This is to certify that the

dissertation entitled

PART I. An Approach to Tricyclo$[7.3.0.0^{4,12}]$-
Dodeca-2,5,7,10-Tetraene
PART II. An Approach to Dodecahedrane
PART III. Lithium Bromide-Lithium Diethylamide
Induced Rearrangment of Epoxides

presented by

Peter Yain-Tain Gur

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Donald G Farnum
Major professor

Date May 6, 1987

PART I. AN APPROACH TO TRICYCLO[7.3.0.$0^{4,12}$]DODECA-2,5,7,10-TETRAENE

PART II. AN APPROACH TO DODECAHEDRANE

PART III. LITHIUM BROMIDE-LITHIUM DIETHYLAMIDE INDUCED REARRANGEMENT OF EPOXIDES

By

Peter Yain-Tain Gur

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
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DOCTOR OF PHILOSOPHY

Department of Chemistry

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ABSTRACT

PART I. AN APPROACH TO TRICYCLO[7.3.0.0^{4,12}]DODECA-2,5,7,10-TETRAENE

PART II. AN APPROACH TO DODECAHEDRANE

PART III. LITHIUM BROMIDE-LITHIUM DIETHYLAMIDE INDUCED REARRANGEMENT OF EPOXIDES

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Tricyclo[7.3.0.0^{4,12}]dodeca-2,5,7,10-tetraene has been made in low yield. It is predicted to undergo a series of structurally degenerate Cope rearrangements. Alternate syntheses through the key intermediate tricyclo[7.3.0.0^{4,12}]dodeca-2,6,10-triene using sulfide contraction/elimination, titanium-induced intramolecular dicarbonyl-coupling, or _bis_-ylide autoxidation, were unsuccessful.

Dodecahedrane is a carbon representative of the five Platonic solids. _Cis_,_endo_-2,6-_bis_(iodomethyl)bicyclo-[3.3.0]octa-3,7-diene and _cis_,_endo_-2,6-_bis_-

(mercaptomethyl)bicyclo[3.3.0]octa-3,7-diene were synthesized, corresponding to two halves of dodecahedrane. However, coupling of the diiodide with dithiol could not be achieved.

The rearrangement of *cis*-cyclooctene oxide with lithium bromide-lithium diethylamide gave a higher yield than with lithium diethylamide alone. The ratio of *cis*,*endo*-bicyclo[3.3.0]octan-2-ol, the major product, to 2-cyclooctenol was also increased. The generality of this effect of lithium bromide was examined with some other epoxides. In most cases added lithium bromide improved the yield and purity of the final product.

To My Parents
and to My Wife, Phoebe Wei-Tsu,
for Their Love and Understanding

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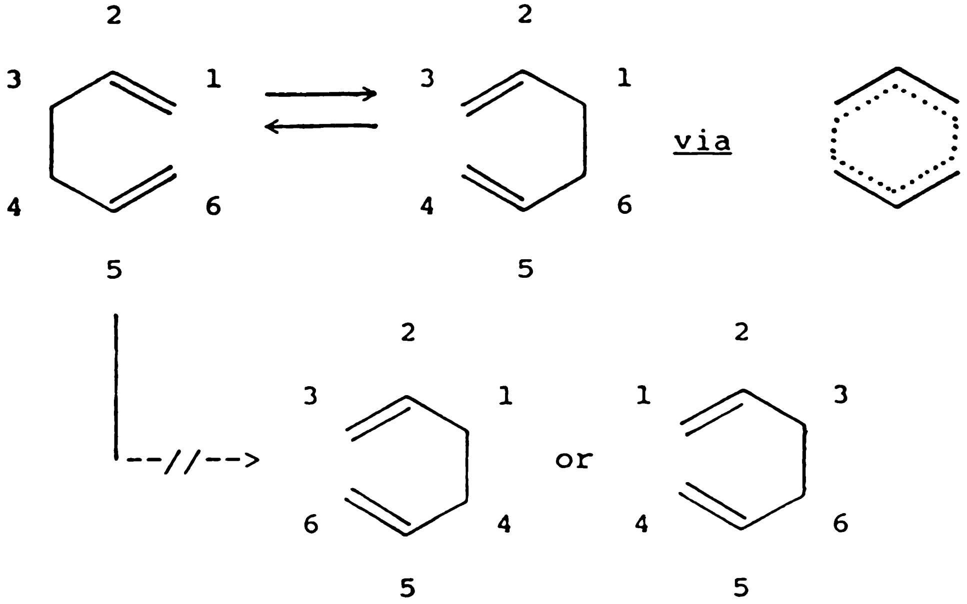
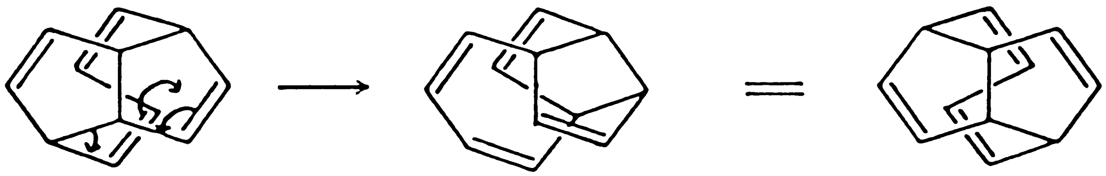
INTRODUCTION

Tricyclo$[7.3.0.0^{4,12}]$dodeca-2,5,7,10-tetraene 1 was synthesized in 1974 by Hagadorn and Farnum[1] in order to test the Cope rearrangement theory.

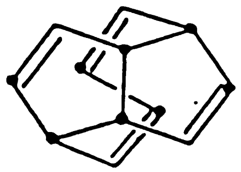
The Cope rearrangement,[2] shown below, has been extensively studied.[3] It is a suprafacial $[_{\pi}2+_{\sigma}2+_{\pi}2]$ concerted reaction which proceeds through a cyclic complex.[4]



Tetraene 1 contains two 1,5-hexadiene units, so it is predicted to undergo a series of structurally degenerate Cope rearrangements.

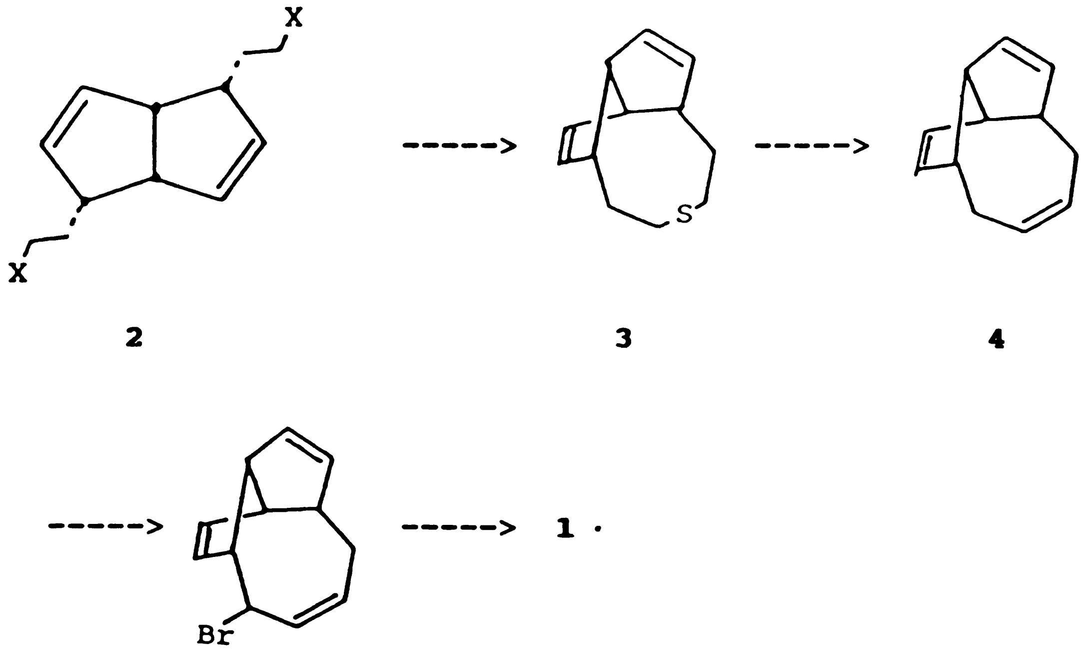


The degenerate Cope rearrangement might be detected from the proton NMR spectrum. Thus, at low temperature, if the rate of equilibration of 1 is slow enough, the spectrum would consist of eight olefinic protons and four allylic protons. If the temperature is raised and the rate of equilibration increases sufficiently, it is predicted that four of the olefinic protons would remain unchanged in respect to their chemical shift, while the remaining eight protons (marked•) would coalesce.



However, the nmr spectrum of 1 was unchanged from 35° to 141°. Therefore, the Cope rearrangement of 1 is slow on the nmr time scale. This slow rate is probably due to the absence of a small ring and its accompanying strain. The goal of this project was to explore an alternate synthesis in order to obtain sufficient material easily, and to use another method to study the kinetics and mechanism of the Cope rearrangement.

Our strategy for the synthesis of 1 is outlined below:

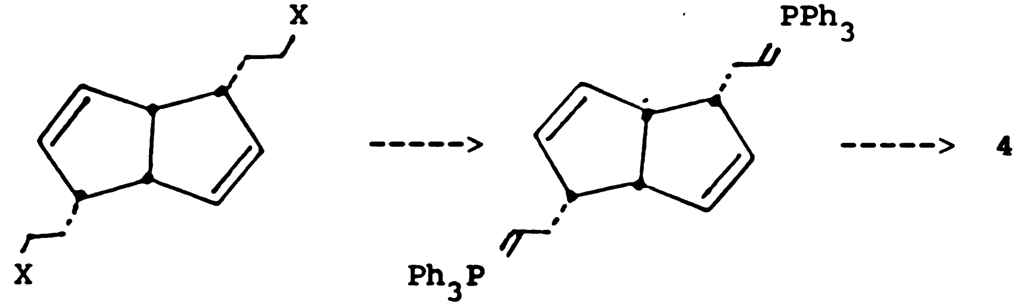


2 3 4

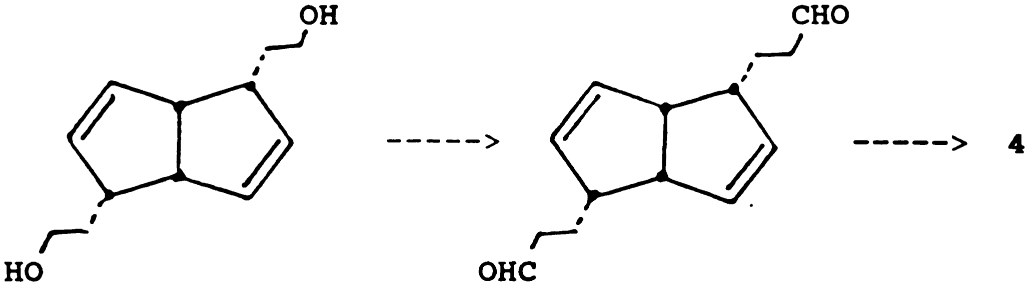
5

Cyclization of dihalide 2 with sodium sulfide might afford sulfide 3. Ring contraction of 3 via a Stevens rearrangement,[5] followed by Hofmann elimination[6] might yield triene 4. Treatment of 4 with NBS might give halide 5. Removal of the halide in 5 with a base might produce 1.

Triene 4 might also be produced by another way:



2 6



7 8

Treatment of dihalide **2** with triphenyl phosphine might produce <u>bis</u> ylide **6**. Cyclization of **6** through an autoxidation process might afford triene **4**.

Oxidation of dialcohol **7** might afford dialdehyde **8**. Coupling of **8** with titanium (III) chloride might also give triene **4**.

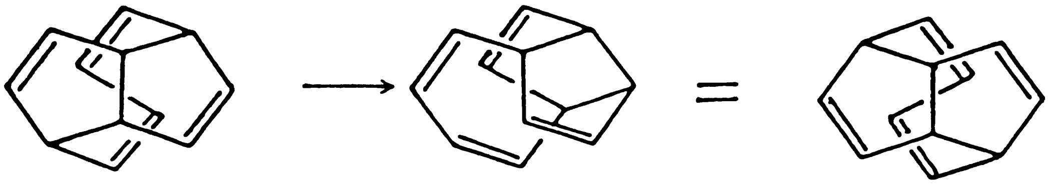
Since the Cope rearrangement of **1** is slow on the nmr time scale, racemization studies might provide information on the rate. Thus, treatment of racemic **1** with an optically active complexing agent, such as Cope's platinum complex **9**,[7] might lead to complete formation of the more stable (or less soluble) diastereomeric complex. Repeated crystallization of the diastereomeric Pt complexes **10** might give the optically pure **1**:

$$\underset{\mathbf{9}}{[\mathrm{PtCl_2(C_2H_4)(+)\text{-}C_6H_5CH_2CH(CH_3)NH_2}]} + \text{racemic } 1$$

$$\longrightarrow \underset{\mathbf{10}}{[\mathrm{PtCl_2(1)(+)\text{-}C_6H_5CH_2CH(CH_3)NH_2}]} + \mathrm{C_2H_4}$$

10 + 4 KCN --> optically pure 1 + $K_2Pt(CN)_4$ + 2 KCl + (+)-$C_6H_5CH_2CH(CH_3)NH_2$

As shown below, each Cope rearrangement converts the starting molecule into its enantiomer, so the Cope rearrangement could be observed by monitoring the loss of optically activity in the initially resolved 1:



1(R) 1(S)

RESULTS AND DISCUSSION

Tricyclo[7.3.0.0^{4,12}]dodeca-2,6,10-triene **4** was the key intermediate in our approach toward 1. Therefore, firstly we concentrated our effect to produce **4**.

1. The Fate of the Sulfide Contraction/Elimination Approach

Triene **4** might be produced by treating dibromide **11** with sodium sulfide, then eliminating the sulfide in **3** (Figure 2).

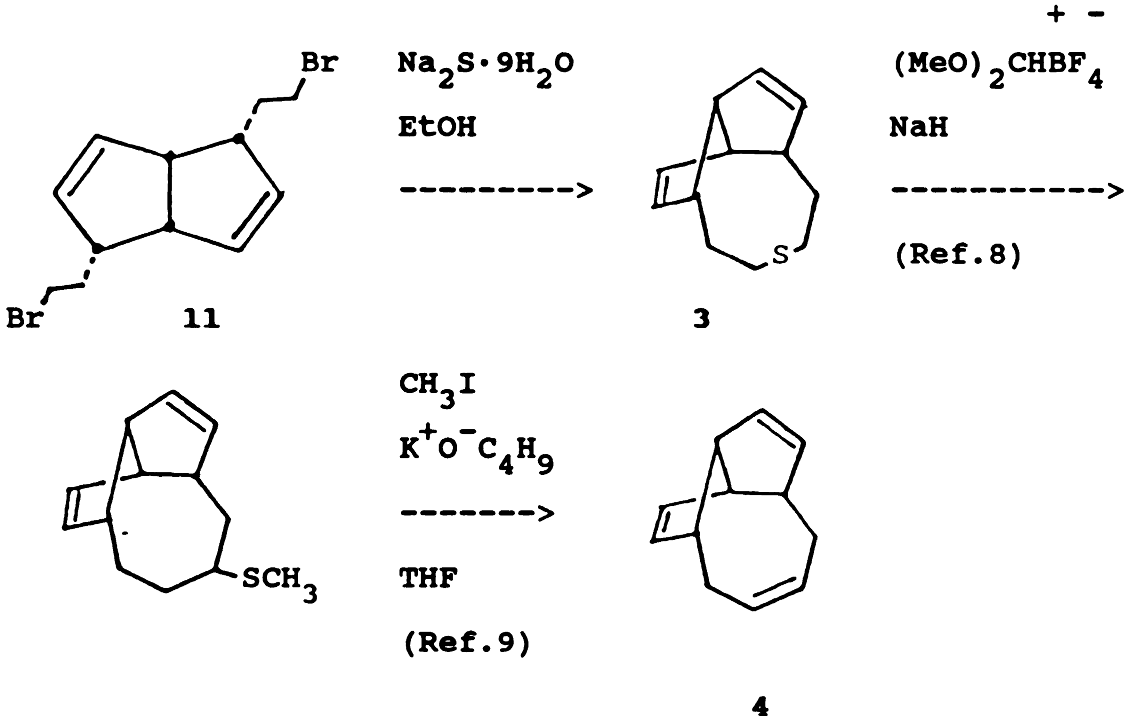
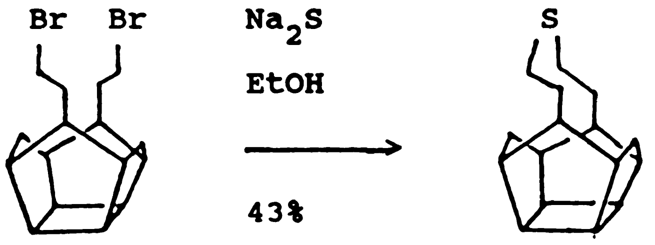


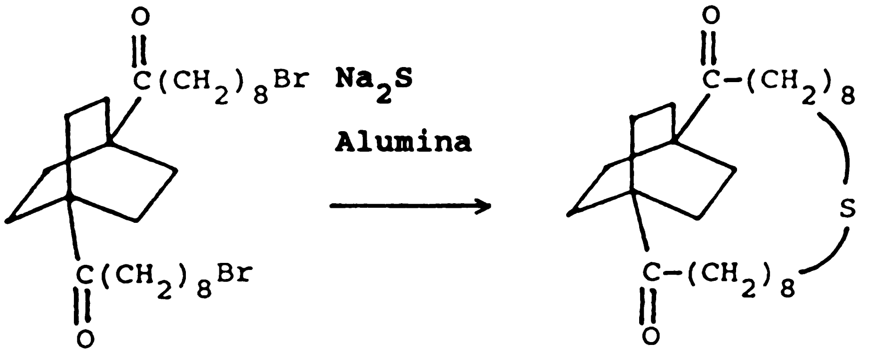
Figure 1. Proposed route to **4** from **3**.

Mirmohammad had reported the preparation of sulfide 3,[10] albeit in low yield (1%).

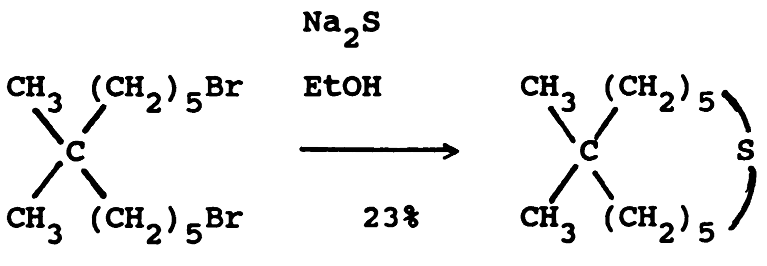
Succcessful synthesis of sulfide rings *via* cyclization of dibromide normally requires high dilution conditions. Some examples are shown below:



(Reference 11)

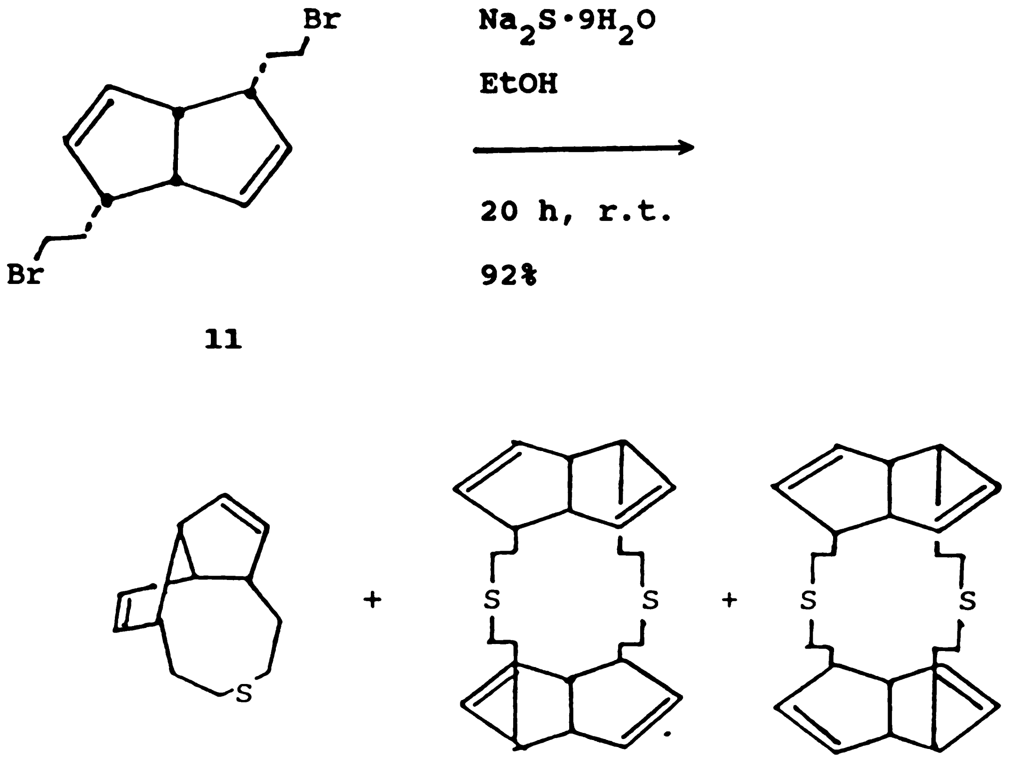


(Reference 12)



(Reference 13)

We modified Mirmohammad's procedure and treated dibromide 11 with sodium sulfide in absolute ethanol in concentrated solution.[14] After twenty hours the reaction was complete and gave a mixture. The major product was a white solid, identified as sulfide dimer 12 (74% yield, m.p. 110-112°). The minor product was the wanted sulfide 3 (18% yield) which was a yellow oil. We believed that 12 was two isomers.



11

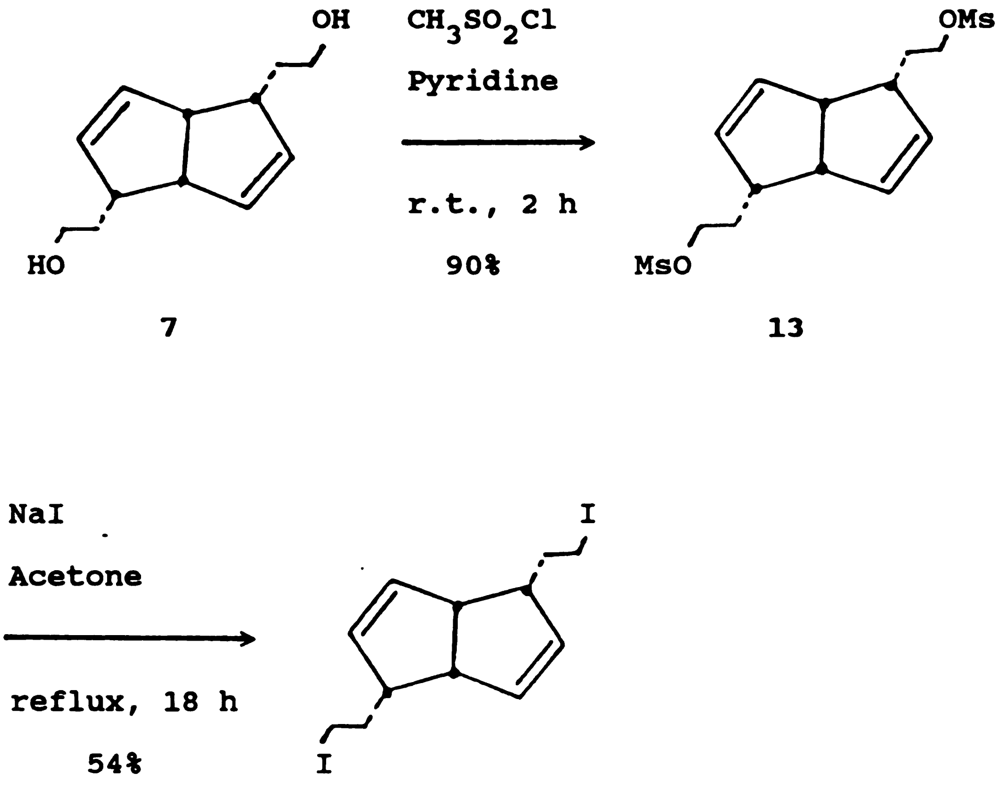
3

12

1 : 4

Because the yield of sulfide **3** from dibromide **11** was very low, we synthesized other dihalides and treated them with sodium sulfide in the hope of producing higher yield of sulfide **3**.

Treatment of diol **7** with mesyl chloride in pyridine[15] gave a 90% yield of the dimesylate **13**, which slowly solidified on standing. Exposure of this material to sodium iodide in refluxing acetone provided diiodide **14** in 54% yield after chromatography.

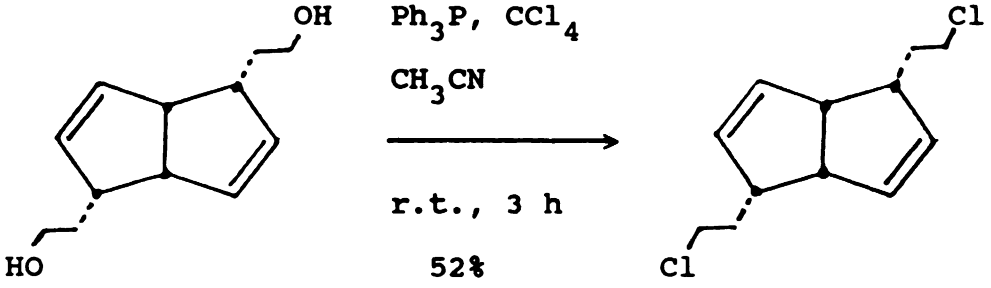


7

13

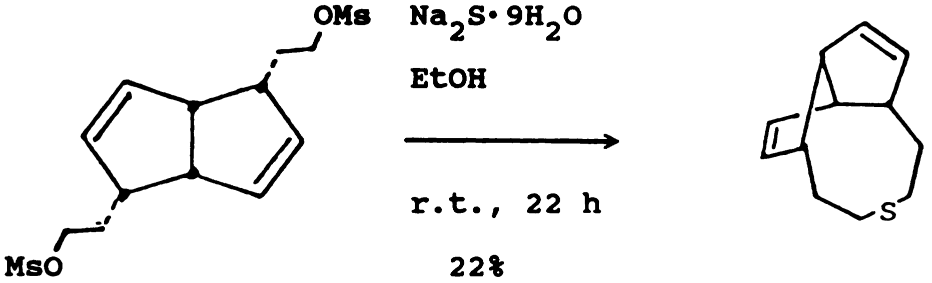
14

Diol 7 was converted to the dichloride 15 by reacted with triphenylphosphine/carbon tetrachloride.[16] After flash chromatography, dichloride 15 was obtained as a yellow oil in 52% yield.



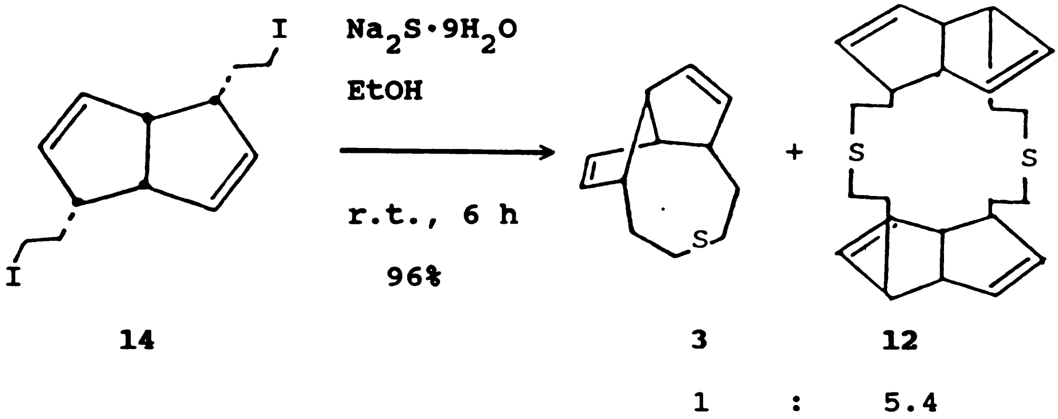
7 15

However, reaction of dimesylate 13 with sodium sulfide still gave sulfide 3 in low yield (22%). There was no trace of sulfide dimer 12.



13 3

Reaction of diiodide 14 with sodium sulfide gave a mixture. The major product still was sulfide dimer 12 (81%, m.p. 95-97 ^{0}), and the minor product was the desired sulfide 3 (15%).



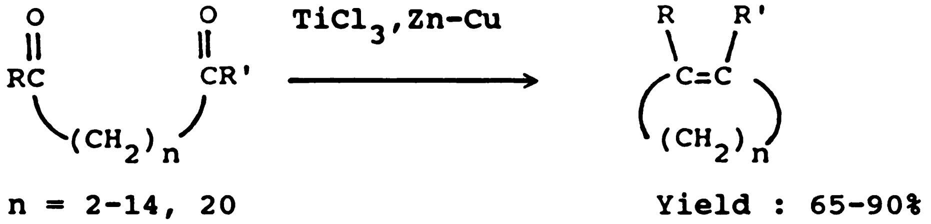
The results of cyclization are summarized in Table 1.

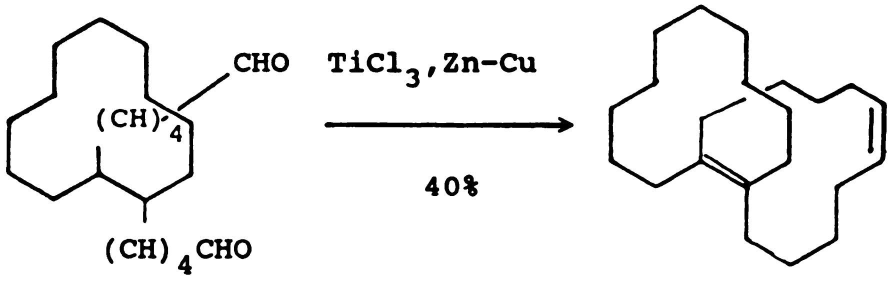
Table 1. Synthesis of Sulfides

Reactant	Product	Yield, % (ratio)
Dibromide 11	Sulfide 3 & Sulfide dimer 12	92 (1 : 4)
Dimesylate 13	Sulfide 3	22
Diiodide 14	Sulfide 3 & Sulfide dimer 12	96 (1 : 5.4)

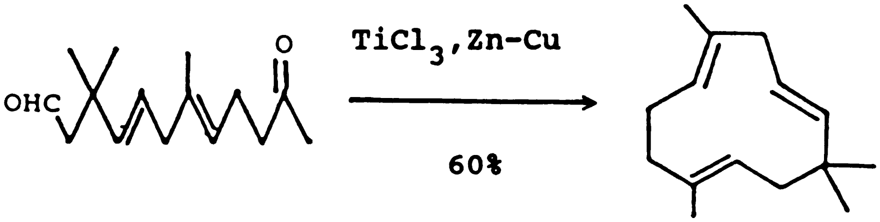
2. The Fate of the Titanium-Induced Intramolecular Dicarbonyl-Coupling Reaction

Intramolecular couplings of dicarbonyl compounds have been obtained by the McMurry reagent[17], $TiCl_3$-Zn-Cu, as shown in the following examples:

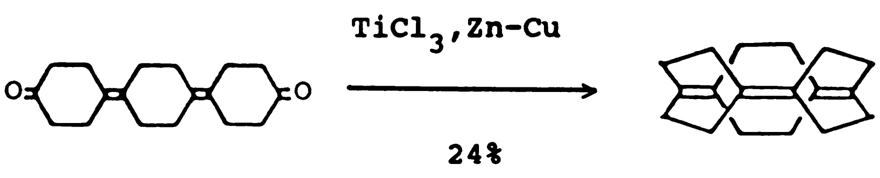




(Ref. 18)



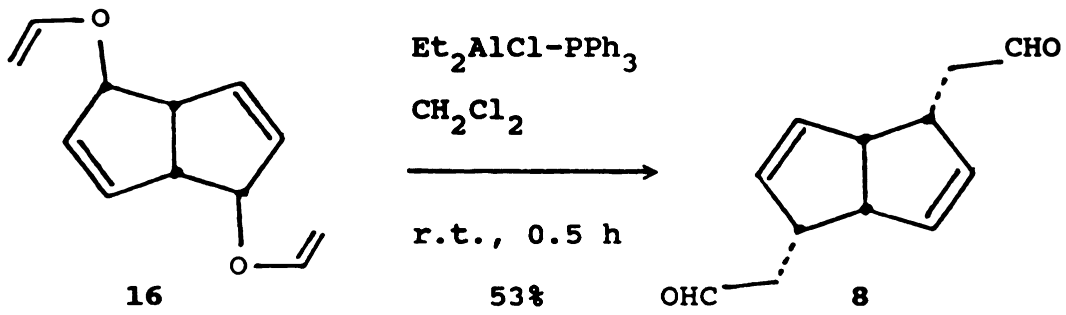
(Ref. 19)

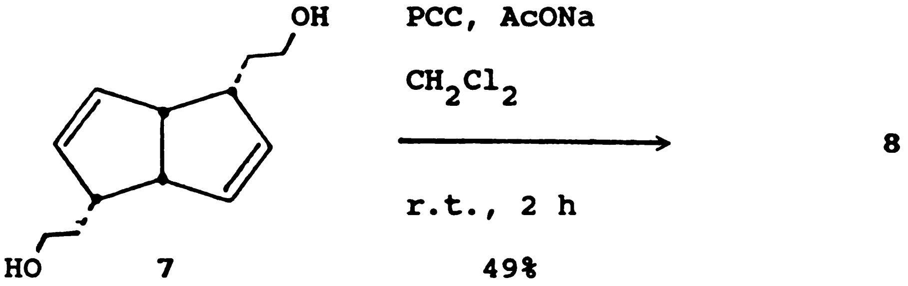


(Ref. 20)

Since there are relatively few other methods of carbocyclic ring synthesis, this titanium-induced coupling reaction might be useful for our synthesis.

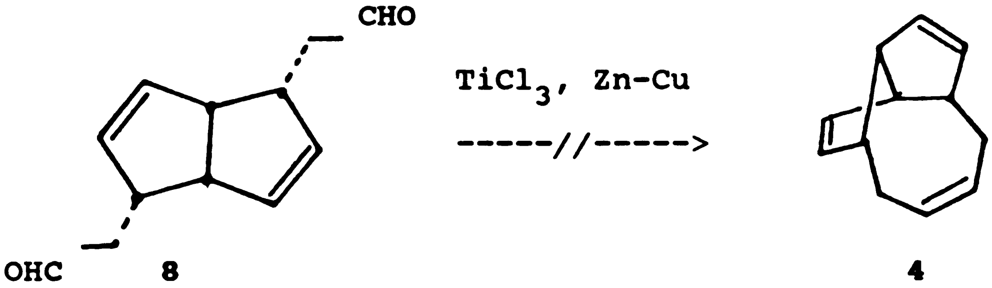
Dialdehyde 8 was produced from vinyl ether 16 by $Et_2AlCl-PPh_3$ in methylene chloride[21] in 53% yield. For comparison, 8 was also prepared from diol 7 by pyridinium chlorochromate,[22] $C_5H_5NHCrO_3Cl$, in 49% yield, and pyridinium dichromate,[23] $(C_5H_5NH^+)_2Cr_2O_7^{-2}$ in 50% yield.





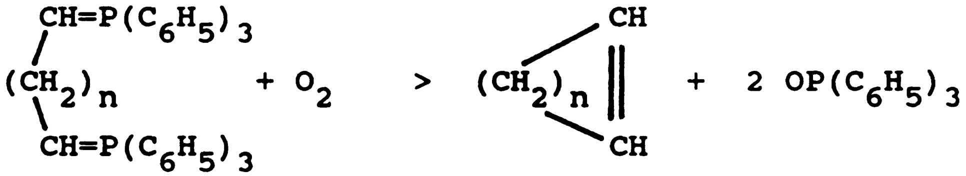
$$7 \xrightarrow[\text{50\%}]{\text{PDC, } CH_2Cl_2 \text{, r.t., 24 h}} 8$$

However intramolecular coupling of dialdehyde **8** by $TiCl_3$-Zn-Cu, did not work; neither the starting material, nor the desired product was found. We only got elimination products.



3. The Fate of the Bis-Ylide Autoxidation

Cycloolefins can be obtained by autoxidation of bis(alkylidenephosphoranes).[24]

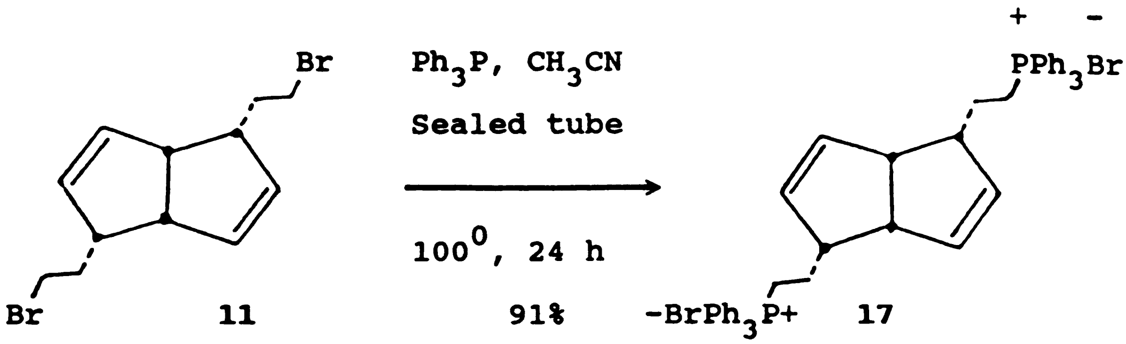


$$(CH_2)_n\begin{cases} CH{=}P(C_6H_5)_3 \\ CH{=}P(C_6H_5)_3 \end{cases} + O_2 \;>\; (CH_2)_n\begin{cases} CH \\ \| \\ CH \end{cases} + 2\ OP(C_6H_5)_3$$

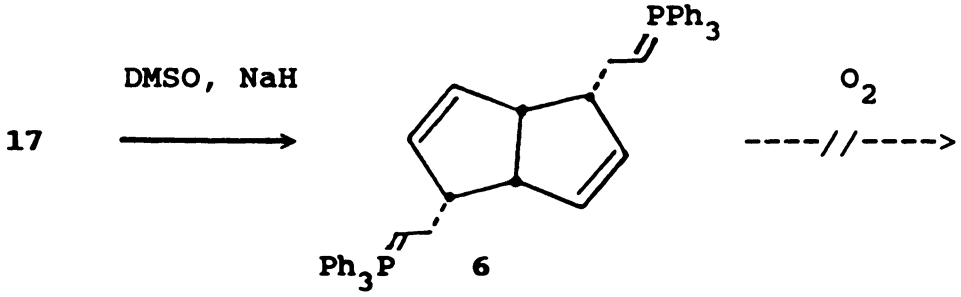
n = 3,4,5

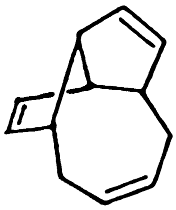
Yield : 58-61%

Treatment of dibromide **11** with triphenylphosphine in a sealed tube afforded the 2,6-bistriphenylphosphonium bromide **17** in 91% yield.



Bis-yliqde 6 was produced by adding 17 dropwise into a NaH/DMSO base solution. Passing the oxygen gas through the solution, however, did not afford any trace of the desired triene 4.



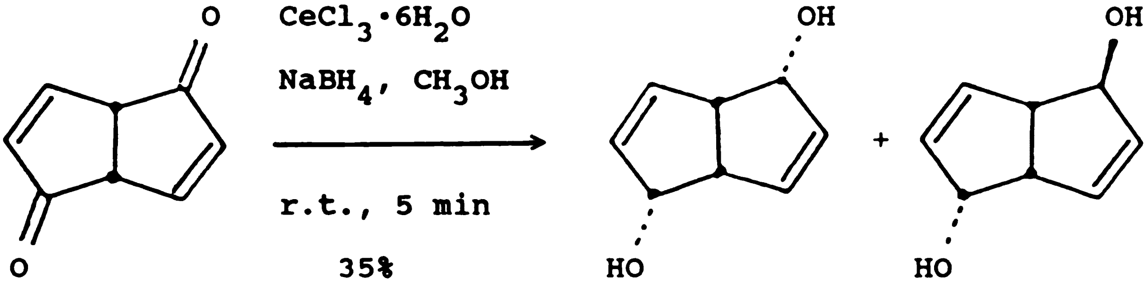


4

Although we tried many methods such as cyclization with sodium sulfide, intramolecular coupling with McMurry reagent $TiCl_3$-Zn-Cu, and autoxidation of bis- ylide, triene 4 was never realized.

4. Reduction of Dienedione 18 and Oxidation of the Epimeric Dienediol 19

Dienedione **18** was our starting material.[1a] Reduction of **18** by cerous chloride mediated with sodium borohydride[25] gave dienediols **19** and **20** in 35% yield.



18 **19** **20**

However, Mirmohammad found at 0^0 this reaction gave a mixture in 100% yield, and the ratio of **19** : **20** was 5 : 1 (GLC analysis). After crystallization from acetone, **19** was isolated in 78% yield.[10]

The residual oil from the crystallization of **19** still contained a certain amount of **19** and **20**, and could be recycled to **18**. Oxidation of the residual oil with PCC in methylene chloride afforded **18** in 35% yield.

$$\text{Residual oil of } \mathbf{19} \text{ and } \mathbf{20} \xrightarrow[\text{r.t., 2 h} \\ 35\%]{\text{PCC, NaOAc} \\ CH_2Cl_2} \mathbf{18}$$

Oxidation of the residual oil with PDC in methylene chloride afforded **18** in 36% yield.

$$\text{Residual oil of } \mathbf{19} \text{ and } \mathbf{20} \xrightarrow[\substack{\text{r.t., 24 h} \\ 36\%}]{\substack{\text{PDC, CH}_2\text{Cl}_2 \\ \text{4A Sieves}}} \mathbf{18}$$

The recycled **18** was a white solid and pure enough to use in the next step.

EXPERIMENTAL

General. Melting points were measured in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Proton nuclear magnetic resonance (H NMR) spectra were obtained on Varian T-60 or Bruker WM-250 spectrometers at 60 MHz and 250 MHz, respectively. Chemical shifts are reported in parts per million downfield from tetramethylsilane internal standard. Infrared spectra (IR) were measured on a Perkin-Elmer 137 spectrometer and a Perkin-Elmer 599 spectrometer, and were calibrated with the polystyrene 1601 cm^{-1} peak. Mass spectra (MS) were obtained on a Finnigan 4000 instrument with ionizing voltage of 70eV, or, when noted, with ionized methane (CI). Gas liquid chromatography (GLC) was performed on an F & M model 700 chromatograph equipped with a thermal conductivity detector. Component ratios were determined by a comparison of peak areas (determined by triangulation) and are uncorrected for detector response. Columns used for analysis were 6' x 1/4" aluminum columns packed with the following stationary phased on Chromosorb G (acid and base washed and silanized, 60/80 mesh): column A, 5% Carbowax 20 M; column B, 4% QF-1; column C, 3% SE-30. Thin layer chromatograms (TLC) were run on Machery-Nagel Polygram SIL G/UV_{254} precoated 0.25 mm silica gel plates, and were developed with either iodine vapor, or an anisaldehyde spray reagent, or identified under UV light. Flash column chromatography was accomplished with either Watman LPS-2 (37-53 um) or EM 9385 (40-63 um) silica gel. Normal column chromatography was performed on EM reagents silica gel 60, 70-230 mesh (EM Cat. #7734) rated at activity 2-3.

Unless otherwise noted, reagents and solvents were reagent grade materials and were used as received. Ether and THF were dried by distillation from sodium or potassium benzophenone ketyl. Diisopropylamine, DMSO and DMF were dried by distillation from calcium hydride. _n_-Butyllithium was obtained from Aldrich as a 2.6 M solution in hexane, and was titrated according to the method of Watson and Eastham.[26]

4-Thiatricyclo[8.3.0.0^{7,11}]trideca-8,12-diene 3. Reaction of dibromoethyldiene 11 with sodium sulfide. Dibromoethyldiene **11** (1.37 g, 4.3 mmol) dissolved in 21 mL of absolute ethanol was stirred with sodium sulfide ($Na_2S \cdot 9H_2O$, 2.06 g, 8.6 mmol) at room temperature for 20 hours. Then, the solution was diluted with 50 mL of distilled water. The aqueous solution was extracted with pentane (2 x 50 mL). The organic phase was washed with saturated aqueous NaCl solution (1 x 10 mL), and dried over anhydrous Na_2SO_4. Removal of solvent left a purple oil (0.166 g) with a somewhat sharp sulfur containing smell. A substantial amount of sulfide dimer **12** remained in the aqueous phase as a white solid (1.065 g), and it was collected by suction filtration. The crude oil and white solid were combined and flash chromatographed on a 1 cm diameter column containing silica gel (20 g, Whatman LPS-2) pack with 4% ethyl acetate/hexane. Elution of the column led to sulfide **3** (0.146 g, 17.6%) and sulfide dimer **12** (0.621 g, 74.5%, m.p. 110-112^0). The spectral properties of both materials were identical to those reported earlier.[10]

<u>Cis</u>,<u>endo</u>-2,6-<u>bis</u>(hydroxyethyl)bicyclo[3.3.0]octa-3,7-diene Dimethanesulfonate 13. Diol **7** (0.97 g, 0.005 mol) was dissolved in dry pyridine (10 mL) in a 25 mL round bottom flask, and cooled to 0^{0}C. Methanesulfonyl chloride (3.9 mL, 0.05 mol, previously distilled (b.p. 54.5-55^{0}C/10 mm)), was added to the stirred solution. The reaction was stirred for 2 h, and then poured onto ice. Extraction with chloroform (2 x 10 mL) was followed by multiple extractions of the combined organic phase with cold 5% NaOH (3 x 10 mL), cold 1 M HCl (4 x 10 mL), saturated $NaHCO_3$ (1 x 10 mL), and saturated NaCl solution (1 x 10 mL). The extract was dried over $MgSO_4$ and the solvent removed to afford dimesylate **13** (1.57 g, 90%) as a brown oil which solidified on standing. This material was not characterized or purified further, but was used directly in the next step. A ^{1}H NMR of this material ($CDCl_3$, 60 MHz) was as follows: δ5.15 (4H, s), 4.38 (4H, d, J=7 Hz), 3.60-3.40 (4H, m), 3.05 (6H, s), 2.30-1.70 (4H, m); MS m/e 350 (M^+, 0.06%), 254 (5.94%), 158 (55.94%), 143 (58.39%), 130 (67.9%), 79 (100%).

Cis,endo-2,6-_bis_(iodoethyl)bicyclo[3.3.0]octa-3,7-diene 14. To a solution of crude dimesylate **13** (1.40 g, 4.0 mmol) in acetone (18 mL) was added sodium iodide (1.80 g, 12 mmol). The reaction was refluxed with stirring for 16 h, after which time an additional portion of sodium iodide (0.45 g) was added and refluxing continued for an additional 6 h. The reaction was cooled, filtered free of precipitated salt, and the solvent removed under reduced pressure. The brown residue was taken up in ether (150 mL) and washed with saturated sodium sulfite (2 x 20 mL) and saturated NaCl solution (20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed to give crude diiodide **14** as a brown oil. Flash chromatography on silica gel packed with 3% ethyl acetate/hexane yielded diiodide **14** (0.90 g, 54%, m.p. 63-65^0) as a white solid. The spectral characteristics were as follows: ^{1}H NMR ($CDCl_3$, 60 MHz) δ5.58 (4H, s), 3.40-3.05 (4H, t, J=10 Hz), 3.04-2.40 (4H, m), 2.10-1.70 (4H, m); MS m/e 415 (M+1, 1.23%), 414 (M^+, 12.55%), 287 (36.44%), 259 (47.26%), 155 (24.09%), 131 (37.71%), 117 (55.05%), 91 (100%).

__*Cis*__, __*endo*__-2,6-__*bis*__(chloroethyl)bicyclo[3.3.0]octa-3,7-diene 15. Reaction of Diol 7 with Carbon Tetrachloride/ Triphenylphosphine. Diol 7 (0.97 g, 5 mmol) was dissolved in acetonitrile (100 mL) in a 250 mL three necked flask equipped with a good magnetic stir bar, a condenser with a drying tube, a thermometer, and a stopper. Carbon tetrachloride (10 mL) was added, and the solution stirred until it was all in solution. Triphenylphosphine (1.45 g, 5.5 mmol) was then added all at once, causing the reaction to warm up to 40^{0}C. The solution immediately became a dark red, and was refluxed for 3 h. The flask was then cooled to room temperature and 10 mL of pentane was added to precipitate the bulk of the triphenylphosphine oxide. The solution was filtered through celite packed in a fritted funnel, and the filtered precipitate washed thoroughly with cold pentane. The solvent was removed under reduced pressure and the remaining oil was flash chromatographed on silica gel (Whatman) packed with hexane. The dichloride 15 (0.58 g, 52%) was isolated as a yellow oil with the following spectral properties: ^{1}H NMR ($CDCl_3$, 60 MHz)δ5.58 (4H, s), 3.46 (6H, t), 3.20-2.60 (2H, m), 2.05-1.80 (4H, m); MS m/e 231 (M^+, 0.65%), 195 (35.16%), 167 (31.11%), 159

(14.27%), 153 (37.08%), 131 (100%).

Reaction of Dimesylate 13 with Sodium Sulfide. Dimesylate **13** (1.05 g, 3.0 mmol) dissolved in absolute ethanol (15 mL) was stirred with sodium sulfide ($Na_2S \cdot 9H_2O$, 1.44 g, 6.0 mmol) at room temperature for 22 h. Then, the solution was added with H_2O (15 mL), and extracted with pentane (2 x 10 mL). The combined organic layer was washed with distilled H_2O (10 mL) and saturated NaCl (10 mL), then was dried over $MgSO_4$. Removal of solvent with the rotovap yielded sulfide **3** (0.13 g, 22.5%) as a pink oil. The spectral properties of the material were identical to those reported earlier.[10]

Reaction of Diiodide 14 with Sodium Sulfide. Diiodide **14** (0.414 g, 1 mmol) suspended in absolute ethanol (25 mL) was stirred with sodium sulfide ($Na_2S \cdot 9H_2O$, 0.48 g, 2.0 mmol) at room temperature for 6 h. Then, the solution was diluted with distilled H_2O (50 mL), and extracted with pentane (2 x 50 mL). The combined organic layer was washed with distilled H_2O (20 mL), saturated NaCl (20 mL), and dried over $MgSO_4$. Removal of solvent with the rotovap yielded sulfide **3** (0.028 g, 14.6%) as a pink oil. Suction filtration of the aqueous product mixture yielded sulfide dimer **12** as a white solid (0.156 g, 81.3%, m.p. 95-97^0). The spectral properties of both materials were identical to those reported earlier.[10]

Cis,endo-bicyclo[3.3.0]octa-3,7-diene-2,6-diacetaldehyde 8. Aliphatic Claisen Rearrangement of Vinyl Ether 16 with Diethylaluminum Chloride/ Triphenylphosphine. A solution of diethylaluminum chloride (25 wt% (1.8 M) solution in toluene, 2.2 mL, 4.0 mmol) was added to a solution of triphenylphosphine (1.16 g, 4.4 mmol) in methylene chloride (7.8 mL) at room temperature under nitrogen and the whole reaction was stirred for 15 min. Vinyl ether 16 (0.38 g, 2 mmol) in methylene chloride (5 mL) was added to the solution and stirred for another 30 min. The mixture was diluted with ether (30 mL) and poured into 1 N HCl (15 mL). The organic layer was washed with saturated sodium chloride (10 mL), dried over $MgSO_4$, and concentrated with the rotovap. The residue (0.282 g) was purified by flash chromatography on 20 g silica gel packed in 33% ethyl acetate/hexane. Dialdehyde 8 was obtained as a clear, colorless oil (0.20 g, 53%). The spectral properties of this material were identical to those reported earlier.[1a]

Oxidation of Cis,endo-2,6-dihydroxyethylbicyclo-[3.3.0]octa-3,7-diene 7 with Pyridinium Chlorochromate. A 25 mL round bottomed flask was fitted with a reflux condenser. Pyridinium chlorochromate (0.646 g, 3 mmol, 1.5 eq.) and sodium acetate (0.049 g, 0.6 mmol, 0.3 eq.) was suspended in methylene chloride (2.6 mL). Dienediol 7 (0.194 g, 1.0 mmol) in methylene chloride (2.6 mL) was added in one portion to the magnetically stirred solution. After 2 h ether (10 mL) was added and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly with ether (3 x 5 mL) whereupon it became a black granular solid. The combined organic solution was passed through a short pad of Florisil, and was washed with 5% aqueous $NaHCO_3$ (15 mL) and saturated NaCl (15 mL). The organic solution was dried over $MgSO_4$ and concentrated at the rotovap. The residue was purified by flash chromatography packed in 33% ethyl acetate/hexane and afforded dialdehyde 8 (0.094 g, 49%) as a colorless oil. The spectral properties of this material were identical to those reported earlier.[1a]

Oxidation of <u>Cis</u>,<u>endo</u>-2,6-dihydroxyethylbicyclo-[3.3.0]octa-3,7-diene 7 with Pyridinium Dichlorochromate. Diol 7 (0.388 g, 2 mmol) was dissolved in methylene chloride (5.6 mL). Pyridinium dichlorochromate (2.26 g, 6 mmol) was added in one portion. The solution was stirred at room temperature for 24 h, then diluted with ether (25 mL). The supernatant was decanted, the residue was washed with ether (3 x 25 mL), and the combined solution was washed with saturated $NaHCO_3$ (3 x 10 mL) and saturated NaCl (10 mL). The extract was dried over $MgSO_4$ and the solvent removed to afford a yellow oil. The crude oil was purified by flash chromatography packed in 33% ethyl acetate/hexane and afforded dialdehyde **8** (0.187 g, 50%) as a clear oil. The spectral properties of this material were identical to those reported earlier.[1a]

Titanium-Induced Reductive Coupling of Dialdehyde 8. The Zn-Cu couple was prepared from zinc dust and $CuSO_4$ following the procedure of McMurry.[18] A stirred slurry of $TiCl_3$ (1.03 g, 6.7 mmol) and Zn-Cu (1.0 g, 15.4 mmol) in 1,2-dimethoxyethane (20 mL) was refluxed under nitrogen for 1 h. Dialdehyde **8** (0.171 g, 0.90 mmol) in 1,2-dimethoxyethane (20 mL) was added through an addition funnel over 3 h, followed by a further 24 h period of reflux. The reaction mixture was then cooled to room temperature and filtered through a Florisil pad. Concentration at the rotorvap gave only 1,2-dimethoxyethane. Neither starting material nor product was found in the solvent.

Cis,endo-2,6-_bis_(2-triphenylphosphoniumethyl)-bicyclo[3.3.0]octa-3,7-diene dibromide 17. _Bis_-bromoethyldiene **11** (0.24 g, 0.75 mmol) was dissolved in acetonitrile (10 mL) in a glass tube. Triphenylphosphine

(0.49 g, 1.88 mmol, 1.12 eq.) was added into the mixture and the glass tube was sealed under vacuum. After heating in an autoclave for 24 h, the glass tube was cooled and opened, and the bloody red solution was taken up in chloroform (30 mL). By addition of ether, a heavy red precipitate was formed. The mixture was filtered by suction filtration. The amorphous red precipitate (0.57 g, 91%), was washed several times with ether. Its decomposition point was 205-235^{0}C. The spectral properties of this material were identical to those reported earlier.[10]

Approach to Tricyclo[7.3.0.0^{4,12}]dodeca-2,6,10-triene 4. Sodium hydride (0.054 g, in 50% mineral oil, 1.125 mmol) was weighed out in a dry 250 mL three necked flask. A magnetic stirrer, addition funnel, nitrogen inlet adapter, reflux condenser and thermometer were fitted to the flask, and a nitrogen atmosphere established. The sodium hydride was washed free of mineral oil with pentane (3 x 20 mL), and then suspended in dry DMSO (50 mL). The mixture was heated at 70-80^{0}C for 45 min, then cooled in an ice bath. Bis-phosphoniumbromidediene **17** (0.45 g, 0.53 mmol) in DMSO (20 mL) was added dropwise, and rinsed in with DMSO (5 mL). The mixture was heated to 50^{0}C, and oxygen (dried over P_2O_5, conc. H_2SO_4 and KOH) passed through a bubbler in the solution at 50^{0}C for three days. The deep red color of the solution turned gradually to deep brown and then lighter brown. The solution was poured into distilled H_2O (50 mL) and extracted with pentane (3 x 75 mL). The combined organic layer was washed with 1 : 1 H_2O-DMSO (100 mL), distilled H_2O (100 mL) and dried over $MgSO_4$. Removal of solvent left a clear solution, whose proton NMR showed only the DMSO proton absorptions.

Since the residue contained material other than the expected triene, the experiment was repeated at room temperature for four days. The deep red color of the solution turned to deep brown after one day and then light brown after four days. The result was similar to the above experiment.

Pyridinium Chlorochromate Oxidation of the Epimeric Dienediols 19 and 20. In a 250 mL round bottomed flask fitted with a reflux condenser was suspended pyridinium chlorochromate (16.15 g, 75 mmol) and sodium acetate (1.23 g, 15 mmol) in methylene chloride (100 mL). The residual dienediols from crystallization of **19** (6.9 g) in methylene chloride (10 mL) was added in one portion to the magnetically stirred solution. After 2 hours dry ether (100mL) was added and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly with ether (3 x 25 mL) whereupon it became a black granular solid. The combined organic solution was passed thorough a short pad of Florisil, and was washed with 5% NaOH (2 x 10 mL), 5% HCl (2 x 10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL). Removal of the solvent gave a thick brown residue, which was sublimed (using a kugelrohr apparatus) to give **18** as a white solid (2.36 g, 35.2%, m.p. 77-79^0). The spectral properties of this material were identical to those reported earlier.[1a]

Pyridinium Dichromate Oxidation of the Epimeric Dienediols 19 and 20. The residue diols **19** and **20** from crystallization of **19** (4.14 g,) was dissolved into methylene chloride (85 mL). Pyridinium dichromate (33.84 g) and 4A molecular sieves were added into the solution. After stirring at room temperature for 24 hours the solution was diluted with ether (170 mL) and the supernatant decanted. The residue was washed with ether (3 x 170 mL), and the combined organic solution was filtered through a small amount of silica gel in order to remove last traces of Cr species. Then, the organic solution was washed with 5% NaOH (2 x 10 mL), 5% HCl (2 x 10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL). Removal of the solvent gave brown needles, which was sublimed (using a kugelrohr apparatus) to give **18** as a white solid (1.44 g, 35.8%, m.p. 77-79^0). The spectral properties of this material were identical to those reported earlier.[1a]

<u>Cis,endo</u>-2,6-dihydroxybicyclo[3.3.0]octa-3,7-diene 19. Reduction of dienedione 18 with Cerous Chloride Mediated Sodium Borohydride. Dienedione **18** (1.34 g, 10 mmol) was dissolved in a 0.4M $CeCl_3 \cdot 6H_2O$ methanol solution (25 mL, 10 mmol) in a 100 mL erlenmeyer flask and $NaBH_4$ (0.378 g, 10 mmol) was added within five minutes with stirring. The mixture was allowed to react at room temperature for thirty minutes. Water (10 mL) was added to the flask and the mixture was stirred for five more minutes. The aqueous solution was extracted with chloroform (2 x 25 mL). The combined organic solution was washed with water (10 mL), saturated aqueous NaCl (10 mL), and dried over Na_2SO_4. Removal of solvent left a yellow oil which was recrystallized from acetone (10 mL) to give dienediol **19** as a white solid (0.477 g, 34.6%, m.p. 92-93^0). The spectral properties of the material were identical to those reported earlier.[1a]

PART II. AN APPROACH TO DODECAHEDRANE

INTRODUCTION

Dodecahedrane **21** was realized by Paquette in 1983.[27,28] Plato wrote in <u>Timaeus</u> "... of the earth arising from the cubane, fire from the tetrahedrane, air from the octahedrane, water from the icosahedrane, and the sphere of the universe from the dodecahedrane" (Figure 2). For the organic chemist, it is a great challenge to translate the Platonic solids into real molecules.[29]

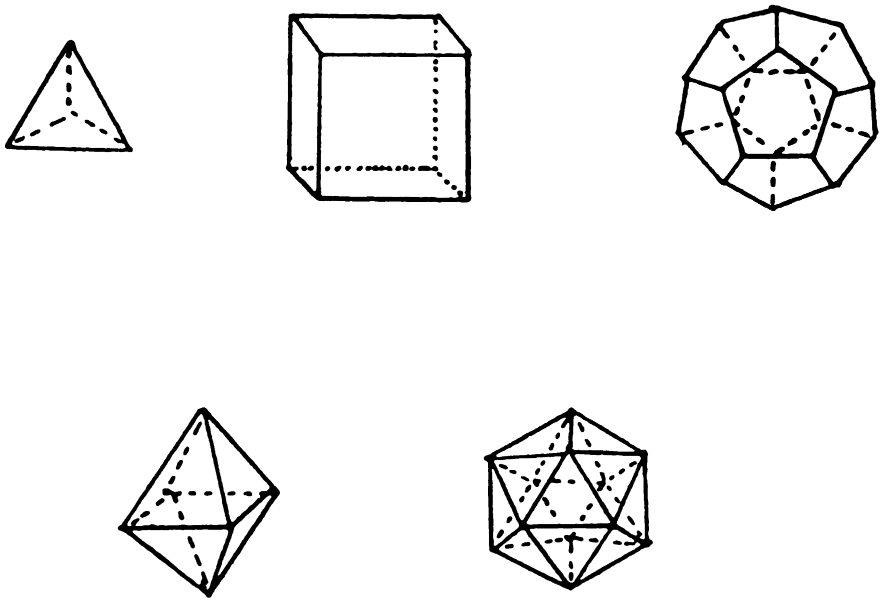
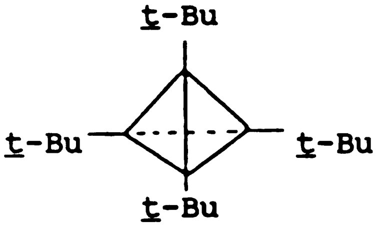


Figure 2. The Platonic solids : (top) tetrahedron, cube, dodecahedron, (bottom) octahedron, icosahedron.

Indeed, Maier succeeded in 1978 in preparing tetra-*tert*-butyl tetrahedrane **22**,[30,31] and Schleyer prepared tetralithiotetrahedrane **23**.[32]



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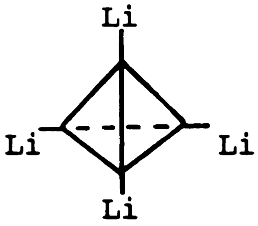

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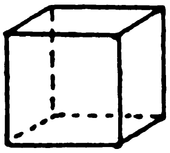
Cubane **24** was achieved by Eaton[33] as early as 1964, and the perfluorooctamethylcubane **25** was obtained by Miller[34] in 1976.



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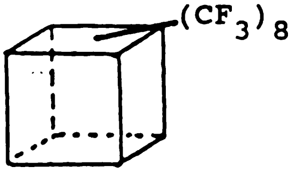


25

In the 1960's, Woodward[35] and many other groups[36] began to pursue **21**. However, octahedrane and icosahedrane are excluded because they exceed the valence of carbon.

Dodecahedrane **21** is a highly symmetric and rigid molecule. The ^1H and ^{13}C NMR of **21** (in $CDCl_3$) are characterized by singlets, the former at δ 3.38 and the latter at 66.93 ppm. Although **21** is very rigid, the angle strain is minimal.

Dodecahedrane **21** and all other above moleculars are achiral molecules, but **21** can be bisected into two isomeric homochiral halves. This kind of disection is called la coupe du roi, the King's cut, (Figure 3).[37] **21** is cut halfway from the top, then perpendicularly cut another halfway from the bottom. Two horizontal quarter-cuts give two homochiral halves which have an identical absolute stereochemical configuration. However, a left-handed segment and a right-handed segment cannot be reassembled to form an apple.

To synthesize **21** is a tough task, because it requires placing twenty identical methine units, thirty C-C bonds, and twelve five-membered rings together properly. Besides, each of the thirty ring fusions must be cis and syn to one another.

The strategy to synthesize **21** can be divided into the linear approach and the convergent approach.

Paquette has synthesized **21** by a linear approach (figure 4).[28] The domino Diels-Alder reaction of 9,10-dihydrofulvalene **26** with dimethyl acetylene dicarboxylate provided the cornerstone intermediate **27**, in which fourteen carbon atoms were already installed into proper position. For the next step, he introduced the remaining six carbon atoms. The so-called closed dilactone **28** contained all requisite twenty carbon atoms and had twelve of the all-important cis-locked methine stereocenters properly installed. Treatment of **28** with methanolic hydrogen chloride provided dichloro diester **29**. Firstly, he shelved **29** for about 30 months while he pursued other aspects. Lately, however, **29** was shown to be a pivotal intermediate. Finally, **21** was realized in twenty-three steps.

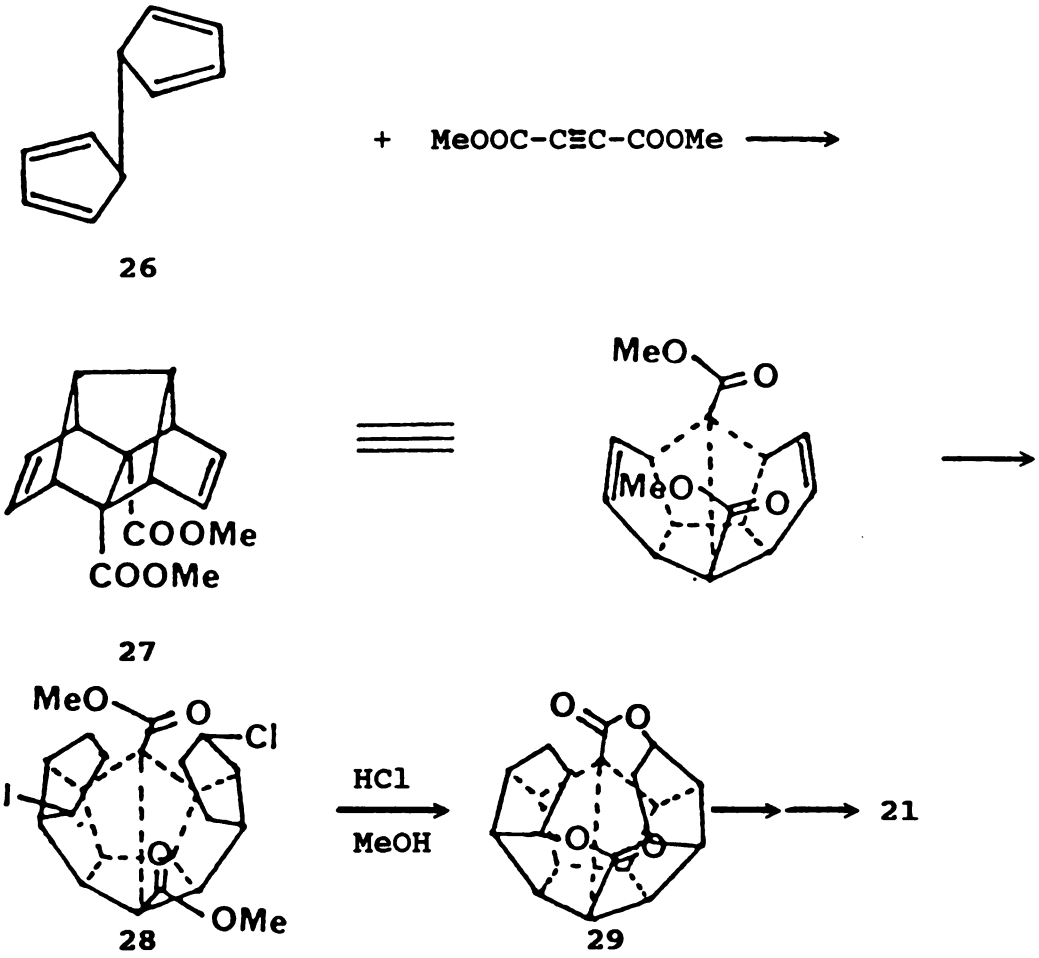
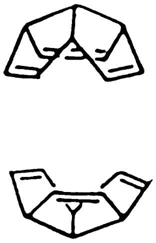


Figure 4. The Linear Approach of 21 by Paquette.

For the convergent approach, dodecahedrane **21** has been pursed by dimerizing of triquinacene **30**,[38] coupling of peristylane **31** with a five-membered ring,[39] and dimerizing of bivalvane **32**.[40]

21 ====>



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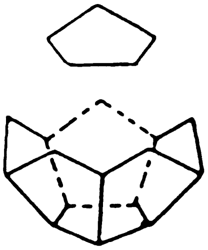

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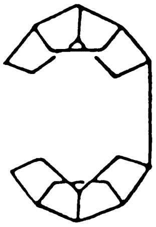
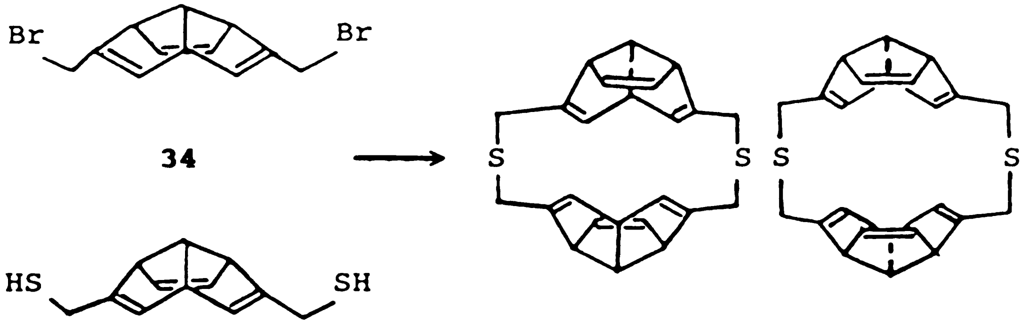


32

Recently, Roberts completed **33** from dibromide **34** and dimercaptan **35**.[41] His target molecule is the doubly annelated dodecahedrane **36**.



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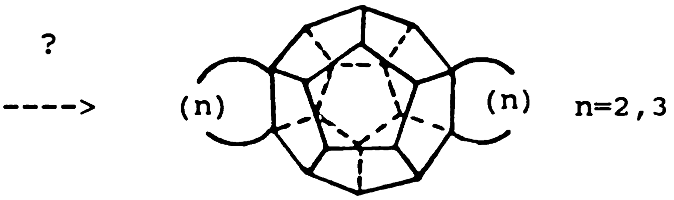
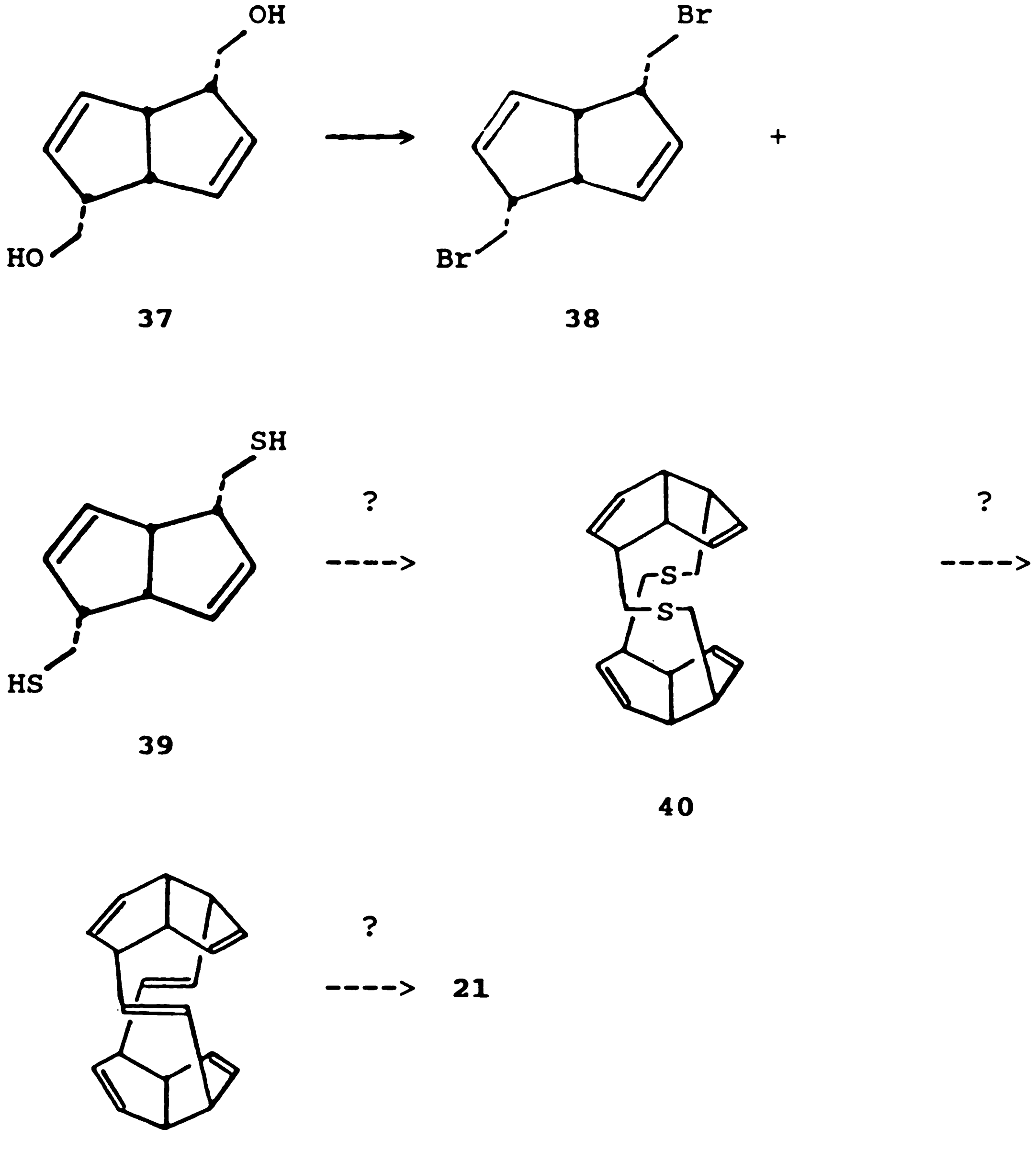


36

We are interested in the convergent synthesis, because it will take fewer steps to realize **21**.

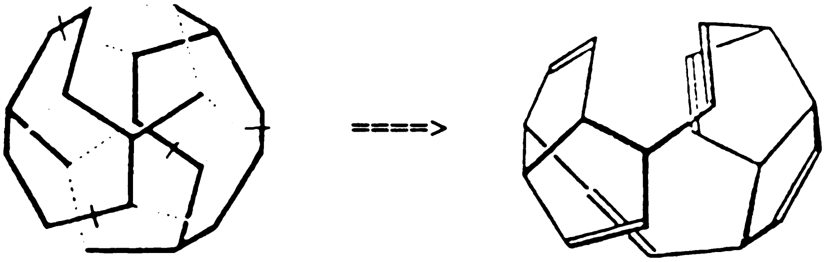
Diol **37** was available in our labratories. Following Monego's model study, we might couple **38** and **39** together to give **40**.[42]



37 38 39 40 41

Treatment of **41** with a small, cationic species,[43] such as H^+, or Li^+, might give a stable inclusion compound of **21**.

21 has four isoprene units, and **41** is a biogenetic-like precursor (Fig. 5).[44] Connecting two bicyclo[3.3.0]octa-3,7-diene fragments of the dodecahedrane framework by two <u>trans</u> double bond bridges will give **41**.



21 **41**

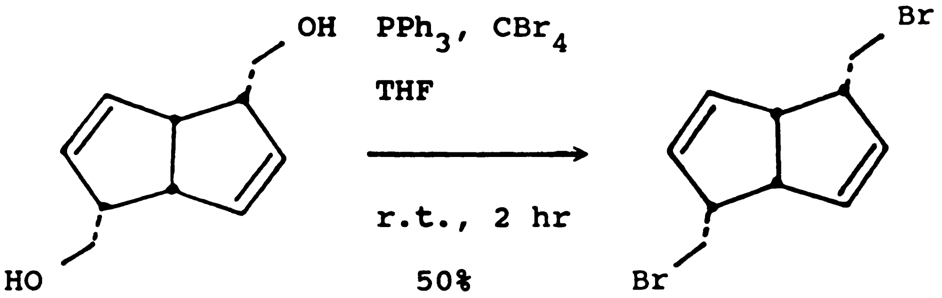
Figure 5. **41** is a Biogenetic-like Precursor of **21**.

RESULTS AND DISCUSSIONS

The Fate of The Coupling Reactions

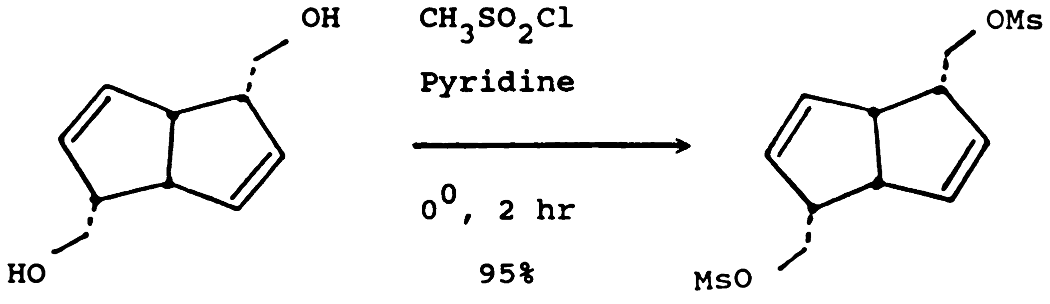
Our immediate goal of this project was to synthesize hexaene **41**. Based upon Monego's model study, we could easily make dibromide **38** and dithiol **39**.

Thus, treatment of diol **37** with triphenylphosphine/ carbon tetrabromide in THF gave dibromide **38** in 50% yield. However, **38** was easily decomposed and hard to purify. Therefore, we decided to make another compound such as diiodide **42** to replace dibromide **38**.

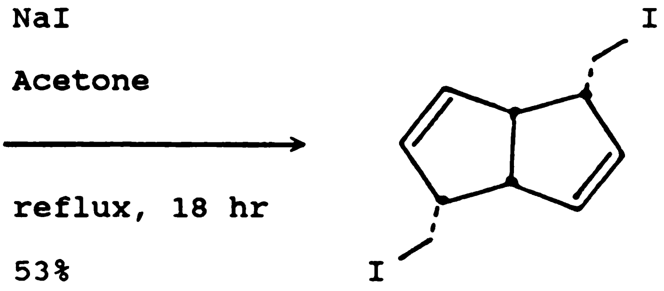


37 **38**

Treatment of diol **37** with mesyl chloride in pyridine afforded dimesylate **43** in 95% yield. Treatment of **43** with sodium iodide in refluxing acetone gave diiodide **42** in 53% yield after chromatography.



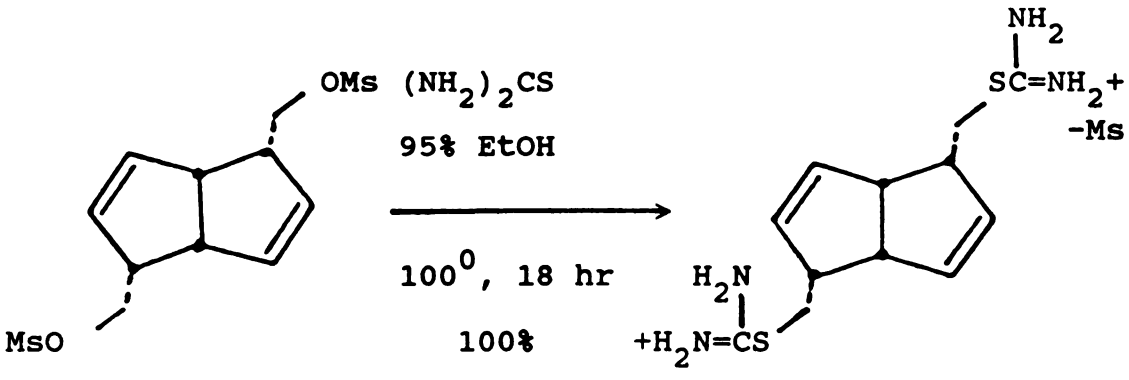
37 43



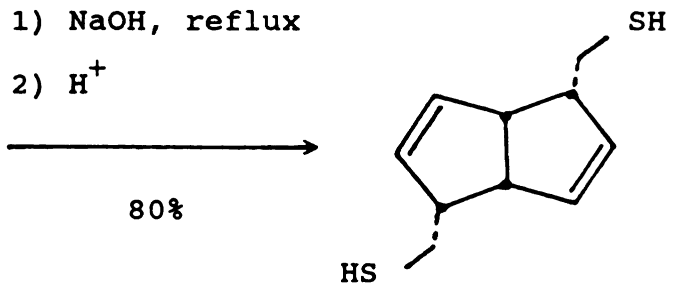
42

Now, we have succeeded in producing one half segment of **21**. We needed to make the other half segment.

The reaction of dimesylate **43** with thiourea in 95% ethanol afforded the <u>bis</u>-thiouronium mesylate **44** in quantitative yield. Alkaline hydrolysis of **44** followed by acidification gave dithiol **39** in 80% yield.



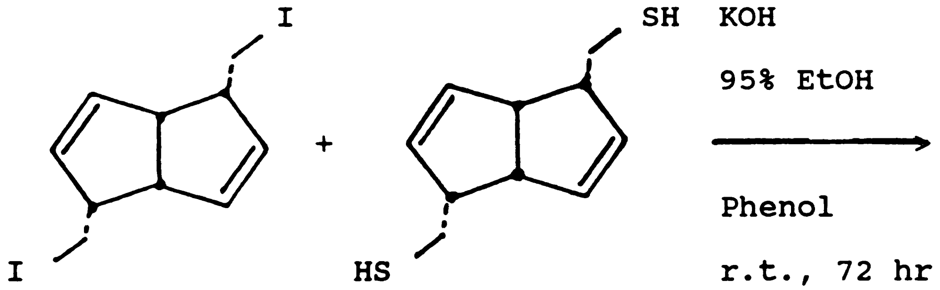
43 44



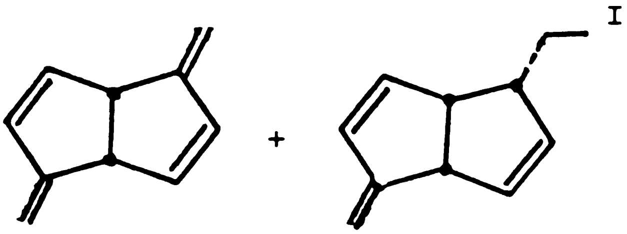
39

It's time to do the coupling reaction. However, we never succeeded.

A 1:1 mixture of diiodide **42** (<0.1M) and dithiol **39** (<0.1M) in benzene was added dropwise over 72 hours to 2.5 molar equivalents of potassium hydroxide in 95% ethanol buffered with 4 equivalent of phenol under nitrogen at room temperature.[41] The reaction was monitored by GC every twelve hours. However, we only recovered some starting materials and got some decomposed compounds. If we increased temperature, we only got



42 **39**

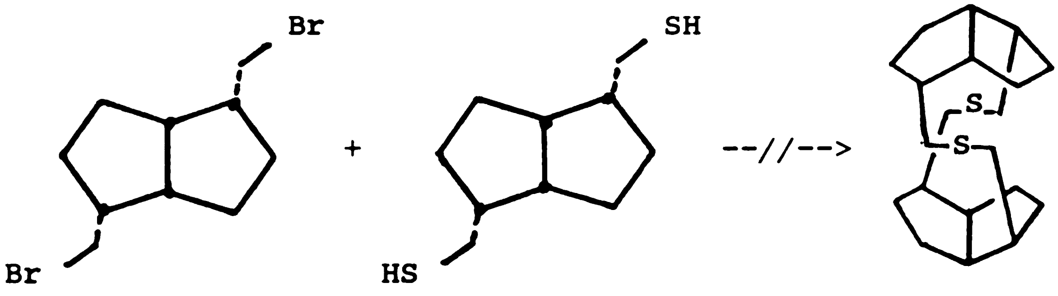


45 **46**

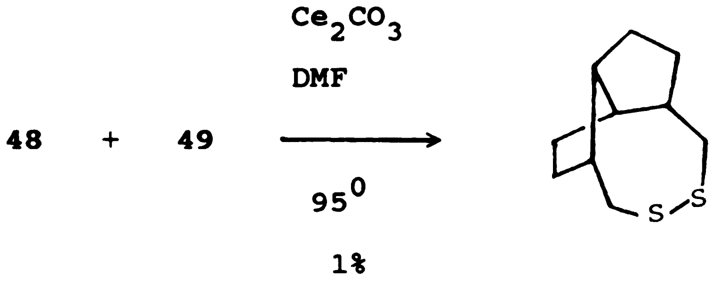
elimination products, such as **45** and **46**.

We changed the base from potassium hydroxide to potassium hydride, the solvent from benzene and 95% ethanol to DMF, and even the starting material from diiodide **42** to dimesylate **43**. However, when we ran this coupling reaction again and again, we still could not get sulfide dimer **40**.

In Monego's model study, the target molecule was sulfide dimer **47**. However, coupling of dibromide **48** with dithiol **49** gave disulfide **50** in 1% yield. There was no trace of sulfide **47**.

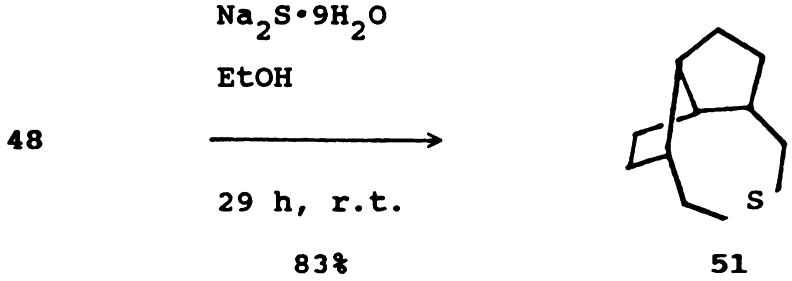


48 **49** **47**



50

Curiously, we treated dibromide **48** with sodium sulfide. If the product was the sulfide dimer **47**, we would use sodium sulfide in our project to approach dodecahedrane **21**. Unfortunately, the product was sulfide **51**.



51

EXPERIMENTAL

General. Melting points were measured in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Proton nuclear magnetic resonance (H NMR) spectra were obtained on Varian T-60 or Bruker WM-250 spectrometers at 60 MHz and 250 MHz, respectively. Chemical shifts are reported in parts per million downfield from tetramethylsilane internal standard. Infrared spectra (IR) were measured on a Perkin-Elmer 599 spectrometer, and were calibrated with the polystyrene 1601 cm^{-1} peak. Mass spectra (MS) were obtained on a Finnigan 4000 instrument with an ionizing voltage of 70 eV. Gas liquid chromatography (GLC) was performed on a Hewlett Packard 5880 instrument. Thin layer chromatograms (TLC) were run on Machery-Nagel Polygram SIL G/UV_{254} precoated 0.25 mm silica gel plates, and were developed with either iodine vapor, or an anisaldehyde spray reagent, or identified under UV light. Flash column chromatography was accomplished with Watman LPS-2 silica gel. Normal column chromatography was performed on EM reagents silica gel 60.

Unless otherwise noted, reagents and solvents were reagent grade materials and were used as received. Ether, THF and benzene were dried by distillation from sodium or potassium benzophenone ketyl. DMF was dried by distillation from calcium hydride. n-Butyllithium was obtained from Aldrich as a 2.6 M solution in hexane, and was titrated according to the method of Watson and Eastham.[26]

Cis,endo-2,6-bis(bromomethyl)bicyclo[3.3.0]octa-3,7-diene 38. Reaction of Diol 37 with Carbon Tetrabromide/Triphenylphosphine. Diol **37** (0.51 g, 3.1 mmol) was dissolved in THF (20 mL) in a 50 mL three necked flask equipped with a magnetic stir bar, thermometer, stopper and under a nitrogen atmosphere. Carbon tetrabromide (4.13 g, 12.4 mmol, 2 eq.) was added, and the solution stirred until it was all dissolved. Triphenylphosphine (3.27 g, 12.4 mmol, 2 eq.) was added all at once, causing the reaction to warm up to 50^0. The solution immediately became a dark red, and began to turn brown as triphenylphosphine oxide precipitated. After stirring at room temperature for 2 hr, the solution was filtered through a fritted funnel, and the filtered precipitate washed thoroughly with hexane. The TLC of this mixture indicated that it contained carbon tetrabromide which is visible on TLC only under UV light, the dibromide **38**, and triphenylphosphine oxide. The solvent was removed under reduced pressure. The remaining product was flash chromatographed on silica gel packed with hexane. When carbon tetrabromide and triphenylphosphine oxide were no longer detected in the eluate, the solvent was changed to 20% ethyl acetate/hexane whereupon the dibromide **38** eluted and was isolated as a very pale yellow liquid (0.45 g, 50.2%). Dibromide **38** was very unstable and decomposed into a dark green solution at room temperature on standing. Dibromide **38** had the following properties: ^{1}H NMR ($CDCl_3$, 60 MHz) δ5.70 (4H, q), 3.60-3.00 (4H, d), 2.10-1.85 (4H, m); MS m/e 294 (M+2, 1.12%), 292 (M^+, 2.30%), 290 (M-2, 1.44%), 131 (82.11%), 117 (52.11%), 91 (100%), 55 (57.52%), 39 (89.07%).

<u>Cis</u>,<u>endo</u>2,6-<u>bis</u>(hydroxymethyl)bicyclo[3.3.0]octa-3,7-diene Dimethanesulfonate 43. Diol 37 (0.102 g, 0.614 mmol) was dissolved in dry pyridine (10 mL) in a 25 mL round bottom flask, and cooled to 0^0. Methanesulfonyl chloride (0.5 mL, 6.4 mmol) previously distilled (b.p. $54.5-55^0$/10 mm), was added to the stirred solution. The reaction was stirred for 2 h, and then poured onto ice. Extraction with chloroform (2 x 10 mL) was followed by multiple extractions of the combined organic phases with cold 5% NaOH (3 x 10 mL), cold 1 M HCl (4 x 10 mL), saturated $NaHCO_3$ (10 mL), and saturated NaCl (10 mL). The extraction was dried over $MgSO_4$ and the solvent removed to afford dimesylate (0.190 g, 95%) as a brown oil which solidified on standing. A ^{1}H NMR of this material ($CDCl_3$, 60 MHz) was as follows: δ5.70 (4H, q), 4.20 (4H, d), 3.70-3.20 (4H, m), 3.00 (6H, s).

<u>Cis</u>,<u>endo</u>-2,6-<u>bis</u>(iodomethyl)bicyclo[3.3.0]octa-3,7-diene 42. To a solution of crude dimesylate **39** (1.26 g, 4.0 mmol) in acetone (18 mL) was added sodium iodide (1.80 g, 12 mmol). The reaction was refluxed with stirring for 16 h, after which time an additional portion of sodium iodide (0.45 g) was added and refluxing continued for an additional 6 h. The reaction was cooled, filtered free of precipitated salt, and the solvent removed under reduced pressure. The brown residue was taken up in ether (150 mL) and washed with saturated sodium sulfite (2 x 20 mL) and saturated NaCl solution (20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed to give crude diiodide **42** as a brown oil. The crude product was recrystallized from pentane to give diiodide **42** (0.90 g, 53%, m.p. 61-64^0) as a white solid. The spectral characteristics were as follows: ^{1}H NMR ($CDCl_3$, 60 MHz) δ5.85-5.40 (4H, q), 3.60-2.50 (12H, m); MS m/e 386 (M^+, 1.77%), 259 (29.31%), 181 (6.09%), 132 (80.23%), 117 (63.99%), 91 (86.6%), 39 (100%).

<u>Cis</u>,<u>endo</u>-2,6-<u>bis</u>(amidinothio)methylbicyclo[3.3.0]-octa-3,7-diene Dimethanesulfonate 44. The Addition of

Thiourea to Dimesylate 43. Dimesylate 43 (0.161 g, 0.5 mmol) and thiourea (0.114 g, 1.5 mmol, 50% excess) were placed in a screw-capped reaction tube, and 95% ethanol added (1.7 mL, i.e., to make the solution 0.3 M in dimesylate). The tube was filled with nitrogen gas, tightly capped and heated on a steam bath for 18 h. The color of the solution became blood red. The solution was allowed to cool to room temperature, and then chilled to -15^0 for 4 h. The resultant solid was filtered, washed with cold ethanol, and air dried to give a yellow solid (0.227 g, 95.6%, m.p. $104-109^0$).

Cis,endo-2,6-bis(mercaptomethyl)bicyclo[3.3.0]octa-3,7-diene 39. Hydrolysis of Bis-thiouronium Dimesylate 44. The crude thiouronium salt 44 from last step (0.227 g, 0.5 mmol) was placed in a 50 mL round bottom flask, and suspended in aqueous NaOH (10 mL of a 1.5 N solution). A serum cap was fitted to the flask and the suspension stirred as nitrogen was bubbled through the solution with a syringe needle (another needle served as a vent). After 5 minutes, a nitrogen purged condenser was fitted to the flask, and the whole system kept under nitrogen for the duration of the reaction. The solution was refluxed for 12 h, whereupon the suspension dissolved. After cooling to 0^0, the reaction was acidified to pH 1-2 with cold HCl (4 N) in the hood. The mixture was transferred to a separatory funnel, and extracted with ether (2 x 20 mL). The organic phase was washed with water (2 x 10 mL), saturated aqueous NaCl (10 mL), and dried over Na_2SO_4. Removal of solvent left a yellow oil which was then flash chromatographed on silica gel with 5% ether in hexane. Dithiol **39** was obtained as a clear colorless oil (0.076 g, 80%). Dithiol **39** had the following properties: ^{1}H NMR ($CDCl_3$, 60 MHz) 5.60 (4H, s, two isotope satellite peakes, J = 18 Hz), δ3.30 (2H, t), 3.00-2.60 (2H, m), 2.40 (4H, t), 1.20 (2H, t); MS m/e 199 (M+1, 4.34%), 198 (M^+, 23.83%), 165 (38.8%), 117 (95.44%), 105 (66.71%), 91 (77.47%), 85 (100%).

The Coupling Reaction of Diiodide 42 and Dithiol 39. Potassium hydroxide (0.126 g, 2.25 mmol) and phenol (0.338 g, 3.6 mmol) were dissolved in 95% ethanol (45 mL) in a 250 mL round bottom flask equipped with a magnetic stir bar, condenser, addition funnel, and nitrogen inlet. A 1:1 mixture of diiodide **42** (0.350 g, 0.9 mmol) and dithiol **39** (0.180 g, 0.9 mmol) in dry benzene (90 mL) was slowly added over a period of three days under a nitrogen atmosphere at room temperature. Then, potassium iodide was removed by filtration, and solvent removed by the rotovap. The residue was flash chromatographed on silica gel with 10% ether/pentane. Removal of solvent afforded a yellow oil (0.409 g) which contained starting material

42 (0.090 g, 21.8% GC yield), decomposed compound **45** (0.093 g, 23.2% GC yield) and other unidentified compounds. There was no trace of the desired sulfide dimer **40**.

If the base was changed from potassium hydroxide to potassium hydride and the reaction was run without phenol it gave diiodide **42** (0.031 g, 7.61% GC yield) and decomposed compound **45** (0.016 g, 3.94% GC yield).

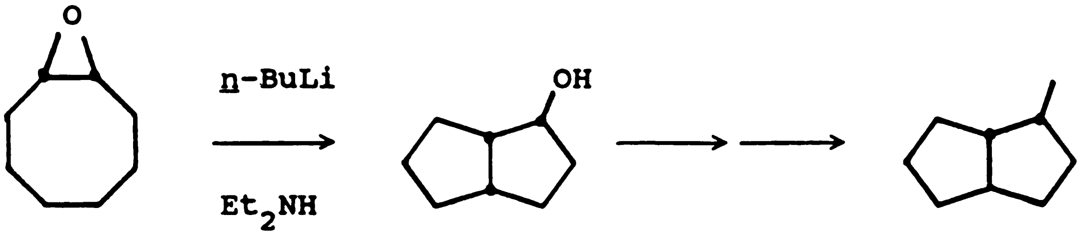
If we changed the solvents to DMF and ran the reaction without phenol, we got diiodide **42** (0.120 g, 29.2% GC yield) and decomposed compound **45** (0.049 g, 12.3% GC yield).

3-Thiatricyclo[6.3.0.0^{5,9}]undecane 51. Reaction of <u>Cis</u>,<u>endo</u>-2,6-<u>bis</u>(bromomethyl)bicyclo[3.3.0]octane 48. Dibromide **48** (0.148 g, 0.5 mmol) dissolved in absolute ethanol (5 mL) was stirred with sodium sulfide ($Na_2S\cdot9H_2O$, 0.24 g, 1.0 mmol) at room temperature for 29 h. The solution was added to distilled H_2O (10 mL), and extracted with pentane (2 x 25 mL). The combined organic layer was washed with distilled H_2O (10 mL), saturated NaCl (10 mL), and dried over $MgSO_4$. Removal of solvent with the rotovap yielded sulfide **51** (0.07 g, 83%) as a pale yellow oil. The spectral characteristics were as follows: ^1H NMR ($CDCl_3$, 60 MHz) δ2.40 (4H, d), 2.38-0.90 (12H, two m centered at 2.36 and 1.50); MS m/e 169 (M+1, 6.36%), 168 (M^+, 28.23%), 135 (100%), 121 (59.55%), 93 (53.65%), 79 (60.02%).

PART III. LITHIUM BROMIDE-LITHIUM DIETHYLAMIDE INDUCED REARRANGEMENT OF EPOXIDES

INTRODUCTION

In a project for the MSU Synthesis Laboratory, we required 2-methylbicyclo[3.3.0]octane with *cis*-cyclooctene oxide **52** as the starting material.



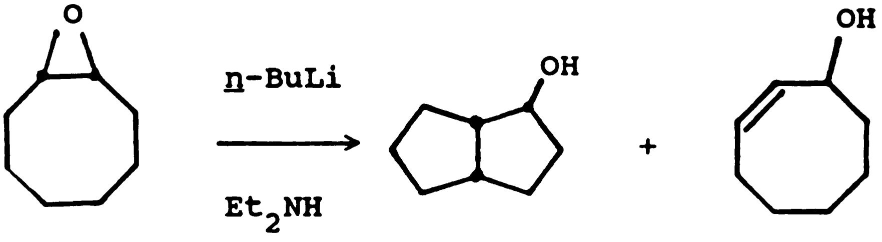
52 **53**

However, the yield of *endo*-*cis*-bicyclo[3.3.0]octan-2-ol **53** (39%) was far below the reported yield (70%).[45] From the literature, Cope prepared *n*-butyllithium from *n*-butyl bromide and lithium wire, and there was a substantial amount of lithium bromide left in the solution. Our *n*-butyllithium was bought from Aldrich Chemical Company and was free from lithium bromide. Therefore, it seemed likely that lithium bromide influenced the reaction. A more detailed experimental study showed to be the case.

The base-induced rearrangement of epoxides was first discovered by Cope,[46] then extensively studied by Crandall[47-52] and Rickborn.[53-58].

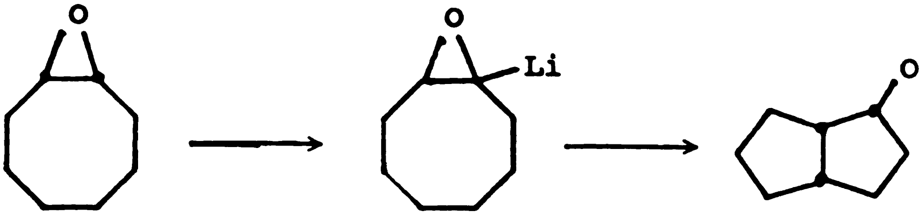
Generally, this rearrangement produces four kinds of products: allylic alcohols, ketones, saturated alcohols, and amino alcohols.

Cope reported that treatment of cis-cyclooctene oxide **52** with lithium diethylamide[45] gave endo-cis-bicyclo[3.3.0]octan-2-ol **53** as the major product, and a small amount of 2-cyclooctenol **54**.



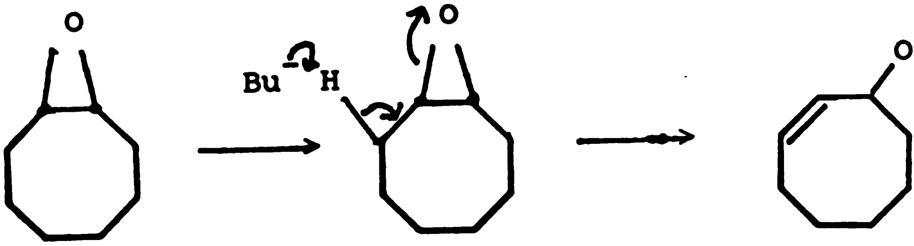
52 **53** **54**

Bicyclic alcohol **53** was proposed to arise from α-elimination, followed by a transannular carbene insertion (eq. 1).[59] Allylic alcohol **54** was proposed to arise from β-elimination (eq. 2).[60]



(eq. 1)

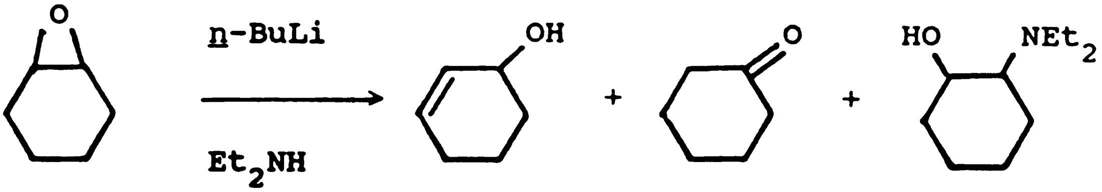
52 **53**



(eq. 2)

52 **54**

Crandall reported that reaction of cyclohexene oxide 55 with lithium diethylamide produced 2-cyclohexenol 56, cyclohexanone 57, and 2-(N,N-diethylamino)cyclohexanol 58.[47,56] Allylic alcohol 56 could be derived from β-elimination, ketone 57 by isomerization of allylic



55 56 57 58

alcohol 56, and amino alcohol 58 from nucleophilic ring opening.

However, we found that when lithium bromide was added to the lithium diethylamide solution, the yield of the rearrangement was improved and the ratio of products was changed.

RESULTS AND DISCUSSION

The rearrangement of epoxide 52 was reinvestigated. Lithium bromide was suspended in 2.5 equiv of lithium diethylamide solution, and 1 equiv of epoxide 52 was added dropwise into this cold solution. The results are shown in Table II.

Table II. LiBr-LiN(C_2H_5)$_2$ Induced Rearrangement of Epoxide 52

LiBr (equiv)	Total Yield (%)	Recovered 52 (%)	Ratio of 52 : 53 : 54
0.0	72	15	0.4 : 1 : 1
0.5	63	28	1 : 1 : 1
1.25	68	23	1 : 2 : 1
2.0	74	17	1 : 4 : 1
2.5	75	16	1 : 5 : 1
5.0	90	3	0.4 : 9 : 1
10.0	80	10	1 : 9 : 1

As the amount of lithium bromide was increased, the total yield was improved, the yield of the major product 53 was increased, and the yields of the minor product 54 and the recovered starting material 52 were decreased. With 5 equiv of lithium bromide added, the rearrangement of 52 gave the best result.

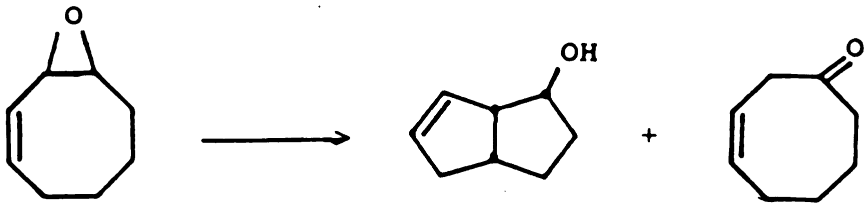
Then we suspended 5 equiv of lithium perchlorate or tetra-_n_-butylammonium bromide in 2.5 equiv of lithium diethylamide solution. The results are shown in Table III. Our purpose was to investigate the role of lithium cation and bromide anion in this reaction. The lithium cation apparently could influence the rearrangement. However, the reaction of 52 with a tetra-*n*-butylammonium bromide-lithium diethylamide solution only gave recovered 52, so the role of bromide anion in this reaction was not clear.

Table III. $LiClO_4$-$LiN(C_2H_5)_2$ or ($\underline{n}$-$C_4H_9)_4NBr$-$LiN(C_2H_5)_2$ Induced Rearrangement of Epoxide 52

	Total Yield (%)	Recovered 52 (%)	Ratio of 52 : 53 : 54
$LiClO_4$	48	42	8 : 8 : 1
($\underline{n}$-$C_4H_9)_4NBr$	0	95	1 : 0 : 0

Because the treatment of 52 with a cold (5 equiv) lithium bromide-(2.5 equiv) lithium diethylamide solution gave the best result, other epoxides were also treated with the same solution in order to test the generality of the reaction

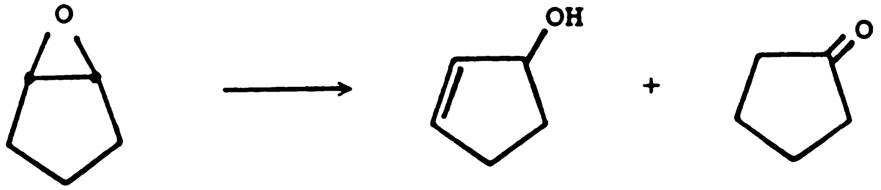
3,4-Epoxycyclooctene 59 was reacted with lithium diethylamide to produce bicycloalcohol 60 (44%), cyclooctenone 61 (14%), and recovered starting material 59 (7%).[48] However, with the lithium bromide-lithium diethylamide, the transformation of 59 gave exclusively 60 (60%) and a small amount of unreacted 59 (2%). 61 was not found.



59 **60** **61**

	Total Yield (%)	Recovered **59** (%)	Ratio of **59 : 60 : 61**
$LiN(C_2H_5)_2$	58	7	1 : 6 : 2
$LiBr-LiN(C_2H_5)_2$	60	2	1 : 28 : 0

The rearrangement of cyclopentene oxide **62** with lithium diethylamide was carried out to give 2-cyclopentenol **63** (10%) and cyclopentanone **64** (2%).[47] With the lithium bromide-lithium diethylamide solution, however, **62** afforded **63** (22%) and **64** (1%) in higher total yield.

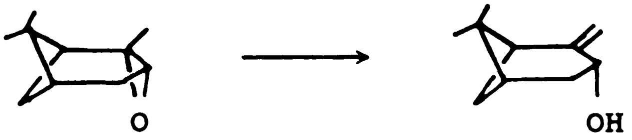


62 **63** **64**

	Total Yield (%)	Ratio of **63 : 64**
$LiN(C_2H_5)_2$	12	5 : 1
$LiBr-LiN(C_2H_5)_2$	23	22 : 1

The reaction of α-pinene oxide **65** with lithium diethylamide afforded allylic alcohol **66** in 91% yield.[47]

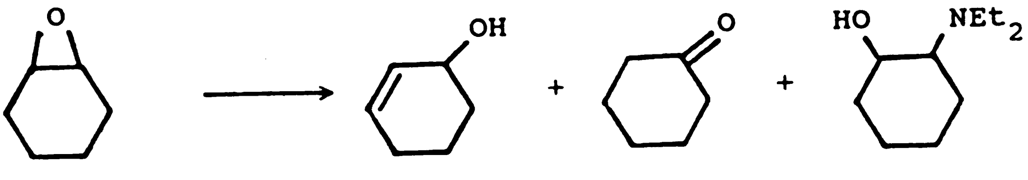
With lithium bromide-lithium diethylamide, **65** produced more **66** in 96% yield with a small amount of recovered **65** (4%).



65 **66**

	Yield (%)	Recovered **65** (%)
$LiN(C_2H_5)_2$	91	0
$LiBr-LiN(C_2H_5)_2$	96	4

Treatment of cyclohexene oxide **55** with lithium diethylamide produced 2-cyclohexenol **56** (59%), cyclohexanone **57** (2%), and 2-(N,N-diethylamino)cyclohexanol **58** (8%).[47,56] But, with lithium bromide-lithium diethylamide, **55** gave a lower amount of major product **56** (50%) and a higher amount of by-product **58** (11%). Ketone **57** was not present.

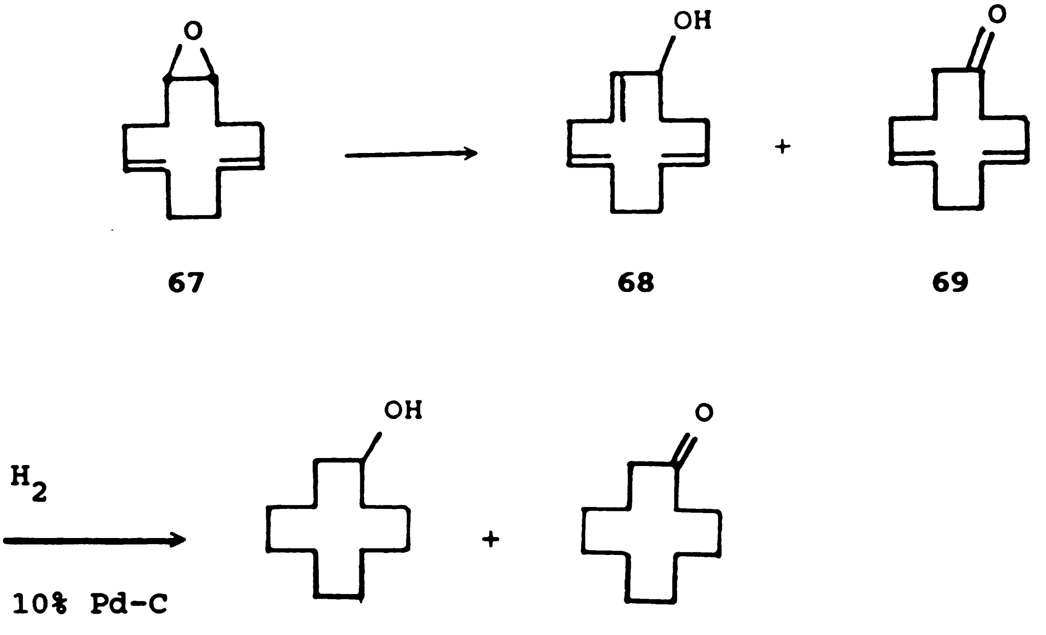


55 **56** **57** **58**

	Total Yield (%)	Ratio of **56** : **57** : **58**
$LiN(C_2H_5)_2$	69	7 : 0.2 : 1
$LiBr-LiN(C_2H_5)_2$	61	5 : 0 : 1

With lithium diethylamide, 1,2-epoxy-5,9-cyclododecadiene **67** produced a mixture of allylic alcohol **68** and unsaturated ketone **69**. The starting material **67** was complete consumed. After hydrogenation on 10% Pd-C under hydrogen atmosphere, the mixture afforded cyclododecanol **70** (37%) and cyclododecanone **71** (42%).

Isomerization of epoxide **67** with lithium bromide-lithium diethylamide, followed by hydrogenation, produced alcohol **70** (61%) and ketone **71** (19%). Apparently, the lithium bromide-lithium diethylamide solution increased the yield of allylic alcohol **68** and decreased the yield of unsaturated ketone **69**.

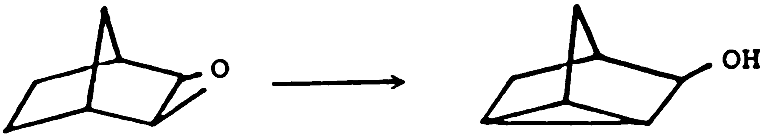


67 **68** **69**

70 **71**

	Total Yield (%)	Ratio of 70 : 71
$LiN(C_2H_5)_2$	79	1 : 1
$LiBr-LiN(C_2H_5)_2$	80	3 : 1

Exo-2,3-epoxynorbornane **72** produced nortricyclanol **73** as a single product.[61] With lithium diethylamide or lithium bromide-lithium diethylamide, the results were the same (55% yield). Therefore, lithium bromide had no influence upon **72**.

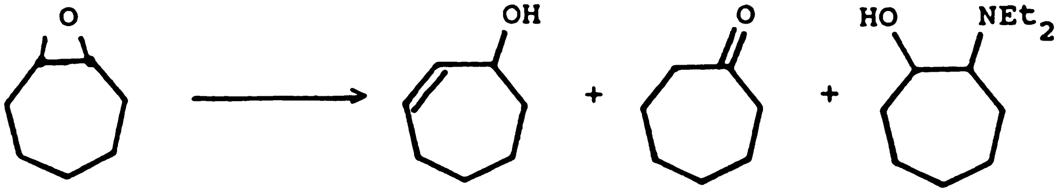


72 73

	Yield (%)
$LiN(C_2H_5)_2$	55
$LiBr-LiN(C_2H_5)_2$	55

The rearrangement of cycloheptene oxide **74** in ether with lithium diethylamide gave allylic alcohol **75** (20%), ketone **76** (7%), amino alcohol **77** (3%), and a lot of recovered starting material **74** (47%).[47] With lithium bromide-lithium diethylamide, the starting material was complete consumed to give **75** (17%), **76** (24%), and **77** (32%).

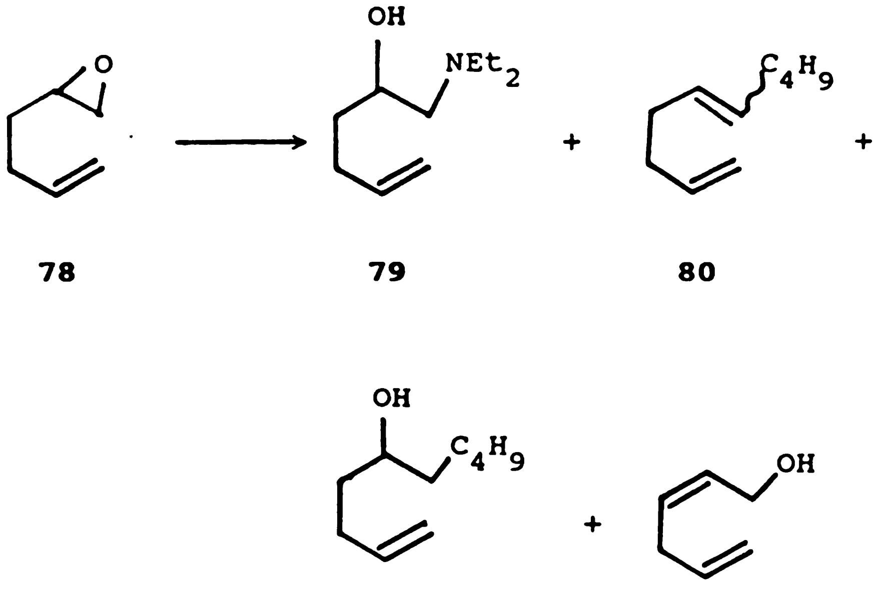
The rearrangement of cycloheptene oxide **74** with lithium diethylamide was repeated in benzene, instead of ether, to give amino alcohol 77, and two minor products in 36% yield.[47] There was no trace of the starting material 74. With lithium bromide-lithium diethylamide, the rearrangement of 74 in benzene gave amino alcohol 77 and two minor products in 46% yield.



74 75 76 77

	Total Yield (%)	Recovered 74 (%)	Ratio of 74 : 75 : 76 : 77
(Ether was used as the solvent)			
$LiN(C_2H_5)_2$	30	47	7 : 3 : 1 : 0.5
$LiBr-LiN(C_2H_5)_2$	73	0	0 : 2 : 3 : 4
(Benzene was used as the solvent)			
$LiN(C_2H_5)_2$	36	0	0 : 0 : 0 : 1
$LiBr-LiN(C_2H_5)_2$	46	0	0 : 0 : 0 : 1

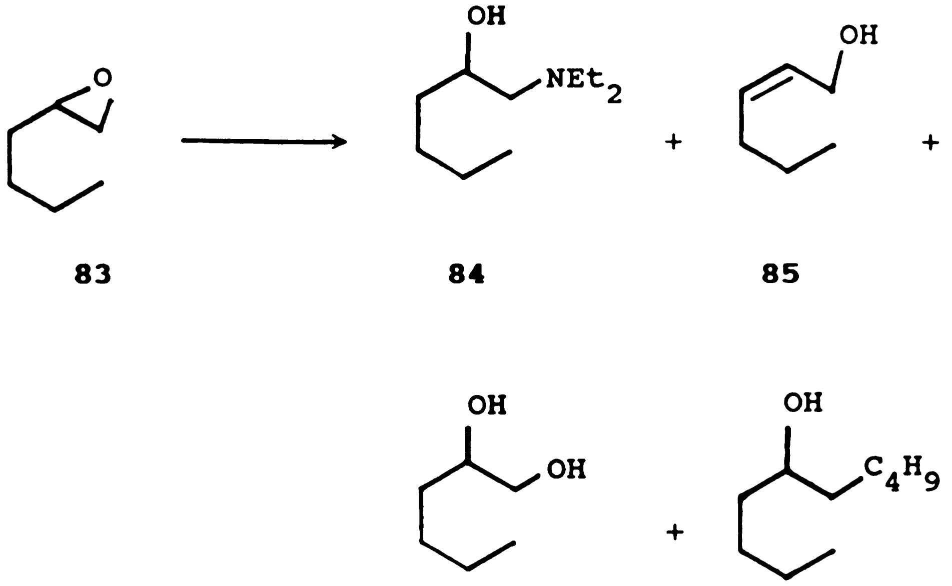
Treatment of 1,2-epoxy-5-hexene oxide 78 with lithium diethylamide produced a mixture in 64% yield.[55] We did not separate the mixture, but the major product was quite possibly the amino alcohol 79 (26%) and the minor products were _cis_- and _trans_-1,5-decadiene 80 (23%), 1-decen-5-ol 81 (12%), and 2,5-hexa-dien-1-ol 82 (3%) based upon the spectra of GC-MS and ^1H NMR of the mixture. With lithium bromide-lithium diethylamide, 78 gave 79 (50%), 80 (27%), 81 (4%), and 82 (2%).



78 79 80 81 82

	Total Yield (%)	Ratio of 79 : 80 : 81 : 82
LiN(C_2H_5)$_2$	64	9 : 8 : 4 : 1
LiBr-LiN(C_2H_5)$_2$	83	25 : 14 : 2 : 1

Lithium diethylamide transformed 1,2-epoxyhexane **83** into a 83% yield of a mixture which was not separated. Based upon the spectra of GC-MS and ^{1}H NMR of the mixture, the major product was probably the amino alcohol **84** (49%) and the minor products were 2-hexen-1-ol **85** (10%), 1,2-hexanediol **86** (9%), and 5-decanol **87** (15%). Lithium bromide-lithium diethylamide transformed **83** into a mixture of amino alcohol **84** (73%), 2-hexen-1-ol **85** (10%), and 5-decanol **87** (5%).



83 **84** **85**

86 **87**

	Total Yield (%)	Ratio of **84 : 85 : 86 : 87**
$LiN(C_2H_5)_2$	83	5 : 1 : 1 : 2
$LiBr\text{-}LiN(C_2H_5)_2$	88	7 : 1 : 0 : 0.5

Lithium bromide is a useful modification in the rearrangement of epoxides. It can improve the yield, increase the ratio of the major product, and increase the amount of bicyclic products. However, sometimes it may increase the yield of the undesired amino alcohol for simple epoxides.

It can complement the use of HMPTA reported by Apparu[62] which tends to inhibit the formation of bicyclic products and favor unsaturated alcohol products. The role of lithium cation in effecting these changes is confirmed by Apparu's results.

The lithium bromide-lithium diethylamide solution should have some synthetic potential. Bicyclo[3.3.0]oct-7-en-endo-2-ol **60** has served as the starting material for Whitesell's synthesis of sarracenin,[63] Ikegami's synthesis of dl-coriolin,[64] and Trost's synthesis of plumericin, allamcin, and allamandin.[65]

EXPERIMENTAL

General. Proton nuclear magnetic resonance (NMR) spectra were obtained on Varian T-60 or Bruker WM-250 spectrometers at 60 MHz and 250 MHz, respectively. Chemical shifts are reported in parts per million downfield from tetramethylsilane internal standard. Infrared spectra (IR) were measured on a Perkin-Elmer 599 spectrometer, and were calibrated with the polystyrene 1601 cm^{-1} peak. Mass spectra (MS) were obtained on a Finnigan 4000 instrument with an ionizing voltage of 70 eV. Gas liquid chromatography (GLC) was performed on a Hewlett Packard 5880 instrument. The INJ TEMP was 250^0, and the DET TEMP was 300^0.

Unless otherwise noted, reagents and solvents were reagent grade materials and were used as received. Ether and benzene were dried by distillation from sodium or potassium benzophenone ketyl. Diethyl amine was dried by distillation from lithium aluminum hydride. *n*-Butyllithium was obtained from Aldrich as a 2.6 M solution in hexane. Lithium bromide and lithium perchlorate were dried in a drying pistol heated with refluxing xylene under vacuum pressure.

General Procedure for Base-Promoted Rearrangements. To an ice-cold solution of 2.5 equiv of diethylamine and the required amount of lithium bromide in anhydrous ether in a three necked flask equipped with a rubber stopper, addition funnel, condenser, and nitrogen inlet was added 2.5 equiv of 2.6 M n-butyllithium in hexane under a nitrogen atmosphere. After 15 min a solution of 1 equiv of the appropriate epoxide in anhydrous ether was added and the mixture was heated to reflux for 2 days. The reaction mixture was cooled and poured into water, and the organic layer separated. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated aqueous ammonium chloride, water, and saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was removed from the product by distillation through a column and the residue was purified by distillation. Product identification was by comparison of spectral data with those in the literature.

Rearrangement of Cis-Cyclooctene Oxide 52.

a) with five equiv of lithium bromide. The rearrangement of 52 was carried out as described in the general procedure. Thus, diethylamine (9.10 g, 0.125 mole) was dissolved in dry ether (100 mL) in a 500 mL three-necked flask equipped with a rubber stopper, addition funnel, condenser, and nitrogen inlet. Lithium bromide (21.71 g, 0.250 mole) was suspended in the reaction mixture which was then cooled in an ice bath. n-butyllithium (48.0 mL x 2.6 M, 0.125 mole) was added through a syringe during five minutes under a nitrogen atmosphere, and the ethereal solution was stirred for an additional fifteen minutes. A solution of cis-cyclooctene oxide **52** (6.30 g, 0.05 mole) in ether (100 mL) was added and the solution was stirred and refluxed under a nitrogen atmosphere for forty eight hours. The reaction mixture was cooled and poured into ice water (350 mL), and the organic layer was separated. The aqueous layer was extracted with ether (2 x 100 mL) and the ethereal solutions were combined and extracted with saturated ammonium chloride (4 x 75 mL) to remove diethylamine. After a final washing with water the ethereal solution was dried over magnesium sulfate and concentrated. The residue was distilled through a short path distillation unit to give a mixture (5.86 g, 93% wt. recovered). The spectral data were compared with those reported before,[45] and the distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 100^0
OVEN TEMP PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 130^0

b) without lithium bromide. The rearrangement of 52

(6.30 g, 0.05 mole) without lithium bromide was carried out as described in the general procedure. The weight of the distilled product was 5.46 g (86.6% wt. recovered).

c) with half equiv of lithium bromide. The rearrangement of **52** (6.30 g, 0.05 mole) with lithium bromide (2.17 g, 0.025 mole) was carried out as described in the general procedure. The weight of the distilled product was 5.75 g (91.2% wt. recovered).

d) with one and one quarter equiv of lithium bromide. The rearrangement of **52** (6.30 g, 0.05 mole) with lithium bromide (5.43 g, 0.0625 mole) was carried out as described in the general procedure. The weight of the distilled product was 5.74 g (91.1% wt. recovered).

e) with two equiv of lithium bromide. The rearrangement of **52** (6.30 g, 0.05 mole) with lithium bromide (8.86 g, 0.200 mole) was carried out as described in the general procedure. The weight of the distilled product was 5.70 g, (90.5% wt. recovered).

f) with two & half equiv of lithium bromide. The rearrangement of **52** (6.30 g, 0.05 mole) with lithium bromide (10.86 g, 0.125 mole) was carried out as described in the general procedure. The weight of the distilled product was 5.71 g, (90.7% wt. recovered).

g) with ten equiv of lithium bromide. The rearrangement of **52** with lithium bromide (43.42 g, 0.500 mole) was carried out as described in the general procedure. The weight of the distilled product was 5.67 g, (90.0% wt. recovered).

h) with five equiv of lithium perchlorate. The rearrangement of **52** with lithium perchlorate (26.60 g, 0.250 mole), in stead of lithium bromide, was carried out as described in the general procedure. The weight of the distilled product was 5.66 g, (89.8% wt. recovered).

i) with five equiv of tetrabutylammonium bromide. The rearrangement of **52** with tetrabutylammonium bromide (80.60 g, 0.250 mole), instead of lithium bromide, was carried out as described in the general procedure. The only product (5.99 g, 95.1% wt. recovered) was recovered cis-cyclooctene oxide **52**.

Rearrangement of 3,4-Epoxycyclooctene 59. The isomerization of 3,4-epoxycyclooctene **59** (1.24 g, 0.01 mol) in ether (70 mL) at reflux temperature for 22 hr was performed and worked up according to the general procedure. The spectral data was compared with those reported before,[48] and the distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 100^0
OVEN TEMP PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 130^0

a) without lithium bromide. The weight of the distilled product was 0.818 g, (66.0% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 0.776 g, (62.6% wt. recovered).

Rearrangement of Cyclopentene Oxide 62. A solution of cyclopentene oxide **62** (1.68 g, 0.02 mol) in ether (100 mL) was treated according to the general procedure. The spectral data were compared with those reported before,[47] and the distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 40^0
OVEN PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 60^0

a) without lithium bromide. The weight of the distilled product was 0.202 g, (12.0% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 0.428 g, (25.5% wt. recovered).

Rearrangement of α-Pinene Oxide 65. The rearrangement of α-pinene oxide **65** (3.04 g, 0.02 mol) in ether (100 mL) was treated according to the general procedure. The spectral data were compared with those reported before,[47] and the product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 100^0
OVEN TEMP PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 120^0

a) without lithium bromide. The weight of the distilled product was 2.982 g, (98.1% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 2.964 g, (97.5% wt. recovered).

Rearrangement of Cyclohexene Oxide 55. The rearrangement of cyclohexene oxide 55 (1.963 g, 0.02 mol) in ether (100 mL) was treated according to the general procedure. The spectral data were compared with those reported before,[47] and the distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 100^0
OVEN TEMP PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 120^0

a) without lithium bromide. The weight of the distilled product was 1.354 g, (69.0% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 1.197 g, (61.0% wt. recovered).

Rearrangement of 1,2-Epoxy-5,9-cyclododecadiene 67 and Hydrogenation of its Products. Rearrangement of 1,2-

epoxy-5,9-cyclododecadiene **67** (3.56 g, 0.02 mol) in ether (100 mL) was treared according to the general procedure. The distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 140^0
OVEN PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 160^0

a) without lithium bromide. The weight of the distilled product was 2.784 g (78.6% wt. recovered). The product (2.56 g, 14 mol) was hydrogenated with 10% Pd/C (250 mg) in 95% ethanol (150 mL) under a hydrogen atmosphere. After 36 mmol of hydrogen was consumed, the solid was filtered and the ethanol solution was added to water (50 mL). The aqueous solution was extracted with pentane (3 x 50 mL), and the combined organic layers were washed with water (2 x 20 mL), saturated aqueous NaCl (20 mL), and dried over $MgSO_4$. Removal of solvent gave a white solid (2.51 g, 99%, m.p. 58-62^0), which was analyzed by GLC. The solid was flash chromatographied with 10% ether/pentane to give cyclododecanol **70** (R = 0.26, m.p. 59-61^0) and cyclododecanone 71 (R = 0.74, m.p. 75-77^0). The spectral data were identical with those of authentic samples obtained from commercial source.

b) with five equiv of lithium bromide. The yield of the distilled product was 2.847 g (80.0%), and the product (2.56 g, 14 mol) was hydrogenated with 10% Pd/C (250 mg) in 95% ethanol (150 mL) under a hydrogen atmosphere. After 48 mmol of hydrogen was consumed, the solution was treated as above to give a solid (2.50 g, 99% wt. recovered, m.p.62-70^0) which was analyzed by GLC as above.

Rearrangement of exo-2,3-Epoxynorbornane 72. Rearrangement of exo-2,3-epoxynorbornane **72** (2.20 g, 0.02 mol) in benzene (50 mL) was treated according to the general procedure. The spectral data were compared with those reported before.[61] The distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 30^0
OVEN PRGM RATE 25^0/min
OVEN TEMP FINAL VALUE 250^0

a) without lithium bromide. The only product was nortricyclanol **22** (1.217 g, 55.3% yield).

b) with five equiv of lithium bromide. The only product was nortricyclanol **73** (1.199 g, 54.5% yield).

Preparation of Cycloheptene Oxide 74. To an ice-cold mechanically stirred mixture of cycloheptene (9.61 g, 0.1 mol) and anhydrous sodium carbonate (31.8 g, 0.3 mol) in methylene chloride (90 mL) was added dropwise 8.6%

peracetic acid (100 g, 0.105 mol).[66] The mixture was stirred at room temperature until the methylene chloride solution gave a negative test with starch-iodide paper. The solid salts were removed by suction filtration and washed well with additional methylene chloride (3 x 10 mL). The solvent was removed from the filtrate by distillation through a Vigreux column and the residue was redistilled through a short distillation unit to give cycloheptene oxide **74** as a colorless oil (5.714 g, 50.9%, b.p. 154-156^0).

Rearrangement of Cycloheptene Oxide 74 in Ether. The rearrangement of cycloheptene oxide **74** (2.24 g, 0.02 mol) in ether (100mL) was treated according to the general procedure. The spectral data were compared with those reported before.[47] The distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 35^0
OVEN PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 55^0

a) without lithium bromide. The weight of the distilled product was 1.298 g (77.3% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 1.622 g (72.4% wt. recovered).

Rearrangement of Cycloheptene Oxide 74 in Benzene. The rearrangement of cycloheptene oxide (2.24 g, 0.02 mol) in benzene (50mL) was treated according to the general procedure. The spectral data were compared with those reported before.[47] The distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 30^0
OVEN PRGM RATE 1^0/min
OVEN TEMP FINAL VALUE 50^0

a) without lithium bromide. The weight of the distilled product was 0.869 g (38.8% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 1.357 g (61.3% wt. recovered).

Rearrangement of 1,2-Epoxy-5-hexene 78. The rearrangement of 1,2-epoxy-5-hexene 78 (1.963 g, 0.02 mol) in ether (100mL) was treated according to the general procedure. The spectral data were compared with those reported before.[49] The distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 35^0
OVEN PRGM RATE 10^0/min
OVEN TEMP FINAL VALUE 200^0

a) without lithium bromide. The weight of the distilled product was 1.250 g (63.7% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 1.630 g (83.1% wt. recovered).

Rearrangement of 1,2-Epoxyhexane 83. Rearrangement of 1,2-epoxyhexane **83** (2.00 g, 0.02 mol) in ether (100 mL) was treated according to the general procedure. The distilled product was analyzed by GLC under the following conditions:

OVEN TEMP INITIAL VALUE 30^0
OVEN PRGM RATE 10^0/min
OVEN TEMP FINAL VALUE 160^0

a) without lithium bromide. The weight of the distilled product was 1.662 g (83.1% wt. recovered).

b) with five equiv of lithium bromide. The weight of the distilled product was 1.767 g (88.4% wt. recovered).

APPENDIX

Figure A1. Proton NMR spectrum ($CDCl_3$, 60 MHz) of *cis*,*endo*-2,6-*bis*(hydroxyethyl)bicyclo[3.3.0]octa-3,7-diene Dimethanesulfonate **13**.

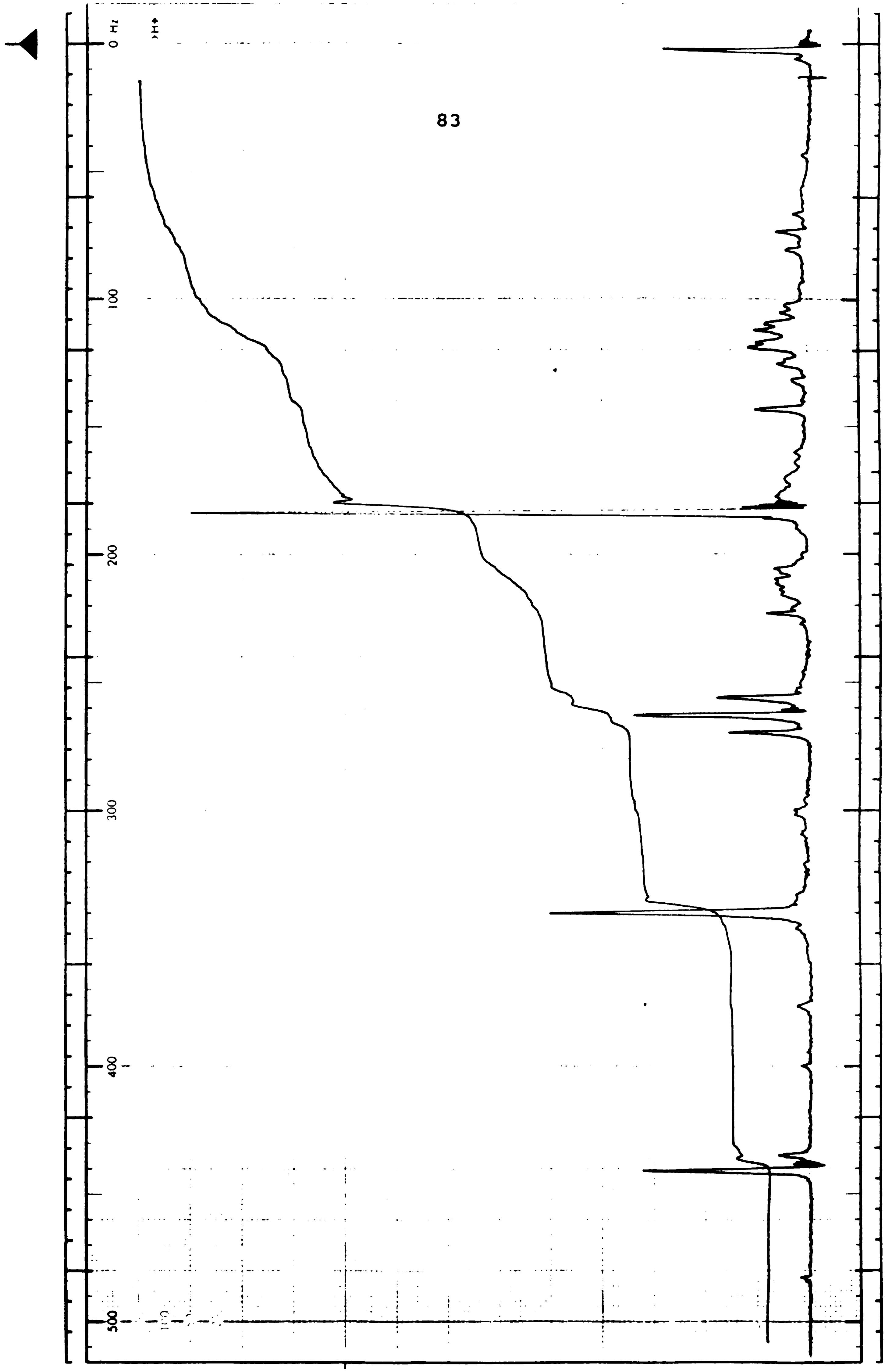

0 Hz
100
200
300
400
500

Figure A2. Proton NMR spectrum ($CDCl_3$, 60 MHz) of *cis*,*endo*-2,6-*bis*(iodoethyl)bicyclo[3.3.0]octa-3,7-diene **14**.

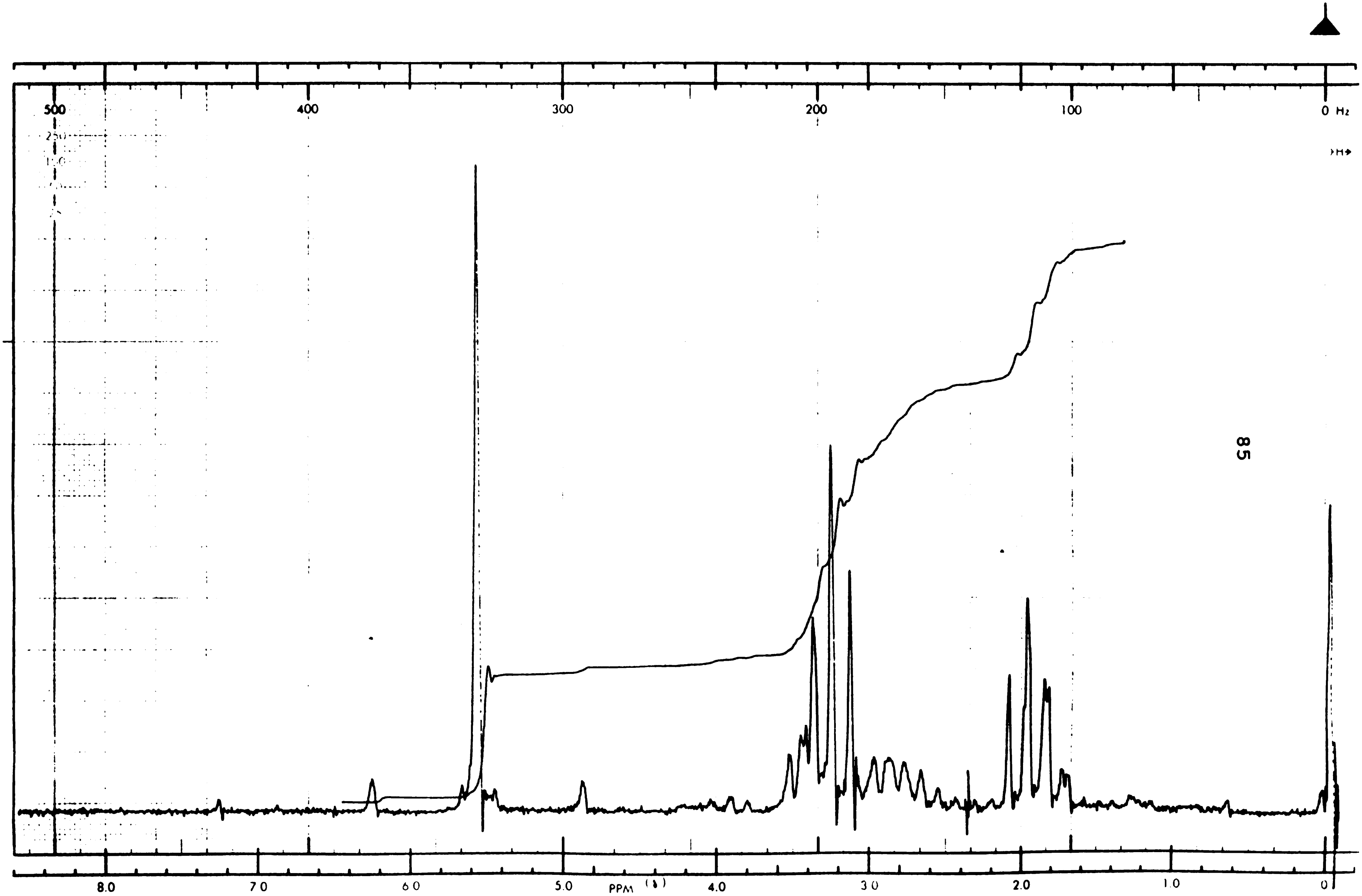

85

Figure A3. Proton NMR spectrum ($CDCl_3$, 60 MHz) of _cis_,_endo_-2,6-_bis_(chloroethyl)bicyclo-[3.3.0]octa-3,7-diene **15**.

) of

clo-

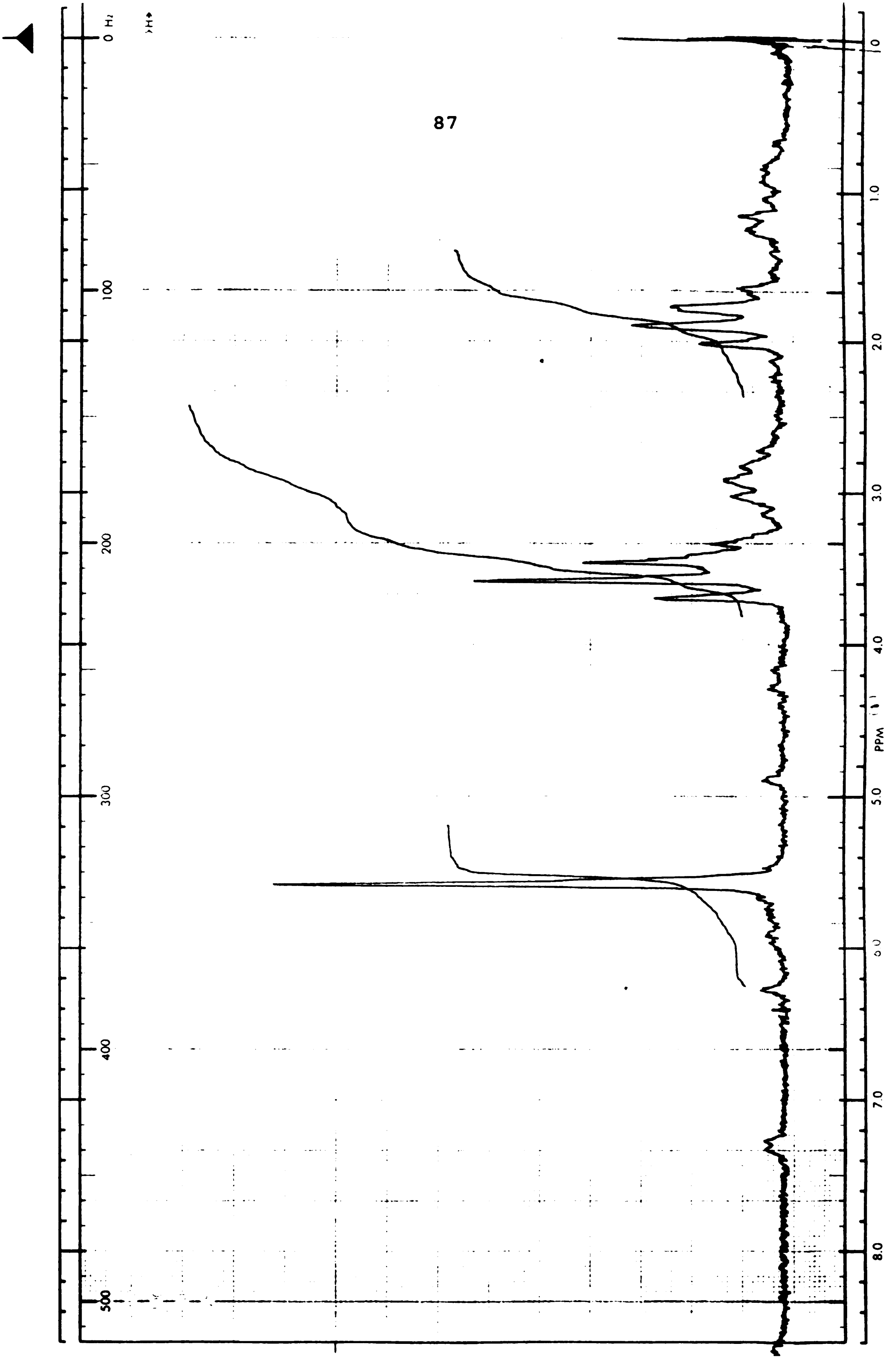


Figure A4. Proton NMR Spectrum ($CDCl_3$, 60 MHz) of Cis, endo-2,6-bis(bromomethyl)bicyclo[3.3.0]octa-3,7-diene **38**.

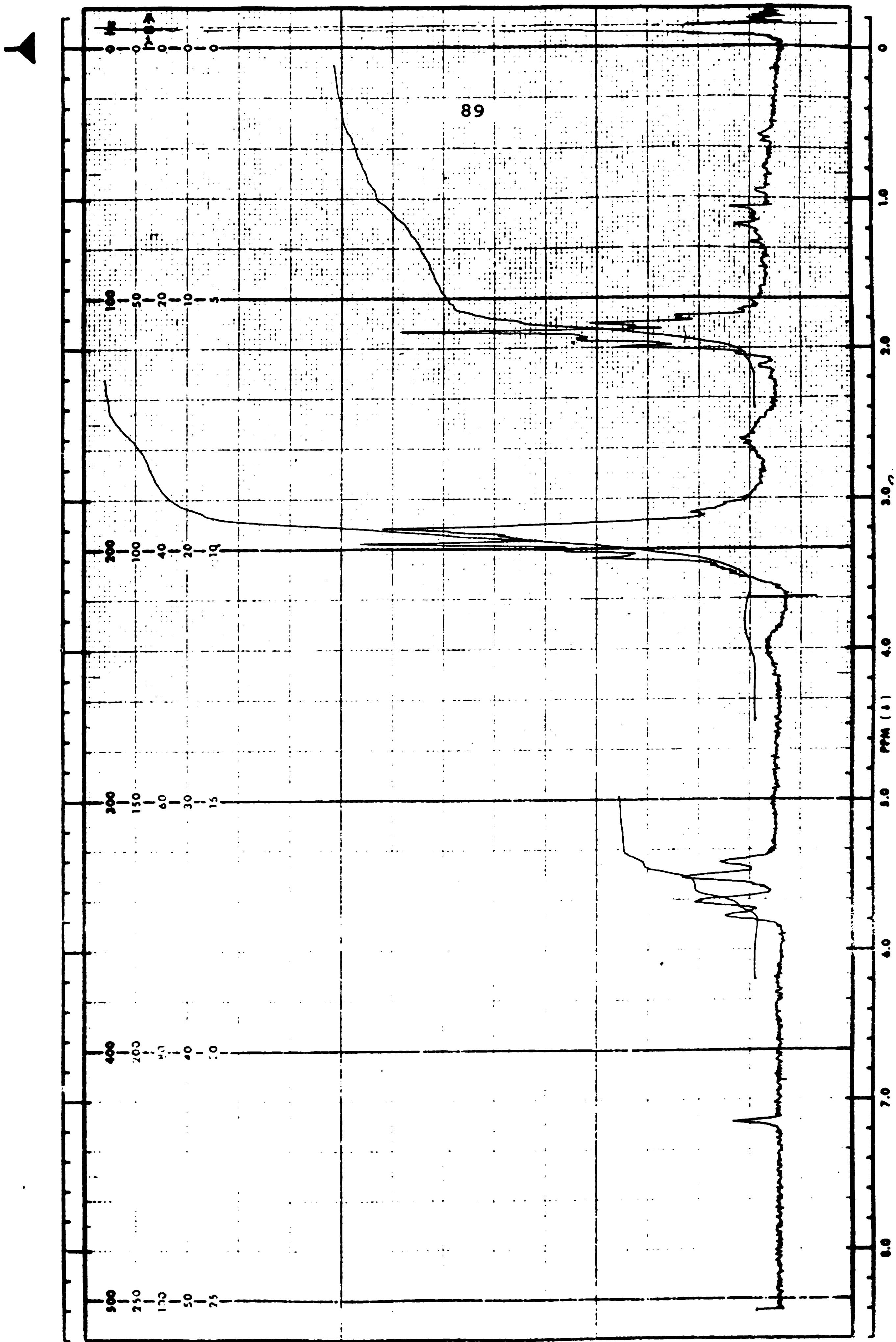

0
1.0
2.0
3.0
4.0
PPM (δ)
5.0
6.0
7.0
8.0
100 50 20 10 5
200 100 40 20 10
300 150 60 30 15
400 200 80 40 20
500 250 100 50 25

Figure A5. Proton NMR spectrum ($CDCl_3$, 60 MHz) of Cis, endo-2,6-bis(mercaptomethyl)bicyclo[3.3.0]-octa-3,7-diene **39**.

of Cis,

[3.3.0]-

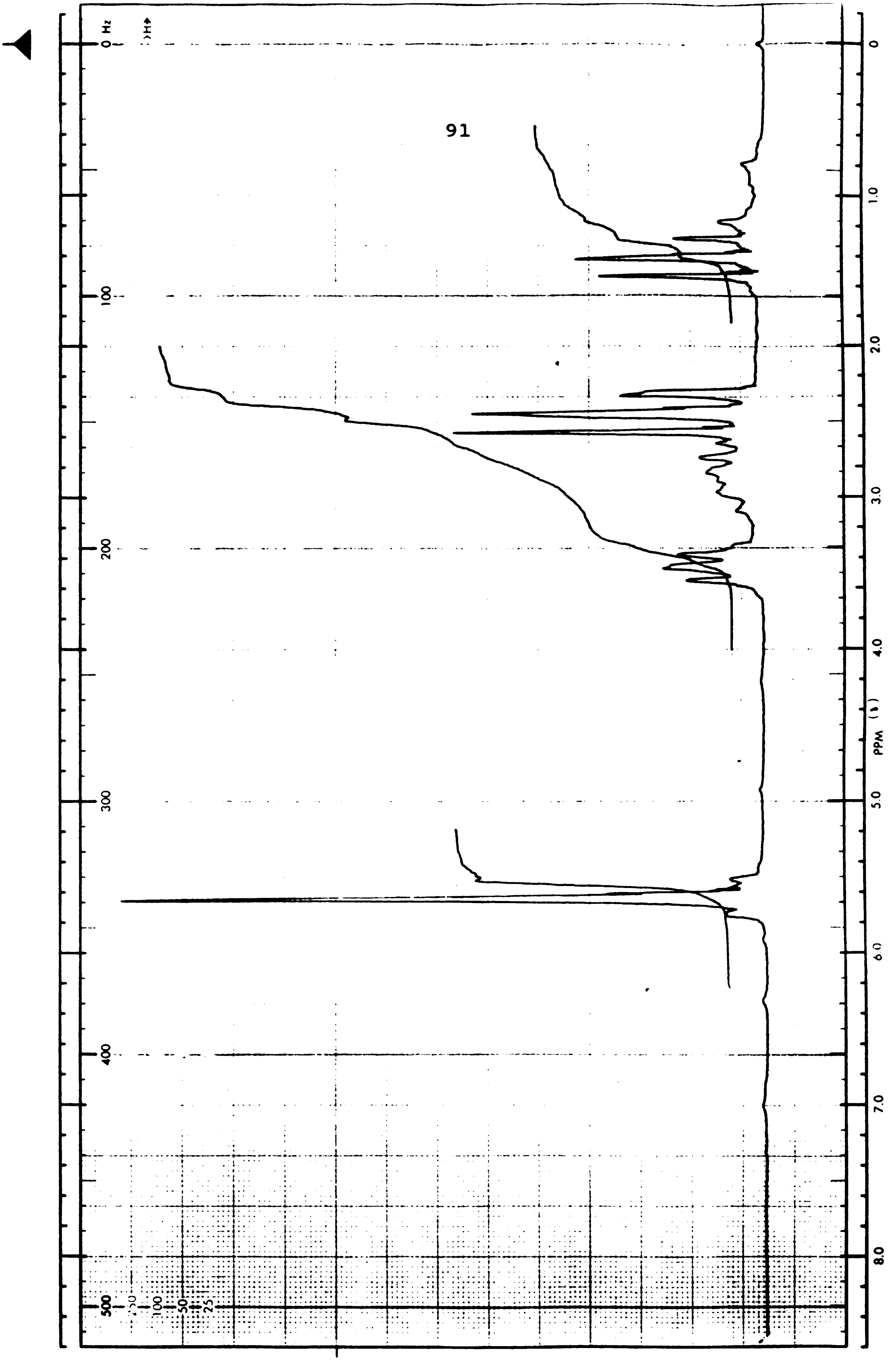
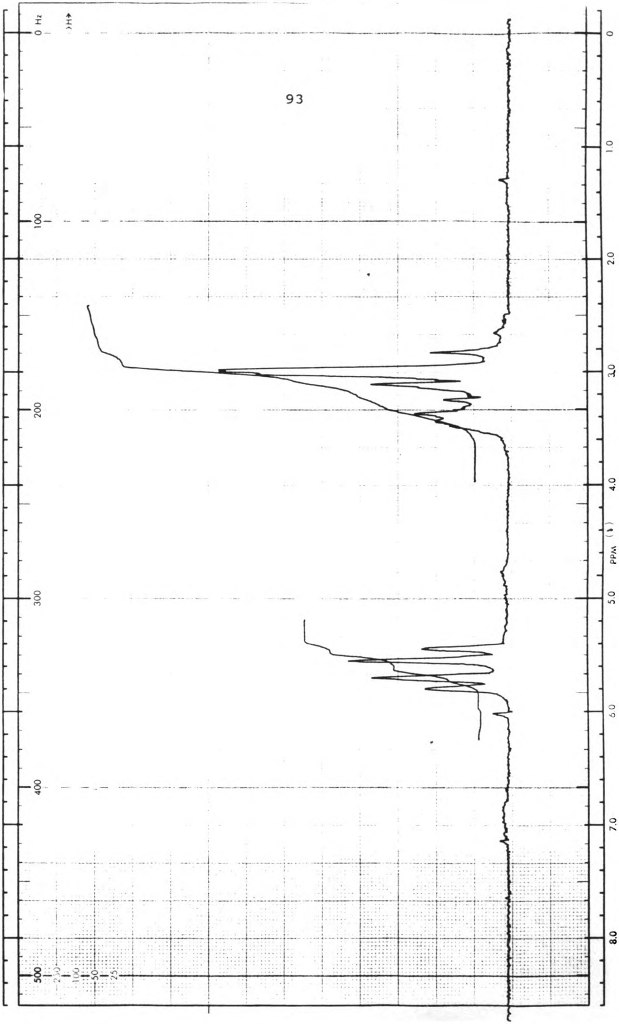


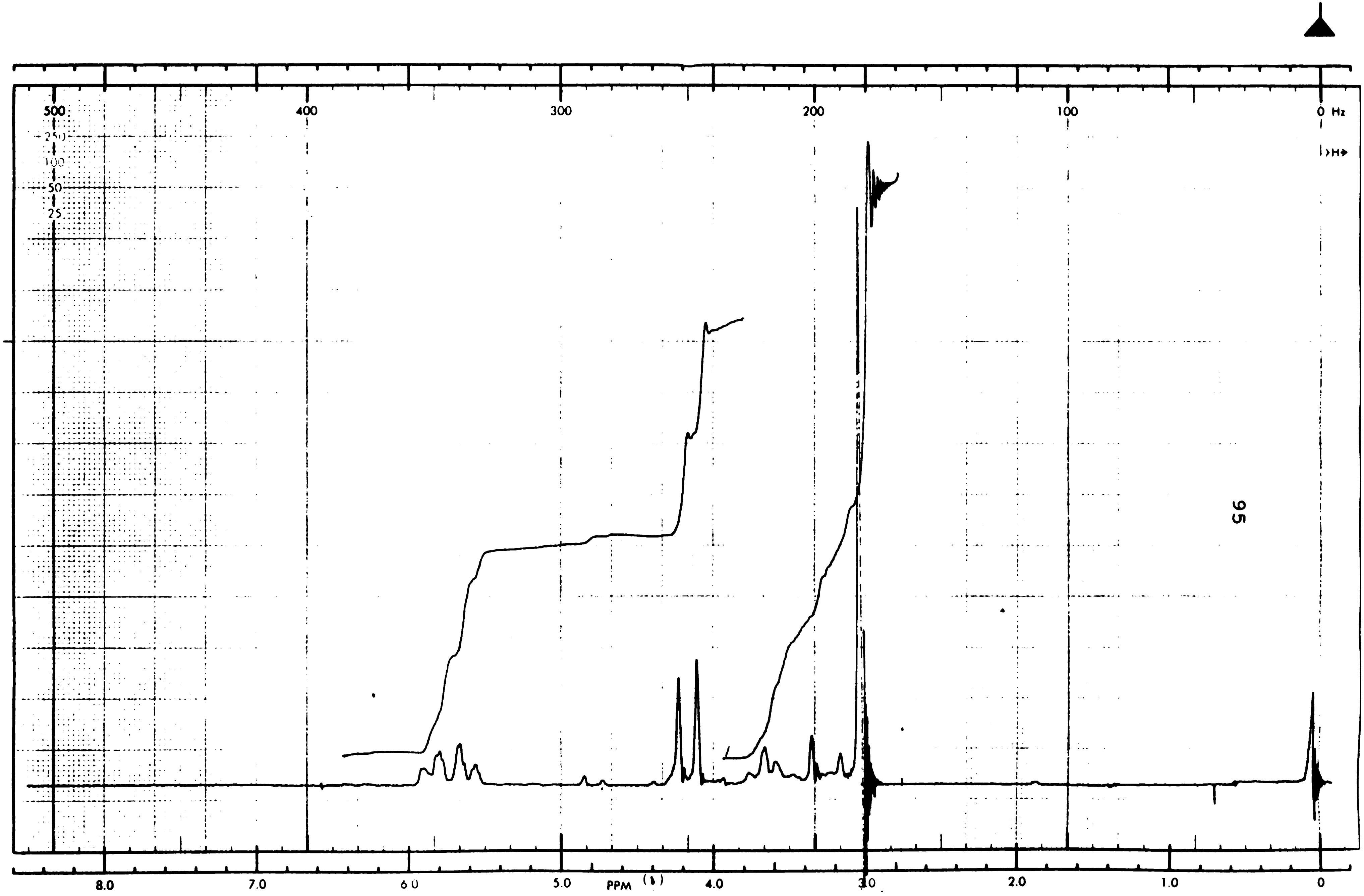
Figure A6. Proton NMR spectrum ($CDCl_3$, 60 MHz) of *Cis*, *endo*-2,6-*bis*(iodomethyl)bicyclo[3.3.0]octa-3,7-diene **42**.



of Cis,

.0]octa-

Figure A7. Proton NMR spectrum ($CDCl_3$, 60 MHz) of Cis, endo-2,6-bis(hydroxymethyl)bicyclo[3.3.0]-octa-3,7-diene Dimethanesulfonate **43**.


500
400
300
200
100
0 Hz
250
100
50
25
95
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

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