1982

I. Synthetic approaches to 1, 1-dilithiocyclopropanes ll. A method for the synthesis of functionalized 2, 4-dimethyl-1, 3-pentadienes III. Electrophilic additions to [4.3.1] propellenes

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Iowa State University

Le, Diem Duy

I. SYNTHETIC APPROACHES TO 1,1-DILITHIOCYCLOPROPANES. II. A METHOD FOR THE SYNTHESIS OF FUNCTIONALIZED 2,4-DIMETHYL-1,3-PENTADIENES. III. ELECTROPHILIC ADDITIONS TO (4.3.1)PROPELLENES

Iowa State University PH.D. 1982

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by

Diem Duy Le

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1982

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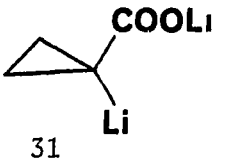
GENERAL INTRODUCTION

Organolithium chemistry encompasses a myriad variety of compounds. Their synthetic utilities are tremendous. Except for a few simple alkyllithiums, the structures of organolithium compounds, which usually exist as aggregates, are generally unknown. Recent *ab initio* calculations on several polylithio compounds have revealed startling structural features. For instance, 1,1-dilithiocyclopropane, 21, was predicted to have a planar geometry at C-1.

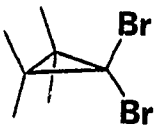
21



31

Planar tetracoordinate carbon has long been a fascinating subject, but an elusive target. The predicted planarity in 21 is of special interest since the carbon may be stabilized in the planar geometry, in contrast to other systems where planarity may be attained by "forceful" bending and twisting of the C-C bonds, or by homoconjugation with a surrounding aromatic network. As a possible precursor to 21, lithium α-lithiocyclopropanecarboxylate, 31, was examined. Some of its nucleophilic reactions were found to be contradictory to published results. Derivatives of 21 were also approached via lithium-bromine exchange of

1,1-dibromotetramethylcyclopropane, 40, and 1,1-dibromo-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 63. The ^{13}C enriched analog of 63, 83 , was employed to allow direct ^{13}C NMR observation of the organolithium intermediates, including the carbenoid 90.



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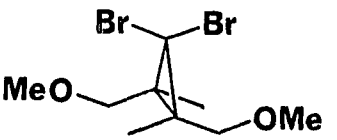

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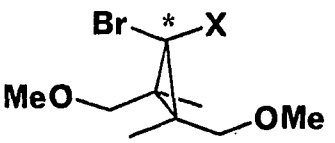


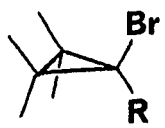
83: X=Br
90: X=Li

*: 45% Carbon 13

Direct spectroscopic observations of α-halolithium carbenoids are very few, despite their long standing as well-studied reactive intermediates. The first ^{13}C NMR observation of an α-bromolithium cyclopropylidene was reported very recently. ^{13}C NMR studies of 90 provided in addition the first direct evidence for the inversion process at the cyclopropylidene carbenoid carbon. A hitherto unknown reactive intermediate, a carbenoid: alkyllithium complex, was unexpectedly discovered. Also reported are the first successful ^{7}Li-decoupled ^{13}C NMR and ^{7}Li NMR spectra of an α-Bromolithium cyclopropylidene carbenoid and other organolithiums resulting from the

treatment of 63 with excess alkyllithium.

Derivatives of cyclopropyl halides are known to undergo various ring-opening reactions to give olefinic compounds. Several alkyl substituted 1-bromo-2,2,3,3-tetramethylcyclopropanes, 99, were observed to extrude a molecule of HBr upon gas chromatography. The products were thought to be the corresponding 3-alkyl-2,4-dimethyl-1,3-pentadienes, 116. Further investigation was pursued



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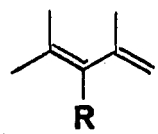
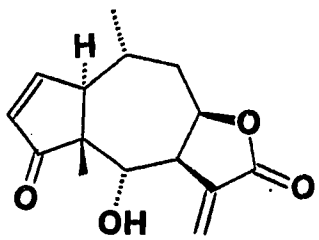


116

because it was recognized that functionalized derivatives of 116 were not known, but are potentially valuable synthetic precursors to several classes of natural products. Reported in Part II is a convenient method for the synthesis of the functionalized dienes.

Ring openings of cyclopropyl halides have also been employed to generate bridgehead olefins from systems such as the 10,10-dibromo[4.3.1]propellenes and derivatives. The stereochemistry of electrophilic additions to [4.3.1] propellenes were not well-established. As part of an effort toward the total synthesis of helenalin, 156, electrophilic additions to [4.3.1]propell-3-ene 158 and 152, and allylic derivatives of [4.3.1]propell-2-ene, 157,

were investigated. Several epimeric pairs of 157 and its derivatives were synthesized. A definite trend in the splitting patterns of H_4 in the ^1H NMR was observed. The patterns were employed to support assignments of stereochemistry in other derivatives.



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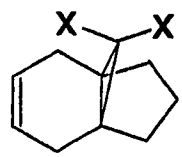
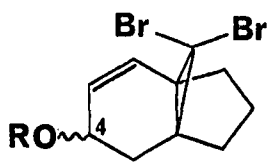


152, X=Br
158, X=H



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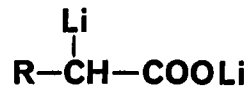
I. SYNTHETIC APPROACHES TO 1,1-DILITHIOCYCLOPROPANES

INTRODUCTION

Polylithium organic compounds have recently attracted attention for synthetic applications, physico-chemical studies, and theoretical calculations. Examples of well-known synthetic intermediates include dianions of carboxylic acids[1], 1, of arenesulfonylhydrazones[2], 2, and of thioacids[3], 3. These simple systems are actually



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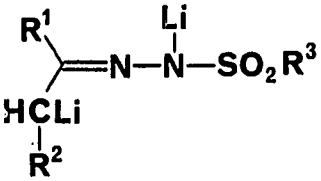

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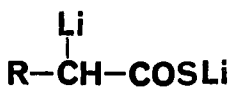
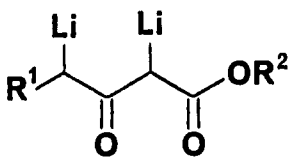


3

monocarbanionic, since one of the anion centers is the heteroatom. Their formation was effected by proton abstraction of the two most acidic hydrogens. Similar proton abstraction was employed to generate 1,3-dianions or polyanions of 1,3-dicarbonyl compounds[4], 4, and β-ketophosphonates[5], 5, although the second or third abstraction was usually more difficult. These polylithium compounds



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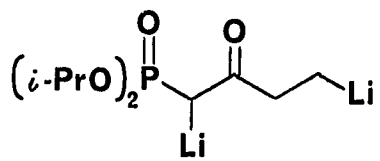
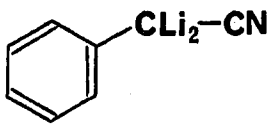


5

have their carbanion centers separated, and also stabilized by neighboring heteroatoms.

Heteroatom-stabilized organopolylithiums also include *gem*-polyanion compounds[6,7,8] such as 6-8. α-Polylithio esters[9] and α-keto dianions[6a,10] have also been reported.



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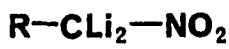

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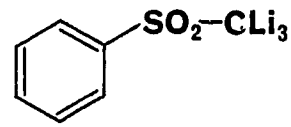

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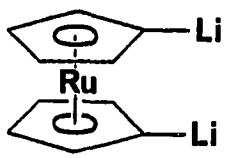
Organopolylithiums containing no stabilizing heteroatoms are also numerous. The carbanionic centers, almost always unsaturated or allylic, are often widely separated[11,12] as exemplified in 9 and 10, or participating in delocalization[13] as shown in 11 and 12, or involved in the newly conceptualized Y-aromaticity[14] as shown in 13.



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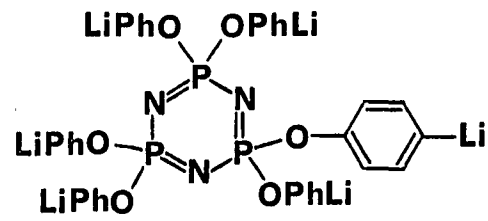

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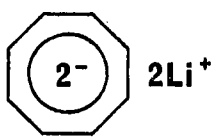

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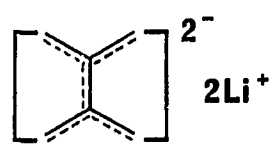

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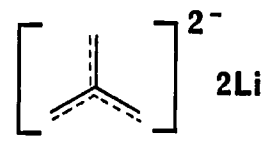
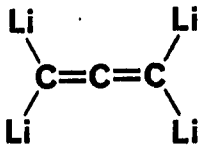


13

Allenic and acetylenic polylithiums have been reported[15]. Treatment of propyne with four equivalents of *n*-butyllithium, followed by trapping with $ClSiMe_3$, provided 15 in good yield. Although the organolithium intermediate was reported as the tetralithio allene, 14, it was conceded later that the actual structure is not known[16].



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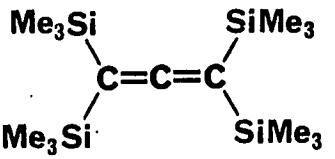
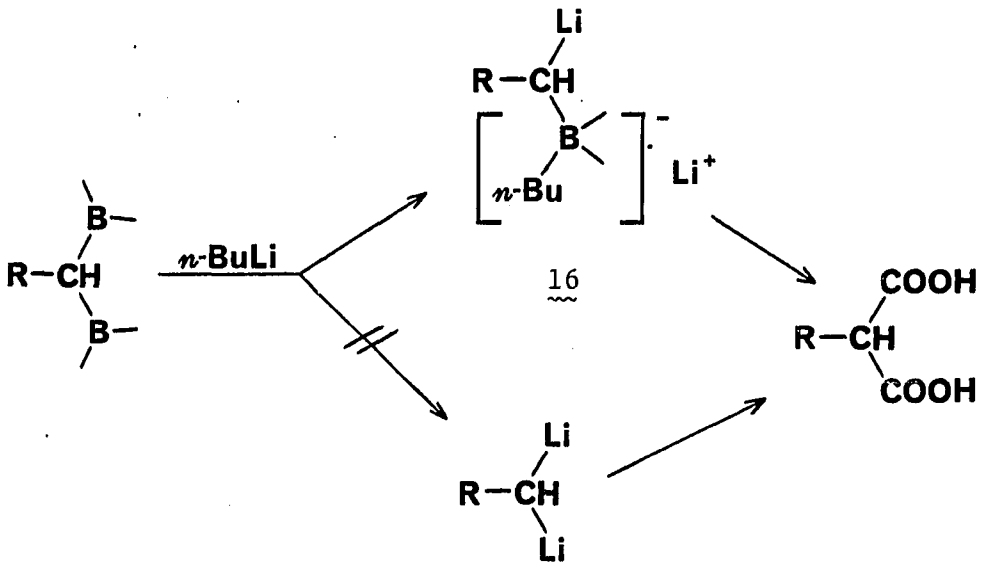


15

The intermediacy of a saturated *gem*-alkyldilithium was suggested[17] when treatment of a 1,1-diboraalkane with two equivalents of *n*-butyllithium followed by trapping with carbon dioxide gave the corresponding diacid (Scheme 1).

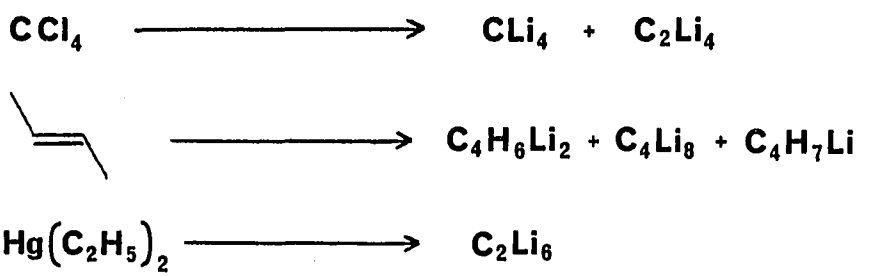
Scheme 1



However, further investigation[18] showed that a consecutive two-fold transmetallation did not occur. The most likely intermediate appeared to be 16.

Preparations of hitherto-mentioned polylithium compounds were effected by the familiar methods of proton abstraction, lithium-halogen exchange, or a combination of the two[10]. Transmetallation following proton abstraction can offer advantageous results[5d,19]. A rather unconventional preparative method has been recently introduced by Lagow and coworkers. At 800°C, lithium vapor reacted with alkyl halides[20,21], simple hydrocarbons[22], carbon vapor[23], or organomercurials[24] to give numerous highly unusual

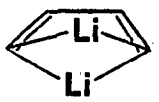
Scheme II



organolithium compounds (Scheme II).

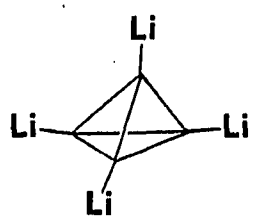
While the presence of more than one anionic center in the molecule was found helpful in preventing undesirable side reactions[25,26] or convenient in providing one-pot tandem alkylation[27,28], or simply essential for the compounds' stability[29], lithium's ability to form electron-deficient

multi-center bonds[30] and to function as an excellent σ-donating, π-accepting substituent[31] have led to predictions of highly unusual structures for polylithium organic compounds. For instance, monomeric *cis,cis*-1,4-dilithiobutadiene and 1,2-dilithiocyclopropene[32] have been predicted to have the bridged structures shown in 16 and 17, respectively. Calculations on several other polylithiums also indicated



16

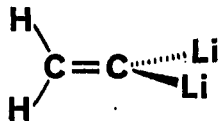
17



18

bridged structures[33,34]. Tetralithiotetrahedrane, 18, is predicted to be a relatively stable species as compared to its hydrocarbon counterpart[31,35]. This has been attributed to the "strain-relieving" properties of lithium. High level of *ab initio* calculations by several groups, most notably Schleyer, Pople, and co-workers, have pointed to a perpendicular structure, 19, for 1,1-dilithioethylene[36], and a near degeneracy for tetrahedral and planar geometries of dilithiomethane[37], 20. The 1,1-dilithiocyclopropane, 21, was calculated (RHF/STO-3G) to be more stable with a planar rather than tetrahedral geometry at C-1[38].

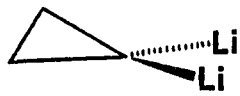
Planar tetracoordinate carbon has long been a fasci-



19

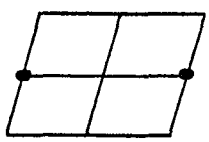
CH_2Li_2

20



21

nating subject. The carbon may exist as such[39] or undergo planar inversion with a sufficient low energy barrier so that its planarity may be detected experimentally[40]. Several highly strain hydrocarbon compounds such as tetracyclo[3.3.1.$0^{3,9}$.$0^{7,9}$]nonane[41], 22, [2.2.2.2]paddlane[42], 24, and the aromatic compound 25[43] have been proposed as candidates containing a planar tetracoordinate carbon.



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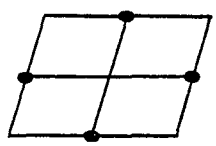

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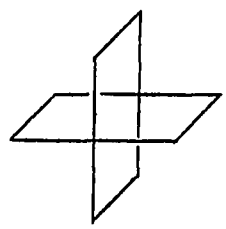

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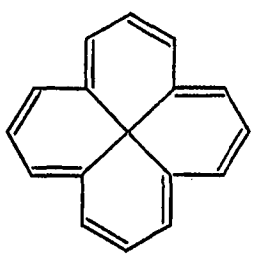

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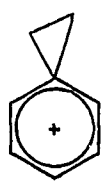


26

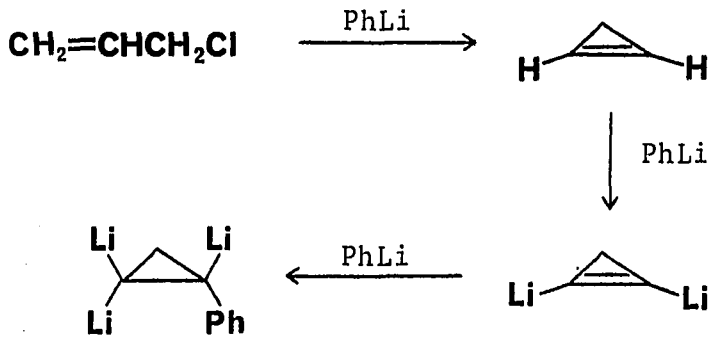
While reports of progress toward the synthesis of fenestranes[44], 22 and 23, are promising, recent semi-empirical calculations have cast doubt on their ultimate realization[45]. Similar pessimistic predictions[45] have also been reached for 24. A low barrier to planar inversion has been suggested for the phenonium ion 26, but never verified experimentally[46].

Experimental verification of the predicted planarity in 1,1-dilithiocyclopropane, 21, is of particular interest since the molecule represents a new approach to planar tetracoordinate carbon. The planar geometry is induced by appropriate substituents, not brutally imposed by ring size as in 22 and 24, or contingent upon aromaticity as in 25. This difference also makes the synthesis of 21 appear more attainable than the others'.

While Lagow's lithium-vapor method is effective in generating various organopolylithiums, it lacks regioselectivity and control over the degree of lithiation, and its harsh conditions seem to exclude delicate molecules such as 21. Compound 28 was proposed as an intermediate formed by the addition of phenyllithium to 17 (Scheme III) in the reaction of allyl chloride with phenyllithium[47]. However, there is no direct evidence for 28, and the evidence for the formation of 17 is inconclusive at best.

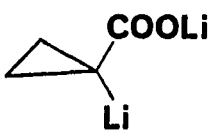
Considered a potential precursor to 21 was lithium α-lithiocyclopropanecarboxylate, 31. Some nucleophilic reactions of 31 were found to conflict with a published account.

Scheme III

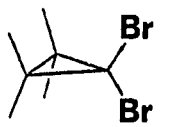


28 17

Attempted syntheses of an alkyl substituted 21 were carried out via a consecutive two-fold Li-Br exchange on 40.



31

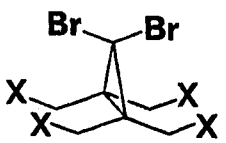


40

It should be emphasized that the predicted planarity in 21 was based on calculations for a hypothetical monomeric structure[38]. In reality, organolithiums exist as aggregates in the condensed phase[48] and, in some cases, even in the gas phase[49]. In only a few instances, monomeric alkyllithiums may be obtained in solution in the presence of complexing agents such as TMEDA[50] or DABCO[51]. Thus, it is equally important as the synthesis itself that 21, or

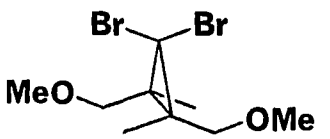
its derivatives, be generated under conditions such that it may exist in the monomeric state.

The synthesis and the problem of the monomeric state of *gem*-dilithiocyclopropanes were approached simultaneously by employing intramolecular coordinating groups as shown in 58. As a stepping stone, reactions of 63 with excess alkyllithiums were studied. Direct observation of the organolithium intermediates with ^{13}C NMR was achieved by employing the ^{13}C-labeled compound 83. The observations also led to an unexpected discovery of a cyclopropylidene carbenoid:alkyllithium complex, and direct evidence for the inversion at the cyclopropylidene carbenoid carbon.

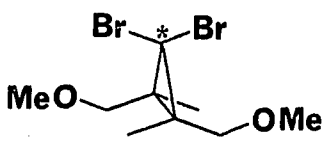


58

X=OR, NR_2



63



83

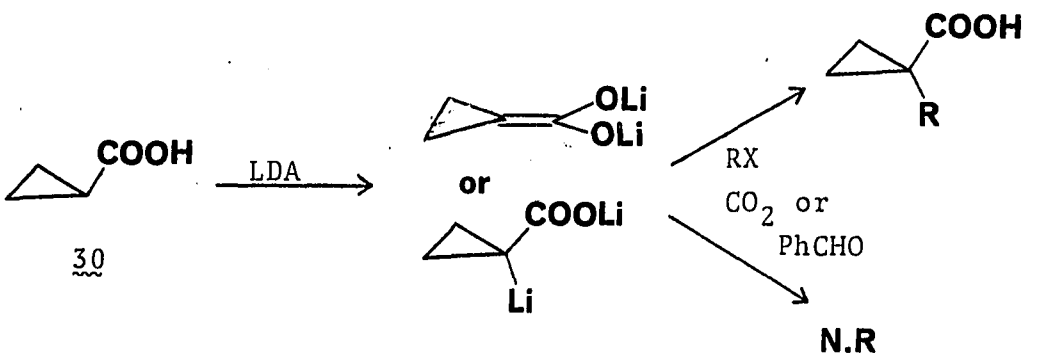
*=45% Carbon-13

RESULTS AND DISCUSSION

Lithium α-Lithiocyclopropanecarboxylate

Generated from the corresponding carboxylic acid by treatment with LDA, the above-named compound was found to undergo alkylation with various alkyl halides, but showed no tendency to add to carbonyl compounds such as carbon dioxide or benzaldehyde (Scheme IV).

Scheme IV



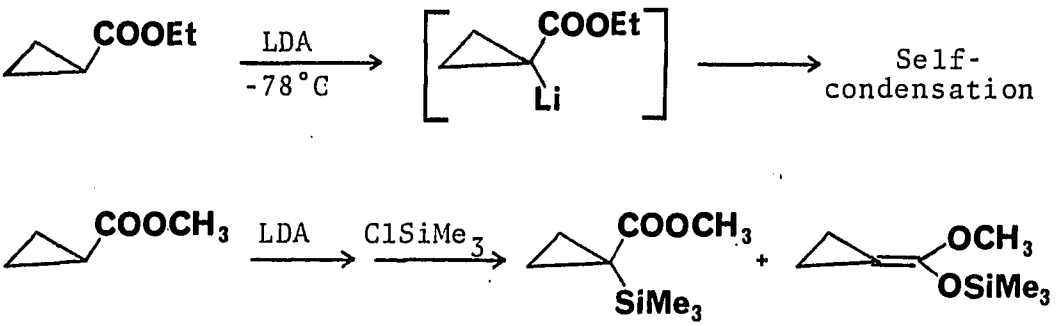
30

31

The lack of reactivity of 31 toward carbonyls was rather surprising. The α-lithiated ethyl ester analog was reported to undergo self-condensation very rapidly even at low temperature[52] (Scheme V). The methyl ester counterpart is less prone to attacking itself and has been trapped with chlorotrimethylsilane to give a mixture of C- and O-silylated products[53]. More recently, 31 was reported not

to undergo alkylation with methyl iodide or benzyl bromide[54].

Scheme V

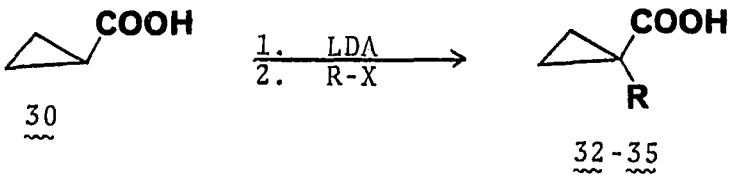


This is contrary to our findings.

The results of alkylation and silylation of 31 are summarized in Table I. Chlorotrimethylsilane seems to be the most effective in trapping the dianion and afforded exclusively the C-silylated product[55]. Alkylation with methyl iodide or allyl bromide gave good yields of the alkylated product, but the percent conversions were rather low. Increased reaction time up to 24 hr. did not result in any improvement. Apparently, proton abstraction was competing with alkylation.

Reaction with benzyl bromide or chloride gave several side products. Three of them were isolated and identified as *trans*-stilbene, 1,2-diphenylethane, and 1,2,3-triphenylpropane. Formation of the first compound from the reaction of alkyllithiums and benzyl halides have been reported previously, and different mechanisms involving carbene intermediates[56] or Wurtz coupling[57] have been proposed. 1,2,3-Triphenylpropane and 1,2-diphenylethane, on the

TABLE I. Yields of products from α-substitution reactions of 30



30 32-35

R-X	Compound	% Yield
$ClSiMe_3$	32	90
MeI	33	90[a]
$BrCH_2CH=CH_2$	34	70[b]
$BrCH_2Ph$	35	17
n-BuI		SM recovered

[a]By NMR.

[b]Based on 30% conversion.

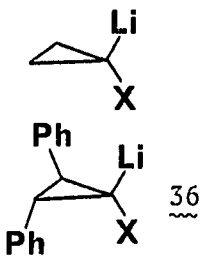
other hand, are known products from the benzyl radical[58].

Treating 31 with *n*-butyl iodide or bromide resulted in only recovered 30, although substantial amounts of LiI or LiBr were observed to precipitate out. Apparently elimination was the main route in these reactions.

Attempts to increase the per cent conversion or to minimize side reactions by treating 31 with copper(I) iodide[59] before adding the alkyl halide, or by using HMPT

as co-solvent[60], were unsuccessful. Also unsuccessful were efforts to effect the additions of 31 to carbon dioxide or benzaldehyde. Treating 31 with $MgBr_2$ or $ZnCl_2$[61] before adding the carbonyl compound still gave no reaction. Perhaps 31 is a very strong base but very poor nucleophile, or else the addition is reversible.

The apparently poor nucleophilicity of 31 as compared to the ester analog is in sharp contrast to that of the diphenyl substituted derivative 36 (X=COOLi). Studies of derivatives of the 2,3-*trans*-diphenylcyclopropyllithium[62] have shown that the system is most reactive[63] when X is



36

TABLE II. Relative stability of cyclopropyl lithiums

X = COOLi < CN < COOR
X = CN < COOMe < COOLi

a lithium carboxylate, and least reactive when X is a nitrile; somewhere in between is the carbomethoxy derivative (Table II). In the unsubstituted cyclopropyllithiums, X = COOLi causes the system to be the least reactive, and the carbanion is most reactive when X is an ester group. Not much is known about the α-cyanocyclopropyllithium except that it has been alkylated at low temperature with allyl bromide[54].

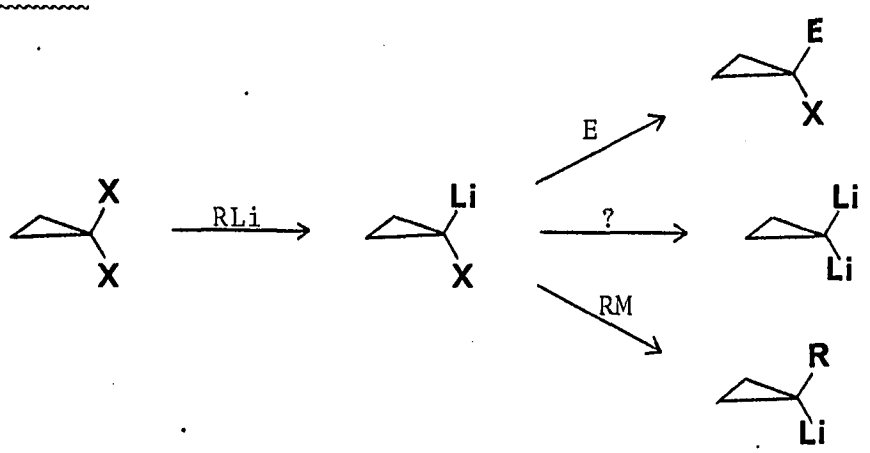
A possible interpretation for 31's unexpectedly poor

reactivity may be that it stabilizes itself by forming highly unreactive aggregates, whereas when phenyl substituents are present as in 36, steric hindrance may prevent the formation of such aggregates.

1,1-Dibromotetramethylcyclopropane

Reactions of *gem*-dihalocyclopropanes with alkyllithiums to generate the cyclopropylidene carbenoid intermediate and subsequent reactivities have been extensively investigated[64]. Due to its combination of functionality, the

Scheme VI



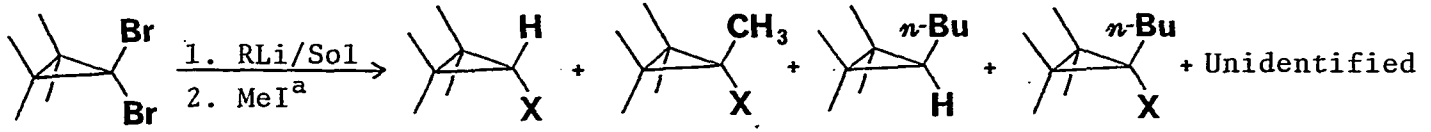
carbenoid has been shown to be capable of undergoing both nucleophilic and electrophilic reactions[65] (Scheme VI). It is not known, however, if the carbenoid can be converted to a *gem*-dilithio species by a consecutive two-fold lithium-halogen exchange. To explore this possibility, 40 was treated with excess alkyllithium reagent in various

solvents, followed by trapping with methyl iodide or CH_3OD.

1,1-Dibromotetramethylcyclopropane, 40, was chosen for the investigation for the following reasons. First of all, there are no cyclopropyl hydrogens. This is important because, due to the high s character[66] of the C-H bond, hydrogens on a cyclopropane may be sufficiently acidic to destroy the alkyllithium reagent[67]. Secondly, 40 is the simplest fully alkyl-substituted *gem*-dihalocyclopropane. Organolithiums generated from 40 when trapped with MeI or MeOH would give known products[68]. And finally, it is economical. Tetramethylethylene is less expensive than other fully substituted alkenes, and dibromocarbene addition was reported to go cleanly and in good yield[69].

Compound 40 prepared according to a slightly modified version of the published procedure[69], was treated with 4 equivalents of *n*-BuLi in various solvents at -95°C, followed by the addition of excess MeI slowly along the inside wall of the reaction flask. The crude product mixtures obtained after work-up were analyzed by NMR and GC.MS. Observed product distributions are summarized in Table III. Compounds 41a and 41b, 42a and 42b were confirmed by independent syntheses (Scheme VIII). Compounds 50 and 51 were not fully characterized. Their structures were deduced from low resolution mass spectra. The formation of 41b and 42b are unexpected and require explanation.

TABLE III. Product ratios from reactions of 40 with *n*-BuLi and MeI



40 41[b] 42[b] 50 51[b]

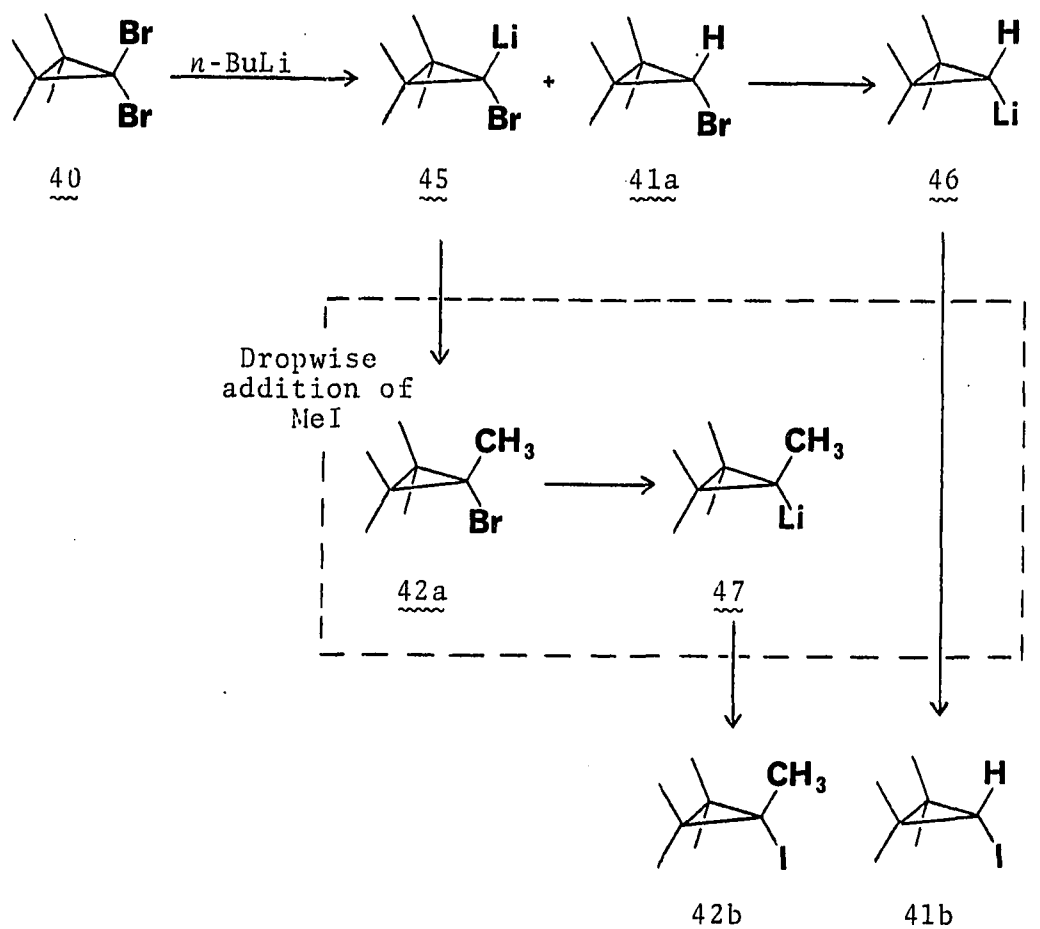
RLi/Solvent	41	42	50	51	Unidentified (m/e)
4 eq. *n*-BuLi/THF	0.3	10.6 42a, 14% 42b, 86%	1.0	2.1	0.3 (168) 0.4 (112)
4 eq. *n*-BuLi. TMEDA (1:1) THF	0.2 41a, 67% 41b, 33%	17.7 42a, 9% 42b, 91%	1.0	0.3	0.5 (168)
4 eq. *n*-BuLi. TMEDA (1:1) Hexane	0.6	None detected	1.0	8.9	None detected

[a]Added dropwise.

[b]a, X=Br; b, X=I.

Scheme VII summarizes the mechanism for the formation of 41b and 42b from 40. Treatment of 40 with *n*-BuLi gave 41a via disproportionation[70], and the major product 45 via exchange. The formation of 41a from 45 via cleavage of THF is believed unlikely due to the relatively short reaction time, 40 min., and the low reaction temperature, -95°C[71]. Besides, 41 were still obtained in comparable amount when THF was replaced by hexane (Table III).

Scheme VII



In the presence of excess *n*-BuLi, 41a was immediately converted to 46. During the dropwise addition of MeI, 45 was methylated to 42a, some of which underwent a second Li-Br exchange with excess *n*-BuLi to give 47. Both 46 and 47 were iodinated instead of methylated by MeI to provide 41b and 42b.

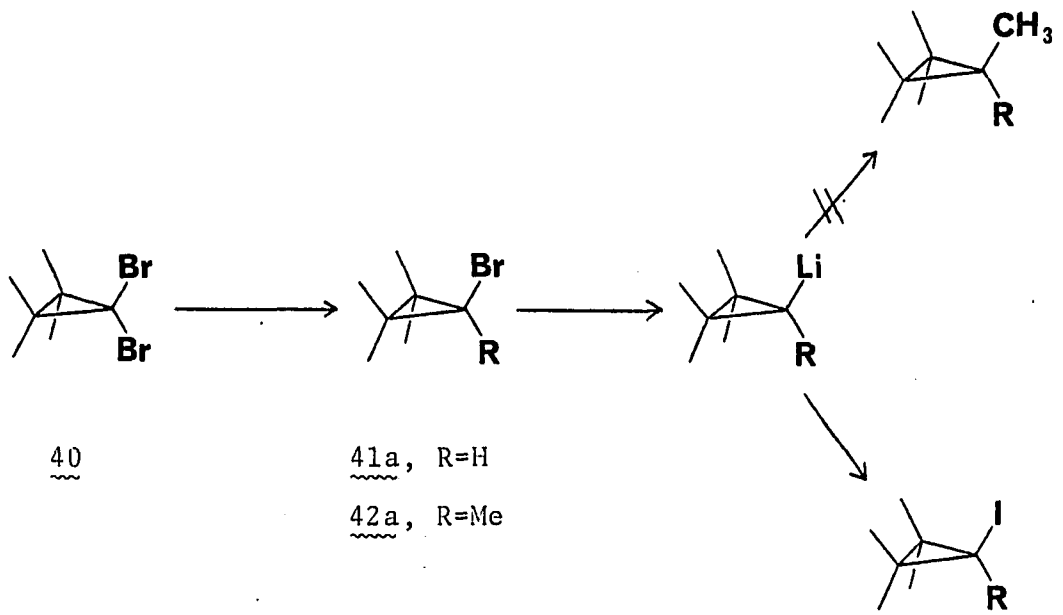
The second Li-Br exchange during the addition of MeI was greatly reduced when MeI was added rapidly as reflected in the reduced yield of 42b (Table IV). This reduction was attributed to the rapid consumption of excess *n*-BuLi by MeI before 42a, a tertiary halide, could effectively compete. Reaction of *n*-BuLi with CH_3I has been shown to generate $CH_3\cdot$[72] besides CH_3Li and others. The results from the fast quench experiments (see also Table IV) also argue against the possibility of 47 being formed by reaction of CH_3Li or $CH_3\cdot$ with 45.

To confirm the conversion of 41a and 42a to 41b and 42b, respectively, pure 41a and 42a were prepared from 40 (see Part II) and treated individually with *t*-BuLi and then MeI (Scheme VIII). In each case, only the iodinated product, 41b or 42b, was detected. The unexpected iodination was confirmed by repeating the same reaction sequence with I_2 in place of MeI to obtain the same product.

The reaction of 46 or 47 with MeI observed is certainly not thermodynamically correct and in conflict with an earlier reported reaction of cyclopropyllithium with MeI[73].

It is suspected that the treatment of 41a or 42a with Butyllithium had given intermediates of different structure from the cyclopropyllithium, 46 or 47, shown. The reaction deserves further investigation.

Scheme VIII



40

41a, R=H

42a, R=Me

41a, R=H

42b, R=Me

Both cyclopropyl iodides 41b and 42b are very unstable in neat form. They turned immediately from colorless to dark red as the solvents were removed. For comparison, ^{1}H NMR of 41a and 41b, 42a and 42b are shown in figures 1 and 2 respectively. While the α-CH_3 in 42b is further downfield than that in 42a, the α-H in 41b is further

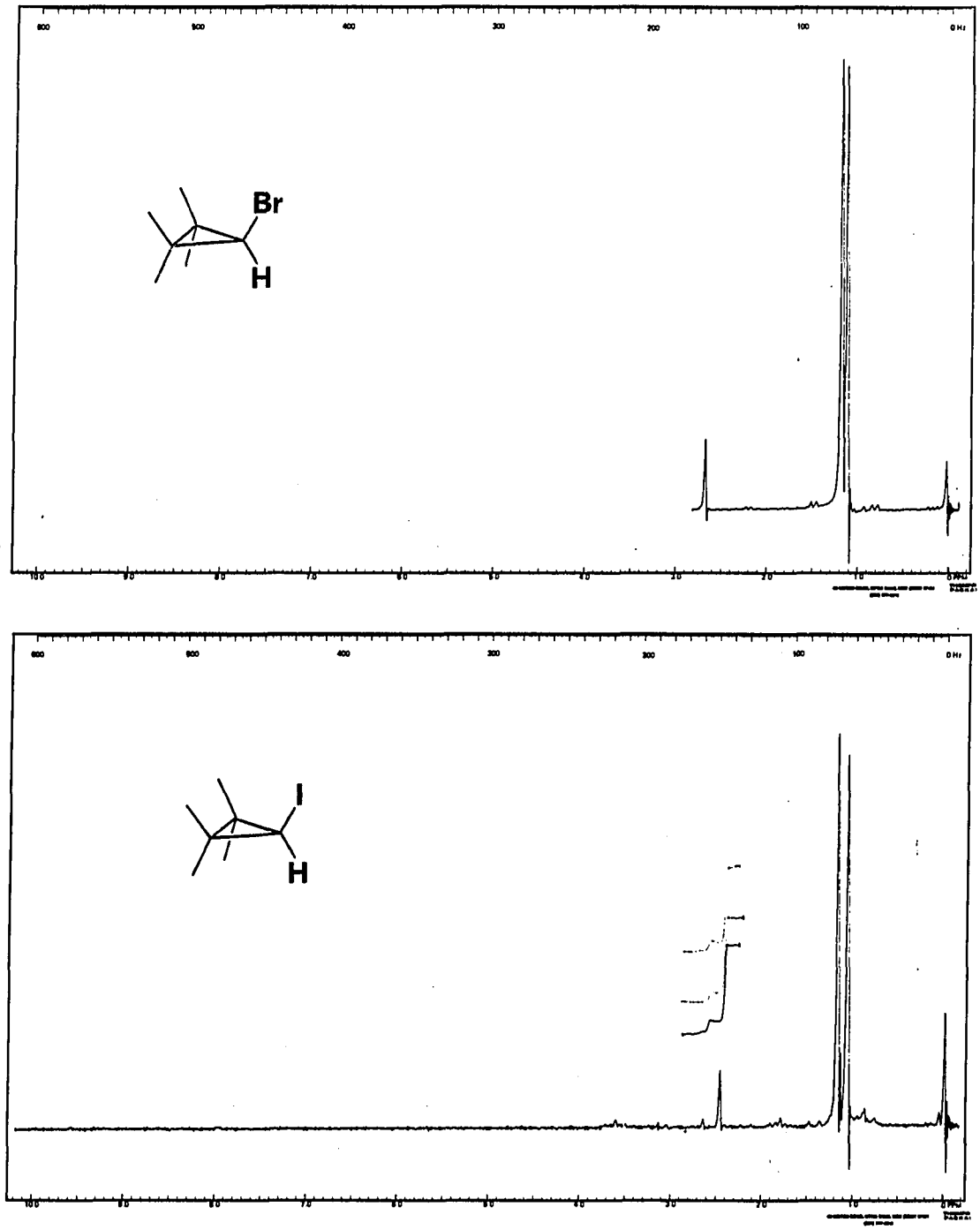


Figure 1. ^{1}H NMR of 41a (top) and 41b (bottom)

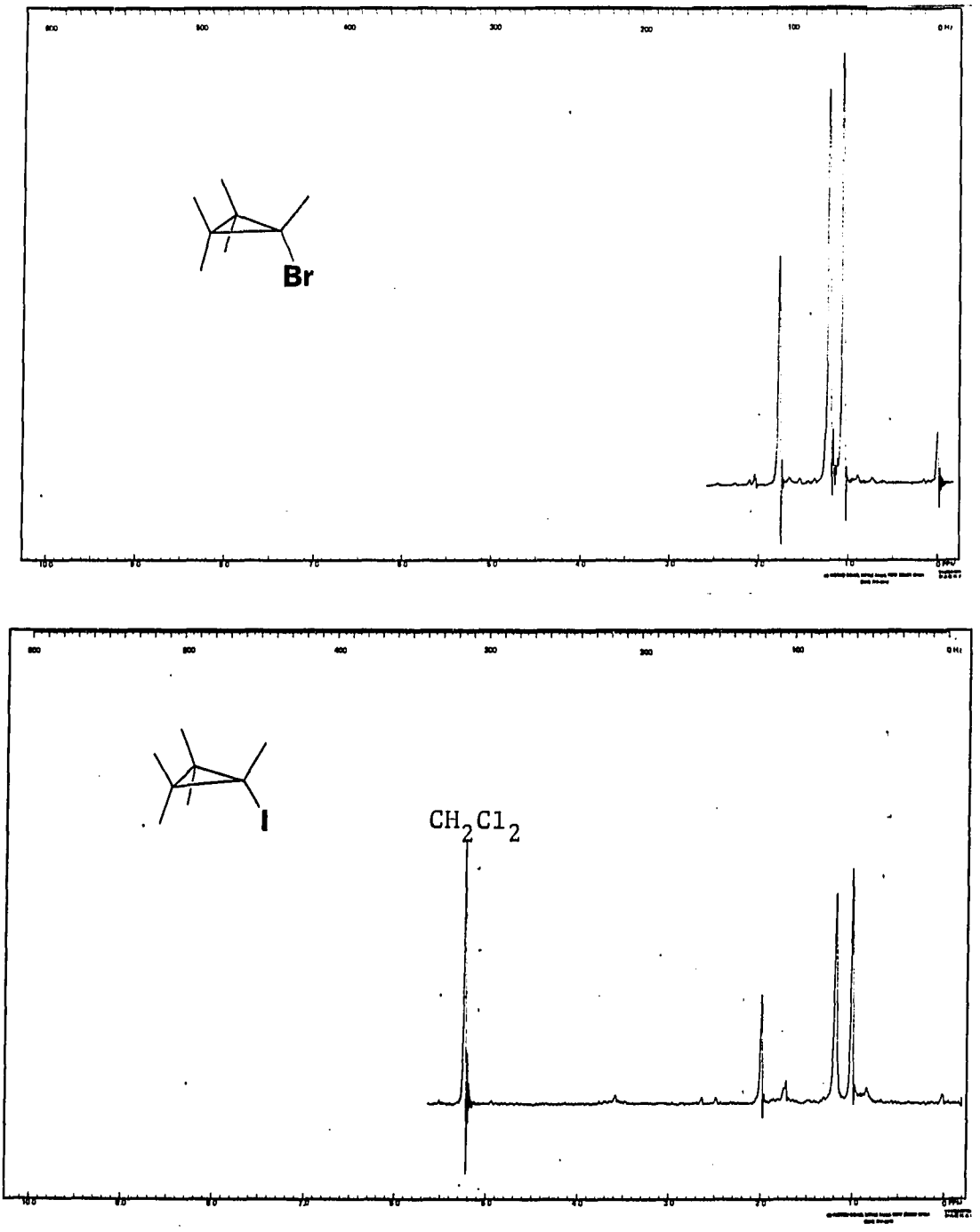
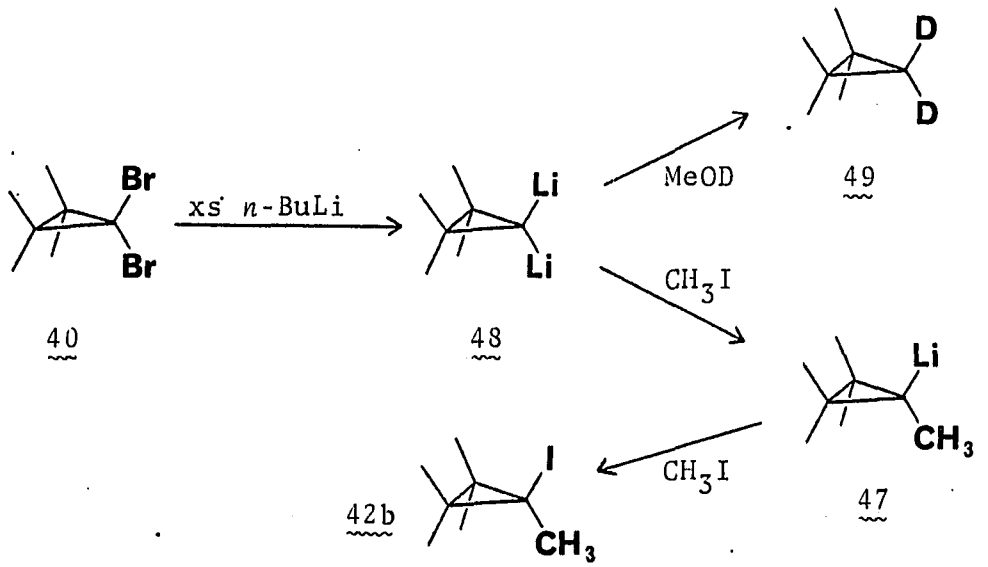


Figure 2. ^1H NMR of 42a (top) and 42b (bottom)

upfield than its counterpart in 41a.

One must consider another possible mechanism by which 42b may be formed from 40 by sequential treatment with excess *n*-BuLi and MeI. It is possible that the dilithio species 48 may have been formed and provided 42b upon addition of MeI (Scheme IX). However, this possibility was eliminated when MeI was replaced by MeOD and no dideutero 49 was detected.

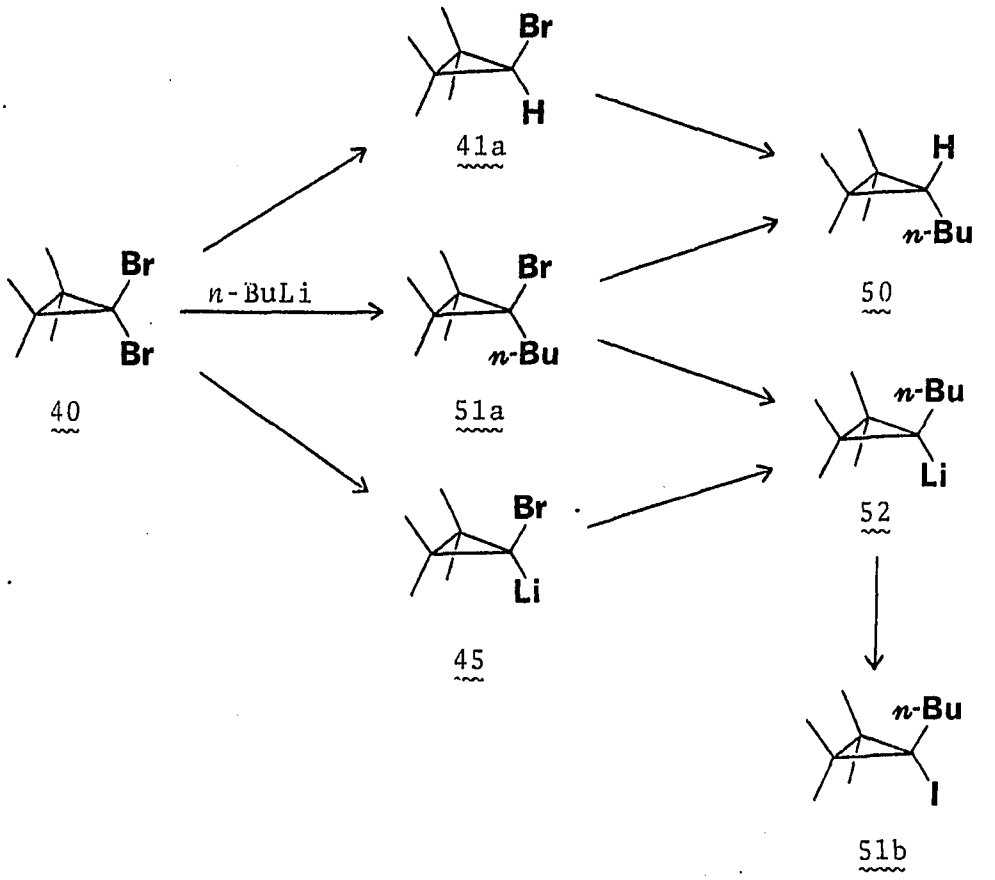
Scheme IX



40 48 49 47 42b

The formation of 50 and 51 can be explained as shown in Scheme X. It seems likely that 40 reacted with *n*-BuLi to give initially 41a via disproportionation, 51a via coupling, and 45 via Li-Br exchange[70]. Under conditions such that the consumption of 40 by *n*-BuLi is slow (see below), 51a may also be formed by reaction of 52 with 40.

Scheme X



In the presence of excess *n*-BuLi, 41a may couple to give 50, which, however, may also be obtained via disproportionation of 51a. Li-Br exchange on 51a or nucleophilic substitution on 45 would have given 52, which then yield 51b upon the addition of MeI.

Solvent effects on the product distribution were dramatically illustrated when THF was replaced by hexane.

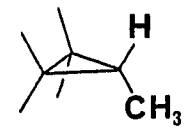
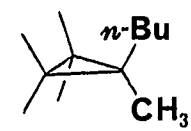
None of the carbenoid trapping product 42 was detected, and 51 was obtained almost exclusively (Table III). THF is known to enhance the Li-Br exchange rate[74] and stabilize the α-halolithium carbenoid[64,75]. Thus, 45, if formed, could have rapidly been converted to 52, which afforded 51a via reaction with 40, and 51b with MeI.

Selected ions observed in the mass spectra of the two unidentified products (m/e112 and 168) are listed in Table IV along with possible lost fragments and structures. If the structure shown for m/e168 is correct, its formation should be intriguing since 47 was found not to undergo alkylation with MeI, and 52 is expected to behave similarly.

Further attempts to generate a 1,1-dilithiocyclopropane via Li-Br exchange involved treating 40 with 5 equivalents of *t*-butyllithium in various solvents at -95°C, followed by quenching with MeI. The results are summarized in Table V.

Normal addition means the *t*-butyllithium was added to the solution of 40 in the solvents indicated. Inverse addition signifies addition to the substrate solution to the *t*-BuLi. Quenching was done by adding excess MeI either all at once directly into the alkyllithium mixture ("all at once"), or by letting it slowly down the inside wall of the reaction flask ("slowly"). Note that whenever MeI was added all at once, 42b was not found in the product mixture.

TABLE IV. Mass spectra of unidentified products

Unidentified Product	Selected ion (intensity)	Lost fragments	Possible structure
m/e 112	112 (15.22)	-	 (m/e 112)
	97 (48.63)	$CH_3^{\cdot}$	
	80 (0.74)	C_2H_6	
	69 (20.05)	$C_3H_7^{\cdot}$	
	57 (base)	$C_4H_7^{\cdot}$	
	55 (94.81)	$C_4H_9^{\cdot}$	
m/e 168	168 (4.26)	-	 (m/e 168)
	111 (81.13)	$C_4H_9^{\cdot}$	
	97 (16.97)	$C_5H_{11}^{\cdot}$	
	83 (32.23)	$C_6H_{13}^{\cdot}$	
	69 (78.92)	$C_7H_{15}^{\cdot}$	
	57 (base)	$C_8H_{15}^{\cdot}$	
	55 (66.54)	$C_8H_{17}^{\cdot}$	

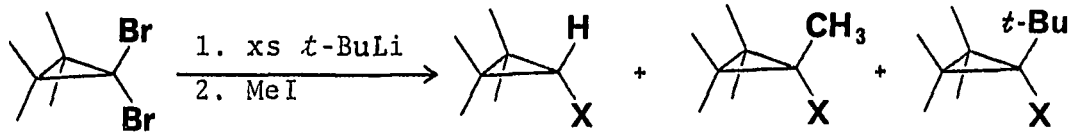
When the solvent was THF alone, normal or inverse addition of *t*-butyllithium did not cause any significant change in the product distribution. In the presence of HMPT, inverse addition yielded substantially less 42 and no detectable amount of 53. It should be pointed out that *t*-butyllithium was reported to lithiate HMPT rapidly at -60°C[76]. Thus, in this case, the alkyllithium reagent may no longer be *t*-butyllithium.

The carbenoid trapping product 42 was still the major product when THF was replaced by hexane with HMPT as the co-solvent. This is in sharp contrast to the reaction using *n*-BuLi.TMEDA in hexane (Table III), where 42 was not detected in the product mixture. Apparently, HMPT effectively acted "in place" of THF.

Another noteworthy observation is that, with one exception, the ratio of 41:42 obtained when *t*-BuLi was used instead of *n*-BuLi under comparable conditions, increased about 3-30 times. This increase is attributed to the preponderance of β-hydrogens in *t*-BuLi which kinetically favored disproportionation.

Since the primary concern was to look for products that may have been formed from *gem*-dilithio compound 48, and as it turned out, MeI was not a satisfactory trapping reagent, the reaction of 40 with excess *t*-BuLi was repeated using MEOD for quenching. As was the case when *n*-BuLi was used, no doubly deuterated 49 was detected.

TABLE V. Product ratios from reactions of 40 with *t*-BuLi



40 41 42 53

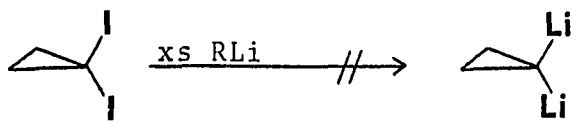
\+ unidentified

Solvents	Addition Methods[a]	Product Ratio				
		41b	42a	42b	53	Unident'd
THF	1. Inverse 2. All at once	1	10	-[c]	-	-
THF	1. Normal 2. Slowly	4	10	16	-	-
THF/HMPT	1. Normal 2. All at once	10	1	-	0.6	5.5
THF/HMPT	1. Inverse 2. All at once	3[b]	10	-	-	0.1
Hex/HMPT	1. Normal 2. Slowly	3[b]	10	6	0.2	-

[a]See text for explanations.
[b]Included both 41a and 41b.
[c]Not detected.

In summary, no evidence was gained for 1,1-dilithiocyclopropane formation upon treatment of 40 with excess *n*-BuLi or *t*-BuLi. Obtained were the expected products from exchange, coupling, and disproportionation. The product distribution depended on the choice of solvents and alkyllithium reagents. When the reaction mixture was quenched with MeI, initial methylation of the carbenoid intermediate 45 was followed by a second Li-Br exchange during the quenching. Lastly, some tetramethylcyclopropyllithiums were iodinated instead of alkylated when treated with MeI.

The failure of 40 to undergo a consecutive two-fold Li-Br exchange was not so surprising once it was learned that even the more reactive *gem*-diiodocyclopropane showed no tendency to undergo such an exchange[77].



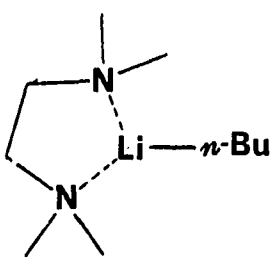
1,1-Dibromo-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane. Reactions with *n*-Butyllithium

The reactions of 40 with excess *n*-butyllithium or *t*-butyllithium described in the preceding section did not yield a 1,1-dilithiocyclopropane because the carbenoid intermediate 45 would not undergo a second Li-Br exchange under the conditions employed. Unfortunately, the thermal

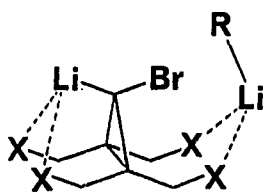
lability of 45 required that it be kept below -78°C; perhaps higher temperatures would be more conducive to the second Li-Br exchange. Also, recall that it is as important as the synthesis itself that the *gem*-dilithio compound be in the monomeric state. Heretofore, no consideration has been given to this latter problem.

Electron donating solvents such as ethers and trialkylamines are known to reduce the degree of aggregation of alkyllithiums[78]. *n*-Butyllithium is hexameric in hydrocarbon solvents, but tetrameric in THF and monomeric in the presence of TMEDA[50]. Unfortunately, not all alkyllithiums are monomeric with TMEDA. Nevertheless, the coordination in the *n*-BuLi TMEDA complex, shown in 55, inspired the multiple intramolecular coordination concept for generating a *gem*-dilithiocyclopropane.

The strategy was to incorporate groups on the ring which coordinate with lithium, *e.g.*, alkoxy or dialkylamino, as illustrated in 56. Advantages provided by this strategy are as follows. First of all, the intermediate carbenoid

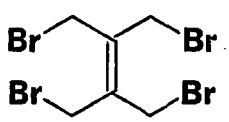


55

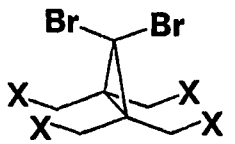


56

is stabilized by intramolecular coordination with the X groups[79]. The reaction may, therefore, be run at higher temperatures, if necessary[80]. Secondly, the second Li-Br exchange is assisted by coordination of the X groups with the incoming alkyllithium reagent. Lastly, once formed, the *gem*-dilithio compound would be stabilized by coordination and would have a good chance to be monomeric. Notice that the X-Li coordination in 56 resembles that in the *n*-BuLi TMEDA complex. The particular side chains shown in 56, with a methylene group between X and the ring, were chosen since the tetramethylcyclopropylidene analog, 45, was investigated, as described in the preceding section. Thus, any new developments observed in this system can be logically attributed to the presence of the X groups. Furthermore, coordination via a five-membered ring has been reported to be more favorable than via other ring sizes[81].



57

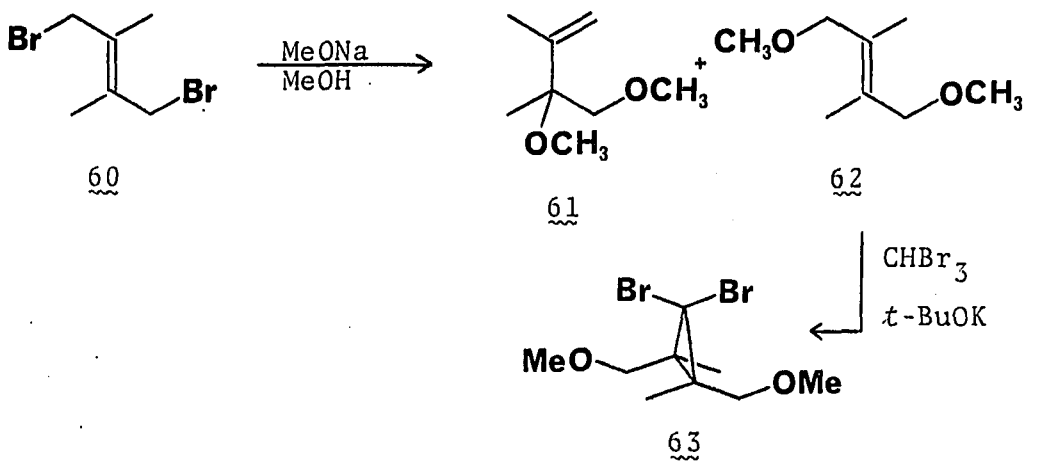


58

Gem-dibromocyclopropanes of type 58 are not known, although the alkene precursor 57 has been reported[82]. Since the concept is relatively new, it seemed desirable to test the strategy initially on a simpler, readily accessible system, namely one with only two *trans*-X groups

in place.

SCHEME XI



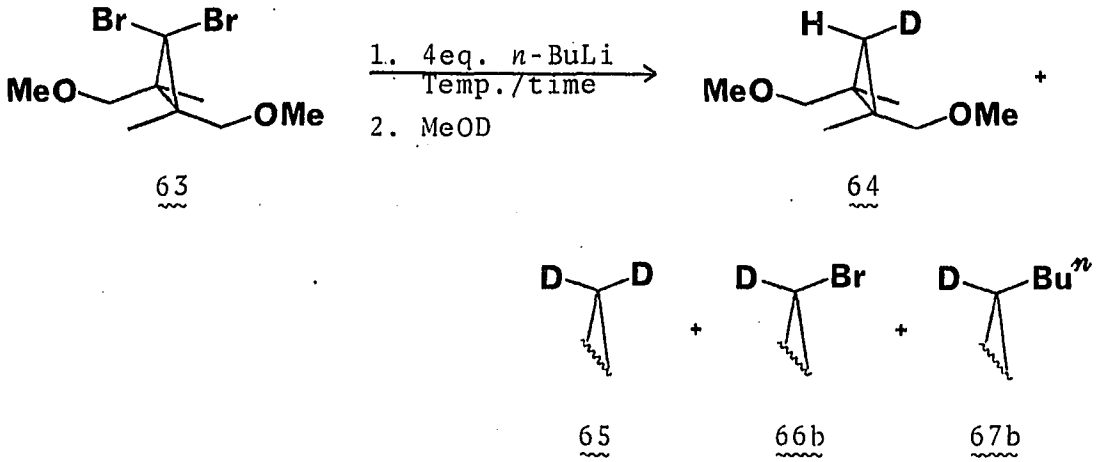
60 61 62 63

The dimethoxycyclopropane 63 was chosen for the exploratory studies since it could be readily obtained from the known dibromoalkene 60 (Scheme XI). Conversion of 60 to the corresponding dimethoxy alkene 62 by treatment with sodium methoxide in methanol was achieved in 31% yield. Repeated spinning bond distillation served to separate 62 from isomeric 61; 62 was then subjected to dibromocarbene addition to afford 63 in the 87% yield.

Treatment of 63 with 4 equivalents of *n*-butyllithium in THF under the conditions specified (Table VI) was followed by rapid quenching with MeOD. The results are summarized in Table VI. It is important to emphasize that the reactions were carried out on a less than 1mmole scale. The amount of MeOD required was no more than 0.1ml and, therefore, could be added all at once. Also, the total

volume of the reaction mixture was less than 5ml, so that very effective stirring was possible. These measures were aimed at eliminating the sequential deuteration-exchange-deuteration process[83] during quenching (see Table V for the success of this approach when quenching with MeI).

TABLE VI. Yields of products from reactions of 63 with *n*-BuLi

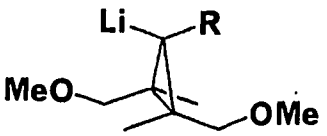


63 64 65 66b 67b

Temp./time	64	65	66b	67b
-78°C/30 min	6%	19%	60%	15%
-78°C→-40°C/30 min	5%	0	0	90%

All percent yields were determined by a combination of GC and GC.MS, or GC and ^{13}C NMR (using internal standard) methods. The initial reaction of 63 with *n*-BuLi is expected to proceed via the familiar disproportionation, exchange, and coupling as discussed in the previous section. Dispro-

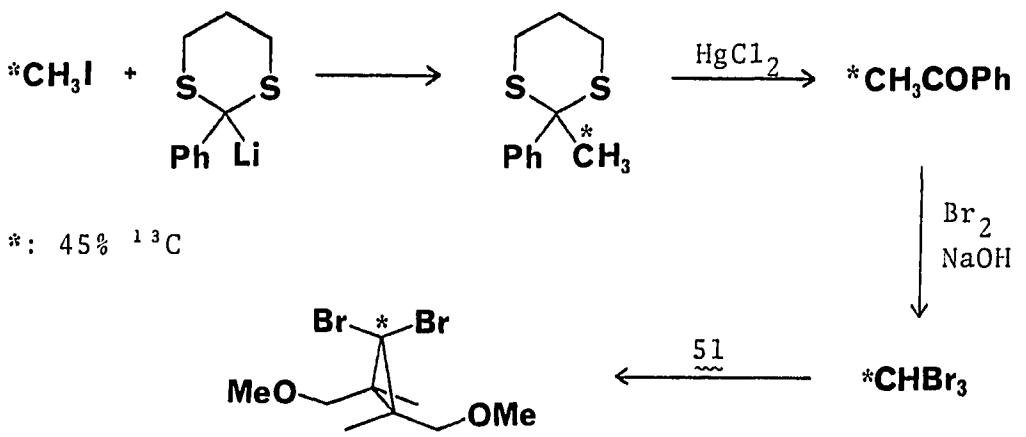
portionation followed by a Li-Br exchange would provide 70, which gave 64 upon the addition of MeOD.



70 R=H
72 R=Br
73 R=*n*-Bu

The formation of, and the lack of, dideutero 65 was very intriguing and invited efforts to observe the organolithium intermediates spectroscopically. Thus, ^{13}C-enriched 83 was synthesized in 24% yield from 45% ^{13}C MeI by the reaction sequence [84] shown in Scheme XII. Separate samples of 83 were treated with 1 equivalent and 4 equivalents of *n*-butyllithium at -78°C, and the reaction mixtures were examined by ^{13}C NMR at the various temperatures indicated in Figures 3 and 5.

SCHEME XII



*: 45% ^{13}C

83

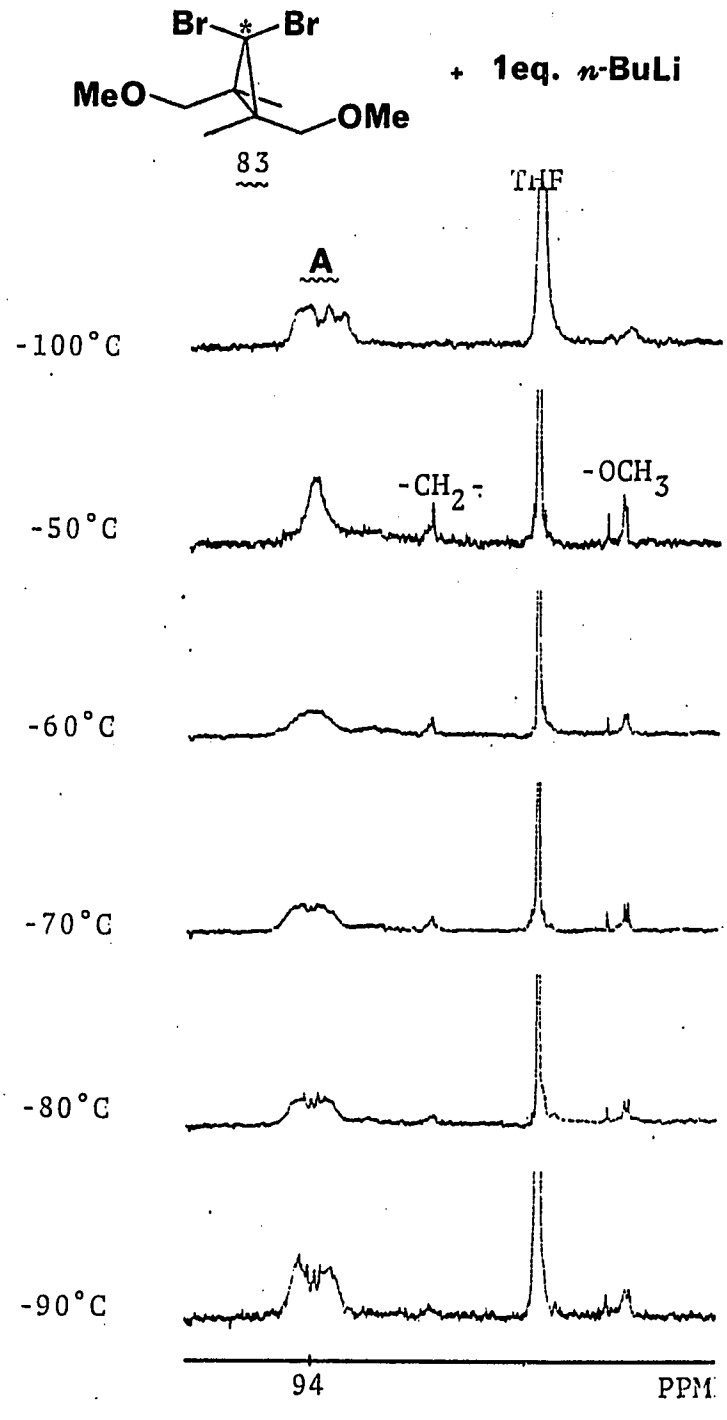


Figure 3. ^{13}C NMR of 83 treated with leq. of *n*-BuLi

^{13}C NMR spectra of 83 plus one equivalent of *n*-butyllithium are shown in Figure 3. Relative to the spectrum of a sample prepared using the unenriched 63, the only new peak observed is a broad multiplet labeled A appearing at δ94. At -80°C, multiplet A is about 8ppm wide at half-height. At higher temperature, A gradually coalesced until it became a singlet about 4ppm wide at -50°C. Upon cooling back to -100°C, A appeared as a quartet with a coupling constant of 45Hz. When irradiated at 38.887Mhz, the quartet structure collapsed into a sharp singlet as shown in Figure 4. The result of this unprecedented ^{7}Li-decoupled ^{13}C NMR experiment eliminates the possibility, which may have been suggested by the poorly defined shape of A (Figure 3), that A is an overlap of two peaks representing different organolithium species.

Since A would also be sharpened up by an increase in the temperature, and the sample's temperature could not be monitored internally, the possibility that the sharpening of peak A shown in Figure 4 was simply due to an increase in the sample's temperature caused by rf irradiation has to be considered. It should be pointed out that at higher temperature, the methylene peak at 81ppm would also sharpen up (Figure 3). By comparing the relative heights of A and the methylene peak in Figure 3 to that shown in Figure 4, one has to conclude that the singlet observed for A in Figure 4 is a result of ^{7}Li decoupling

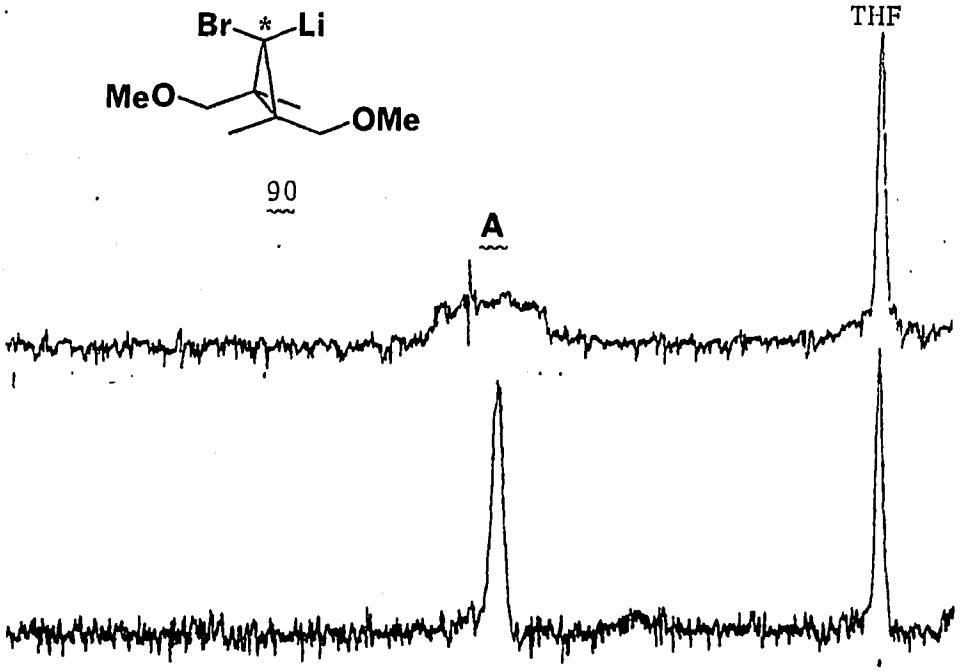
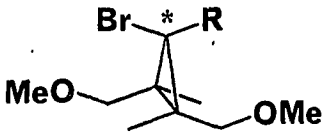


Figure 4. Non decoupled (top) and ^{7}Li-decoupled (bottom) ^{13}C NMR of a sample of A

and not of increased temperature. When the sample used to obtain the spectra in Figure 3 was poured into MeOH, 86a was the exclusive product.

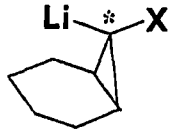
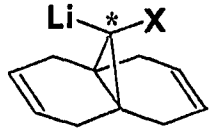
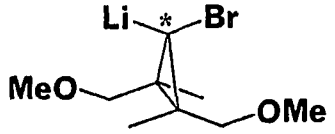


Compound	R	C-1
83	Br	δ51
86a	H	39
90	Li	94

Peak A may be assigned to the carbenoid carbon of 90. Its chemical shift is substantially downfield from that of C-1 in 86a or 83. Similar large downfield shifts for other

cyclopropylidene carbenoids have been reported[85]. Some of these are tabulated in Table VII.

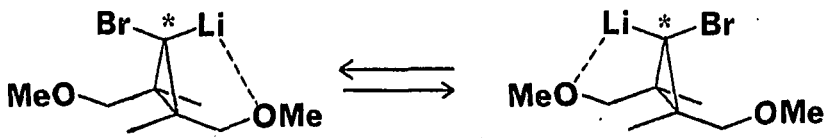
Table VII. ^{13}C Chemical shifts of carbenoid

Compound		δ(ppm)	$J_{^7Li-^{13}C}$
	(X=Br)	87	undefined
	(X=I)	83	45Hz
	(X=Cl)	86	45
	(X=Br)	102	undefined
$CH_3-\overset{*}{C}Br_2Li$		147	45
$\overset{*}{C}HBr_2Li$		101	43
		94	45

Since the ^7Li nucleus has a spin of 3/2, the quartet structure of A indicates C-1 of 90 is bonded to only one lithium on the NMR time scale. The sharpening of the A resonance at higher temperatures is attributed to lithium

exchange which averages the ^{7}Li-^{13}C coupling[86].

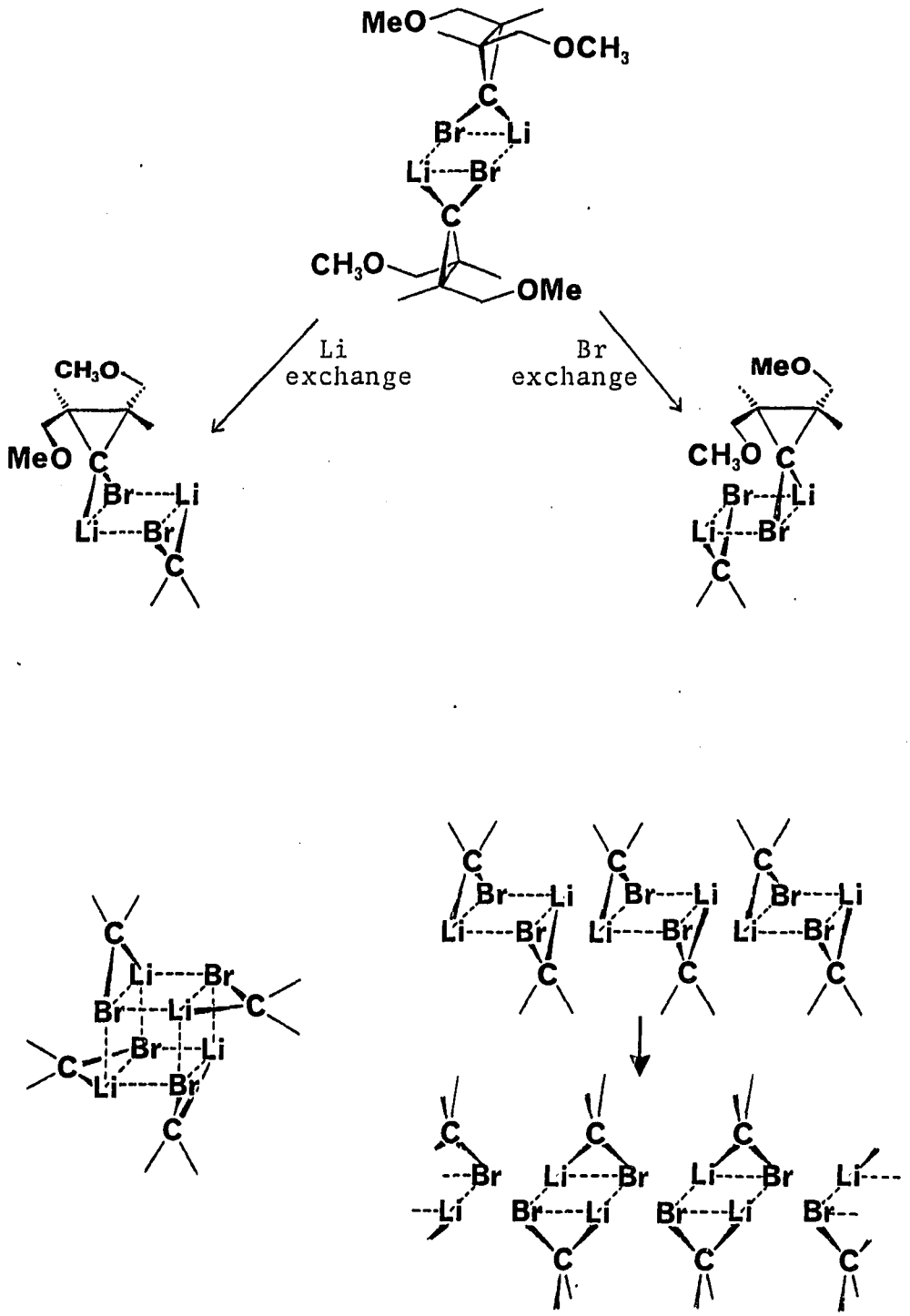
Further scrutiny of the ^{13}C NMR Spectra provided an additional important observation. At -80°C and -70°C, the two MeO- in 90 appeared as two well-distinguished singlets at 57.08 and 56.56ppm. They coalesced into a broad singlet of about 1ppm wide at -60°C to -50°C.



Apparently, between -80 and -70°C, the inversion process at the carbenoid carbon is sufficiently slow compared to the NMR time scale so that each MeO- can be observed individually. At -60°C and up, the process is fast enough to cause the two peaks to coalesce. The two MeO- were observed as a broad peak at -90°C and below due to a general peak broadening caused by high viscosity and poorer resolution. Rapid inversion at a cyclopropylidene carbenoid carbon has been inferred from the stereochemistry of trapping products[87]. To my knowledge, the above observation is the first spectroscopic evidence for this process.

The mechanism of inversion at C-1 in alkyllithium is not known. It may be a completely different process from the inter-aggregate or intra-aggregate lithium exchange[86].

Scheme XIII


MeO
OCH3
C
Br
Li
Li
Br
C
CH3O
OMe
Li
exchange
Br
exchange
CH3O
MeO
C
Br
Li
Li
Br
C
MeO
CH3O
C
Br
Li
Li
Br
C
C
Li
Br
Br
Li
C
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C
Br
Li
Br
Li
C

Nevertheless, one may expect a different mechanism for the inversion at the α-bromolithium carbenoid carbon due to the highly labile bromine.

The inversion at the carbenoid carbon in 90 is proposed to involve the lithium and bromine exchange. For the sake of clarity, the mechanism is illustrated using a dimer of 90 (Scheme XIII), although the tetrameric state may be equally probable. The intra-aggregate exchange resembles a [1,3] sigmatropic shift with inversion at the migrating center[88]. This "[1,3] shift" would make either one of the OMe groups alternate between *syn-/anti-* to the Li (or the Br) bonded to the carbenoid carbon. The inter-aggregate exchange may occur between a pair of aggregates resulting in a "new" pair or take place in a chain-reaction fashion. In case of the tetramer, the Li and Br exchange results in the carbenoid carbon "walking" on the cube formed by the four pairs of Li-Br.

Once the ^{13}C NMR of the carbenoid 90 generated from 83 and one equivalent of *n*-BuLi had been obtained, ^{13}C NMR observation of a solution generated from 83 and four equivalents of *n*-BuLi was carried out. The spectra obtained at 10°C intervals from -90°C to -50°C and then again at -80°C are shown in Figure 5.

Besides A, a new multiplet was observed at 88ppm. At -90°C, this new multiplet, labeled B, is about 6ppm wide measured at mid-height and exhibits a smaller coupling

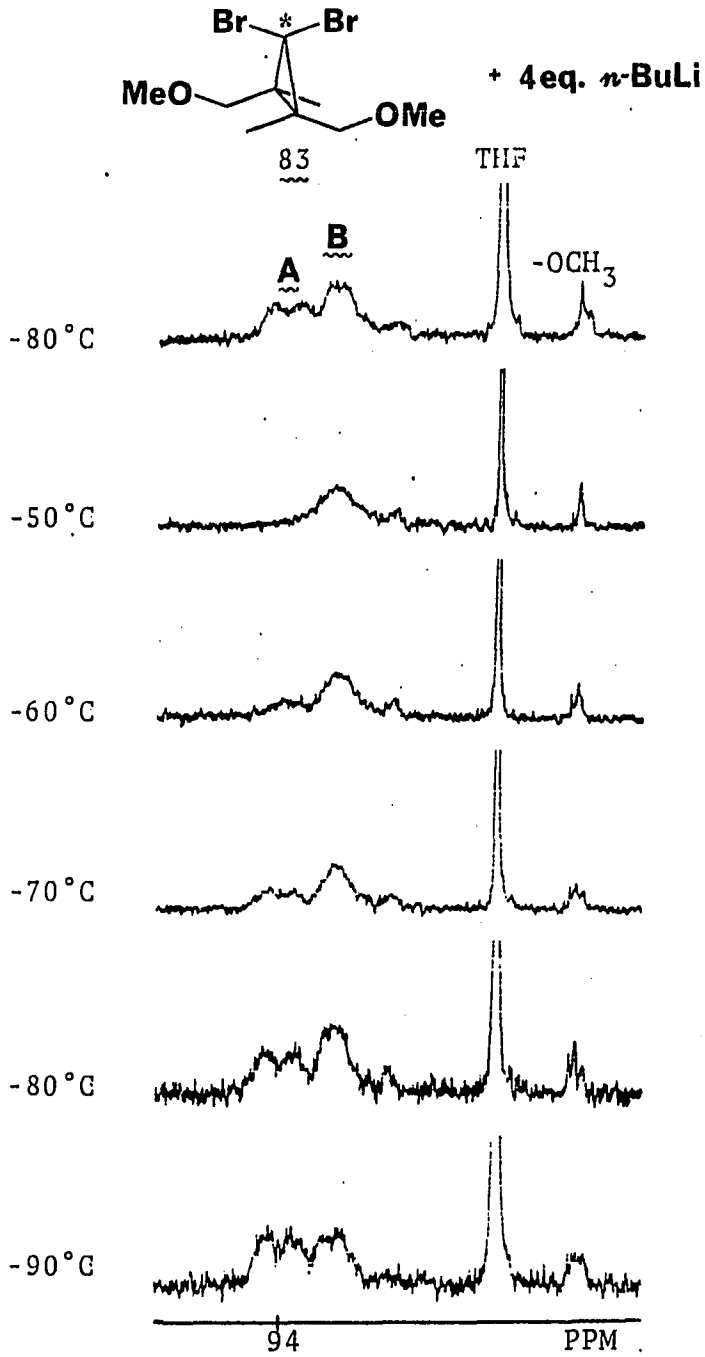
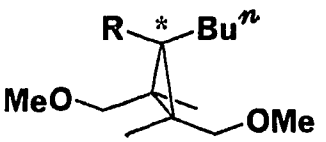
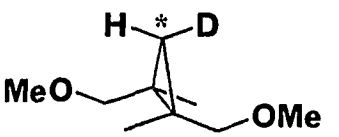


Figure 5. ^{13}C NMR of 83 treated with 4eq. of *n*-BuLi

constant than A. As the temperature increased, the relative intensity of B to A also increased. At -50°C, A had disappeared completely; only B remained. At this point, the sample was cooled back to -80°C, whereupon A reappeared in approximately the same intensity relative to B as before. When the sample, however, was warmed to -40°C, B started to diminish; and a new peak, labeled C, was observed at 30ppm (Figure 6). After 30 minutes at -40°C, the sample was cooled back to -60°C, but neither A nor B reappeared; only C remained. Quenching the sample at this point with MeOD gave mainly 87b; 84 was also detected in about 5% by ^{13}C NMR.



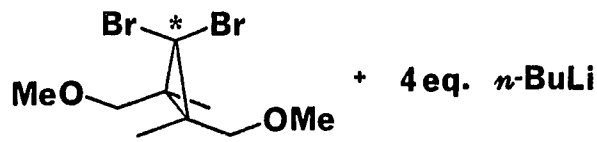
87b, R=D
92, R=Li



84

Evidently, C corresponds to the organolithium 92. Its chemical shift of 30ppm as compared to 32.4ppm for 87b is as expected for the variation between an alkyllithium and its hydrocarbon analog. The formation of C is rationalized in Scheme XIV.

This in the presence of excess *n*-BuLi, 90 was converted into a carbenoid:*n*-BuLi mixed aggregate, which was responsible



83

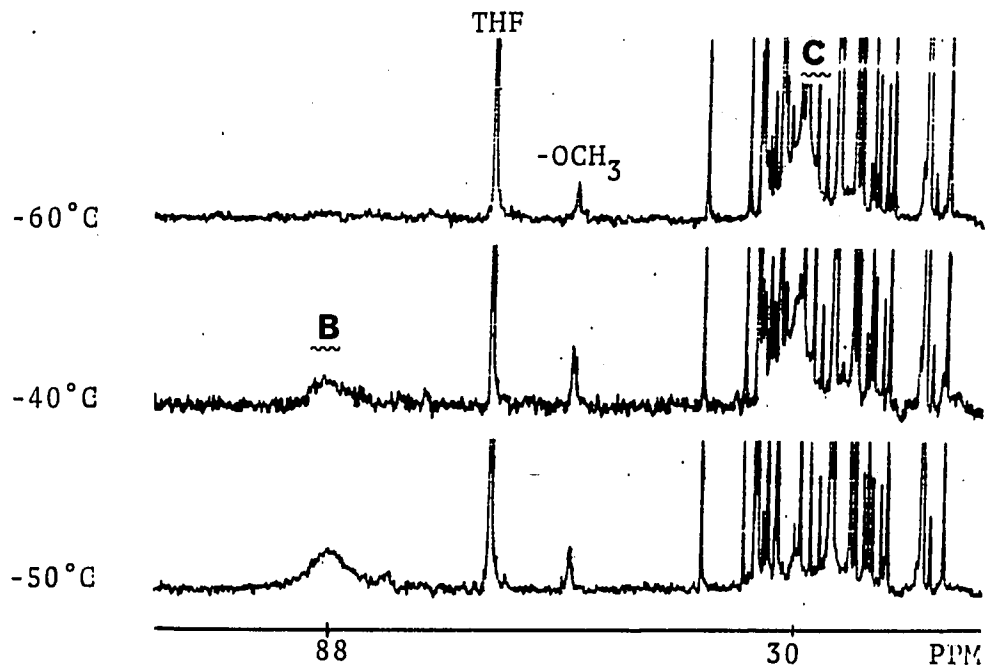
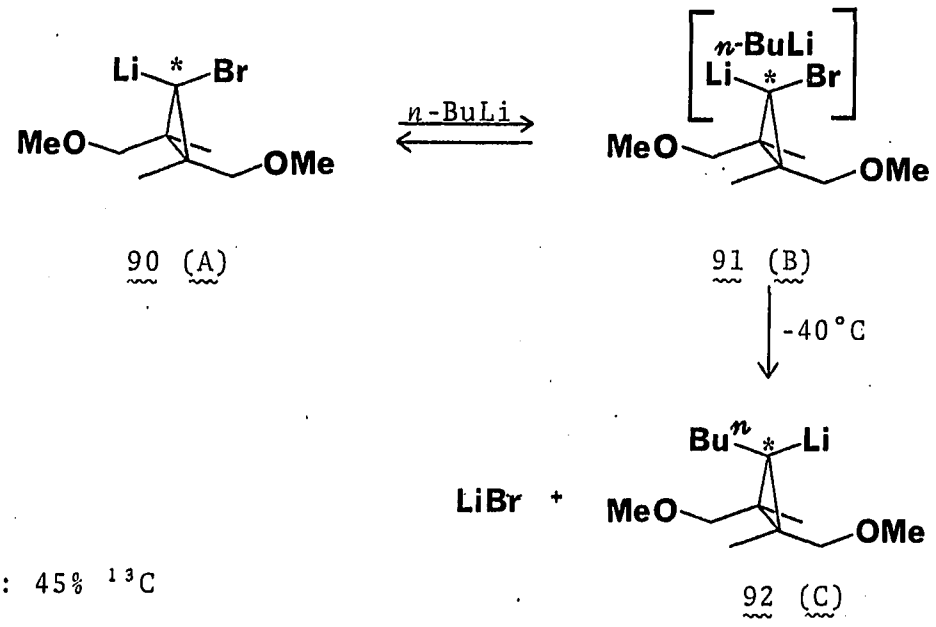


Figure 6. ^{13}C NMR of 83 treated with 4eq. of *n*-BuLi in THF-hexane

Scheme XIV



for the multiplet B. Between -90°C and -50°C, 90 and 91 interconvert with 91 favored at higher temperature. Above -50°C, 91 collapsed rapidly into 92.

The discovery of 91, a hitherto unknown carbenoid: alkyllithium complex, deserves further scrutiny. Due to the bulky structure of 90, an aggregation order greater than four for 91 seems unlikely[89]. B was also observed when only 1.5eq. of *n*-butyllithium was used, although its intensity relative to A was reduced by a factor of two (Figure 7). Although qualitative, these observations support a 1:1 complex of A and *n*-butyllithium as the composition of the species responsible for B.

The favoring of B relative to A at the higher

temperatures may be related to the increased stability of *n*-BuLi tetramers at lower temperatures[86b], but their increased dissociation at higher temperatures which would then favor the presumably less-aggregated B.

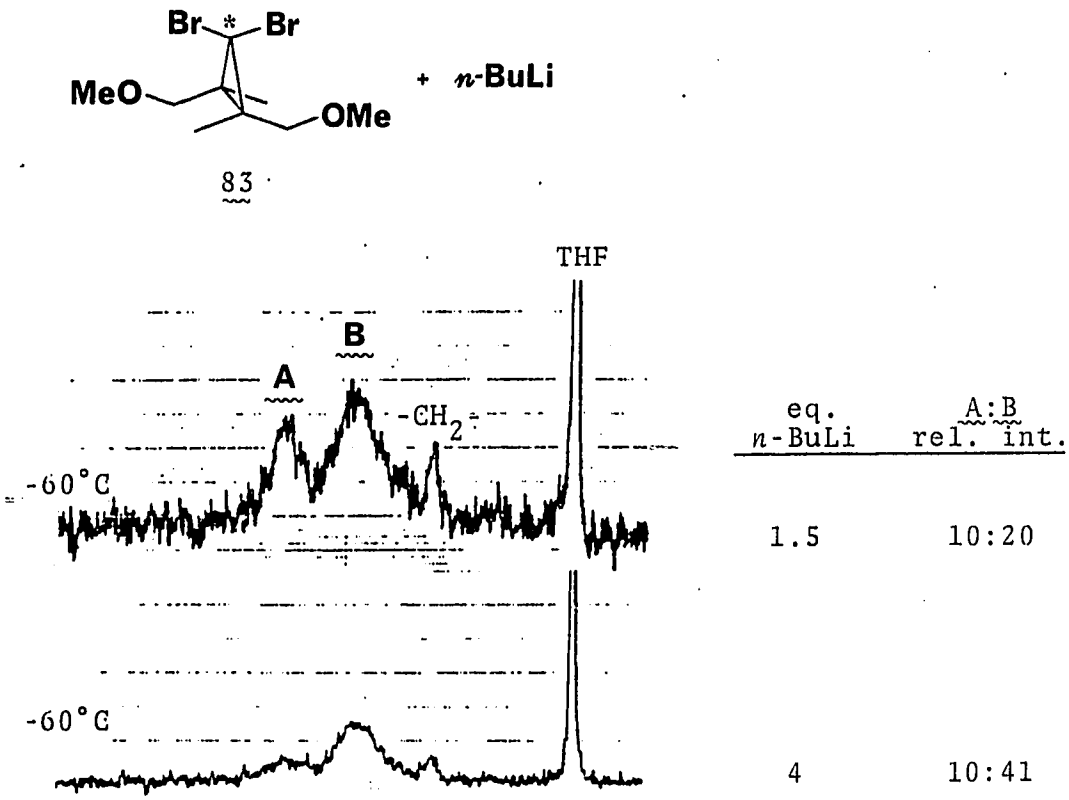


Figure 7. ^{13}C NMR of 83 treated with various amounts of *n*-BuLi

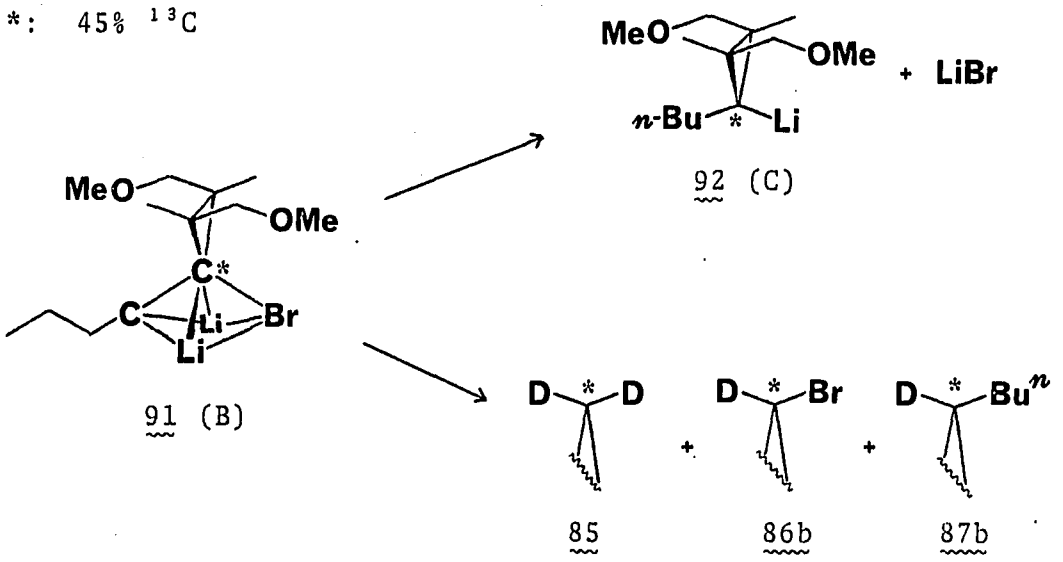
At -90°C, the ^{13}C-^{7}Li coupling constant in multiplet B can be roughly observed, and appears to be smaller than that of A. The persistent shape of B, narrow at the top and broad at the base, as compared to the rectangular shape of A, suggests a coupling to more than one lithium.

Since the complex contains a 1:1 ratio of 90 and *n*-BuLi, this suggests C-1 in 91 is bonded to two lithiums on the NMR time scale. Also worth emphasizing is the large downfield chemical shift of B which indicates a significant carbenoid character for 91.

A proposed structure for 91 is shown in Scheme XV. Several important features should be noted as follows. The carbenoid carbon and C-1 of *n*-BuLi in 91 each has six ligands, a feature very common for carbons involved in electron-deficient bonding in alkyllithium aggregates[90]. Bromine with three ligands has been reported in the structures of $(MeLi)_{4-n}(LiBr)_n$[91]. Furthermore, organic species having a formal trivalent bromine have been recently synthesized[92].

Perhaps most significant is the fact that 91 resembles the transition state of an S_n2 displacement at the carbenoid carbon by *n*-BuLi to provide 92. Conversion of 91 to 92 proceeds by a simple elimination of LiBr with a minimum movement of all nuclei. While it satisfies the principle of least motion, the "S_n2 structure" also requires the two lithiums to be on, or nearly so, the same plane with the cyclopropane ring. Fortunately, a Dreiding model of 91

Scheme XV



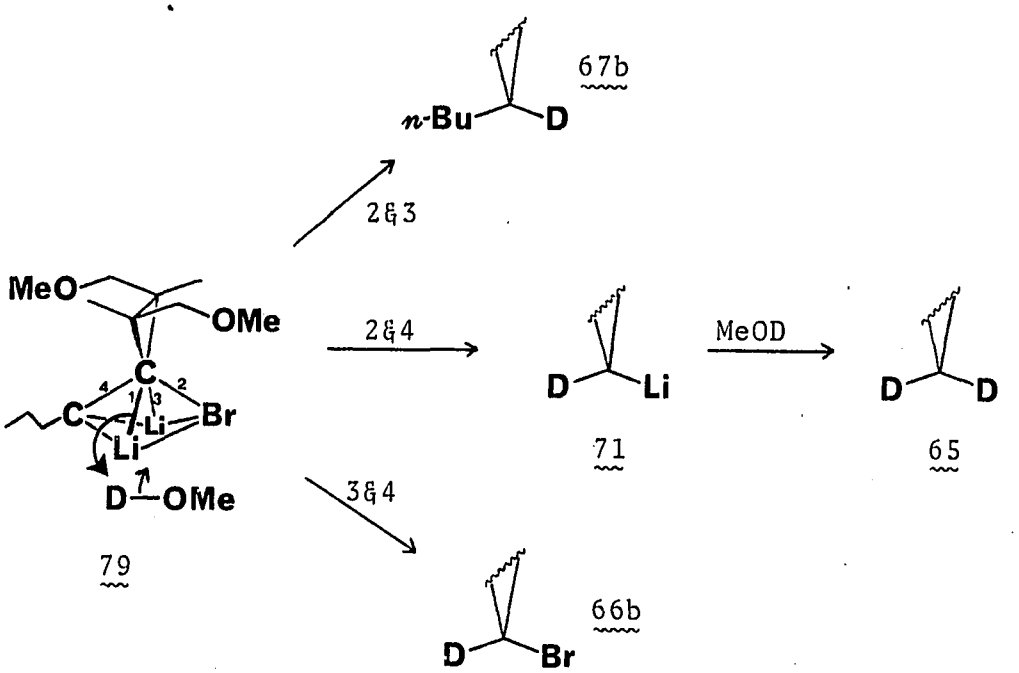
indicated this geometry to be most sterically favorable. Also very significant is that the proposed structure for 91 reflects the carbenoid's characteristic of being both nucleophilic and electrophilic. The carbenoid carbon is bonded to both the electropositive lithium and the carbanion center of *n*-BuLi.

Recall that a THF solution of 63 treated with 4eq. of *n*-BuLi at -78°C provided dideutero 65 in 19% yield when quenched with MeOD at -78°C (Table V). The formation of 65 likely occurs from the complex 79, and can be rationalized as illustrated in Scheme XVI.

As one of the C-Li bonds in 79, bond number 1, for

example, is replaced by a C-D bond, either bonds 2 and 3, 2 and 4, or 3 and 4 collapse. Collapsing bonds 2 and 3 would give rise to 67b, bonds 3 and 4 to 66b, and bonds 2 and 4 to the alkyllithium intermediate 71, which, upon further deuteration with MeOD, gives 65.

Scheme XVI



Although 66b may be formed from trapping of 79, much of the 60% obtained at -78°C is formed via trapping of the carbenoid 72, since, at this low temperature, 72 is also present in a comparable amount with 79 (Figure 5). By contrast, most of 67b obtained, 15%, must have come from 79 instead of 73 for, at -78°C and after 30 minutes reaction

time, the conversion of B to C does not occur to any detectable extent as indicated by the ^{13}C NMR (Figure 5). Of course at higher temperature (-40°C) 67b does originate from 73, the unenriched analog of 92 (C).

The formation of 65 can arise from a *gem*-dilithiocyclopropane such as 79. Another possibility, a sequential deuteration-exchange-deuteration of carbenoid 72 during the addition of MeOD, has been eliminated by employing the inverse quenching technique, and other quenching experiments[83]. However, sequential exchange within aggregates is very difficult to firmly exclude.

In summary, treatment of 83 with excess *n*-butyllithium at -78°C in THF gives an equilibrium mixture of carbenoid 90 and an *n*-BuLi:90 complex, 91. This new reactive intermediate, 91, is favored at higher temperature and is stable up to -50°C. Between -50°C and -40°C, 91 is rapidly converted irreversibly to the coupling product 92. Dideutero 85, obtained by quenching the mixture at below -50°C, was formed from the complex 91. Based on the tendency of alkyllithiums to aggregate via multi-center electron deficient bonding, the electrophilicity and nucleophilicity of carbenoids, ^{13}C NMR data, and the observed chemistry, a structure for 91 is proposed in which the carbenoid carbon is bonded via electron-deficient bonding to two lithium atoms, the carbanion center of *n*-butyllithium, and a bromine. The two lithiums are

located on the same plane with the cyclopropane ring. Although the structure of 91 is thus a 1,1-dilithiocyclopropane, its C-1 is not a tetracoordinate carbon.

1,1-Dibromo-2,3-*trans*-dimethoxymethyl-2,3 dimethylcyclopropane. Reactions with *t*-Butyllithium

In the preceding section, it was shown that reaction of 63 with excess *n*-BuLi provided a carbenoid:*n*-BuLi complex. Since the carbenoid showed no tendency to undergo a second Li-Br exchange, the use of a more reactive alkyllithium reagent seemed in order. Reactions of 63 and *t*-butyllithium are described in this section.

Samples of the ^{13}C-enriched analog of 63, 83, were treated individually with various amounts of *t*-BuLi and studied by ^{13}C NMR to observe the organolithium intermediates directly. The ^{13}C NMR spectra of 83 and 2 equivalents of *t*-BuLi obtained at 10°C intervals from -80 to -50°C, and again at -80°C, are shown in Figure 8. The second equivalent of *t*-BuLi was necessary due to the rapid reaction of *t*-BuLi with the *t*-BuBr generated during the Li/Br exchange. The organolithiums formed were expected to be mainly 90, the carbenoid.

As expected, multiplet A was observed at δ94; it was about 8ppm wide at -80°C, and sharpened up at higher temperature. By comparison with spectra of a non-enriched

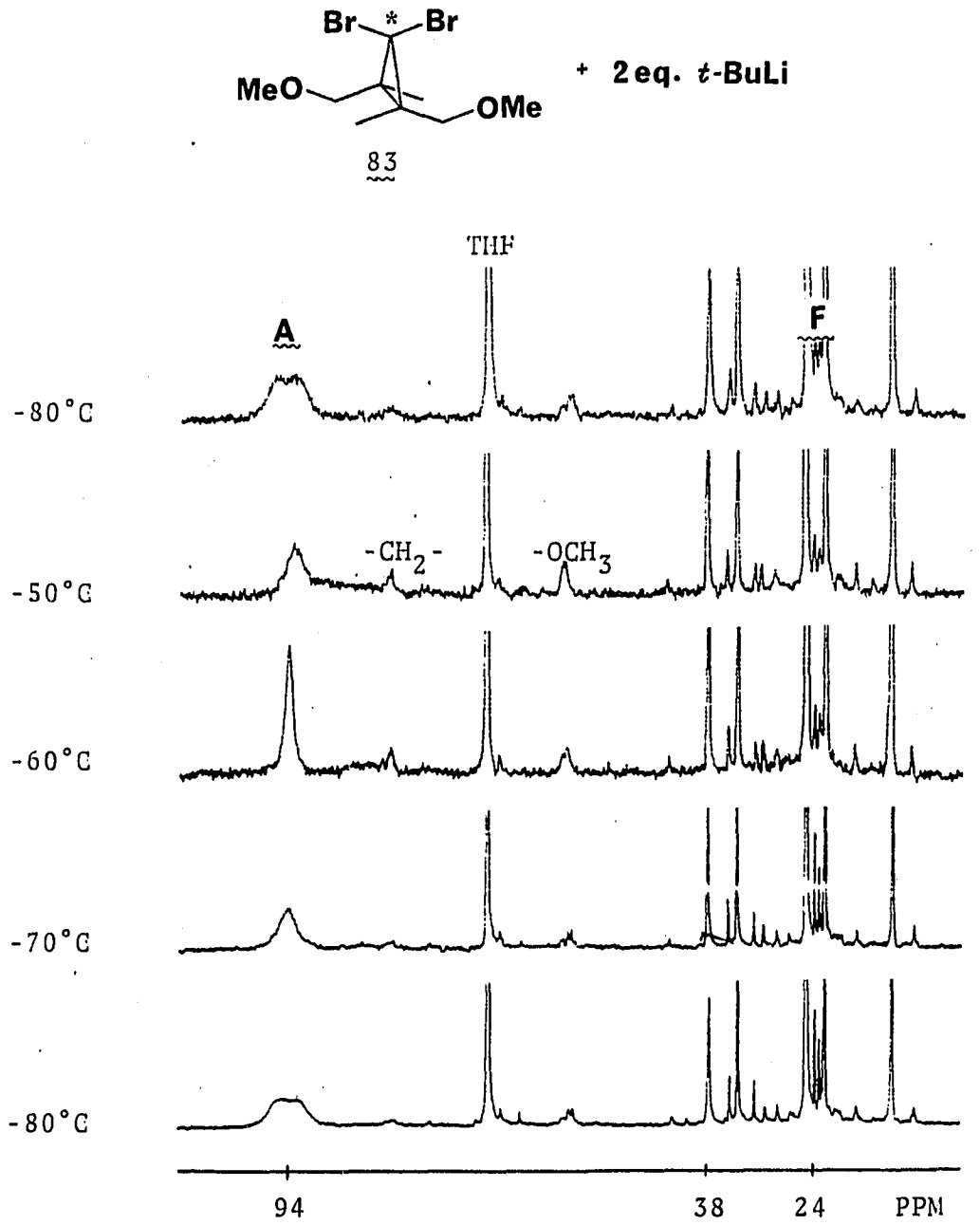
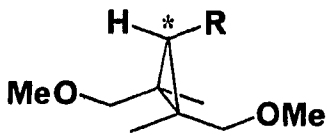


Figure 8. ^{13}C NMR of 83 treated with 2eq. of *t*-BuLi

sample, and a blank control consisting of THF, pentane, d_6-benzene, and *t*-BuLi, an additional peak was found at δ38.4 and assigned to 86a. The assignment was based on the finding that quenching the sample with MeOH afforded exclusively 86a (presumably mainly from 90) whose C-1 appeared at δ40.0 when its ^{13}C NMR was recorded at room temperature in $CDCl_3$. A small amount of 83 disproportionates with *t*-BuLi would account for the pre-quench production of 86a.



86a, R=Br
94, (F), R=Li
89, R=H

As in the spectra of samples prepared with 1 equivalent of *n*-BuLi (Figure 3), two sharp singlets at 57.1 and 56.6ppm were observed at -80°C and -70°C, and are attributed to the two methoxy groups in 90. As before, the two singlets coalesced at -60 to -50°C.

The spectrum taken after the sample was cooled back to -80°C from -50°C showed a small multiplet at δ24. This multiplet, labeled F, was assigned to 94. Pouring the sample at this point into a well-stirred large excess of MeOH afforded mainly 86a, and also about 1% of 89 (detected by ^{13}C NMR), which is consistent with the observation of

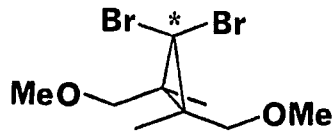
a minor amount of F.

It is interesting to compare the A produced with *t*-BuLi to that formed using *n*-BuLi. As shown in Figure 9, multiplet A in the sample using 2 equivalents of *t*-BuLi became sharper much more rapidly as the temperature increased than in the *n*-BuLi-produced case.

An interpretation for this difference is that using 2eq. of *t*-BuLi to generate the carbenoid also generated 1eq. of LiBr. The carbenoid is likely to aggregate and then undergo lithium exchange with LiBr rather than with another carbenoid molecule since there is less steric hindrance and more ionic character associated with LiBr. The inter-species lithium exchange should thus be more facile and, consequently, A became sharper at lower temperature.

Multiplet A from the sample using *t*-BuLi observed at -50°C seems to be out of line. The top of the peak is now at 93ppm instead of 94ppm. It is also broader instead of sharper than it was at -60°C. This unexpected deviation is attributed to the formation of a new mixed aggregate of A and LiBr at this temperature. Further observations supporting this interpretation are provided by ^{7}Li NMR and discussed in the subsequent section.

In the presence of excess *t*-BuLi, additional reactions of carbenoid 90 were observed. Figure 10 shows the ^{13}C NMR of 83 after treatment with 5 equivalents of *t*-BuLi at -78°C



83

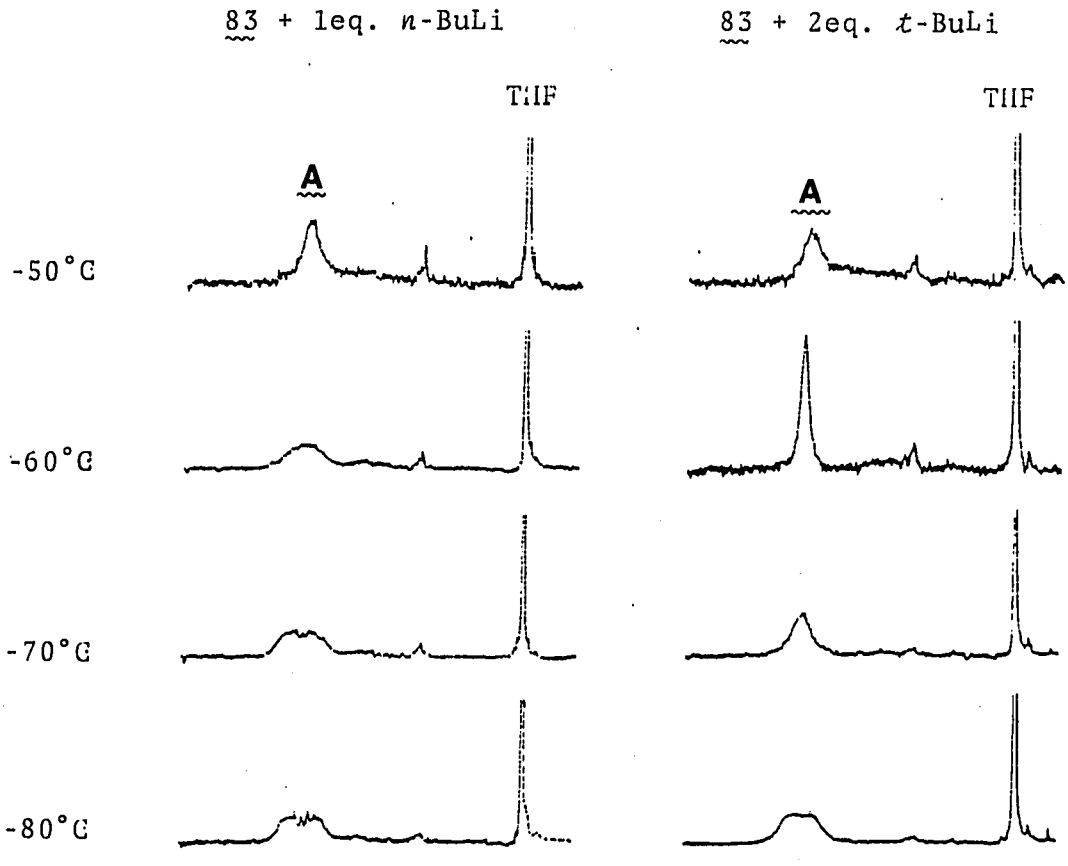
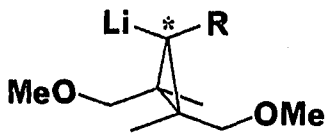


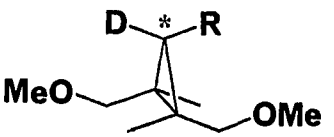
Figure 9. ^{13}C NMR of 90 (A) generated from 83 and *n*-BuLi or *t*-BuLi

in THF. The spectra were obtained at 10°C intervals from -80 to -50°C, and again at -80°C.

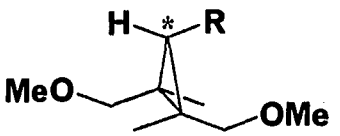
Initially at -80°C, two new multiplets, E at 44ppm and F at 24ppm were observed besides A. Both E and F were unstructured, about 6ppm wide at mid height, and did not change width appreciably with temperature. The prominent sharp singlet protruding from the center of E is assigned to 88a.



Compound	R
93 (E)	*t*-Bu
94 (F)	H
90 (A)	Br



84	H
85	D
88b	*t*-Bu



89	H
88a	*t*-Bu

As the temperature was increased, A was observed to diminish in intensity while E increased. At -50°C, A had disappeared completely and did not return upon recooling to -80°C. Only E and F remained[93]. Quenching the sample at this point by pouring it into a well-stirred large excess of MeOD afforded a mixture of 84, 85, 88a, 88b,

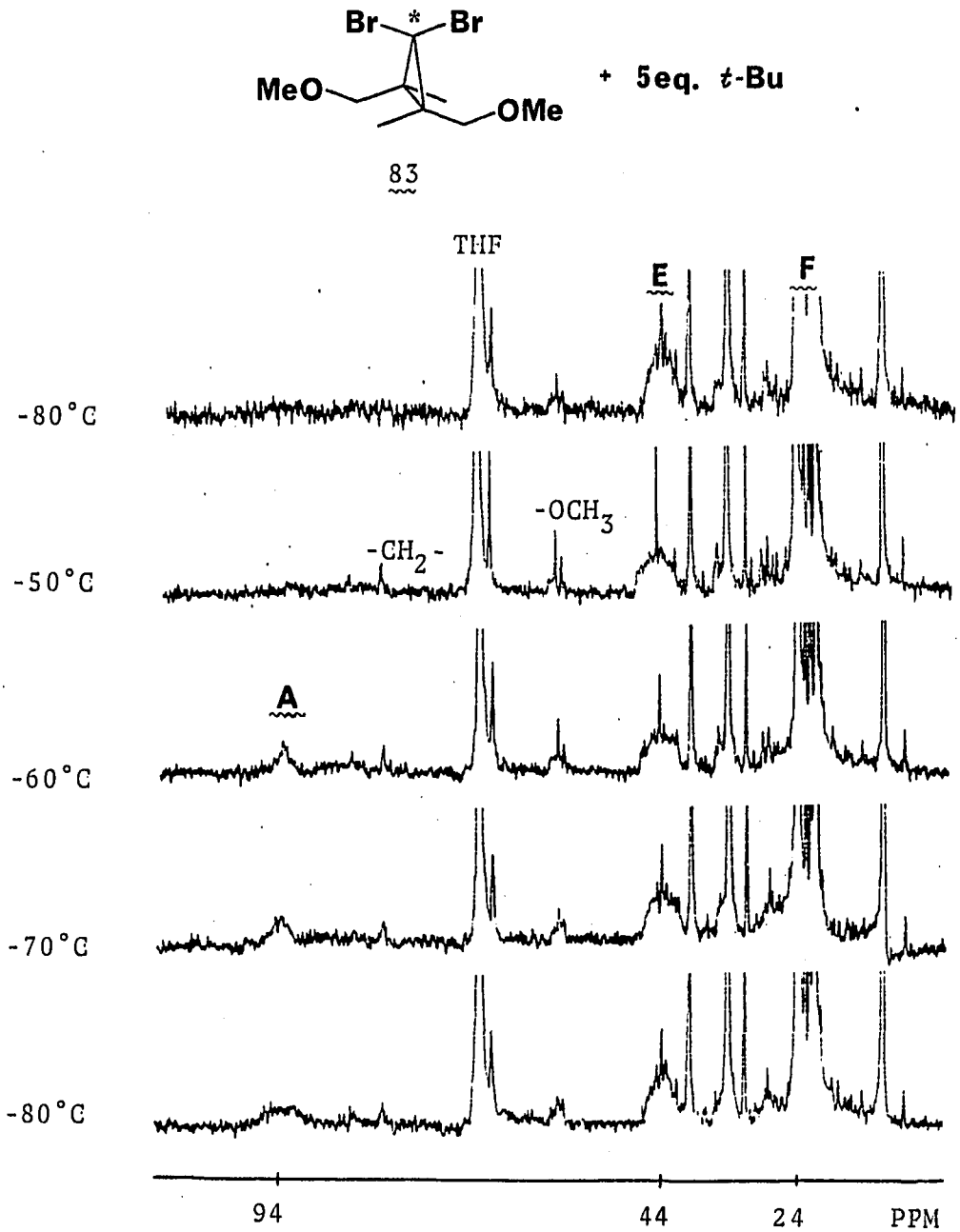


Figure 10. ^{13}C NMR of 83 treated with 5eq. of *t*-BuLi

and 89, as indicated by GC.MS, ^{13}C NMR, and comparisons with authentic samples obtained from preparative scale syntheses.

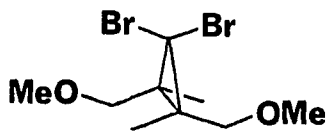
Thus, E and F were assigned as the alkyllithium 93 and 94, respectively. Their ^{13}C chemical shifts are very similar to that of their hydrocarbon analogs, 88a at 44.8ppm and 89 at 23.3ppm, in accord with the reported trend that an alkyllithium and its corresponding hydrocarbon do not differ appreciably in their carbon chemical shift[85,94].

The formation of 85 is very intriguing, especially since, unlike in the case where excess *n*-BuLi was used to form an observable carbenoid:*n*-BuLi complex which was trapped with MeOD to give 85, there was no carbenoid:*t*-BuLi complex observed. Furthermore, A was irreversibly transformed as the temperature increased.

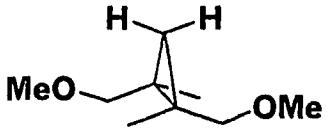
For quantitative determinations, samples of 63 were treated with 5 equivalents of *t*-butyllithium at various temperatures, followed by rapid quenching with excess MeOD. Known amounts of *p*-di-*t*-butylbenzene were then added as internal standards. Crude product mixtures obtained after work-up were analyzed by a combination of GC and GC.MS, or GC and ^{13}C NMR spectroscopy, using an internal standard. The results are summarized in Table VIII.

Several important observations should be noted. When the reaction temperature was raised to -50°C, there was a

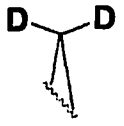
Table VIII. Yields of products from reactions of 63 with *t*-BuLi

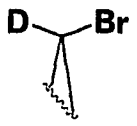


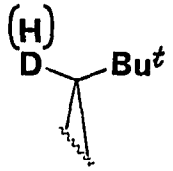
1. 5eq. *t*-BuLi
2. MeOD, quench



63 69





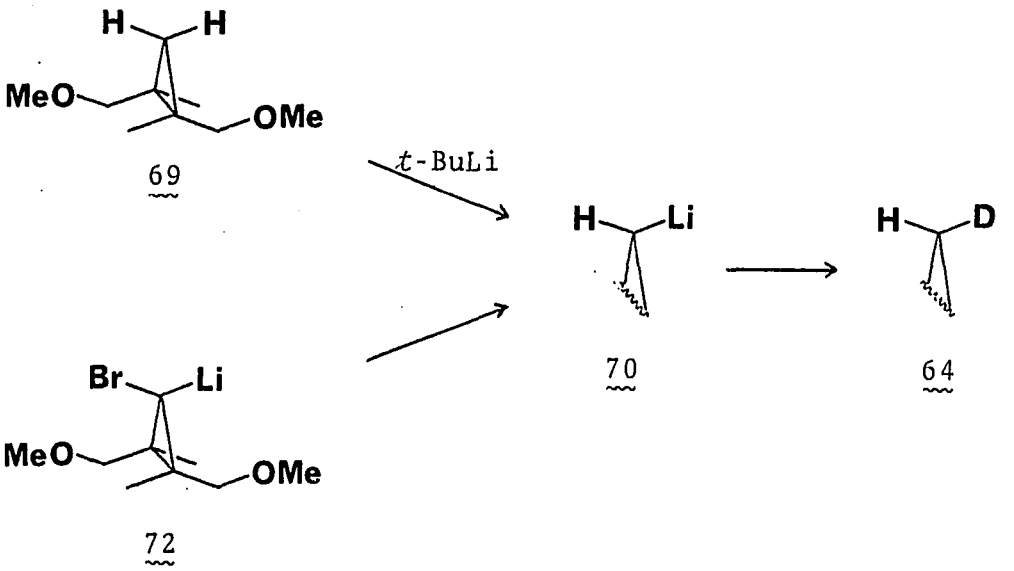


64 65 66b 68

Method of Quenching	Yield (%)				
	69	64	65	66b	68
A. Normal[a]	6	21	16	52	3
B. Inverse[b]	6	21	15	36	4
C. Inverse[b]	7	20	14	44	3
D. Inverse[c]	9	23	16	15	4
E. Normal (warmed to -50°C)	4	24	23	15	30

[a]Rapid addition.
[b]Via stainless-steel tube.
[c]Dual-vessel.

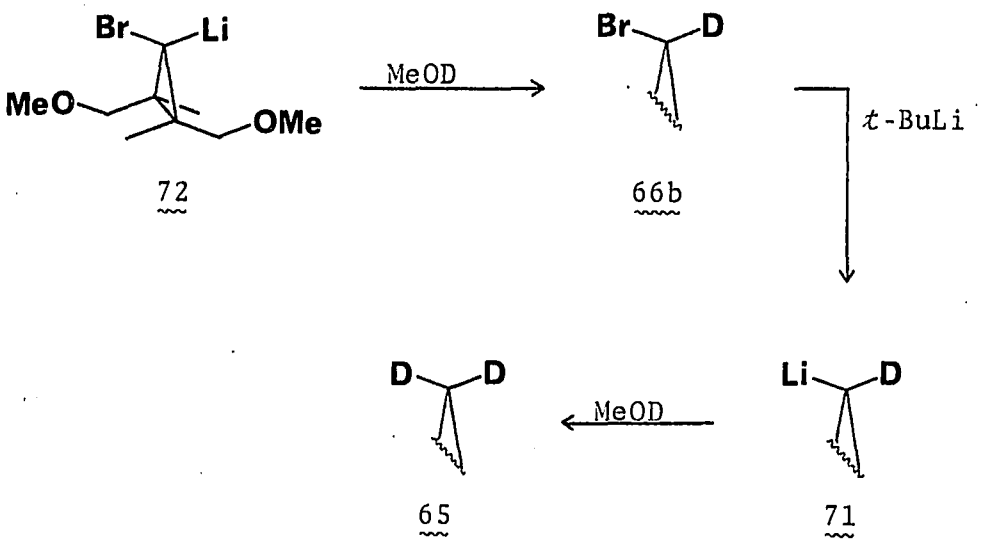
slight decrease in the yield of 69 and a slight increase of 64, but substantial increase of 65 and 68 at the expense of 66b. The slight change in the amounts of 69 and 64 with temperature is attributed to a slow lithiation of 69 by *t*-BuLi[95] to 70 which gave 64 upon quenching with MeOD. However, minor disproportionation of the carbenoid intermediate, 72, with *t*-BuLi could not be excluded.



The large increase in 68, decrease in 66b, and relative constancy of 64 are consistent with the ^{13}C NMR observation that A diminished in favor of E while F remained essentially unchanged. However, the formation of 65 and its increased yield at higher temperature were not paralleled by a spectroscopic observation. It was suspected that there might be a hidden peak, X, corresponding to the organolithium

from which 65 was formed and to which A was converted in addition to E. There is also a possible mechanism for the formation of 65 which does not require the intermediacy of X. This mechanism is considered first (Scheme XVI).

Scheme XVI



72 66b 65 71

According to this mechanism, 65 was formed from 72 during quenching by a sequence of deuteration-exchange-deuteration. Compound 66b, formed by deuteration of 72, may undergo a second Li-Br exchange with excess *t*-butyllithium to give 71 which was trapped with MeOD to yield 65. The second Li-Br exchange was possible since there was a higher concentration of the alkyllithium than MeOD when the latter was first added to the alkyllithium mixture. In fact, the amount of 65 increased about two times when quenching was done by letting the MeOD run down slowly

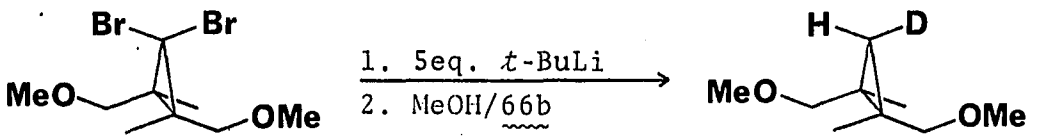
along the inside wall of the reaction flask.

This consecutive deuteration-exchange-deuteration mechanism was eliminated by the following experimental techniques and quenching experiments. As mentioned earlier, all reactions were carried out on less than 1mmole. The total volume of the alkyllithium mixture was no more than 5ml. This small volume made very effective stirring possible. Also, the amount of MeOD required was less than 0.1ml and, therefore, could be added all at once via syringe injection directly into the mixture.

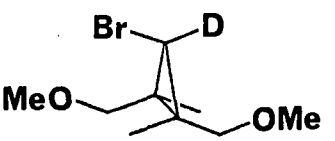
In other experiments, the solution of organolithiums was transferred via a stainless steel tubing into a flask containing a large excess of well-stirred MeOD; or the reaction was carried out in a special dual-vessel apparatus[96] that allowed the alkyllithium mixture to be transferred dropwise to a well-stirred large excess of MeOD and, at the same time, kept at the desired low temperature. By this inverse addition method, the concentration of MeOD is always much larger than that of the alkyllithium, and of 66b, so that the second Li-Br exchange had no reasonable chance to occur. The yield of 65 obtained was essentially the same as that afforded by using the normal addition method (Table VIII). This indicates that running the reaction on less than 1mmole scale and adding the MeOD all at once are sufficient to prevent the consecutive deuteration-exchange-deuteration process during quenching.

An additional experiment designed to show the sequential deuteration-exchange-deuteration mechanism did not occur was to use MeOH containing 1eq. of 66b for quenching. Had the second Li-Br exchange taken place during quenching, some of 66b would have been converted to 64. As expected, no amount of 64 was detected.

Lastly, if a consecutive deuteration-exchange-deuteration of 90 were indeed occurring, it is difficult to understand why 90 was no longer observable by ^{13}C NMR. If it were only broadened by a dynamic process at -50°C, it would necessarily reappear at -80°C. It does not, and consequently cannot be the source of 65.



63 64



66b

Thus, it appeared that there was indeed present a new organolithium intermediate X, which was formed by reaction of A with excess t-butyllithium, and which yielded 65 upon quenching with MeOD, but was not observed by routine ^{13}C NMR. A possible reason for the apparent unobservability of X

is that the labeled carbon was coupled to several lithiums, and thus suffered from broadening due to quadrupole-induced relaxation[86,97]. Also, coupling with several lithiums would split the peak into a multi-line multiplet due to the lithium nuclear spin quantum number of 3/2. It is known that quadrupole induced relaxation can be severe enough to render the carbon unobservable[97] under conditions routinely employed.

These interpretations were supported by ^{7}Li-decoupled ^{13}C NMR experiments. Thus, a sample of 83 in THF was treated at -78°C with 5eq. of *t*-butyllithium in a 12mm NMR tube. The ^{13}C NMR spectra of the sample taken with and without ^{7}Li decoupling are shown in Figure 11. The broad multiplet E at δ44 became a sharp singlet in the decoupled spectrum. Multiplet F at δ24 was not clearly defined in the non-decoupled spectrum due to the solvent peaks, but can be easily observed in the decoupled spectrum as a sharp, distinct singlet. Most important is the appearance of a new singlet coincident with a solvent peak at δ28, which increased in intensity upon decoupling. Significantly, other solvent peaks did not sharpen or otherwise change, indicating that the decoupling did not serve to alter the temperature in the NMR tube. Evidently, this new peak corresponds to the organolithium X. It should be noted that when the solvent peak is substracted from this peak, the intensity of X is about the same as

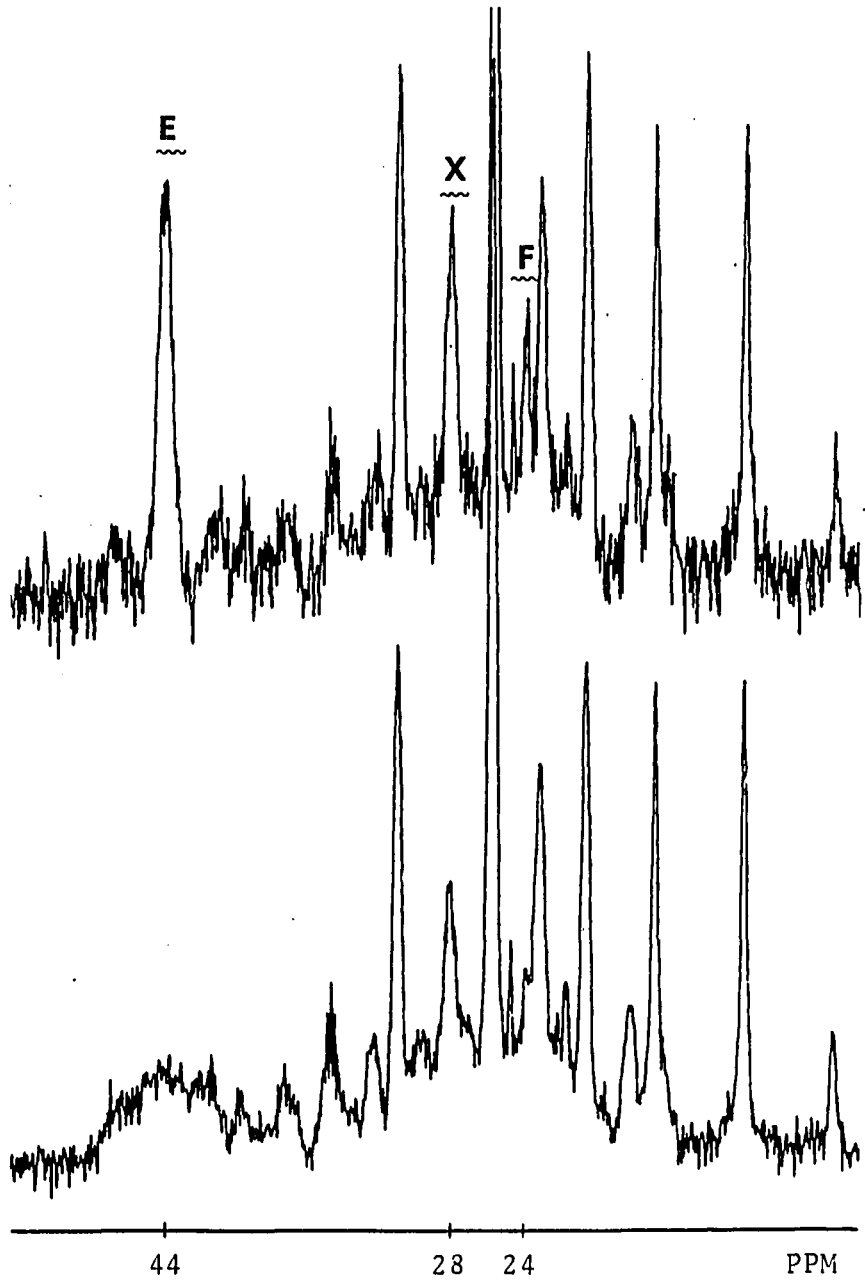


Figure 11. ^{7}Li decoupled (top) and non-decoupled (bottom) ^{13}C NMR of 83 treated with 5eq. of *t*-BuLi

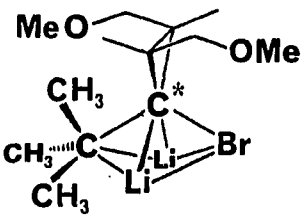
that of F. Since there is no Overhauser effect in the ^{7}Li-decoupled spectrum, the similar intensities of X and F serves to indicate similar amounts of each species[98]. Indeed, the trapping products expected from X and F, namely 65 and 64, respectively, were obtained in the same yield (Table VIII).

With the existence of X established, attention can be turned to its structure. An obvious possibility for X is a carbenoid:*t*-BuLi complex analogous to the previously described carbenoid:*n*-BuLi complex. However, this possibility seems remote, for unlike in the *n*-BuLi case, there was no temperature dependent equilibration between A and X. A was observed to transform into E as indicated by the increase in E's intensity in the NMR, and X, as indicated by the increase in the yield of 65. Moreover, the chemical shift of X, δ28, is significantly upfield from that of B or any other known carbenoid[85,99], thereby excluding any structure having carbenoid character[100].

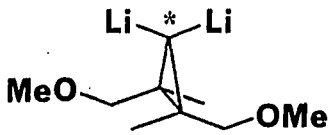
The failure of A and *t*-BuLi to form an observable complex is attributed to both the high reactivity and bulkiness of *t*-BuLi. Indeed, a simple model of an A:*t*-BuLi complex, as shown in 96, indicates a very severe crowding problem for the *t*-Butyl and the side chains on the cyclopropane ring.

Thus, with the possibility of a carbenoid-type structure dismissed, we favor the *gem*-dilithio cyclopropane 97, or its aggregates (e.g.,98) for X (note that structure 98 would be

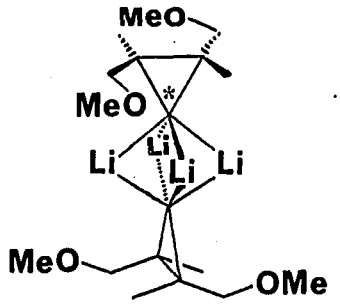
expected to show a 13 line multiplet for C-1 due to ^{7}Li coupling). An additional observation supporting the *gem*-dilithio structure was obtained as follows.



96



97



98

Recall that C-1 in 97 (X) was not observable with ^{13}C NMR unless ^{7}Li-decoupled. The reasons cited were a combination of coupling to several lithiums and quadrupole induced line broadening. Possibly a replacement of the lithiums with comparable nuclei would also render C-1 unobservable.

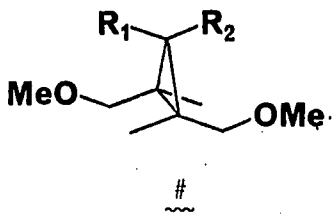
Deuterium is perhaps the perfect replacement, as it has a similar electronic structure (group IA) and size as lithium. More importantly, with a nuclear spin quantum number of 1, deuterium also possesses a quadrupole moment and has been reported to broaden an adjacent carbon resonance via quadrupole induced relaxation[101]. Therefore, a routine ^{13}C NMR spectrum of 65 was obtained which, as predicted, did not show the C-1 peak[102].

The C-1 chemical shifts of a series of *trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropanes are summarized in Table IX. It is noteworthy that the chemical shifts of 77, and 69 do not differ significantly (compare the large difference between 66a and 72). Evidently the C-Li bonds in 77 have the overall appearance of normal sigma bonds.

In summary, while treatment of 63 with excess *n*-BuLi provided a carbenoid:*n*-BuLi complex, reaction with excess *t*-BuLi generated an organolithium intermediate X which (a) was formed from irreversible reaction between carbenoid 72 and *t*-BuLi; (b) afforded 65 upon quenching with MeOD, and (c) could not be observed with routine ^{13}C NMR, but appeared at δ28 (C-1) when ^{7}Li decoupled. The observations led to the assignment of a *gem*-dilithiocyclopropane structure for X, as shown in 77.

An overall scheme summarizing the reactions of 63 with excess *t*-BuLi is shown in Scheme XVII. Alkyl halides, including *gem*-dihalocyclopropanes, are known to react with alkyllithiums via coupling, exchange, and disproportionation[70,72,103]. Thus, the disproportionation reaction of 63 and *t*-BuLi gave 66a (66a probably did not arise appreciably from solvent cleavage, save during formation due to local heating, since the amount of 94 remained essentially constant over time and with increased temperature), the exchange reaction 72, and the coupling reaction 75. In the presence

Table IX. ^{13}C chemical shifts of C-1

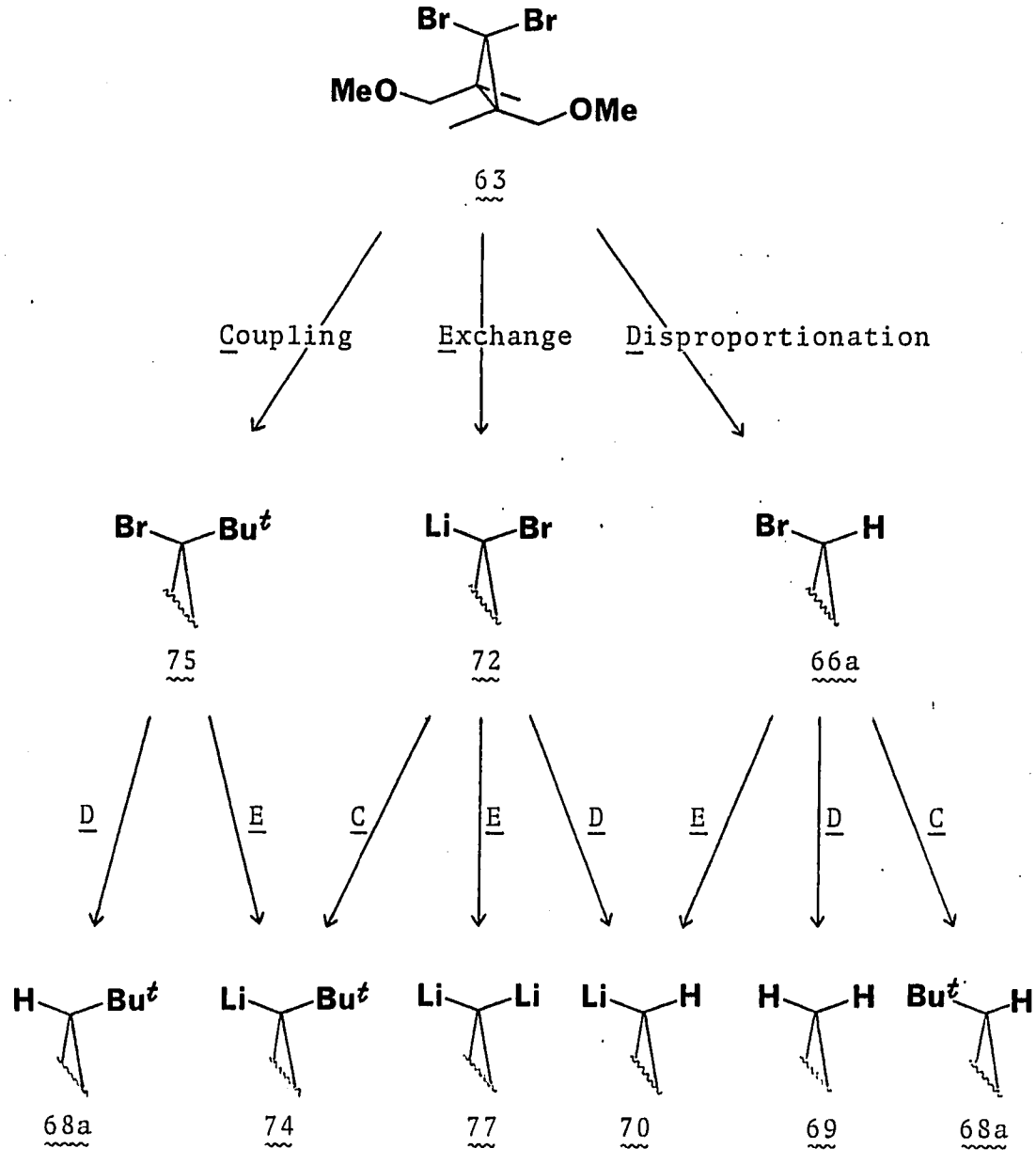


#

#	R_1	R_2	C-1
69	H	H	23.3ppm
64	H	D	23.0
65	D	D	Not observed
70	Li	H	24
77	Li	Li	28
63	Br	Br	51.0
66a	Br	H	39.1
72	Br	Li	94
67a	*n*-Bu	H	32.4
73	*n*-Bu	Li	30
68a	*t*-Bu	H	44.8
74	*t*-Bu	Li	44

of excess *t*-BuLi, both 75 and 66a were converted rapidly into the products of, again, coupling, exchange, and disproportionation. No coupling product from 75, however, was formed, likely due to the bulkiness of the *t*-butyl group. Carbenoid 72 underwent similar reactions although at slower rates and higher temperature. The disproportionation of 72 to 70 was insignificant, since the amount of 70 remained relatively unchanged while 72 was converted to 74 and 77. The ability of 72 to undergo an exchange

Scheme XVII


Br
Br
MeO
OMe
63
Coupling
Exchange
Disproportionation
Br
Bu^t
75
Li
Br
72
Br
H
66a
D
E
C
E
D
E
D
C
H
Bu^t
Li
Bu^t
Li
Li
Li
H
H
H
Bu^t
H
68a
74
77
70
69
68a

reaction with *t*-BuLi is attributed to the directing and stabilizing effects of the methoxy groups.

^{7}Li NMR of 1,1-Dibromo-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane after Treatment with Alkyllithiums

It was hoped that ^{7}Li NMR studies of the reaction mixtures from 63 and *n*-BuLi or *t*-BuLi would provide further insights into the structures of the organolithium intermediates. This spectroscopic method was used to probe the structures of simple alkyllithium aggregates as early as 1965 by T. L. Brown and Seitz[89b,104]. It was instrumental in observing the lithium exchange between MeLi and LiBr, and the formation of their mixed aggregate[105]. Studies of aryllithiums and the effects of substituents on ^{7}Li chemical shifts have also been reported[106]. More recently, ^{6}Li NMR has also been utilized and reportedly provided advantageous results[107]. In general, the literature in this field has been sparse.

Several general features of ^{7}Li NMR deserve mention. The ^{7}Li chemical shifts, usually reported in ppm relative to an external standard of LiBr dissolved in THF or methanol, are not found more than 2ppm on either side of the reference, and are sensitive to solvent, concentration, and temperature. Spectra of multi-component samples generally show only a single peak due to rapid lithium exchange, unless the

temperature is sufficiently low to slow down the rate of exchange.

The ^{7}Li NMR spectra of 63 treated with *n*-BuLi or *t*-BuLi were unexceptional. The spectra were, unless specified otherwise, obtained at 10°C intervals from -80°C to -50°C and again at -80°C with a Bruker WM300 spectrometer at 116.644MHz. The chemical shifts are reported in ppm relative to an external standard of 3M LiBr solution in THF. Due to condensation on the outside of the NMR tube, the samples occasionally did not spin during observation. Spectra of non-spinning samples are noted as such.

A sample of 63 and 1 equivalent of *n*-BuLi gave the ^{7}Li NMR spectra shown in Figure 12. The prominent singlet corresponding to 72 was about 46Hz wide at -80°C and 20Hz wide at -50°C, and appeared at δ0.5±0.2. Two additional minor peaks were also observed at δ2.2 and δ1.8 at temperatures between -80°C and -60°C. However, they did not reappear after the sample was warmed to -50°C and recooled to -80°C. These two peaks may result from different aggregates of 72 that were formed when hexameric *n*-BuLi was added to 63. The peaks disappeared once equilibrium was reached.

^{7}Li NMR spectra of 63 treated with 4 equivalents of *n*-BuLi are included in Figure 13. The large excess of *n*-BuLi produced a very prominent singlet (*n*-BuLi) which largely obscured all other peaks. Consequently, it was

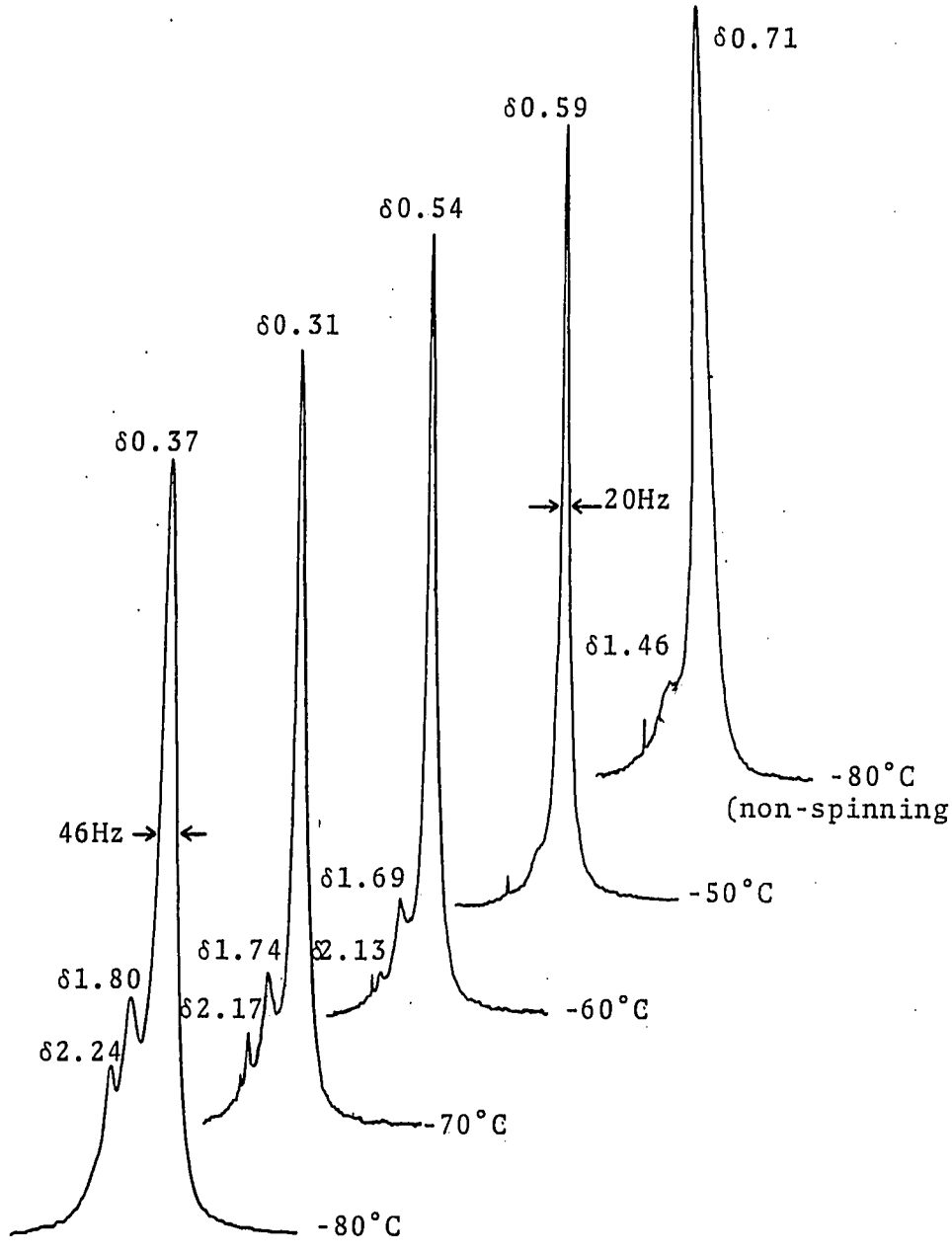
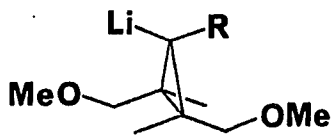


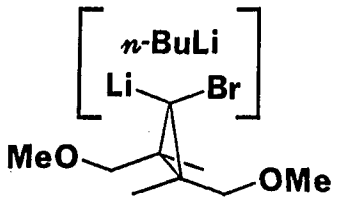
Figure 12. ^{7}Li NMR of 63 after treatment with 1eq. of *n*-BuLi

decided to observe a sample using only 2 equivalents of *n*-BuLi. The spectra thus obtained were much better defined, and are shown in Figure 14.

The peaks observed represent a mixture of *n*-BuLi, carbenoid 72, complex 79, and minor amounts of 73 and LiBr at temperatures below -50°C. Due to the complexity



72, R=Br
73, R=*n*-Bu



79

arising from lithium exchange and possible mixed aggregate formation exchange between these species, a thorough interpretation of the spectra must await further investigation. It may be pointed out, nevertheless, that the peak at δ-0.2(-80°C) increased at the expense of those at δ0.94 (*n*-BuLi) and δ0.56(72) as the temperature increased. It became the only prominent peak at -50°C. This peak must correspond to the complex 79. The observation also supports the earlier conclusion that 79 is a 1:1 complex of 72 and *n*-BuLi. Recooling to -90°C regenerated the carbenoid peak, but with the complex 79 still in excess. This is in accord with the CMR results (Figure 5). Also, only a small amount

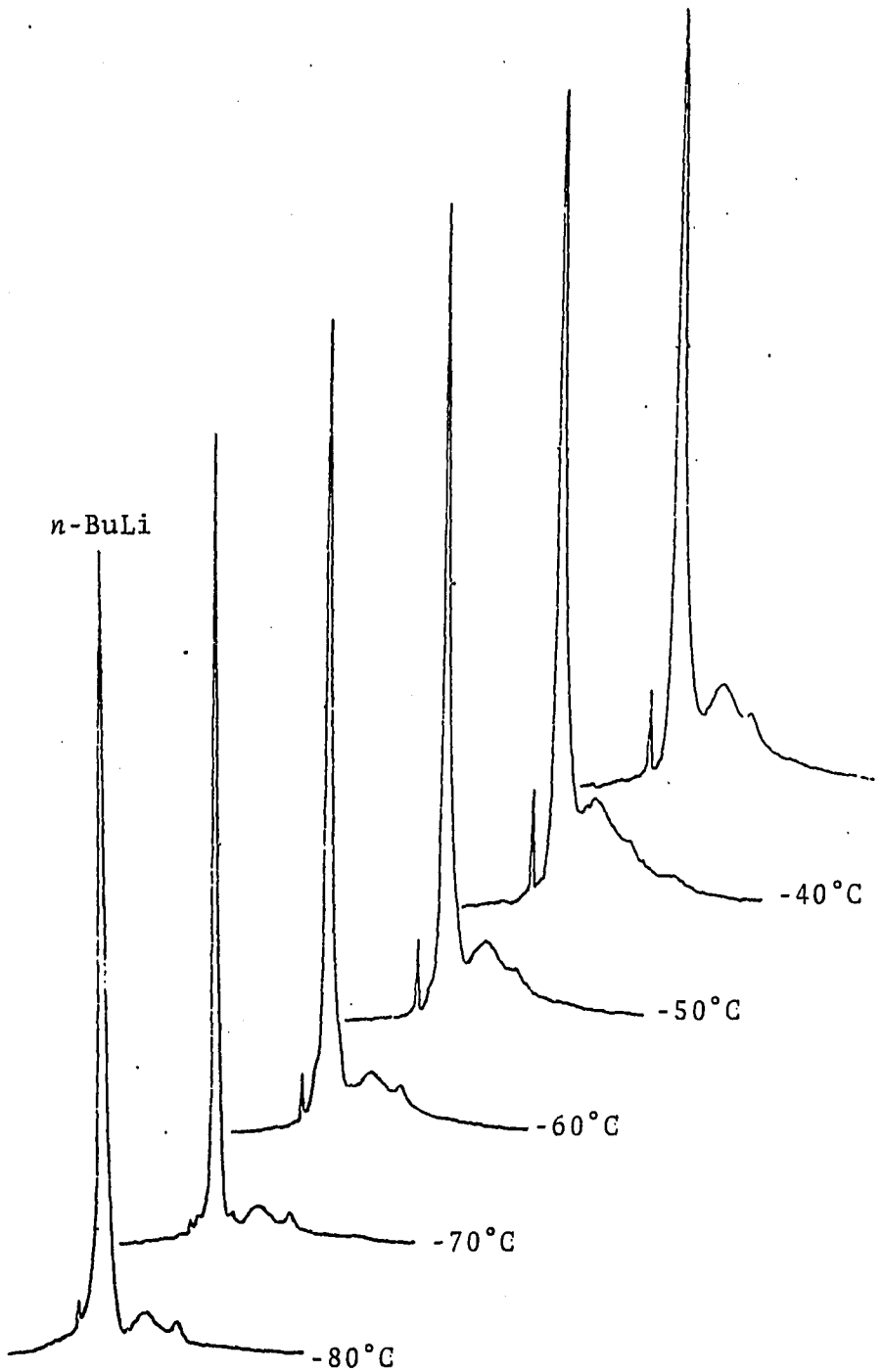


Figure 13. ^{7}Li NMR of 63 after treatment with 4eq. of *n*-BuLi

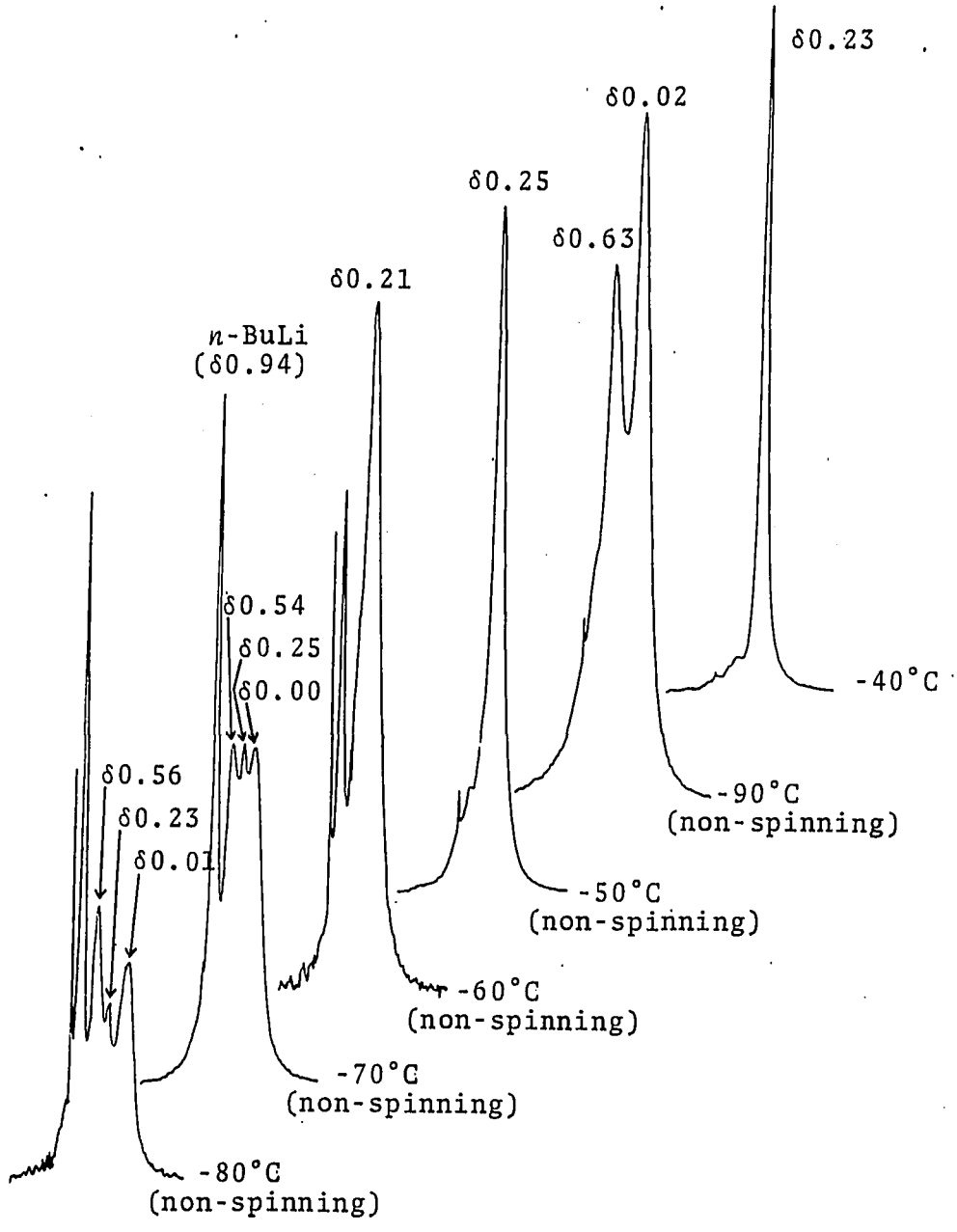


Figure 14. ^{7}Li NMR of 63 after treatment with 2eq. of *n*-BuLi

of *n*-BuLi can be seen upon recooling. A combination of factors may be responsible, including initially incomplete reaction of starting material, increased reaction to provide by-product 73 (thus consuming *n*-BuLi), and aggregation and exchange with LiBr.

At -40°C, where 79 had completely collapsed into 73 and LiBr, the singlet at δ0.23 was the weighted average resulting from rapid lithium exchange between 73 and LiBr. Since 73 and LiBr were present in about the same amount and the chemical shift of LiBr is approximately δ0.0 (see below), the calculated chemical shift for 73 is about δ0.5, but could be as low as δ0.9-δ1.0 (see below).

^{7}Li NMR spectra of 63 treated with 2 equivalents of *t*-BuLi are shown in Figure 15. There are two main components namely carbenoid 72 and LiBr, in equal amounts. However, only one major peak was observed throughout the temperature range from -90°C to -50°C. Apparently, the lithium exchange between 72 and LiBr is very rapid even at -90°C. (Remember that the CMR supports this and shows the adjacent carbon is coupled to only one lithium thereby excluding a static structure.) With the exception at -50°C, the chemical shifts are all δ0.0, which puts LiBr at δ-0.4 if 72 is assumed to be at about δ0.4 (Figure 12).

At -50°C, the singlet appeared at δ0.17. Recall that the ^{13}C NMR similarly showed that the ^{13}C chemical shift of 72 (90) deviated at -50°C (Figure 9). If the chemical shift

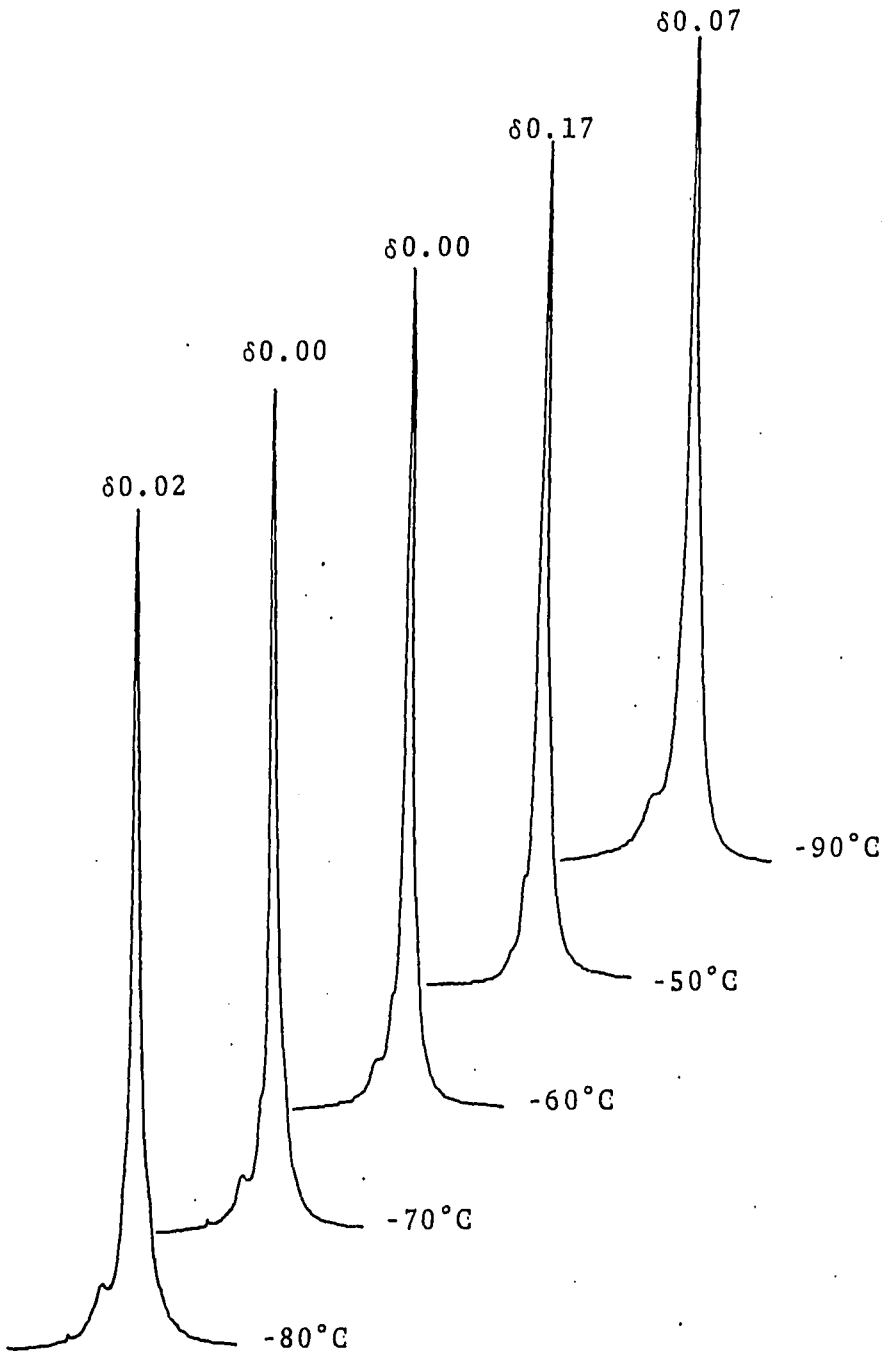
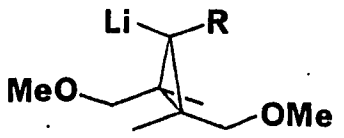


Figure 15. ^{7}Li NMR of 63 after treatment with 2eq. of *t*-BuLi

difference is real (see the shift variations in Figure 12), then it may well be that a new mixed aggregate of 72 and LiBr predominated at this temperature. Another possibility would be co-aggregation with F (70); this point needs further study.

^{7}Li NMR spectra of 63 and 5 equivalents of *t*-BuLi are shown in Figure 16. Despite the presence of several organolithium compounds such as 72, 74, 70, and 77, in addition to LiBr, the spectrum consisted of only a broad singlet at δ0.63 at -80°C, which appeared to shift slightly upfield as the temperature was increased to -50°C. Recall that as the temperature is increased, 72 is irreversibly converted to 74, 77, and LiBr. Equilibration with the



72 : R = Br
74 : R = Bu^{t}
70 : R = H
77 : R = Li

increasingly concentrated and upfield resonating LiBr would serve to explain the upfield drift of the observed resonance.

Upon recooling to -90°C from -50°C, the main peak now appeared at δ0.10 with minor shoulders at δ0.38 and δ0.79. Again, due to the complex dynamic processes in a multi-component system, meaningful interpretations of these spectra must await further investigation. It is clear,

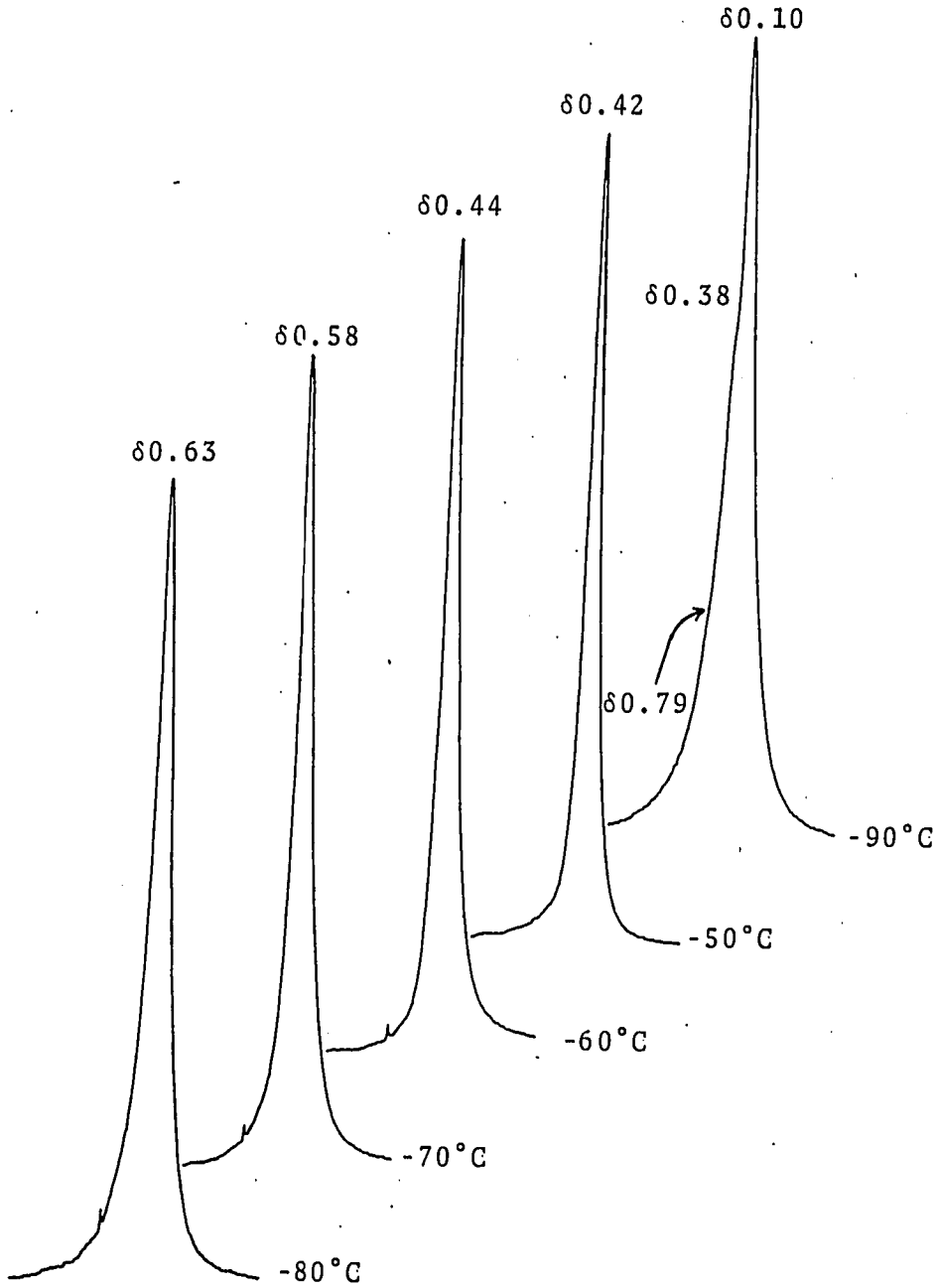


Figure 16. ^{7}Li NMR of 63 after treatment with 5eq. of *t*-BuLi

however, that the presence of LiBr is not particularly helpful.

In summary, the products from reactions of 63 with *n*-BuLi and *t*-BuLi have been examined with ^{7}Li NMR. Similarly to the other few examples reported in the literature, the ^{7}Li chemical shifts observed were confined to a narrow range of less than 3ppm. Also, the resonance lines were often very broad, causing severe overlap. Spectra of multi-component samples are devastatingly simplified by rapid lithium exchange. Despite these limitations, some observations consistent with the ^{13}C NMR data were recognized.

As mentioned earlier, ^{7}Li NMR as a structural tool is still in its early developmental stages. It is suggested that simpler systems of halolithium carbenoids, alkyllithiums with vicinal coordinating groups, and polylithioorganic compounds be examined. Hitherto, there has been no report of ^{7}Li NMR studies of any of these systems, despite the fact that they are increasingly important classes of reactive intermediates.

EXPERIMENTAL

General

Infrared spectra were recorded on a Beckman IR-18A or IR-4250 Spectrophotometer, ^{1}H NMR spectra on a Varian HA-60 or Hitachi Perkin-Elmer R20-B Spectrometer using the indicated solvents and TMS as the internal standard, and ^{13}C NMR spectra on a Jeol FX-90 Spectrometer using the solvents indicated. Chemical shifts are reported in ppm downfield from TMS (δ units). GC-MS analyses were performed on an automated Finnigan Quadrupole Mass Spectrometer. High resolution mass spectra were measured on a AEI M5902 Mass Spectrometer. Quantitation by GC was done on a Varian 3700 Gas Chromatograph with a glass column of 3%OV1 on Chromosorb W, 12 in. x 2mm, using an internal standard. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Alkyllithium reagents were purchased from Ventron and standardized periodically according to published procedures[108]. All reactions involving alkyllithiums were carried out under a blanket of Argon. Additions of liquid reagents were done via syringes inserted through the rubber septum capping the reaction vessel. Reaction vessels were flame dried cooled under Nitrogen. THF was freshly distilled over LAH. Alkyl halides, HMPT, diisopropylamine, and chlorotrimethylsilane were freshly distilled over CaH_2. Other reagents were purified as specified.

p-Di-*t*-Butylbenzene, used as an internal standard, was sublimed twice and stored under Nitrogen.

Syntheses

Lithium-α-Lithiocyclopropanecarboxylate, 31

The procedure is similar to that of Ainsworth and Kuo[55]. To a solution of 31.ml (22mmole) of diisopropylamine in 10ml of THF at 0°C was added 9.2ml of a 2.4M *n*-BuLi solution in hexane, and the resulting mixture stirred for 10 minutes. A solution of cyclopropanecarboxylic acid (10mmoles) in 10ml of THF was then added dropwise. After the addition was completed, the mixture was stirred for another 10 minutes at 0°C.

1-Trimethylsilylcyclopropanecarboxylic acid, 32

To a solution of 10mmole of 31, prepared as described above, was added dropwise at 0°C a solution of 2.5ml (20mmole) of chlorotrimethyl-silane in 2.5ml of THF. After the exothermic reaction subsided, the ice bath was removed and stirring continued for 3 hours. The mixture was then quenched with 10ml of water. The organic layer was extracted once with 20ml of 1M NaOH solution. The combined aqueous layers were cooled in an ice bath, acidified with concentrated HCl, and extracted three times with Et_2O. The combined extracts were washed with sat'd. NaCl solution, dried over $MgSO_4$, and stripped of solvents in vacuo to afford 1.165g

of crude 32 as colorless crystals, which were recrystallized from pentane (70% yield), mp131-134°C. IR (CCl_4): 3500-2500 (broad), 1675, 1400 an^{-1}. ^1H NMR (CCl_4): δ11.3 (s,1H), 1.6-0.3 (m,4H), 0.1 (s,9H). ^{13}C NMR ($CDCl_3$): δ183.52 (int.1565), 13.27 (10881), 10.67 (1475), -2.60 (102.74). Anal. Calc'd for $C_7H_{14}O_2Si$: m/e 143.05283. Found: m/e 143.05359.

1-Methylcyclopropanecarboxylic acid, 33

To a solution of 10mmole of 31 prepared as described above was added dropwise at 0°C a solution of 1.3ml (20mmole) of freshly distilled MeI in 2ml of THF. The ice bath was removed after completion of the addition. The usual work up after 1 hour additional reaction time afforded 0.874g of an oily residue which, by comparison with an authentic sample purchased from Aldrich, was identified as a 1:1 mixture of the starting material and 33. An 89% yield of 33, based on 53% conversion, was calculated from ^1H NMR integration.

1-Allylcyclopropanecarboxylic acid, 34

To a solution of 10mmole of 31, prepared as described above was added dropwise at 0°C a solution of 20mmole of allyl bromide in 3ml of HMPT and 2ml of THF. The ice bath was removed after completion of the addition, and the mixture was further stirred for 3 hours. The usual work up afforded 0.782g of a mixture of the starting material and 34 (70% yield of 34 based on 30% conversion found by NMR

integration). For characterization, pure 34 was obtained by fractionating distillation (68°C, 0.2Torr) of the crude mixture. IR (CCl_4): 3400-2400 (broad), 1690, 1635 cm^{-1}. ^1H NMR (CCl_4): δ11.2 (s, 1H), 6.1-5.5 (m, 1H), 5.2 (br s, 1H), 4.8 (br s, 1H), 2.3 (d, 2H, J=6Hz), 1.3-0.7 (m, 4H) ^{13}C NMR ($CDCl_3$): δ182.16 (int. 1052), 135.24 (2687), 116.44 (3641), 36.70 (4342), 22.62 (1650), 15.74 (7647). Anal. Calc'd for $C_7H_{10}O_2$: m/e 126.06808. Found: m/e 126.06838.

1-Benzylcyclopropanecarboxylic acid, 35

Method A To a solution of 10mmole of 31 prepared as described above was added dropwise at 0°C a solution of 1.5ml (12mmole) of benzyl bromide in 1.5ml of THF. The mixture turned dark brown, then light yellow toward the end of addition. The reaction mixture was stirred for an additional 2 hours at room temperature. The usual work up afforded crude 35 which was recrystallized from hexane to give 0.303g of 35 (17% yield), m.p 102-104°C. IR (CCl_4): 3400-2400, 1700, 1610, 1500 an^{-1}. ^1H NMR (CCl_4): δ12.3 (s, 1H), 7.2 (s, 5H), 3.0 (s, 2H), 1.4-0.8 (m, 4H) ^{13}C NMR ($CDCl_3$): δ182.09 (int. 1220), 139.16 (1535), 129.28 (7425), 128.17 (8434), 126.29 (4975), 37.78 (5236), 23.61 (1171), 16.00 (9822). Anal. Calc'd for $C_{11}H_{12}O_2$: m/e 176.08373. Found: m/e 176.08356.

The organic layer, after extraction with base, was

washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacus to yield an oily residue. Components of this crude mixture were isolated by G.C prep chromatography using a 3%OVI on Chromosorb W glass column (12'x8mm). Three of them were identified by NMR, IR, low resolution mass spec, and/or by comparison with authentic samples, as 1,2-diphenylethane (ca. 5%), *trans*-stilbene (ca. 10%) and 1,2,3-triphenylpropane (ca. 3%).

Method B The normally-prepared solution of 31 (10mmole) was added dropwise via syringe under a blanket of nitrogen to 3ml of benzyl bromide in 17ml of THF. An ice bath was used intermittently during the addition to calm the exothermic reaction. The reaction was then stirred for 3 hours at room temperature, following which the usual work up afforded 0.307g of 35 (17% yield) after recrystallization.

1,1-Dibromotetramethylcyclopropane, 40

In a dried three-necked flask equipped with a mechanical stirrer and an addition funnel were placed 19g of potassium, 200ml of *t*-butyl alcohol and 200ml of hexane. The mixture was stirred until all the potassium had dissolved, and then was cooled to below 10°C with an ice bath. To this was added 20.429g of tetramethylethylene, followed immediately by dropwise addition of 61.353g of bromoform in 50ml of hexane. Near the end of the addition, when the reaction was no longer appreciably exothermic, the ice bath was removed and stirring continued for 2 hours. The light yellow

suspension was then quenched with saturated NH_4Cl solution, after which pentane and water were added. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo. The crude crystalline product was purified by sublimation at 0.7 Torr to afford 42.1g (68% yield) of dibromide 40, m.p 78-79°C (lit.[69]: 54% yield, m.p 77-78°C).

1-Iodo-2,2,3,3-tetramethylcyclopropane, 41b

Method A Under anhydrous conditions, a solution of 0.697g (4mmole) of 41a (see Part II) in 10ml of THF was cooled to -95°C (liquid N_2/Skelly B slurry), following which 5ml of a 1.5M *t*-BuLi solution in pentane was added. After stirring for 20 minutes, a solution of 1.5eq of I_2 in 10ml of THF was added dropwise. After warming to room temperature, the mixture was washed with, in sequence, 5% $NaHSO_3$ and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo to yield 0.625g of an oily residue. A small sample of the residue was immediately diluted with CCl_4 for ^1H NMR observation since, in neat form, the residue rapidly turned dark red and more viscous. ^1H NMR (CCl_4): δ2.45 (s, 1H), 1.20 (s, 6H), 1.06 (s, 6H). About 10% of 41a was also observed. Due to its instability, purification of 41b was not attempted and no further characterization was made.

Method B A solution of 0.359g (2.03mmole) of 41a (see Part II) in 10ml of THF was cooled to -95°C, following

which 3ml of a 1.5M *t*-BuLi solution in pentane was added. After 20 minutes, 1.2eq of MeI in 3ml of THF was added dropwise. Usual work up after warming to room temperature afforded 0.332g of an oily residue whose ^{1}H NMR was essentially identical to that obtained by Method A.

Iodopentamethylcyclopropane, 42b

Under anhydrous conditions, a solution of 0.296g (1.5mmole) of 42a (see Part II) in 5ml of THF was cooled to -95°C (liquid N_2/Skelly B slurry), after which 1.2eq of *t*-BuLi was added dropwise and the reaction stirred for 20 minutes. A solution of 0.11ml of MeI in 2ml of THF was then added dropwise. After warming to room temperature, the usual work up afforded 0.165g of crude 42b which turned rapidly into dark brown viscous liquid in neat form. ^{1}H NMR (CCl_4): δ2.00 (s, 3H), 1.15 (s, 6H), 1.00 (s, 6H). Due to its instability, further purification and characterization of 42b were not attempted.

In an otherwise identical procedure, 0.5ml of HMPT was used as a co-solvent in 5ml of THF. 0.325g (1.7mmole) of 42a yielded 0.290g of crude 42b whose ^{1}H NMR is essentially identical to that obtained as above. A small amount (ca. 5%) of 42a was also observed.

Reactions of 1,1-Dibromotetramethylcyclopropane, 40 with excess *n*-Butyllithium

A solution of 1.253g of 40 in 20ml of THF was

cooled to -95°C. A white suspension resulted, to which 9ml of a 2.2M *n*-BuLi solution in hexane was slowly added along the inside wall of the reaction flask. The addition took 20 minutes. After an additional 20 minutes, the clear homogenous mixture was quenched by dropwise addition of a solution of 4 equivalents of MeI in 1.5ml of THF. The cold bath was then removed. After warming to room temperature, the mixture was diluted with pentane, washed with sat'd NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to afford 1.273 of crude residue. An aliquot was accurately weighed and mixed with a known amount of benzophenone as the internal standard for GC.MS analysis, which showed a mixture of 41, 42, 50, 51, and two unidentified products of m/e 112 and 168 in ratios of ca. 0.3:10.6:1.0:2.1:0.4:03, respectively. Compounds 41 and 42 were identified by comparison of their mass spectra and the crude ^1H NMR with that of authentic samples obtained from independent syntheses. The ratio of 42a:42b, which varies between 2.5:1 to 6.0:1, were determined by ^1H NMR integration using their unobstructed α-CH_3 singlets. The structures of 50 and 51 were deduced from their low resolution mass spectra. The major m/e are summarized and interpreted in Table X and XI, respectively. Both compounds show the typical fragmentation of hydrocarbons, i.e. clusters of peaks with the major peak in each cluster 14 mass unit apart. As in the case of 41 and 42, most of 51 was

Table X. Major fragments from the mass spectrum of 50

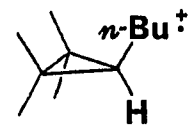
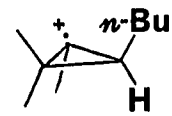
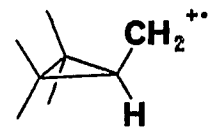
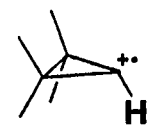
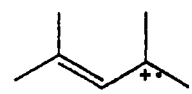
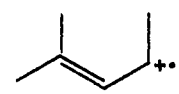
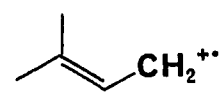
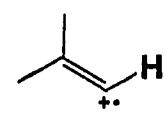
m/e	Relative Intensity	Ion Structure	Lost Fragment
154	4.20		none
139	0.42		$\cdot CH_3$
111	13.56		$C_3H_7\cdot$
97	87.22	 or 	$C_4H_9\cdot$
83	20.83		$C_5H_{11}\cdot$
69	67.46		$C_6H_{13}\cdot$
55	Base		CH_2=CH-CH_3 (from m/e 97)

Table XI. Major fragments from the mass spectrum of 51

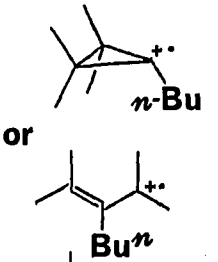
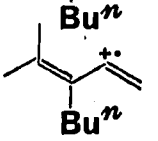
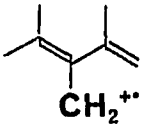
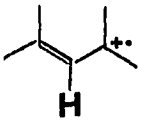
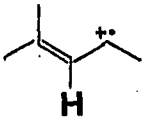
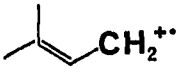
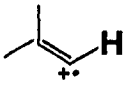
m/e	Relative Intensity	Ion	Lost Fragment
153	16.13		Br· or I·
137	7.41		CH_4
109	11.02		$CH_3CH_2CH_3$
97	34.56		C_4H_8
83	47.81		C_5H_{10}
69	77.24		C_6H_{12}
55	Base		$CH_3CH{=}CH_2$ (from m/e 97)

Table XII. Major fragments from the mass spectrum of 119

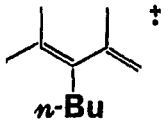
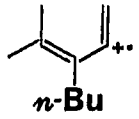
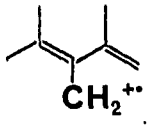
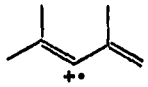
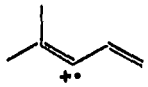
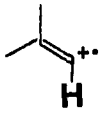
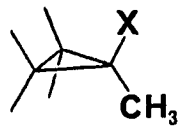
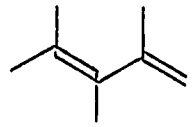
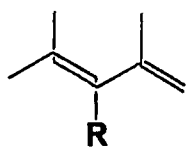
m/e	Relative Intensity	Ion Structure	Lost Fragment
152	13.58		none
137	22.90		$\cdot CH_3$
109	26.84		$C_3H_7\cdot$
95	46.54		$C_4H_9\cdot$
81	Base		$C_5H_{11}\cdot$
67	91.05		$C_6H_{13}\cdot$
55	55.63		HC=CH (from m/e 81)

Table XIII. Major m/e from the mass spectra of 42 and 118

 42		 118	
m/e	Relative Intensity	m/e	Relative Intensity
97	49.38	95	90.99
81	13.26	81	12.29
69	14.11	67	base
55	base	55	72.90

dehydrohalogenated during the GC stage (see Part II) and, thus, appeared as a component having a shorter retention time than 51's and an apparent parent ion of 152, which was assigned the structure shown in 119. Major fragments from



R = H
= Me
119, = *n*-Bu

the mass spectrum of 119 are shown in Table XII. As an additional supporting evidence for the structures of 51 and 119, it is noted that they show very similar fragmentation patterns at m/e lower than 97 to that of the known compounds 42 and 118 (Table XIII), respectively.

Under anhydrous conditions (see General section), 9ml of a 2.2M *n*-BuLi in hexane solution was diluted with

5ml of THF at -78°C, to which was added a molar equivalent of TMEDA, and the mixture was stirred for 10 minutes. After cooling to -95°C (liquid N_2/Skelly B slurry), 1.231g (4.8mmole) of 40 dissolved in 15ml of THF was added. The addition took 20 minutes. After an additional 20 minutes, a solution of 4 equivalents of MeI in 2ml of THF was added dropwise. The cold bath was then removed to warm the reaction mixture to room temperature. Saturated NH_4Cl solution and pentane were added. The organic layer was washed with 1N HCl and then with sat'd $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo to afford 1.140g of an oily residue. An aliquot was accurately weighed and mixed with a known amount of benzophenone as the internal standard for GC.MS analysis, which indicated a mixture of 41, 42, 50, 51, and an unidentified product of an apparent parent ion of m/e 168 in the ratio of ca. 0.2:17.7:1.0:0.3:0.5. From ^1H NMR, the ratio of 41a:41b and 42a:42b were found to be 2:1 and 1:10, respectively.

Under anhydrous conditions (see General section) at -78°C, 3.1ml of TMEDA was added to 9.3ml of a 2.2M *n*-BuLi in hexane solution. The resulting solution was stirred for 10 minutes then cooled to -95°C (liquid N_2/Skelly B slurry). A solution of 1.315g (5.1mmole) of 40 dissolved in 15ml of hexane was added dropwise. The mixture was stirred for 20 minutes after completion of the addition, then 4 equivalents of MeI in 2ml of THF was added dropwise.

The cold bath was then removed to warm the mixture to room temperature. The usual work-up afforded 1.968g of an oily residue. An aliquot was mixed with a known amount of benzophenone as the internal standard for GC.MS analysis, which indicated a mixture of 41, 50, 51 in ratios of ca. 0.6:1:0:8.9.

Reaction of 1,1-Dibromotetramethylcyclopropane, 40, with excess *t*-Butyllithium

Inverse addition of *t*-BuLi and rapid addition of MeI were employed. Under anhydrous conditions, 5.5ml of a 1.8M *t*-BuLi in pentane solution was diluted with 5ml of THF at -95°C. To this was added dropwise 0.512g (2mmole) of 40 dissolved in 5ml of THF. The addition took 20 minutes. After an additional 20 minutes, 5 equivalents of MeI were added all at once. The mixture was then allowed to warm up to room temperature by removing the cold bath. Crude product obtained after the usual work-up was analyzed with GC.MS and crude ^{1}H NMR to show a mixture of 41b, 42a in ca. 1:10 ratio.

Normal addition of *t*-BuLi and slow addition of MeI were employed. Under anhydrous conditions, a solution of 1.261g (4.9mmole) of 40 in 20ml of THF was cooled to -95°C (liquid N_2/Skelly B slurry). To this was added dropwise 14ml of a 1.5M *t*-BuLi solution in pentane. The resulting mixture was stirred for 20 minutes and then quenched with 4 equivalents of MeI. After warming up to room temperature, the usual work-up afforded 0.538g of an oily residue which

was shown by GC.MS and ^{1}H NMR to consist of 41b, 42a and 42b in ca. 4:10:16 ratio.

Normal addition of *t*-BuLi and rapid addition of MeI were employed. Under anhydrous conditions, a solution of 1.321g (5.2mmole) of 40 in 20ml of THF and 5ml of HMPT was cooled to -95°C. To the resulting slurry was added dropwise 14ml of a 1.5M *t*-BuLi solution in pentane. After completion of the addition, the mixture was stirred for 15 minutes and quenched by rapid addition of 5 equivalents of MeI. After warming up to room temperature, the mixture was washed twice with 3N HCl solution. The combined aqueous layers were extracted once with Et_2O. The combined organic layers were washed consecutively with sat'd $NaHCO_3$ solution and sat'd NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to yield 0.886g of crude product which was shown by GC.MS and ^{1}H NMR to consist of 41b, 42a, and two unidentified components with m/e 168 and 208 in ca. 10:1:5.5:5.5 ratio. About 8 other minor components of unobvious origin or parent ions were also observed.

THF-HMPT with inverse addition of *t*-BuLi and rapid addition of MeI were employed. Under anhydrous conditions, 7.3ml of a 1.5M *t*-BuLi solution in pentane were added dropwise to 20 ml of THF and 5ml of HMPT at -95°C. To this light orange mixture was added slowly along the inside wall of the reaction flask a solution of 0.561g (2.2mmole) of 40 in 10ml of THF. After completion of the addition, the mixture

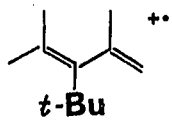
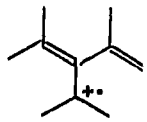
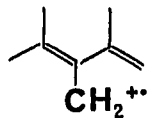
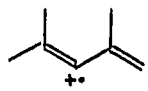
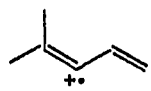
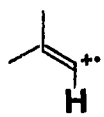
was stirred for 15 minutes and then quenched by rapid addition of 5 equivalents of MeI. After warming up to room temperature, the usual work-up yielded 0.293g of crude product which was shown by GC.MS and ^{1}H NMR to consist of 41, 42a and m/e 168 in ca. 3:10:0.1 ratio. About 10 other minor components of unobvious parent ions or origin were also observed by GC.MS.

Hexane-HMPT with normal addition of *t*-BuLi and slow addition of MeI were employed. Under anhydrous conditions a solution of 1.288g (5.0mmole) of 40 in 20ml of hexane and 5ml of HMPT was cooled to -95°C. To this mixture was added 13.4ml of a 1.5M *t*-BuLi solution in pentane, and the resulting mixture stirred for 20 minutes, following which 5 equivalents of MeI were added dropwise. After warming up to room temperature, the mixture was worked up as usual to yield 0.740g of crude product which was shown by GC.MS and ^{1}H NMR to consist of 41b, 42a, 42b, 53, and m/e 168 in ca. 3:10:6:0.2:0.1 ratio. About 7 minor peaks that are poorly resolved and of unobvious parent ions or origin were also observed by GC.MS. The structure of 53 was deduced from the mass spectrum of its dehydrohalogenated form (120). Its fragmentation pattern (Table XIV) is closely matched with that of 118 or 119.

1,4-Dimethoxy-*trans*-2,3-dimethyl-2-butene, 62

Method A 21.8g (265mmole) of 2,3-dimethyl-1,3-buta-

Table XIV. Major fragments from the mass spectrum of 120

m/e	Relative Intensity	Ion Structure	Lost Fragment
152	6.84		none
137	61.18		$CH_3^{\cdot}$
109	2.96		$C_3H_7^{\cdot}$
95	56.19		$C_4H_9^{\cdot}$
81	90.57		$C_5H_{11}^{\cdot}$
67	30.13		$C_6H_{13}^{\cdot}$
57	base	t-Bu$^{\cdot}$	$C_7H_{11}^{\cdot}$
55	48.61		HC=CH (from m/e 81)

diene were converted to 60 according to the published procedure[109]. The crude dibromide 60 was immediately dissolved in 400ml of MeOH and stirred with 31.5g of MeONa for 16 hours. Most of the MeOH was removed in vacuo and replaced by water. The mixture was then extracted three times with 200ml portions of pentane. The combined extracts were washed with sat'd NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The NMR of the crude product showed a mixture of the desired 62 and the allylic rearrangement product 61 in a 1:1 ratio. Spinning band distillation of the crude product provided 7.944g (21% yield) of 61 (bp 53°C/7Torr). IR (CCl_4): 3080, 2900, 1670, 1630, 1440, 1120, 900 cm^{-1}; ^1H NMR (CCl_4): δ4.85 (br m, 2H), 3.23 (s, 3H), 3.20 (s, 2H), 3.00 (s, 3H), 1.65 (br m, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$): δ145.48 (Int. 932), 113.90 (4334), 79.06 (929), 77.60 (4477), 59.35 (3168), 49.92 (3410), 19.26, (5293), 1866 (3511). Anal. Calc'd for $C_8H_{16}O_2$: m/e 144.11503. Found: m/e 144.11515. Further distillation gave 9.240g (31% yield) of 62 (bp 53 C/5 Torr). IR (CCl_4): 2800-3000 (br), 1450, 1150, 950, 900 cm^{-1}; ^1H NMR (CCl_4): δ3.85 (s, 4H), 3.20 (s, 6H), 1.70 (s, 6H); ^{13}C NMR ($CLCl_3$): δ129.93 (int. 2864), 7278 (7497), 57.34 (6520), 15.74 (3164). Anal. Calc'd for $C_8H_{16}O_2$: m/e 144.11503. Found: m/e 144.11515.

Method B The crude dibromide 60 was dissolved in 250ml of MeOH and the solution added dropwise to a well-

stirred mixture of 4 equivalents of MeONa and 200ml of MeOH at 70-80°C. The addition took 4 hours. After another 4 hour stirring, the usual work-up yielded a mixture of 61 and the desired 62 in a 1:12 ratio, as indicated by ^{1}H NMR.

1,1-Dibromo-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane, 63

In 20ml of *t*-butanol and 100ml of hexane were dissolved 2.64g of potassium, and the resulting solution cooled to -40 to -47°C, after which 4.862g (20mmole) of the dimethoxybutene 62 were added. To this slurry mixture was added dropwise a solution of 6ml of bromoform in 25ml of hexane. The addition took 2 hours. After stirring for an additional 2 hours, the mixture was quenched with saturated NH_4Cl solution, warmed up to room temperature, diluted with hexane, washed with sat'd NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to afford 20.351g of crude product. This was distilled at 80°C and 0.75 Torr to give 9.333g (87% yield) of 63. IR (CCl_4): 3000-2800 (br m), 1450, 1380, 1200, 1100, 960 cm^{-1}; ^{1}H NMR (CCl_4): δ3.40 (s, 4H) 3.30 (s, 6H), 1.30 (s, 6H); ^{13}C NMR ($CDCl_3$): δ75.87 (Int. 7655), 58.80 (4748), 50.95 (978), 32.86 (1685), 16.66 (5170). Anal. Calc'd for $C_6H_8Br_2$: m/e 239.89723. Found: m/e 239.89890.

1-^{13}C-1,1-Dibromo-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 83

Under anhydrous conditions, 1.8g of potassium was dissolved in 20ml of hexane and 30ml of *t*-butanol. The resulting slurry was cooled to -40°C. To this was added 5.14g (32.4mmole) of 62 followed by the dropwise addition of a solution of 2.7g (10.8mmole) of ^{13}C-bromoform[84] in 5ml of hexane. The resulting mixture was stirred at -36 to -32°C for 1 hour, and at -20°C for another hour. Crude product obtained after the usual work-up was distilled to recover 3.205g of 62 (bp 51°C/7 Torr) and to afford 2.228g of 83 (bp 87°C/1.5 Torr). IR (CCl_4): 2930, 1450, 1380, 1200, 1115, 970 cm^{-1}; ^{1}H NMR (CCl_4): δ3.35 (triplet, J_{C-H}=2Hz, 4H), 3.30 (s, 6H), 1.30 (triplet, J_{C-H}=2Hz, 6H); ^{13}C NMR (d_6-benzene): δ75.64 (Int. 919), 58.18 (543), 51.47 (8376), 16.68 (473), the quaternary carbon appeared as a very weak broad peak at ca. 33ppm. Anal. Calc'd for $C_6H_8{}^{79}Br^{81}Br$: m/e 239.89723. Found: m/e 239.89696.

Trans-1,2-Dimethoxymethyl-1,2-dimethylcyclopropane, 69

A mixture of 2.6g of zinc dust, 0.396g of CuCl, and 100ml of Et_2O were refluxed under nitrogen for 30 minutes[110]. To the resulting Zn/Cu couple were added 2.894g (20mmole) of 62 and 3ml of CH_2I_2, and the mixture refluxed for 24 hours. The mixture was then filtered, washed with water and sat'd NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to give 3.657g of a 10:46 mixture of the starting material

and 69. Pure 69 was obtained by distillation of the crude product (bp 50°C/5 Torr). IR (CCl_4): 3000 to 2800 (br m), 1450, 1380, 1200, 1120, 970, 950 cm^{-1}; ^1H NMR (CCl_4): δ3.22 (s, 10H), 1.12 (s, 6H), 0.25 (s, 2H); ^{13}C NMR ($CDCl_3$): δ78.36 (Int. 6704), 58.53 (7120), 24.13 (2161), 23.27 (4466), 17.63 (5972). Anal. Calc'd for $C_8H_{14}O$ (P^+-CH_3OH): m/e 126.10446. Found: m/e 126.10491.

1-Bromo-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane, 66a

To a solution of 0.978g (3.1mmole) of dibromide 63 in 10ml of THF at -78°C was added dropwise 1.3ml of a 2.5M *n*-BuLi solution in hexane. After 5 minutes, the mixture was quenched with MeOH and worked up as usual to afford 0.789g of crude 66a. For characterization and response factor determination, crude 66a was purified by distillation (bp 63-64°C/1.8 Torr); 0.412g (56% yield) of 66a were collected. IR (CCl_4): 3000-2800 (br m), 1450, 1375, 1200, 1100, 960 cm^{-1}; ^1H NMR (CCl_4): 3.40 (br m, 10H), 2.88 (s, 1H), 1.20 (s, 6H); ^{13}C NMR (d_6-benzene): δ76.39 (int. 10870), 75.41 (10852), 58.19 (8780), 57.92 (9700), 39.12 (7666), 27.63 (3052), 26.55 (2136), 16.91 (5691), 14.90 (4859).

1-Deutero-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane

To 0.591g (2.5mmole) of 66a in 8ml of THF at -78°C were added slowly 1ml of a 2.5M *n*-BuLi solution in hexane. After

15 minutes, the mixture was quenched with CH_3OD, allowed to warm up to room temperature, diluted with Et_2O, washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to yield 0.412g of 64. For characterization and response factor determination, crude 64 was purified by distillation, followed by preparative gas chromatography using a 3% OV1 on Chromosorb W 12'x8mm glass column. IR (CCl_4): 3000-2800, 1450, 1375, 1190, 1100, 950, 940 cm^{-1}; ^1H NMR (CCl_4): δ3.20 (s, 10H), 1.10 (s, 6H), 0.25 (s, 1H); ^{13}C NMR (d_6-benzene): δ78.12 (int. 4640), 57.92 (3930), 24.11 (1192), 22.65 (1655, triplet, J_{C-D}=24.41Hz), 17.72 (3807).

1,1-Dideutero-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane, 65

To a solution of 0.751g (2.4mmole) of dibromide 63 in 20ml of THF at -78°C was added dropwise 1.1ml of a 2.2M *n*-BuLi solution in hexane. After 5 minutes, the mixture was quenched with CH_3OD, allowed to warm up to room temperature, washed with sat'd NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to afford 0.628g of crude 66b. Anal. Calc'd for $C_9H_{15}O_2D$: m/e 157.12131. Found: m/e 157.12211. A solution of 0.412g of 66 in 15ml of THF was similarly treated with 1eq. of *n*-BuLi at -78°C for 15 minutes followed by quenching with MeOD. After the usual work-up, 0.172g of 65 was obtained. IR (CCl_4): 3000-2800, 1450, 1380, 1200, 1105, 960 cm^{-1}; ^1H NMR (CCl_4): δ3.25 (s, 10H),

1.15 (s, 6H); ^{13}C NMR (d_6-benzene): 78.12 (int. 3632), 57.97 (3911), 24.00 (1054), 17.66 (3308), C-1 was not observed.

1-*n*-Butyl-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane, 67a

To a solution of 0.709g (2.24mmole) of dibromide 63 in 15ml of THF at -78°C were added dropwise 4ml of a 2.2M *n*-BuLi solution in hexane. After completion of the addition, the mixture was warmed up to -40°C, stirred at this temperature for 30 minutes, and then quenched with MeOH. After warming up to room temperature, the usual work-up afforded 0.628g of crude 67a. For characterization and response factor determination, 67a was purified by distillation followed by preparative G.C. using a 3% OV1 on Chromosorb W, 8mmx12' glass column. IR (CCl_4): 3000-2800 (br m), 1450, 1370, 1180, 1100, 950 cm^{-1}; ^1H NMR (CCl_4): δ3.10 (br m, 10H), 0.80-1.40 (br m with s at 0.20 and 0.10, 16H); ^{13}C NMR (d_6-benzene): δ79.53 (300), 74.60 (294), 58.19 (218), 57.92 (225), 32.36 (1200), 26.49 (125), 25.74 (118), 24.22 (250), 22.76 (225), 19.18 (264), 14.14 (260), 12.52 (174). Anal. Calc'd for $C_{12}H_{22}O$: m/e 182.16707. Found: m/e 182.16740.

1-*t*-Butyl-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane, 68a

To 1.431g of 63 in 15ml of THF at -78°C were added

11.3ml of a 2.0M *t*-BuLi solution in pentane. After the addition, the mixture was warmed up to -50°C, stirred at this temperature for 30 minutes, and then quenched with MeOH. After warming up to room temperature the usual work-up afforded 0.924g of a mixture of 69 and 68a. The crude product was distilled to yield 0.179g of 69 (bp 58-59°C/8 Torr) contaminated with a small amount of 68a, and 0.565g of mainly 68a (bp 58°C/1.5 Torr). For characterization and response factor determination purposes, pure 68a was obtained by preparative G.C. using a 3% OV1 on Chromosorb W, 2mmx12' glass column. IR (CCl_4): 3000-2800 (br, m), 1460, 1380, 1200, 1110, 960 cm^{-1}; ^1H NMR (d_6-benzene): δ3.33 (s, 2H), 3.05 (br s, 8H), 1.25 (m, 6H), 1.00 (s, 9H), 0.27 (s, 1H); ^{13}C NMR (d_6-benzene): δ80.67 (Int. 170), 74.44 (240), 58.03 (226), 44.75 (757), 32.40 (73), 31.32 (634), 28.17 (100), 27.90 (95), 21.02 (135), 13.28 (188). Anal. Calc'd for $C_{12}H_{22}O$: m/e 182.16707. Found: m/e 182.16754.

Reactions of 63 with excess *n*-Butyllithium

To a solution of 0.218g (0.69mmole) of 63 and 0.0111g of *p-di-t*-Butylbenzene standard in 2.3ml of THF at -78°C was added dropwise 1.2ml of a 2.5M *n*-BuLi solution in hexane. After 30 minutes, 0.1ml of MeOD was injected all at once directly into the well-stirred mixture, which was then allowed to warm up to room temperature followed

by the usual aqueous work-up. The products were identified as 64 and 65 (25%), 66b (60%), and 67b (15%) by GC.MS and comparison with authentic samples obtained by independent syntheses; the yields were determined by gas chromatography using the internal standard.

The fraction, y, of 64 in the mixture of 64 and 65 was calculated from the equation:

$$y(2.30) + (1-y)\ 23.23 = 16.84$$

where 2.30 is the relative intensity of m/e 115 of pure 64, 23.23 pure 65, and 16.84 mixture of 64 and 65. By solving this equation, y = 0.305. Thus, the yield of 64 is 8% and that of 65 17%.

To a well-stirred solution of 0.0314g of *p*-di-*t*-butylbenzene standard and 0.186g of 63 in 3ml of THF at -78°C, was added dropwise 1.2ml of 2M *n*-BuLi solution in hexane. The mixture was warmed up to -40°C and kept at this temperature for 30 minutes, after which it was quenched by adding, all at once, 0.1ml of MeOD. The crude product mixture obtained after the usual work-up was found by GC.MS and comparison with authentic samples to contain 67b (90%) and 64 (5%). The yields were determined by gas chromatography using the internal standard method.

Reactions of 63 with excess *t*-Butyllithium

To 0.287g of 63 and 0.0254g of *p*-di-*t*-butylbenzene in 10ml of THF at -78°C were added 5 equivalents of *t*-BuLi in

pentane. After stirring for 10 minutes, 0.2ml of MeOD was squirted rapidly directly into the well-stirred mixture. The light yellow color disappeared instantly. After warming up to room temperature, the resulting mixture was worked-up as usual. The crude was found to consist of 69+64+64 (43%), 66b (15%), and 68 (4%) by GC.MS and comparison with authentic samples. The yields are the averages of results determined by gas chromatography and by GC.MS (appropriate response factors employed) using the internal standard method. The ratio of 69:64:65 was determined from the mass spectra (see below), and their yields were found to be 7%, 22%, and 18%, respectively.

To a solution of 0.207g (0.66mmole) of 63 and 0.0208g of *p-di-t*-Butylbenzene in 10ml of THF at -78°C were added 2ml of a 1.8M *t*-BuLi solution in pentane. After 10 minutes, the light yellow solution was transferred via argon pressure through a 22-gauge 5in. long stainless steel tube into a well-stirred large excess of MeOD at room temperature. The crude product mixture obtained after the usual work-up was analyzed as before to show 69 (6%), 64 (21%), 65 (15%), 66b (36%), and 68 (4%).

Similarly, a solution of 0.299g (0.946mmole) of 63 and 0.0249g of *p-di-t*-butylbenzene in 10ml of THF at -78°C was treated with 5 equivalents of *t*-BuLi for 10 minutes and then quenched by adding to a large well-stirred excess of MeOD at room temperature. The crude obtained

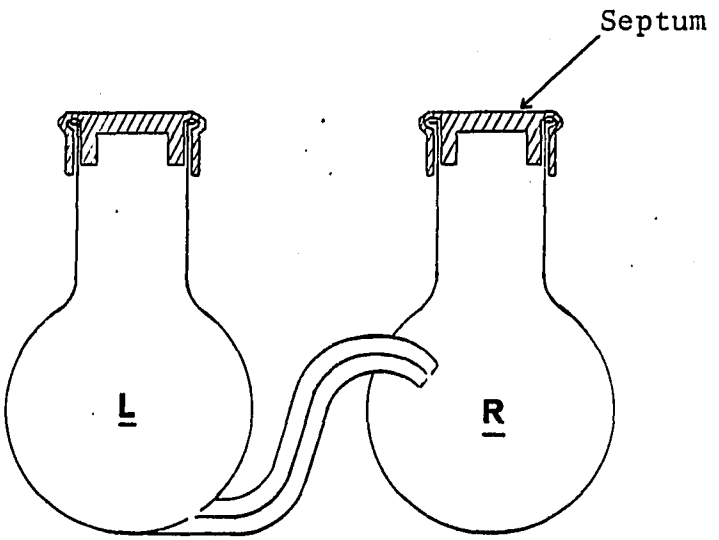


Figure 17. Apparatus employed for inverse addition in reactions of 63 with excess *t*-BuLi

after the usual work-up was analyzed as before to show 69 (7%), 64 (20%), 65 (14%), 66b (44%), and 68 (3%).

Since the reaction mixture would inevitably warm up somewhat during the transfer as described in B and C, a dual-vessel illustrated in Figure 17 was used to carry out the reaction. In vessel L was placed a solution of 0.231g (0.73mmole) of 63 and 0.0175g of *p-di-t*-butylbenzene in 10ml of THF. A slight pressure of argon was applied to vessel R to prevent premature transfer from vessel L to R. Both vessels were then immersed in dry ice-acetone bath, and the temperature was allowed to equilibrate. 2.0ml of a 1.8M *t*-BuLi solution in pentane were added to vessel L dropwise. After the resulting mixture was stirred for 10 minutes, 2ml of MeOD was introduced into vessel R. The organolithium solution in L was then transferred dropwise into R by applying a slight pressure of argon to L. After warming up to room temperature, the reaction mixture was worked-up as usual. The crude was analyzed as described above to show 69 (9%), 64 (23%), 65 (16%), 66b (15%), and 68 (4%).

The ratio of 69:64:65 was calculated from the mass spectra of the mixtures as follows.

Let x = fraction of 69 in the mixture

y = " " 64 " "

z = " " 65 " "

Then

$$x + y + z = 1 \quad (1)$$

$$1.49\,x + 29.43\,y + 2.40\,z = M \quad (2)$$

$$0.42\,x + 2.30\,y + 23.23\,z = M \quad (3)$$

where M and N are the relative intensity of m/e 114 and 115, respectively, of the mixture. The coefficients are obtained from the mass spectra of the pure compounds as

	69	64	65
m/e 114	1.49	29.43	2.40
m/e 115	0.42	2.30	23.23

shown above. By solving equations (1) to (3) by the matrix method,

$$y = \frac{1}{635.60}\,(22.81\,M - 0.91\,N - 33.60) \quad (4)$$

$$z = \frac{1}{635.60}\,(-1.88\,M + 27.94\,N - 8.93) \quad (5)$$

and $$x = 1 - y - z \quad (6)$$

The calculated values for x, y, and z are shown in Table XV. The yields were determined simply by multiplying the fraction by the total yield of the three compounds.

Since the total yields of 69+64+65 were determined from GC and GC.MS with the assumption that the response factor of the mixture is the same as that of 64, the major component, and the difference in their molecular weights is negligible, it seems desirable to check the results by another method. Thus, the yields were recalculated using a combination of ^{1}H NMR and mass spectral

Table XV. The yields of 69, 64, and 65 as determined by GC-GC.MS

Experiment	M	N	x (% yield)	y (% yield)	z (% yield)
A	14.376	9.933	0.135 (7%)	0.479 (21%)	0.386 (17%)
B	14.777	9.468	0.141 (6)	0.495 (21)	0.364 (15)
C	14.558	8.866	0.174 (7)	0.487 (20)	0.339 (14)
D	14.458	8.550	0.192 (9)	0.483 (23)	0.325 (16)

data as follows.

Let Y = mmole of 64 in the mixture

X = " " 69 " "

then:

$$2X + Y = P \tag{7}$$

where P is the total mmole of cyclopropylic proton and was obtained from ^{1}H NMR integration using the internal standard method.

Also, $$\frac{X}{Y} = Q \tag{8}$$

where Q is determined from the ratio of x:y (Table XV).

From equations (7) and (8),

$$Y = \frac{P}{1 + 2Q}$$

Once Y is known, X and Z, the mmole of 65, are determined using the x:y and z:y ratios. The yields of 69, 64, and

65 thus calculated (Table XVI) are essentially the same as those determined earlier from GC and GC.MS data (Table XV).

Another method of calculation using ^{13}C NMR and GC.MS data was carried out as follows. The crude products of A, B, C, D, and other similar experiments were combined to give sufficient amount of 69+64+65 mixture for distillation. From the ^{13}C NMR of the distilled mixture and each pure compound the following quantities were obtained.

		Intensity of MeO-	Intensity of C-1	Intensity ratio C-1/MeO-
69		7120	4466	0.627
64		3930	1655	0.421
69	Mixture	6122	515	0.084
64			1491	0.244
65			Not observed	N.A

Thus, the fraction of 69, x, was determined by 0.084/0.627 or 0.134, that of 64, y, 0.244/0.421 = 0.579, and z = 1-0.134 - 0.579 or 0.287. With the average yield of the mixture at 43%, the yields of 69, 64, and 65 are 6%, 25%, and 12%, respectively. The slight differences between the yields calculated here from those determined earlier by GC and GC.MS, or by ^{1}H NMR and GC.MS are attributed to errors in measuring the intensities of C-1 in the mixture's ^{13}C NMR.

Table XVI. The yields of 69, 64, and 65 calculated from ^{1}H NMR-GC.MS

Experiment	P	Q	X (% yield)	Y (% yield)	Z (% yield)
A	0.301	0.282	0.054 (8%)	0.192 (24%)	0.155 (19%)
B	0.249	0.285	0.045 (7)	0.158 (24)	0.116 (18)
C	0.360	0.357	0.074 (8)	0.206 (22)	0.143 (15)
D	0.300	0.396	0.066 (9)	0.167 (23)	0.112 (15)

The triplet from C-1 of 64 overlaps slightly with the singlet from the C-1 of 69 and that of the quaternary carbon.

In conclusion, all three different methods of per cent yield calculation described above give essentially the same results and are reliable.

To a solution of 0.129g (0.41mmole) of 63 and 0.0226g of *p-di-t*-butylbenzene in 5ml of THF at -78°C was added dropwise 1.1ml of a 2.0M *t*-BuLi solution in pentane. The resulting mixture was then warmed up to -50°C and kept at this temperature for 30 minutes, and then quenched by injecting 0.2ml of MeOD all at once directly into the mixture. The light yellow color disappeared instantly. Warming up to room temperature followed by the usual work-up afforded the crude mixture which was analyzed by GC and GC.MS as described earlier to show 69 (4%), 64 (24%),

65 (23%), 66b (15%), and 68 (25%). By the ^{13}C NMR-GC.MS method, the yields of 69, 64, and 65 were found to be 2%, 24%, and 24%, respectively.

To a solution of 0.255g (0.81mmole) of 63 in 10ml of pentane, freshly distilled from LAH, at -78°C was added dropwise 2.1ml of a 2.0M *t*-BuLi solution in pentane. White solid, presumably LiBr, appeared instantly. The resulting mixture was kept at -78°C for 5 days, during which time it was stirred for at least 8 hours per day. The mixture was then quenched by injecting all at once 0.5ml of MeOD directly into the well-stirred solution, followed by warming up to room temperature and the addition of 0.0374g of *p-di-t*-butylbenzene standard. The crude product mixture obtained after the usual work-up was analyzed with GC-GCMS as described earlier to show 69 (6%), 64 (21%), 65 (23%), 66b (36%), and 68 (6%). By the ^{1}H NMR-GC.MS method, the yields of 69, 64, and 65 were found to be 6%, 22%, and 24%.

Preparation of samples of 83 for ^{13}C NMR studies

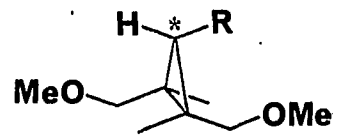
In a 5mm NMR tube were placed 0.05ml of d_6-benzene, 0.045g of 83, and 0.3ml of THF under a blanket of argon. After cooling to -78°C, 0.06ml of a 2.5M *n*-BuLi solution in hexane was added dropwise. The sample tube was then sealed with a torch. At the end of the ^{13}C NMR observation, the tube was opened and its contents poured into a well-stirred large excess of MeOH at -78°C. After warming up

to room temperature, the mixture was worked up as usual and analyzed by GC.MS, ^{1}H NMR, and ^{13}C NMR to confirm the major presence of 86a.

In a 5mm NMR tube were placed 0.039g of 83, 0.05ml of d_6-benzene and 0.15ml of THF under argon. After cooling to -78°C, 0.2ml (4 equivalents) of a 2.5M *n*-BuLi solution in hexane was added dropwise. The tube was then sealed with a torch. At the end of the ^{13}C NMR observation, the tube was opened and its contents poured into a well-stirred large excess of MeOD at -78°C. The usual work-up followed by GC.MS analysis of the crude showed the presence of 86b, 84, 85, and 87.

In a 25ml RB flask were placed 0.07g of 83, 0.05ml of d_6-benzene, and 0.2ml of THF under argon. After cooling to -78°C, 0.2ml of a 2.2M *t*-BuLi solution in pentane was added dropwise. The resulting mixture was transferred to a 5mm NMR tube via a 20-gauge 5in. long stainless steel tubing under a slight pressure of argon. The NMR tube was then sealed off with a torch. After the ^{13}C NMR observation had been completed, the tube was opened and its contents poured into a well-stirred large excess of MeOH at -78°C. The crude product obtained after the usual work-up was analyzed by GC.MS and ^{13}C NMR, and found to contain mainly 86a. About less than 1% of 89 and 88a were also detected.

In an apparatus described by Casey et al.[111] were



86a = R = Br
89 = R = H
88a = R = *t*-Bu

placed 0.035g of 83, 0.05ml of d_6-benzene, and 0.4ml of THF under argon. After cooling to -78°C, 0.3ml of a 2.2M *t*-BuLi solution in pentane was added dropwise. The mixture was then transferred into the NMR tube by the method given above, after which the tube was sealed with a torch. At the end of the ^{13}C NMR observation, the sample tube was opened and its contents poured into a well-stirred large excess of MeOD. The crude product obtained after the usual work-up was analyzed by GC.MS and ^{13}C NMR to which showed the presence of 89, 84, 85, and 88b.

Preparation of samples for ^{7}Li-decoupled ^{13}C NMR studies

In a 12mm NMR tube was placed 1ml of a solution of 0.791g (2.5mmole) of 83 in 5ml of 4:1 THF/d_8-THF. After cooling to -78°C, 0.2ml of a 2.5M *n*-BuLi solution in hexane were added dropwise. An additional 1.3ml of THF was then added. To eliminate the problem of vortex formation due to spinning, a supported glass float shown in Figure 18 was introduced, and the sample tube was sealed with a torch. ^{7}Li-decoupled ^{13}C NMR spectra were obtained on a Varian XL-100 spectrometer at 25.2 MHz, with the decoupling power set at 12 watts at 38.887197 MHz[112].

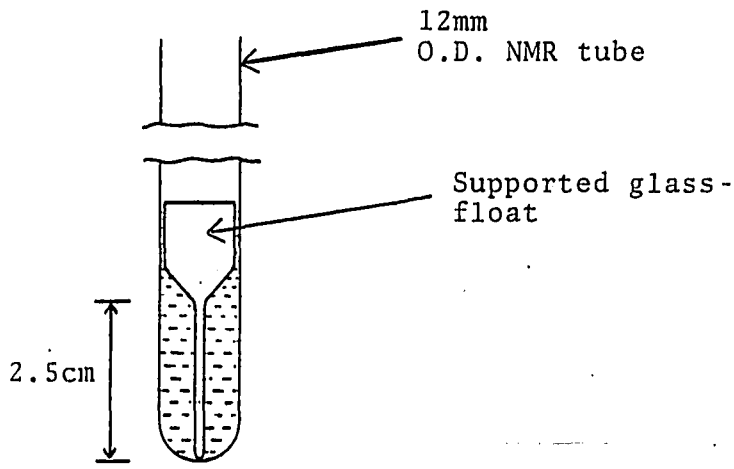


Figure 18. Sample tube for the ^{7}Li-decoupled ^{13}C NMR

In a 12mm NMR tube was placed 1ml of a solution prepared from 0.791g of 83 and 5ml of 4:1 THF/d_8-THF. After cooling to -78°C, 0.2ml of a 2.5M *n*-BuLi solution in hexane was added. While the mixture was stirred with a glass rod, 1ml of a 2M *t*-BuLi solution in pentane was added dropwise. A supported glass-float was then inserted, and the tube sealed with a torch. ^{7}Li-decoupled ^{13}C NMR were obtained with a broad band decoupling frequency of 38.887197 MHz and a power of 8 watts[112].

Preparation of samples for ^{7}Li NMR

In a 10mm NMR tube were placed 0.234g (0.74mmole) of 63, 1.5ml of THF and 0.25ml of d_6-benzene. After cooling to -78°C, 0.3ml of a 2.5M *n*-BuLi solution in hexane was

added. The tube was capped and sealed with parafilm. ^{7}Li NMR spectra were immediately taken on a Bruker WM300 Spectrometer at 116.644 MHz.

In a 10mm NMR tube were placed 0.244g (0.77mmole) of 63, 1ml of THF, and 0.25ml of d_6-benzene. After cooling to -78°C, 0.6ml of a 2.5M *n*-BuLi solution was added dropwise. The tube was capped and sealed with parafilm. ^{7}Li NMR spectra were immediately taken as before.

In a 10mm NMR tube were placed 0.236g (0.74mmole) of 63, 1ml of THF, and 0.25ml of d_6-benzene. After cooling to -78°C, 0.6ml of a 2M *t*-BuLi in pentane was added slowly with vigorous shaking. The tube was capped and sealed with parafilm. ^{7}Li NMR spectra were immediately taken as before.

In a 10mm NMR tube were placed 0.132g (0.42mmole) of 63, 0.7ml of THF, and 0.25ml of d_6-benzene. After cooling to -78°C, 1ml of a 2M *t*-BuLi solution in pentane was added slowly with vigorous shaking. The tube was capped and sealed with parafilm. ^{7}Li NMR spectra were immediately taken as before.

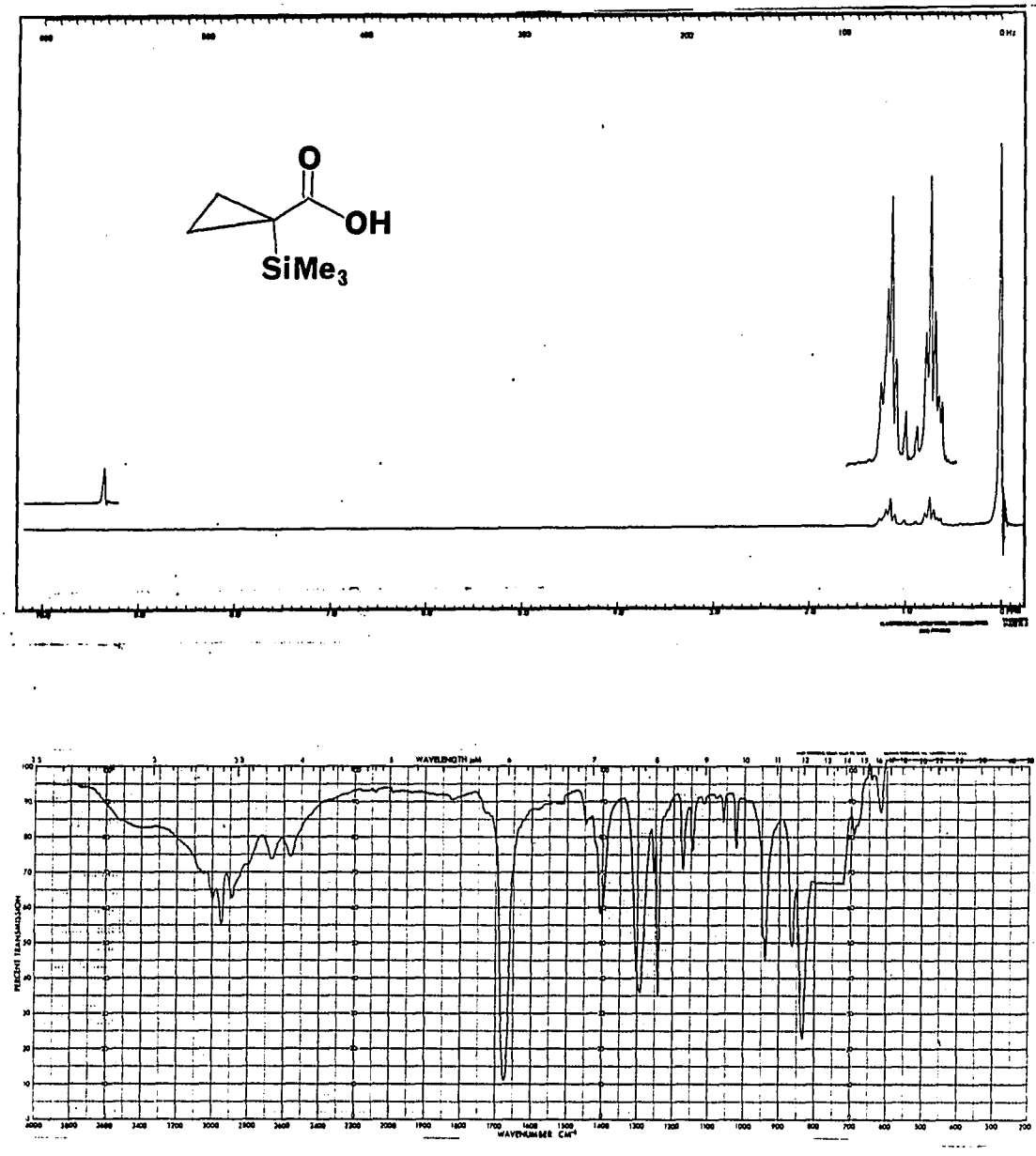


Figure 19. ^1H NMR (CCl_4) and IR (CCl_4) of 1-Trimethysilyl-cyclopropanecarboxylic acid, 32

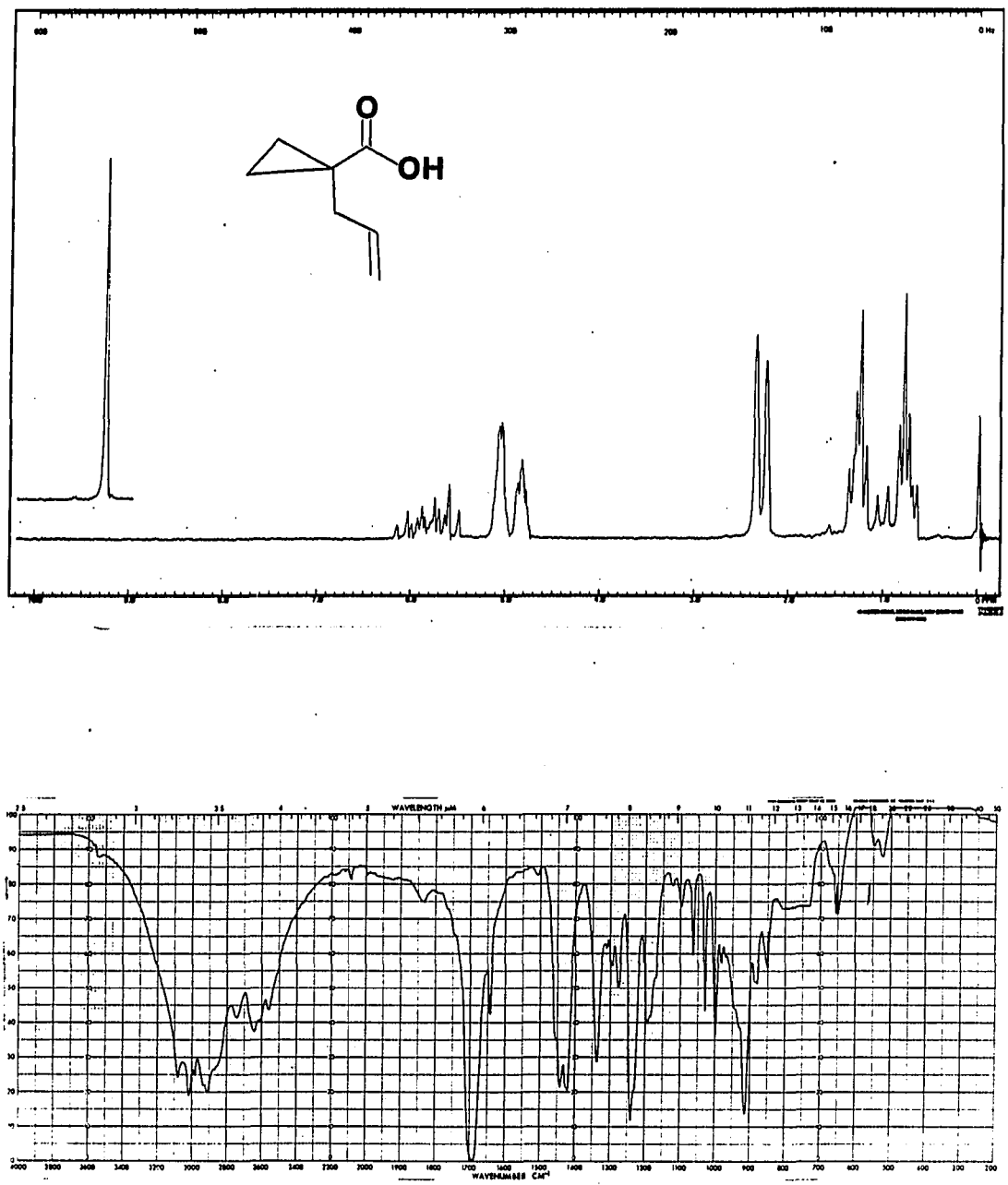
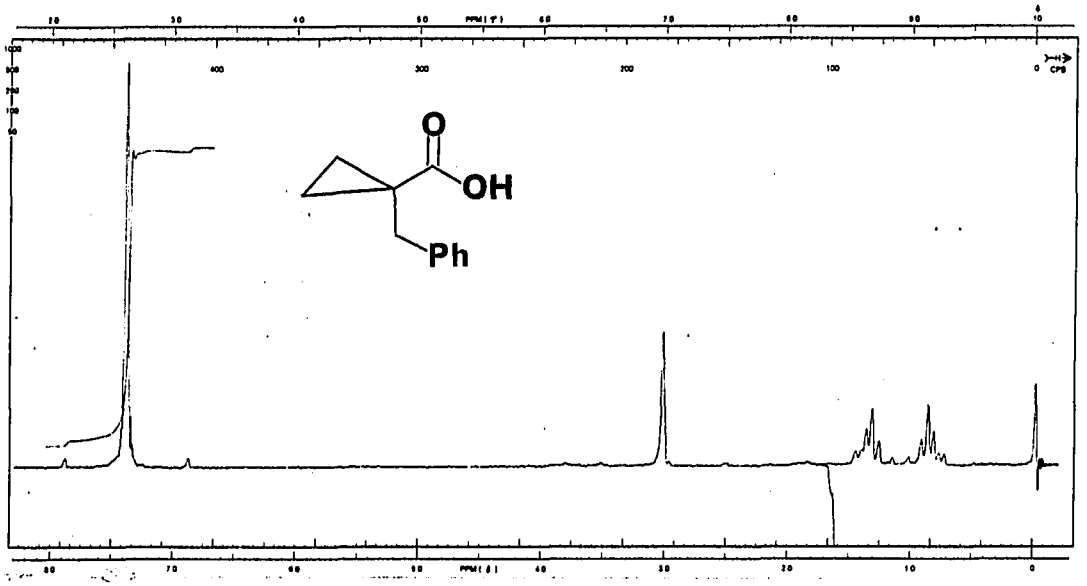


Figure 20. ^{1}H NMR (CCl_4) and IR (CCl_4) of 1-Allylcyclopropanecarboxylic acid, 34



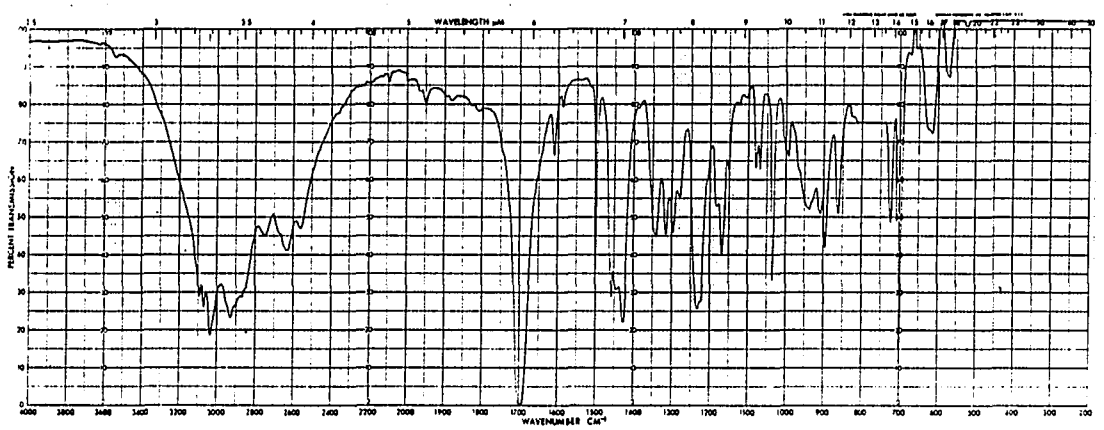
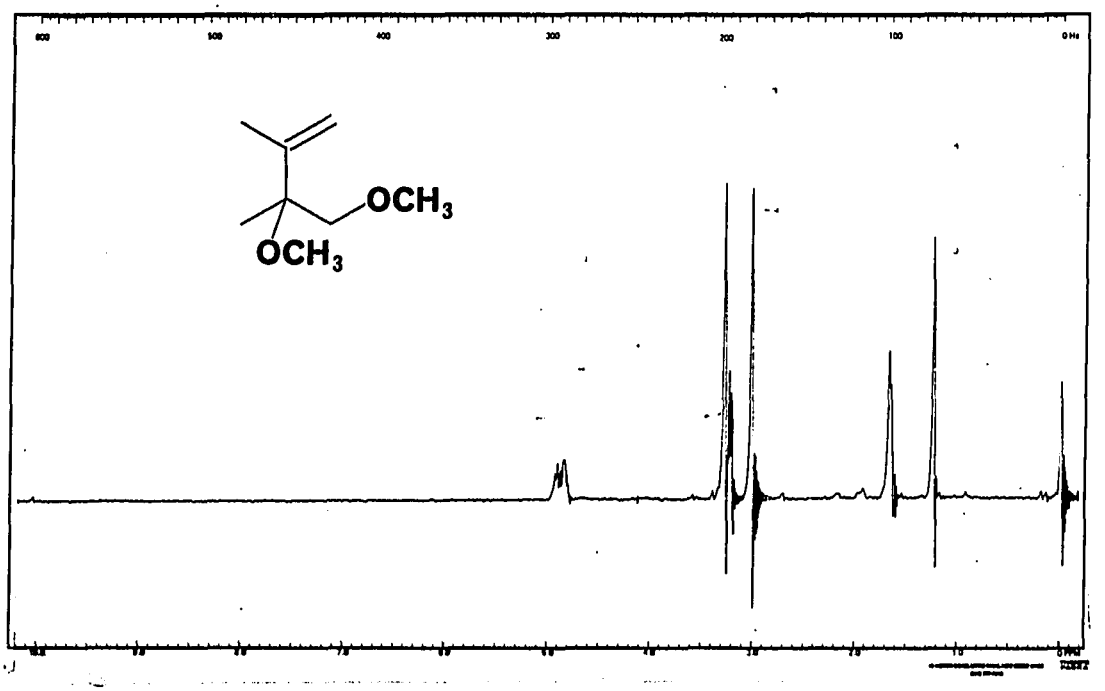


Figure 21. ^1H NMR (CCl_4) and IR (CCl_4) of 1-Benzylcyclopropanecarboxylic acid, 35



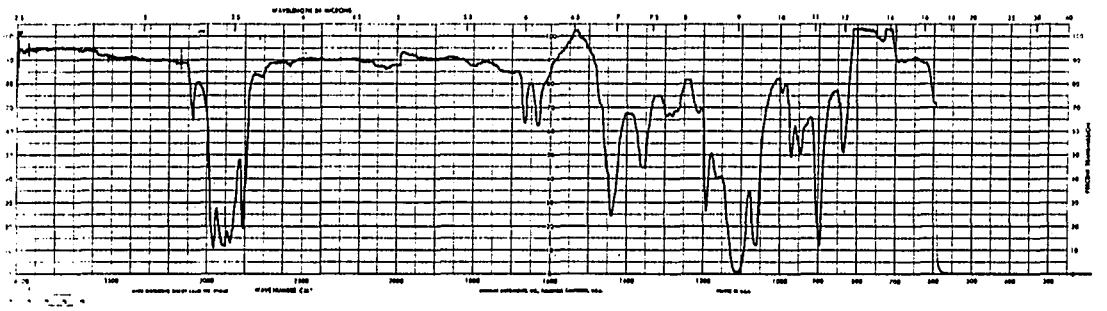


Figure 22. ^1H NMR (CCl_4) and IR (CCl_4) of 2,3-Dimethyl-3,4-dimethoxy-1-butene, 61

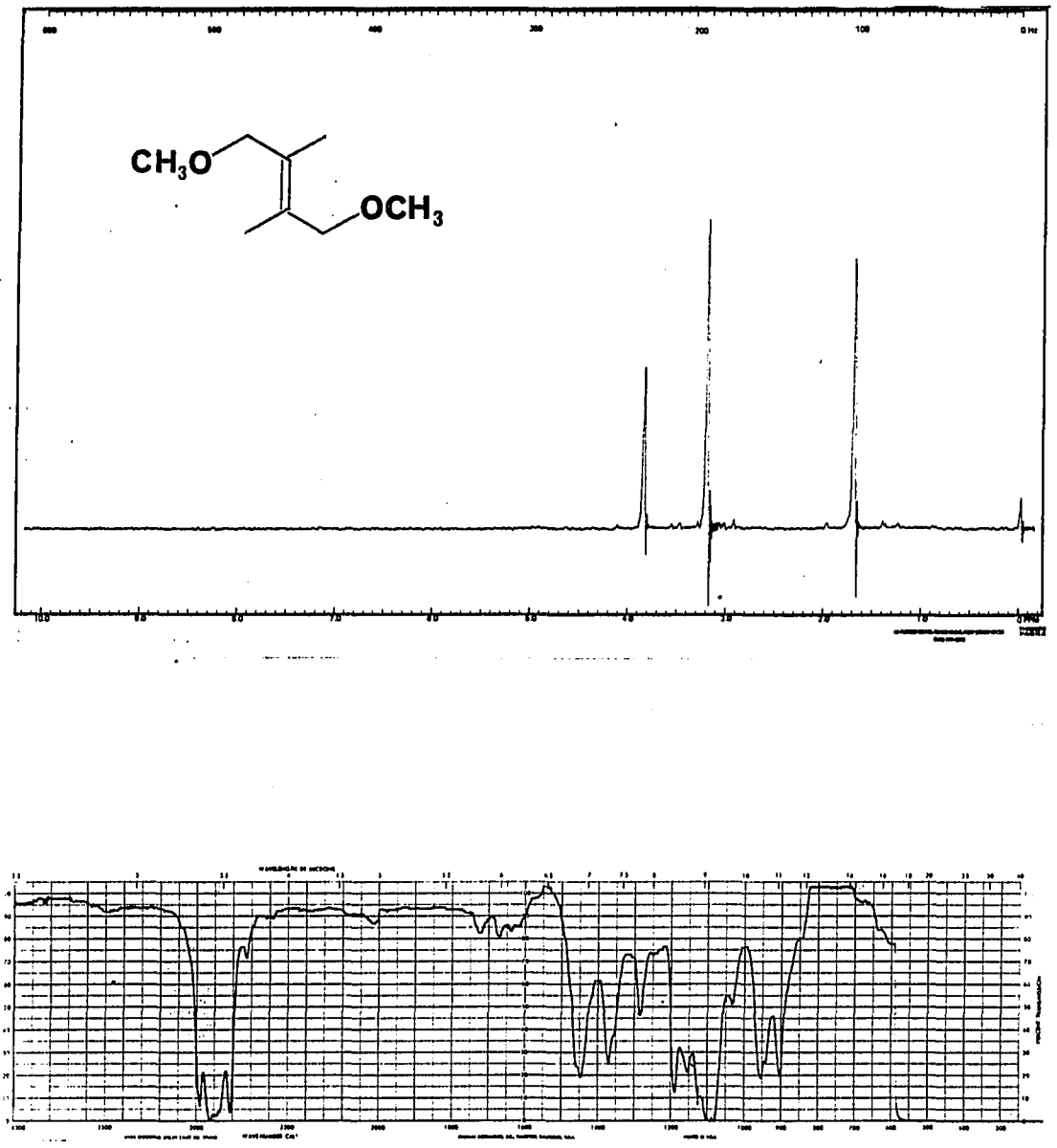


Figure 23. ^{1}H NMR (CCl_4) and IR (CCl_4) of 1,4-Dimethoxy-2,3-*trans*-dimethyl-2-butene, 62

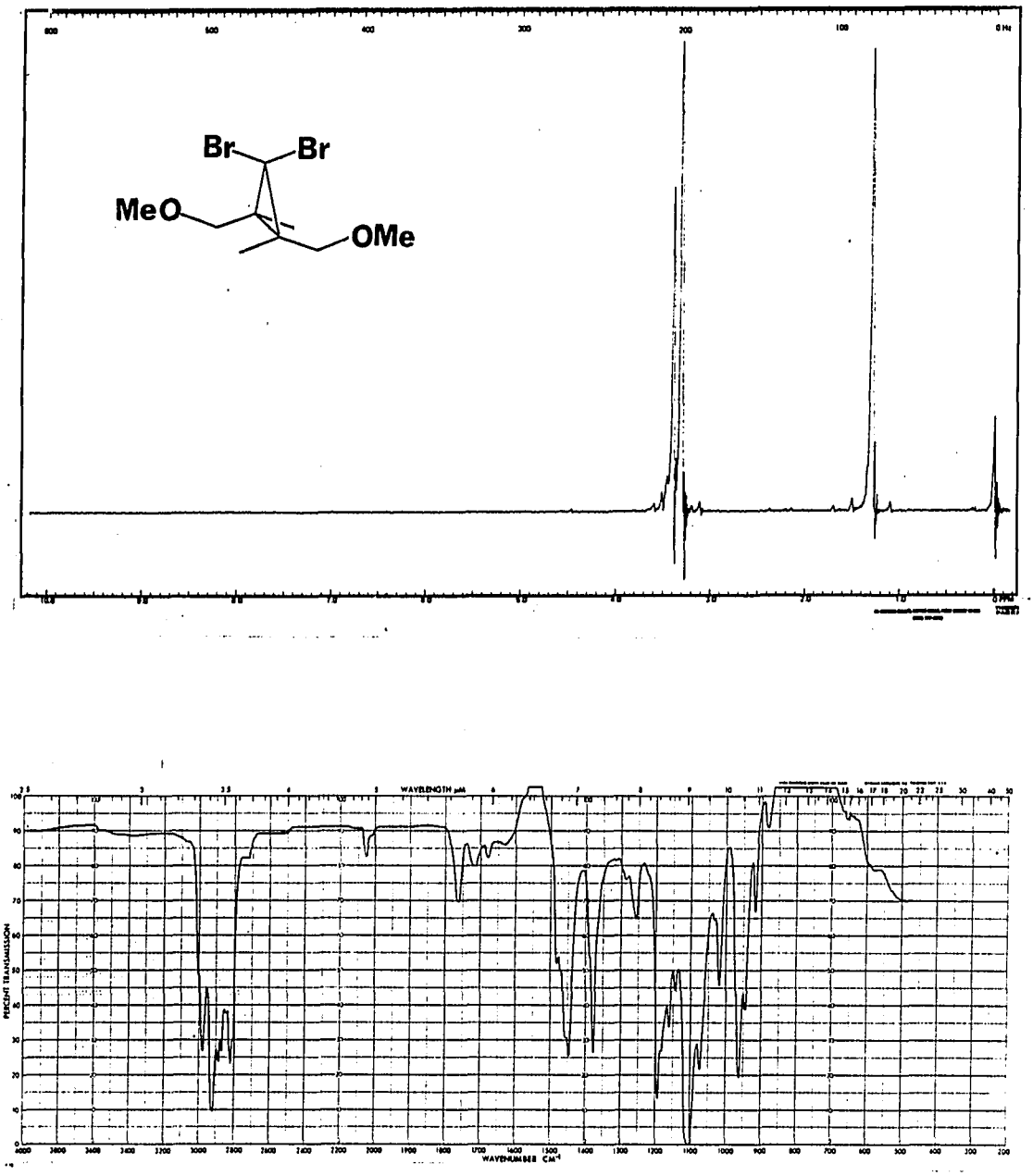
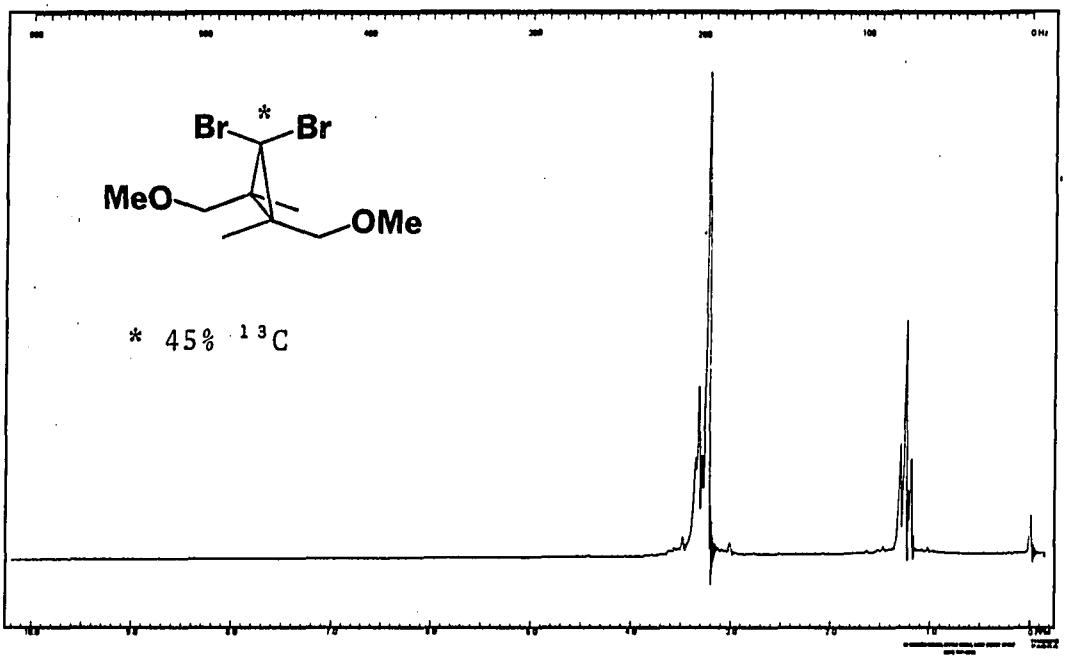


Figure 24. ^{1}H NMR (CCl_4) and IR (CCl_4) of 1,1-Dibromo-2,3-*trans*-dimethoxymethyl dimethylcyclopropane



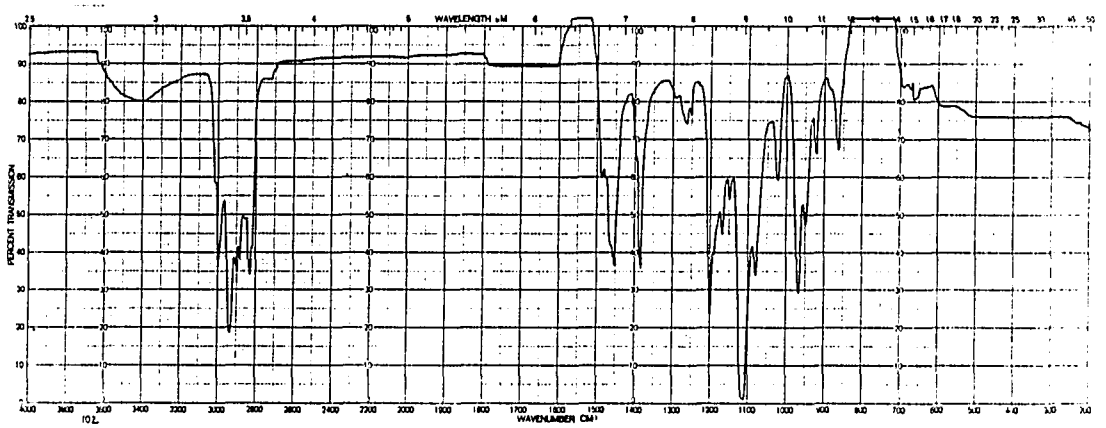


Figure 25. ^{1}H NMR (CCl_4) and IR (CCl_4) of 1-^{13}C-1,1-Dibromo-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 83

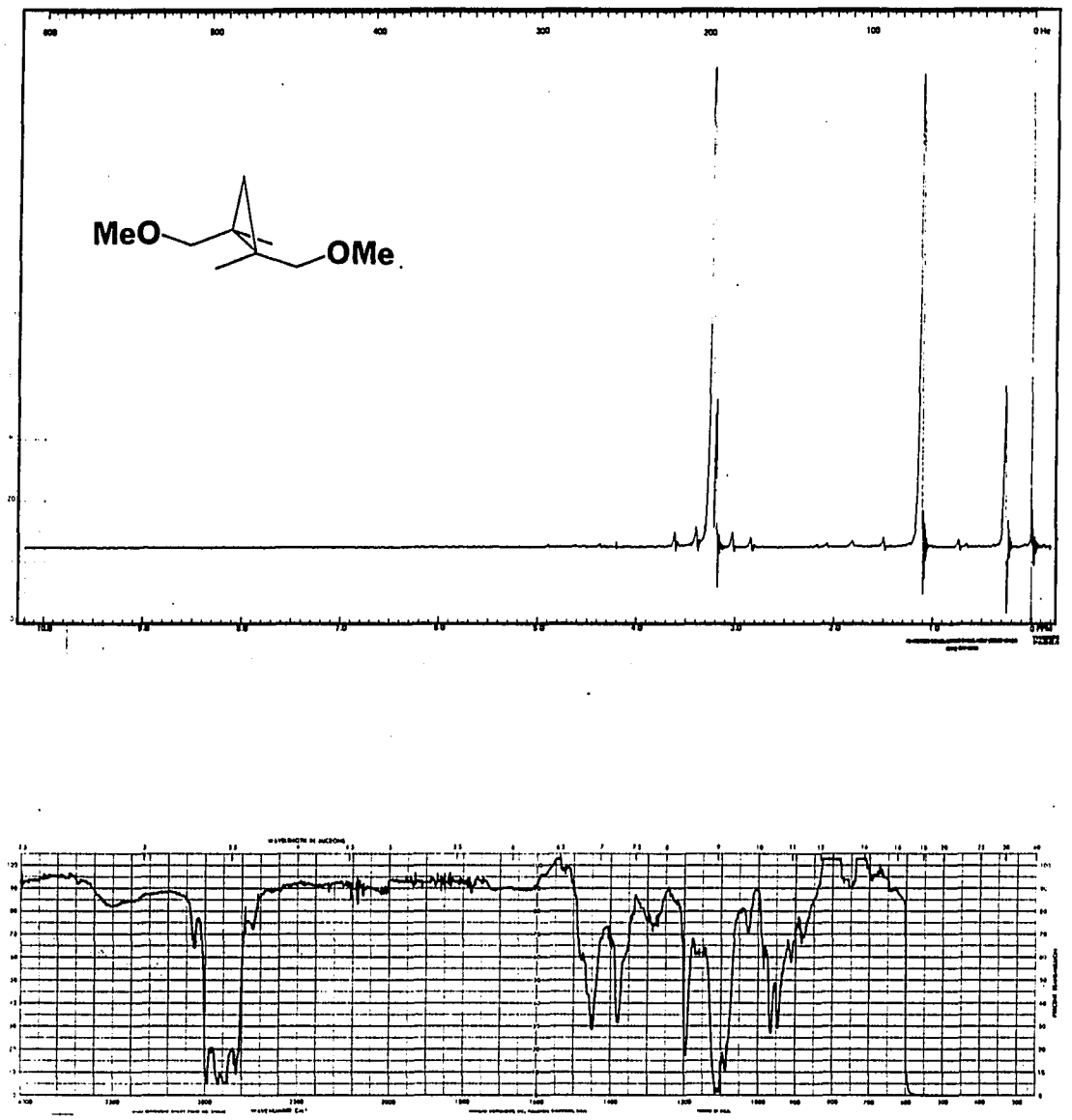


Figure 26. ^1H NMR (CCl_4) and IR (CCl_4) of 1,2-*trans*-Dimethoxymethyl-1,2-dimethylcyclopropane, 69

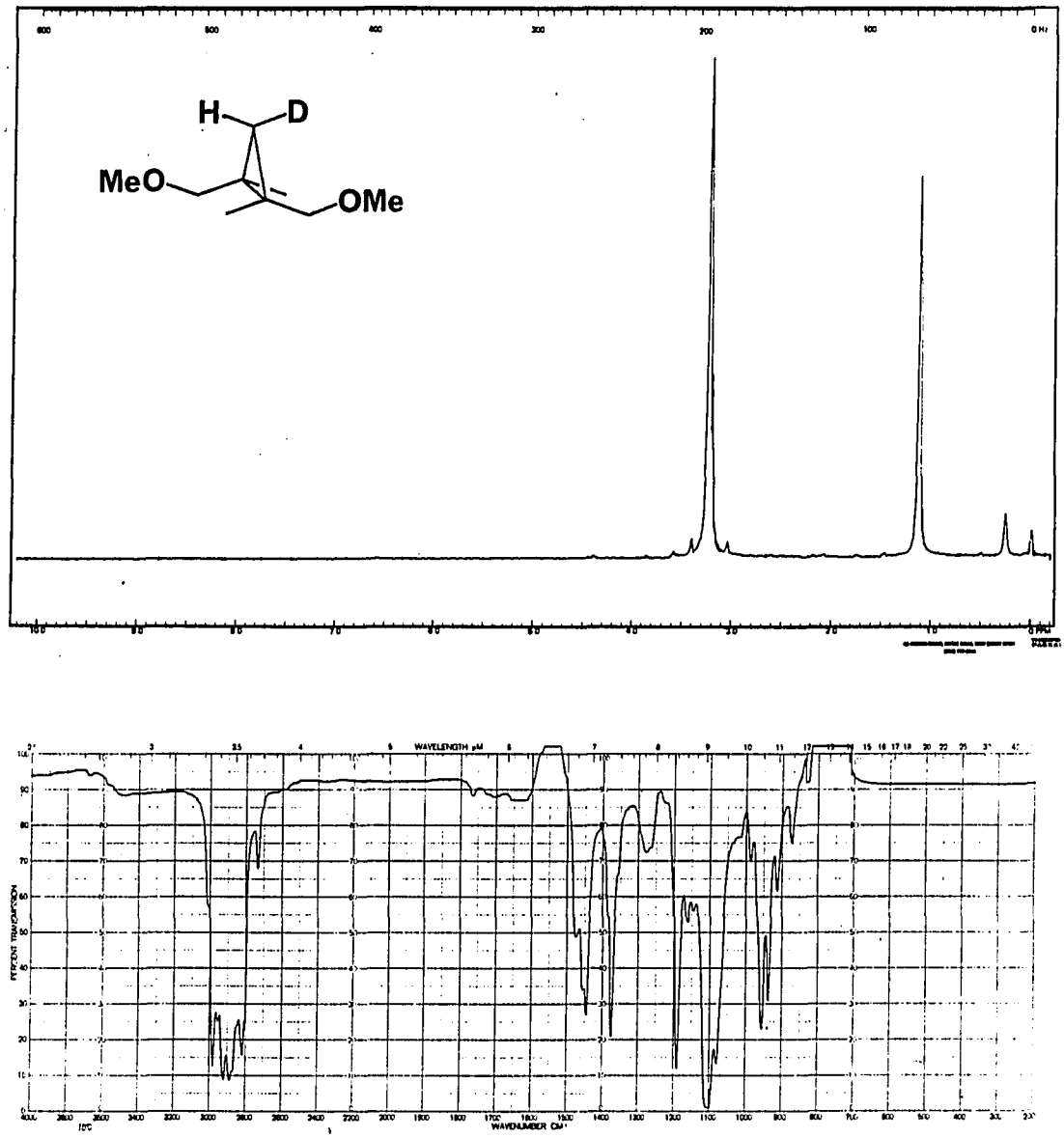


Figure 27. ^1H NMR (CCl_4) and IR (CCl_4) of 1-Deutero-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane, 64

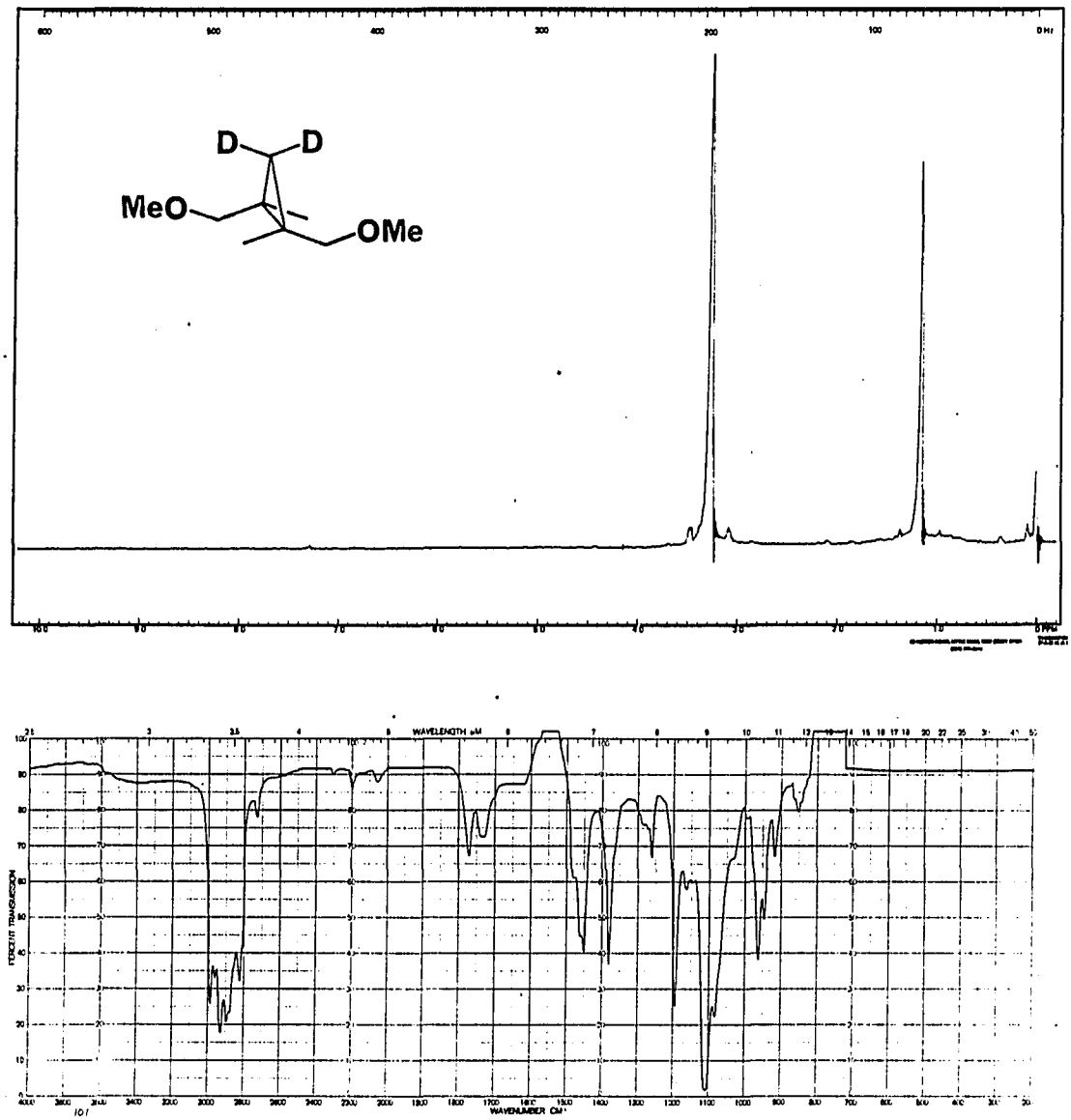


Figure 28. ^1H NMR (CCl_4) and IR (CCl_4) of 1,1-Dideutero-2,3-*trans*-dimethoxymethyl dimethylcyclopropane, 65

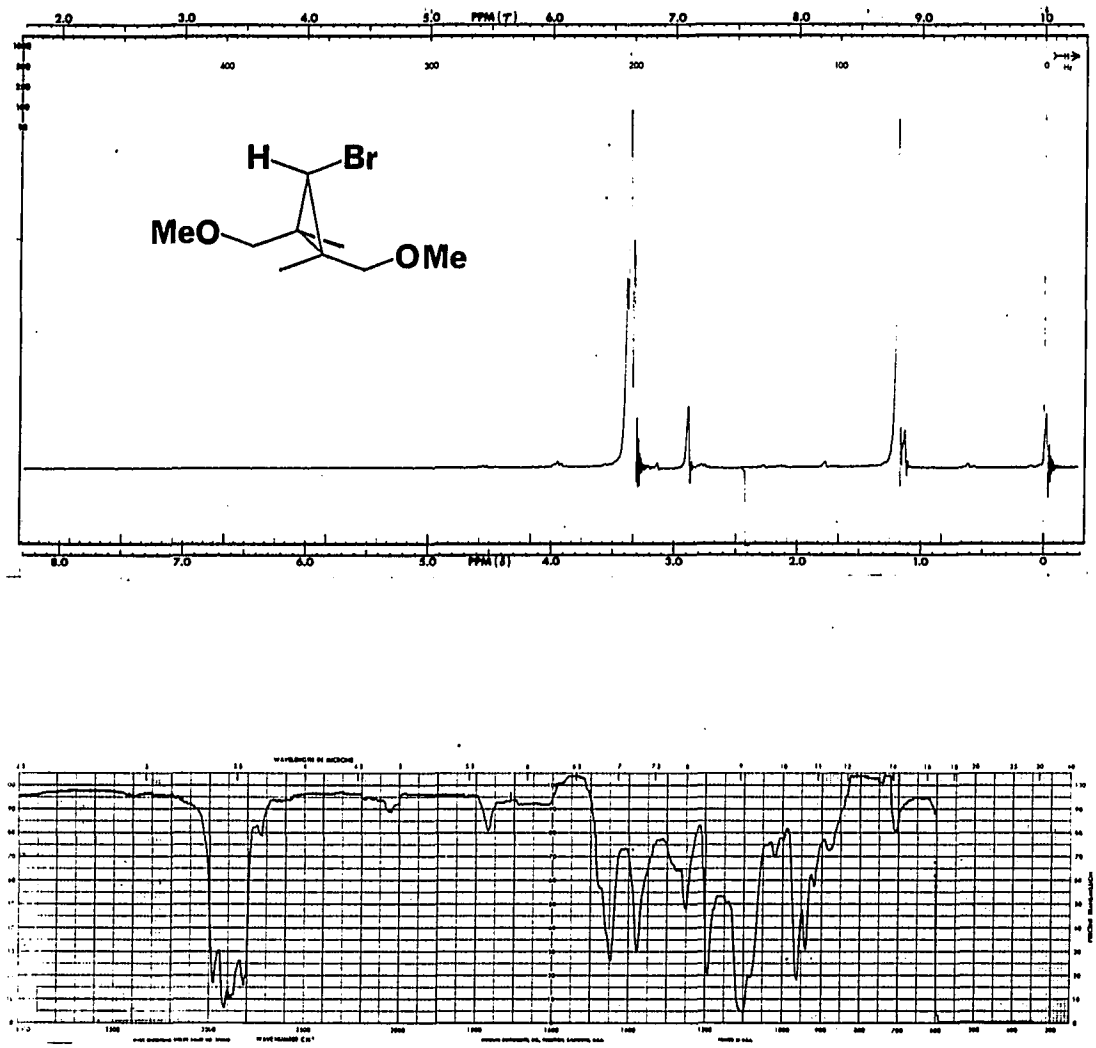
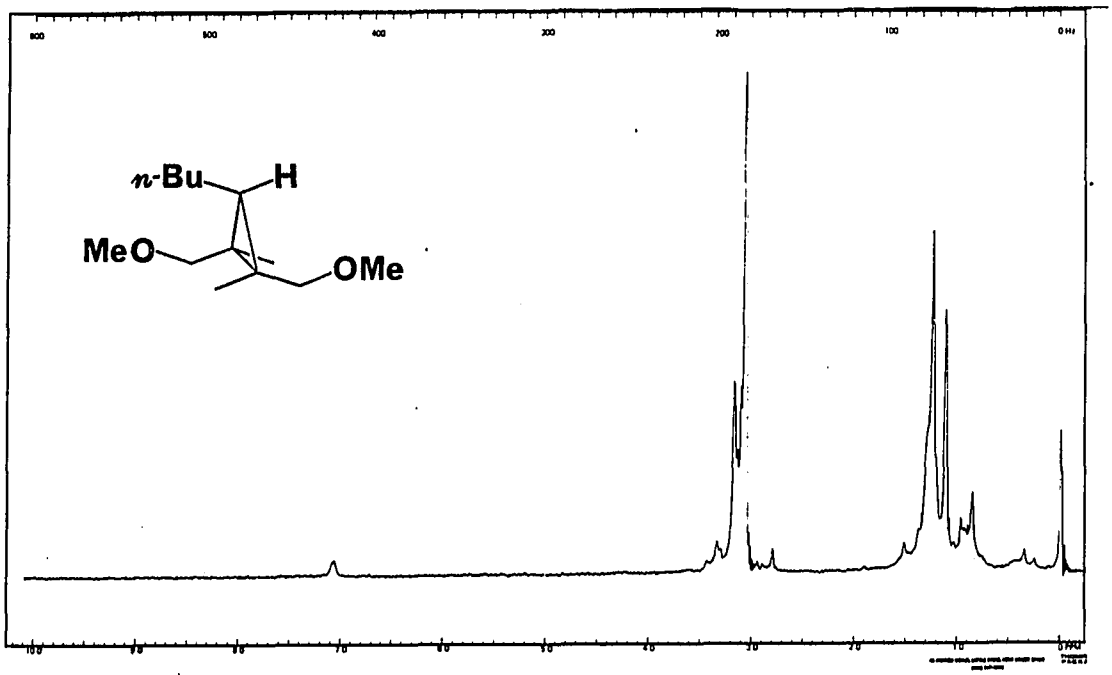


Figure 29. ^1H NMR (CCl_4) and IR (CCl_4) of 1-Bromo-2,3-*trans*-dimethoxymethyl dimethylcyclopropane, 66a



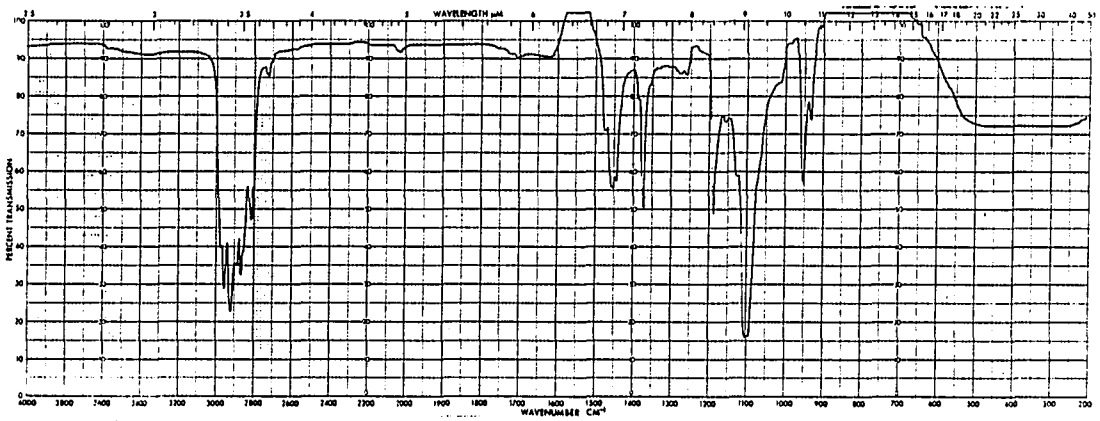
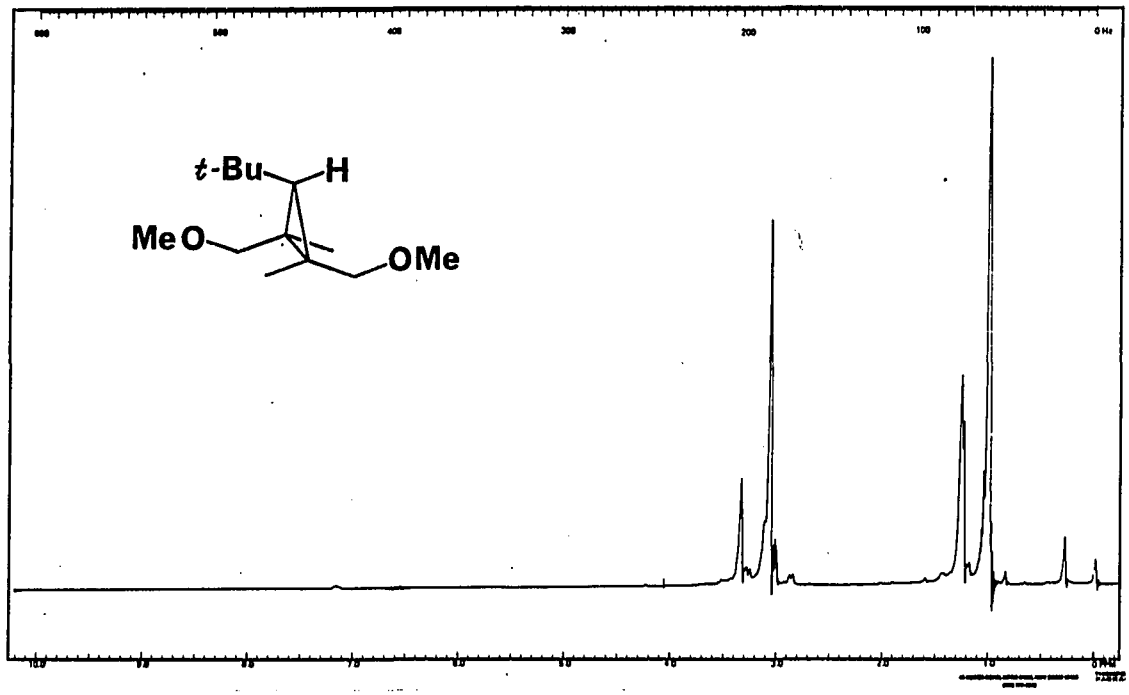


Figure 30. ^{1}H NMR (CCl_4) and IR (CCl_4) of 1-*n*-Butyl-2,3-*trans*-dimethoxymethyl dimethylcyclopropane, 67a



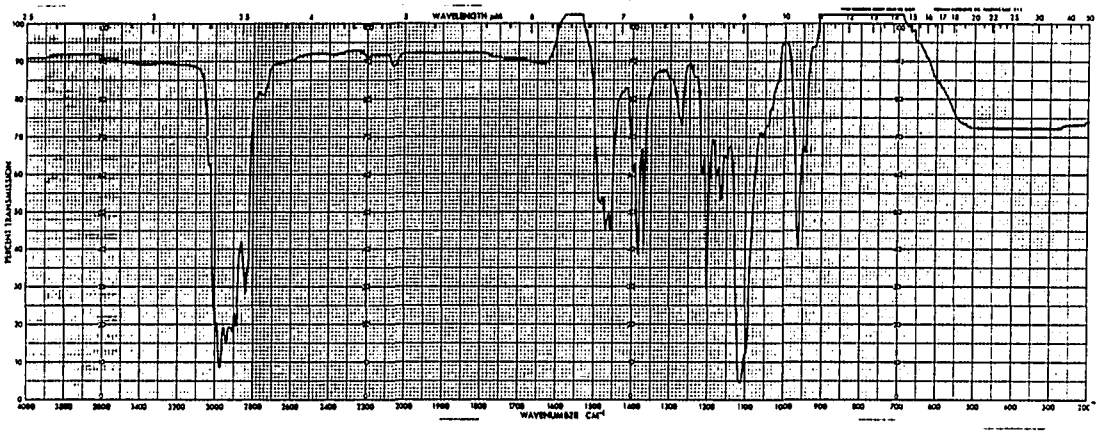


Figure 31. ^{1}H NMR (CCl_4) and IR (CCl_4) of 1-*t*-Butyl-2,3-*trans*-dimethoxymethyl dimethylcyclopropane, 68a

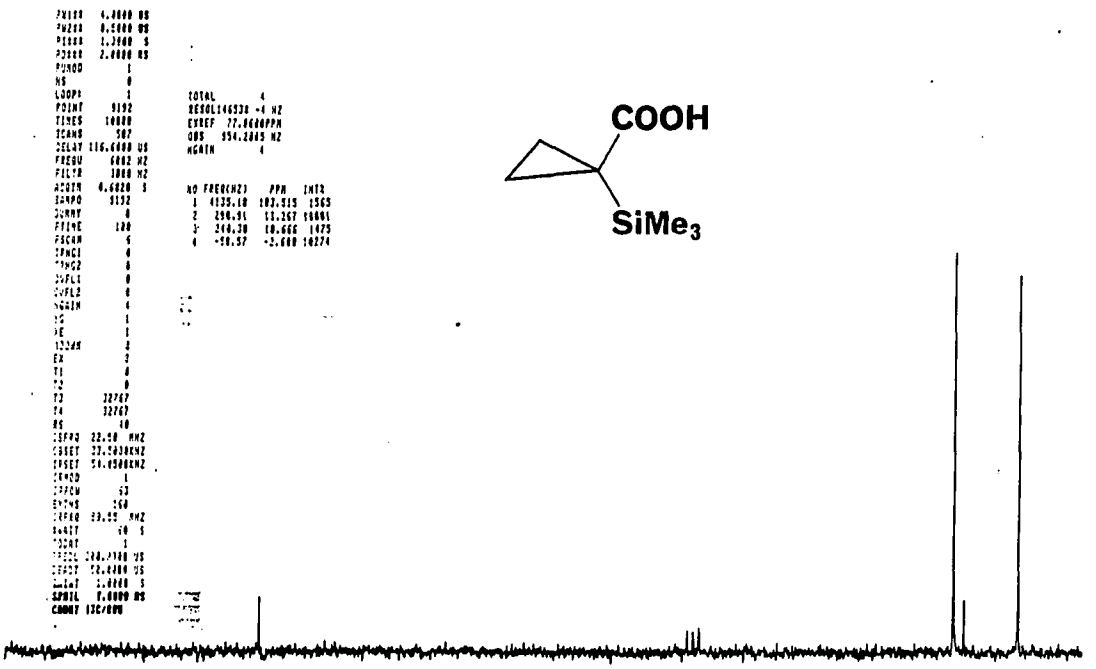


Figure 32. ^{13}C NMR ($CDCl_3$) of 1-Trimethylsilylcyclopropanecarboxylic acid, 32

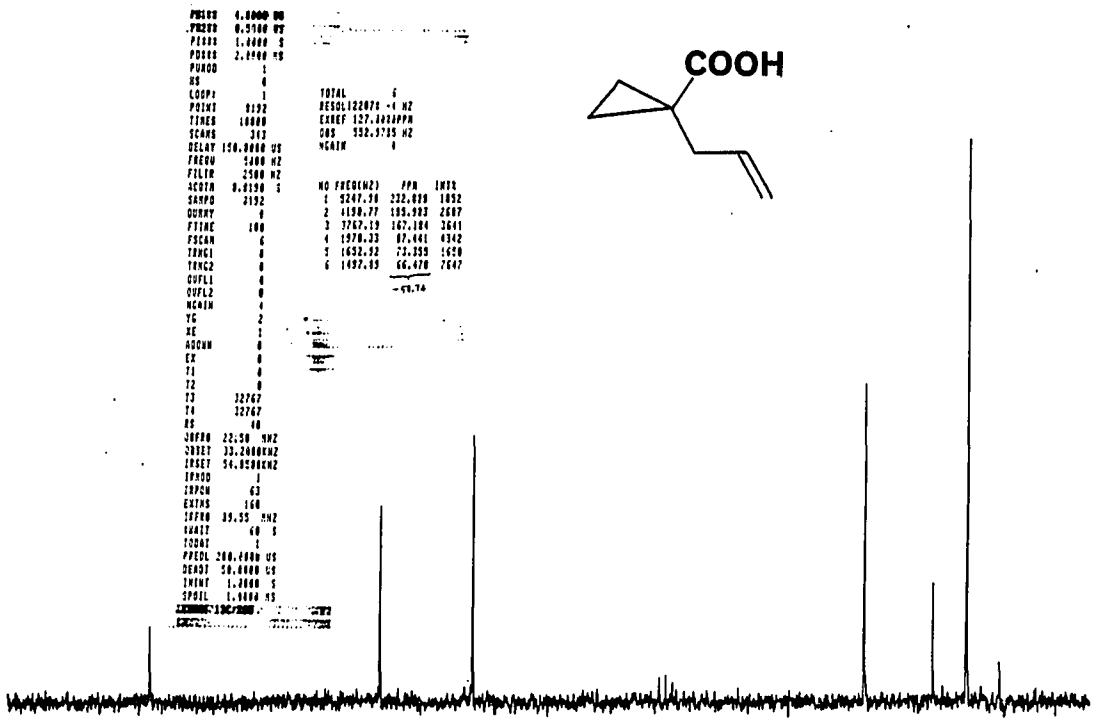


Figure 33. ^{13}C NMR ($CDCl_3$) of 1-Allylcyclopropanecarboxylic acid, 34

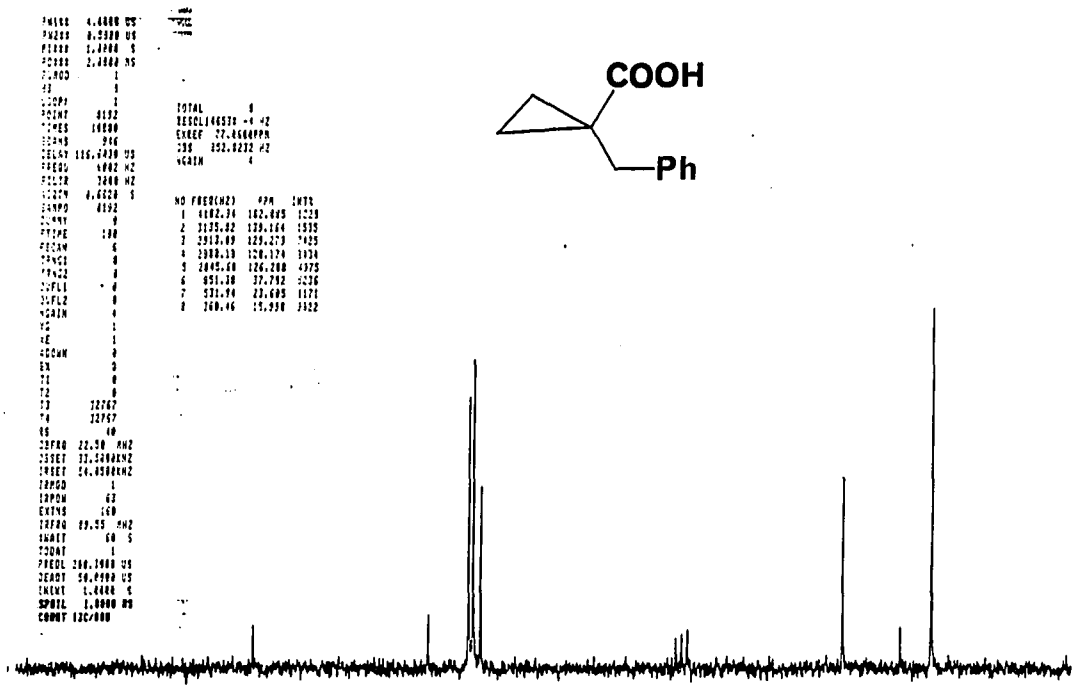


Figure 34. ^{13}C NMR ($CDCl_3$) of 1-Benzylcyclopropane-carboxylic acid, 35

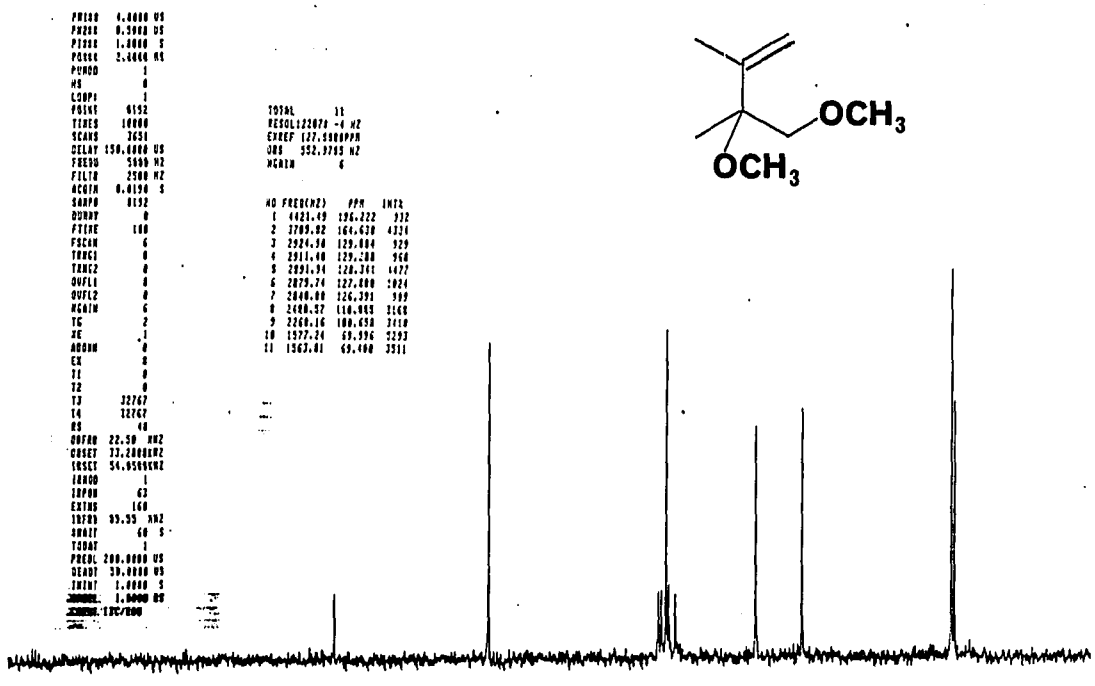


Figure 35. ^{13}C NMR ($CDCl_3$) of 2,3-Dimethyl-3,4-dimethoxymethyl-1-butene, 61

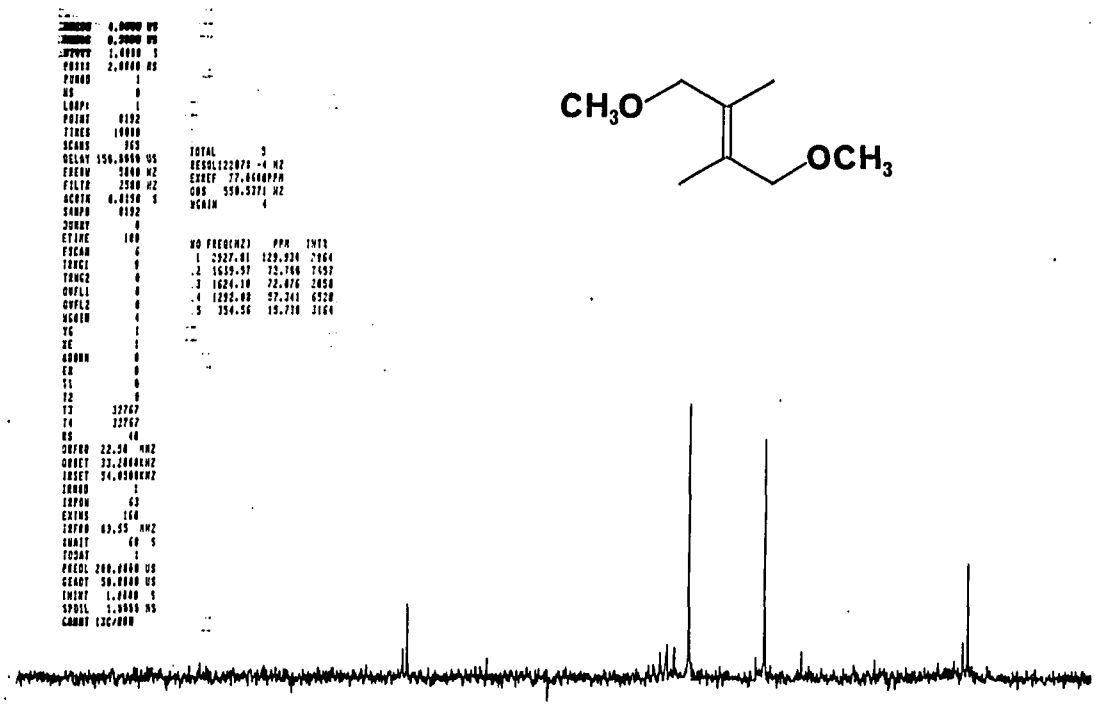


Figure 36. ^{13}C NMR ($CDCl_3$) of 2,3-*trans*-Dimethyl-1,4-dimethoxy-2-butene, 62

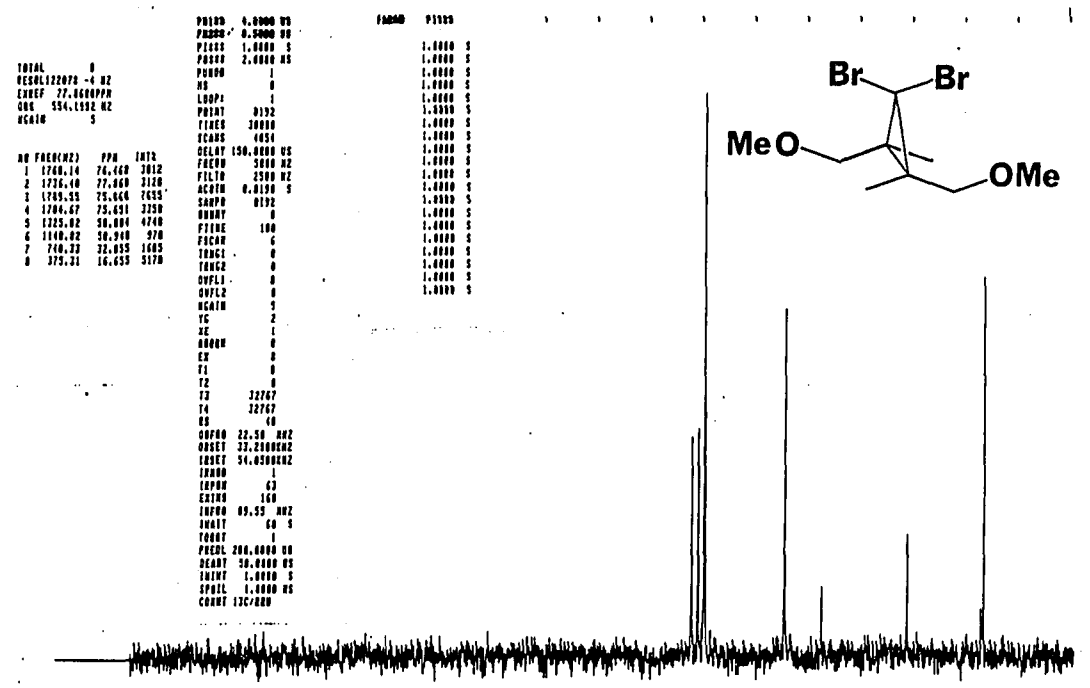


Figure 37. ^{13}C NMR ($CDCl_3$) of 1,1-Dibromo-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 63

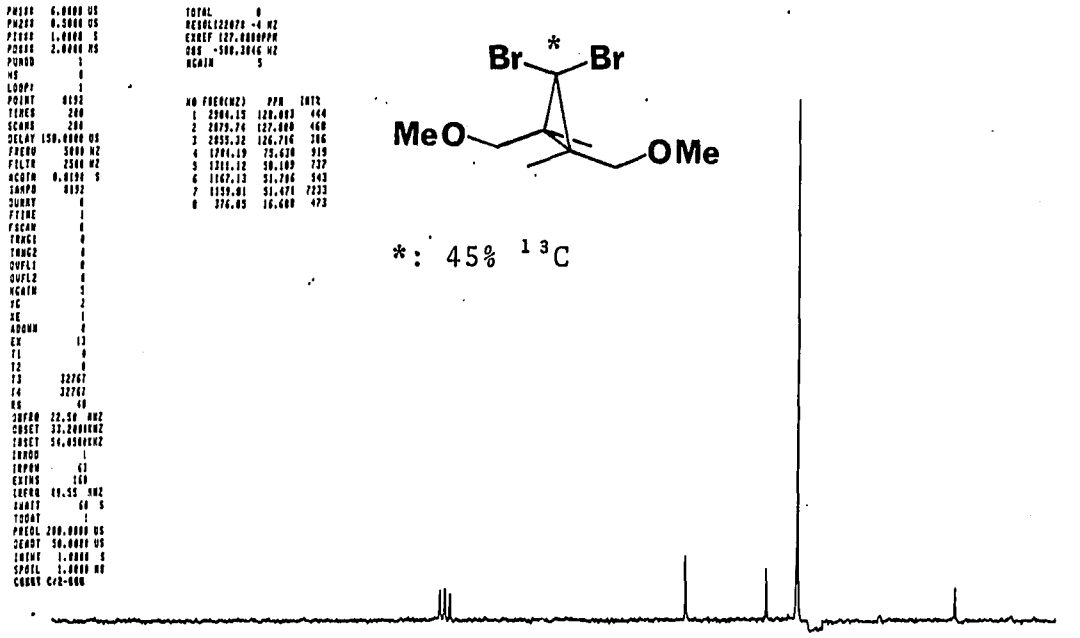


Figure 38. ^{13}C NMR (d_6-Benzene) of 1-^{13}C-1,1-Dibromo-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 83

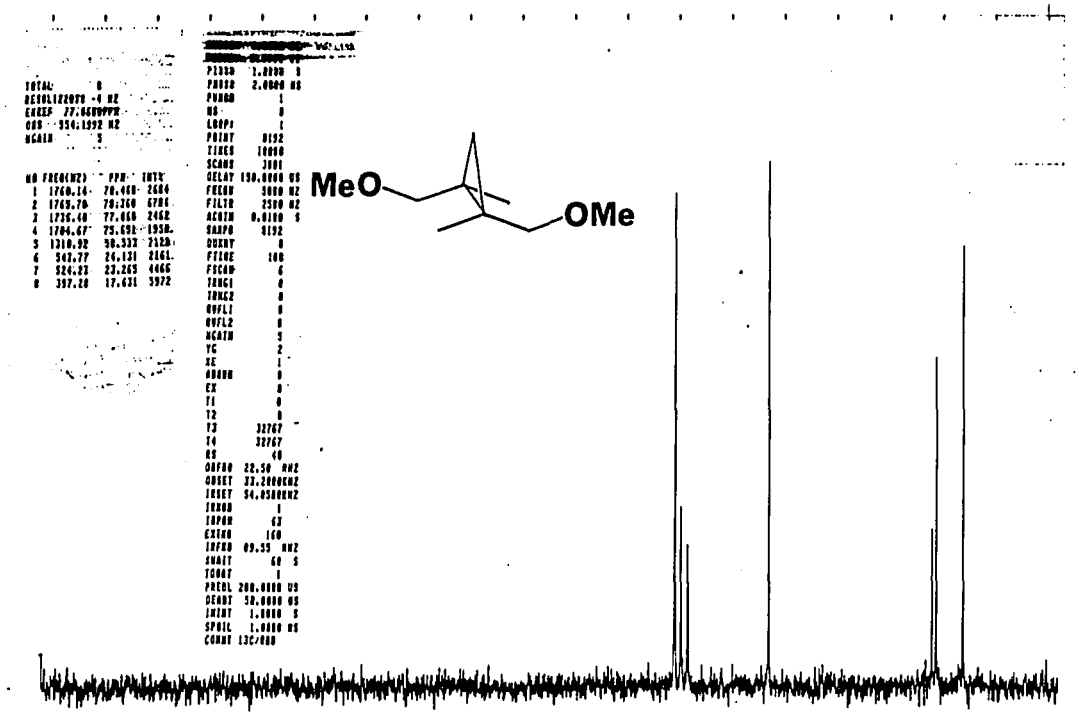


Figure 39. ^{13}C NMR ($CDCl_3$) of 1,2-*trans*-dimethoxymethyl-1,2-dimethylcyclopropane, 69

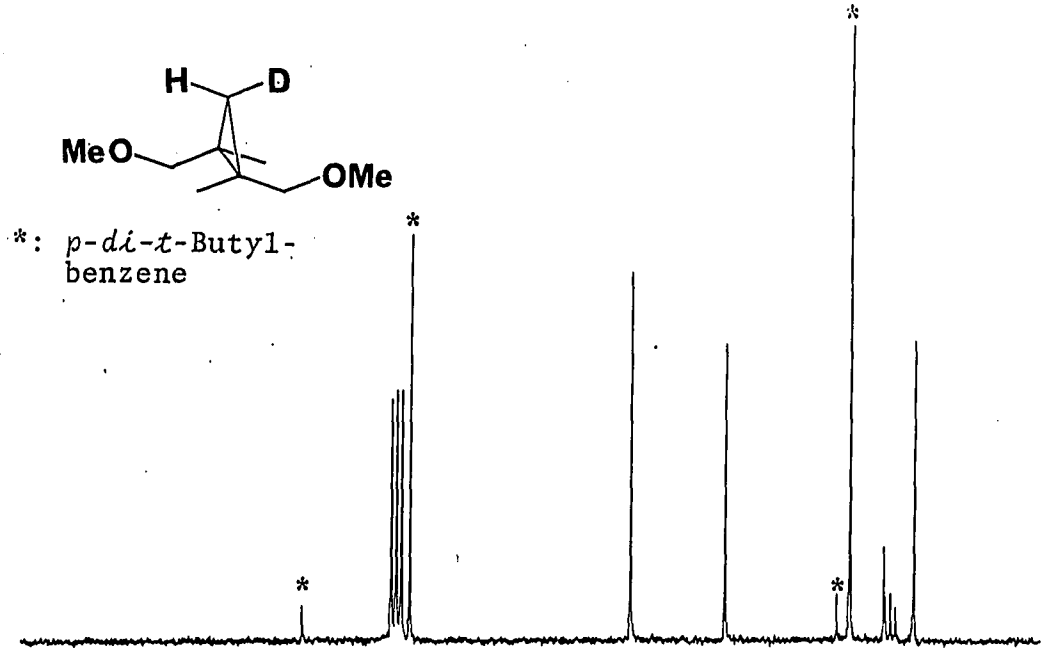


Figure 40. ^{13}C NMR (d_6-Benzene) of 1-Deutero-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 64, and *p-di-t*-Butylbenzene

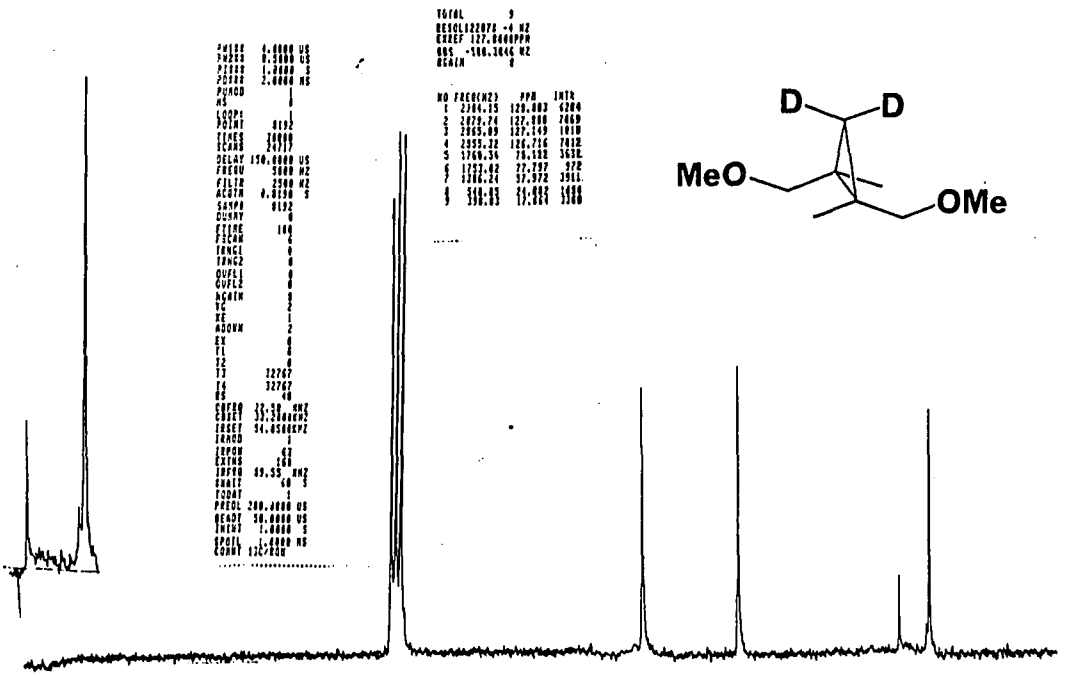


Figure 41. ^{13}C NMR (d_6-benzene) of 1,1-Dideutero-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 65

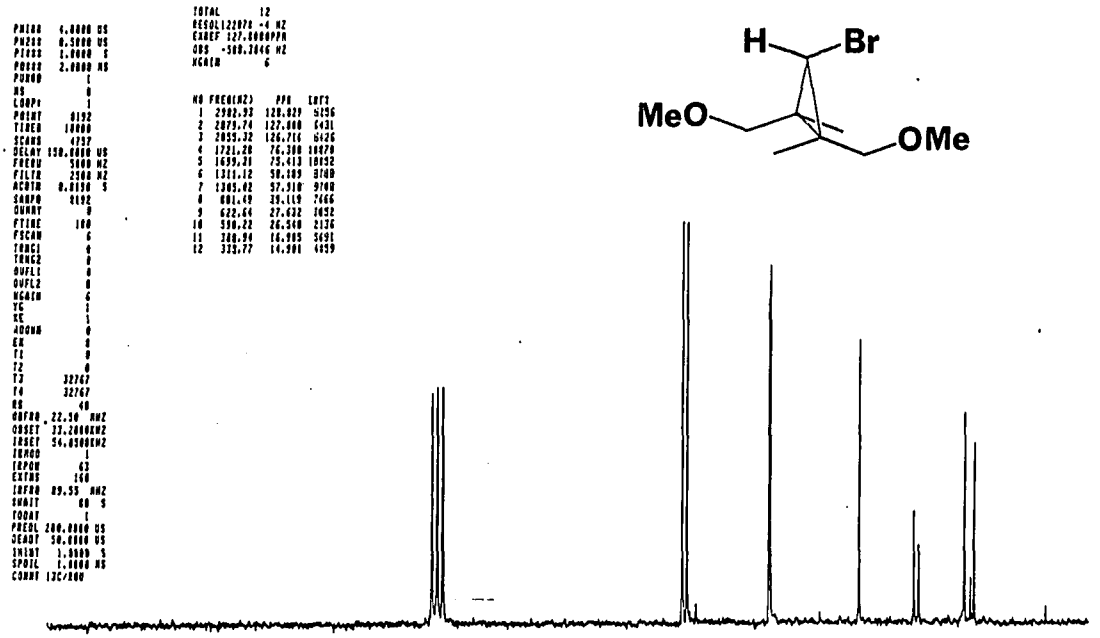


Figure 42. ^{13}C NMR (d_6-Benzene) of 1-Bromo-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 66a

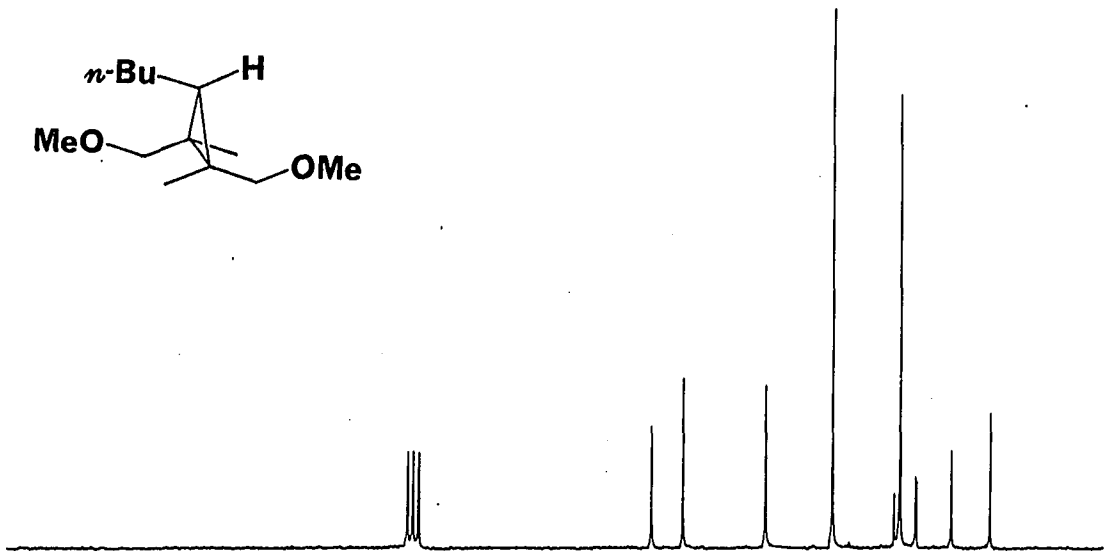


Figure 43. ^{13}C NMR (d_6-Benzene) of 1-*n*-Butyl-*trans*-2,3-dimethoxymethyl-2,3-dimethylcyclopropane, 67a

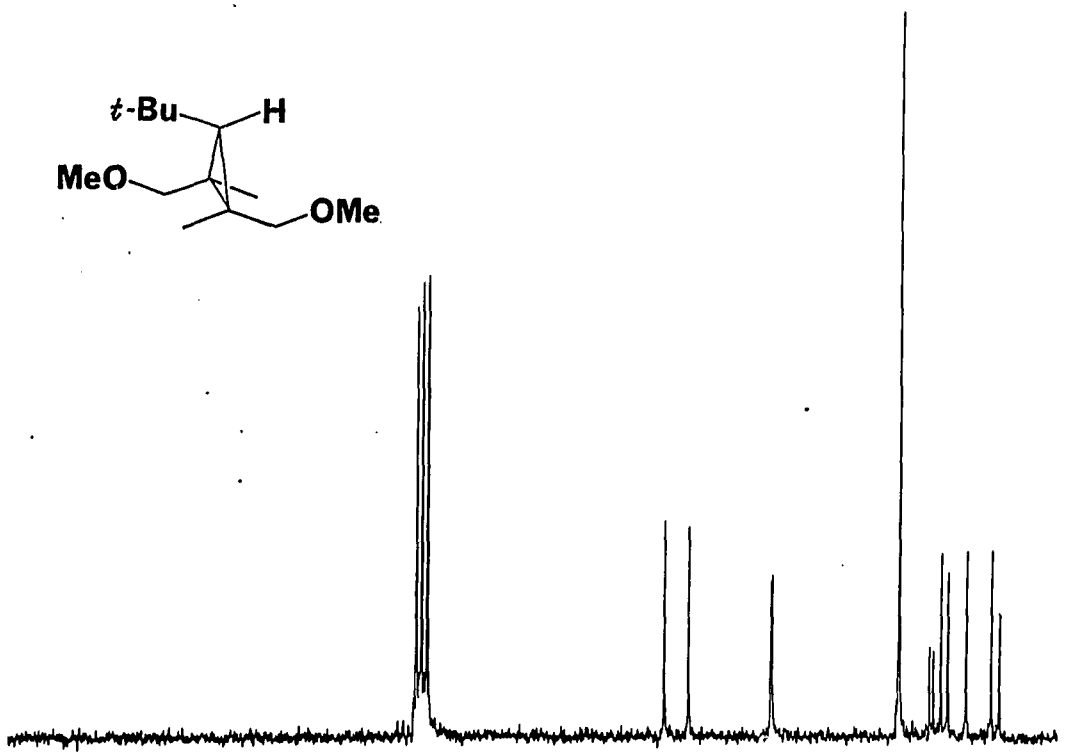
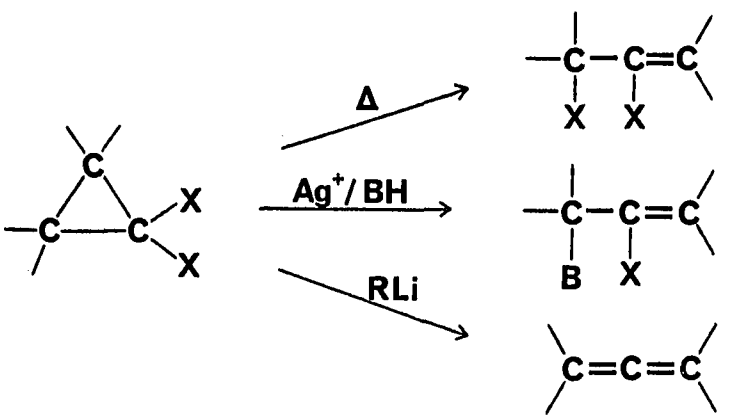


Figure 44. ^{13}C NMR (d_6-Benzene) of 1-*t*-Butyl-2,3-*trans*-dimethoxymethyl-2,3-dimethylcyclopropane, 68a

II. A METHOD FOR THE SYNTHESIS OF FUNCTIONALIZED 2,4-DIMETHYL-1,3-PENTADIENES

INTRODUCTION

Ring opening reactions of cyclopropyl halides have been mostly studied using *gem*-dihalo compounds[113]. Under thermal or solvolytic conditions, the reactions afforded allylic derivatives and, occasionally, 1,3-dienes[113a]. By treatment with alkali or alkaline metals or alkyllithiums, allenes and, in the presence of appropriate vinyl substituents, novel products from rearrangement[114] were obtained. Alkoxy derivatives of *gem*-dihalocyclopropanes have been

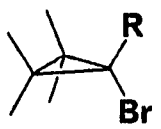


reported to give alkynes when solvents with appropriate nucleophilic reagents[113a] are used.

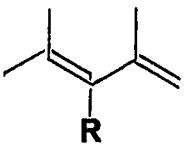
Monohalocyclopropanes undergo similar ring opening reactions during solvolyses or thermolyses[113c,115] to provide olefinic derivatives. The mode of ring opening relative to the orientation of the halogen has been

extensively investigated[116].

It was observed that G.C. traces of mixtures containing monobromide 41a, or its alkyl derivatives, 42a, 51a, and 53a, always showed an extra peak which had a molecular weight corresponding to the loss of HBr from the monobromide (see Part I). Apparently, the monobromide had



41a, R = H
42a Me
51a *n*-Bu
53a *t*-Bu



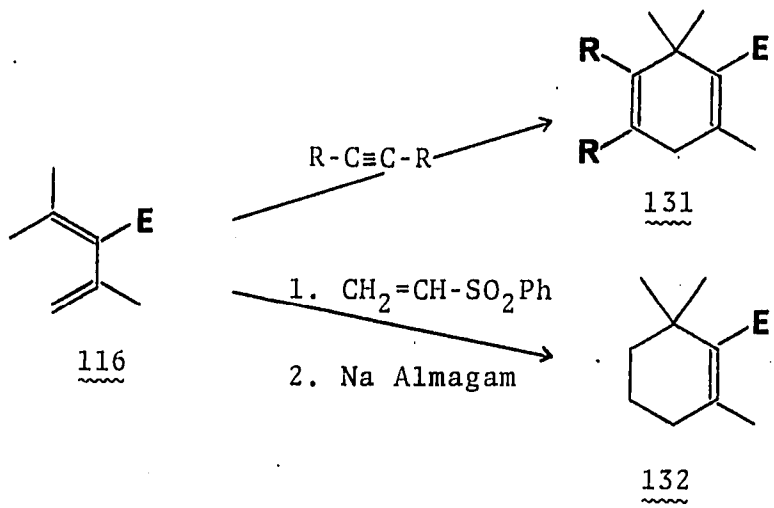
117, R = H
118 Me
119 *n*-Bu
120 *t*-Bu

undergone dehydrohalogenation following ring opening to give the corresponding 1,3-diene, 101[117]. This interpretation was found to be correct, as described in the following section.

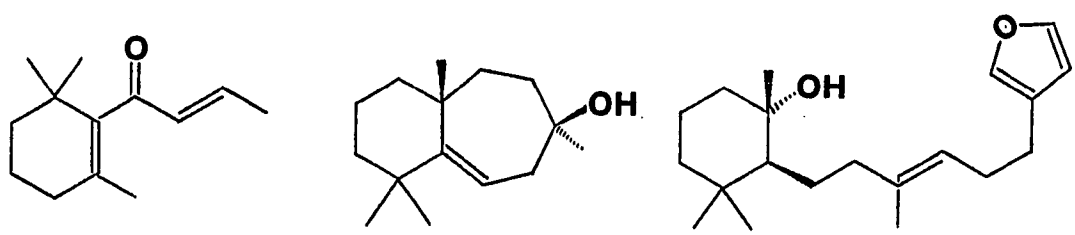
Besides the parent compound, only a few derivatives of 101 have been reported[118]. Thermal decomposition of Me_3SnCl_2Ph[119] or $CHCl_3$[120] in the presence of tetramethylethylene and pyrolyses of methylated *gem*-dichlorocyclopropanes[121] have been shown to give the corresponding dienes. Further development of the thermal dehydrohalogenation approach to the general class of 2,4-dimethyl-1,3-pentadienes seemed desirable. In cases where R is a functionalized substituent which would allow further elaboration,

such dienes may be synthetically useful. Diene 117 has been reported to undergo Diels-Alder reactions with α,β-unsaturated aldehydes[122]. Cycloaddition of functionalized diene 116 with appropriate dienophiles[123] (Scheme XVIII) would provide the highly substituted cyclohexadiene 131 or the

Scheme XVIII



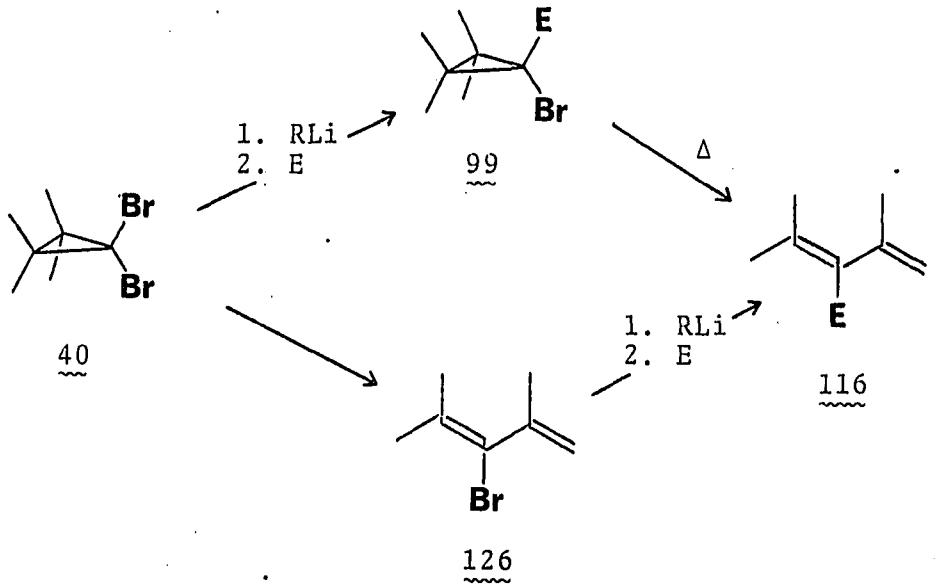
1,3,3-trimethylcyclohexene 132 which is found in several classes of natural products, *e.g.* β-Damascone[124], Widdrol[125], and Ambliol-A[126].



β-Damascone Widdrol Ambliol-A

RESULTS AND DISCUSSION

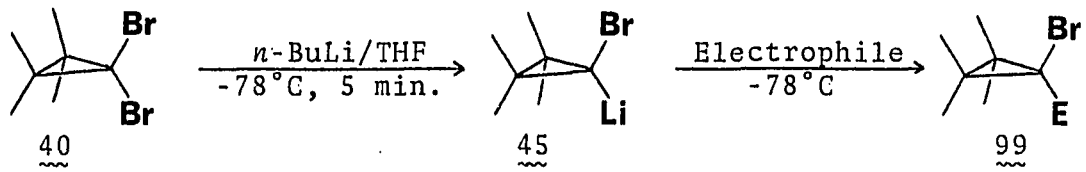
Of the two apparent routes to diene 116 starting from 40 (Scheme XIX), the derivatization of 40 via a carbenoid intermediate followed by pyrolysis was found to be more advantageous. The synthetic methodology developed is Scheme XIX



convenient and economical.

Several derivatives of 116 were synthesized from 40[127] by trapping the carbenoid intermediate 45 with the appropriate electrophiles. The results are summarized in Table XVII. Except for the ester 103 and the carboxylic acid 104, the products were obtained in moderate to good yields. Reaction conditions were not fully optimized.

Table XVII. Summary of the syntheses of 99



40 45 99

Electrophile	Compound	E	mp or bp	Yield (%)
MeOH	41a	H	30°C @ 20Torr	78
MeI	42a	Me	39 → 40°C	65
$ClSiMe_3$	100	$SiMe_3$	85°C	79
HCOOEt	101	CHO	39 → 41°C	58
Ac_2O	102	$COCH_3$	39°C @ 1Torr	61
ClCOOEt	103	COOEt	64°C @ 0.9Torr	18
CO_2	104	COOH	115 → 120°C	12

Carbenoid 45 has been generated and hydrolyzed with concentrated HCl or trapped with $ClSiMe_3$ below -100°C[128]. It was found that the generation and MeOH hydrolysis of 45 at -78°C (dry-ice/acetone bath) gave similar results. At -78°C, however, a much better yield of 100 was obtained from trapping 45 with $ClSiMe_3$.

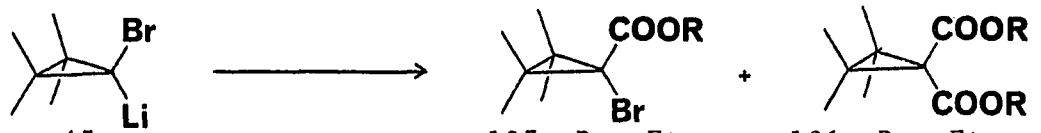
Compound 42a was reasonably unstable. Crude 42a turned completely into a dark black oily liquid at room temperature in a matter of hours. Purified crystalline 42a kept in a freezer showed appreciable signs of decomposition in about six months. Aldehyde 101 was oxidized slowly by the air at room temperature to the corresponding

carboxylic acid 104. It was, therefore, stored in a freezer under nitrogen.

Reactions of 45 with electrophiles leading to α-bromo-ester 103 deserve some discussion. Side products obtained were identified by GC.MS as the *gem*-diester 106 and the starting material 40. The product distribution is sensitive to how the electrophiles and 45 were mixed together, as shown in Table XVIII.

Rapid addition of ethyl chloroformate to 45, termed rapid normal addition, gave a mixture of 103, 106, and 40 in a 1:3:4 ratio as determined by ^{1}H NMR. The ratio changed

Table XVIII. Carboxylation of 45



45

103: R = Et
105: R = Me

106: R = Et
107: R = Me

XCOOR (eq.)	Addition method[a]	Product Ratio Monoester:Diester:40
ClCOOEt (1)	Rapid normal	1:3:4[b]
ClCOOEt (5)	Dropwise inverse	1:1:1[b]
$(MeO)_2CO$ (1)	Dropwise normal	<5%:57%:28%[c]

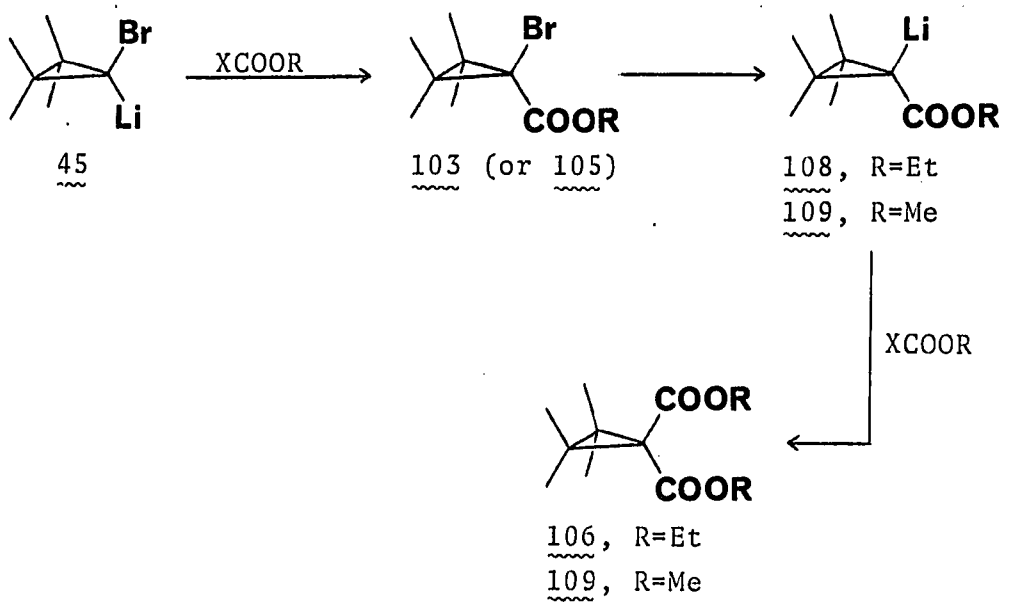
[a]See text for explanation.
[b]By ^{1}H NMR.
[c]Isolated yields.

to 1:1:1 when the solution of 45 was added dropwise to 5eq. of well-stirred ethyl chloroformate, termed dropwise

inverse addition. Trapping 45 by dropwise normal addition of dimethylcarbonate afforded only 107 and 40 in the isolated yields shown. Less than ca. 5% of 105 was detected by GC.MS of the crude mixture.

Apparently, slow addition of XCOOR to 45 enhanced the chance for α-bromoester 103 (or 105) to undergo a second LiBr exchange with remaining carbenoid 45 (see Scheme XX) to give the cyclopropyl lithium 108 (or 109) and 40. Further reaction of 108 (or 109) with XCOOR afforded the

Scheme XX



45

103 (or 105)

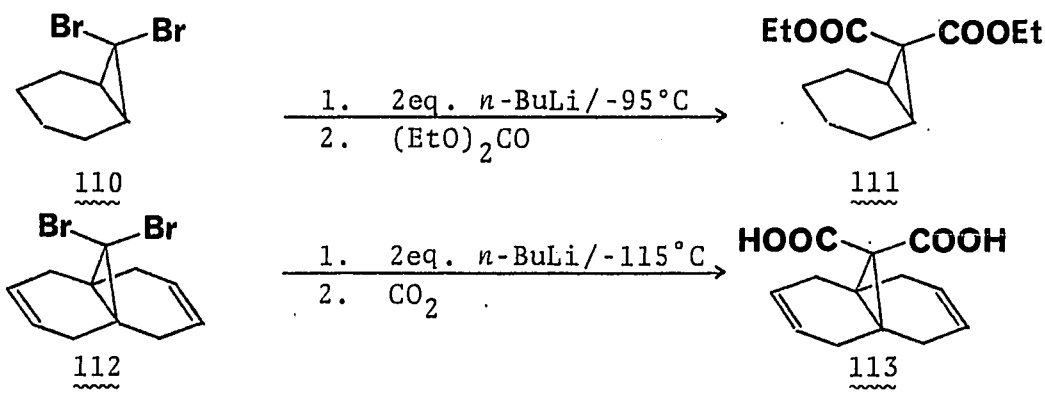
108, R=Et
109, R=Me

106, R=Et
109, R=Me

corresponding diester 106 (or 107). Rapid normal addition of XCOOR minimized the amount of 103 (or 105) which could undergo a second Li-Br exchange with 45. Slow inverse addition using excess XCOOR was even more effective in

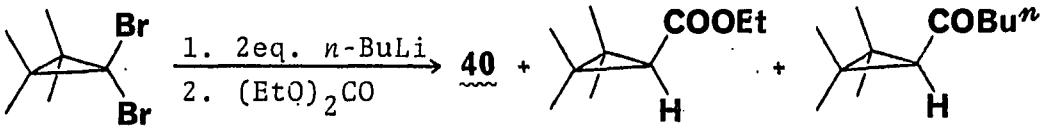
preventing the second Li-Br exchange during quenching, since the concentration of XCOOR was always several times higher than that of the α-bromoester.

It is interesting, however, that even with inverse addition, the amounts of 106 and 103 formed were still equal. A reasonable explanation is that, like other organolithiums, carbenoid 45 exists as an aggregate under the conditions employed. It was the aggregate that reacted with ethyl chloroformate or carbonate, with intra-aggregate scrambling of lithium and bromine to give the diester and 40. Thus, despite the large excess of ethyl chloroformate and inverse addition, the diester was always formed preponderantly. It is to be noted that this type of process was not seen when the more powerful electrophiles (e.g., MeOH) were used.



The preference for diester formation has been utilized

in the syntheses of several cyclopropane *gem*-diesters from the corresponding *gem*-dihalocyclopropanes. Treatment of 110 with 2eq. of *n*-BuLi, followed by the addition of diethyl carbonate, gave diester 111 in good yield[129]. Dibromide 112 was converted to 113 similarly, in 70% yield[130]. Similar treatment of 40, however, gave a mixture of 40, the monoester 114, and ketone 115 in ca. 20%, 33%, and 40% yields, respectively, as determined by NMR and GC.MS. Further investigations



40 114 (33%) 115 (40%)

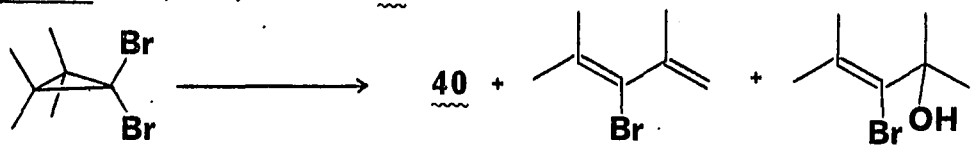
are necessary before final interpretation can be proposed.

It should also be pointed out that the preference for exchanging both bromines in one treatment with *n*-BuLi seems to be confined to the cases leading to diester or diacid formation. Reactions of 45 with other carbonyl compounds, such as ethyl formate or acetic anhydride, gave the corresponding aldehyde or ketone (see Table XVII) in a preponderant amount. Other derivatives of α-bromocyclopropyl lithium have been reported to give bromohydrins or subsequent rearranged products upon reaction with aldehydes or ketones[129,131]. Obviously, the carbonyl group itself does

not play a significant role in affecting the diester formation.

In search of an efficient set of conditions for the thermal conversion of 99 to diene 116, dibromide 40 and monobromide 41a were pyrolyzed using different types of columns at various temperatures. The ratios of products obtained under different conditions are shown in Tables XIX and XX.

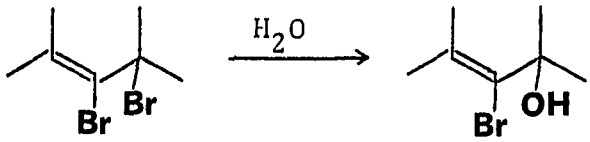
Table XIX. Pyrolysis of 40



Column	Temp (°C)	Ratio 40:126:128
Glass helices	300	.04: 1 : 2
Glass helices	400	None: 1 : 1
Quartz chips	500	None: 1 :1.4
Quartz chips	600	None: 1 :None
Copper turnings	300	None: 1 :None

Using a 12in. long column packed with glass helices or quartz chips, complete ring opening of 40 required temperatures above 300°C, and complete loss of HBr required at least 600°C. However, if copper turnings were used to peak the column, conversion of 40 to 126 was obtained at 300°C. The bromohydrin 128 might be formed by attack of moisture on the allylic bromide 127 when

warming the reaction mixture from cold trap to room temperature. Alternatively, H_2O adhered to the glass surface may

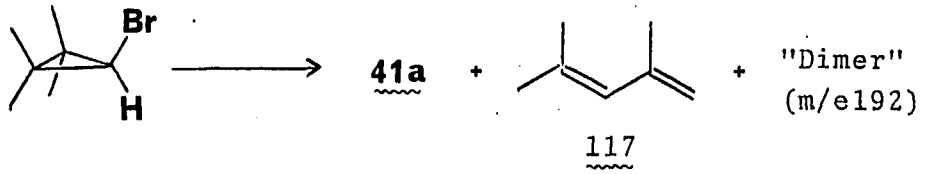


127 128

have been responsible for the formation of 128.

As expected, 41a undergoes the thermal ring opening less readily than 40. A dimer of unknown structure was

Table XX. Pyrolysis of 41a



117

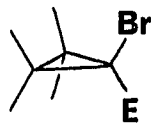
Column	Temp (°C)	Ratio 41a:117:Dimer
Glass helices	300	3: 1 : 2
Quartz chips	600	None: 1 : 2
Copper turnings	300	None: 1 :None

obtained at temperatures up to 600°C using a glass helices- or quartz chips-packed column. As in the case of 40, using a copper turning-packed column resulted in a clean and complete conversion of 41a to the diene. Apparently, the hot surface of metallic copper catalyzed the ring opening and subsequent dehydrohalogenation of 40 and 41a.

The copper catalyzed method was found to work well

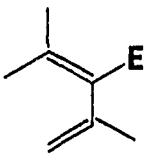
with other derivatives of 41a as shown in Table XXII, and should be an improvement over the more expensive silver-assisted solvolysis method[131a]. Diene 126 was converted

Table XXI. Pyrolysis of 99



99

300°C, 0.25Torr
Copper turnings

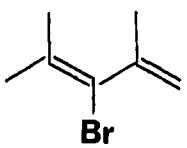


116

Compound	E	b.p(°C)	% Yield
117	H	94	84
118	Me	95	70[a]
121	$SiMe_3$	39°C & 7Torr	90[b]
122	CHO	57°C & 5.5Torr	71[a]
123	$COCH_3$	82°C & 35Torr	73
124	COOEt	55°C & 9.5Torr	16[a]
126	Br	35°C & 9.5Torr	74

[a]Total yield from 30.
[b]Using a quartz column at 600°C.

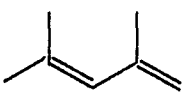
to the known 117 in 62% yield by treatment with *n*-BuLi followed by hydrolysis with MeOH. Exploratory experiments



126

n-BuLi
THF
-78°C

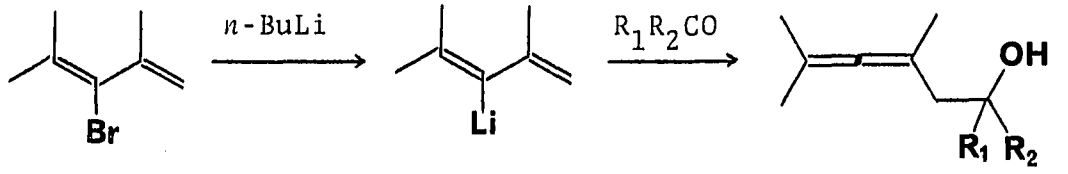
MeOH



117

aimed at converting 126 into other derivatives of 117 via

the allyl-vinyllithium 129 seemed to indicate a tendency of 129 to form allene derivatives. This finding may deserve further investigation since, upon reacting with aldehydes or ketones, 129 may be a convenient precursor to the



126 129 130

β-hydroxyallene 130. Several β-hydroxyallenes have been reported to undergo various novel transformations to β-lactones[132].

Diene 121 is also both an allyl and vinyl silane. Allyl[133] and vinyl silanes[134], each with its own set of reactions, have been shown to be valuable synthetic intermediates. It would be interesting to explore the behavior of 121.

EXPERIMENTAL

General

Infrared spectra were recorded on a Beckman IR-18A or IR-4250 spectrophotometer, ^{1}H NMR and ^{13}C NMR spectra on a Varian HA-60 or Hitachi Perkin-Elmer R20-B spectrometer and a Jeol FX-90 spectrometer, respectively, in the solvents indicated with TMS or $CDCl_3$ as the internal standard. GC.MS analyses were performed on an automated Finnigan Quadrupole Mass Spectrometer. High resolution mass spectra were measured on an AEI MS-902 Mass Spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. All reactions involving alkyllithium were carried out under anhydrous conditions, which means the reaction vessels were flame-dried, cooled under nitrogen, and capped with rubber septa. THF was freshly distilled from LAH. Additions of liquid reagents were effected via syringes inserted through the septum under a blanket of argon or nitrogen. Liquid reagents were dried as described. All pyrolyses were carried out at 0.25Torr and the temperature specified through a horizontal 12in. column packed with copper turnings, unless specified otherwise, in a Lindberg split tube furnace. Products were collected in a dry ice/acetone-cooled trap. External heat was applied

to the flask containing the starting material whenever necessary to facilitate vaporization.

Syntheses

1-Bromo-2,2,3,3-tetramethylcyclopropane, 41a

Under anhydrous conditions, a solution of 5.220g (20.4mmole) of 40 in 100ml of THF was cooled to -78°C. To this was added 1eq. of *n*-BuLi in hexane and the resulting solution stirred for 5 minutes, following which 2ml of MeOH were slowly added along the inside wall of the flask. After warming up to room temperature, the mixture was diluted with pentane, washed with water and saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo. The crude product, 3.816g, was distilled to afford 2.799g (78% yield) of 41a (bp 30°C/20Torr; lit.[128]:86-88°C/100Torr, 76% yield).

Bromopentamethylcyclopropane, 42a

Under anhydrous conditions, a solution of 6.096g (23.8mmole) of 40 in 100ml of THF was cooled to -78°C. To this was added 1eq. of *n*-BuLi in hexane and the resulting solution stirred for 5 minutes, followed by the dropwise addition of a solution of 1.5ml of MeI in 3.5ml of THF. A white suspension appeared in about 5 minutes. After stirring for 1 hour, the mixture was warmed up to room temperature, diluted with pentane, washed with water and

saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo to afford 5.395g of crude 42a which was immediately dissolved in 1ml of EtOH and let stand in a freezer (-20°C) for 20 hours to allow crystallization. Colorless crystalline 42a was collected and washed with cold EtOH (65% yield, m.p 39-40°C). IR (CCl_4): 3000, 2940, 1460, 1380, 1000; ^1H NMR (CCl_4): δ1.78 (s, 3H), 1.23 (s, 6H), 1.07 (s, 6H). Anal. Calc'd for C_8H_{15} (P^+-Br): m/e 111.11738. Found: m/e 111.11725.

1-Bromo-1-trimethylsilyl-2,2,3,3-tetramethylcyclopropane, 100

Under anhydrous conditions, a solution of 7.900g (30.9 mmole) of 40 in 150ml of THF was cooled to -78°C. To this was added 1eq. of *n*-BuLi in hexane, and the resulting solution stirred for 5 minutes, followed by the slow addition of a solution of 4ml of $ClSiMe_3$, freshly distilled from CaH_2, in 10ml of THF. After 1 hour, the mixture was allowed to warm up to room temperature, diluted with pentane, washed with water and saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo. The oily crude product was distilled (bp 42°C/0.6Torr) and the distillate recrystallized from EtOH to afford 6.042g (79% yield) of 100, mp 85°C (lit.[128]: 31% yield, mp 87-88°C). IR (CCl_4): 3000, 1450, 1240, 910, 840 cm^{-1}; ^1H NMR (CCl_4): δ1.32 (s, 3H), 1.27 (s, 3H), 0.32 (s, 9H). Anal. Calc'd for $C_9H_{18}BrSi$ (P^+-CH_3): m/e 233.03611. Found: m/e 233.03537.

1-Bromo-2,2,3,3-tetramethylcyclopropanecarboxaldehyde, 101

A solution of 6.205g (24.2mmole) of 40 in 100ml of THF was cooled to -95°C. Most of 40 precipitated and formed a white suspension, whereto 1eq. of *n*-BuLi in hexane was added dropwise, and stirring continued for 5 minutes. Ethyl formate (9.7ml, 5eq.), freshly distilled over CaH_2, was then added rapidly along the inside wall of the reaction vessel. After stirring at -95°C for another ½ hour, the vessel was transferred to a dry-ice-acetone bath and stirred for 3 hours at -78°C. After warming up to room temperature, the mixture was diluted with pentane, washed with water and saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo. The crude crystalline 101, 3.057g, was immediately sublimed, under nitrogen to avoid air-oxidation, to afford 2.853g (58% yield), mp 39-41°C. IR (CCl_4): 2960, 2920, 1710, 1450, 1380, 1090, 980, 870 cm^{-1}; ^1H NMR (CCl_4): δ9.78 (s, 1H), 1.33 and 1.30 (2 overlapping singlets, 12H). Anal. Calc'd. for $C_8H_{13}OBr$: m/e 204.01497. Found: m/e 204.01495.

1-Bromo-1-acetyl-2,2,3,3-tetramethylcyclopropane, 102

A solution of 6.017g (23.5mmole) of 40 in 100ml of THF was cooled to -95°C. To this was added dropwise 1eq. of *n*-BuLi in hexane, and the resulting solution stirred for 5 minutes. Then 5eq. of Ac_2O, which had stood over CaH_2 for 20 hours, was added rapidly along the inside wall of the flask. After stirring the reaction mixture at -95°C for

½ hour, the flask was transferred to a dry-ice-acetone bath, and the reaction stirred at -78°C for 3 more hours. After warming up to room temperature, the mixture was diluted with pentane, washed twice with 50% K_2CO_3 solution, once with water, and once with saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo. The residue was distilled to afford 3.137g (61% yield) of 102 (bp 39°C/1Torr). IR (CCl_4): 3000, 2940, 1705, 1450, 1370, 1215, 840 cm^{-1}; ^1H NMR (CCl_4): δ2.26 (s, 3H), 1.23 (s, 6H), 1.17 (s, 6H). Anal. Calc'd. for $C_8H_{12}OBr$ (P^+-CH_3): m/e 203.00714. Found: m/e 203.00619.

Ethyl 1-bromo-2,2,3,3-tetramethylcyclopropanecarboxylate, 103, and 1,1-Dicarboethoxy-2,2,3,3-tetramethylcyclopropane, 106

Method A In order to generate the carbenoid solution and then add it dropwise to ethyl chloroformate while always keeping the solution at -95°C, the apparatus illustrated in Figure 18 was used. Under anhydrous conditions, a solution of 5.940g (23.7mmole) of 40 in 125ml of THF was placed in vessel L. A small stream of argon, which was blown into vessel R and escaped through vessel L, served to prevent premature transferring of the mixture from vessel L to R. The apparatus was immersed in a Skelly B/liquid N_2 slurry bath. After 15 minutes, 1eq. of *n*-BuLi in hexane was added dropwise to the 40 solution in vessel L and stirred for 15 minutes. Then 5eq. of ClCOOEt was introduced via syringe into vessel R. The carbenoid solution in vessel L was

transferred to R by applying a slight pressure of argon at the top of L. The resulting mixture was stirred for ½ hour at -95°C and 3 hours at -78°C. After warming up to room temperature, the mixture was diluted with Et_2O, washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo. NMR of the residue showed approximately a 1:1:1 mixture of 103, 106, and the starting material. Distillation of the residue afforded a fraction containing 103 (bp 64°C/0.9Torr) in about 80% purity, and the diester 106 (bp 77°C/0.9Torr) in about 90% purity. For characterization, 103 and 106 were further purified by TLC. For 103: IR (CCl_4): 2960, 1730, 1450, 1370, 1250, 900 cm^{-1}; ^1H NMR (CCl_4): δ4.10 (q, 2H, J=7.5Hz), 1.37-1.14 (m from a t overlapping two s at 1.20 and 1.14, 15H). Anal. Calc'd. for $C_{10}H_{17}O_2Br$: 248.04119. Found: m/e 248.04163. For 106: IR (CCl_4): 3000, 2940, 1730, 1450, 1380, 1220, 1120, 1080, 1060 cm^{-1}; ^1H NMR (CCl_4): δ4.07 (q, 4H, J=7.5Hz), 1.34-1.10 (m from a t overlapping a s at 1.20, 18H). ^{13}C NMR ($CDCl_3$): δ168.17 (Int. 879), 60.41 (3259), 43.51 (462), 3206 (1445), 18.99 (6669), 13.98 (4418). Anal. Calc'd. for $C_{12}H_{19}O_4$ (P^+-CH_3): m/e 227.12834. Found: m/e 227.12824.

Method B A solution of 0.525g (2.1mmole) of 40 in 25ml of THF was cooled to -78°C, followed by the addition of 1eq. of *n*-BuLi in hexane, and 5 minutes of stirring. Then 1eq. of ClCOOEt was injected through the septum onto the inside wall of the reaction vessel as fast as possible.

The yellow color of the carbenoid solution disappeared instantly. NMR of the crude product obtained after the work-up described above showed approximately a 1:3:4 mixture of 103, 106, and starting material.

1,1-Dicarbomethoxy-2,2,3,3-tetramethylcyclopropane, 107

Under anhydrous conditions, a solution of 2.714g (10.6 mmole) of 40 in 40ml of THF was cooled to -78°C, followed by the dropwise addition of 1eq. of *n*-BuLi in hexane. After 5 minutes, a solution of 1eq. of dimethyl carbonate in 2ml of THF was added dropwise. A white suspension appeared in about 1 hour. Stirring was continued for an additional 2 hours. The mixture was then allowed to warm up to room temperature, diluted with Et_2O, washed with water and saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo to afford 2.475g of an oily residue. Upon standing overnight in the freezer (-20°C), most of the starting material precipitated out and was collected and washed with a 50:50 EtOH:water mixture (0.771g, 28% recovered). The liquid portion was then distilled and 0.919g of 107 was collected (bp 57°C/0.8Torr, 57%). IR (CCl_4): 2980, 1735, 1435, 1265, 1230, 1085, 1065 cm^{-1}; ^1H NMR (CCl_4): δ3.63 (s, 6H), 1.22 (s, 12H). Anal. Calc'd. for $C_{10}H_{15}O_4$ (P^+-CH_3): m/e 199.09703. Found: m/e 199.09653.

1-Bromo-2,2,3,3-tetramethylcyclopropanecarboxylic acid, 104

Under anhydrous conditions, a solution of 0.793g (3.0

mmole) of 40 in 30ml of THF was cooled to -78°C, followed by the addition of 1eq. of *n*-BuLi in hexane; the resulting solution was stirred for 5 minutes. Carbon dioxide gas was then bubbled through the carbenoid solution for 15 minutes. Stirring was continued under a slight pressure of CO_2 for 3 hours. After warming up to room temperature, the mixture was diluted with Et_2O and extracted twice with a 1M NaOH solution. The combined extracts were acidified with concentrated HCL, and extracted twice with Et_2O. The combined ethereal extracts were dried over $MgSO_4$ and stripped of solvent in vacuo to yield 0.150g (12% yield) of 104, mp 115-120°C. IR ($CDCl_3$): 3600-2500 (broad, COOH), 1700, 1400, 1275, 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.26 (s, 12H); ^{13}C NMR ($CDCl_3$): δ173.57 (Int. 1172), 28.16 (3220), 21.46 (8074), 0.00 (2313). Anal. Calc'd. for $C_7H_{10}O_2Br$ (P^+-CH_3): m/e 204.98641. Found: m/e 204.98570.

2,4-Dimethyl-1,3-pentadiene, 117

Pyrolysis of 0.453g of 41a afforded 0.209g (85% yield) of 117 which was not further purified, but found identical to an authentic sample (Aldrich).

2,3,4-Trimethyl-1,3-Pentadiene, 118

After 5.136g of 40 were converted to 42a as described, crude 42a was pyrolyzed directly. The pyrolysate was distilled at 95°C to afford 1.776g of 118 (70% yield). IR (CCl_4): 3600-3200 (br), 3080, 2920, 1630, 1440, 890

cm^{-1}; ^1H NMR (CCl_4): δ4.80 (br m, 1H), 4.50 (br m, 1H), 1.80-1.60 (m with a s at 1.15, 12H). Anal. Calc'd. for C_8H_{14}: m/e 110.10955. Found: m/e 110.10922.

2,4-Dimethyl-3-trimethylsilyl-1,3-pentadiene, 121

An aliquot of 2.046g (8.2mmole) of 100 was pyrolyzed at 600°C and 0.25Torr through a 12in. quartz-tube packed with quartz chips. The pyrolysate was distilled to afford 1.215g (90% yield) of 121 (bp 39°C/7Torr). IR (CCl_4): 3080, 2960, 1630, 1610, 1440, 1250, 910, 830 cm^{-1}; ^1H NMR (CCl_4): δ4.77 (br m, 1H), 4.32 (br m, 1H), 1.90-1.50 (m with s at 1.80 and 1.70, 9H), 0.13 (s, 9H). Anal. Calc'd. for $C_{10}H_{20}Si$: m/e 168.13340. Found: m/e 168.13342.

2,4-Dimethyl-3-formyl-1,3-pentadiene, 122

The pyrolysis apparatus was flushed with nitrogen three times. Then 2.857g of 101 were pyrolyzed to afford 1.539g of pyrolysate, which was purified by distillation to give 1.220g (71% yield) of 122 (bp 57°C/5.5Torr). IR (CCl_4): 3100, 2930, 2760, 1685, 1630, 1450, 1380, 1320, 1135, 910 cm^{-1}; ^1H NMR (CCl_4): δ9.93 (s, 1H), 5.08 (br m, 1H), 4.58 (br m, 1H), 2.18 (s, 3H), 1.93 (s, 3H), 1.75 (br m, 3H); ^{13}C NMR ($CDCl_3$): δ189.30 (3824), 153.99 (677), 140.86 (1574), 140.27 (1140), 115.75 (4690), 23.74 (3133), 22.63 (4122), 18.66 (1990). Anal. Calc'd. for $C_8H_{12}O$: m/e 124.08882. Found: m/e 124.08875.

2,4-Dimethyl-3-acetyl-1,3-pentadiene, 123

An aliquot of 0.367g of 102 were pyrolyzed, and the pyrolysate distilled to give a 73% yield of 123 (bp 82°C/ 35Torr). IR (CCl_4): 3080, 2905, 1680, 1635, 1600, 1430, 1370, 1350, 1200, 900 cm^{-1}; ^1H NMR (CCl_4): δ5.05 (br m, 1H), 4.73 (br m, 1H), 2.02 (s, 3H), 1.75-1.65 (m, 9H). Anal. Calc'd. for $C_9H_{14}O$: m/e 138.10449. Found: m/e 138.10442.

2,4-Dimethyl-3-carboethoxy-1,3-pentadiene, 124

After 5.893g of 40 were converted to 103 by Method A, 5.377g of the crude product mixture were pyrolyzed and the pyrolysate was distilled to afford 0.636g of 124 (bp 55°C/ 9.5Torr, 16% yield). IR (CCl_4): 3080, 2980, 1715, 1625, 1445, 1370, 1240, 1210, 1100, 1050, 900 cm^{-1}; ^1H NMR (CCl_4): δ5.00 (br m, 1H), 4.65 (br m, 1H), 4.10 (q, 2H, J=7.5Hz), 1.97 (s, 3H), 1.80 (br s, 6H), 1.24 (t, 3H, J=7.5Hz); ^{13}C NMR ($CDCl_3$): δ167.64 (955), 142.94 (880), 142.18 (2409), 131.40 (880), 115.52 (5223), 59.73 (4000), 22.72 (5420), 21.86 (3875), 13.95 (5042), 13.63 (1025). Anal. Calc'd. for $C_{10}H_{16}O_2$: m/e 168.11503. Found: m/e 168.11544.

2,4-Dimethyl-3-bromo-1,3-pentadiene, 126

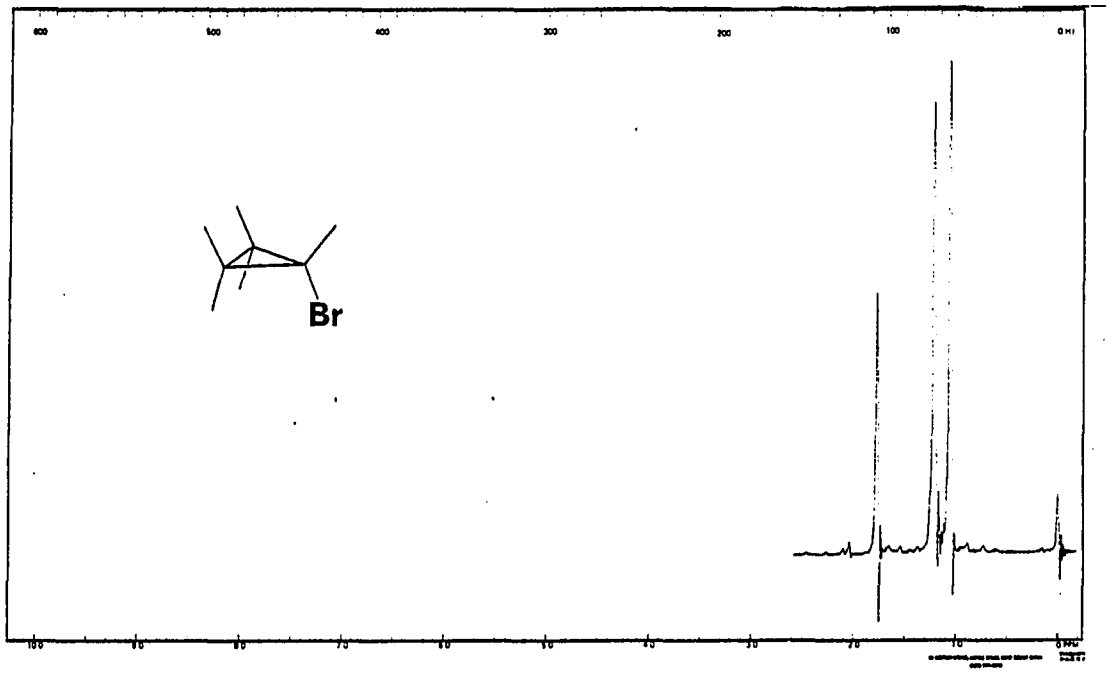
An aliquot of 9.813g of 40 were pyrolyzed. The pyrolysate was dried over K_2CO_3 and distilled to afford 6.271g of 126 (bp 35°C/9.5Torr, 74% yield). IR (CCl_4): 3080, 2920, 1625, 1440, 1370, 1090, 980, 905, 850 cm^{-1}; ^1H NMR

(CCL_4): δ4.95 (br m, 1H), 4.85 (br m, 1H), 1.88 (br s, 6H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ144.02 (1549), 130.64 (830), 120.24 (2091), 116.28 (6461), 24.29 (3261), 21.64 (5357), 21.53 (6165). Anal. Calc'd for $C_7H_{11}Br$: m/e 174.00441. Found: m/e 174.00376.

A sample of 0.204g of 126 was converted to 2,4-dimethyl-1,3-pentadiene, 117, by treatment with 1.2eq. of *n*-BuLi at -78°C for 5 minutes, followed by dropwise addition of MeOH. The usual work-up afforded crude 117, in 62% yield, as determined by the internal standard NMR method.

2,4-Dimethyl-3-bromopent-2-ene-4-ol, 128

An aliquot of 5.059g of 40 was pyrolyzed at 400°C and 0.25Torr through a horizontal column packed with glass helices. The liquid portion of the pyrolysate was withdrawn with a pipet and found to be mainly 126 by NMR. The crystalline portion was washed with cold hexane and sublimed to obtain a colorless crystalline compound, mp 47-48°C, which was identified as 128. IR (CCl_4): 3600 (s, free -OH), 3460 (br, -OH), 2980, 1620, 1450, 1360, 1160, 1100, 840 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.35 (s, 1H), 2.00 (s, 3H), 1.87 (s, 3H), 1.50 (s, 6H); ^{13}C NMR ($CDCl_3$): δ132.48 (int. 15), 128.42 (24), 75.65 (26), 31.12 (168), 29.01 (41), 22.29 (54). Anal. Calc'd. for $C_7H_{11}Br$ (P^+-H_2O): m/e 174.00441. Found: m/e 174.00493.



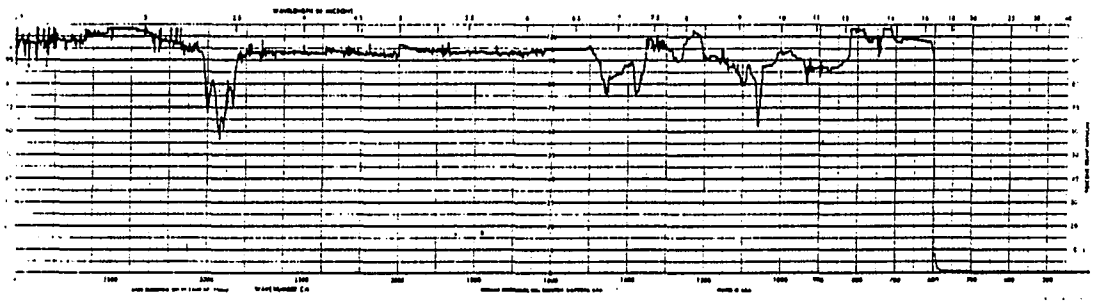


Figure 45. ^1H NMR (CCl_4) and IR (CCl_4) of Bromopentamethylcyclopropane, 42a

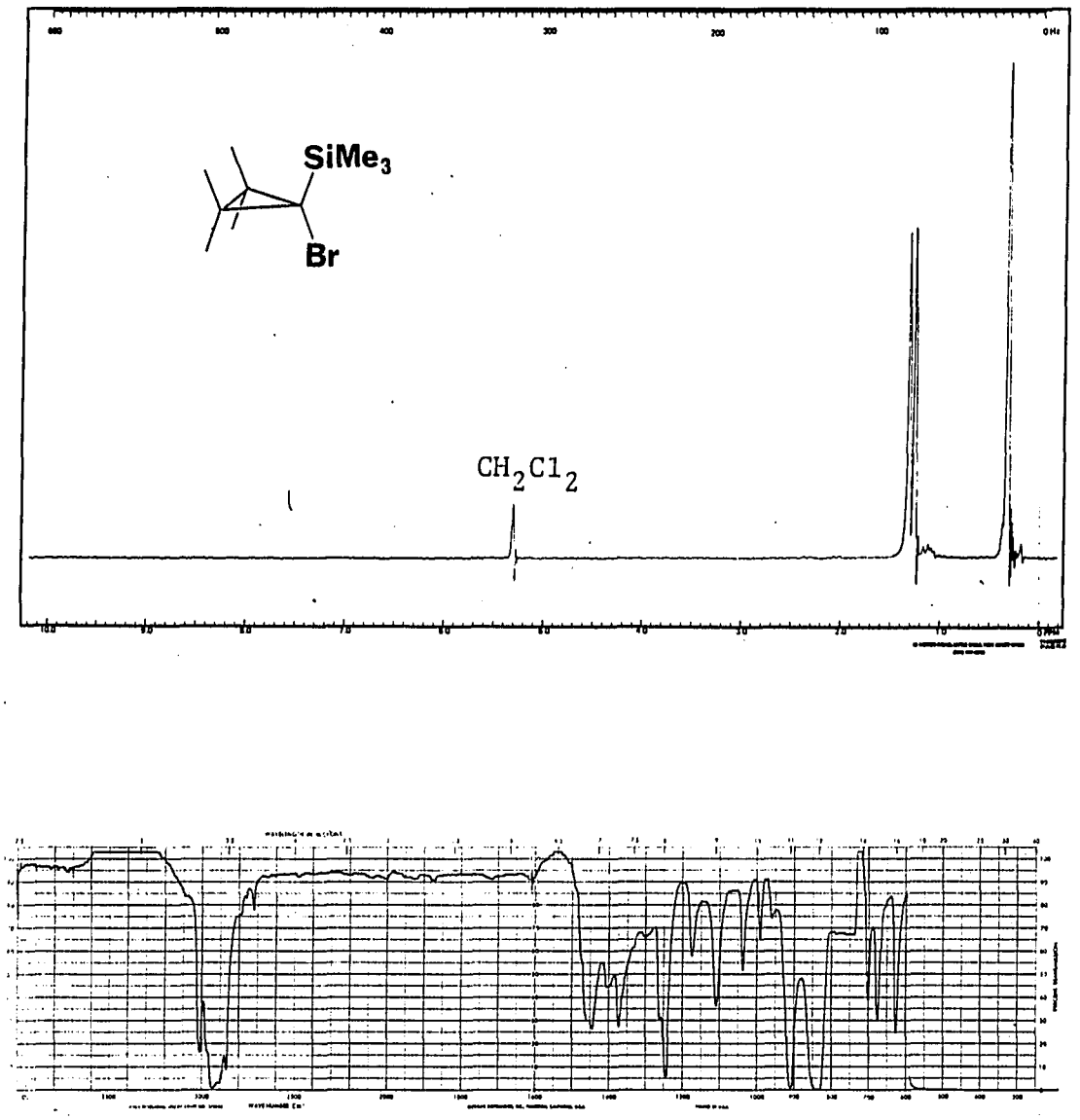
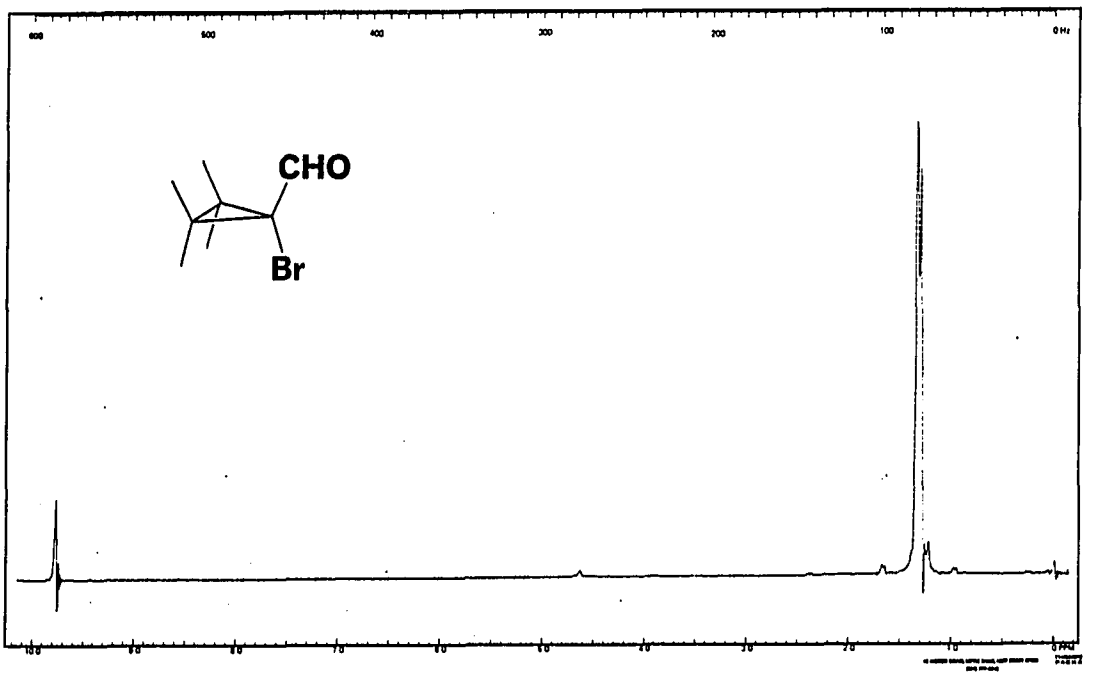


Figure 46. ^1H NMR (CCl_4) and IR (CCl_4) of 1-Bromo-1-trimethylsilyl-2,2,3,3-tetramethylcyclopropane, 100



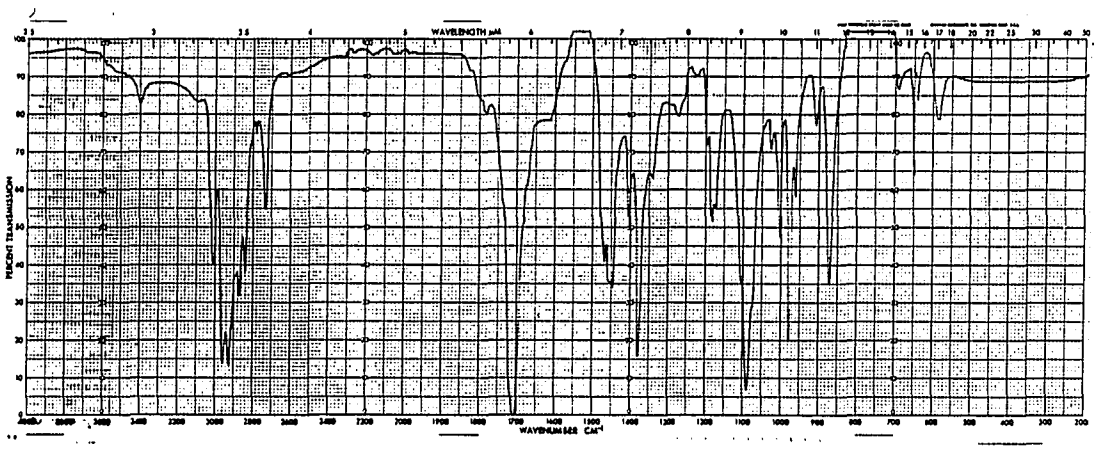


Figure 47. ^{1}H NMR (CCl_4) and IR (CCl_4) of 1-Bromo-2,2,3,3-tetramethylcyclopropanecarboxaldehyde, 101

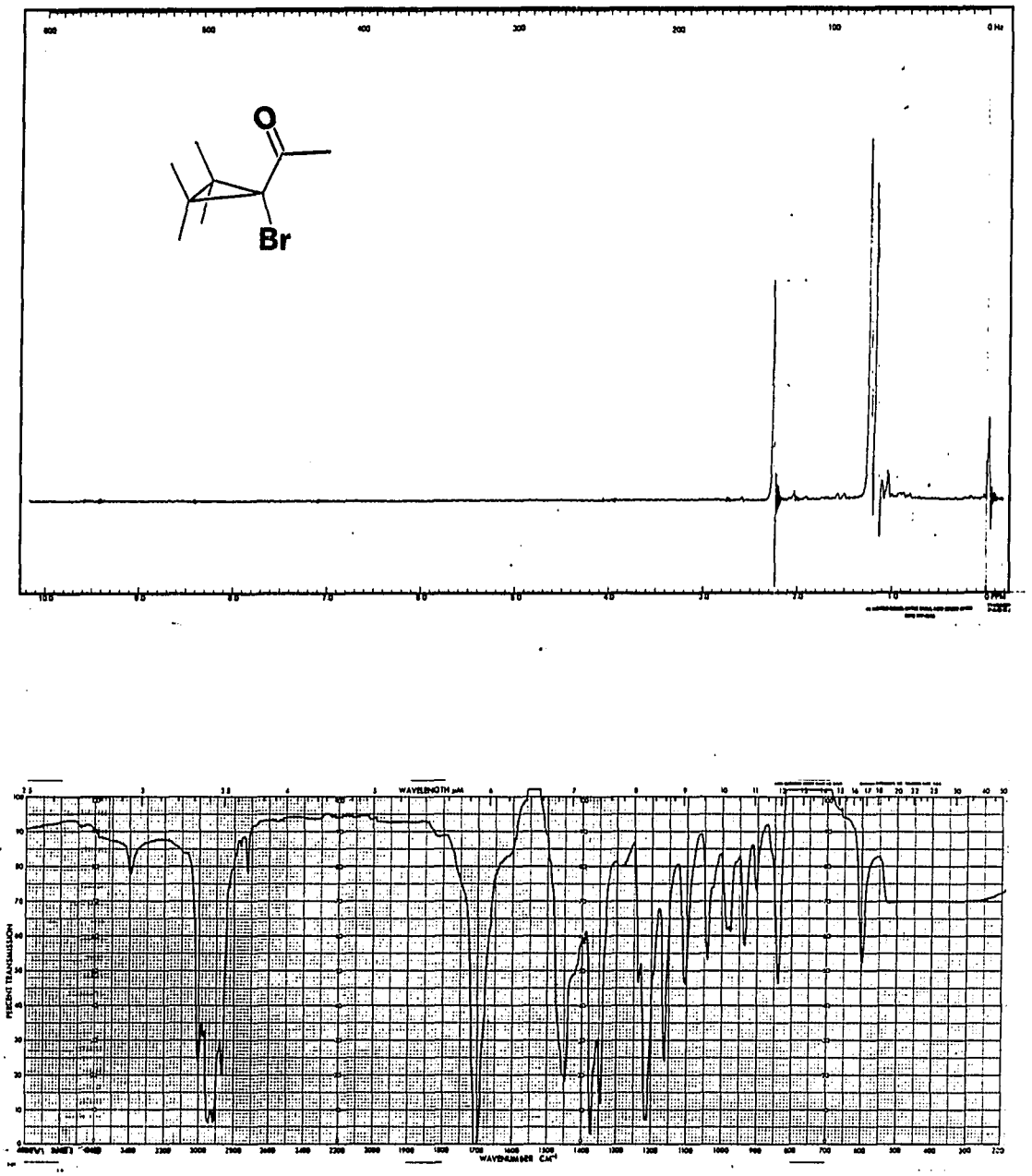


Figure 48. ^1H NMR (CCl_4) and IR (CCl_4) of 1-Bromo-1-acetyl-2,2,3,3-tetramethylcyclopropane, 102

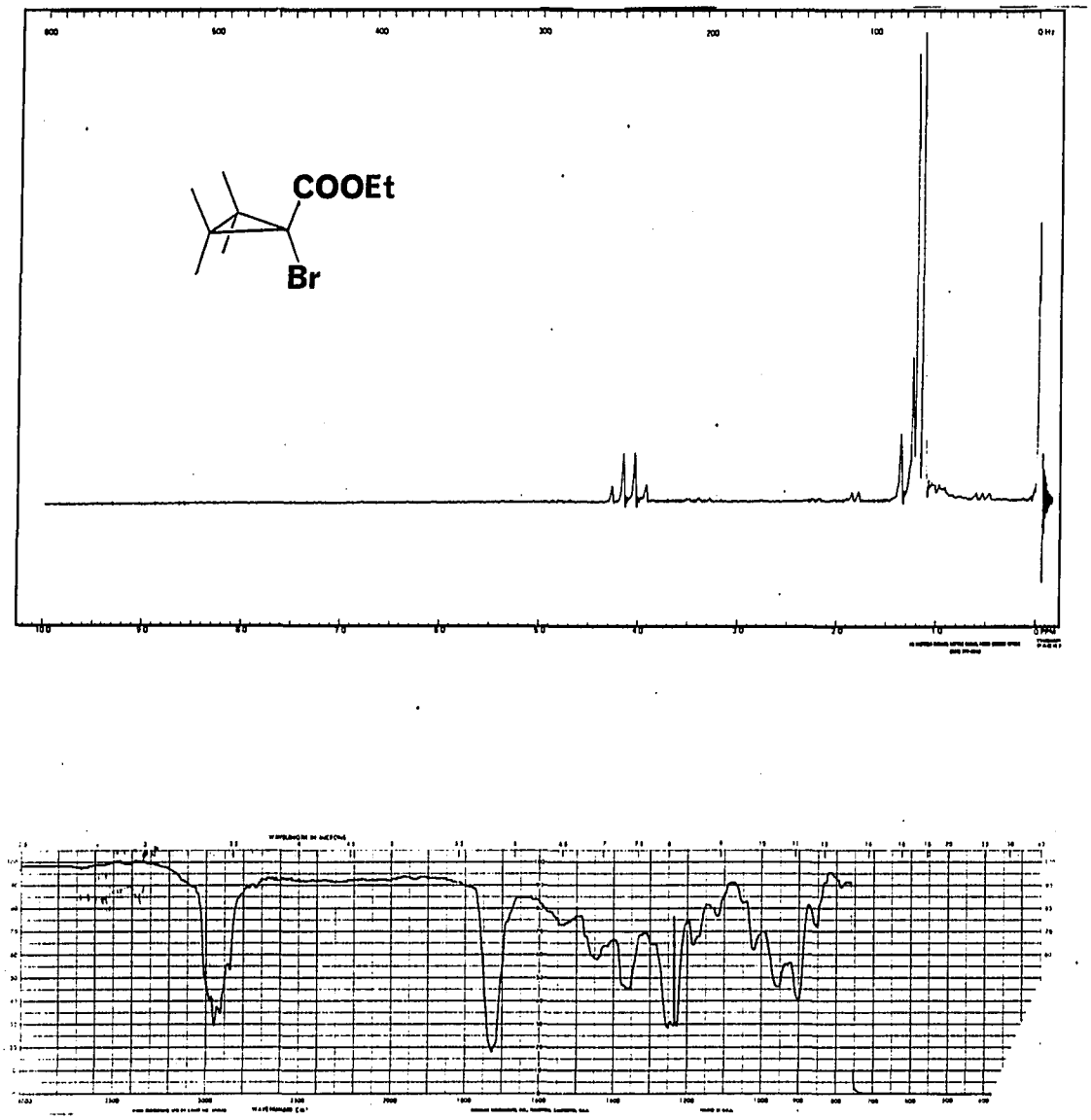
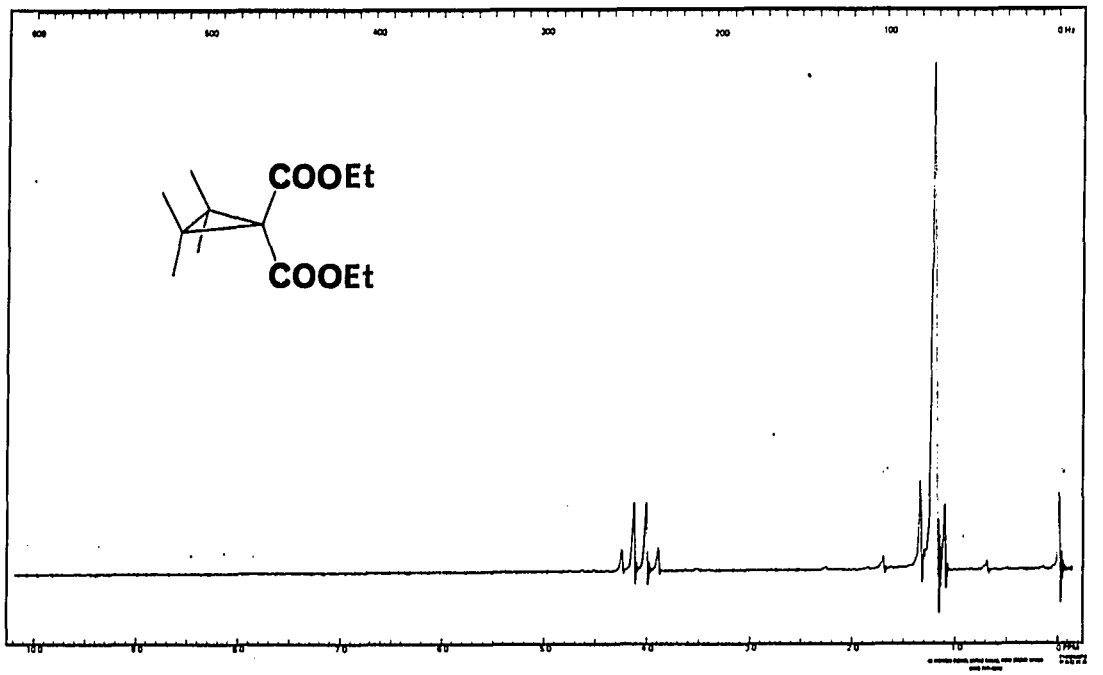


Figure 49. ^1H NMR (CCl_4) and IR (CCl_4) of Ethyl 1-Bromo-2,2,3,3-tetramethylcyclopropanecarboxylate, 103



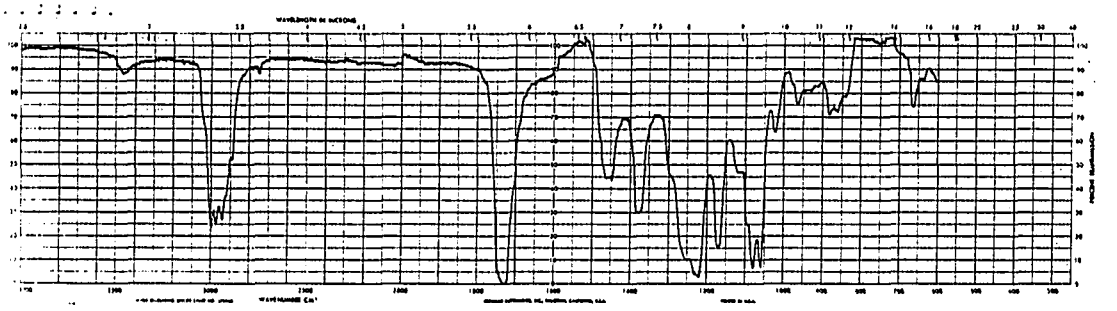


Figure 50. ^1H NMR (CCl_4) and IR (CCl_4) of 1,1-Dicarboethoxy-2,2,3,3-tetramethylcyclopropane, 106

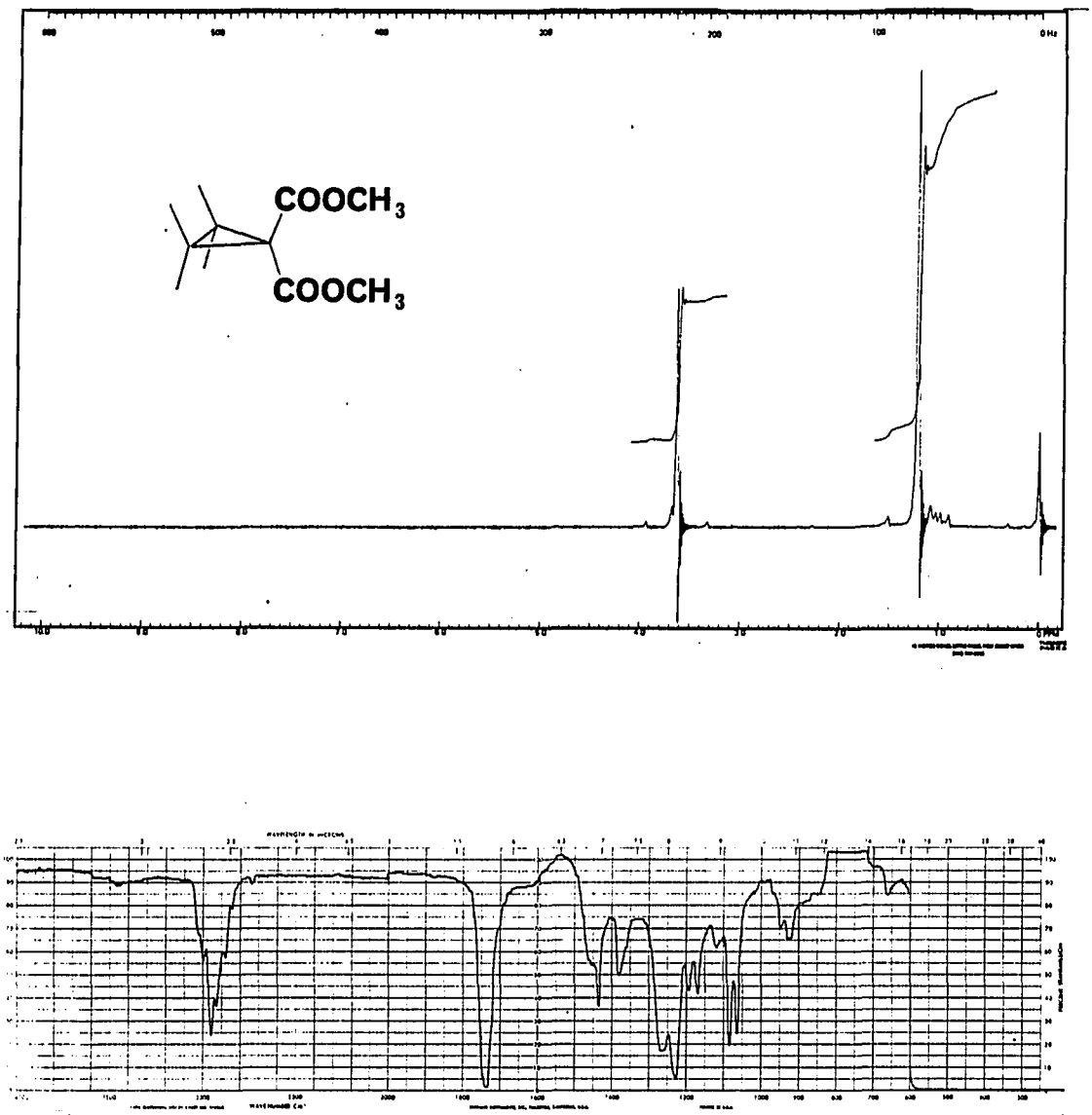
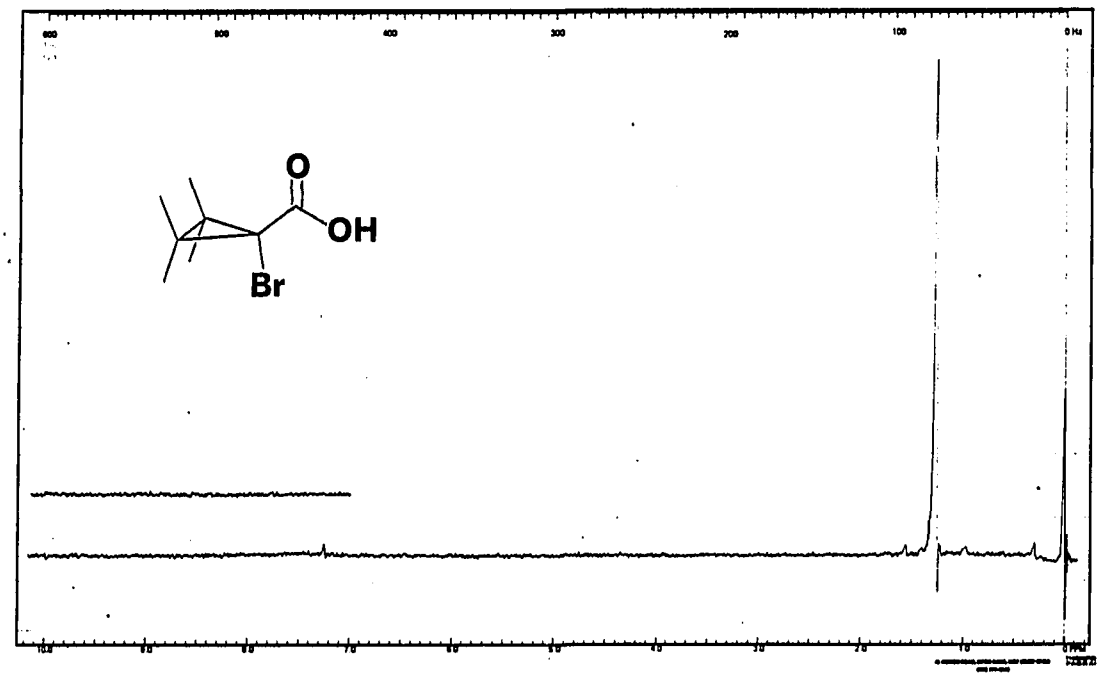


Figure 51. ^1H NMR (CCl_4) and IR (CCl_4) of 1,1-Dicarbomethoxy-2,2,3,3-tetramethylcyclopropane, 107



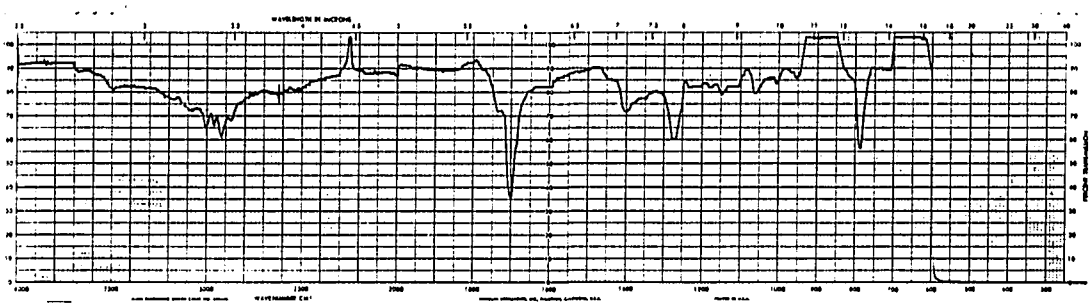


Figure 52. ^{1}H NMR ($CDCl_3$) and IR ($CDCl_3$) of 1-Bromo-2,2,3,3-tetramethylcyclopropanecarboxylic acid, 104

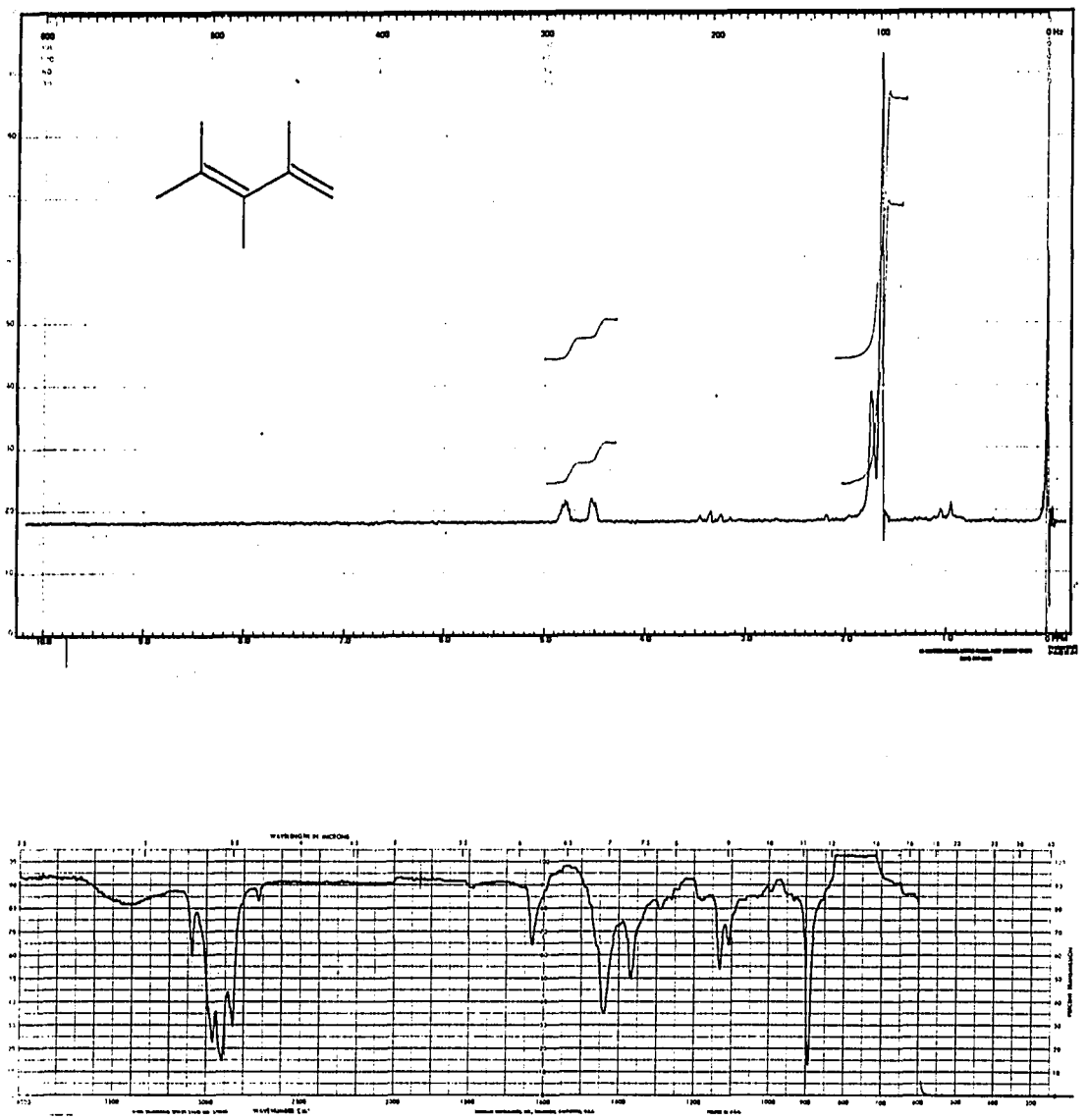


Figure 53. ^1H NMR (CCl_4) and IR (CCl_4) of 2,3,4-Trimethyl-1,3-pentadiene, 118

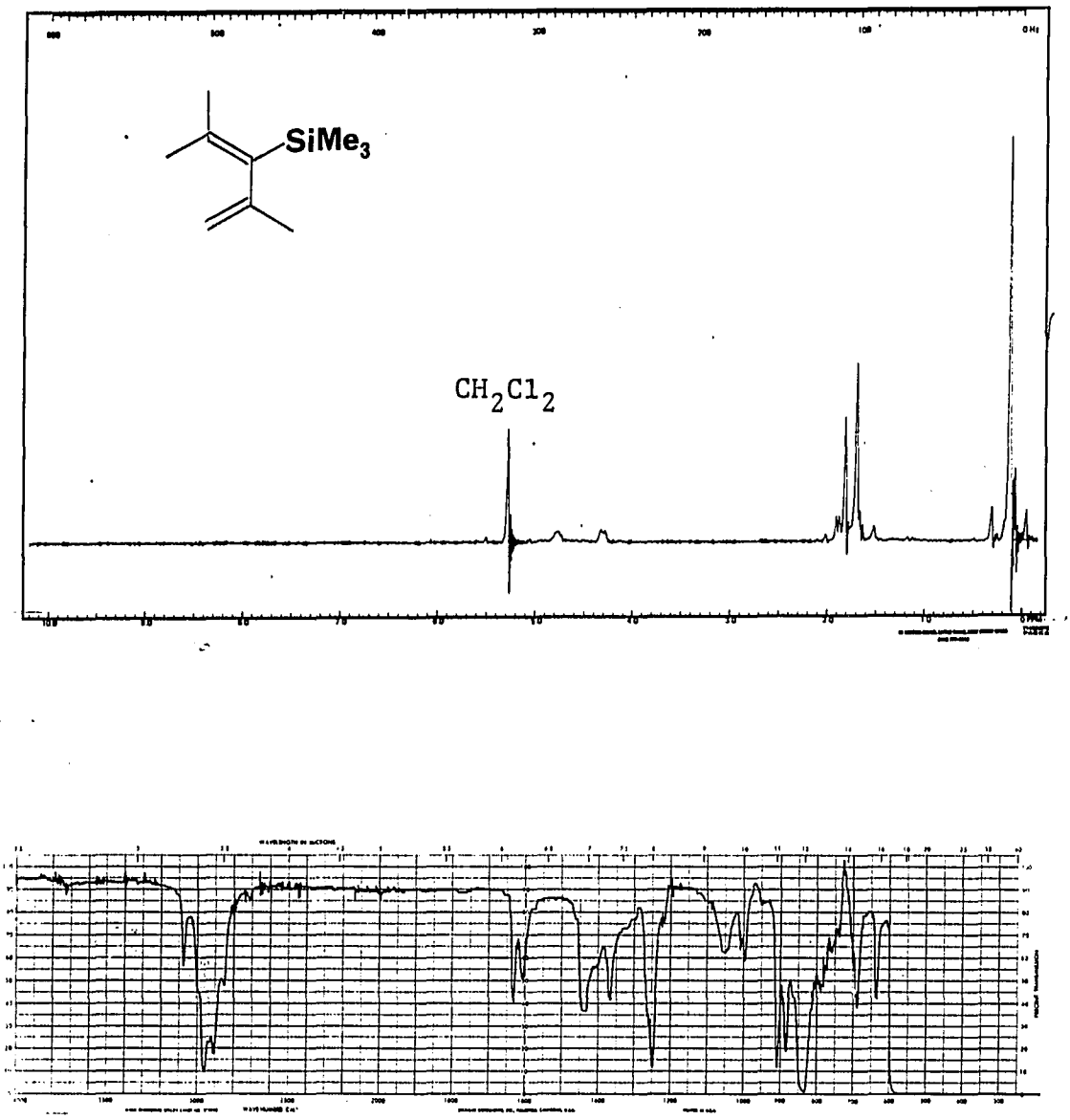
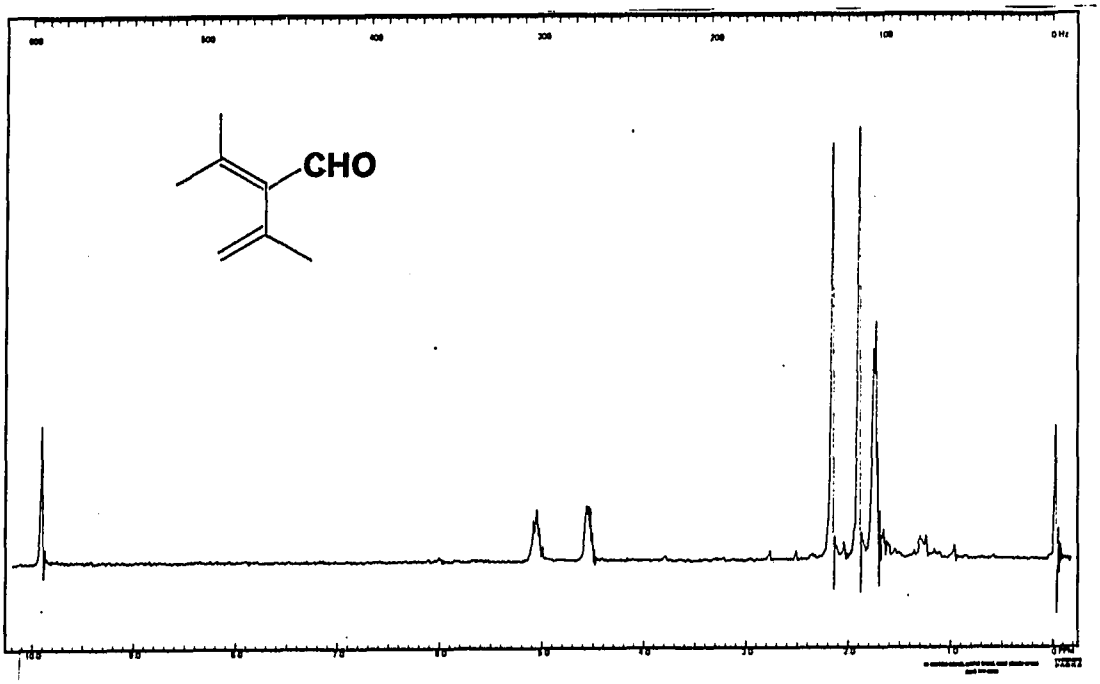


Figure 54. ^1H NMR (CCl_4) and IR (CCl_4) of 2,4-Dimethyl-3-trimethylsilyl-1,3-pentadiene, 121



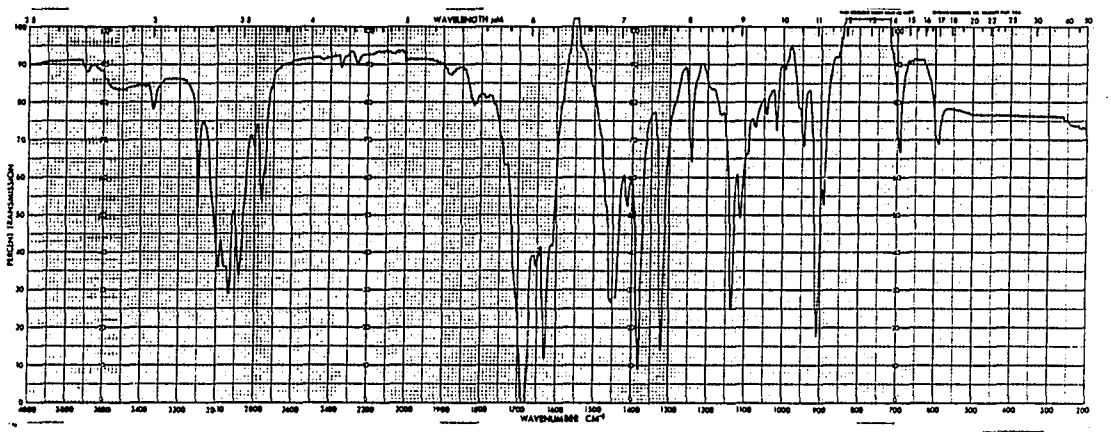
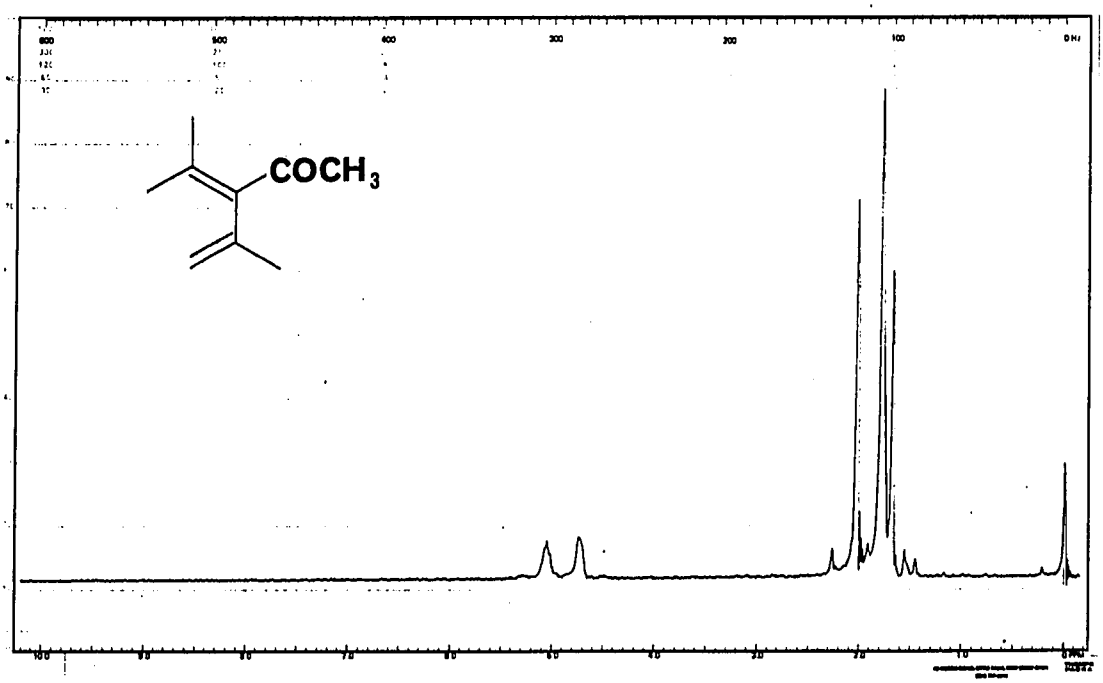


Figure 55. ^1H NMR (CCl_4) and IR (CCl_4) of 2,4-Dimethyl-3-formyl-1,3-pentadiene, 122



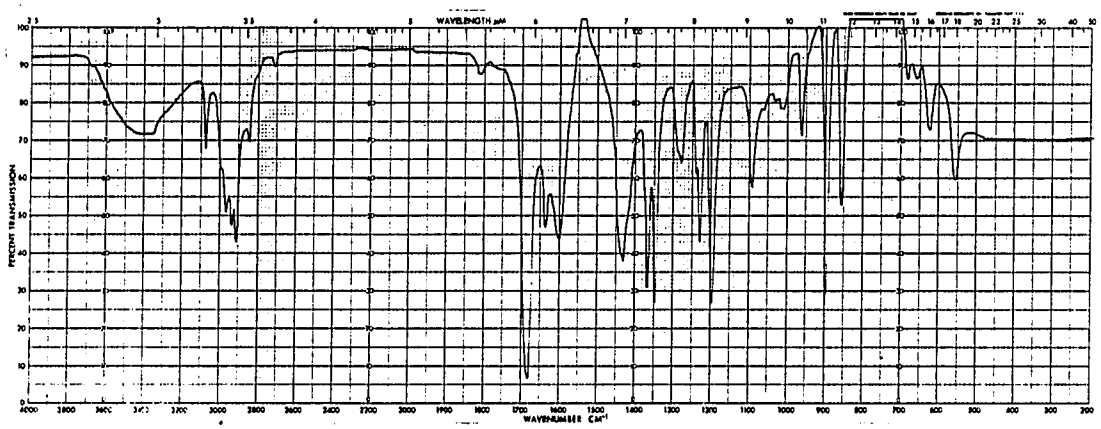


Figure 56. ^1H NMR (CCl_4) and IR (CCl_4) of 2,4-Dimethyl-3-acetyl-1,3-pentadiene, 123

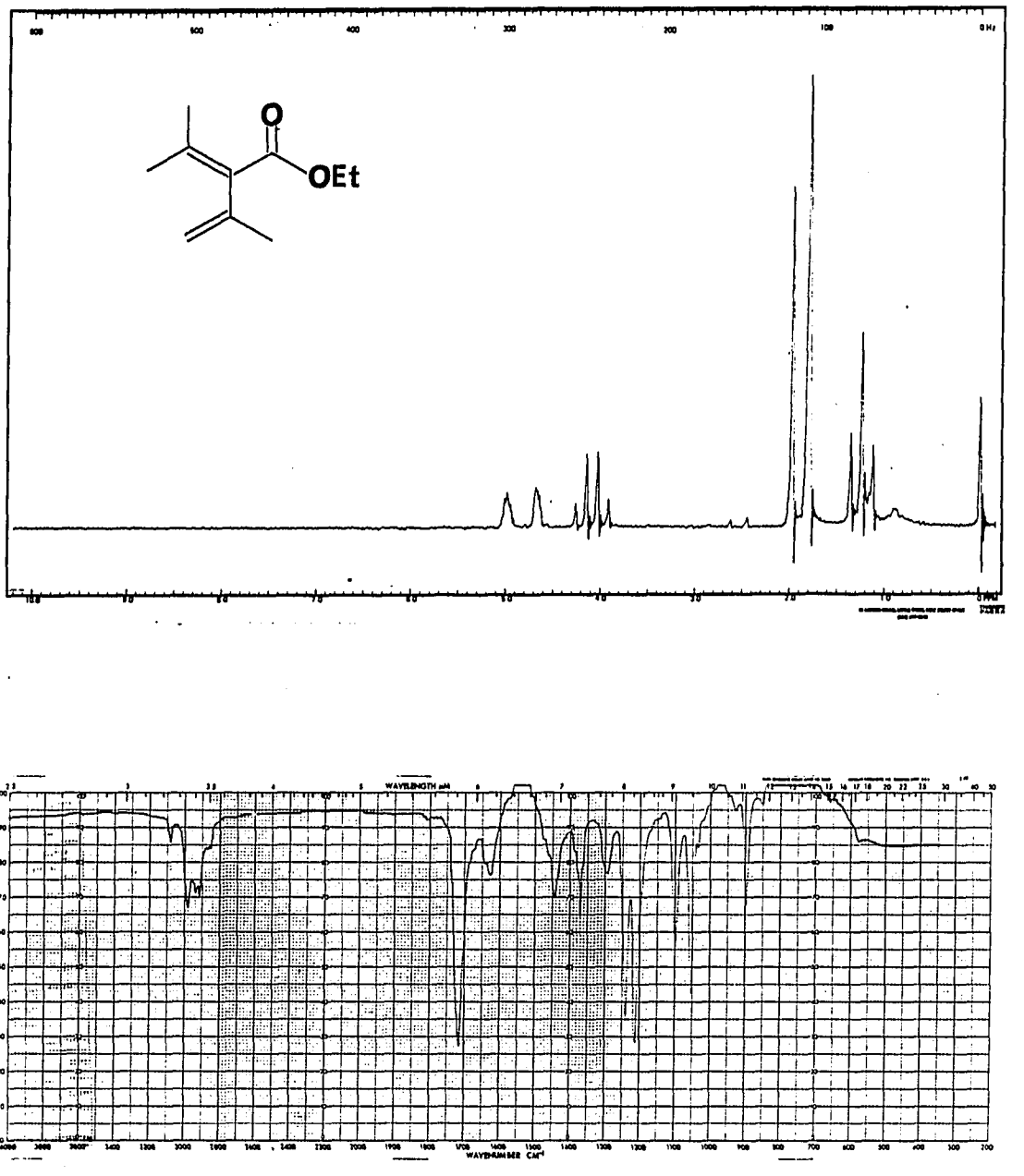
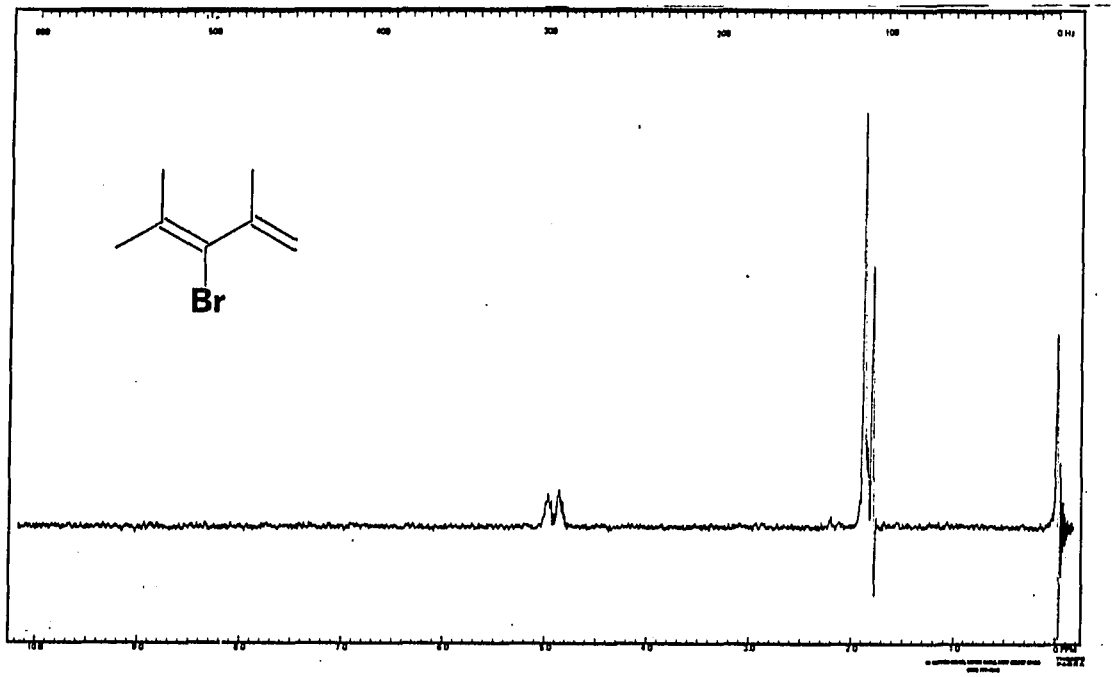


Figure 57. ^1H NMR (CCl_4) and IR (CCl_4) of 2,4-Dimethyl-3-carboethoxy-1,3-pentadiene, 124



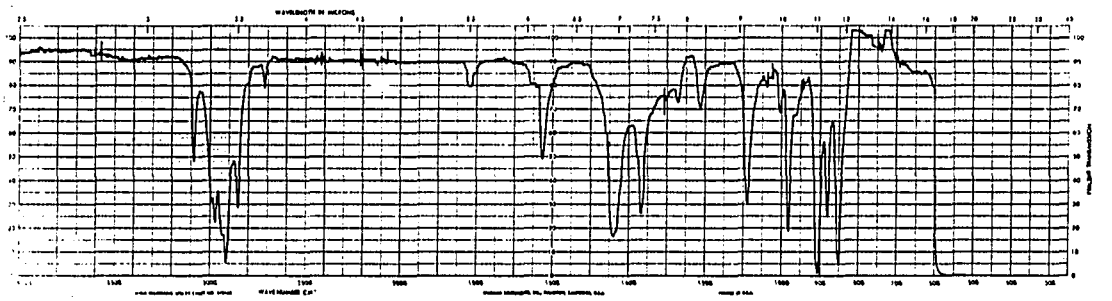


Figure 58. ^{1}H NMR (CCl_4) and IR (CCl_4) of 2,4-Dimethyl-3-bromo-1,3-pentadiene, 126

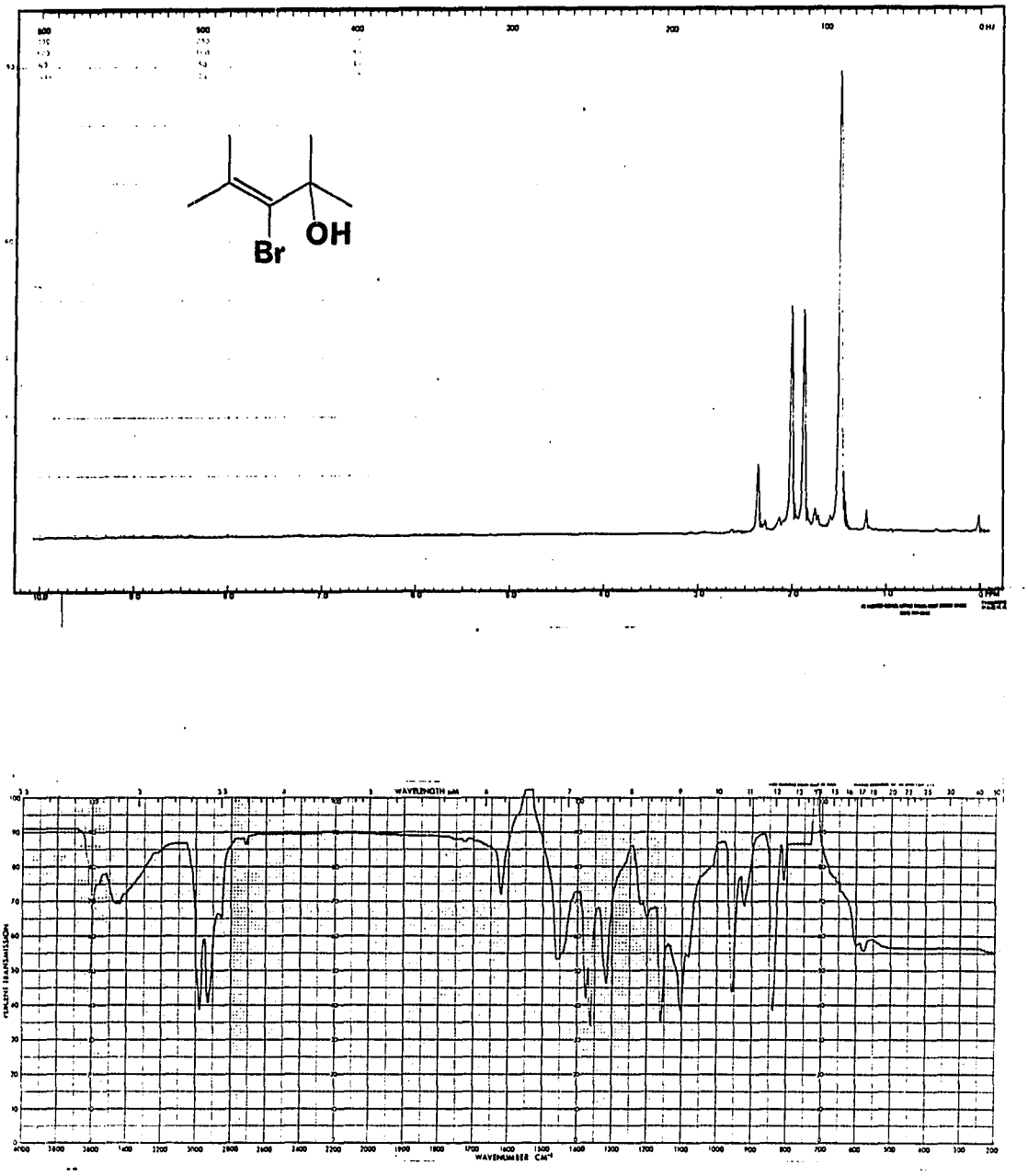


Figure 59. ^1H NMR ($CDCl_3$) and IR (CCl_4) of 2,4-Dimethyl-3-bromopent-2-ene-4-ol, 128

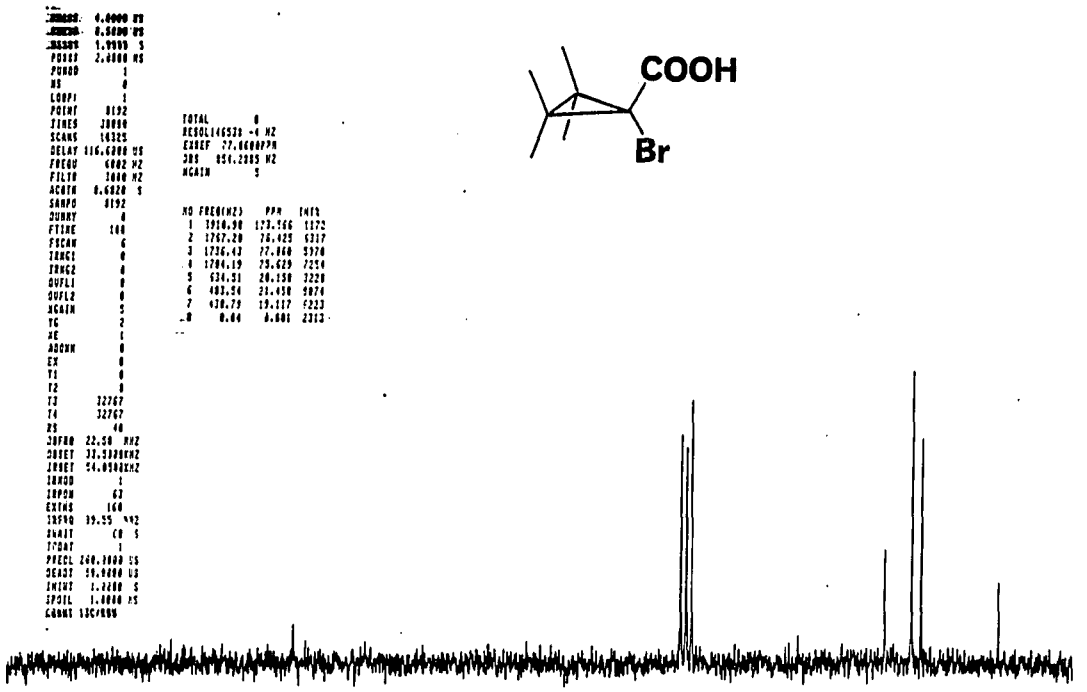


Figure 60. ^{13}C NMR ($CDCl_3$) of 1-Bromo-2,2,3,3-tetramethyl-cyclopropanecarboxylic acid, 104

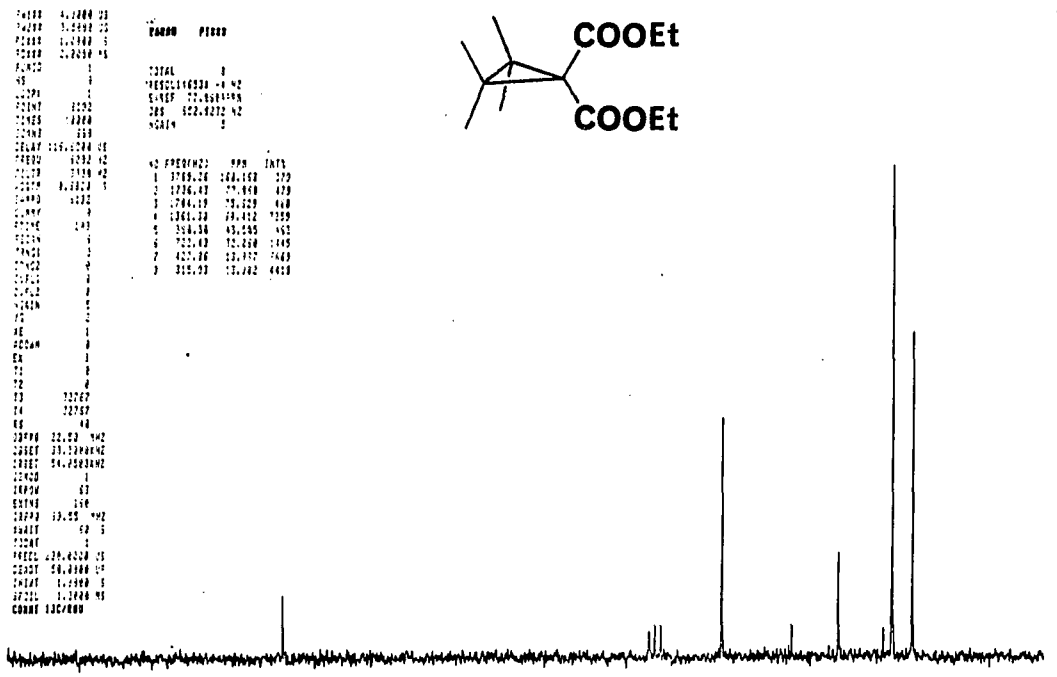


Figure 61. ^{13}C NMR ($CDCl_3$) of 1,1-Dicarboethoxy-2,2,3,3-tetramethylcyclopropane, 106

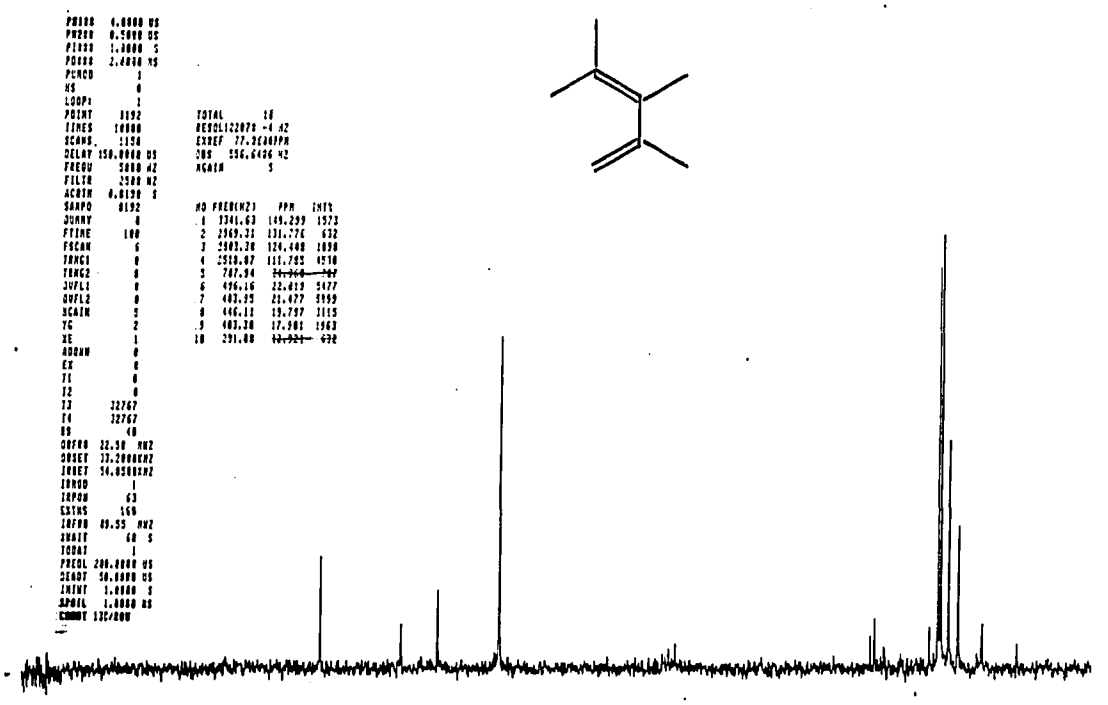


Figure 62. ^{13}C NMR ($CDCl_3$) of 2,3,4-Trimethyl-1,3-pentadiene, 118

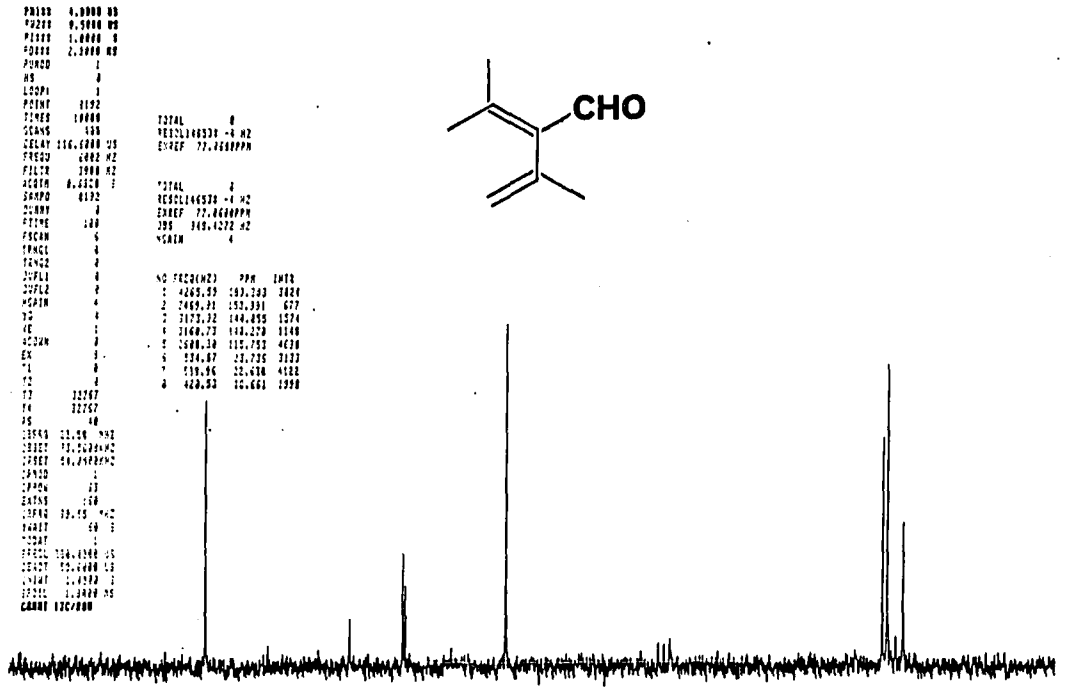


Figure 63. ^{13}C NMR ($CDCl_3$) of 2,4-Dimethyl-3-formyl-1,3-pentadiene, 122

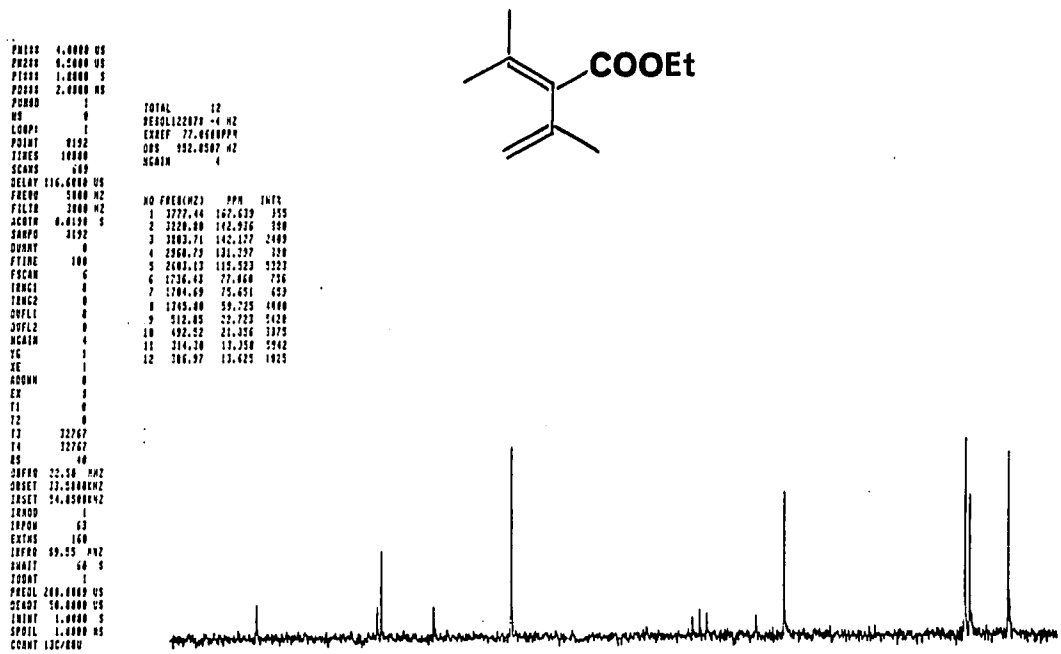


Figure 64. ^{13}C NMR ($CDCl_3$) of 2,4-Dimethyl-3-carboethoxy-1,3-pentadiene, 124

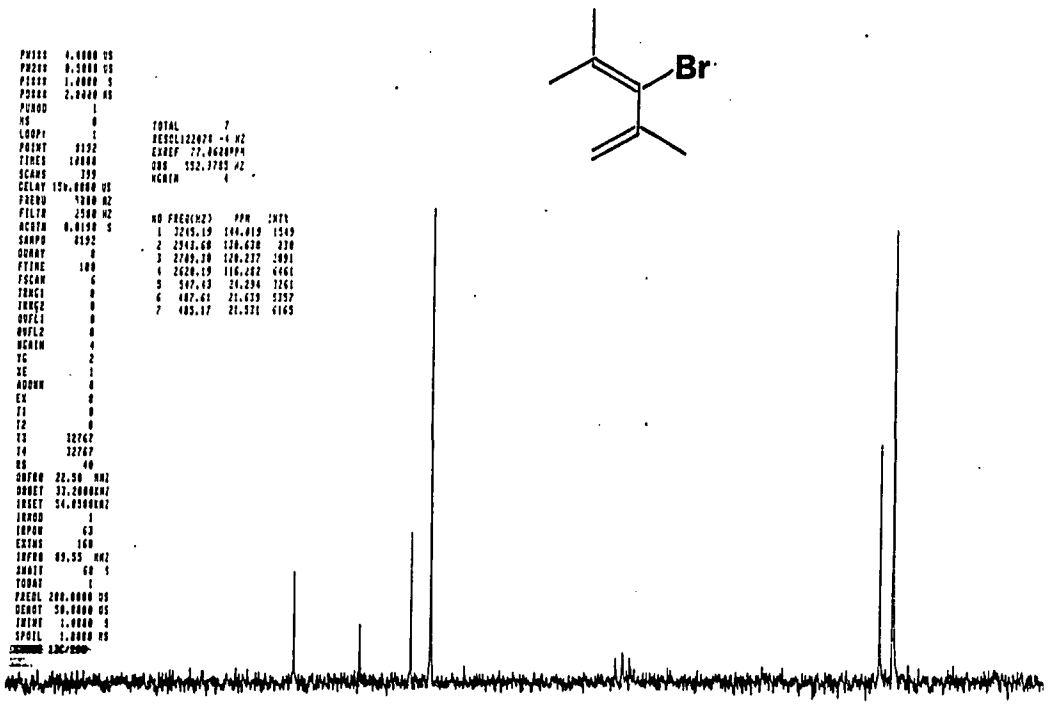
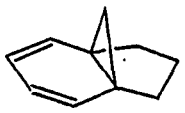


Figure 65. ^{13}C NMR ($CDCl_3$) of 2,4-Dimethyl-3-bromo-1,3-pentadiene, 126

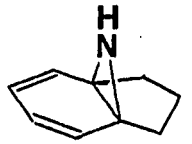
III. ELECTROPHILIC ADDITIONS TO [4.3.1]PROPELLENES

INTRODUCTION

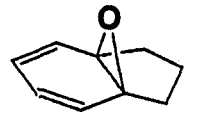
[4.3.1]Propellenes are well-studied members of the Propellane family[135]. The diene 140[136] and its derivatives[137,138] have been extensively investigated with respect to the cycloheptatriene-norcaradiene equilibrium problem. Singlet oxygen addition[139], Diels-Alder reactions[140], protonation[141], and transition-metal complexes[142] of 140



140



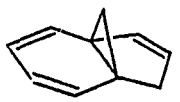
141



142

have also been reported, as have studies of the heterocyclic analogs 141[143] and 142[144].

Triene 143 has received attention for its conversion to the tetraenyl anion 144[145], a 10π-electron aromatic system. Reactions of 144 with electrophiles were reported



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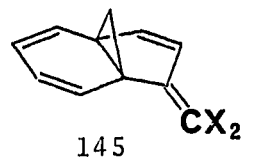
144

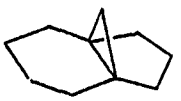


145

to be highly stereoselective[146]. The methylenated derivatives 145 were found to prefer a tricyclic structure[147].

Spectroscopic studies of [4.3.1]propellane systems

have appeared in the last two decades. The effects of the cyclopropane ring on the chemical shifts of the olefinic protons in 140 were examined using a mathematical model[148].



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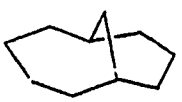
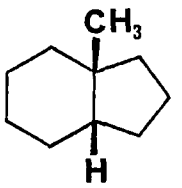


148



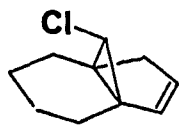
149

Comparison of the ^{13}C NMR of 147 and its relatives 148 and 149 was made to examine the effects of ring strain on the carbon chemical shifts[149].

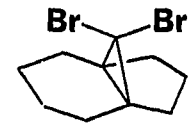
Hydrogenolysis of 147 led to side-bond cleavage of the cyclopropane ring[150], giving almost exclusively the *cis*-isomer, 149. A similar side-bond cleavage during free radical bromination[151] has been reported, but the product stereochemistry is not known.

Reports of halogenated derivatives of [4.3.1]propellanes are abundant. The halo-derivatives were often employed to generate *anti*-Bredt' bridgehead olefins. A rather unexpected reaction occurred when 150 was treated with strong base[152]. Solvolyses of 151 and 152 have been shown to proceed via bridgehead olefinic intermediates[153]. The organolithiums obtained from treating 153 and 154 with alkyllithiums gave the corresponding alcohols upon oxyenation[154]. Retention

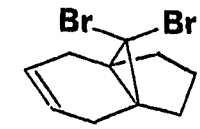
was observed in acetolyses of 153 or 154 and their saturated



150

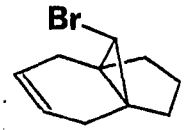


151

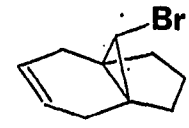


152

counterparts[155]. However, reductions of either 153 or 154 with Bu_3SnD provided only the epimer 155[156]. Lithiocyclopropylidene carbenoids generated from 151 or 152 and its



153



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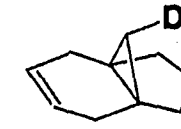
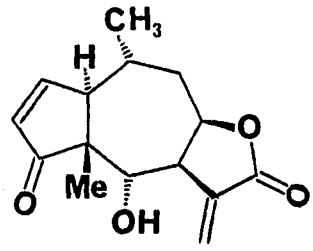
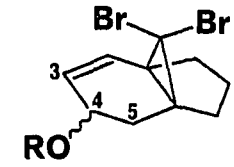


155

derivatives have been shown to undergo various reactions such as insertion, dimerization, or rearrangements[157].





157

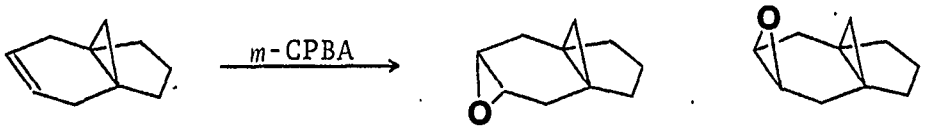
In our laboratories, electrophilic additions to 152, 157, and their derivatives were investigated in studies toward the total synthesis of Helenalin[158,159]. Unexpected chemistry was observed and attributed to conformational

effects. ^{1}H NMR of several pairs of epimers of 157 and its derivatives revealed a well-defined trend in the splitting patterns of H_4, which was applied to support stereochemical assignments in a related system.

RESULTS AND DISCUSSION

[4.3.1]Propell-3-ene and Derivatives

Epoxidization of 158[160] with *m*-CPBA provided a 2.7:1.0 mixture[161] of two isomeric epoxides, from which pure 159 and 160 were isolated by column chromatography. The



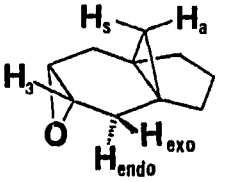
158 159 160

stereochemistry was established by studying the Lanthanide-Induced-Shifts of each isomer using $Eu(pdm)_3$[162].

As expected, H_s in 160 is shifted downfield more rapidly with each increment of $Eu(pdm)_3$ than H_s in 159, due to its proximity to the oxygen. The LIS of H_s and other protons in the vicinity of the epoxy ring are summarized in Tables XXIII and XXIV. Several observations deserve mention.

H_s in 159 was so shielded that it appeared at -0.2ppm. This remarkable shielding effect has been rationalized in terms of a long-range anisotropy effect by the epoxy ring[161], but the unusual effectiveness is not well-understood. H_s in 160 was shifted even more readily than H_{exo}. This seems to indicate a closer proximity of H_s to the oxygen and,

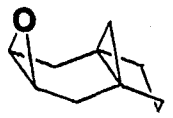
Table XXII. Proton Lanthanide-Induced-Shifts of 159



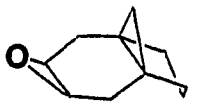
159

[Eu(pdm)$_3$] / [159]	LIS (ppm)				
	H_s	H_a	H_3	H_{exo}	H_{en}
0	-0.2	0.6	3.1	2.1	
0.1	0.4	1.0	5.0	2.7	3.3
0.2	1.2	1.6	7.8	3.7	4.8
0.3	2.1		10.3	4.1	6.2
0.4	2.8	2.6	12.9	5.4	7.6

consequently, a concave boat or approximately planar conformation shown in 160a and 160b, respectively, but not a convex conformation, 160c, as previously suggested[161].



160a

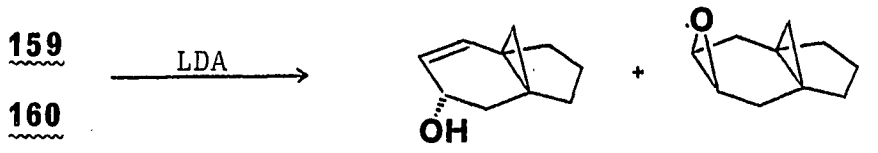


160b

160c

It is interesting to note that when a mixture of 159 and 160 was treated with LDA, only 159 was opened up to the allylic alcohol. Since conversion of an epoxide into an allylic alcohol by a strong base proceeds via *syn* elimination[163], it is apparent that 160 remained intact

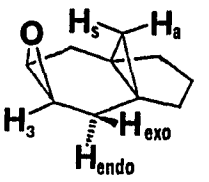
because in conformer 160a or 160b it is difficult for LDA to complex with the oxygen and, at the same time, be in a



161 160

position to abstract H_{exo}. The stability of 160 toward LDA provides a convenient way to isolate this minor epoxide

Table XXIII. Proton Lanthanide-Induced-Shifts of 160



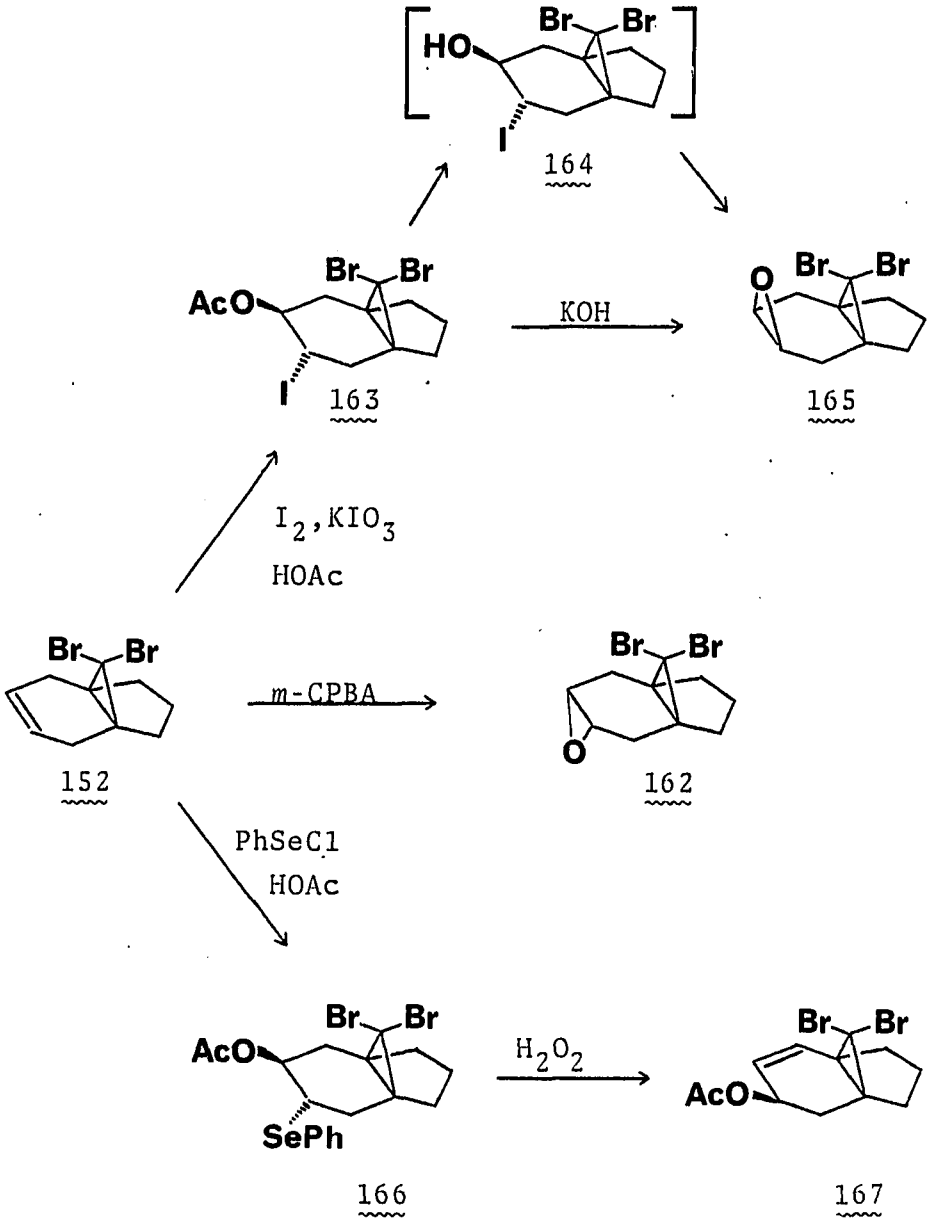
160

[Eu(pdm)$_3$] / [160]	LIS (ppm)				
	H_s	H_a	H_3	H_{exo}	H_{en}
0	0.7	0.2	3.1	2.6	2.0
0.1	2.2	0.7	5.0	3.5	2.7
0.2	4.1	1.3	7.8	4.7	3.6
0.3	7.4	2.3	12.3	7.0	5.1
0.4	9.2	2.9	14.7	8.2	6.0

from the major one, 159, since separating 160 from 161 by column chromatography is understandably much easier than from 159.

Since additions to the double bond in 158 prefer the *endo* approach, it was expected that electrophilic additions

Scheme XXI


HO
Br
Br
I
164
AcO
Br
Br
I
163
KOH
O
Br
Br
165
I_2, KIO_3
HOAc
Br
Br
152
m-CPBA
Br
Br
O
162
PhSeCl
HOAc
AcO
Br
Br
SePh
166
H_2O_2
AcO
Br
Br
167

to 152 would occur exclusively from the *endo* side (Scheme XXI) due to the overwhelming steric effect of the bromine atoms. Accordingly, epoxidization of 152[164] gave only 162, whose structure was confirmed by reduction with n-Bu_3SnH to the known compound 159. The epimeric epoxide 165 (Figure 66) was obtained serendipitously by iodination[165] of 152 in acetic acid followed by basic hydrolysis of the acetate 163. The structure of 165 was confirmed by reducing it with n-Bu_3SnH to the known epoxide 160. Apparently, iodination of 152 took place exclusively from the *endo* side to give 163. Hydrolysis of 163 with KOH provided 164 which eliminated HI spontaneously to yield 165.

Selenenylation[166] of 152 in acetic acid proceeded similarly to give 166. Oxidative elimination of 166 with hydrogen peroxide provided exclusively 167. The structure of 167 was confirmed by hydrolysis to the alcohol 168 followed by oxidation to the α,β-unsaturated ketone 170 (Scheme XXII) which is identical in all respects to that obtained from similar oxidation of 169. Since 169 was provided by a base-catalyzed expoxide ring-opening of 162, its hydroxyl group must be *endo*. Therefore, 168 is undoubtedly the *exo* epimer.

The conversion of 162 to 169 using a strong base deserves some discussion. When the usual base (LDA) was used, only a complex mixture of unidentified products plus unreacted 162 was obtained. Similar treatment of 159,

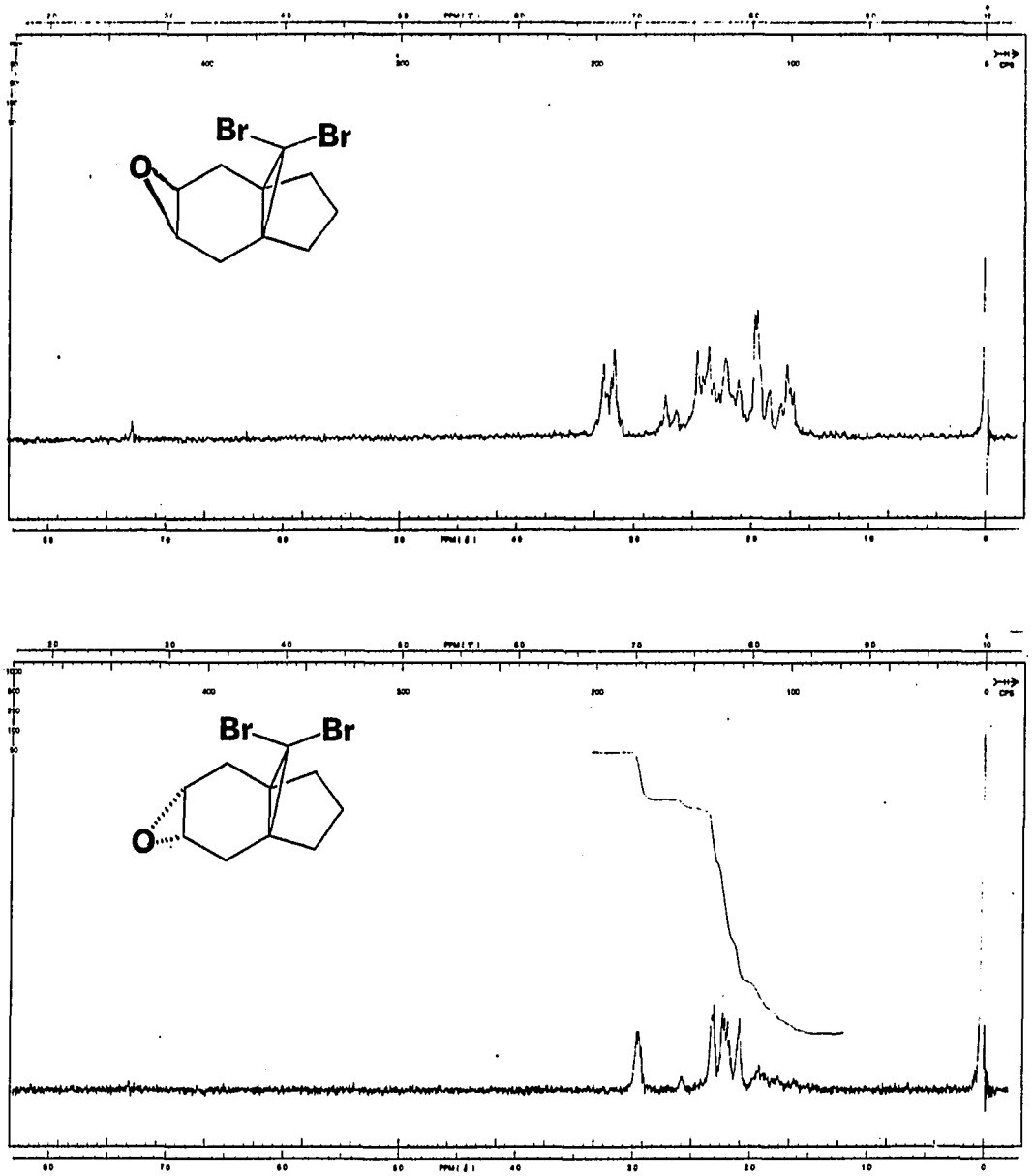
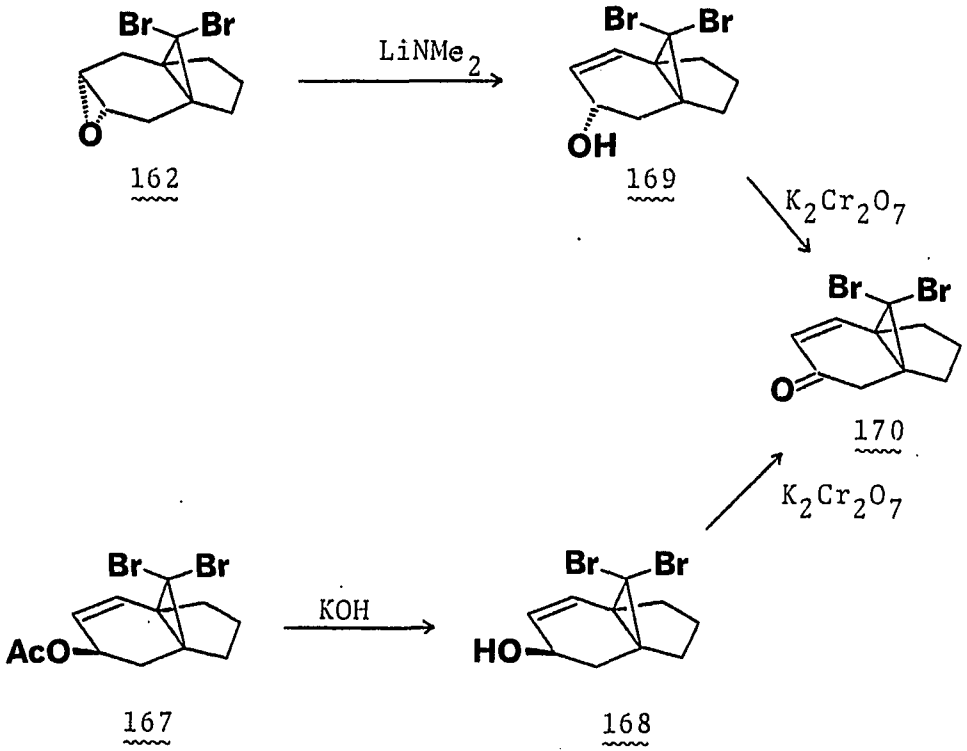


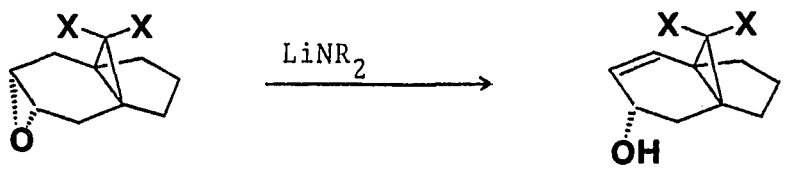
Figure 66. ^{1}H NMR of (top) *exo*-2,3-Epoxy-10,10-dibromo[4.3.1] propellane, 165, and (bottom) *endo*-2,3-Epoxy-10, 10-dibromo[4.3.1]propellane, 152

Scheme XXII



162 169 170 167 168

however, gave the alcohol 161 in satisfactory yield. When the less bulky base $LiNMe_2$ was used, a 78% yield of 169 was obtained from 162. Apparently, replacing the two C-10



159	X = H	161	X = H	66% yield
162	X = Br	169	X = Br	None

hydrogens in 159 with bromine atoms (162) makes approaches to the *endo* side more sterically hindered. The bromine atoms may have accomplished this by forcing both or either the six and five-membered ring to bend more toward each other.

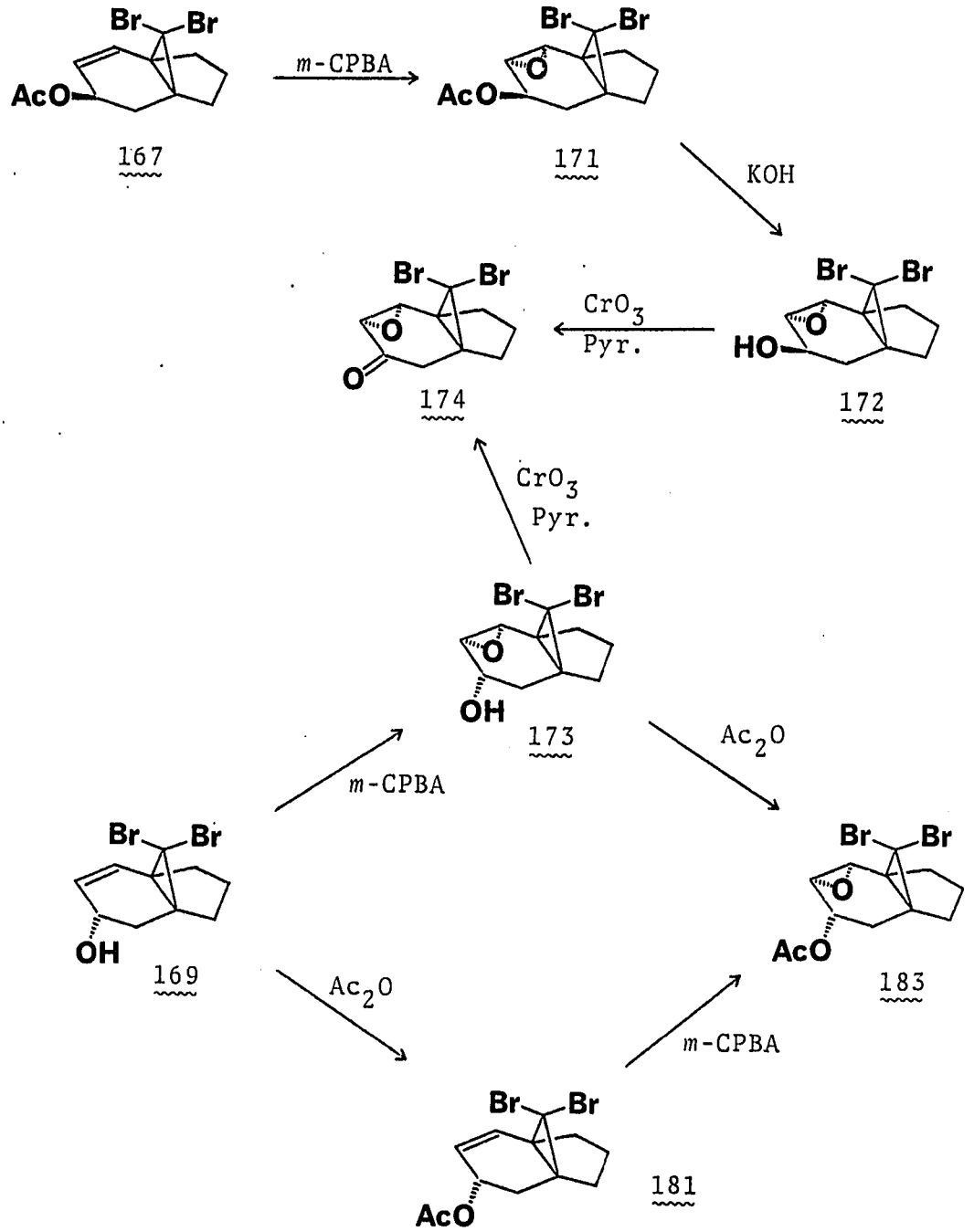
[4.3.1]Propell-2-ene and Derivatives

Similar to the [4.3.1]propell-3-enes, allyl derivatives of [4.3.1]propell-2-ene also undergo electrophilic additions preferentially from the *endo* side.

Epoxidization of 167 produced only one isomer which, based on steric considerations of a model of 167, was assigned the structure shown in 171 (Scheme XXIII). The stereochemical assignment was supported by the following results. First, 171 was hydrolyzed to the alcohol 172 followed by oxidation to the ketone 174. The identical ketone was also obtained from oxidation of 173. Since epoxidization of 169 undoubtedly provided 173 due to the directive effect[167] of the hydroxyl group, and both 172 and 173 were oxidized to the same ketone, 172 must be the *endo*-epoxide shown.

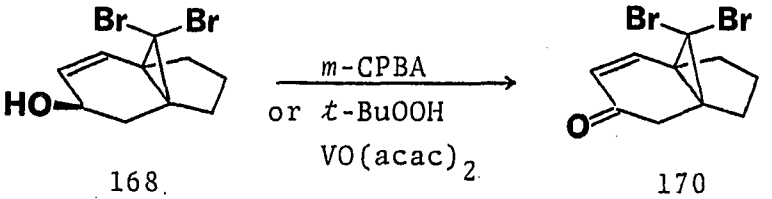
It is interesting to note that even after masking the hydroxyl group in 169 as the acetate, epoxidization of the system still produced exclusively the *endo* epoxide 183. The *endo* stereochemistry was confirmed by treating

Scheme XXIII



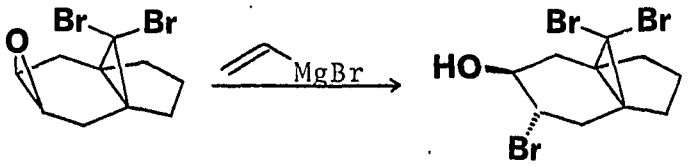
173 with Ac_2O to give 183. Apparently, the steric effect of the *syn* bromine is overwhelming as in 152.

This overwhelming effect was also illustrated in an attempted epoxidization of 168. Treatment of 168 with either CPBA or *t*-BuOOH in the presence of $VO(acac)_2$[168] provided only the known ketone 170.



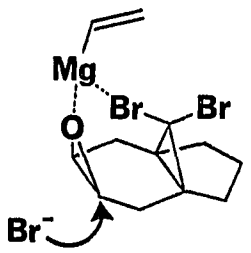
168 170

Another unexpected result attributed to the presence of the bromine atoms was observed in the reaction of 165 with vinyl magnesium bromide. Instead of the predicted

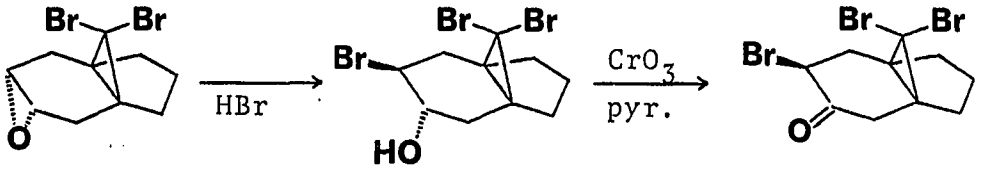


165 177

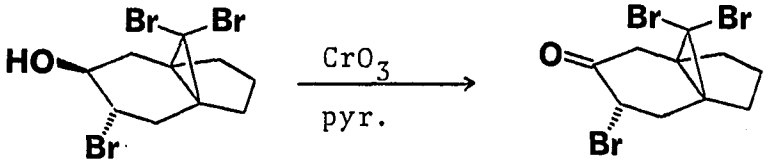
alkylation product, only the bromohydrin 177 was isolated. This unexpected formation of 177 can be nicely explained by a complexation of the magnesium with both the oxygen and bromine of 165 followed by an attack from the *endo* side by the bromide anion.



An isomer of 177 was prepared by treating 162 with HBr to obtain the bromohydrin 178. Both 177 and 178 were



162 178 180



177 179

oxidized to produce the pair of epimeric ketones 179 and 180. A close examination of their ^{1}H NMR proved interesting. While H_4 in 179 appeared as a "triplet", that in 180 was found as an XBA pattern (Figure 67). Apparently the *exo* proton at C_4 in 179 is almost equally coupled to the two protons

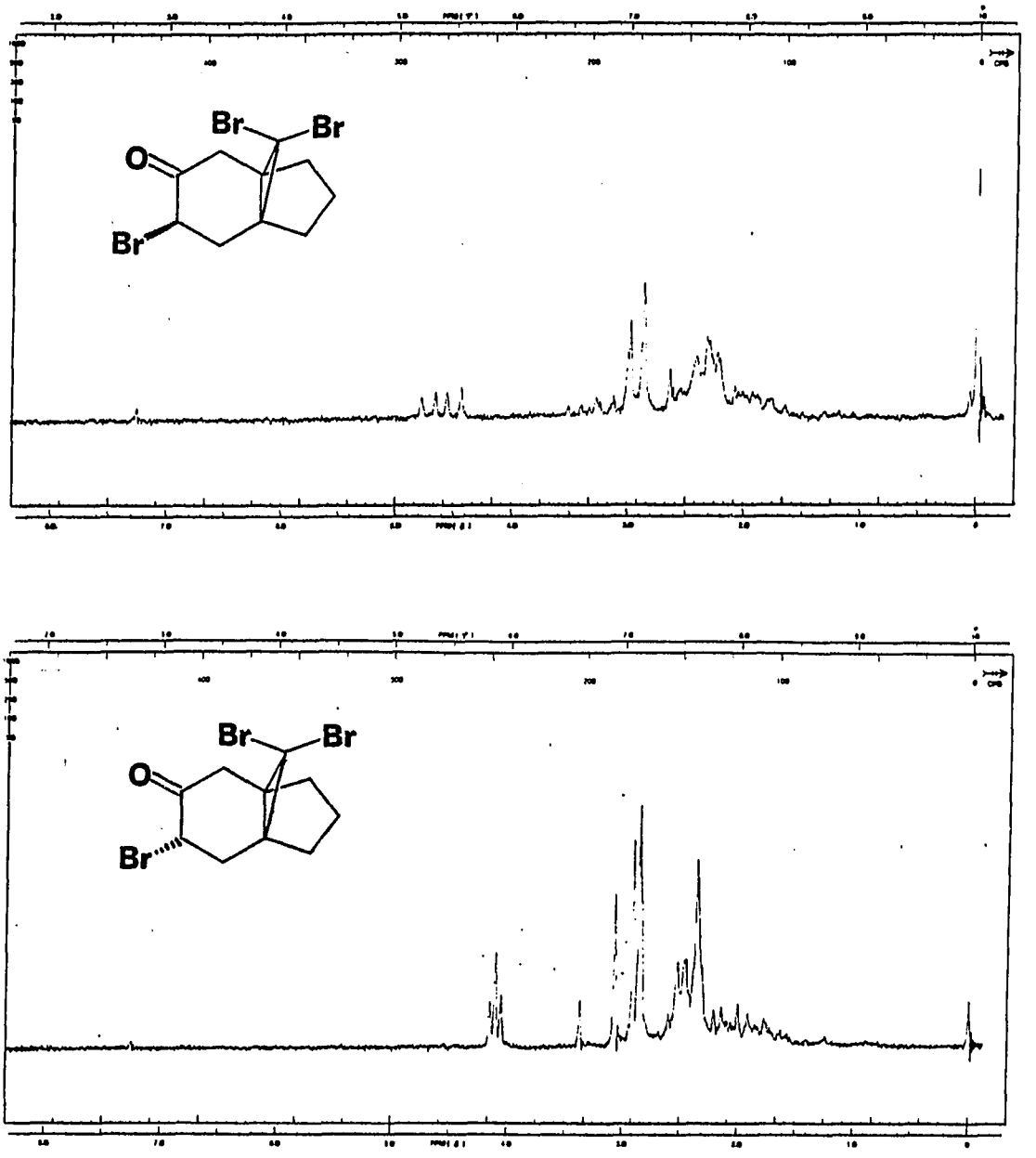
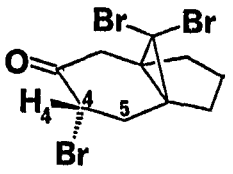
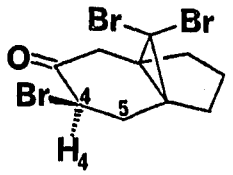


Figure 67. ^{1}H NMR of (top) *exo*-4,10,10-Tribromo[4.3.1]prope11-3-one, 180, and (bottom) *endo*-4,10,10-Tribromo [4.3.1]prope11-3-one, 179

at H_5, whereas the *endo* proton at C_4 in 180 is not.

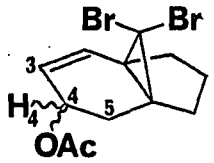


179

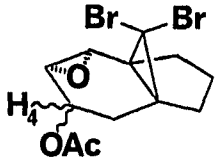


180

Similar coupling patterns were also observed for the related systems 181, 167, and 183, 171. However, due to further coupling with the proton at C-3, the appearance of H_4 in these systems is more complex. H_4 in 181 is represented



167, *exo*-OAc
181, *endo*-OAc



171, *exo*-OAc
183, *endo*-OAc

by two overlapping triplets, whereas in 182, it appears as an XBA with fine splitting (Figure 68). Similarly, H_4 in 183 is a double "triplet" and in 171, it is an XBA with further fine splitting (Figure 69).

The splitting patterns and coupling constants of H_4 in various epimeric pairs are tabulated in Table XXV. In all *exo* epimers, there is observed essentially the same coupling constants of about 12Hz for J_{XB} and 6-7Hz

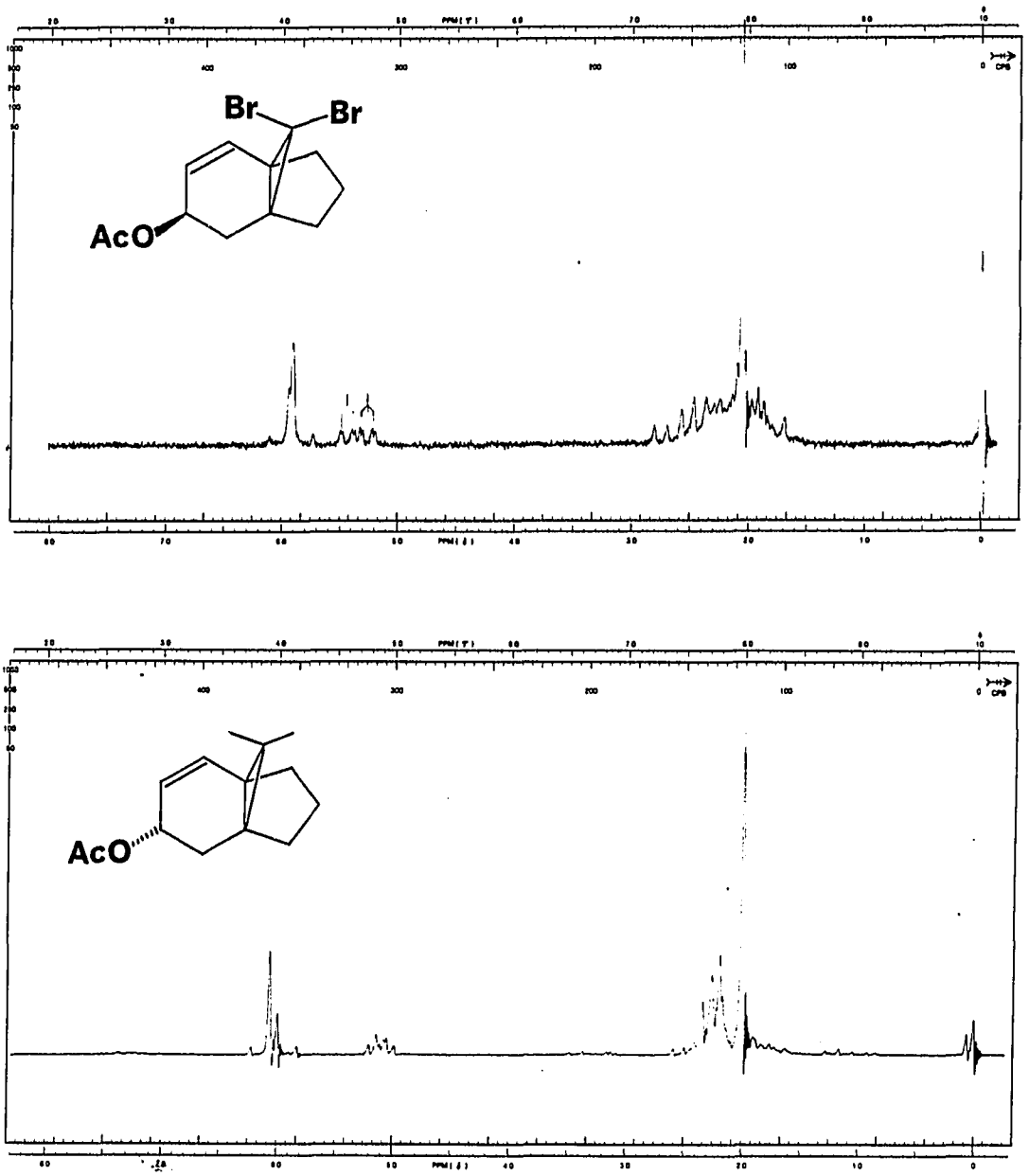


Figure 68. ^{1}H NMR of *exo*-4-Acetoxy-10,10-dibromo[4.3.1] propell-2-ene, 167 (top), and *endo*-4-Acetoxy-10,10-dibromo[4.3.1]propell-2-ene, 181

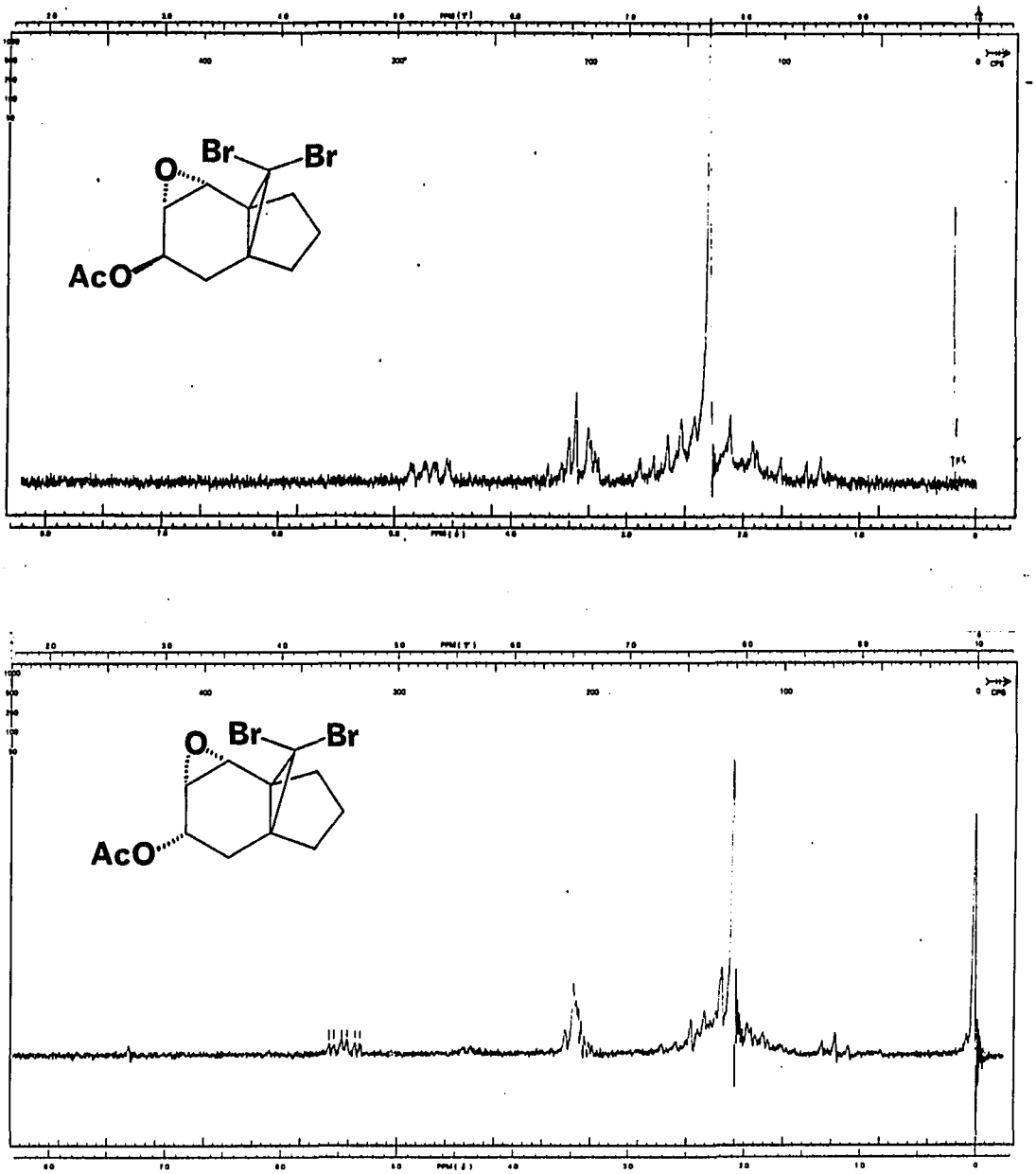
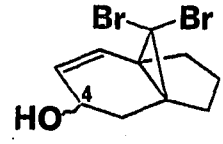
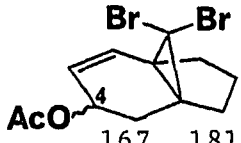
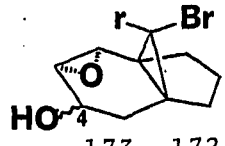
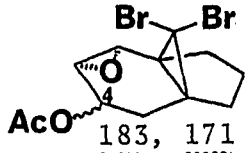
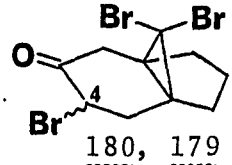
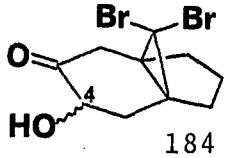
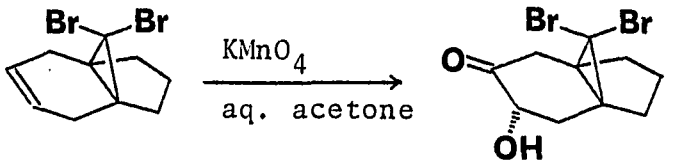


Figure 69. ^{1}H NMR of (top) *exo*-4-Acetoxy-2,3-*endo*-epoxy-10,10-dibromo[4.3.1]propellane, 171, and (bottom) *endo*-4-Acetoxy-2,3-*endo*-epoxy-10,10-dibromo [4.3.1]propellane, 183

Table XXIV. Splitting patterns and coupling constants of H_4

Compound	H_4	
	Endo epimer	*Exo* epimer
 169, 168	Broad, Unstructured	XBA J_{XB} = 11Hz, J_{XA} = 6Hz
 167, 181	Overlapping triplets	XBA J_{XB} = 11Hz, J_{XA} = 6Hz
 173, 172	Broad, Unstructured	XBA J_{XB} = 11Hz, J_{XA} = 6Hz
 183, 171	XBA J_{XM} = 7Hz, J_{XA} = 3Hz	XBA J_{XB} = 12Hz, J_{XA} = 7Hz
 180, 179	"Triplet" J_{XA} = 3Hz	XBA J_{XB} = 13Hz, J_{XA} = 7Hz
 184	"Triplet" J_{XA} = 11Hz	Unknown.

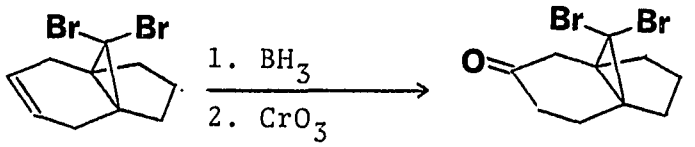
for J_{XA}. The general splitting pattern of H_4 was utilized to support the assignment of stereochemistry in 184. The α-hydroxy ketone 184 was obtained from oxidation of 152 with neutral $KMnO_4$ in aqueous acetone[169]. Although the preference for the *endo* approach to the double bond in 152 has been established, the stereochemistry at C-4 in 184 was questionable due to a possible base-catalyzed epimeri-



152 184

zation during the reaction. However, ^1H NMR of 184 showed H_4 as a "triplet" indicating the hydroxyl group was indeed *endo* and the epimerization had not occurred.

Another derivative of 152 prepared by an electrophilic addition to the olefin is 115. Hydroboration of 152 followed



152 185

by oxidation[170] gave 185 in 52% yield. Compound 185 was unstable at room temperature. Purified white crystals of 185 turned completely dark green in about a week.

In summary, [4.3.1]propell-2-enes and -3-enes undergo electrophilic additions preferentially from the *endo* side. In the case of the 10,10-Dibromo derivatives, the steric effect of the bromine atoms is overwhelming and responsible for some unexpected chemistry. Several epimeric pairs of allylic derivatives of [4.3.1]propell-2-ene were synthesized. The proton at C-4 in these compounds was observed to have a general splitting pattern which depends on the stereochemistry at C-4. The splitting pattern was applied to assign the stereochemistry in a related system.

EXPERIMENTAL

General

Infrared spectra were recorded on a Beckman IR-18A or IR-4250 spectrophotometer, and NMR spectra on a Varian HA-60 or Hitachi Perkin-Elmer R-20B spectrometer using deuterated chloroform as the solvent and tetramethylsilane as the internal standard. High resolution mass spectra were measured using an AEI MS-902 mass spectrometer. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Syntheses

endo-3,4-Epoxy[4.3.1]propellane, 159, and *exo*-3,4-Epoxy [4.3.1]-propellane, 160

To a solution of 3.451g of *m*-CPBA (20mmole) dissolved in 75ml of $CHCl_3$ was added dropwise 2.68g of 158[154] (20mmole) in 5ml of $CHCl_3$. An exothermic reaction took place instantly, and precipitation of *m*-Chlorobenzoic acid was observed. Work-up after 15 minutes stirring consisted of diluting with Et_2O, washing with saturated $NaHCO_3$, water, and saturated NaCl, drying over $MgSO_4$, and stripping of solvent on a rotary evaporator. The oily residue was chromatographed on a silica-gel column, which was eluted initially with hexane to afford 0.212g of the starting material, and then with

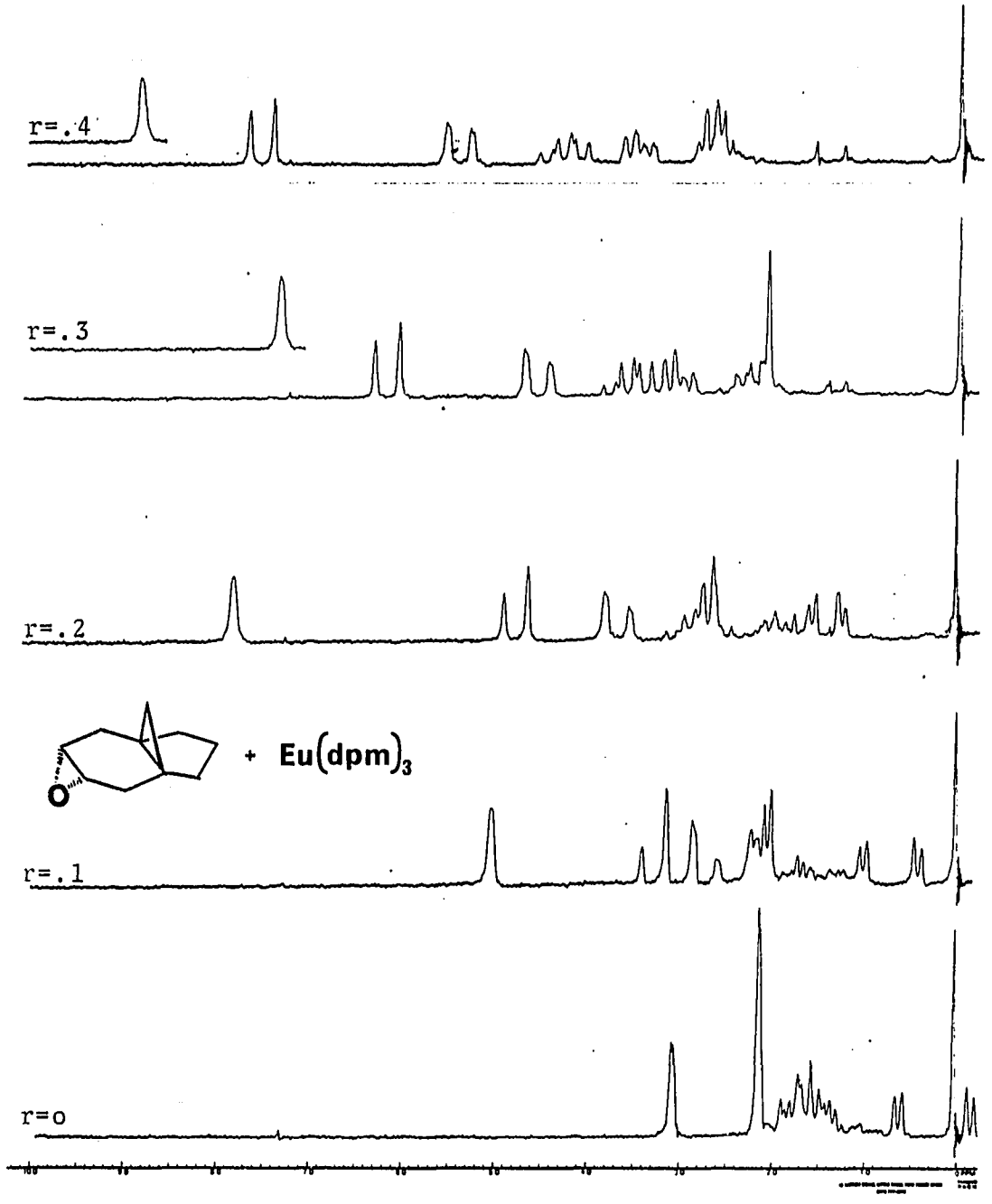


Figure 70. LIS of *endo*-3,4-Epoxy[4.3.1]propellane, 159, at various r, $Eu(dpm)_3$ to 159 molar ratio

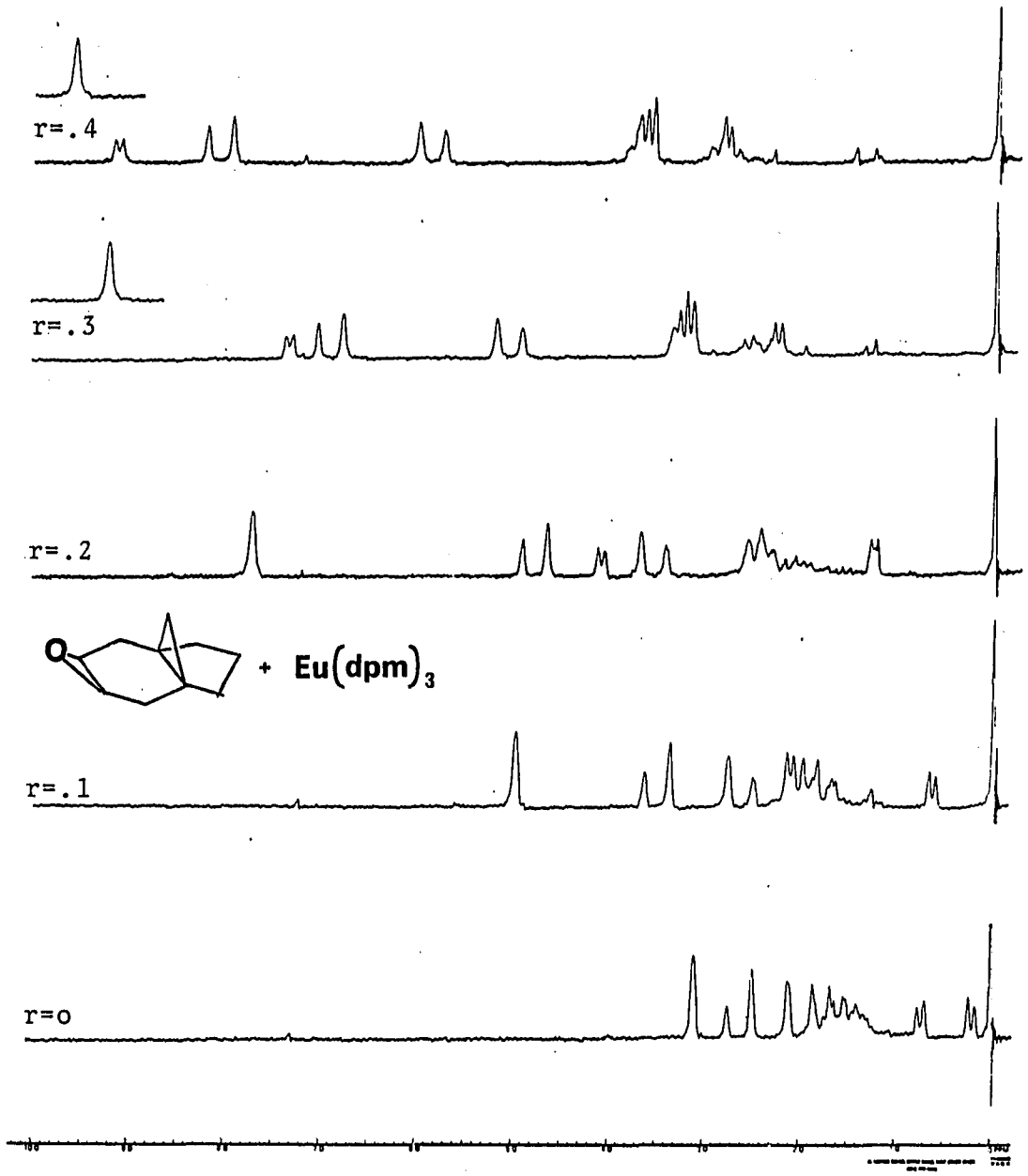


Figure 71. LIS of *exo*-3,4-Epoxy[4.3.1]propellane, 160, at various r, $Eu(dpm)_3$ to 160 molar ratio

20% ethereal hexane to yield 1.924g of a 10:27 mixture of the two isomeric epoxides (64% yield).

Each isomer was obtained in pure form by column chromatography of the mixture on a 71in.x½in. silica-gel column eluted with 10% ethereal hexane. After 250ml of solvent had passed through, 30 5ml fractions were collected. Fraction 8 was found to contain only the major isomer, and fractions 28 to 30 only the minor one.

To 0.0308g (0.205mmole) of the minor product in 0.55ml of $CDCl_3$ was added 0.0144g of $Eu(dpm)_3$ (0.205mmole). The mixture was shaken well and let stand until all undissolved impurities settled down. The ^1H NMR of the mixture was measured. Another 0.0144g portion of the $Eu(dpm)_3$ was again added and the same subsequent steps were carried out. A total of four portions of the $Eu(dpm)_3$ were used. The spectra obtained are shown in Figure 71.

The same procedure was utilized for a sample of 0.0434g (0.289mmole) of the major epoxide dissolved in 0.55ml of $CDCl_3$ using four portions of 0.0203g of $Eu(dpm)_3$. The minor component was then identified as the *exo*-epoxide, 160; IR (neat): 2900, 2850, 1450, 1430, 1010, 860 cm^{-1}; ^1H NMR (CCl_4): δ3.00 (s, 2H), 2.57 and 1.95 (AB, 4H, J= 16hz), 1.90-1.20 (m, 6H), 0.77 and 0.16 (AB, 2H, J=4Hz). Anal. Calc'd for $C_{10}H_{14}O$: C, 79.96%; H, 9.39%. Found: C, 80.02%; H, 9.31%. The major epoxide was the *endo*-isomer, 159; IR (neat): 3040, 2900, 2850, 1440, 1430, 1020, 860

cm^{-1}; ^1H NMR (CCl_4): δ3.04 (s, 2H), 2.10 (s, 4H), 1.9-1.2 (m, 6H), 0.60 and 0.20 (AB, 2H, J=6Hz). Anal. Calc'd for $C_{10}H_{14}O$: C, 79.96%; H, 9.39%. Found: C, 79.94%; H, 9.30%.

endo-[4.3.1]Propell-2-en-4-ol, 161

In a flame-dried flask equipped with a magnetic stirring bar and a septum, kept below -10°C and under dry N_2, were placed 0.55ml (3.9mmole) of diisopropyl amine, 5ml of THF freshly distilled from LAH, and 2.8ml of a 1.4M solution of *n*-Buli in hexane. After 15 minutes stirring, 0.189g (1.3mmole) of 159 in 5ml of THF were injected through the septum. The mixture was allowed to warm up to room temperature and stirred for 8 hours. Work-up consisted of washing with 1M HCl solution, water, and saturated NaCl followed by drying over $MgSO_4$. After stripping of the solvent in a rotary evaporator, the oily residue was chromatographed on a silica-gel column to afford 0.126g (66% yield) of 161. IR (CCl_4): 3600-3100, 3070, 3030, 2920, 2860, 1630, 1500, 1095, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ6.05 (AMX, 1H, J_{MX}=2.5Hz, J_{AX}=10Hz), 5.30 (d, J=10Hz), 4.40-3.90 (m. 1H), 2.70-2.30 (apparent AB, 2H), 2.00-0.90 (m, 6H), 0.74 and 0.45 (AB, 2H, J=5Hz). Anal. Calc'd for $C_{10}H_{14}O$: C, 79.96%; H, 9.39%. Found: C, 79.99%; H, 9.40%.

To 0.0729g (0.486mmole) of 161 in 0.55ml of $CDCl_3$ was added 0.034g (0.049mmole) of $Eu(dpm)_3$. The ^1H NMR was

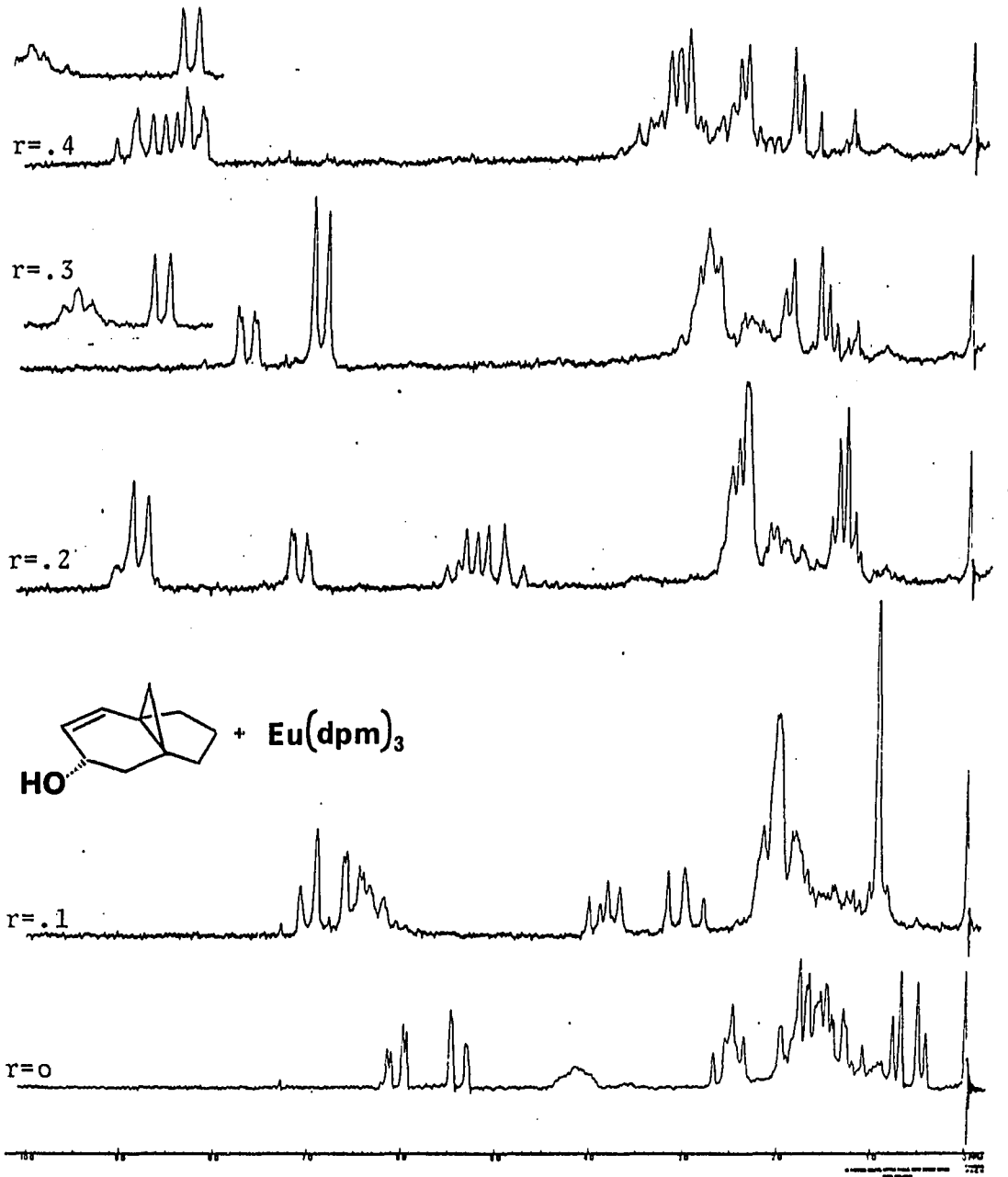


Figure 72. LIS of *endo*-[4.3.1]propell-2-en-4-ol, 161, at various r, $Eu(dpm)_3$ to 161 molar ratio

then taken. The addition of $Eu(dpm)_3$ was repeated until a total of four ^1H NMR spectra corresponding to four different $Eu(dpm)_3$:161 ratios were obtained. The spectra are shown in Figure 72.

exo-3,4-Epoxy-10,10-dibromo[4.3.1]propellane, 165

A solution of 2.015g (6.9mmole) of 152, 0.876g of I_2, and 0.372g of KIO_3 in 35ml of acetic acid was stirred at 50°C for 2 hours. To the mixture was added 0.677g of KOAc and stirring was continued for another 12 hours at 50°C. The mixture was then poured onto an ice-water slurry and extracted twice with CH_2Cl_2. The combined extracts were washed once with water, and concentrated in a rotary evaporator. The residue was dissolved in 50ml of benzene and stirred with 0.774g of KOH in 10ml of MeOH. The dark red mixture turned into light brown, and an oily layer separated on the bottom. More MeOH was added until the two layers became miscible. The mixture was checked for basicity and more KOH was added as necessary. After 4 hours, most of the MeOH was removed in a rotary evaporator and replaced with Et_2O. The ethereal solution was washed with water, saturated $NaHCO_3$, and saturated NaCl, and dried over $MgSO_4$. The dark purple crystalline residue was chromatographed on a silica-gel column; elution with 33% ethereal hexane afforded 1.322g (62% yield) of 165; m.p 127.0-128.5°C. IR (KBr): 2940, 1440, 1050, 815 cm^{-1}.

Anal. Calc'd for $C_{10}H_{12}OBr_2$: 305.92547. Found: 305.92513.

In an oven-dried 5mm NMR tube under N_2 were placed 0.082g of 165 and 0.361g of *n*-Bu_3SnH[171]. The tube was then sealed off with a torch, and became warm when shaken vigorously. After 30 hours, NMR indicated the presence of 160, as shown by a singlet at δ3.00, a doublet at δ2.55 (J=16Hz), and a doublet at δ0.15 (J=4Hz).

endo-10,10-Dibromo[4.3.1]propell-2-en-4-ol, 169

To 5.84g (20mmole) of 152 dissolved in 125ml of $CHCl_3$ were added 1.1eq. (4.27g) of *m*-CPBA. The mixture became perceptibly warm in 1 minute. After 4 hours stirring at r.t, a sat'd solution of $NaHSO_3$ was added. The organic layer was diluted with ether, washed twice with 1M NaOH solution, once with sat'd NaCl, and dried over $MgSO_4$. Evaporation of solvents afforded a white solid identified as 162 (6.047g, 98% yield)[164].

In a flame-dried flask were placed 0.24ml (3.6mmole) of $HNMe_2$ in 5ml of dry THF at 0°C. To this was added 2.7ml (3.6mmole) of a 1.33M *n*-BuLi solution which was previously standardized with diphemylacetic acid. After stirring for 15 minutes at 0°C, 0.74g (2.4mmole) of 162, dissolved in 10ml of dried THF, was added dropwise via syringe. After completion of the addition, stirring was continued for 5 minutes. The mixture was then diluted with ether, washed with 1N HCl solution and then sat'd NaCl solution, dried

over Na_2CO_3, and stripped of solvents on a rotary evaporator. Column chromatography of the residue on silica gel, eluting first with 80% ethereal hexane, afforded 0.16g of the starting material. Further elution with 67% ethereal hexane gave 0.45g (78%) of 169 (m.p 88.5-89.5°C). IR (KBr): 3500-3100 (OH), 3020, 2920, 1630, 1430, 1010 cm^{-1}; ^1H NMR (CCl_4): δ5.98 (apparent d, J=2Hz, 2H), 4.15 (m, 1H), 2.5-1.5 (m, 9H). Anal. Calc'd for $C_{10}H_{12}Br_2O$: C, 39.00; H, 3.95; Br, 51.88. Found: C, 39.17; H, 3.93; Br, 51.83.

The acetate derivative 181 was prepared by refluxing 0.055g (0.18mmole) of 169 with 0.3ml of Ac_2O and 0.02ml of pyridine in Et_2O for 12 hours. The usual work-up and recrystallization (Et_2O-hexane) afforded 0.050g (79% yield) of 181; m.p 81.5-83°C. ^1H NMR ($CDCl_3$): δ6.10 (m, 2H), 5.10 (apparent two overlapping triplet, 1H), 2.5-1.7 (m with an acetate s at 2.0, 8H).

10,10-Dibromo[4.3.1]propell-2-ene-4-one, 170

To a solution of 0.924g (3mmole) of 168 and 1.5eq. of $VO(accac)_2$[168] in 20ml of benzene were added dropwise 1.5eq. of *t*-butylhydroperoxide in benzene. The light green mixture turned dark brown instantly. The reaction was followed by TLC which showed it to be completed in 36 hours. The mixture was then diluted with Et_2O, washed twice with saturated $NaHCO_3$ solution, once with water, dried over K_2CO_3, and concentrated in vacuo. The oily residue solidified and

weighed 0.720g (78% yield); m.p 84°C. IR ($CDCl_3$): 3040, 2940, 1670, 1610, 1445, 1390, 1250; ^1H NMR ($CDCl_3$): δ6.9 (d, 1H, J=10Hz), 6.1 (d, 1H J=10Hz), 2.7 (AB pattern, 2H, J=19Hz), 2.5-1.7 (br m, 6H). Anal. Calc'd for $C_{10}H_{10}OBr_2$: m/e 303.90994. Found: m/e 303.91274.

Compound 170 was also obtained from refluxing 168 with 1.2eq. of *m*-CPBA in $CHCl_3$ for 12 hours, and from oxidation of either 168 or 169 with chromic acid[172].

4-*exo*,2,3-*endo*-Epoxy-10,10-dibromo[4.3.1]propellane-4-acetate, 171

To 3.375g (10mmole) of 167 dissolved in 50ml of $CHCl_3$ were added 3.369g of *m*-CPBA. After refluxing for 12 hours, the mixture was diluted with Et_2O, washed twice with sat'd $NaHCO_3$ solution, once with H_2O, and once with sat'd NaCl solution, and finally dried over $MgSO_4$. Solvent was removed with a rotary evaporator. The crystalline product was recrystallized from hot EtOH/H_2O to afford 2.051g (60% yield) of 171. IR (CCl_4): 2930, 1750, 1440, 1370, 1230, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ4.65-4.35 (XBA, 1H, J_{XB}=12Hz, J_{XA}=7Hz), 3.30-3.05 (apparent AB, 2H, J=3.5Hz), 2.80-1.45 (m including an acetate s at 2.10, 8H).

4-*exo*,2,3-*endo*-Epoxy-10,10-dibromo[4.3.1]propell-4-ol, 172

Acetate 171 (2.876g, 8mmole) was added to 8mmole of KOH dissolved in 130ml of MeOH. The mixture was refluxed for 30 minutes and then concentrated in vacuo. The residue

was dissolved in Et_2O, washed with water and saturated NaCl solution, dried over $MgSO_4$, and stripped of solvent in vacuo. The crude product was recrystallized from Et_2O-Hexane to afford 2.070g (97% yield) of the alcohol 172; m.p 111-114°C. IR (KBr): 3600-3020 (-OH), 2930, 1440, 1500, 1060, 1040, 870, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$): 3.80-3.50 (ABX, 1H J_{AX}=6Hz, J_{BX}=11Hz), 3.38-3.15 (apparent AB, 2H, J=3.5Hz), 2.40-1.50 (m. 8H). Anal. Calc'd for $C_8H_9Br_2$ (P^+-HO=CH-CHO): m/e 262.90710. Found: m/e 262.90632.

4-*endo*,2,3-*endo*-Epoxy-10,10-dibromo[4.3.1]propellane-4-ol, 173

To 0.100g (0.33mmole) of alcohol 169 dissolved in 15ml of $CHCl_3$ was added 0.084g (0.49mmole) of m-CPBA. After refluxing for 13 hours, the mixture was washed twice with saturated $NaHCO_3$ and once with saturated NaCl solution, and dried over K_2CO_3. The solvent was then removed in vacuo. Hexane was added to the oily residue to allow crystallization, following which 0.085g of the epoxide was collected (81% yield), m.p 124-125°C. IR ($CDCl_3$): 3600-3200 (-OH), 2940, 1440, 1250, 1030, 780 cm^{-1}; ^1H NMR ($CDCl_3$): 4.65-4.20 (m, 1H), 3.55-3.35 (m, 2H), 2.55-1.60 (m. 8H). Anal. Calc'd for $C_8H_9Br_2$ (P^+-HO=CH-CHO): m/e 262.90710. Found: m/e 262.90663.

The acetate derivative 183 was prepared by refluxing 0.05g (0.18mmole) of 173 with 1.2eq. of each Ac_2O and pyridine in Et_2O for 12 hours. The crude obtained after

the usual work-up is identical to that provided by epoxidization of 181 with *m*-CPBA (2 hours, reflux) as shown by ^{1}H NMR.

endo-2,3-Epoxy-10,10-dibromo[4.3.1]propellane-4-one, 174

The oxidations of 172 and 173 were carried out following the method of Brown et al.[172]. To 1.971g (6.1mmole) of 172 dissolved in 30ml of Et_2O were added 3ml of a 2N chromic acid solution. After stirring for 48 hours, the aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The crude product was recrystallized from Et_2O-hexane to afford 1.015g (52% yield) of 174; m.p 125.5-126.5°C. IR (KBr): 2910, 1725, 1430, 855, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ3.85 (d, 1H, J=4Hz), 3.38 (d, 1H, J=4Hz), 2.85 (m, 2H), 2.5-1.6 (br m, 6H). Anal. Calc'd for $C_{10}H_{10}O_2Br_2$: m/e 319.90486. Found: m/e 319.90802.

Alternately, a solution of 1.84g (5.73mmole) of 173 in 30ml of CH_2Cl_2 was added to a well-stirred solution of 3.435g (34.35mmole) of CrO_3 and 5.5ml of pyridine[173] in 75ml of CH_2Cl_2. The red solution turned dark brown instantly. After 3 hours stirring, the usual work-up and recrystallization (Et_2O-hexane) afforded 1.140g (62% yield) of 174.

3-*exo*,4-*endo*-4,10,10-Tribromo[4.3.1]propellan-3-ol, 177

To 0.575g of 165 in 100ml of THF was added 1.8ml of a

1.2M solution of vinyl magnesiumbromide in ether. After 8 hours, the mixture was quenched with saturated NH_4Cl, washed with water, dried over $MgSO_4$, and concentrated in vacuo. Hexane was added to the oily residue to induce solidification. After recrystallization, 0.557g (89% yield) of 177 were collected, m.p 100-106°C. IR (KBr): 3600-3040 (-OH), 2920, 1440, 1060, 840 cm^{-1}; ^1H NMR ($CDCl_3$): δ4.30-3.50 (m, 2H), 2.85-1.60 (m, 12H). Anal. Calc'd for $C_{10}H_{12}OBr_2$ (P^+-HBr): 305.92547. Found: 305.92913.

3-*endo*,4-*exo*-4,10,10-Tribromo[4.3.1]propellan-3-ol, 178

To a solution of 0.155g (0.50mmole) of 162 in 30ml of $CHCl_3$ was added 0.09g of a 48% aqueous HBr solution at room temperature. After stirring for 6 hours, the mixture was washed with H_2O, sat'd $NaHCO_3$ solution, and sat'd NaCL solution, and dried over $MgSO_4$. The solvent was removed with a rotary evaporator. About 1ml of hexane was added to the oily residue to induce solidification. After recrystallization, 0.191g of 178 (98% yield) was obtained, m.p 109-110°C. IR (KBr): 3600-3100 (-OH), 2940, 1450, 1190, 1035, 920, and 770 cm^{-1}; ^1H NMR ($CDCl_3$): 4.10-3.80 (m, 2H), 3.10-1.60 (m, 11H).

For conversion to the acetate derivative, 186, 0.989g (2.55mmole) of 178 was refluxed in Et_2O with 1.2eq. each of acetic anhydride and pyridine for 12 hours. The mixture was then diluted with Et_2O and washed with saturated $NaHCO_3$.

After drying with $MgSO_4$, the mixture was concentrated in vacuo and the residue was recrystallized from ethereal hexane to yield 0.848g (77%) of the acetate; m.p 131-133°C. IR (KBr): 2930, 1745, 1440, 1225, 1130, 790 cm^{-1}. ^1H NMR ($CDCl_3$): δ5.25-4.80 (apparent AMX with second splitting, J_{MX}=11.5Hz, J_{AX}=17.5Hz), 4.10-3.60 (apparent B_2MX, 1H, J_{BX}=5Hz, J_{MX}=11.5Hz), 2.95-2.30 (m, 2H), 2.25-1.50 (m with a sharp singlet at 2.00, 12H). Anal. Calc'd for $C_{10}H_{11}Br_3$ (P^+-HOAC): 367.84133. Found: 367.84107.

endo-4,10,10-Tribromo[4.3.1]propellan-3-one, 179

In a flame-dried flask, under N_2, 0.226g of dried CrO_3 was added to a 0.4ml of pyridine[168], freshly distilled from BaO, and 5ml of CH_2Cl_2, freshly distilled from $CaCl_2$, and the resulting mixture stirred for 15 minutes. A solution of 0.129g (0.38mmole) of bromohydrin 177 in 5ml of CH_2Cl_2 was then added all at once. The light orange mixture turned dark brown instantly. After stirring for 20 minutes, the mixture was filtered and concentrated in vacuo. The residue was dissolved in Et_2O and filtered again. The ethereal solution was then washed with solutions of 1N HCl, saturated $NaHCO_3$, and saturated NaCl, and dried over $MgSO_4$. Concentration in vacuo afforded 0.104g of an oily mixture of ketone 179 and the starting material (3:2). For characterization, pure 179 was obtained by preparative TLC. IR (KBr): 2980, 2920, 1720 (C=O), 1440, 1195, 910, 800 cm^{-1}; ^1H NMR ($CDCl_3$): δ4.10

(apparent t, 1H, J=11Hz), 3.20 and 2.75 (AB, 2H, J=18Hz), δ2.85 (apparent s, 2H), 2.55-1.60 (m, 6H). Anal. Calc'd for $C_{10}H_{11}OBr_3$: m/e 383.83599. Found: m/e 383.83540.

exo-4,10,10-Tribromo[4.3.1]propellan-3-one, 180

To a solution of 7.043g (18.1mmole) 178 in 250ml of Et_2O was added 1eq. of Brown's reagent[172] over a period of 20 minutes. After 12 hours, the organic layer was separated and the aqueous layer extracted with a 1:1 Et_2O-THF mixture. The combined organic layers were stirred at room temperature with another 1eq. of Brown's reagent for 12 hours. The above steps were repeated two more times for a total of 4eq. of Brown's reagent. The combined organic layers were washed with water, saturated $NaHCO_3$, saturated NaCl, and dried over $MgSO_4$. The solvent was removed in vacuo. Hexane was added near the end of the evaporation to induce crystallization of 180, whereby 4.547g (78% yield) were collected; m.p 153-154°C. IR (KBr): 2920, 1725 (C=O), 1450, 1395, 1110, 810, 515 cm^{-1}. ^1H NMR ($CDCl_3$): δ4.75-4.4 (ABX, 1H, J_{AX}=7Hz, J_{BX}=13Hz), 3.50-1.05 (m with an apparent AB at 2.90, 10H). Anal. Calc'd for $C_{10}H_{11}OBr_3$: 383.83599. Found: 383.83604.

endo-3-Hydroxy-10,10-dibromo[4.3.1]propellan-4-one, 184

Oxidation of 152 with $KMnO_4$ under neutral condition was accomplished utilizing the published procedure[169]. To a solution of 1.21g of $KMnO_4$ and 0.92g of $MgSO_4$ in 15ml

of H_2O at 0°C was added dropwise a solution of 1.116g (3.82mmole) of 152 in 10ml of acetone. The deep purple color turned dark brown in about 30 minutes. The reaction mixture was filtered and the solid washed well with acetone. The resultant solution was concentrated to about 20ml, diluted with water, and extracted three times with Et_2O. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford 0.601g of a white crystalline mixture of the starting material, 184 and likely the 1,2-diol. To the crude product mixture were added 3ml of Et_2O which dissolved most of the starting material and ketol. This mixture was separated by column chromatography on silica-gel, eluting first with hexane to afford the starting material, and then with 50% ethereal hexane to afford the ketol 184, m.p 111-115°C. IR (KBr): 3600-3020, 2920, 1710, 1435, 1080, 1030; ^1H NMR ($CDCl_3$): δ4.05 (apparent t, 1H, J=5.5Hz), 2.85 (apparent d, 2H), 2.7-1.8 (br m, 8H). Anal. Calc'd for $C_{10}H_{12}O_2Br_2$: m/e 321.92040. Found: m/e 321.92007.

10,10-Dibromo[4.3.1]propellan-4-one, 185

To a solution of 2.82g (9.7mmole) of 152 in 100ml of dry THF at 0°C were added 11ml of a 1M BH_3-THF solution. The resulting mixture was allowed to warm up to room temperature and stirred for 4 hours. Ice chips were then added to destroy any excess BH_3. Most of the aqueous layer was removed with a pipet. The organic layer was then stirred

with 5ml of a 0.7M solution of chromic acid[170] for 38 hours. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed twice with saturated $NaHCO_3$ solution, once with water, dried over K_2CO_3, and concentrated in vacuo. The oily residue was crystallized from hot hexane. Collected were 1.545g (52% yield), m.p 70-71.5°C. IR (CCl_4): 2930, 1720, 1450, 1440, 1150, 1120; ^1H NMR ($CDCl_3$): δ2.05 (apparent s, 2H), 2.4-1.6 (br m, 10H). Anal. Calc'd for $C_{10}H_{12}OBr_2$: m/e 305.92559. Found: m/e 305.92424.

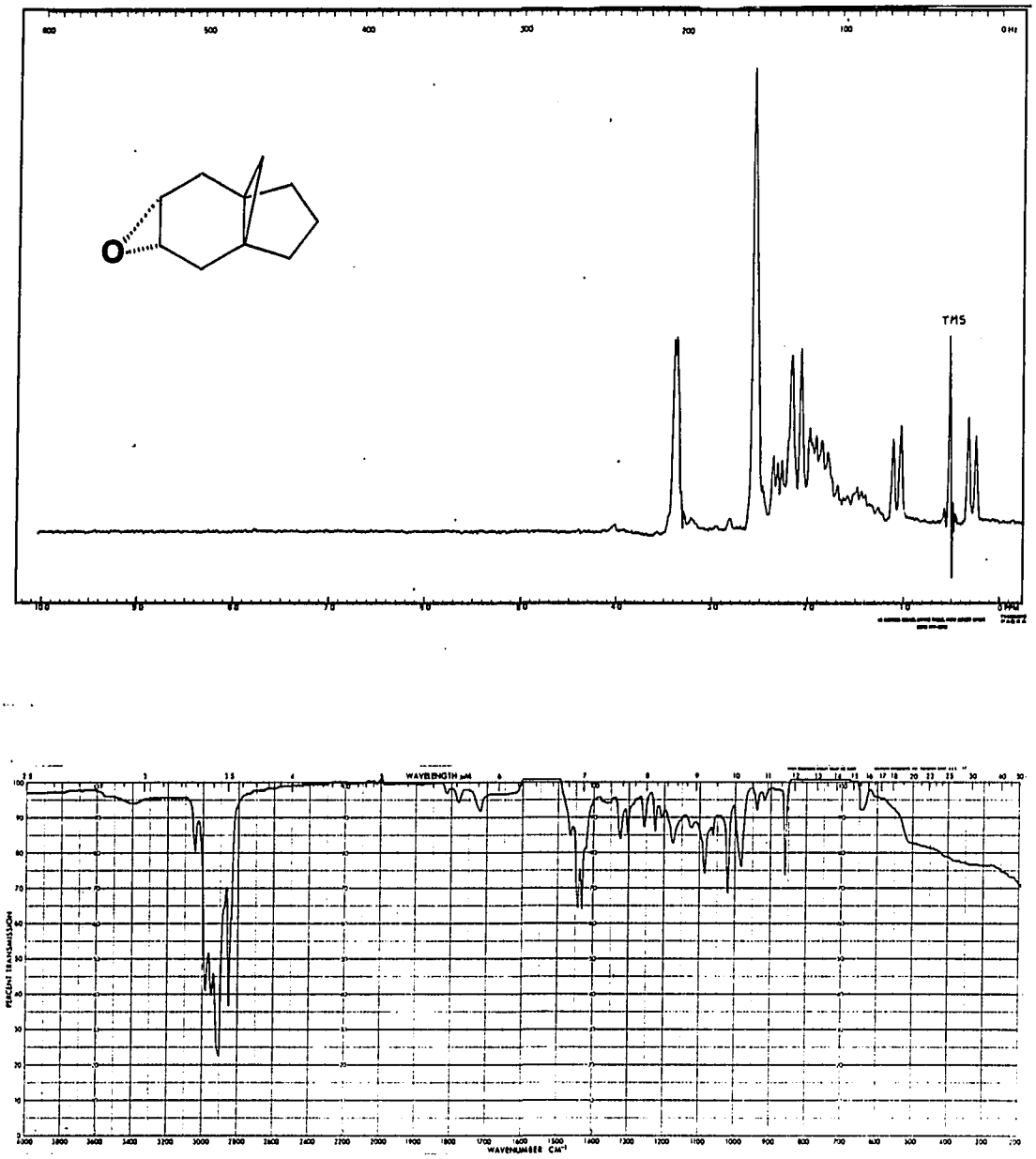


Figure 73. ^{1}H NMR (CCl_4) and IR (CCl_4) of *endo*-2,3-Epoxy[4.3.1]propellane, 159

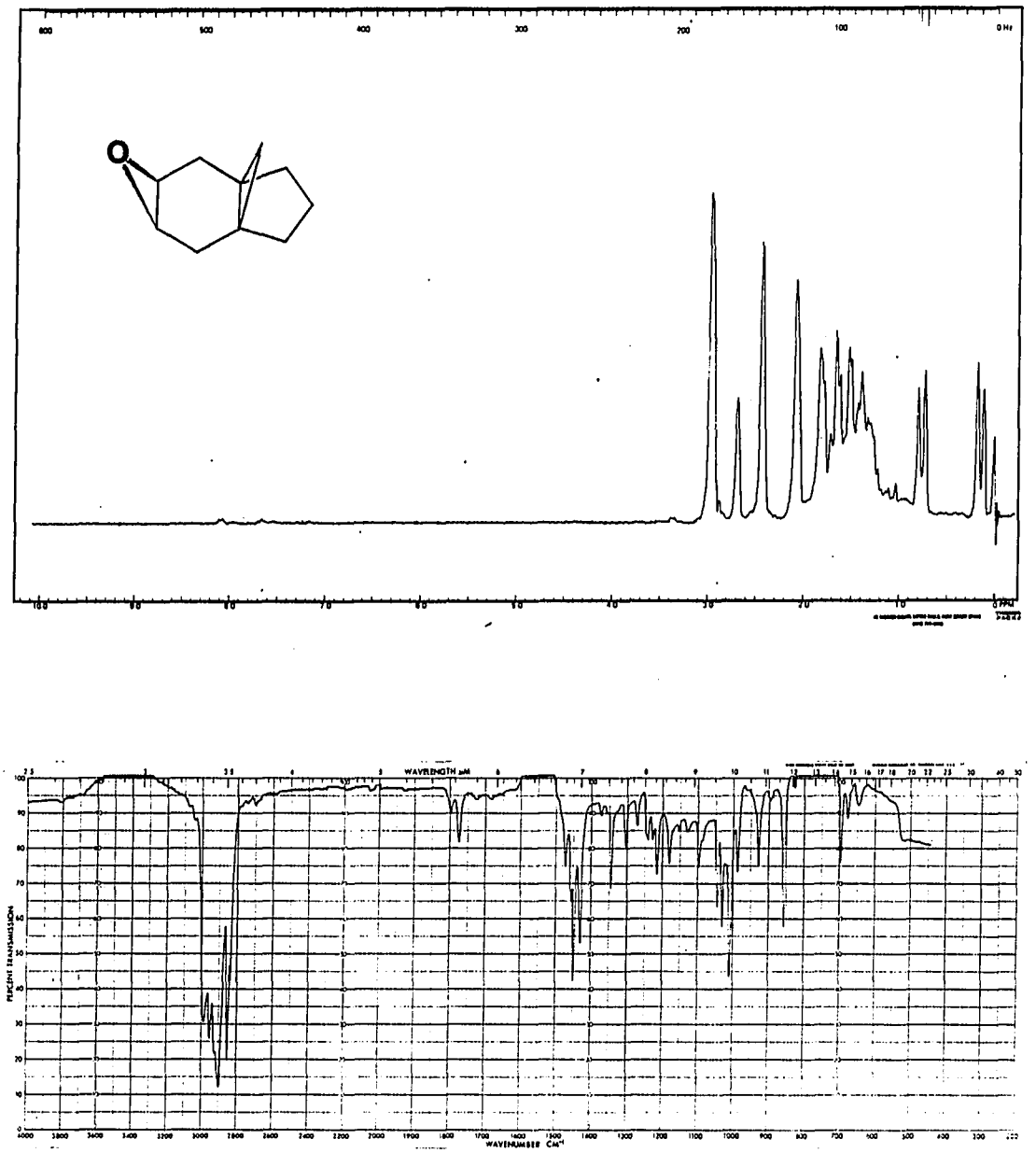
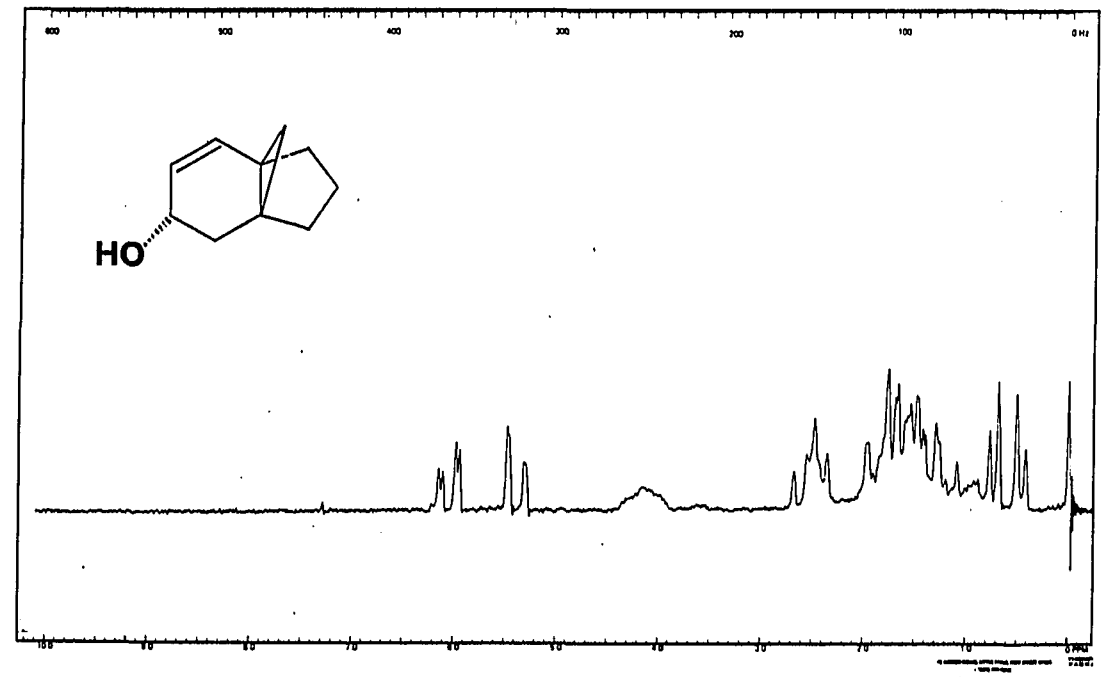


Figure 74. ^1H NMR (CCl_4) and IR (CCl_4) of *exo*-2,3-Epoxy [4.3.1]propellane, 160



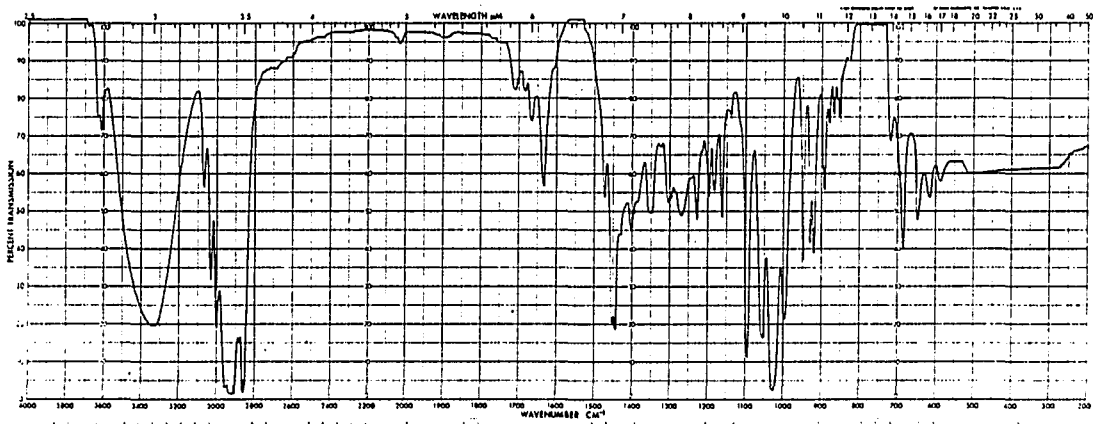
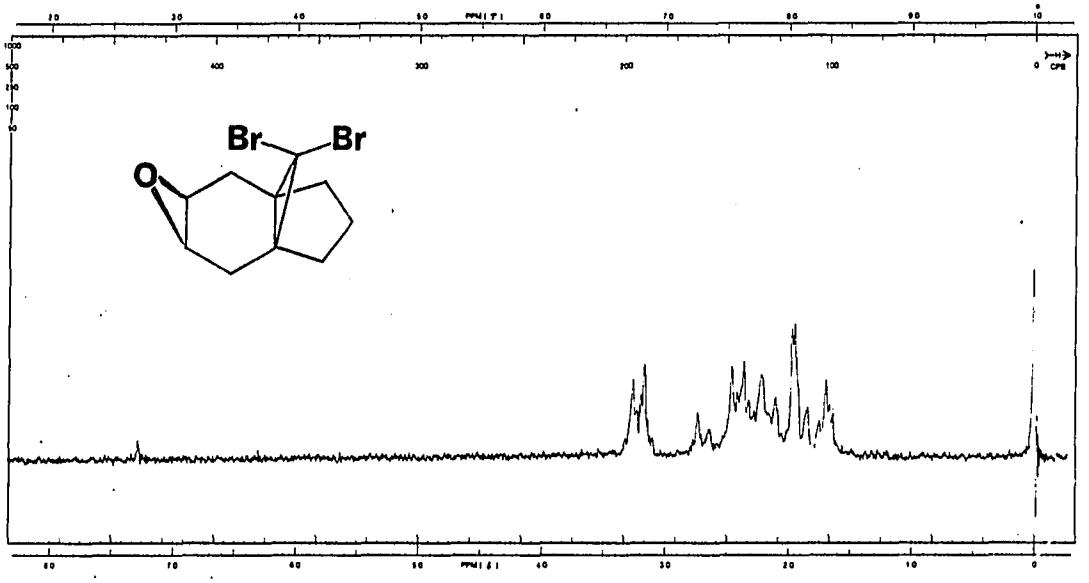


Figure 75. ^1H NMR (CCl_4) and IR (CCl_4) of *endo*-[4.3.1] propell-2-en-4-ol, 161



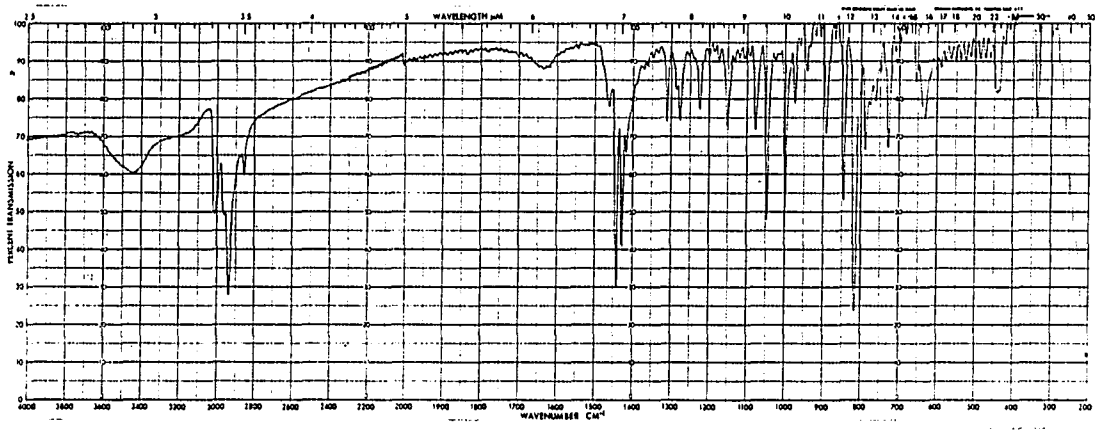
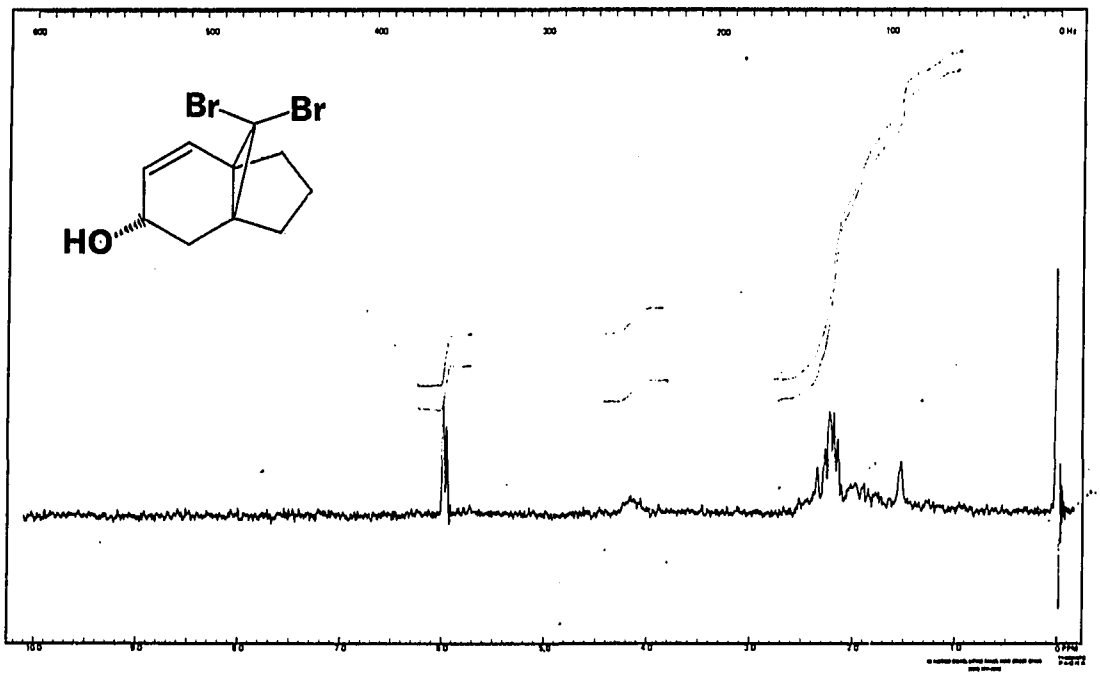


Figure 76. ^{1}H NMR ($CDCl_3$) and IR (KBr) of *exo*-2,3-Epoxy-10,10-dibromo[4.3.1]propellane, 165



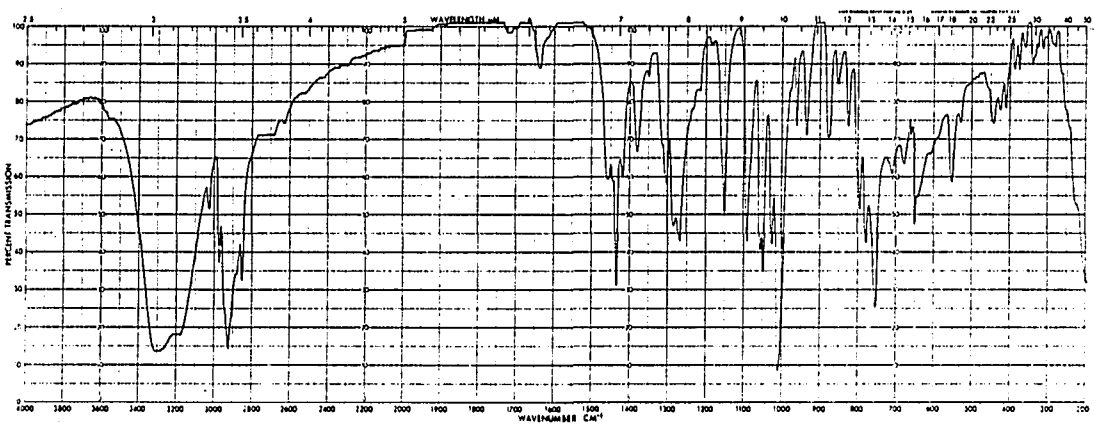
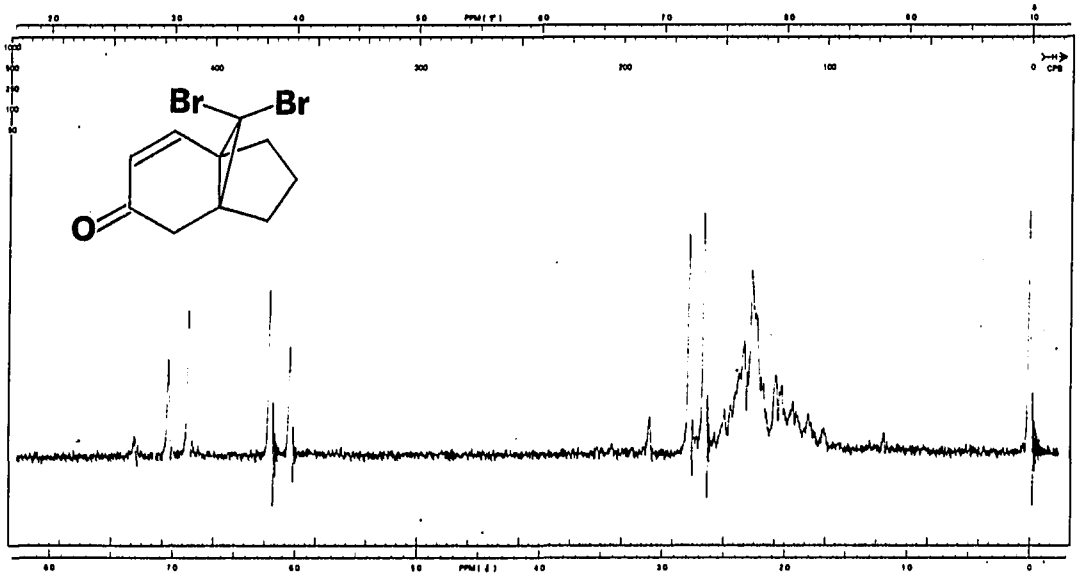


Figure 77. ^{1}H NMR ($CDCl_3$) and IR (KBr) of *endo*-10,10-dibromo[4.3.1]prope11-2-en-4-o1, 169



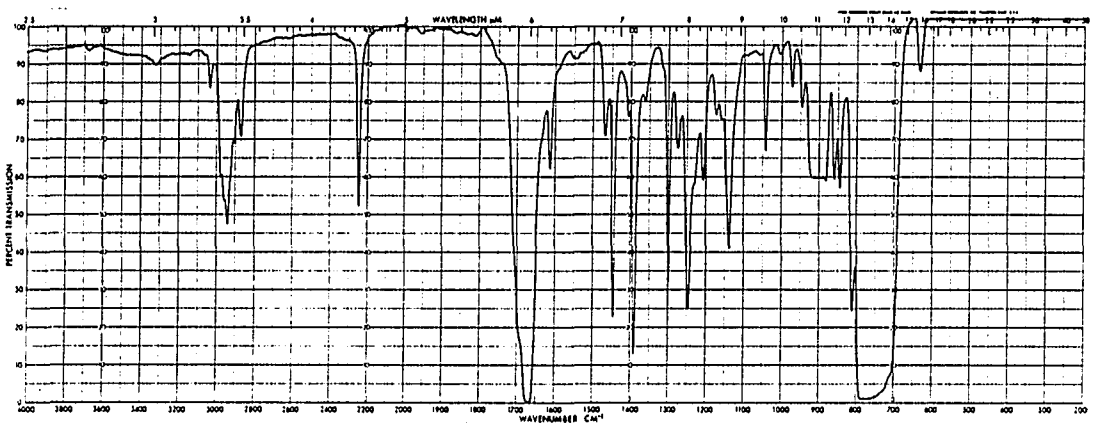
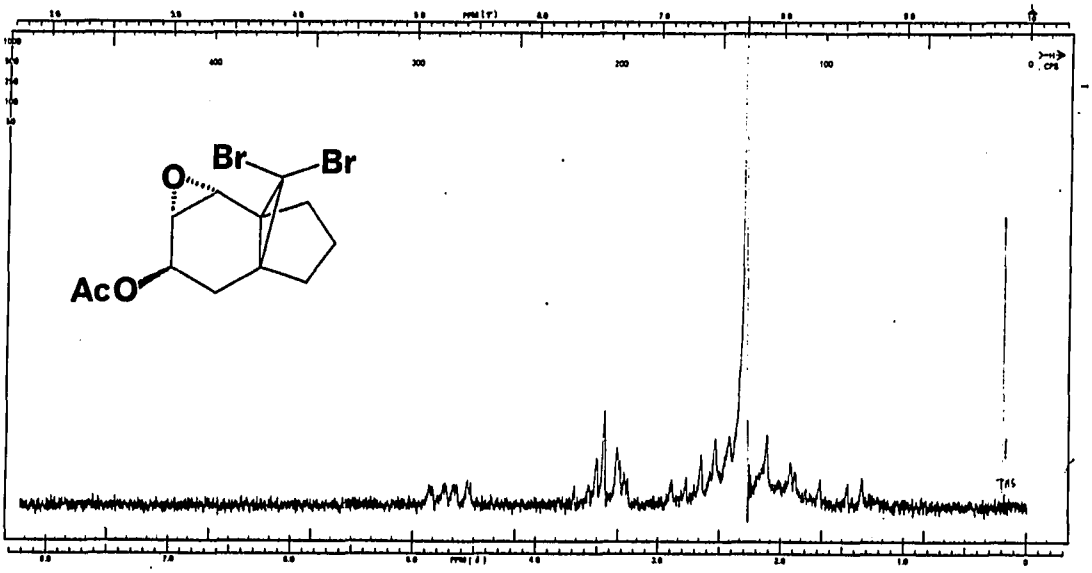


Figure 78. ^1H NMR ($CDCl_3$) and IR ($CDCl_3$) of 10,10-Dibromo [4.3.1]propell-2-en-4-one, 170



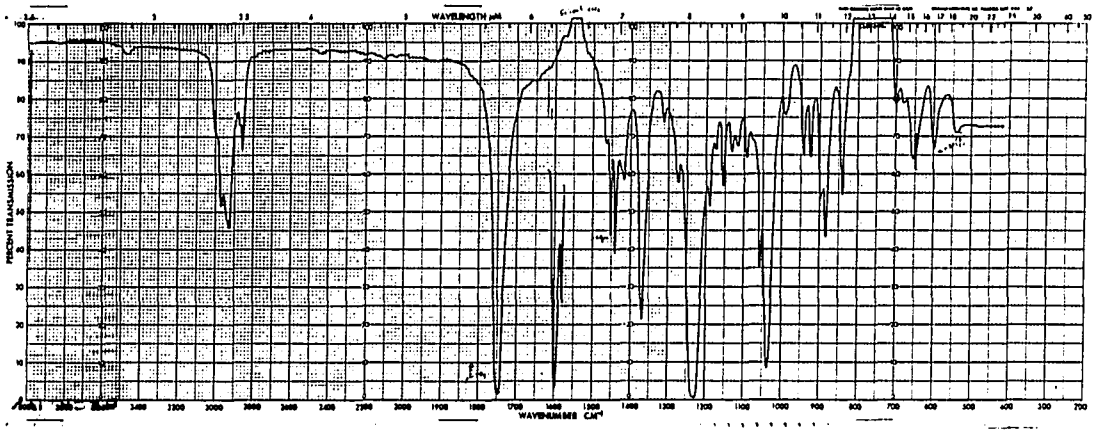
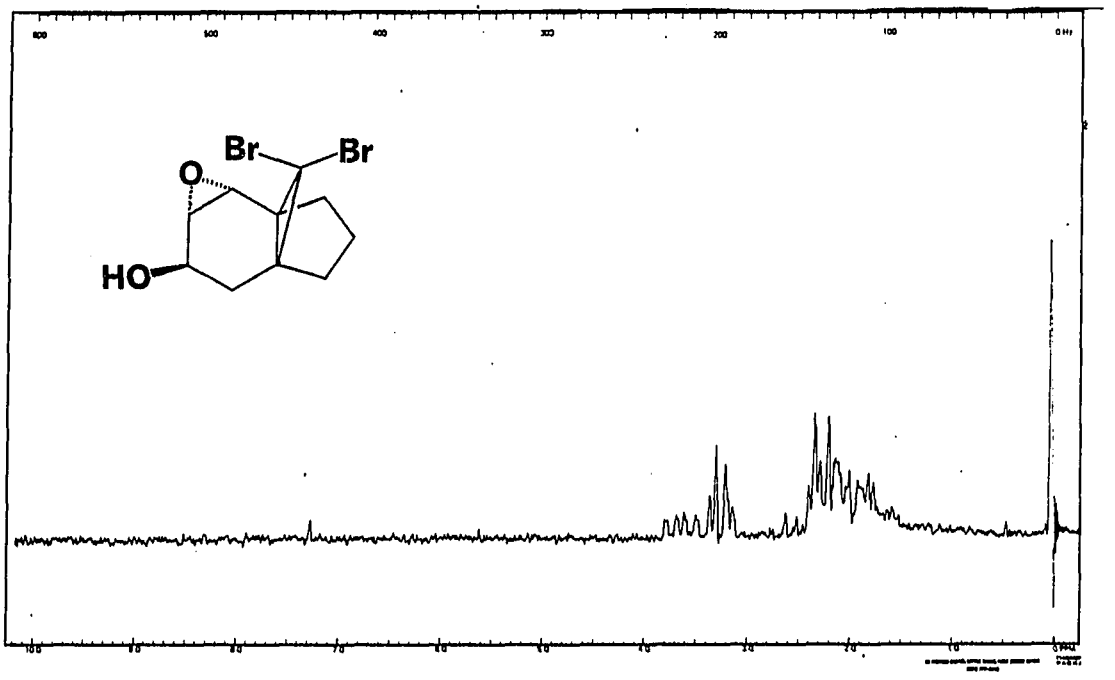


Figure 79. ^1H NMR ($CDCl_3$) and IR (CCl_4) of *exo*,2,3-*endo*-Epoxy-10,10-dibromo[4.3.1]propellan-4-acetate, 171



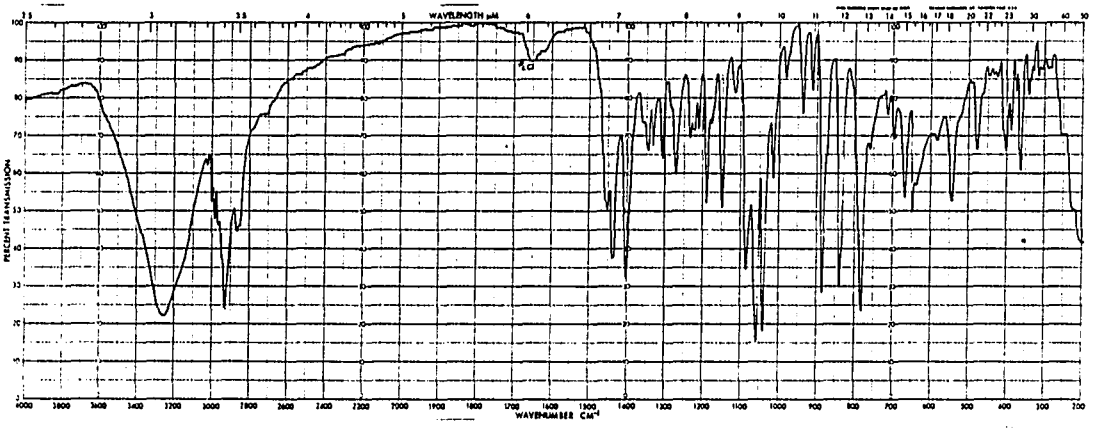


Figure 80. ^{1}H NMR ($CDCl_3$) and IR (KBr) of *exo*,2,3-*endo*-Epoxy-10,10-dibromo[4.3.1]propellan-4-ol, 172

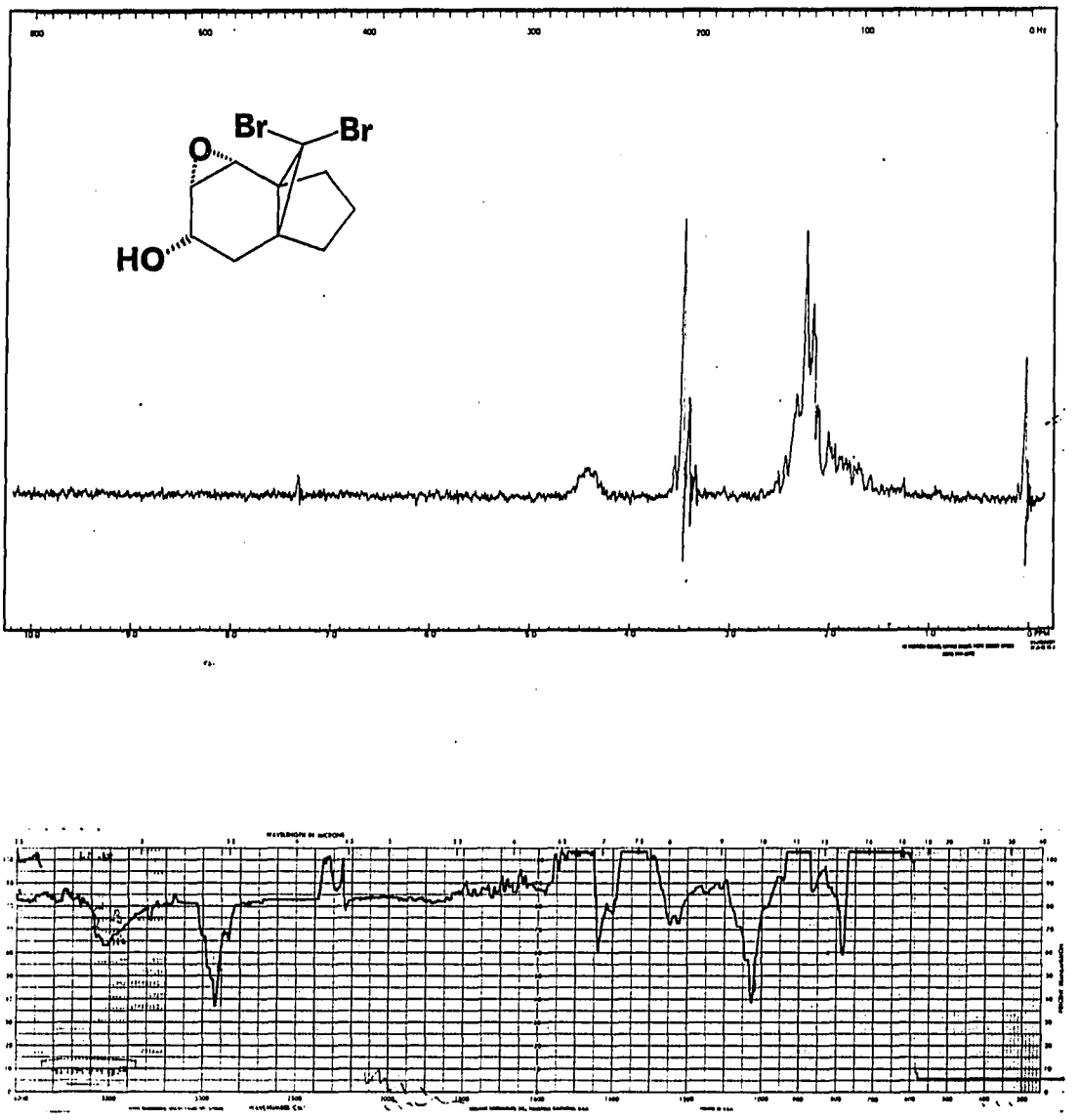


Figure 81. ^{1}H NMR ($CDCl_3$) and IR ($CDCl_3$) of *endo*,2,3-*endo*-Epoxy-10,10-dibromo[4.3.1]propellan-4-01, 173

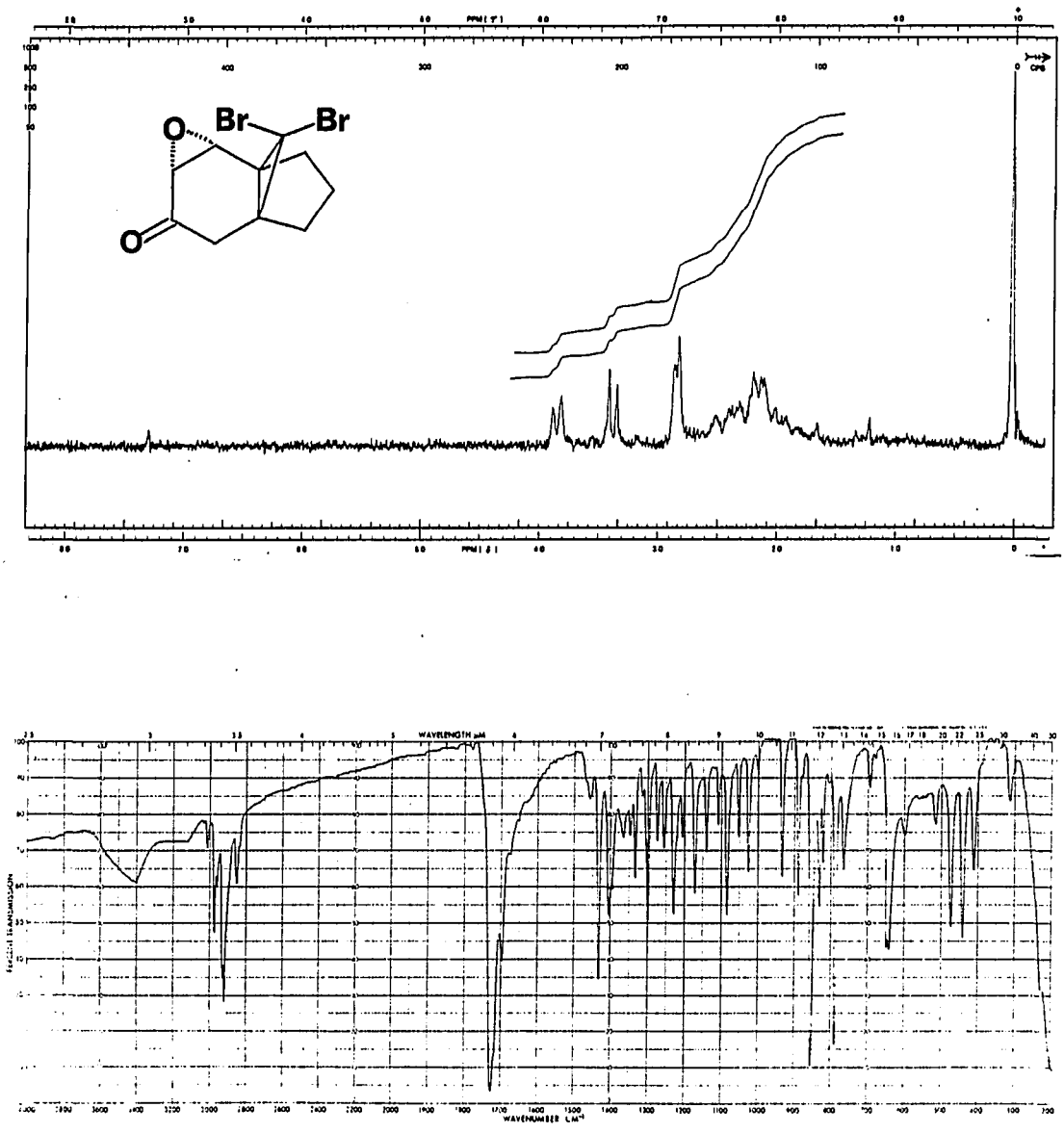
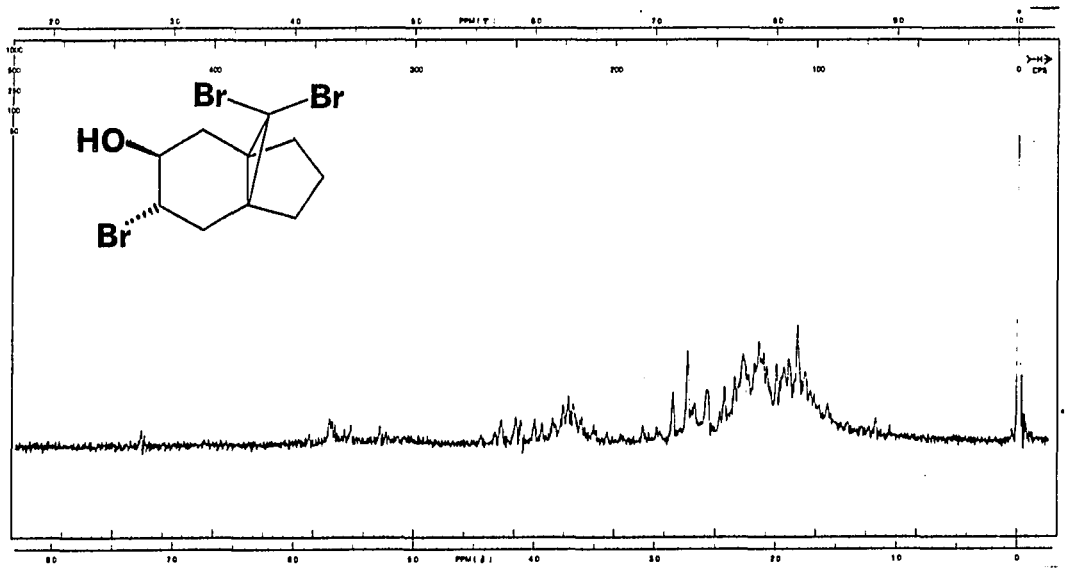


Figure 82. ^1H NMR ($CDCl_3$) and IR (KBr) of *endo*-2,3-Epoxy-10,10-dibromo[4.3.1]propellan-4-one, 174



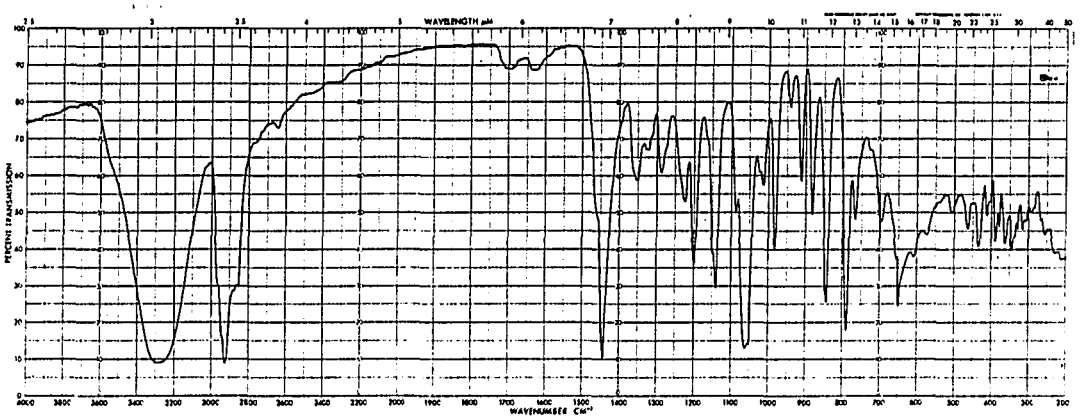


Figure 83. ^{1}H NMR ($CDCl_3$) and IR (KBr) of 3-*exo*,4-*endo*-4,10,10-Tribromo[4.3.1]propellan-3-01, 177

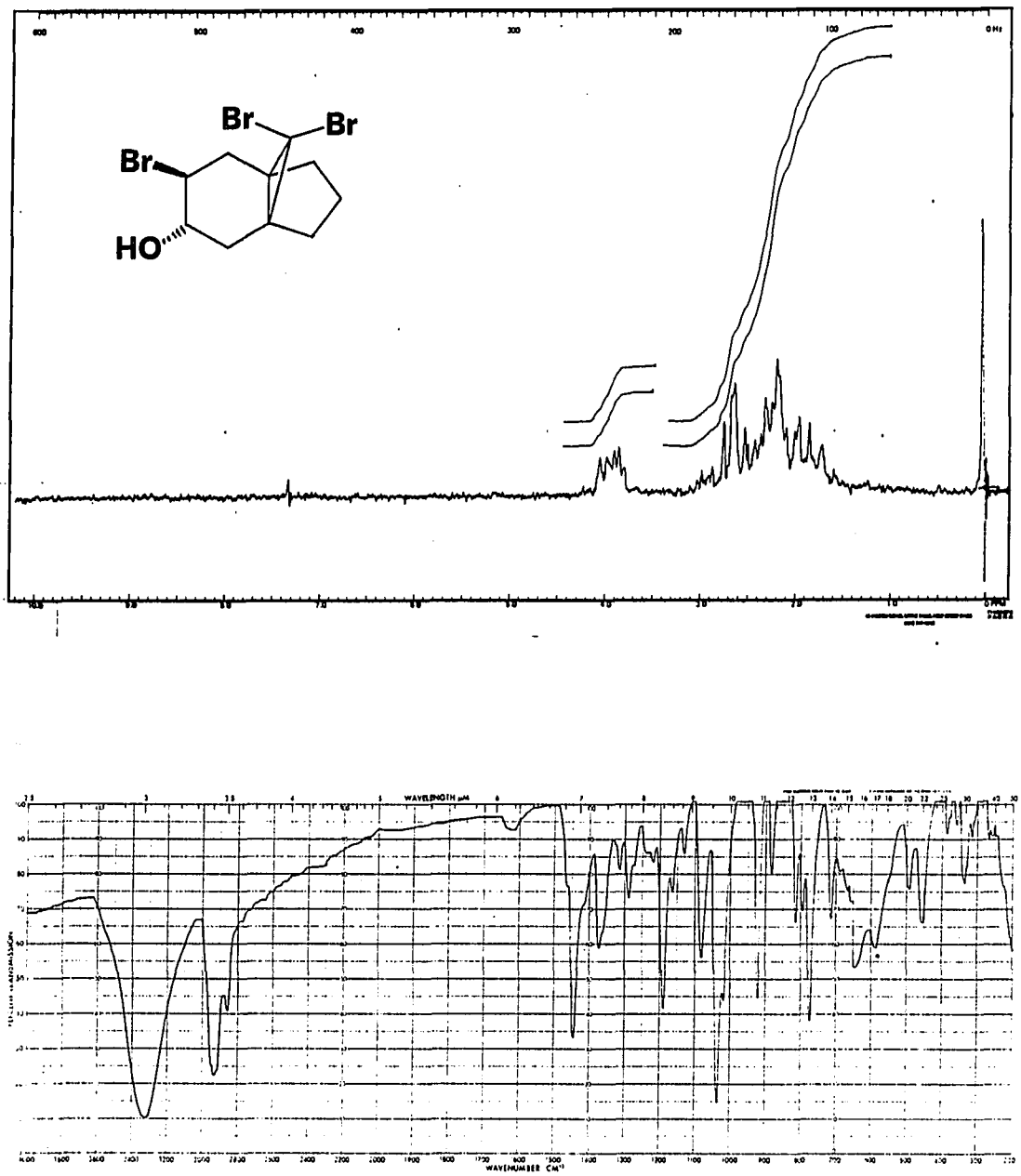
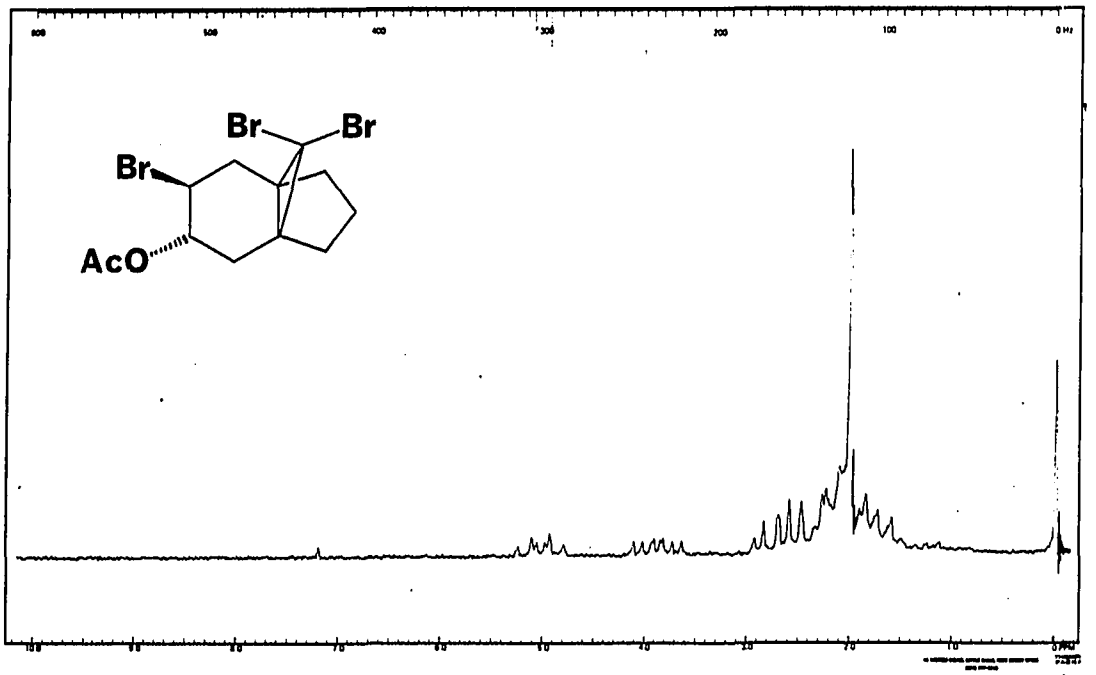


Figure 84. ^{1}H NMR ($CDCl_3$) and IR (KBr) of 3-*endo*,4-*exo*-4,10,10-Tribromo[4.3.1]propellan-3-ol, 178



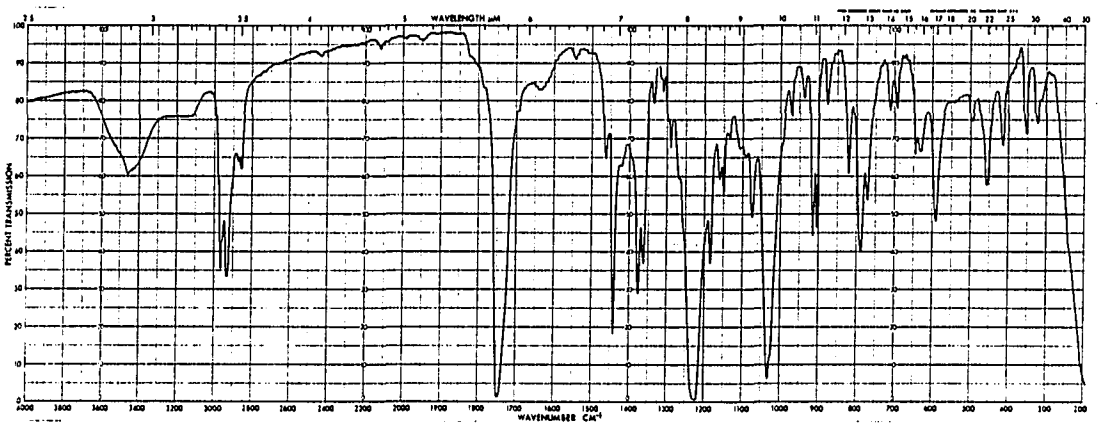
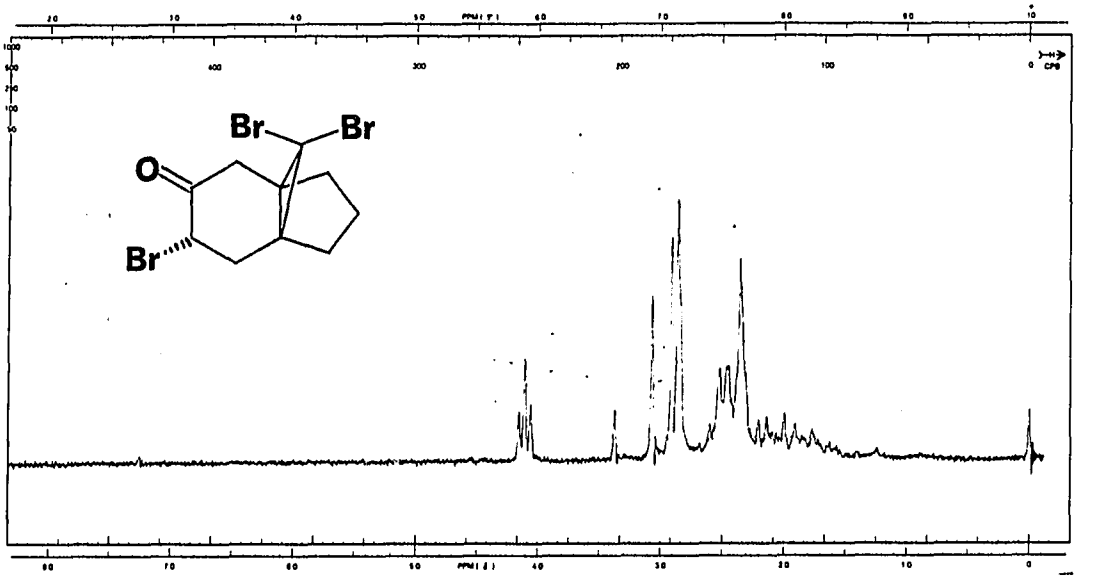


Figure 85. ^{1}H NMR ($CDCl_3$) and IR (KBr) of 3-*endo*,4-*exo*-4,10,10-Tribromo[4.3.1]propellan-3-acetate, 186



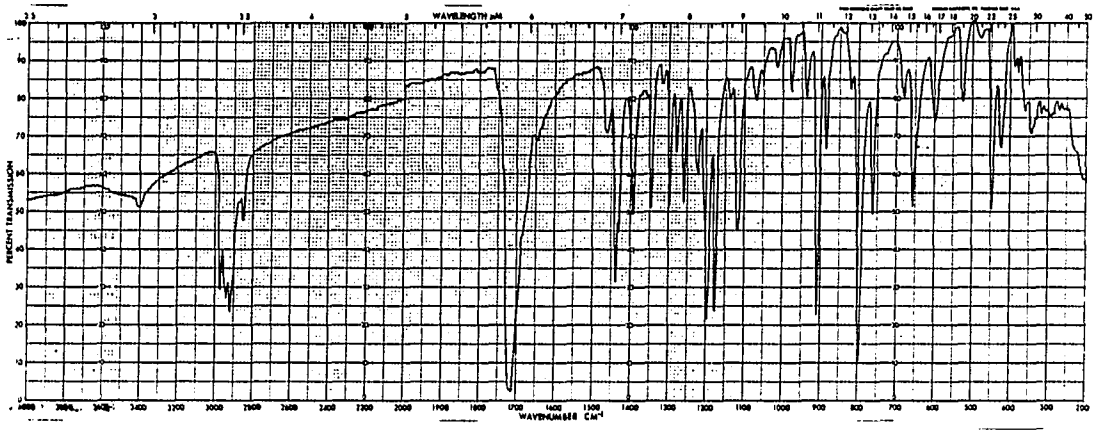


Figure 86. ^{1}H NMR ($CDCl_3$) and IR (KBr) of *endo*-4,10,10-Tribromo[4.3.1]propellan-3-one, 179

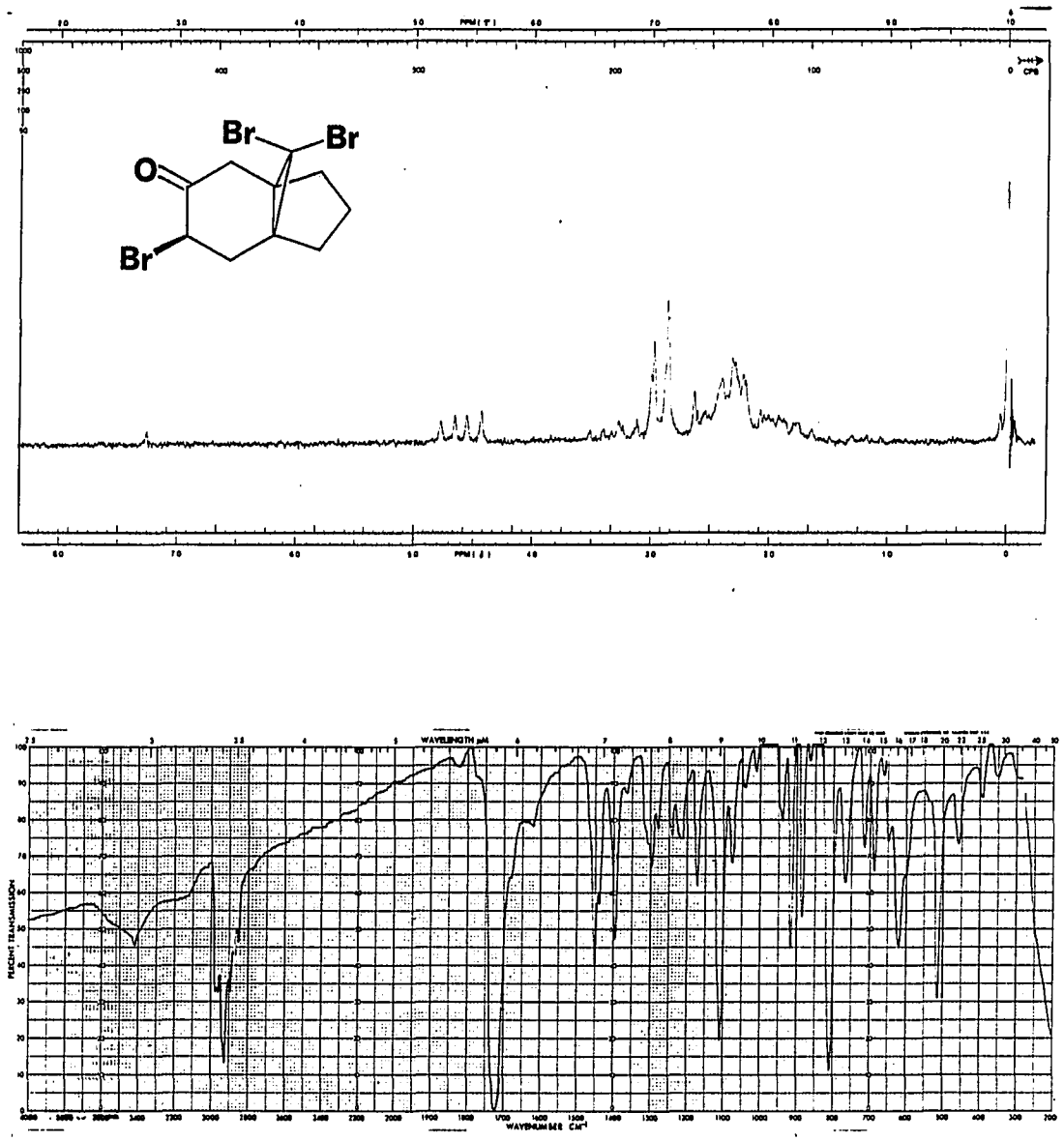
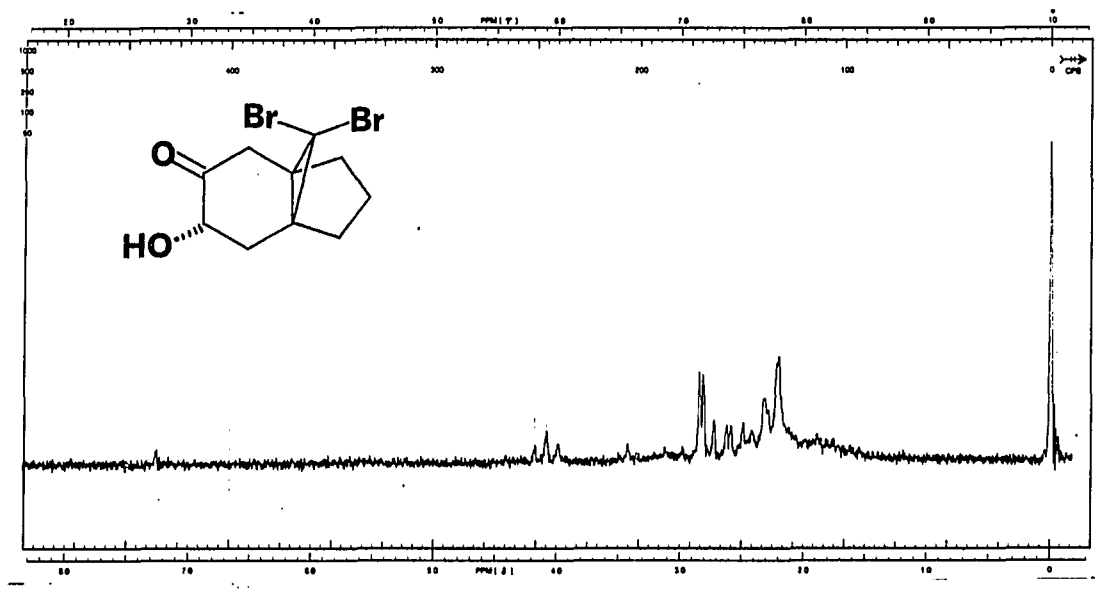


Figure 87. ^{1}H NMR ($CDCl_3$) and IR (KBr) of *exo*-4,10,10-Tribromo[4.3.1]propellan-3-one, 180



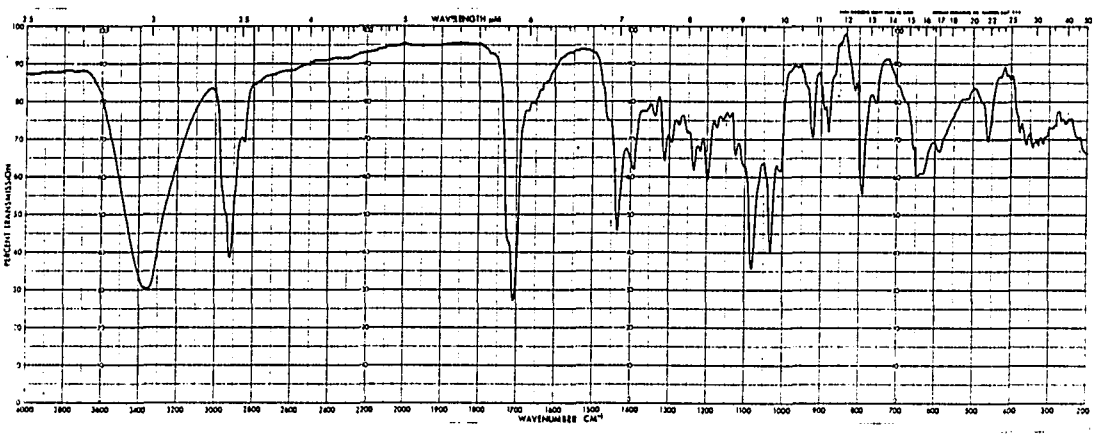


Figure 88. ^{1}H NMR ($CDCl_3$) and IR (KBr) of *endo*-3-Hydroxy-10,10-dibromo[4.3.1]propellan-4-one, 184

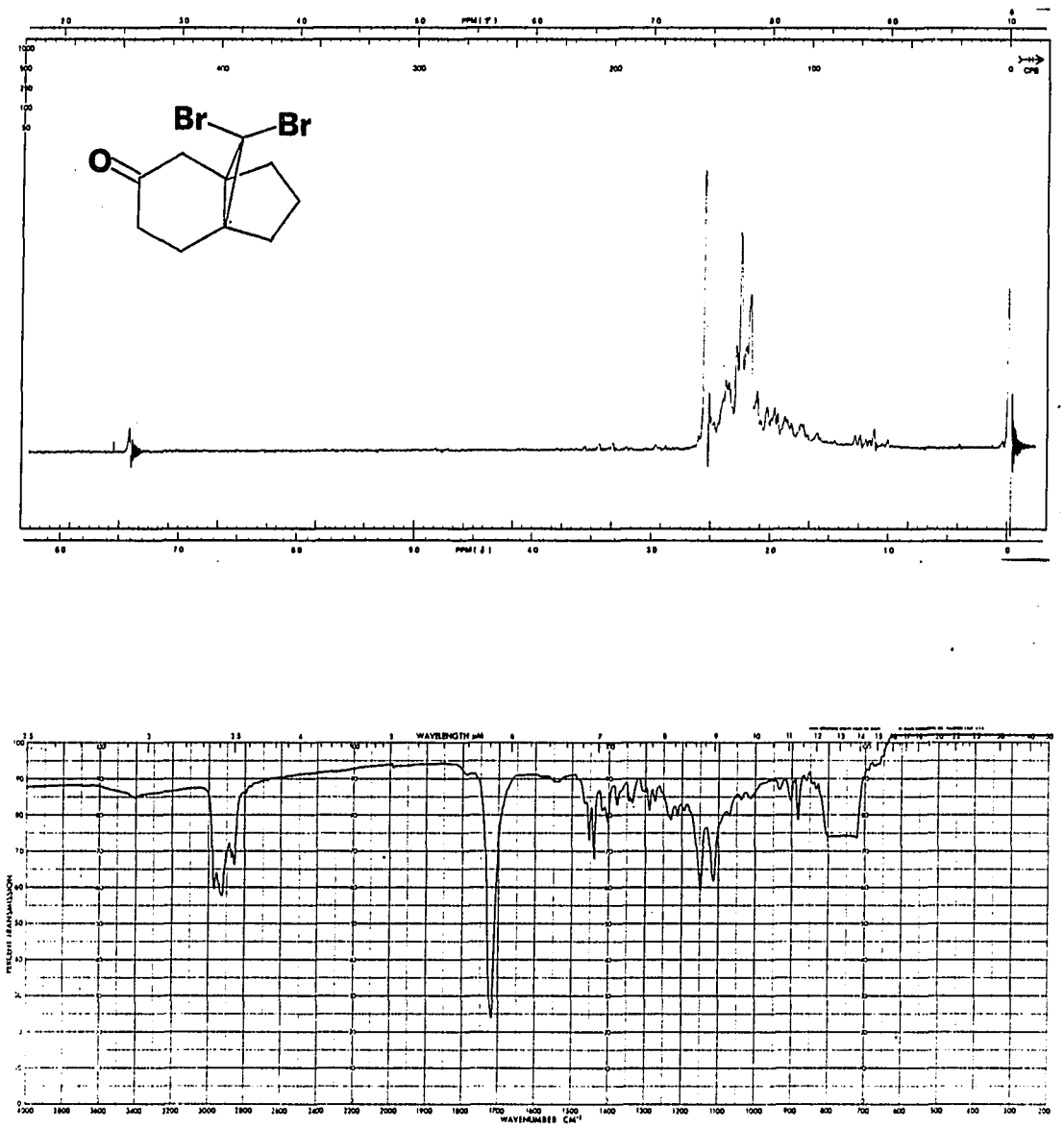


Figure 89. ^1H NMR ($CDCl_3$) and IR (KBr) of 10,10-Dibromo-[4.3.1]propellan-3-one, 185

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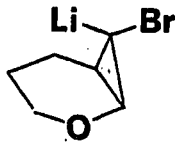

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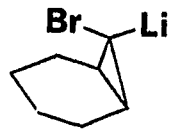

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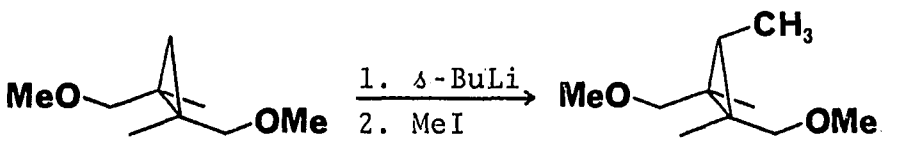

69 ca. 5%

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