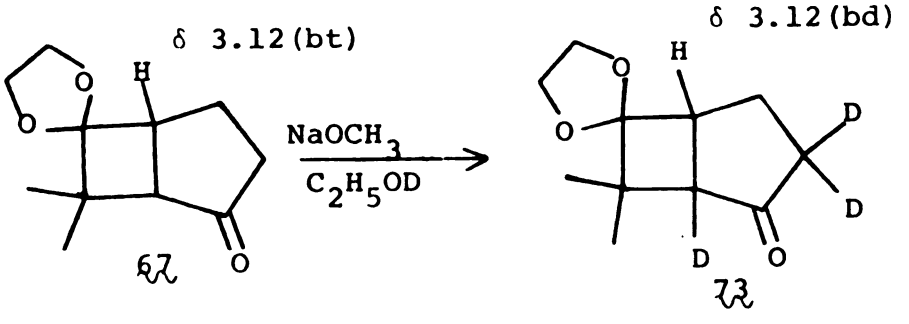


68 69 70

The structural assignment of alcohols 63 and 64 was confirmed by oxidation of the mixture of alcohols to ketones according to Dauben's procedure[39] followed by deketalization. The mixture of 63 and 64 was subjected to oxidation using chromium trioxide-pyridine complex to afford a clean mixture of ketones 55 and 67 in a ratio of 3:7 according to gas chromatographic analysis. This ketone mixture was then separated by column chromatography. Both ir and nmr spectra of these ketones are quite different. The ir spectrum of 55 showed a carbonyl absorption at 1750 cm^{-1} and that of 67 at 1739 cm^{-1}. The nmr spectra were markedly different in the spin-spin coupling. The ethylene ketal protons in 55 showed a broad singlet while those of 67 showed a multiplet. The signals for the protons at C-1, C-2 and C-4 of 55 were less complex than those for the protons at C-1, C-3 and C-4 of 67. However, the evidence collected from nmr and ir spectra would not permit a definite structural assignment for ketones 55 and 67. Therefore both ketones 55 and 67 were subjected to further reactions. Deketalization of 55 and 67 produced diketones 71 and 72 respectively.



The spin-spin coupling of the methine (H-1) proton resolved the conflict between the two structures. A doublet for the H-1 proton at δ 2.60 (j = 8 Hz) which was split by the H-5 proton was consistent only with the diketone 72. A complex signal at δ 2.70 split by 2H-2 and H-5 protons was consistent with the diketone 71. Additional evidence to confirm the structure of 67 was obtained from proton-deuterium exchange. Thus stirring 67 with sodium methoxide in deuterium ethoxide for two hours exchanged up to three protons as determined by the nmr spectrum. The signal of a broad triplet at δ 3.12



(J = 8 Hz) in 67 changed to a broad doublet (J = 8 Hz) in 73. Comparison of the integration ratio based on the methyl protons or ethylene ketal protons revealed that 73 possessed a multiplet of approximately two protons at δ 1.90. This is consistent with the deuterated ketone 73.

It is very unfortunate that the desired ketone 55 was a minor product from hydroboration and oxidation reactions. Since the synthesis of 31 required many reactions, it was clear that a large amount of 55 was required in order to complete the final step. Therefore a new route to 55 was designed.

A thorough search of the chemical literature provided several routes for the conversion of epoxides to ketones or alcohols as shown in Figure 12. Even though acid or salt catalyzed rearrangement of an epoxide to a ketone is well known, base catalyzed transformation may also be possible. In general, the dominant pathway for the reaction of a simple alkyl-substituted epoxide with a strong base is a rearrangement into an allylic alcohol.[46] However Crandrall[47] and coworkers found that ketones were also formed upon treatment of some epoxides with lithium diethylamide as shown in Figure 13.

Figure 12

Various Pathways for Conversion of

Epoxides to Alcohols or Ketones.

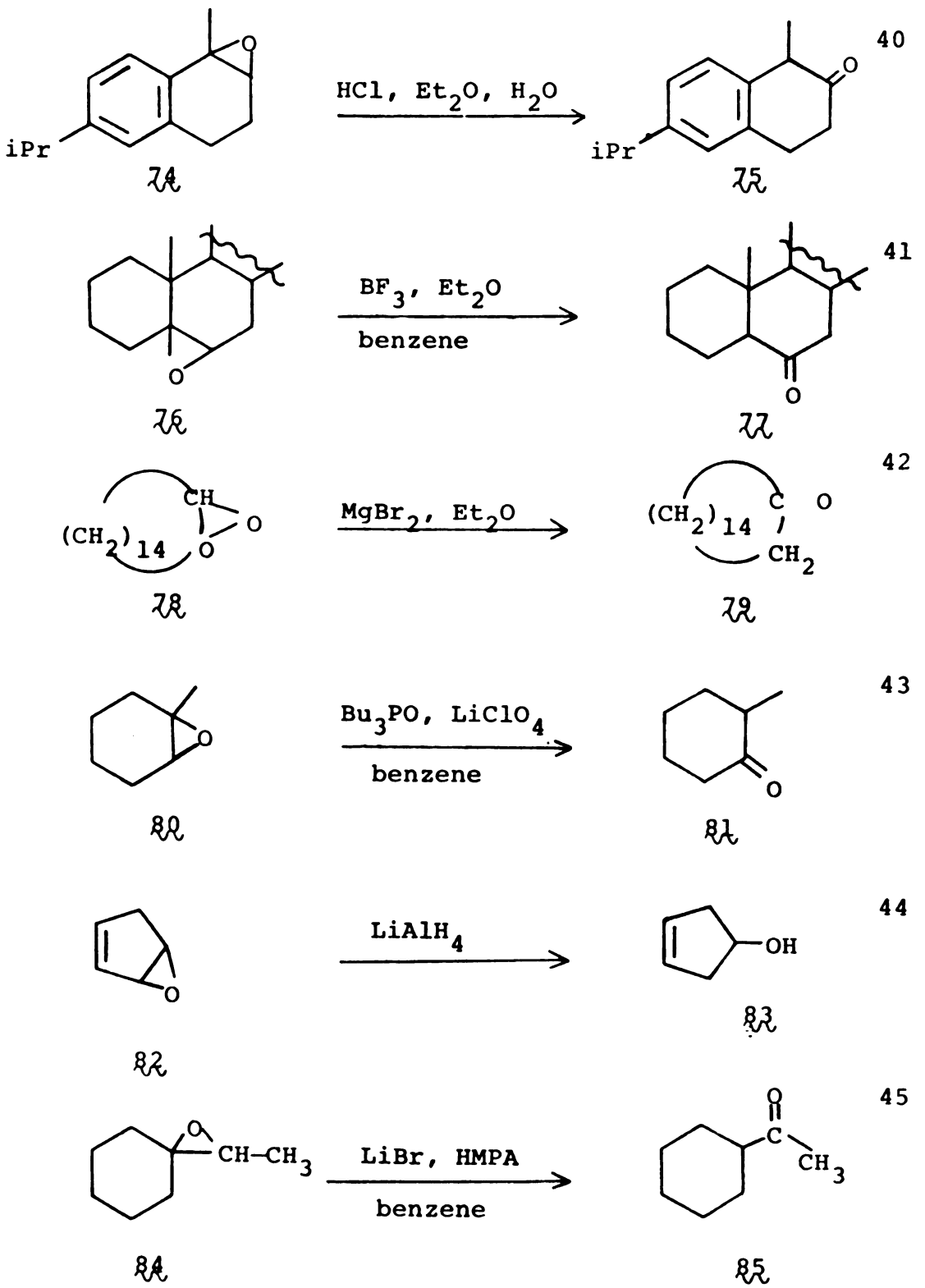
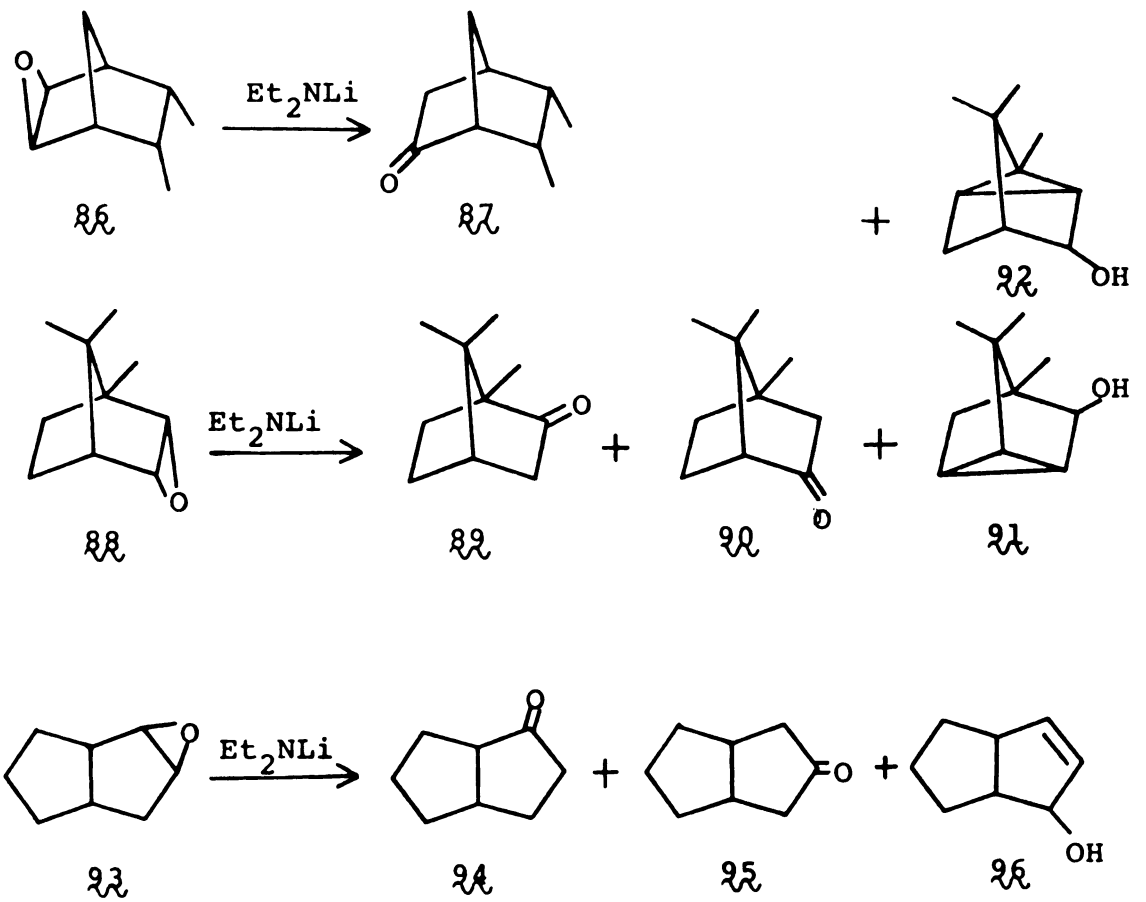
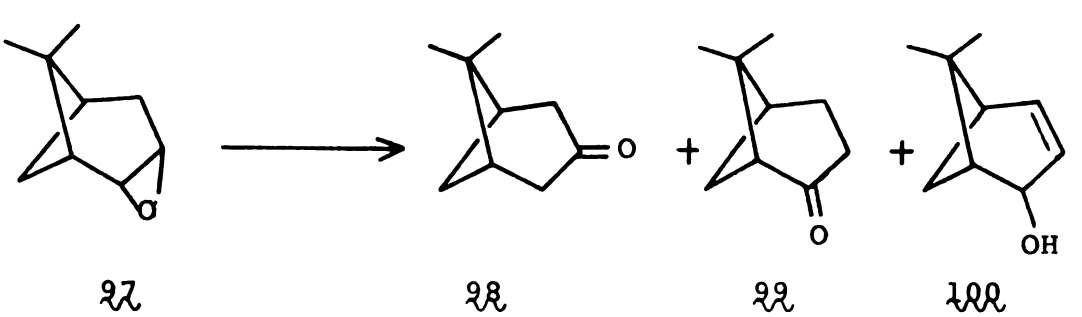


Figure 13

Base Catalyzed Rearrangement of Epoxides to some Ketones



In some cases, rearrangement to ketones was found to predominate over that to allylic alcohols. For example,[48] the reaction of the epoxide 97 with lithium diethylamide gave ketones 98 and 99 as major products while the

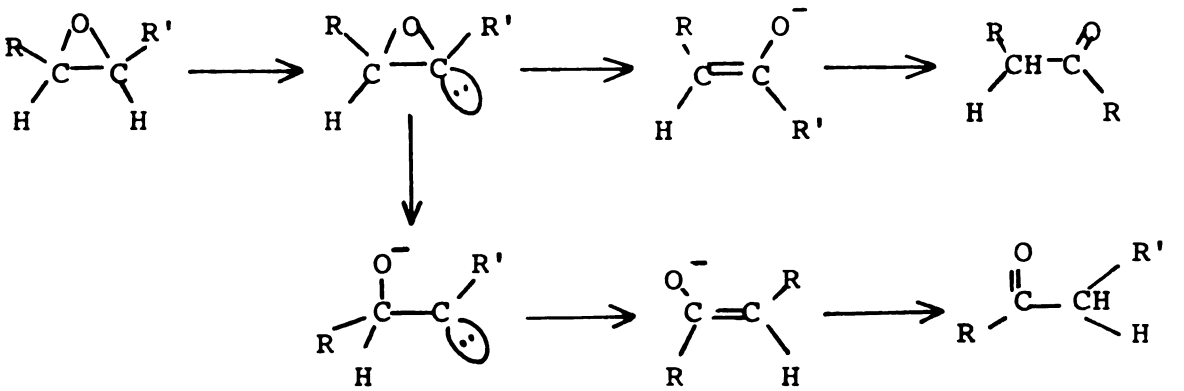


allylic alcohol 100 was found in a small yield. Crandall suggested that the steric effect of the methyl group influenced the course of the transformation.

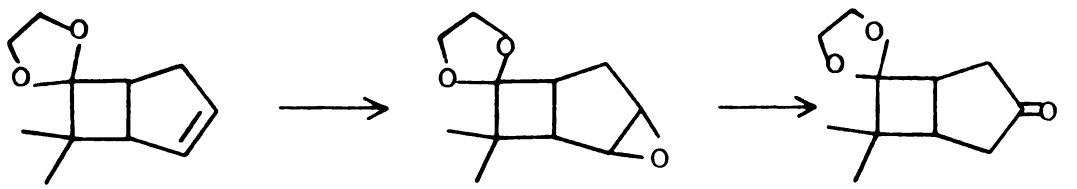
The mechanism for the base catalyzed conversion of an epoxide to a ketone was proposed by Crandall[48] to involve α-proton abstraction followed by rearrangement as depicted in Figure 14.

Figure 14

Proposed Mechanism for Rearrangement of an Epoxide to Ketones.

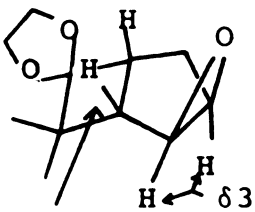


It appears to be very promising that the ketone 55 could be obtained as a major product from rearrangement of the epoxide 101. Thus treatment of the olefin 54 with metachloroperbenzoic acid yielded the epoxide 101 in quantitative yield. The product appeared to be a single isomer as shown from the nmr spectrum and gas



54 101 55

chromatography. The nmr data permitted the stereochemistry of 101 to be established. A doublet at δ 2.13 (J =



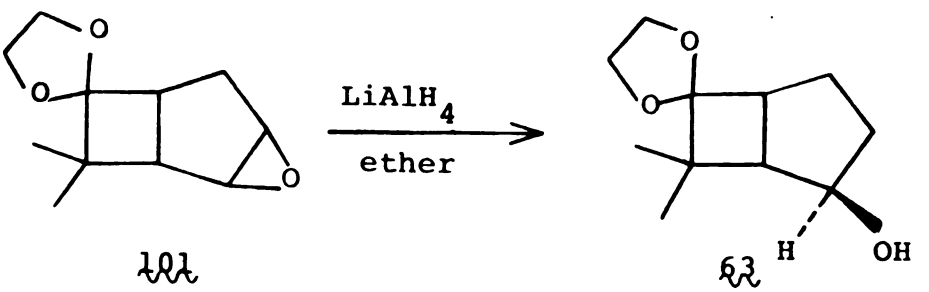
δ3.23, dd, J = 8,2 Hz

δ 2.13, d,J = 8 Hz

101a

8 Hz) and a doublet of doublet at δ 3.23 (J = 8, 2 Hz) confirmed the structure as well as stereochemisty as *exo* epoxide 101a.

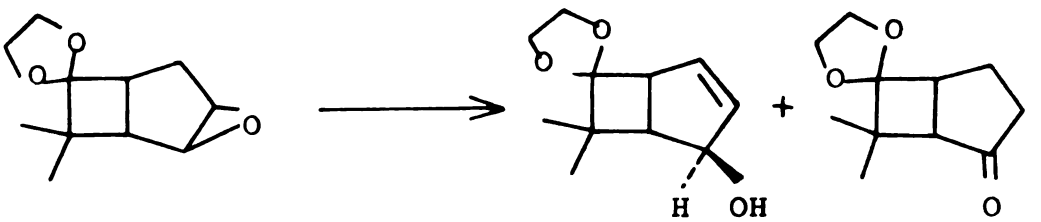
Reaction of the epoxide 101 with lithium aluminum hydride gave only the alcohol 63. This is not very surprising since the less hindered position was attacked



101 63

by the hydride ion. This reaction also confirmed the stereochemical assignment of 63 obtained from hydroboration.

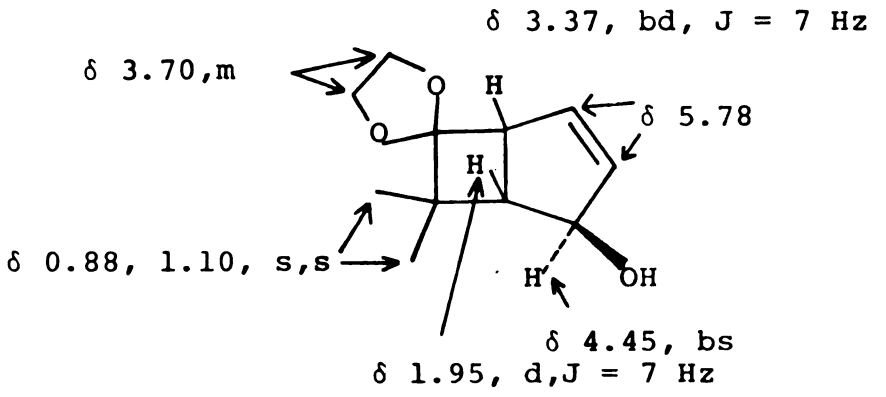
When the epoxide 101 was treated with lithium diisopropylamide in ether at reflux temperature, two products were formed in a ratio of 85:15. The minor



101 102 67

85% 15%

product was found to be 67. The spin-spin coupling in the nmr spectrum allowed us to assign the structure and stereochemistry of the major product to be an *exo* allylic alcohol 102. A broad doublet at δ 3.37 (J = 7 Hz), a doublet at δ 1.95 (J = 7 Hz) and a broad singlet at δ 4.45 were consistent with those expected from the assigned structure.



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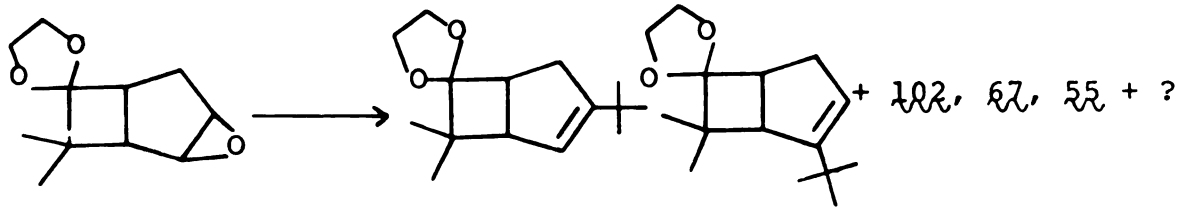
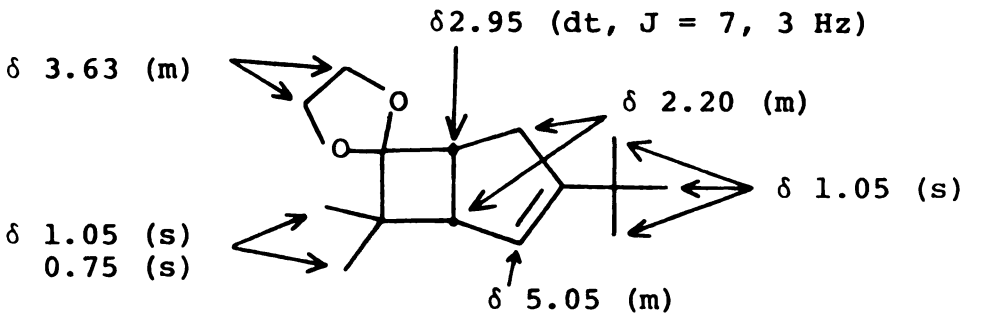
Treatment of the epoxide 101 with *t*-butyllithium at low temperature afforded the desired ketone 55, as well as 67, 102, 103, 104 and another in 71, 3.4, 15.4, 3.4,



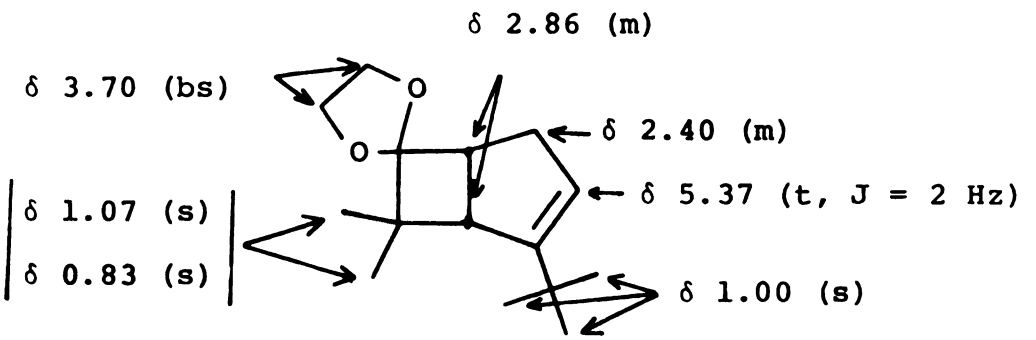
102 103 104

3.4% 4.5% 15.4% 3.4% 71%

4.5 and 2.3% yield as analyzed by gas chromatography. Separation of 67, 55 and 102 from a mixture of 103 & 104 was achieved by column chromatography. However, separation by preparative vpc afforded pure 103 and 104. Structures of both 103 and 104 were assigned mainly on the basis of nmr spectra. However, further evidence to support the correctness of the proposed structures was obtained from nmr decoupling experiments. Irradiation of



103



104

the methylene protons at δ 2.20 in the compound 103 changed the spin-spin coupling of the olefinic proton at δ 5.05 (m) to a doublet (J = 2 Hz). Similarly, irradiation of the methylene protons at δ 2.40 in 104 changed the triplet at δ 5.37 (J = 2 Hz) to a singlet. This was completely consistent with expected results from the proposed structures.

The ketone 55 was also found to predominate over the allylic alcohol 102 and the ketone 67 in a variety of

solvents and butyllithium base catalyzed reactions as shown in Table 2.

TABLE II

Study of Base Catalyzed Rearrangement of Epoxide 101.

base	solvent	% product			
		55	67	102	others
t-BuLi	THF	71.1	3.4	15.4	10.1
t-BuLi	pentane	33.5	13.5	31.3	21.7
n-BuLi	pentane	40.7	10.2	29.8	19.8
n-BuLi	THF-pentane	56.7	2.6	21.9	18.8
n-BuLi	THF	56.0	2.3	22.6	19.1
n-BuLi	ether	59.6	6.7	18.0	15.7

Synthesis of 7,7-dimethyl-3-(2-ethyltosylate)-bicyclo-[3,2,0]heptan-6-one 52

Establishing a carbon sidechain at the C-3 site of the ketone 55 was the next synthetic step. The modified Wittig reaction seemed to be well suited for this transformation. Thus the ketone 55 was converted to the conjugate ester 56 in 67% yield using methyldiethylphosphonoacetate in a Wadsworth-Emmons phosphonate reaction.[49] The nmr spectrum showed a broad singlet for the olefinic

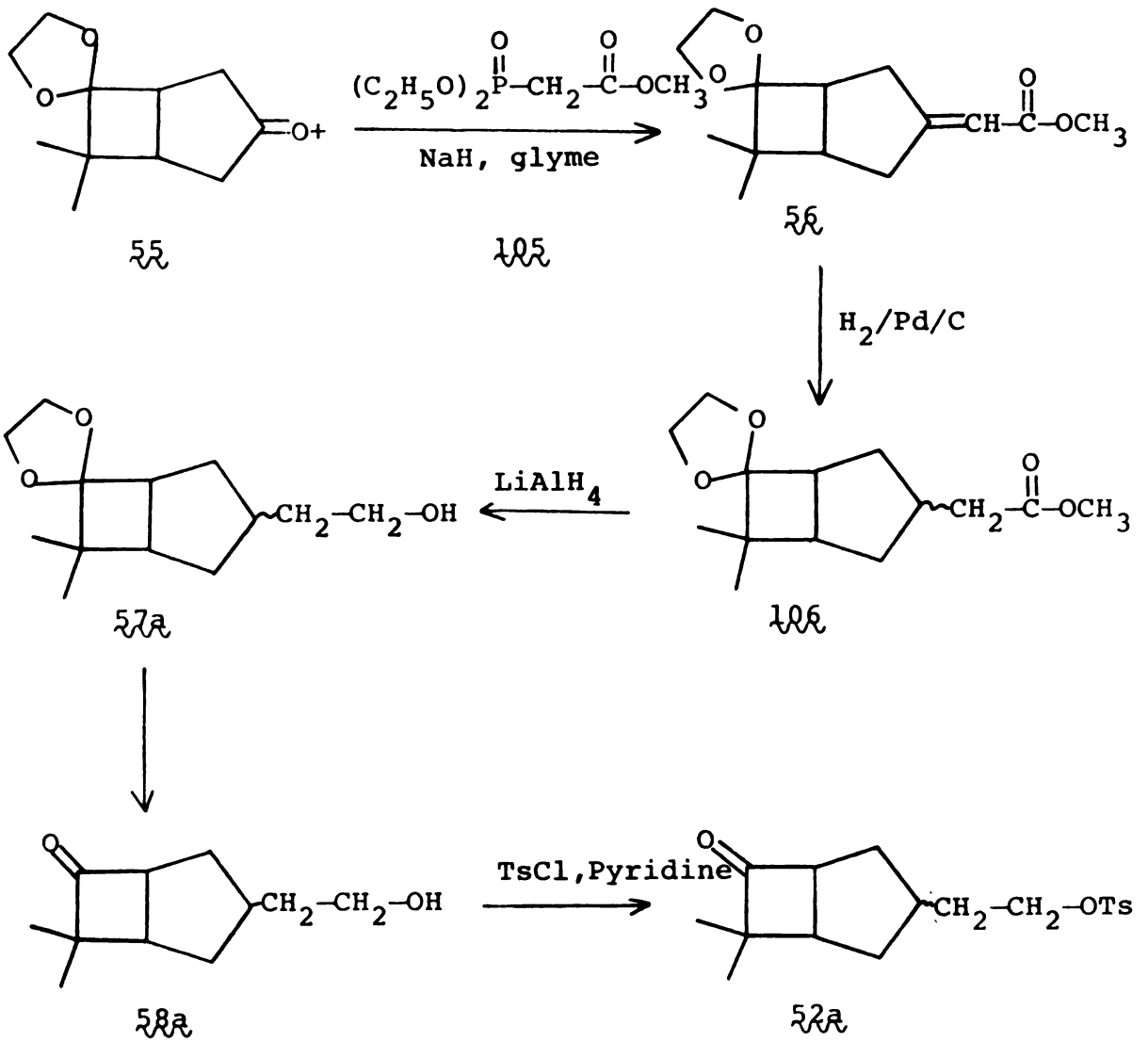
proton and a sharp singlet for the methoxy protons at δ 5.52 and 3.50 respectively. Catalytic hydrogenation of the conjugated ester 56 over 5% palladium-charcoal afforded the saturated ester 106 in 94% yield. Gas chromatographic analysis showed two isomers present in a ratio of 4:1. The saturated ester 106 was also obtained in a similar ratio of isomers from reduction of the conjugated ester 56 with magnesium metal in methanol. The stereochemistry of the isomers could not be established on the basis of nmr and ir spectra.

Transformation of the saturated ester 106 to a mixture of ketal alcohols 57a was achieved by lithium aluminum hydride reduction in quantitative yield. The nmr spectrum of this material showed four different methyl groups at δ 1.03, 1.00, 0.80 and 0.75 with relative intensity 4:1:4:1. The ketal alcohols 57a underwent deketalization very cleanly to a mixture of the keto alcohols 58a. Attempts to separate the isomers as the acetates on column chromatograph by varying the flowrate of eluting solvent, solvents and even the load of solid supports were unsuccessful. Tosylation of the keto alcohols 58a furnished the bicyclo keto tosylates 52a in greater than 90% yield.

Accomplishing the synthesis of the keto tosylates 52a provided an intermediate for cyclization to the tricyclic ketone 31. However this material was a mixture of

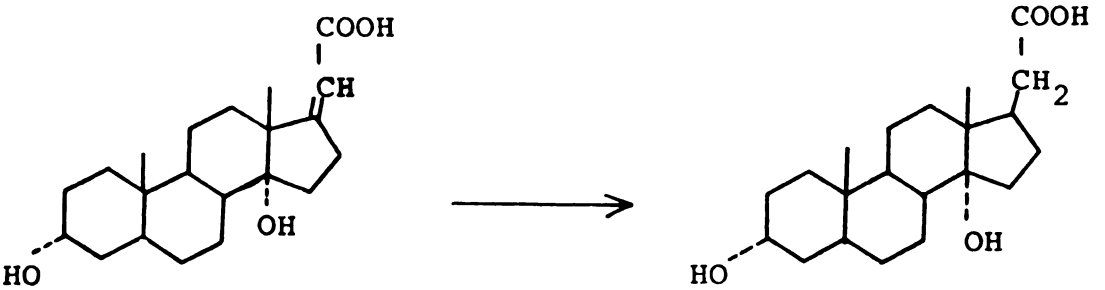
Figure 15

Synthetic Pathway to the Tosylate 52a.



diastereomers of which one isomer was predominant. Furthermore, the stereochemistry of the major isomer could not be determined on the basis of nmr or ir spectra. In the cyclization step, only one isomer of the keto tosylate 52 might cyclize to the tricyclic ketone 31. If the minor isomer in 52a was the right isomer, then detection of the formation of 31 would be very difficult if the reaction proceeded in poor yield. Therefore a new route to improve the isomeric ratio and a single step conversion of the conjugated ester 56 to the ketal alcohol 57 was considered.

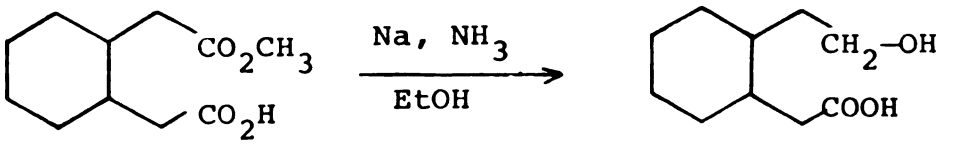
Searching the literature, it was found that conversion of the conjugated ester 107 to the saturated ester 108 was accomplished in good yield using potassium-ammonia solution.[50] Also Paquette[51] showed that the ester 109 could be reduced to the alcohol 110 by metal-ammonia



107 108

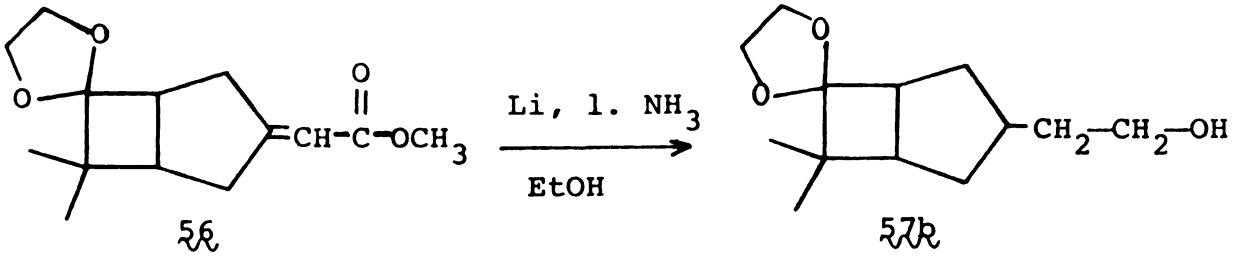
solution. With this information, direct transformation of the conjugated ester 56 to the ketal alcohol 57 by means of lithium-ammonia reduction seemed to be promising. As

expected, when 56 was subjected to lithium-ammonia solu-

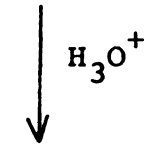


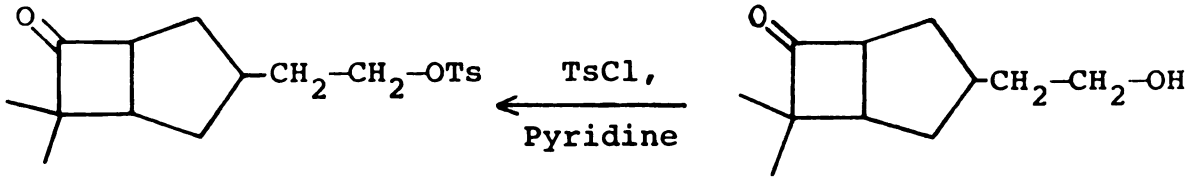
109 110

tion a mixture of isomeric ketal alcohols 57b was formed in 65-70% yield. Gas chromatographic analysis and nmr



56 57b



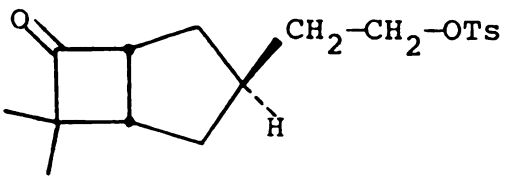


52b 58b

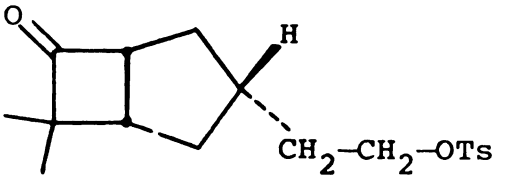
spectrum showed a reversed in isomeric ratio with that obtained from the previous pathways. Conversion of 57b to 58b and then to 52b was accomplished in up to 90% yield.

Attempted synthesis of 3,3-dimethyltricyclo[4,2,1,$0^{1,4}$]-nonan-2-one 31

We had already prepared two sets of mixtures of diastereoisomers 52a and 52b in which one possessed 52c as the major isomer while the other possessed 52d. In order

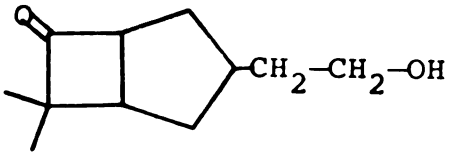


52c

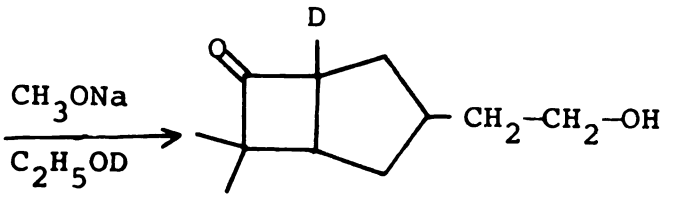


52d

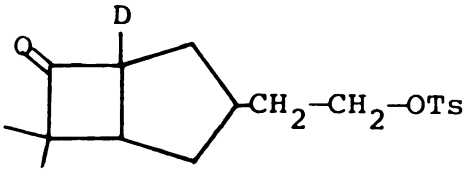
to see whether the methine proton alpha to the ketone function is exchangeable, we treated the keto-alcohols 58a with sodium methoxide in deuterium ethoxide. The nmr spectrum of the product 58c remained almost the same as



58a

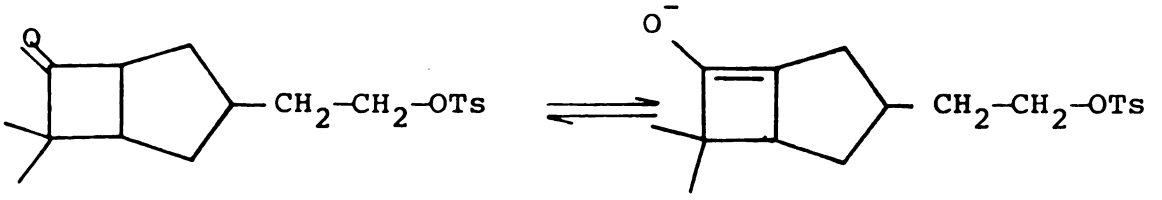


58c



52e

that of 58a except the signal at δ 3.57 disappeared. Calculation from the mass spectrum showed that 99% of one deuterium was incorporated in the molecule. The alcohols 58c were then converted to the tosylates 52e which was purified through column chromatography. Again the mass spectrum showed 90% of deuterium incorporated in the molecule. After the tosylates 52e were treated with sodium methoxide in methanol for approximately one hour, the nmr spectrum showed the appearance of the signal at δ 3.43. This proved to us that the enol form of the tosylate 52 could be formed in the presence of base.



Attempts to cyclize the tosylate 52 to the ketone 31 were carried out with various bases and conditions. Attempts to detect the formation of 31 were unsuccessful. In most of the cases where some products were formed, the ratio of isomers measured from the intensities of the methyl signals in the nmr spectra remained the same as those of the starting material. Most of the attempted reactions, bases used, conditions and % yield are presented in Table 3.

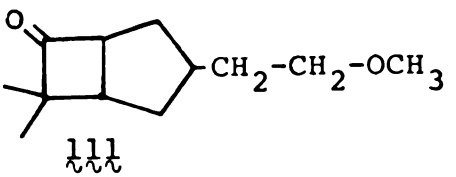
TABLE 3

Attempted Cyclization of the Tosylate 52 with Various Bases and Conditions

starting material	base	condition: solvent, temp., time	product	% yield
52a	NaH	THF, 60 °, 10-24 hrs.	starting material	
52a	NaH	DMF, 25 °, 4 hrs.	starting material	
52a	NaH	DMF, 55-60 °, various	unidentified	
52a	tBuOK	THF, 25 °, 16 hrs.	starting material	
52a	tBuOK	tBuOH, 25 °, 10 hrs.	starting material	
52a	$(\rangle\!\!-\!\!\rangle)_2NLi$	THF, 25 °, 10 hrs.	starting material	
52a	$(\rangle\!\!-\!\!\rangle)_2NLi$	THF, 70°, 24 hrs.	starting material + unidentified	
52a	NaH + 1 drop tBuOH	glyme, 25°, 10 hrs. 45°, 2 hrs.	111	93%
52a	$NaNH_2$	THF, 25°, 18 hrs.	starting material	
52a	$CH_3\overset{O}{\overset{\|\|}{S}}CH_2^-$	DMSO, 25°, 1/2 hr.	112 + unidentified	30%
52a	$CH_3\overset{O}{\overset{\|\|}{S}}CH_2^-$	DMSO, 25°, 2 hrs.	112 + unidentified	40%
52a	tBuLi	hexane, -100°, + 1 1/2 hrs. TMEDA	starting material	
52a	tBuLi	THF, -78 °, 15 min 25 °, 12 hrs.	113	80%

starting material	base	condition: solvent, temp., time	product	% yield
52a	tBuLi	THF, -100°, 2-3 hrs.	113	80%
52a	tBuLi	THF, -100°, 2 hrs. + HMPA	114 ? + unidentified	25%
52b	tBuOK	tBuOH, 25°, 14 hrs.	starting material	
52b	$NaOCH_3$	THF, 25°, 6 hrs. 40°, 12 hrs. 50°, 12 hrs.	starting material	
52b	$(\rangle\!\!\rightarrow)_2NLi$	THF, 25°, 18 hrs.	starting material	
52b	$NaOC_2H_5$	C_2H_5OH, 25°, 108 hrs.	115*	~100%

*structural assignment based on only nmr and ir spectra.



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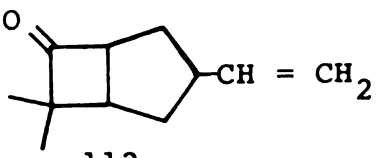

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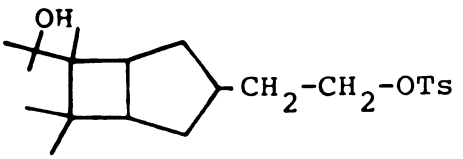

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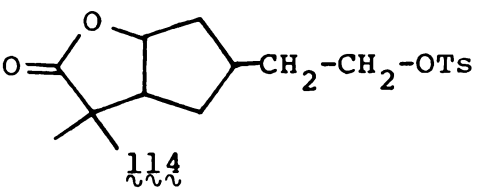

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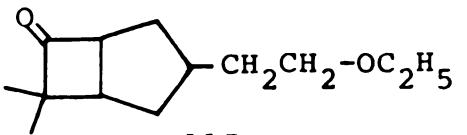

115

It was very unfortunate that the tosylate 52 did not undergo cyclization to the tricyclic ketone 31 under the conditions shown. However it is quite understandable because the transformation may have to proceed through a prohibitively high activation energy in order to achieve the formation of 31 which is a highly strained compound.

EXPERIMENTAL

General

All melting points were measured in open capillaries with a Thomas-Hoover apparatus and were uncorrected; boiling points were also uncorrected. Combustion analysis were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Infrared spectra were recorded on a Perkin-Elmer model 137 spectrophotometer; absorption maxima are reported as frequency (in cm^{-1}), referenced to 1601 cm^{-1} peak of polystyrene. Liquid samples were taken as neat films, and solids as nujol mulls.

Proton nuclear magnetic resonance spectra (HNMR) were run on Varian T-60 instrument (60 MHz); variable temperature nmr spectra were recorded on a Varian A-56/60 spectrometer; Carbon nuclear magnetic resonance spectra were taken on a Varian CFT-20 spectrometer. Chemical shifts are reported in ppm downfield of tetramethylsilane (TMS) or relatively to tetramethylammoniumtetrafluoroborate (TMA) as standard.

Mass spectra were run on a Hitachi RMU-6 instrument with an ionizing voltage of 70 eV. Gas chromatographic separations were run on an F & M model 700 chromatograph.

The percentage of compositions reported were calculated from the peak areas.

Most of the solvents used for reactions were dried in usual manners. For examples: acetonitrile was dried over calcium chloride and refluxed with phosphorus pentoxide overnight and distilled; glyme was refluxed with lithium aluminum hydride and distilled; ether, tetrahydrofuran, and benzene were dried over sodium metal. Hexane used for column chromatography was washed with concentrated sulfuric acid and distilled over calcium chloride.

3,4-Dimethylhexane-3,4-diol 32

Dry magnesium turnings (48 g, 2 moles) and anhydrous benzene (400 ml) were placed in a 2 liter-three necked round bottom flask fitted with mechanical stirrer, reflux condenser and addition funnel. A solution of 43 g (0.15 M) of mercuric chloride dissolved in 437 ml (4.4 moles) of dry ethylmethylketone was slowly added to the stirred mixture at such a rate to maintain a gentle reflux. When the addition was completed, another 200 ml of benzene was added and the mixture was heated on a steam bath for two hours. The solution was then cooled down and added to ice-water containing 120 g of sodium hydroxide. The organic layer was separated, dried over sodium hydride and distilled to remove benzene and unreacted ethylmethylketone. The residue was then distilled under reduced pressure.

The fraction of boiling point 124-126°/10 nm (142 g, 48.6%) was collected. The product has the following spectral properties: nmr (δ, CCl_4): 0.90 (a pair of triplet, J = 7 Hz, 6H), 1.03 (singlet, 6H), 1.41 (a pair of quartet, J = 7 Hz), 2.23 (singlet, 2H); ir (neat): 3465, 1464, 1130, 995 cm^{-1} and others.

1,2,3,6-Tetrahydro-3,4,5,6-tetramethylphthallic anhydride 34

One drop of 20% sulfuric acid was added into 90 grams of 3,4-dimethylhexane-3,4-diol 32 and the solution was then distilled. The distillate which was collected at 98° consisted of two layers, organic and water layers. The mixture was poured into a separatory funnel and the oil was separated and dried over anhydrous calcium chloride. The oil was then redistilled and the fraction of boiling point 72-78°/90-100 mm was collected (37.3 g). The nmr spectrum of this material showed that it was a mixture of olefins. One of these was 33. This mixture was used without further purification.

To a cooled solution of 5 g of maleic anhydride in 20 ml of ethyl acetate and 20 ml of petroleum ether, the mixture of dienes (5.74 g) was added slowly. After the addition was completed, the mixture was then refluxed for an hour and cooled to room temperature. The solid was filtered through aspirator, and washed with petroleum ether, giving the crude anhydride 34 in 23% yield (4.51 g)

from the diol 32. The product which was recrystallized from hexane has the melting point 91.5-94°. The spectral data were consistent with the assigned structure: nmr (δ, CCl_4), 1.40 (d, 6H, J = 7 Hz), 1.65 (s, 6H), 2.40 (m, 2H), 3.05 (dd, 2H, J = 3, 2 Hz); ir (nujol) 1850, 1780, 1192 and 1180 cm^{-1} and others; ms, m/e: 208 (parent peak), 136, 121, 105, 95, 91, and 77 among others.

Dimethyl-1,2,3,6-tetrahydro-3,4,5,6-tetramethylphthallate 35

The anhydride 34, (2.2 g, 10.6 mm) was dissolved in 10 ml of methanol containing one drop of concentrated sulfuric acid. The mixture was boiled under reflux for an hour. The excess of alcohol was removed. The residue was then poured into sodium bicarbonate solution and extracted with ether. The extract was dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give the crude diester 35. This was then recrystallized from petroleum ether to give 2.0 g (74%) of the white solid of 35, m.p. 50-52°. The spectral properties were in accord with the expected structure. The nmr spectrum showed the following absorptions (δ, CCl_4): 1.07 (d, J = 7 Hz, 6H), 1.67 (s, 6H), 2.50 (m, 2H), 3.00 (d, J = 5 Hz, 2H) and 3.63 (s, 6H). The ir spectrum exhibited one carbonyl absorption at 1745 cm^{-1} and others at 1215, 1178, and 1190 cm^{-1}.

Dimethyl-3,4,5,6-tetramethylphthalate 36

The tetrahydroester 35 (2.0 g, 0.78 mm) and 10% palladium-charcoal (1 g) were placed in a round bottom flask fitted with a refluxing condenser. The flask was flushed with nitrogen and inert atmosphere was maintained. The mixture was then heated at 220° for two hours. After cooling, the reaction mixture was washed several times with ether. Removal of the ether yielded 1.28 g of dimethyltetramethylphthallate, 36 (60%). The purified aromatic diester 36 (petroleum ether, m.p. 124-125°) showed the following spectral properties: nmr (δ, $CDCl_3$): 2.20 (s, 6H), 2.23 (s, 6H), 3.77 (s, 6H); ir (nujol), 2899, 1730, 1460, 1379 and 1212 cm^{-1} and other weak bands; ms, m/e: 250 (parent peak), 119, 118, 190, 160 among others.

3,4,5,6-Tetramethylphthallic anhydride 37

A 100 ml round-bottom flask equipped with a refluxing condenser were placed 7.73 g (3.72 mm) of the tetrahydro anhydride 34 and 3.54 g of 10% palladium-charcoal and inert atmosphere was provided. The flask was then heated in an oil bath at 220-230° for four hours. After cooling, the product was extracted with warm chloroform several times. Removal of solvent on rotary evaporator provided a clean desired-anhydride 37 in 50% yield (3.83 g). The product could be used immediately for the next reaction

or recrystallized from ether. The purified 37 has spectral data as follows: ms, m/e: 204 (parent peak); ir (nujol): 1851, 1785, 1219, 913 and 749 cm^{-1} and other weak bands; nmr ($CDCl_3$): 2.33 (s, 6H), 2.63 (s, 6H).

1,2-Bis(hydroxymethyl)-3,4,5,6-tetramethylbenzene 38

a) Lithium aluminum hydride reduction of 36. In a 100 ml three-necked flask fitted with condenser and provided with nitrogen atmosphere, were placed excess lithium aluminum hydride and 40 ml of dry ether. The solid diester 36 (1.52 g, 6.1 mm) was added slowly and carefully. After the addition was completed, the reaction mixture was refluxed overnight (15-20 hours). At the end of the period, the reaction was cooled to room temperature, and water was slowly added to destroy excess lithium aluminum hydride. The solution was then extracted several times with ether. The combined ether layers were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of ether on the rotary evaporator afforded 1.06 g (90%) of the clean alcohol 38. The spectral data of recrystallized product (CCl_4, m.p. 171.5-173°) were as followed: ms, m/e: 194 (parent peak); ir (nujol): 3330 cm^{-1}; nmr (δ, $CDCl_3$): 2.16 (s, 6H), 2.28 (s, 6H), 3.13 (bs, 2H) and 4.72 (s, 4H).

Anal. Calc. for $C_{12}H_{18}O_2$: C, 74.23; H, 9.28

Found : C, 74.27; H, 9.26

b) Two successive reductions of 37 with lithium aluminum hydride. To a stirred solution of excess lithium aluminum hydride in 200 ml of ether, the solid anhydride 37 (5.51 g, 27.0 mm) was added slowly and carefully at room temperature. After the addition, the mixture was refluxed for ten hours. At the end of the reaction, the solution was cooled to room temperature and water was added. The solution was extracted several times with ether. The combined ether layers were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The ether was removed on rotary evaporator to give a solid mixture which was not identified. This solid mixture was repeatedly reduced in a solution of lithium aluminum hydride. At the end of the reaction, 5.02 g (96%) of the diol 38 was collected.

1,2-Bis(bromomethyl)-3,4,5,6-tetramethylbenzene 39

In a 250 ml three-necked flask equipped with a mechanical stirrer, condenser and dropping funnel, were placed 3.0 g (15.5 mm) of the diol 38 and 100 ml of dry benzene. The reaction flask was cooled to 10° and a solution of 4.5 g of phosphorus tribromide in 50 ml of dry benzene was slowly added to the stirred solution of the diol 38. After the addition was completed, the reaction mixture was stirred for additional 20 minutes. The solution was then filtered and poured into a beaker

containing ice-water. The benzene layer was separated and washed with water, saturated sodium chloride and dried over anhydrous magnesium sulfate. Removal of benzene gave 4.51 g (86.6%) of the dibromide 39 which was recrystallized from hexane (m.p. 163-164°). The spectral data were in accord with the expected structure. The mass spectrum showed peaks at m/e 322, 320, 318 and others (Calc. mass of 39, 320). The ir spectrum showed absorptions at 1195 cm^{-1} and several other weak bands. The nmr spectrum exhibited signals at (δ, CCl_4) 2.27 (s, 6H), 2.32 (s, 6H) and 4.67 (s, 4H).

Anal. Calc. for $C_{12}H_{16}Br_2$: C, 45.00, H. 5.00
Found : C, 45.09; H, 5.17

2-Carbomethoxy-1,2,3,4-tetrahydro-5,6,7,8-tetramethyl-naphthalene 40

a) The preparation of activated zinc. Zinc powder (10 g) was put in 50 ml of 10% hydrochloric acid solution and stirred for 15 minutes. The metal was then filtered through suction funnel, washed with water, methanol, acetone and ether and dried under vacuum. This activated zinc was kept under nitrogen before use.

b) Reaction of 39 with methylacrylate in the presence of activated zinc. In a three-necked flask equipped with a mechanical stirrer, dropping funnel and condenser provided with nitrogen atmosphere were placed 5.0 g of

freshly distilled methylacrylate (excess), 200 ml of dry dimethylformamide and 3 g of activated zinc. To the stirred solution, a mixture of 6.1 g (19 mm) of the dibromide 39 in 150 ml of dimethylformamide was added slowly over a period of three hours. During addition time, 1.5 g more of activated zinc was added. After the addition was completed, the reaction was stirred for additional six hours. The solution was then filtered and the residue was washed with ether. The combined filtrates were poured into a solution of 20 ml of concentrated hydrochloric acid in 300 ml of water. The organic layer was separated, washed with water, sodium bicarbonate solution, saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of solvent on the rotary evaporator gave a white solid. The solid was then sublimed very slowly at 60-65°/0.5 mm to afford 3.4 g of the methylester 40 (72%, m.p. 91-92.5°). The spectral properties were consistent with the expected structure. The mass spectrum exhibited the parent peak at m/e 246 (calc. mass for 40, 246). The ir spectrum showed the carbonyl absorption at 1740 cm^{-1} and C—O stretching band at 1176 cm^{-1} and other bands. The nmr spectrum had the following peaks (δ, CCl_4), 3.70 (s, 3H), 2.16 (bs, 12H) and 1.10-3.20 (m, 7H).

2-Hydroxymethyl-1,2,3,4-tetrahydro-5,6,7,8-tetramethyl-naphthalene 29

In a round bottom flask equipped with a refluxing condenser, were placed 2.5 g (10 mm) of the methylester 40, 0.82 g of lithium aluminum hydride and 50 ml of ether. The flask was refluxed for a period of six to eight hours. At the end of reaction, the solution was cooled to room temperature and water was added. The reaction mixture was extracted with ether twice. The combined ether layers were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of ether yielded 2.95 g of the clean alcohol 29 (95%). The sublimed white-solid alcohol 29 (m.p. 101-102°) possessed the following spectral properties: ms, m/e 218 (parent peak, calc. mass for 29, 218); ir (nujol) 3323 cm^{-1}, nmr (δ, CCl_4): 1.40-2.67 (m, 8H), 2.07 (s, 6H), 2.13 (s, 6H) and 3.15 (d, J = 7 Hz, 2H).

1,2-Bis(bromomethyl)benzene 45

In a three-necked flask equipped with a long condenser, addition funnel and magnetic stirrer was placed 50 g (0.47 mole) of *ortho*-xylene. The flask was heated at 110-120° with an oil bath. Bromine (160 g) was very slowly added through dropping funnel to maintain an almost colorless liquid till the end of the operation. Hydrogen bromide evolved was carried out by a stream of nitrogen into a

dilute solution of sodium hydroxide. The time used for addition of bromine was approximately seven to eight hours.

As soon as the reaction was over, the crude dibromide 45 was poured into a small beaker and allowed to stand for 24 hours to solidify. The solid crystal was then spread over paper towels. The solid compound obtained (60 g, 48%) was now almost colorless and sufficiently pure. The pure dibromide was obtained by recrystallizing from hexane, m.p. 92-93°. The spectral data were in accord with the assigned structure. The mass spectrum showed the following peaks, m/e 266, 264, 262, 185, 183, 104, 91 and 78 and others (calc. mass for 45, 264). The nmr spectrum exhibited two singlet signals at δ 6.33 and 7.37 with the same ratio of protons.

2-Carbomethoxy-1,2,3,4-tetrahydronaphthalene 46

In a 500 ml three-necked flask fitted with mechanical stirrer and additional funnel provided with an inert atmosphere were placed 17 g of freshly distilled methylacrylate, 100 ml of dry dimethylformamide and 4 g of activated zinc. To the stirred solution, a mixture of 20.0 g (7.6 mm) of the dibromide 45 in 200 ml of dry dimethylformamide was added dropwise for a period of 3-4 hours. Every hour, 2 g of zinc was added. After the addition was completed, the reaction mixture was stirred for ten more hours. When the reaction period was over, the solution was then

filtered through celite. The filtrate was poured into a solution of 30 ml of concentrated hydrochloric acid in 1 liter of water. The solution was extracted twice with ether (2 x 150 ml). The combined organic layers were washed with water, sodium bicarbonate solution, saturated sodium chloride and dried over anhydrous magnesium sulfate. Removal of ether on the rotary evaporator gave an oily liquid. Molecular distillation at 68-70°/0.5 mm gave 6.93 g of the ester 46 (48.2% yield). The spectral data of this material were as followed: nmr, (δ, CCl_4): 1.70-3.13 (m, 7H), 3.66 (s, 3H) and 7.00 (s, 4H); ir (neat): 1739, 1497, 1190 and 746 cm^{-1} among other bands; ms, m/e: 190 (parent peak), 158, 130, 115, 91, 77 and others (calc. mass of 46, 190).

2-Hydroxymethyl-1,2,3,4-tetrahydronaphthalene 30

To a round bottom flask containing 0.7 g of lithium aluminum hydride and 30 ml of ether, was added slowly the mixture of 1.98 g (10 mm) of ester 46 in 5 ml of ether. The reaction mixture was then stirred at room temperature for eight hours after which water was added slowly to destroy excess lithium aluminum hydride. The solution was extracted with ether. The ether was separated and washed with water, saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of ether on the rotary evaporator gave 1.60 g of the crude alcohol 30 (95%) which was

molecular distilled at 70°/0.5 mm. The spectral properties were consistent with the assigned structure: ms, m/e: 162, 144, 129, 119, 104, 91, 77 and others; ir (neat) 3333, 1494, 1069, 1031 and 743 cm^{-1} and other bands; nmr (δ, CCl_4): 1.15-3.03 (m, 8H), 3.58 (d, J = 6 Hz, 2H) and 7.00 (s, 4H).

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.48; H, 8.64
Found : C, 80.26; H, 8.39

7,7-Dimethylbicyclo[3,2,0]hept-2-ene-6-one 53

The apparatus used for this reaction is shown in Figure 16. Tetramethyl-1,3-butanedione 59 was used as dimethylketene precursor. The dione 59 (25 g) was placed in the ketene generator which was heated at 110-120° with an oil bath and the heating coil was heated to just redness. The dione which was heated to sublime was pyrolyzed to dimethylketene in this region. Over a period of 10-12 hours, dimethylketene was carried by nitrogen stream into a rapidly stirred solution of 50 ml of freshly distilled cyclopentadiene in 100 ml of acetonitrile at 0°. At the end of the period, the reaction mixture was kept under nitrogen at -40° overnight. The excess cyclopentadiene and acetonitrile were then distilled at atmospheric pressure. The residue was distilled under reduced pressure through a 12 inch vigreux column giving 26 g of adduct 53 (57%), b.p. 66-67°/15 mm. The spectral data were in accord with that

expected from 53. The nmr spectrum exhibited the following signals: (δ, CCl_4): 0.90 (s, 3H), 1.30 (s, 3H), 2.30-2.77 (m, 2H), 3.07 (bd, J = 7 Hz, 1H), 3.83 (dt, J = 7, 3 Hz, 1H), and 5.50-5.87 (m, 2H). The ir spectrum showed absorptions at 1775, 1358, 743 cm^{-1} and other several bands.

7,7-Dimethyl-6,6-ethylenedioxybicyclo[3,2,0]hept-2-ene 54

In a one liter round bottom flask was placed a mixture of 16.925 g (124 mm) of ketone 53, 75 ml of ethylene glycol, 100 mg of *p*-toluenesulfonic acid and 300 ml of benzene. The mixture was stirred vigorously in order to mix the two layers. The flask was connected to a Dean-Stark trap and a condenser along with a drying tube. The solution was then heated to reflux for twenty hours (an approximately equivalent amount of water was collected). At the end of the period, the reaction mixture was cooled to room temperature and 5 ml of saturated sodium bicarbonate solution was added and stirred. The benzene layer was separated and washed twice with water. The organic layer was also washed with 200 ml saturated sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled at atmospheric pressure. The residue was then distilled under reduced pressure yielding 21 g of the ketal 54 (94%, b.p. 74-75°/15 mm). The spectral properties of 54 were as follows: ms, m/e: 180 (parent peak), 165, 137, 114, 99 and others (calc. mass of 54, 180); (neat): 1212,

1177, 1134, 1053 and 718 cm^{-1} and other bands; nmr, (δ, CCl_4): 0.77 (s, 3H), 1.10 (s, 3H), 2.07-2.67 (m, 3H), 2.96 (dt, J = 7, 3 Hz, 1H), 3.67 (m, 4H) and 5.27-5.73 (m, 2H).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89

Found : C, 73.25; H, 8.88

7,7-Dimethyl-6,6-ethylenedioxy-exo-bicyclo[3,2,0]heptan-2-ol 63. Reaction of 54 with diborane and hydrogen peroxide.

Into a 500 ml three-necked round bottom flask provided with a nitrogen inlet, dropping funnel, reflux condenser and magnetic stirrer, was introduced a solution of 6.19 g (34 mm) of olefin 54 in 130 ml of tetrahydrofuran. Commercial borane solution (38 ml, 1 M in T.H.F.) was added to the stirred solution of olefin. After the addition was completed, the reaction mixture was stirred for an additional hour. Water was then added to destroy residual borane. After hydrogen evolution had ceased, 8 ml of 6 N sodium hydroxide was added, followed by 8 ml of 30% hydrogen peroxide. The solution was stirred for two hours and 50 ml of water was added. The organic layer was separated and the aqueous layer was extracted with ether for three times (3 x 100 ml). The combined organic solvents were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the ether gave 6.32 g of a clear liquid (93% yield). Gas chromatographic analysis (4% QF-1, 6 ft column, 150°) showed that only two

alcohols were obtained with an approximate ratio of 7:3. Attempts to separate these alcohols by preparative gas chromatograph gave only one pure isomer, the major 63. Reinjection of the minor fraction still showed the presence of the major isomer. The spectral data obtained from the major alcohol were in accord with the structure 63: ms, m/e: 198 (parent peak), 183, 165, 153, 141, 125, 114, 99 and other (calc. mass for 63, 198); ir (nujol): 3247, 1316, 1176, 1031 and others; nmr, (δ, CCl_4): 0.80 (s, 3H), 1.40 (s, 1H exchanged with D_2O), 1.33-2.33 (m, 5H), 2.87 (bt, J = 7 Hz, 1H), 3.67 (m, 4H) and 3.96 (bd, J = 4.5 Hz, 1H).

The minor isomer could not be obtained in pure form. However, it was suggested to have the structure 64.

Reaction of the mixture of 63 and 64 with acetyl chloride in pyridine. Formation of exo-2-acetoxy-7,7-dimethyl-6,6-ethylenedioxybicyclo[3,2,0]heptane 65 and 3-acetoxy-7,7-dimethyl-6,6-ethylenedioxybicyclo[3,2,0]heptane 66.

The mixture of alcohols 63 and 64 (358 mg, 1.8 mm) was dissolved in 2 ml of dry pyridine and cooled to 0°. Acetyl chloride (1 ml, *Ca.* 6 fold excess) was added and the reaction was stirred for 15 minutes. The reaction mixture was then poured into 10 ml of water and the solution was extracted with ether (3 x 10 ml). The

combined ethers were washed with diluted hydrochloric acid, saturated sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give 370 mg of an oil. Gas chromatographic analysis showed that the mixture contained 63% of 65, 29% of 66, 7.2% of unreacted alcohol 63 and 0.8% of olefin 54. This material was adsorbed on alumina column (15 g, activity 2-3). The eluting solvent was gradually changed from pure hexane to 7% ether-hexane. The major acetate 65 had the following spectral properties: ms, m/e: 240 (parent peak 4.08%), 197 (14.64%), 180 (38.40%), 165 (34.78%), 114 (98.55%), 99 (100%) and others; ir (neat): 1738, 1246, 1016 cm^{-1} and other bands; nmr, (δ, CCl_4): 0.80 (s, 3H), 1.12 (s, 3H), 1.83 (s, 3H), 1.40-2.23 (m, 5H), 2.90 (bt, J = 7 Hz, 1 Hz), 3.70 (m, 4H) and 4.88 (bd, J - 4.5 Hz, 1H).

The minor acetate 66 had spectral properties as followed: ms, m/e: 240 (parent peak, 0.34%), 197 (1.19%), 180 (48.57%), 165 (24.29%), 114 (80.7%), 99 (100%) and others; ir (neat): 1739, 1247, 1033 cm^{-1} and other bands; nmr, (δ, CCl_4): 0.85 (s, 3H), 1.08 (s, 3H), 1.10-2.27 (m, 5H), 2.90 (dt, J = 8, 2 Hz, 1H), 3.73 (m, 4H) and 5.17 (t, J = 7 Hz, 1H).

Reaction of the mixture of 63 and 64 with chromium trioxide-pyridine complex. Formation of 7,7-dimethyl-6,6-ethylene-dioxybicyclo[3,2,0]-heptan-2-one 67, and 7,7-dimethyl-6,6-ethylenedioxybicyclo[3,2,0]heptan-3-one 55.

A 1-liter three-necked flask was equipped with a mechanical stirrer, and a dropping funnel, and provided with an inert atmosphere. Chromium trioxide (30 g) was added to the stirred solution of 60 ml of pyridine in 500 ml of methylene chloride. After the addition was completed, the deep-red solution was stirred for additional 15 minutes at room temperature. At the end of this period, a solution of 6.39 g of the alcohol mixture in 50 ml of methylene chloride was added in one portion. After stirring for an additional 15 minutes, the solution was left standing for a period of 6-8 hours to complete oxidation. The solution was decanted and the residue was washed with methylene chloride. The combined methylene chloride solutions were then washed with dilute sodium hydroxide, quickly washed with dilute hydrochloric acid, saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvent on the rotary evaporator gave 5.77 g of a crude material. Gas chromatographic analysis showed that conversion of alcohols to ketones was completed and two ketones were obtained in a ratio of 7:3 (4% QF-1, 6 ft column, 150°).

Separation of these two ketones was achieved on column chromatography using alumina a adsorbent (activity 3) and ether-hexane as eluting solvent which was gradually changed from 5% to 10% ether. The ketone 67 which was the major product had the following spectral properties: ms, m/e: 196 (parent peak), 181, 140, 114, 99 and others; ir, (neat): 1739, 1163, 1031 cm^{-1} and several other bands; nmr (δ, CCl_4): 0.86 (s, 3H), 1.20 (s, 3H), 1.70-2.67 (m, 5H), 3.12 (bt, J = 8 cps, 1H) and 3.87 (m, 4H).

Anal. Calc. for $C_{11}H_{16}O_3$: C, 67.35: H, 8.16
Found : C, 67.26; H, 8.27

The ketone 55, which was the minor product, showed the following spectral data: ms, m/e 196 (parent peak, calc. mass for 55, 196); ir (neat): 1750 cm^{-1}; nmr (δ, CCl_4): 0.90 (s, 3H), 1.23 (s, 3H), 2.20 (m, 5H), 3.20 (dt, J = 8, 3 Hz, 1H) and 3.87 (bs, 4H).

Anal. Calc. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16
Found : C, 67.32; H, 8.27

7,7-Dimethylbicyclo[3,2,0]heptane-2,6-dione 77

In a round bottom flask, 174 mg of ketone 67 in 5 ml of benzene was mixed with 3 ml of 5% of hydrochloric acid solution. The mixture was stirred vigorously for six hours. After the reaction time, the mixture was slowly poured into a solution of sodium bicarbonate. The benzene layer was separated. The aqueous layer was extracted again

with benzene. The combined benzene layers were washed with water, saturated sodium chloride and dried over anhydrous sodium sulfate. Gas chromatographic analysis showed that 94% of the diketone 22 was formed. Separation of 22 was achieved by preparative gas chromatography (20% SE 30, 130°). The spectral data of 22 were as followed: ms, m/e: 152 (parent peak), 124, 109, 95, 83, 70 and others (calc. mass for 22, 152); ir (neat): 1785 and 1739 cm^{-1} and other bands; nmr, (δ, CCl_4): 1.03 (s, 3H), 1.40 (s, 3H), 1.93 (m, 4H), 2.60 (d, J = 8 Hz, 1H), and 3.93 (bt, J = 8 Hz, 1H, 1H).

Anal. Calc. for $C_9H_{12}O_2$: C, 71.05; H, 7.89
Found : C, 70.96; H, 7.78

7,7-Dimethylbicyclo[3,2,0]heptane-3,6-dione 21

The ketone 55 (92 mg) was subjected to deketalization according to the procedure used for deketalization of 67. The diketone 21 which was obtained in 95% yield was separated by preparative gas chromatography. The spectral properties were consistent with 55. The mass spectrum showed the parent peak and the base peak at m/e 152 and 70 respectively (calc. mass for 21, 152). The nmr spectrum exhibited the following signals (δ, CCl_4), 1.05 (s, 3H), 1.37 (s, 3H), 1.95-3.01 (m, 5H), and 3.98 (m, 1H).

7,7-Dimethyl-6,6-ethylenedioxy-1,3,3-trideuterobicyclo-[3,2,0]heptan-2-one 73.

A mixture of 72 mg of the ketone 67, 30 mg of sodium methoxide and 5 ml of deuterium ethoxide was stirred at room temperature for two hours. At the end of the reaction, 1 ml of deuterium oxide was added, with stirring, followed by 10 ml of ether. The organic layer was separated and washed with water, saturated sodiumchloride and then dried over sodium sulfate. Removal of the solvent afforded 70 mg of a clean product. The nmr spectrum showed absorptions at δ 0.83 (s, 3H), 1.20 (s, 3H), 1.56-2.10 (m, 2H), 3.03 (bd, J = 8 Hz, 1H) and 3.85 (m, 4H).

7,7-Dimethyl-6,6-ethylenedioxy-exo-bicyclo[3,2,0]heptane-2,3-oxide 101.

In a 300 ml three-necked flask fitted with a condenser and dropping funnel were placed 4.64 g (23.6 mm) of 62 and 150 ml of dry methylene chloride. To the stirred solution at 0°, 5.23 g of 85% metachloroperbenzoic acid in 40 ml of methylene chloride was added. After the addition was completed, the reaction was stirred for two hours. At the end of this period, the solution was filtered through a suction funnel. The filtrate was washed with dilute sodium hydroxide, water, saturated sodium chloride and dried over anhydrous sodium sulfate. Methylene chloride was removed on the rotary evaporator to give 4.81 g of the crude

epoxide 101 (95%). G. C. analysis showed quantitative conversion of the olefin 54 to the epoxide 101. This epoxide was purified on column chromatography (alumina, act 3) using 7% ether-hexane as eluting solvent. The spectral data supported the assigned structure: ir (neat): 1380, 1050, 835 cm^{-1} and others; ms, m/e: 196, 195, 181, 167, 153, 137, 114, 99 (base) and others (calc. mass for 101, 196); nmr, (δ, CCl_4): 0.97 (s, 3H), 1.07 (s, 3H), 1.88 (m, 2H), 2.13 (d, J = 8 Hz, 1H), 2.60 (dt, J = 8, 3 Hz, 1H), 3.23 (dd, J = 8, 2 Hz, 2H) and 3.72 (bs, 4H).

Reaction of the epoxide 101 with lithium aluminum hydride. Formation of 7,7-dimethyl-6,6-ethylenedioxy-exo-bicyclo-[3,2,0]heptan-2-ol 63.

In a round bottom flask fitted with a condenser were placed 674 mg (3.4 mm) of the epoxide 101, excess lithium aluminum hydride (150 mg) and 30 ml of ether. The mixture was stirred at room temperature for 51 hours, and water was added. The ether layer was separated and the aqueous layer was extracted again with ether. The combined extracts were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The g.c. analysis showed that the epoxide 101 was converted to a single alcohol 63 in 91% yield. The nmr spectrum of the crude material was comparable to that of the pure alcohol 63.

7,7-Dimethyl-6,6-ethylenedioxy-exo-bicyclo[3,2,0]hept-3-ene-2-ol 102. Reaction of the epoxide 101 with lithium diisopropylamide.

A 25 ml three-necked flask was equipped with a condenser and a mercury bubbler connected to an aspirator. The flask was flame-dried and an inert atmosphere was provided. Through a syringe, 1 ml of *n*-butyllithium (15.03% of *n*-butyllithium in hexane) was injected and the flask was cooled to 0°. Diisopropylamine (0.2 ml) was added slowly and the mixture was stirred. After the addition was completed, the hexane was evaporated under reduced pressure to dryness. A nitrogen atmosphere was again provided, and the mercury bubbler was removed. The base was then dissolved with 5 ml of dried ether. To the stirred solution, a mixture of 260 mg of the epoxide 101 in 1 ml of ether was added and the reaction mixture was refluxed for four hours. When the solution was cooled to room temperature, water was added. The organic layer was separated and the aqueous layer was extracted again with ether. The combined extracts were washed with dilute hydrochloric acid, saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the ether yielded 252 mg of a crude material. Gas chromatographic analysis showed two major peaks (ratio, 85:15). Separation was achieved on column chromatograph using alumina as adsorbent

and 20% ether-hexane as eluting solvent. The major product had spectral properties consistent to the allylic alcohol 102; nmr (δ, CCl_4): 0.88 (s, 3H), 1.10 (s, 3H), 1.95 (d, J = 7 Hz, 1H), 2.13 (bs, 1H), 3.37 (bd, J = 7 Hz, 1H), 3.70 (m, 4H), 4.45 (bs, 1H) and 5.78 (m, 2H); ir (neat): 3438 cm^{-1} and others; ms, m/e: 196 (parent peak, calc. mass for 102, 196).

The minor product was identified as the ketone 67.

Reaction of the epoxide 101 with *t*-butyllithium.

A 200 ml three-necked flask fitted with a condenser was flame-dried and a nitrogen atmosphere was provided. Tetrahydrofuran (120 ml) was introduced, cooled to -78° and 16 ml of *t*-butyllithium (0.96 M) was slowly added. To the stirred solution, a mixture of 2.719 g (13.3 mm) of the epoxide 101 in 5 ml of tetrahydrofuran was slowly added. After stirring for 15 minutes at -78°, the solution was allowed to warm up slowly to room temperature and stirred for an additional 30 minutes. The reaction was then quenched with water. The solvent was separated, washed again with water, saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of solvent afforded a mixture of compounds which were assigned as 103, 104, 102, 67 and 55 and others. Analysis by gas chromatograph (4% QF-1, 6 ft, 150°) showed that these components presented in amounts of 3.4%, 4.5%, 15.4%, 3.4%

and 71.1% respectively. The mixture was adsorbed on alumina (activity 2-3) and eluted with hexane and gradually changed to 7% ether-hexane and up to 40% ether-hexane. The compounds 103, 104 and unidentified came out in the same fractions. Separation of 103 and 104 was achieved by preparative gas chromatography (4% QF-1, 6 ft, 110°).

The spectral data of 104 were as followed: ms, m/e: 236 (9.2%), 221 (2.8%), 193 (3.1%), 179 (32.4%), 114 (100%), 99 (62.9%), and others (calc. mass for 104, 236); ir (neat): 1190, 1139 cm^{-1} and others; nmr (δ, CCl_4): 0.83 (s, 3H, 1.00 (s, 9H), 1.07 (s, 3H), 2.10-3.07 (m, 4H), 3.70 (bs, 4H) and 5.37 (t, J = 2 Hz, 1H). Irradiation of the signal at δ 2.40 changed the spin-spin coupling of the olefinic proton at δ 5.37 from a triplet to a singlet. The compound 103 showed the following spectral properties: ms, m/e: 236 (2.2%), 221 (1.6%), 179 (27.8%), 114 (100%), 99 (38.9%) and others (calc. mass for 103, 236), nmr (δ, CCl_4): 0.75 (s, 3H), 1.05 (s, 12H), 2.10-2.70 (m, 3H), 2.95 (dt, J = 7, 3 Hz, 1H), 3.63 (m, 4H) and 5.05 (m, 1H). Irradiation of the signal at δ 2.20 changed the spin-spin coupling of the olefinic proton at δ 5.05 from a multiplet to a doublet (J = 2 Hz).

3-Carbomethoxymethylene-7,7-dimethyl-6,6-ethylenedioxy-bicyclo[3,2,0]heptane 56.

a) Preparation of methyldiethylphosphonoacetate 105. In a three-necked flask equipped with a condenser and a dropping funnel and provided with a slow stream of nitrogen was placed 35.5 g (21.4 mm) of triethyl phosphite. The flask was heated with an oil bath at 110-120°. To the stirred solution, methylbromoacetate (28.5 g, 18.6 mm) was added dropwise to maintain a slow refluxing rate. After the addition was completed, the reaction was heated for an additional three hours. The mixture was then distilled and the fraction of b.p. 130-131°/0.08 mm was collected (34.3 g, 89%). The nmr spectrum showed the following absorptions: (δ, CCl_4): 1.33 (t, J = 7 Hz, 6H), 2.83 (d, J = 22 Hz, 2H), 3.73 (s, 3H) and 4.10 (q, J = 7 Hz, 4H).

b) Reaction of 105 with the ketone 55. In a 250 ml three-necked flask equipped with a condenser and provided with a nitrogen atmosphere were placed 1.32 g of sodium hydride (57% dispersion) and 150 ml of glyme. To the stirred solution, 6.5 ml of 105 was added at 0°. After the evolution of gas had ceased, a solution of 3.57 g (18 mm) of 55 in 2 ml of glyme was added. The solution was then heated under reflux for six hours. The reaction mixture was then cooled to room temperature and water was added. The solution was extracted with ether. The

organic layer was separated, washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvent gave a liquid mixture which was adsorbed on alumina and eluted with 7% ether-hexane to afford 3.04 g of the conjugated ester 56 (67%). The spectral properties were as followed: ms, m/e: 252., 237, 221, 220, 193, 179, 114, 99 and others; ir (neat): 1719, 1666, 1205, 1129 and 1031 cm^{-1} and other bands; nmr, (δ, CCl_4): 0.80 (s, 3H), 1.08 (s, 3H), 1.83-3.37 (m, 6H), 3.53 (s, 3H), 3.67 (m, 4H) and 5.57 (bs, 1H).

Exo-endo-3-carbomethoxymethyl-7,7-dimethyl-6,6-ethylenedioxybicyclo[3,2,0]heptane 106.

a) Reduction of the conjugated ester 56 with magnesium metal in methanol. In a round bottom flask fitted with condenser were placed 2 ml of methanol, 72 mg of the conjugated ester 56 and 61 mg of magnesium metal. The mixture was stirred for 3 hours during which time most of the magnesium was consumed and a gelatinous precipitate was formed. To dissolve the precipitate and the remaining magnesium, 5 ml of dilute hydrochloric acid was added. The solution was extracted with three 10 ml portions of ether. The combined solvents were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The solvents were removed to afford 70 mg of a clean mixture of exo- and endo- ester 106 (96%).

The ester mixture was adsorbed on alumina and eluted with 10% benzene-hexane. The spectral data of this exo- and endo-mixture were as followed: nmr (δ, CCl_4): 3.80 (m, 4H), 3.63 (s, 3H), 2.91 (bt, J = 8 Hz, 1H), 2.46-1.20 (m, 8H), 1.12; 1.07 (s,s; ratio 4:1, 3H) and 0.85 (s, 3H); ir (neat): 1742 and 1190 cm^{-1} and others; ms, m/e: 254 (parent peak).

b) Catalytic hydrogenation of the conjugated ester 56. A solution of 2.73 g of the ester 56 in 150 ml of ethanol was stirred over 1.0 g of 5% palladium-charcoal under a hydrogen atmosphere until hydrogen uptake ceased (1.5 hr). The solution was filtered and the residue was washed with ethanol. Removal of solvent on the rotary evaporator afforded 2.49 g of the exo-endo mixture of ester 106. Gas chromatographic analysis showed that the ratio of exo-endo isomers obtained from catalytic hydrogenation was approximately the same as that obtained from magnesium metal reduction.

7,7-Dimethyl-6,6-ethylenedioxy-3-exo-endo-(2-hydroxyethyl)-bicyclo[3,2,0]heptane 57a. Reduction of the ester 106 with lithium aluminum hydride.

Into a solution of lithium aluminum hydride (0.50 g) in 40 ml of ether was added slowly a mixture of 1.16 g of the ester 106 in 2 ml of ether. After the solution was stirred at room temperature for four hours, water was

added. The ether layer was separated and the aqueous layer was extracted again with ether. The combined ether was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the ether yielded an oil which was then chromatographed on alumina and eluted with 25% ether-hexane giving 1.02 g of 57a (99%). The spectral data were as followed: ms, m/e: 226 (parent peak); ir (neat): 3389, 1379 and 1041 cm^{-1} and others; nmr, (δ, CCl_4): 3.67 (m, 4H), 3.45 (t, J = 6 Hz, 2H), 2.78 (bt, J = 8 Hz, 1H), 2.41 (bs, 1H, D_2O exchangeable), 2.10-1.00 (m, 8H) and four methyl groups at 1.03, 1.00, 0.80 and 0.75 (total 6H).

7,7-Dimethyl-3-exo-endo-(2-hydroxyethyl)-bicyclo[3,2,0]-heptan-6-one 58a.

The ketal alcohol 58a (0.270 g) was dissolved in 7 ml of benzene and 5 ml of dilute hydrochloric acid was added. The reaction was stirred vigorously to mix the two layers for 6 hours. The organic layer was separated and the aqueous layer was washed again with benzene. The benzene extracts were washed with sodium bicarbonate solution, saturated sodium chloride and dried over anhydrous sodium sulfate. The benzene was removed on the rotary evaporator and the residue was chromatographed to give 0.213 g (98%) of 58a: ms, m/e: 182 (parent peak); ir (neat): 3425 and 1770 cm^{-1}; nmr (δ, CCl_4): 3.57 (t,

underneath t at 3.47, 1H), 3.47 (t, J = 6 Hz, 2H), 2.66 (bs, 1H, D O exchanged), 2.60-1.10 (m, 8H) and four methyl groups at 1.23, 1.20, 1.00, 0.93 (total 6H).

7,7-Dimethyl-3-exo-endo-(2-ethyltosylate)-bicyclo[3,2,0]-heptan-6-one 52a.

The alcohol 58a (2.54 g) was dissolved in 20 ml of pyridine and the solution was cooled to 0°. Excess toluenesulfonyl chloride (3.0 g) was added in one portion and the mixture was stirred for 1-2 hours. At the end of the reaction, ice cold water was added and the solution was extracted twice with chloroform (2 x 20 ml). The combined extracts were washed with dilute hydrochloric acid, saturated sodium carbonate, saturated sodium chloride and dried over anhydrous sodium sulfate. The chloroform was removed and the residue was chromatographed on an alumina column to give 4.21 g of 52a (90%): ms, m/e: 336 (parent peak), 242, 181, 164, 155, 136, 121, 108, 93, 70 and others; ir (neat) 1776, 1610 cm^{-1} and several bands; nmr (δ, CCl_4): 7.26 (ABq, J = 8 Hz, 4H), 3.76 (t, J = 6 Hz, 2H), 3.43 (bt, J = 8 Hz, 1H), 2.60-1.00 (m, 8H), 2.30 (s, 3H) and four methyl groups at 1.07, 1.03, 0.83 and 0.73 (total 6H).

7,7-Dimethyl-6,6-ethylenedioxy-3-exo-endo-(2-hydroxyethyl)-bicyclo[3,2,0]heptane 57b. Reduction of the conjugated ester 56 with lithium-ammonia.

Into a 250 ml three-necked flask equipped with a mechanical stirrer and Dry Ice condenser was distilled 150 ml of ammonia. At -78°, a solution of 3.0 g (12 mm) of the conjugated ester 56 in 5 ml of ethanol was added. The mixture was distilled to dryness. The residue was then dissolved with ether and water. The ether layer was separated and the aqueous layer was extracted again with ether. The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the ether gave a crude material which was then chromatographed (Alumina, 20% ether-hexane) to afford 1.92 g of the ketal alcohol 57b (70%). The spectral properties were as followed: ms, m/e: 226, 114, 99 and others; ir (neat): 3395, 1041 cm^{-1} and other bands; nmr (δ, CCl_4): 3.63 (m, 4H), 3.43 (t, J = 7 Hz, 2H), 2.76 (bt, J = 8 Hz, 1H), 2.33-1.00 (m, 8H), 1.00 (s, 3H) and 0.73 (s, 3H).

7,7-Dimethyl-3-exo-endo-(2-hydroxyethyl)-bicyclo[3,2,0]-heptan-6-one 58b.

Procedure used according to preparation of 58a. ms, m/e: 182, 70 and others.

ir, (neat): 3448, 1774, 1058 cm^{-1} and others.

nmr, (δ, CCl_4): 3.57 (t, J = 7 Hz, 2H), 3.46 (t, J = 7 Hz, 1H), 2.50-0.93 (m, 9H), 1.20 (s, 3H) and 1.00; 0.93 (both s, total 3H).

7,7-Dimethyl-3-exo-endo-(2-ethyltosylate)-bicyclo[3,2,0]-heptan-6-one 52b.

Procedure used according to preparation of 52a.

ms, m/e: 336, 70 and others.

ir (neat): 1775 cm^{-1}.

nmr (δ, CCl_4): 7.26 (ABq, J = 8 Hz, 4H), 3.76 (t, J = 6 Hz, 2H), 3.43 (t, J = 8 Hz, 1H), 2.60-1.00 (m, 8H), 2.30 (s, 3H) and four methyl groups at 1.20, 1.16, 0.96, and 0.83 (total of 6H).

5-Deutero-7,7-dimethyl-3-exo-endo-(2-hydroxyethyl)-bicyclo-[3,2,0]heptan-6-one 58c.

The alcohol 58a (0.82 g) was dissolved in 5 ml of deuterium ethoxide and 0.27 g of sodium methoxide was added. After the reaction was stirred for two hours, 0.5 ml of deuterium oxide was added. The mixture was extracted with ether (2 x 15 ml) and the combined extracts were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of solvents on the rotary evaporator gave a clear liquid which was chromatographed on an alumina column (25% ether-hexane) to afford 0.72 g

of the deuterated alcohol 58c: nmr (δ, CCl_4): 3.47 (t, J = 7 Hz, 2H), 2.60-1.10 (m, 9H) and four methyl groups at 1.23, 1.20, 1.00 and 0.93 (total of 6H); ms, m/e: 183 (7.26%), 165 (7.26%), 138 (9.67%), 110 (14.51%), 94 (22.58%), 70 (100%) and others. Calculation from ms showed that 99% of one deuterium was incorporated into the molecule.

5-Deutero-7,7-dimethyl-3-exo-endo-(2-ethyltosylate)-bicyclo[3,2,0]heptan-6-one, 52e.

To the solution of the deuterated alcohol 58c (0.652 g, 3.5 mm) in 5 ml of pyridine at 0°, 0.70 g of toluenesulfonyl chloride was added in one portion. After the reaction was stirred at 0° for two hours, ice-water was added and the mixture was extracted with cold chloroform (2 x 20 ml). The combined extracts were washed quickly with dilute hydrochloric acid, sodium bicarbonate solution, saturated sodium chloride and dried over anhydrous sodium sulfate. The chloroform was removed and the residue was chromatographed on an alumina column (25% ether-hexane) to give 1.05 g of the deuterated tosylate 52e (88%). The nmr spectrum of 52e was similar to that of 52a except the broad triplet at δ 3.43 disappeared. The mass spectrum showed m/e at 337 (1.98%), 242 (1.95%), 182 (1.83%), 165 (7.73%), 155 (4.04%), 109 (33.87%), 91 (32.26%), 70 (100%)

and others. Again, calculation from ms showed 91% of deuterium incorporated in the molecule.

Attempted synthesis of 3,3-dimethyltricyclo[4,2,1,$0^{1,4}$] nonan-2-one 31. Reaction of the tosylate 52a with sodium hydride and *t*-butanol in glyme.

To a suspension of 50 mg of 57% sodium hydride in 9 ml of glyme was added slowly a mixture of 111 mg of the tosylate 52a in 1 ml of glyme followed by a drop of *t*-butanol. The solution was stirred at room temperature for 15 hours and then heated at 45° for 3 hours. The reaction was followed by TLC until the starting material disappeared. After the reaction was completed the solution was cooled to room temperature and poured into ice-water. The mixture was extracted with methylene chloride (2 x 10 ml). The organic extracts were washed with water, saturated sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed to give 60 mg of the clean methyl ether 111 (93%). The spectral data were in accord with the assigned structure: ms, m/e: 196 (parent peak, calc. mass of 111, 196), 70 (base peak) and others; ir (neat): 1776, 1373 and 1124 cm^{-1} and others; nmr (δ, CCl_4): 3.64 (bt, J = 8 Hz, 1H), 3.23 (t, J = 6 Hz, 2H), 3.17 (s, 3H), 2.57-1.00 (m, 8H) and four methyl groups at 1.23, 1.17, 1.00 and 0.92 (total of 6H).

Reaction of the tosylate 52a with *t*-butyllithium in tetrahydrofuran.

In a 25 ml three-necked flask equipped with condenser, stopper and serum cap was placed 5 ml of tetrahydrofuran and 0.5 ml (0.96 M) of *t*-butyllithium was added slowly at -78°. To the stirred solution, a mixture of 156 mg of the tosylate 52a in 1 ml of tetrahydrofuran was added. The reaction mixture was stirred at -78° for 15 minutes and allowed to warm to room temperature. The solution was then quenched with water and extracted with ether (2 x 10 ml). The combined solvents were washed with saturated sodium chloride and dried over sodium sulfate. Removal of solvents gave a crude material which was adsorbed on an alumina column. The material was eluted with 25% ether-hexane to give 140 mg of the adduct 113 (77%): ms, m/e: 394 (very weak), 337 (8.8%), 222 (5.0%), 207 (3.7%), 194 (5.0%), 165 (16.2%), 155 (6.2%), 137 (51.2%), 128 (77.5%), 91 (45.0%), 57 (87.5%), 43 (100%); ir (neat): 3597, 1610, 1470, 1360, 1176, 1099 and others; nmr (δ, CCl_4): 7.37 (ABq, J = 8 Hz, 4H), 3.90 (t, J = 6 Hz, 2H), 2.40 (s, 3H), 2.93-1.10 (m, 10H), 1.20 (s, 3H) and 0.90 (s, 12H).

Reaction of the tosylate 52a with methylsulfinyl carbanion.

A solution of methylsulfinyl carbanion was prepared by the method of Corey[52] from 57 mg of 57% sodium hydride

dispersion (washed with pentane) and 5 ml of dimethyl sulfoxide. To this solution, at 60°, under nitrogen, was added a solution of 244 mg of the tosylate 52a in 6 ml of dimethyl sulfoxide. The resulting solution was stirred for 1.5 hours and then poured into ice-cold water. The mixture was extracted twice with chloroform (2 x 30 ml). The combined chloroform extracts were washed with water and dried over magnesium sulfate. Removal of the chloroform yielded 108 mg of crude material. Thin layer chromatography showed at least two products were formed. Separation on column chromatography (alumina, act 3, 20% chloroform-hexane) gave 24 mg of the olefin 112 (29%). The spectral data were as follows: ms, m/e: 164 (parent peak), 70 and others; ir (neat) 1770, 1647 and 921 cm^{-1} and other bands; nmr (δ, CCl_4): 5.53 (two d, J = 18, 10 Hz, 1H), 4.87 (two bd, J = 18, 10 Hz, 2H), 3.56 (bt, J = 8, 1H), 2.60-1.00 (m, 6H), 1.33 (s, 3H) and 1.03 (s, 3H).

Reaction of the tosylate 52b with sodium ethoxide in ethanol.

In a 25 ml three-necked flask fitted with a condenser were placed 55 mg of the tosylate 52b, 10 mg of sodium and 6 ml of ethanol under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 108 hours. Water was then added and the solution was extracted with ether. The ether layer was separated, washed with

saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of ether afforded 30 mg of the ethyl ether 115. The nmr spectrum showed the following absorptions: δ, 0.90 (s, 3H), 1.10 (t, J = 7 Hz, 3H), 1.17 (s, 3H), 0.80-2.60 (m, 8H), 3.23 (q, J = 7 Hz, 2H), 3.26 (t, J = 6 Hz, 2H) and 3.53 (bt, J = 8 Hz, 1H). The ir spectrum showed the carboxy absorption at 1773 cm^{-1}.

Reaction of the tosylate 52a with *t*-butyllithium in HMPA and tetrahydrofuran.

In a 50 ml three-necked flask, 5 ml of THF and 0.8 ml of HMPA were placed under a nitrogen atmosphere. The flask was cooled to -100° and 0.4 ml of *t*-butyllithium was added. To the stirred solution, 78 mg of the tosylate 52a in a 3 ml of THF was added slowly. The solution which changed from yellow to deep green was stirred for an additional hour and was warmed up to room temperature. The solution was then quenched with deuterium oxide and extracted with ether. The ether was separated and dried over anhydrous sodium sulfate. Removal of the ether gave a crude material which was chromatographed on an alumina column to afford 20 mg of a compound which was suggested to be the lactone 114. The spectral data were as followed: ms, m/e: 352, ir (neat): 1770 cm^{-1}; nmr (δ, CCl_4): 7.33 (ABq, J = 8 Hz, 4H), 3.86 (t, J = 6 Hz, 2H), 3.27 (q,

J = 7 Hz, 1H), 2.37 (s, 3H), 2.35-0.80 (m, 8H), 1.30 (s, 3H) and 1.20 (s, 3H).

General procedure for attempted cyclization of the tosylate 52.

In a three-necked flask fitted with a condenser were placed 5-10 ml of solvent and base. The mixture of the tosylate 52 in 1-2 ml of solvent was added. The reaction solution was stirred for a period of time. Water was then added and the solution was extracted with ether. The organic layer was separated, washed with saturated sodium chloride and dried over anhydrous sodium sulfate.

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APPENDIX

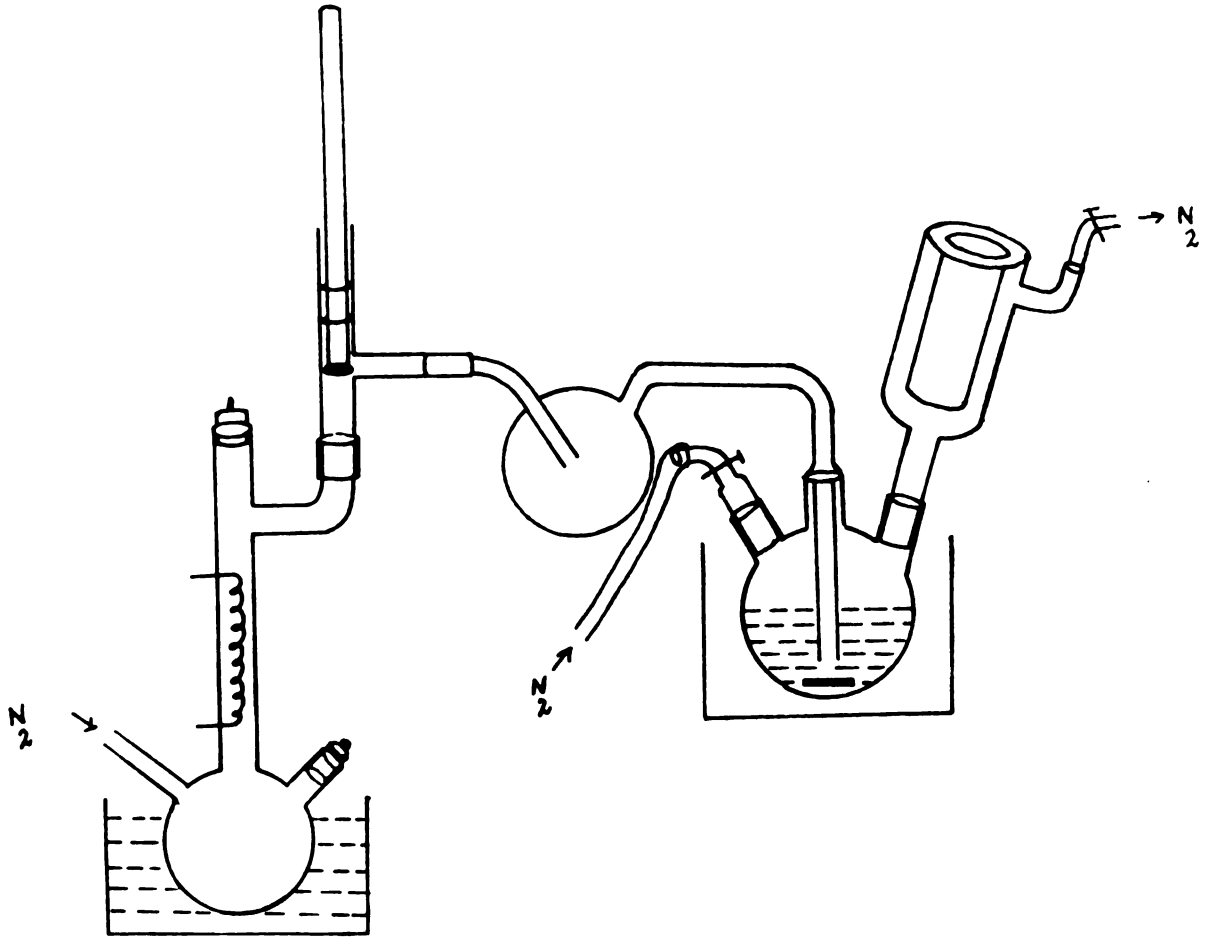


Figure 16

Apparatus Used for Preparation of Ketone 53.

Figure 17

Proton NMR Spectrum of

7,7-Dimethyl-6,6-ethylenedioxy-

bicyclo[3,2,0]hept-2-ene 54

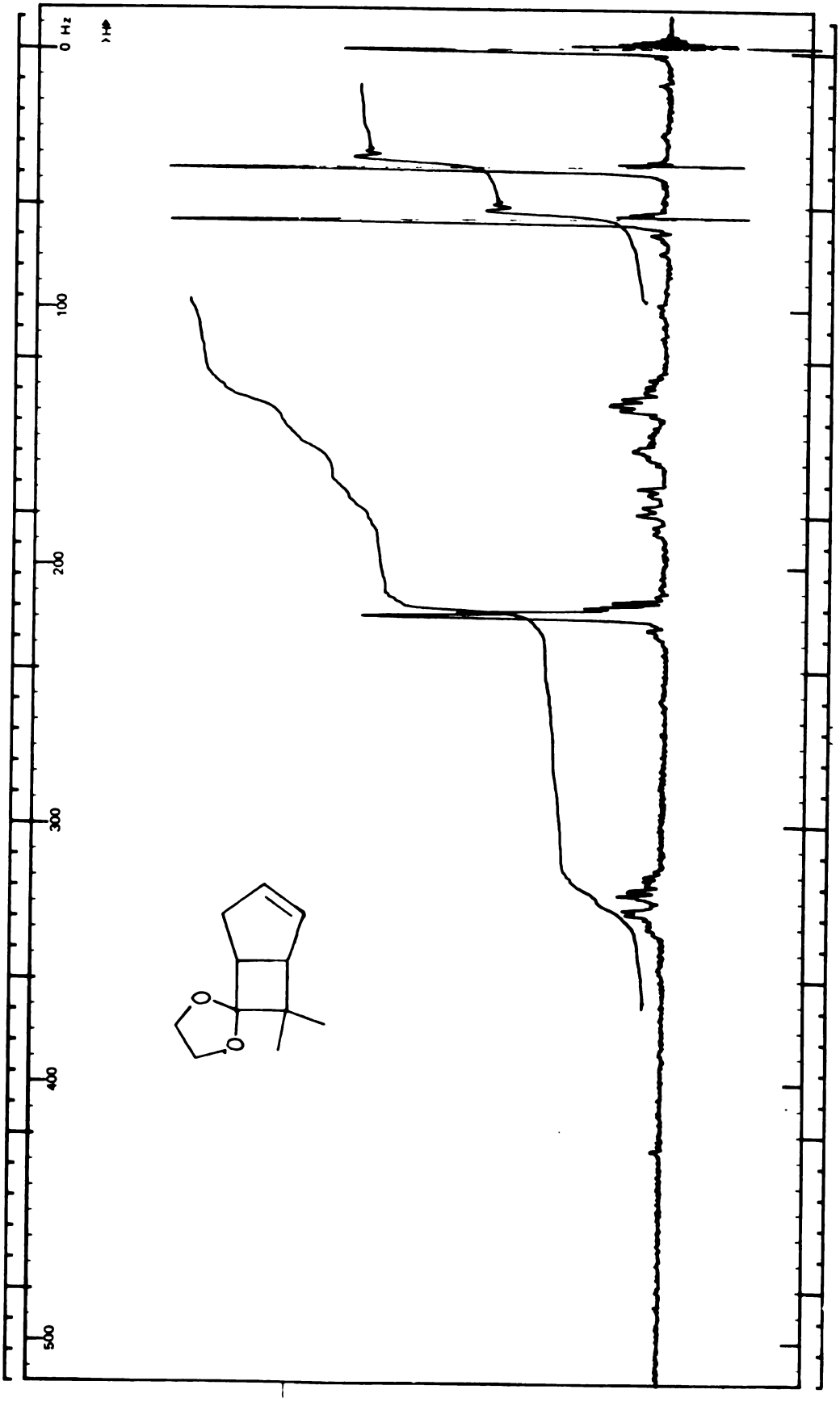


Figure 17

Figure 18

Proton NMR Spectrum of

7,7-Dimethyl-6,6-ethylenedioxy-exo-

bicyclo[3,2,0]heptan-2-ol 63

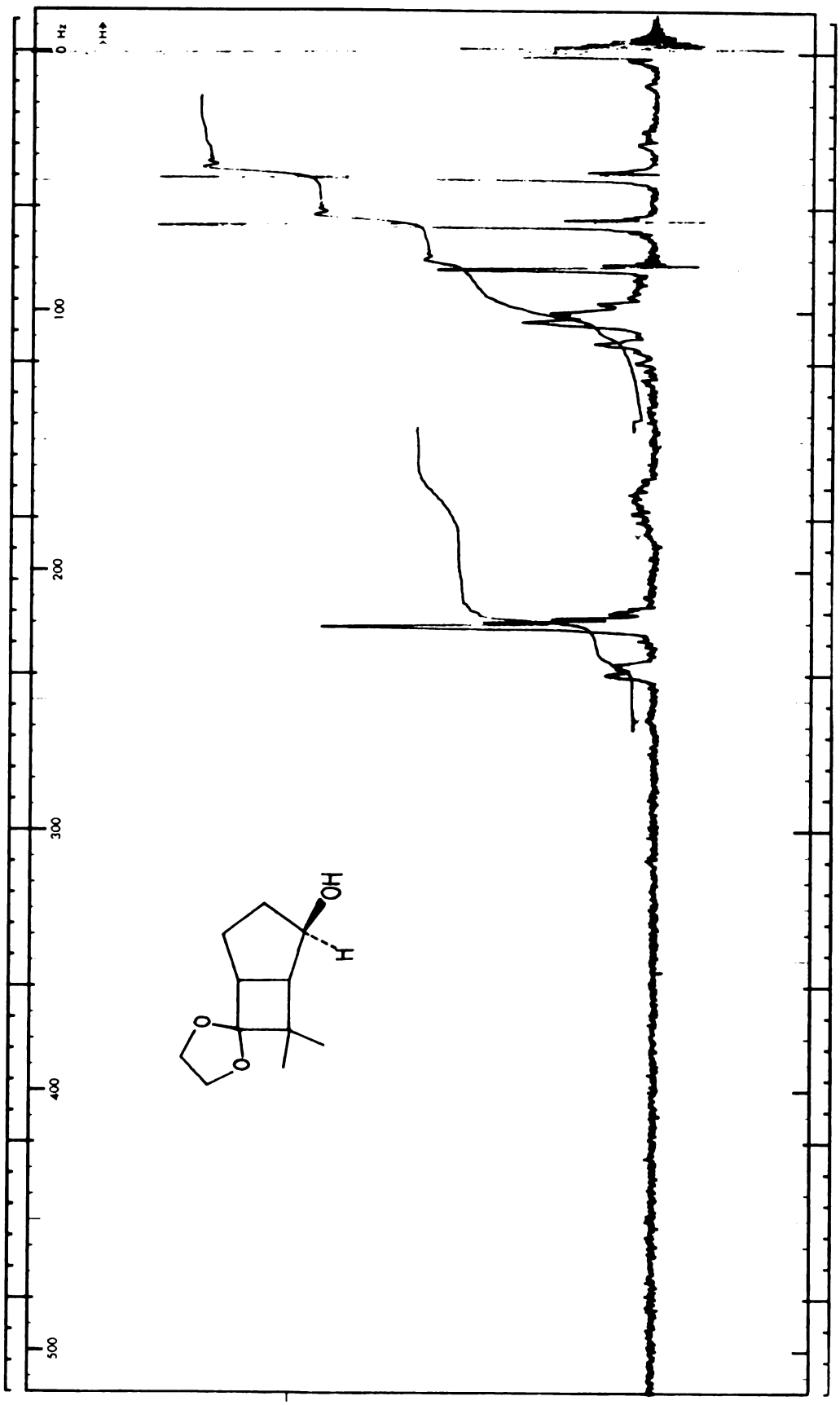


Figure 18

Figure 19

Proton NMR Spectrum of

7,7-Dimethyl-6,6-ethylenedioxy-exo-

bicyclo[3,2,0]heptane-2,3-oxide 101

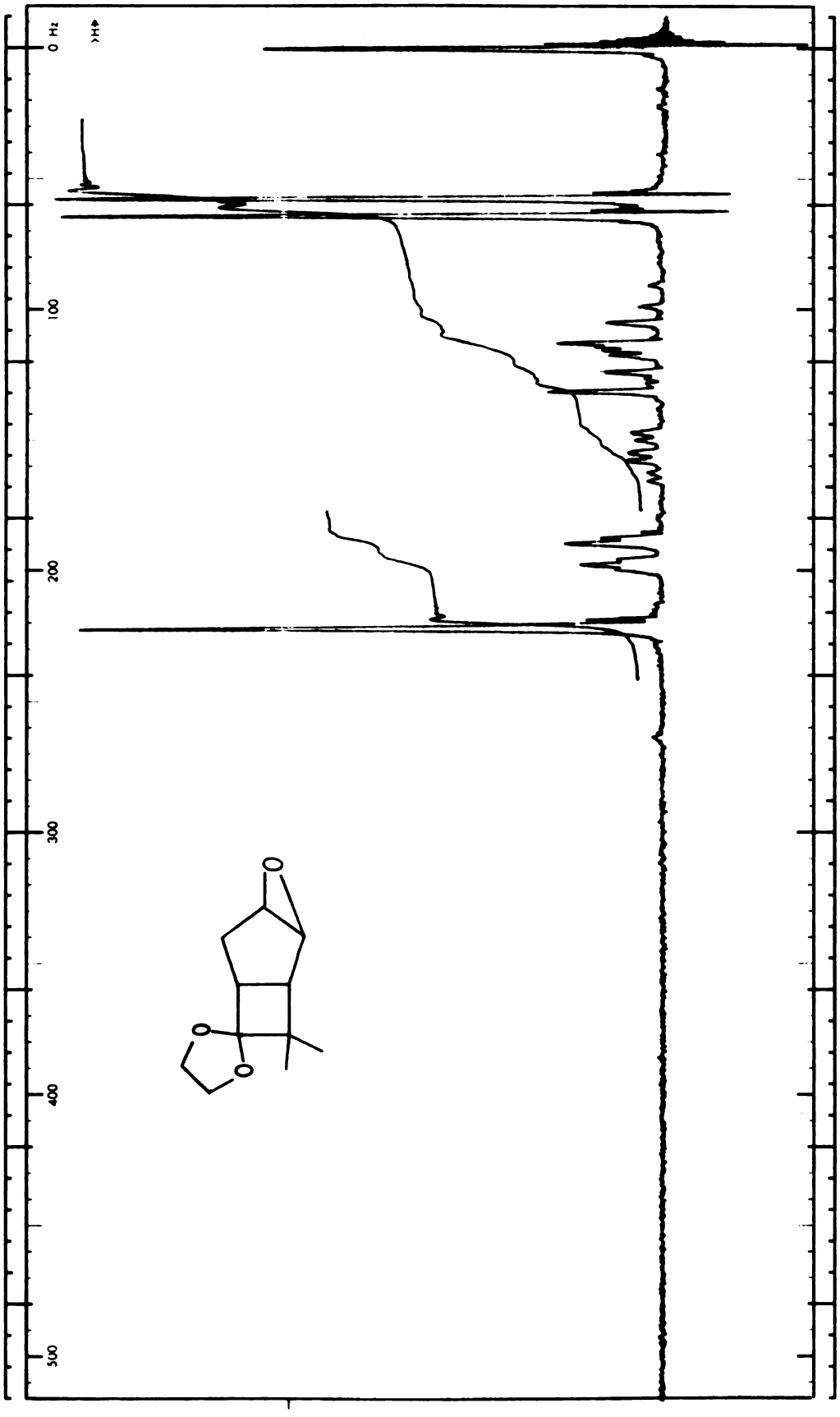


Figure 19

Figure 20

Proton NMR Spectrum of

7,7-Dimethyl-6,6-ethylenedioxy-

bicyclo[3,2,0]heptan-2-one 67

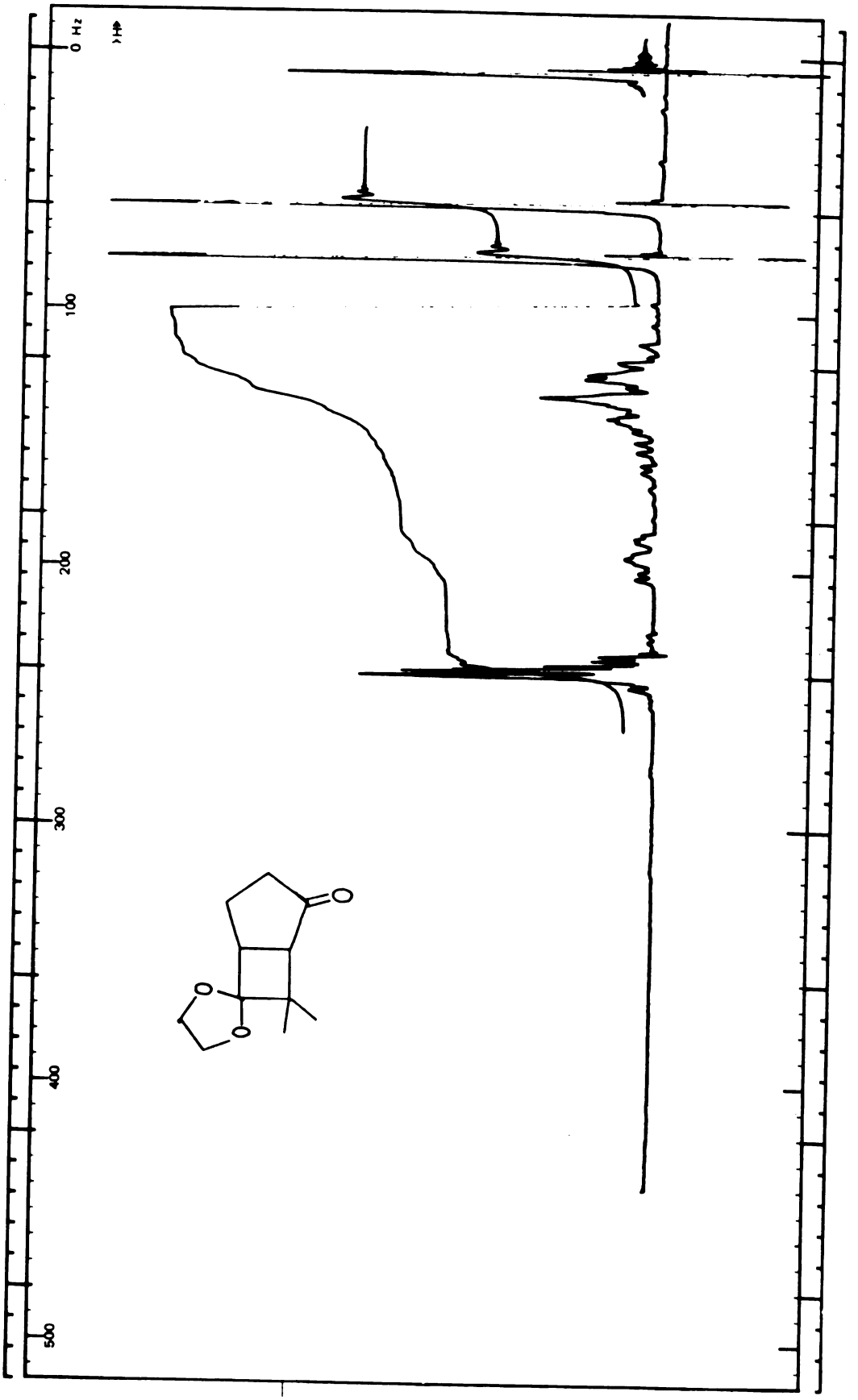


Figure 20

Figure 21

Proton NMR Spectrum of

7,7-Dimethyl-6,6-ethylenedioxy-

bicyclo[3,2,0]heptan-3-one 55

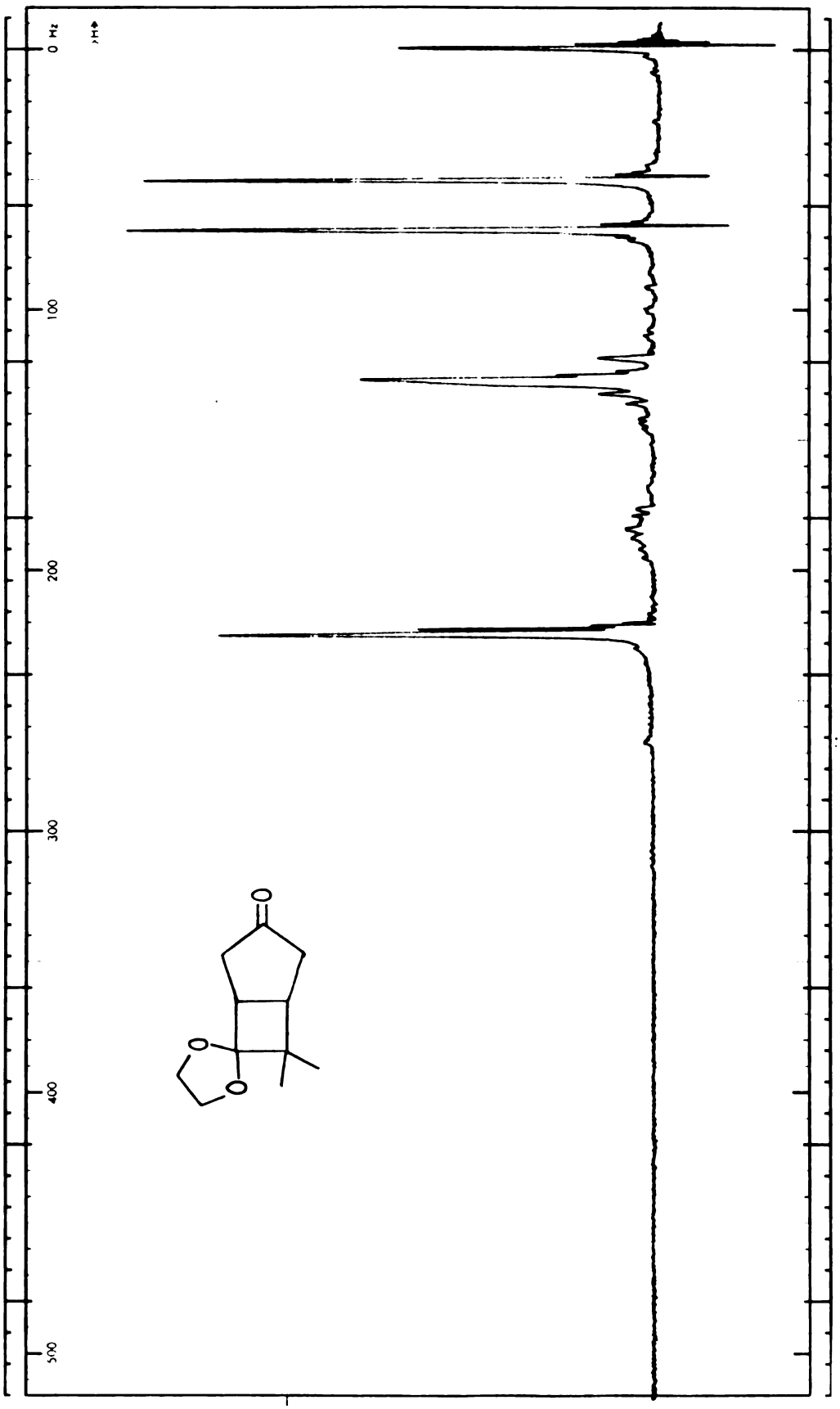


Figure 21

Figure 22

Proton NMR Spectrum of

7,7-Dimethylbicyclo[3,2,0]heptane-2,6-dione 22

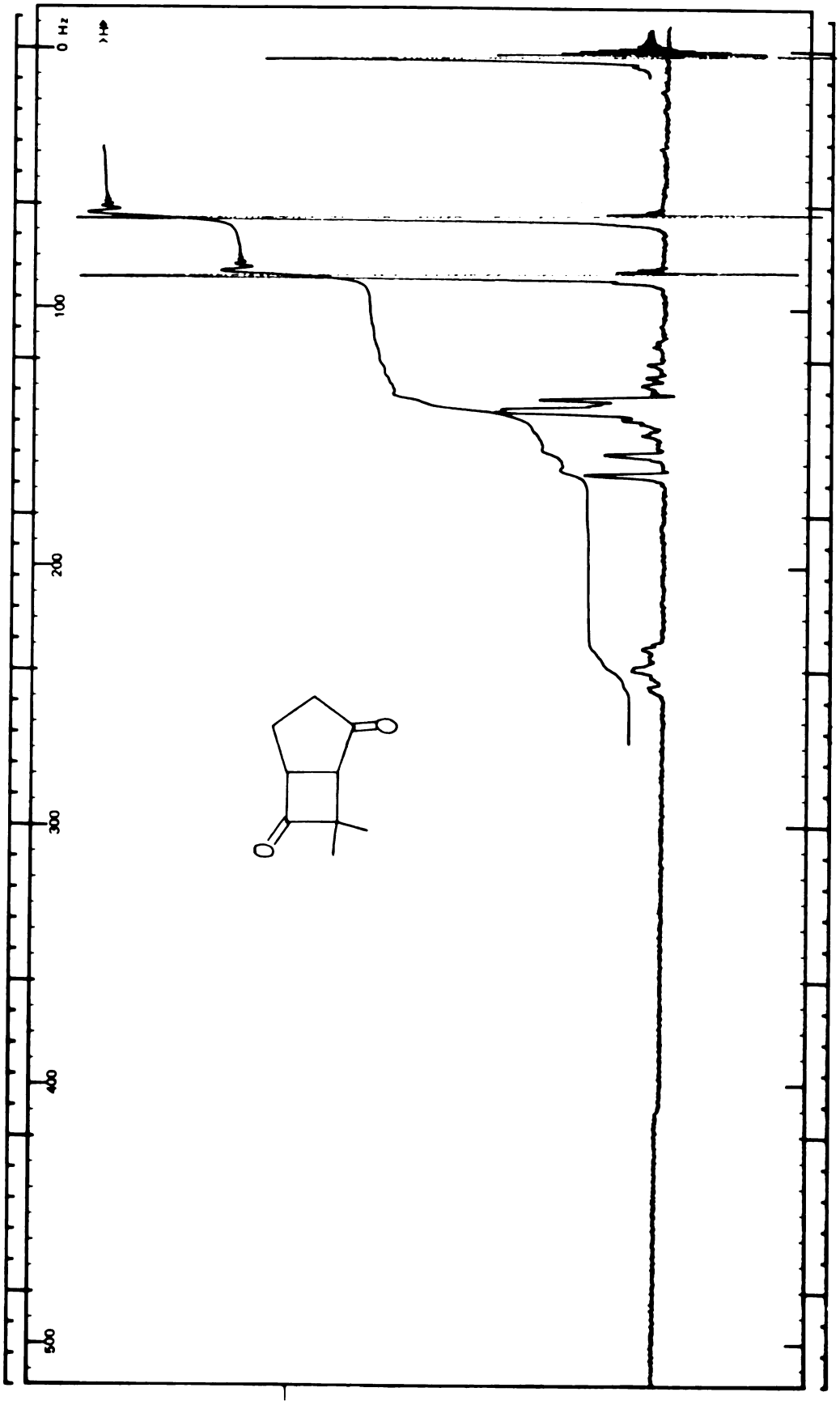


Figure 22

Figure 23

Proton NMR Spectrum of

7,7-Dimethylbicyclo[3,2,0]heptane-3,6-dione 71

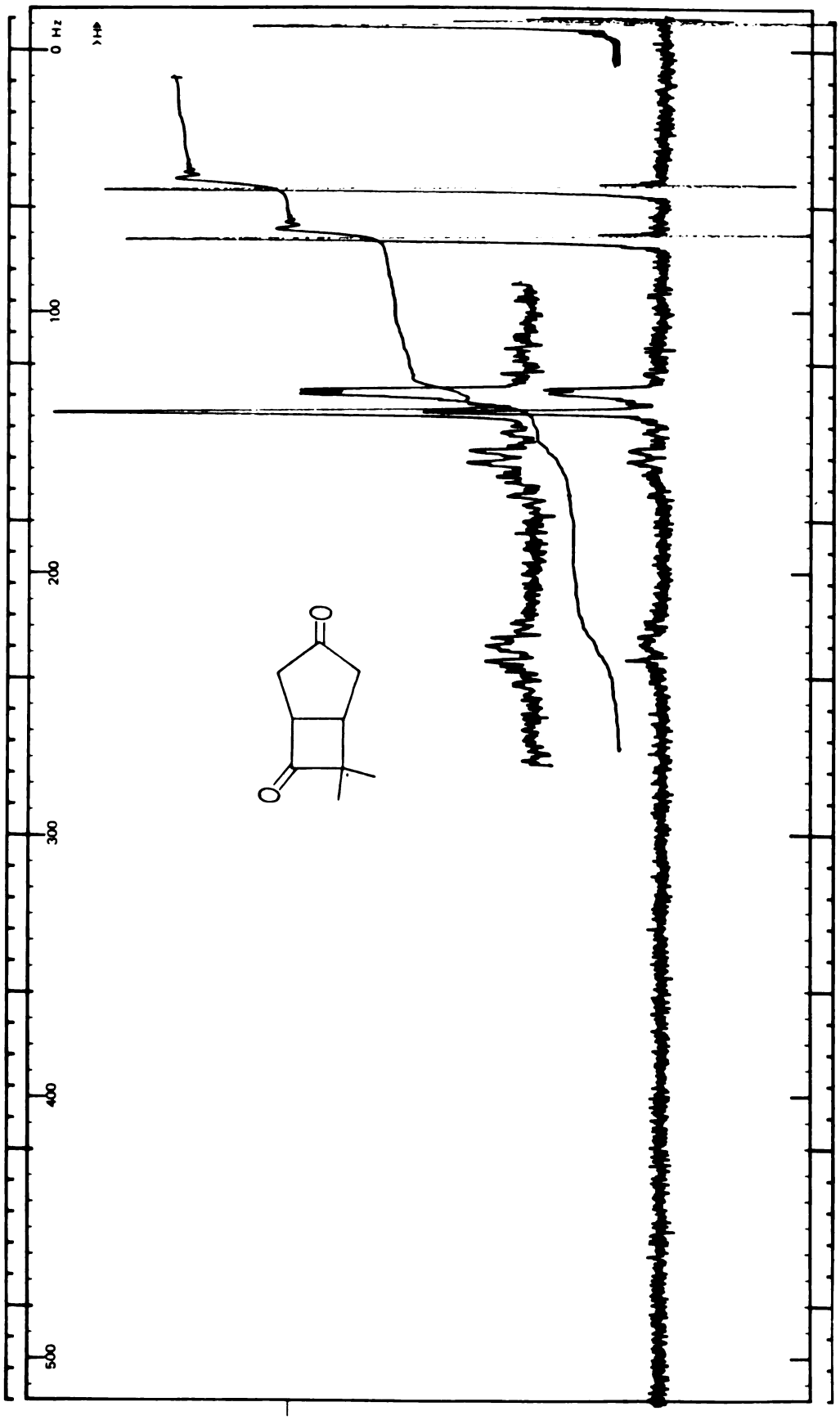


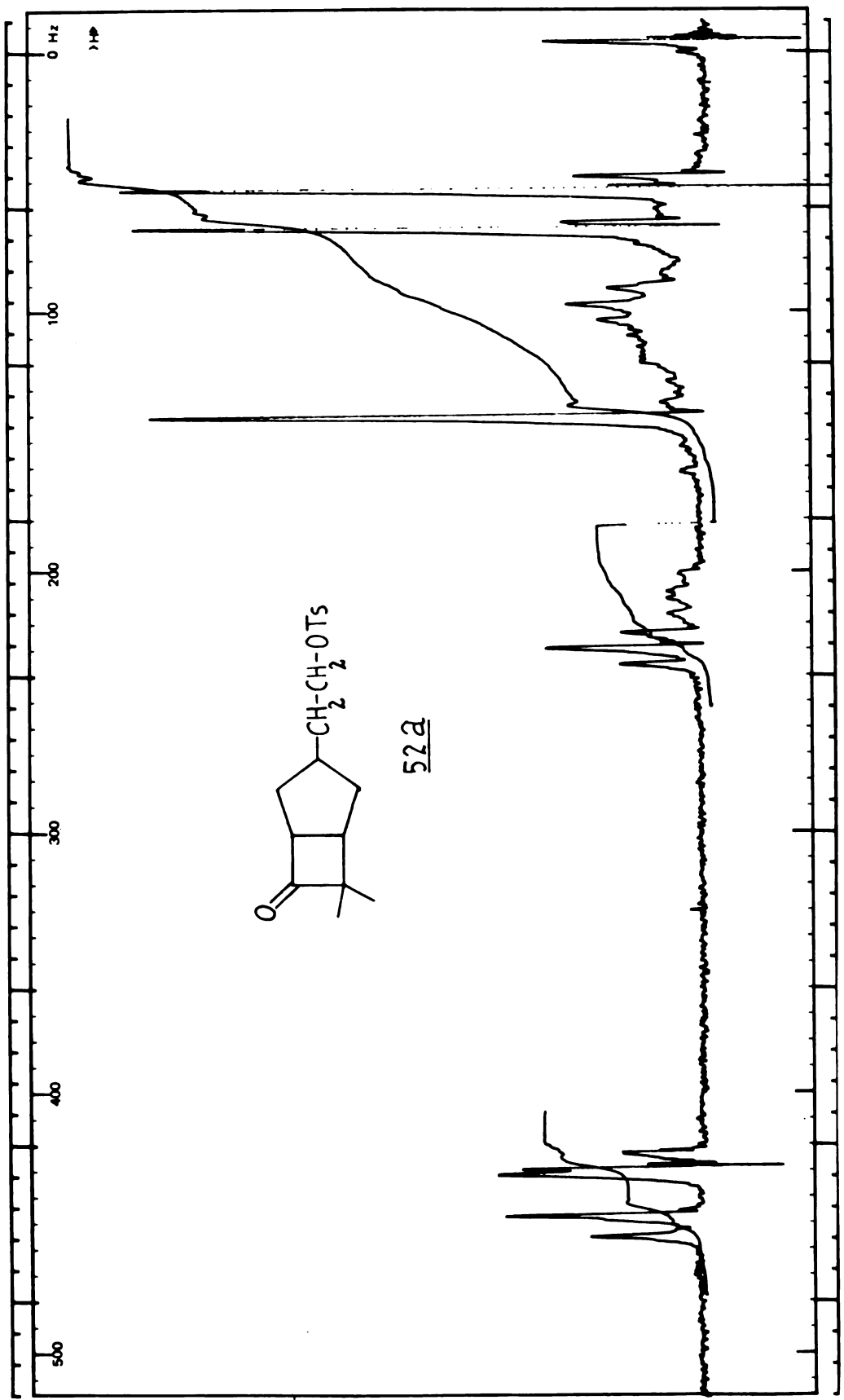
Figure 23

Figure 24

Proton NMR Spectrum of

7,7-Dimethyl-3-exo-endo-(2-ethyltosylate)-

bicyclo[3,2,0]heptan-6-one 52a



52a

Figure 24

Figure 25

Proton NMR Spectrum of

7,7-Dimethyl-3-exo-endo-(2-ethyltosylate)-

bicyclo[3,2,0]heptan-6-one 52b

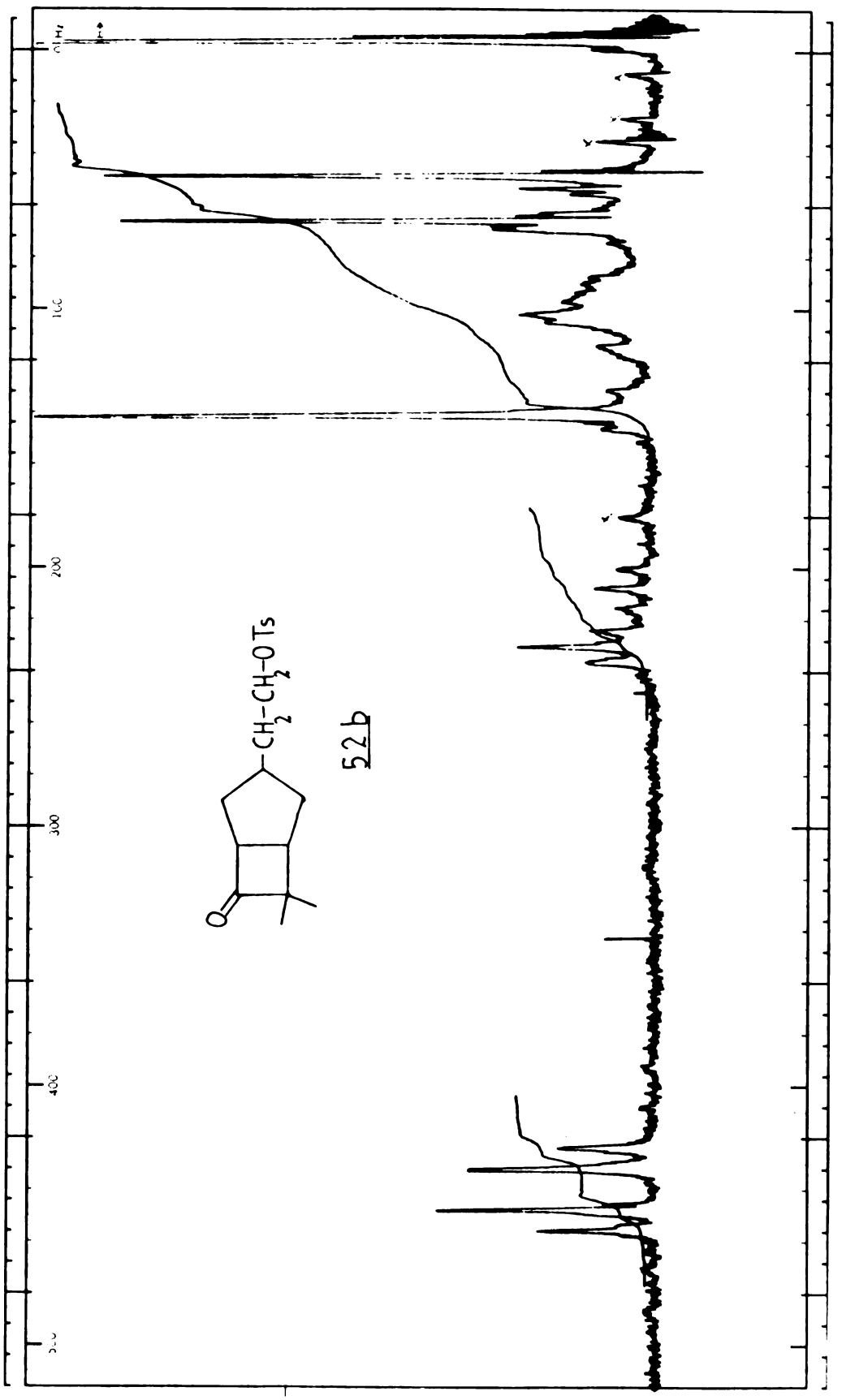


Figure 25

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