A Stereospecific Synthesis of Key Intermediates in the Total Synthesis of Alnusenone

Thesis by

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Abstract

Two approaches to the synthesis of key intermediates in the total synthesis of alnusenone has been outlined and the synthesis of several of these intermediates has been accomplished.

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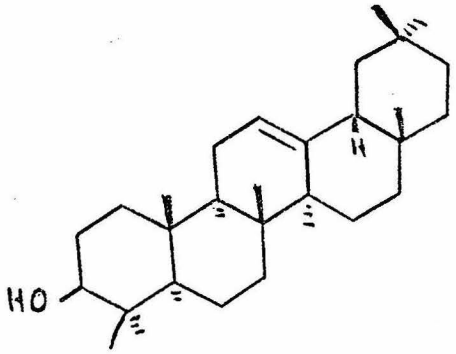
Introduction

The pentacyclic triterpenes are conveniently sub-divided into three groups, based on inter-relationships which have been established with one of three members, β-amyrin, α-amyrin, and lupeol.

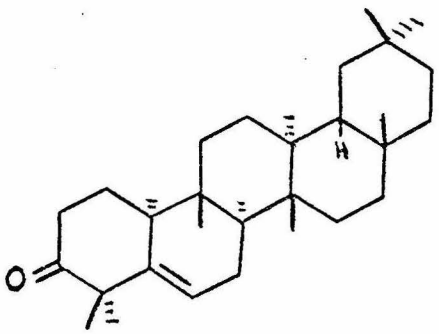
β-amyrin, $C_{30}H_{50}O$, is widely distributed in the latex and resin of many plants, and in particular is a major constituent of Manila elemi resin. Preliminary studies show that it is a pentacyclic secondary alcohol containing a single ethylenic linkage, resistant to hydrogenation. The presence of this grouping is shown by the formation of an epoxide with per-acids, and by the positive color reaction with tetramitromethane. As a result of a complicated series of degradations, β-amyrin is now known to have the constitution (I).



I

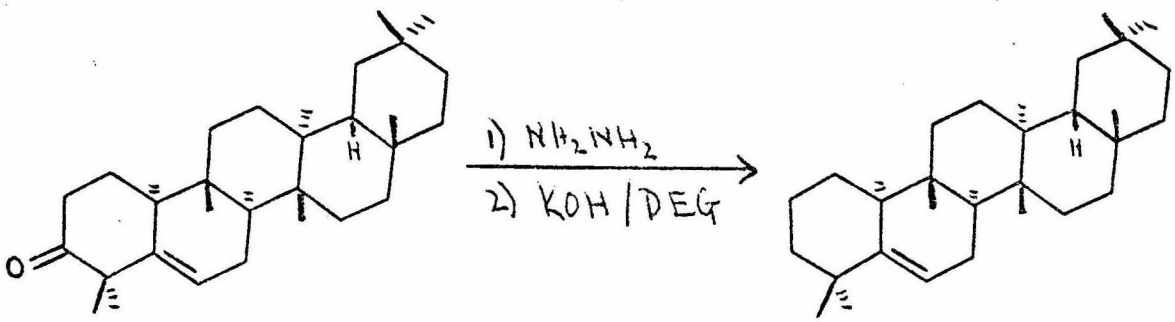
It turns out that β-amyrin is very important in biosynthetic schemes, thus provides partially some impetus for attempting to synthesize it.

A possible precursor to the β-amyrin skeleton is alnusenone (III).



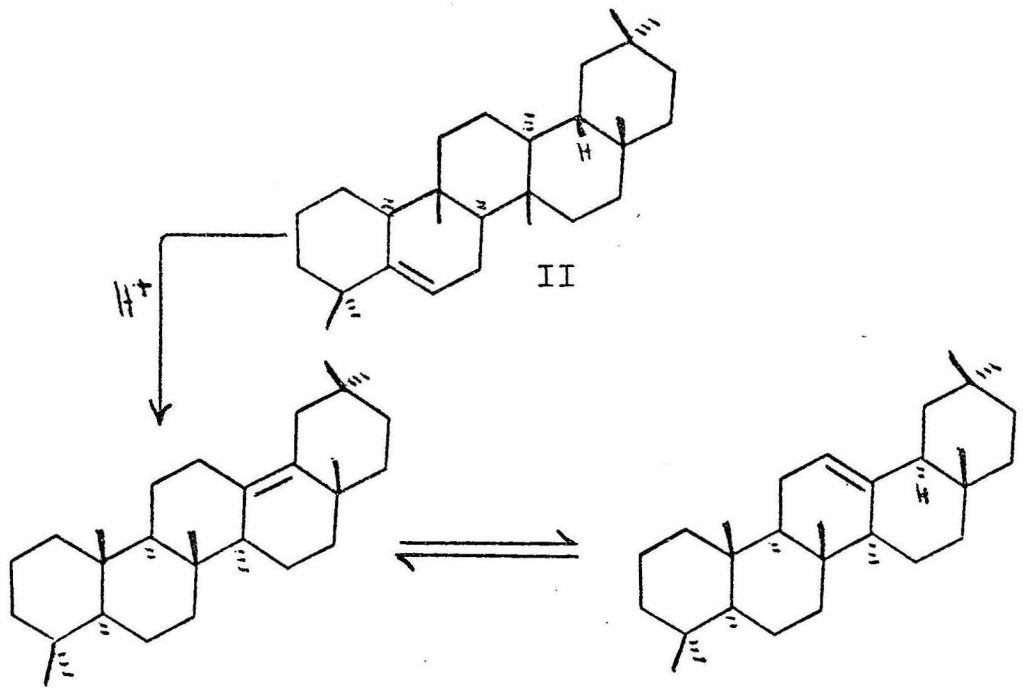
III

If a Wolff-Kishner reduction of alnusenone (III) is carried out, alnusene (II) results.



III II

From (II) it might be possible to synthesize a skeleton (V) closely resembling the basic structure of β-amyrin by treatment of (II) with hydrochloric acid.

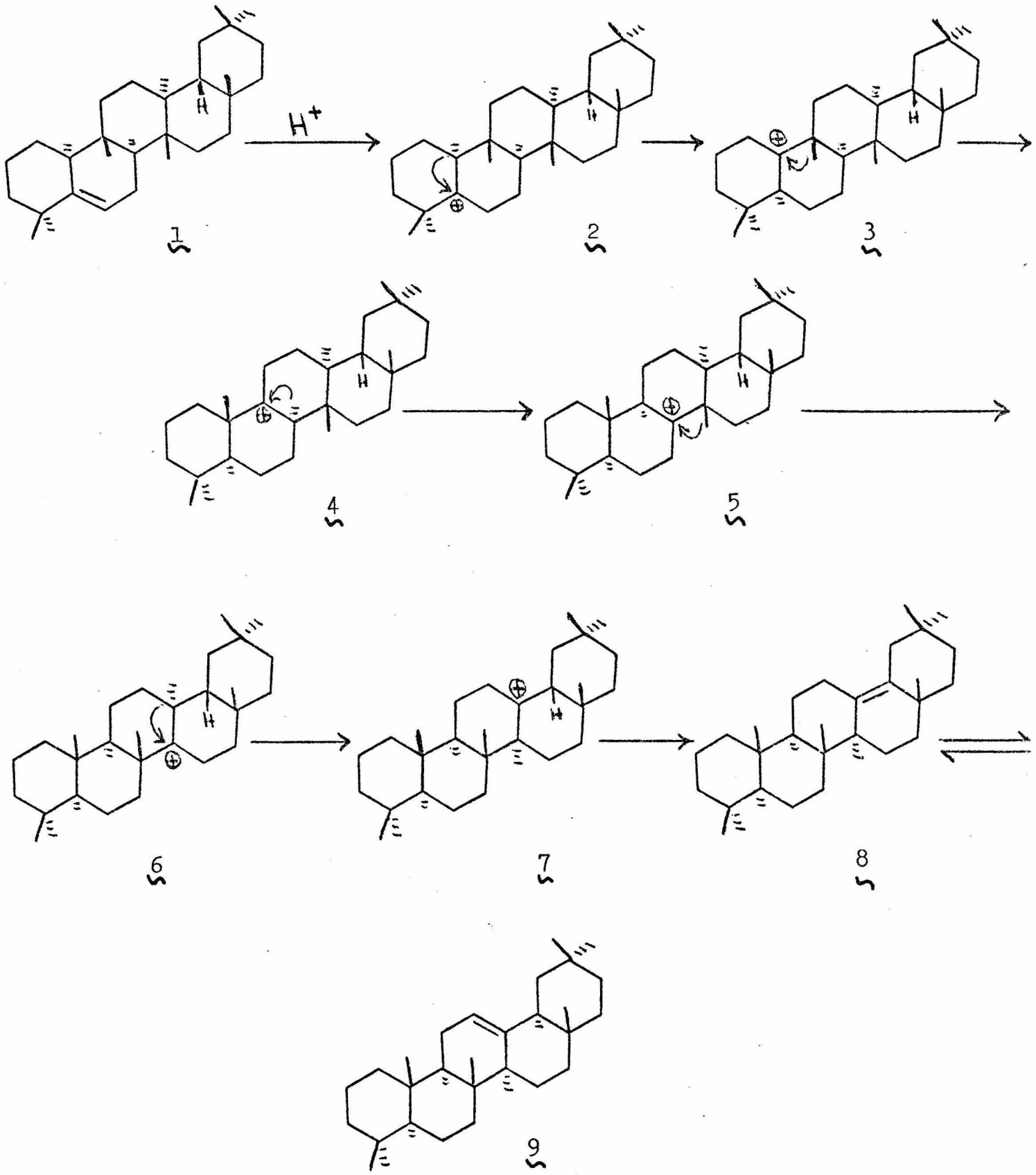


II V IV

The mechanism is an extraordinary series of methyl-hydrogen migrations.[1] Chart A depicts the cationic intermediates that result.

is treated with hydrochloric acid. The transformation occ— ...s by a series of methyl-hydrogen migrations of the [illegible]

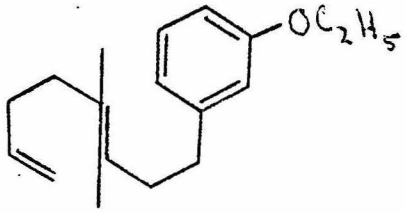
Chart A



Alnusenone now becomes the target molecule, since β-amyrin might be obtained from it.

Discussion

A possible intermediate for the total synthesis of alnusenone is trans-4,5-dimethyl-4,8-nonadienyl-m-ethoxybenzene (VI).



VI

Work was first done on a model system to see if an efficient synthetic sequence could be developed to get into a benzenoid system similar to (VI), If such a method could be developed, then it might be possible to synthesize (VI) along the same route. The proposed sequence on the model system is shown in Chart B, and its application to the synthesis of (VI) is shown in Chart C.

Chart B

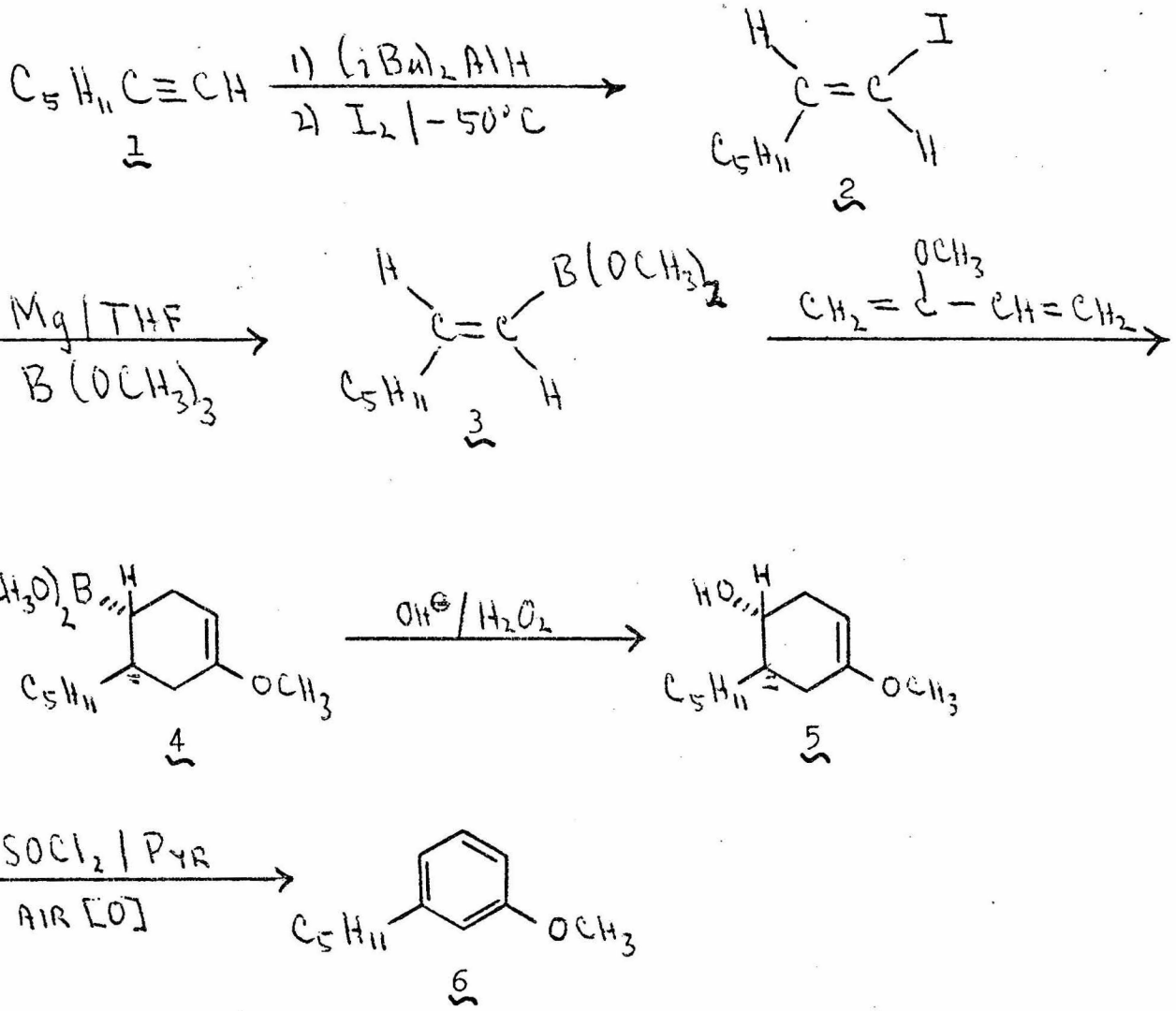
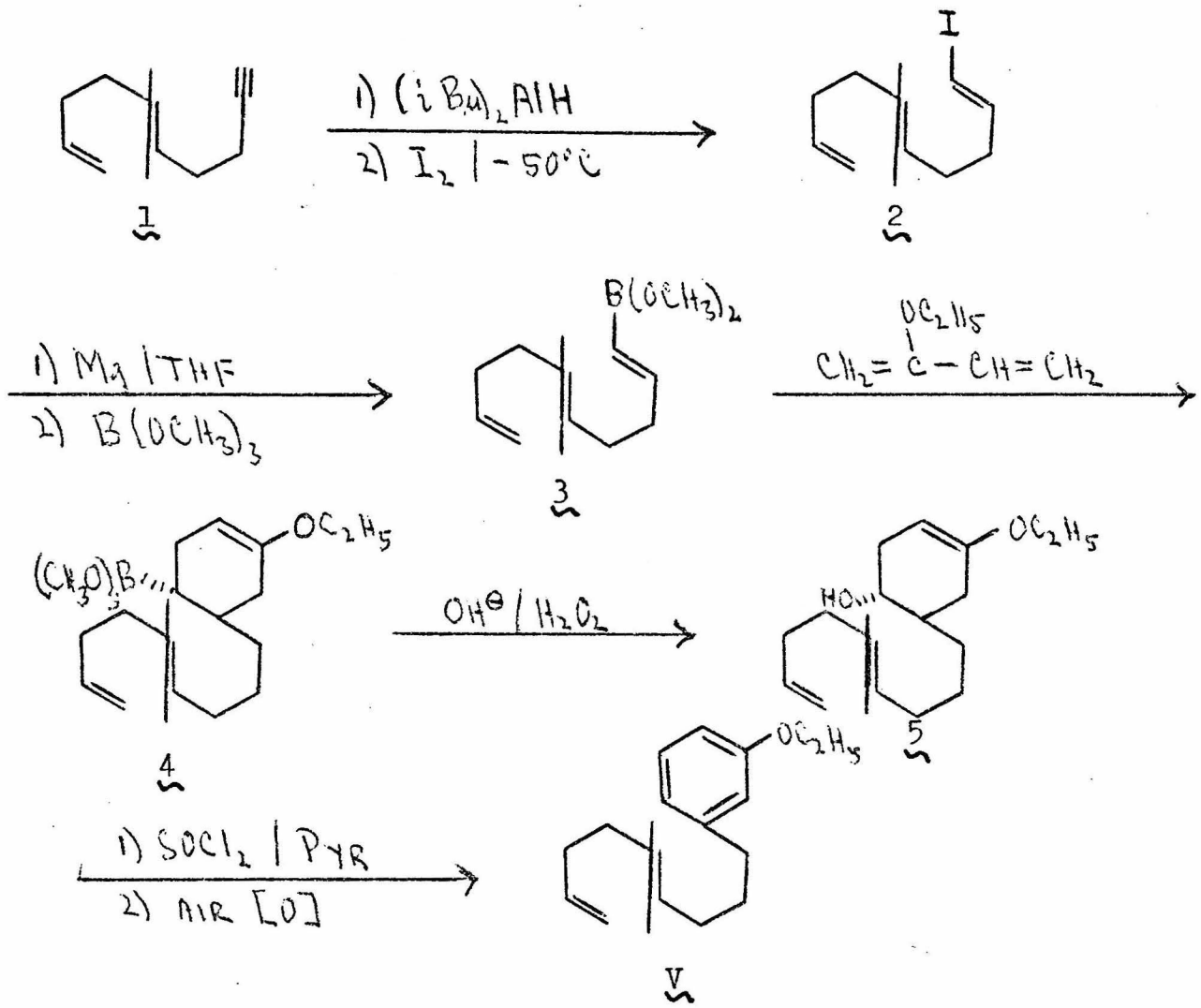

C5H11C≡CH
1
1) (iBu)2AlH
2) I2 | -50°C
2
1) Mg | THF
2) B(OCH3)3
3
CH2=C(OCH3)-CH=CH2
4
OH⊖ / H2O2
5
1) SOCl2 | PyR
2) AIR [O]
6

Chart C


1) (iBu)2AlH
2) I2 | -50°C
I
1
2
1) Mg | THF
2) B(OCH3)3
B(OCH3)2
3
OC2H5
CH2= C – CH= CH2
(CH3O)2B
OC2H5
4
OH⊖ / H2O2
HO
OC2H5
5
1) SOCl2 | PYR
2) AIR [O]
OC2H5
V

The hydroalumination reaction[2] to form trans-1-iodo-1-heptene (B#2) went in 58.6% yield. A slightly colored liquid was obtained which was about 92% pure by VPC.

The formation of the boronic ester (B-3) proved to be unsuccessful, however, Four attempts under various conditions were tried without success. The exact reason or reasons are still not clear at this time.

The problem in the first two attempts was formation of the vinyl Grignard itself. During the formation of the Grignard, large amounts of white precipitate were formed, which were found to be soluble in water. This indicated that it was a magnesium salt of some sort. It was not thought that the salt was MgIOH which would result from the reaction of the Grignard with water, because the apparatus was dried thoroughly in the oven, and too much precipitate was formed.

The only other possibility is the formation of MgI_2 which would result from Grignard coupling.

In both attempts, the addition of trimethyl borate to the Grignard solution was carried out anyway, in the hopes of forming some of the desired boronic ester (B-3). None was ever isolated.

Later, it was discovered in a paper by Matteson[3] that $CH_2=CH-B(OCH_3)_3^{\ominus}{}^{\oplus}MgCl$ is converted to $CH_2=CH-B(OH)_2$, CH_3OH, and MgClOH upon addition of acid. The boronic acid is soluble in water, and polymerizes in a short time.

Consequently, even if the desired boronic ester (B-3) were formed, it was lost in the work-up of the reaction.

Also, Matteson found that if the aqueous layer containing the vinyl boronic acid was shaken with n-butanol, the corresponding butyl ester was readily formed. dissolving in the organic layer, and was stable. Apparently, the methyl ester is quite unstable and therefore, cannot be formed.

If the Grignard could be formed, it would now be attempted tofform the butyl boronic ester by Matteson's procedure.

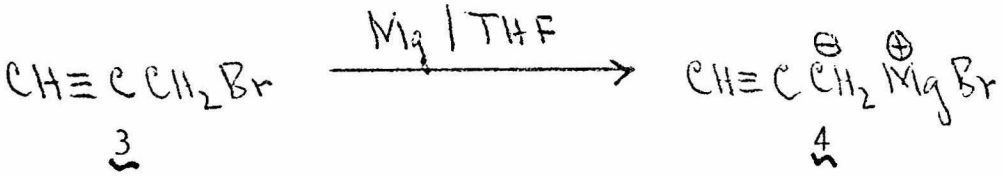
It was found that if excess Mg, excess solvent, and vigorous stirring were employed,in an attemot to minimize Grignard coupling, the Grignard could indeed be formed. The presence of Grignard was confirmed by adding a crystal of 1, 10-phenanthroline to the reaction mixture. A reddish solution resulted.

Matteson's procedure was now followed in an attempt to form the butyl boronic ester. After two attempts, it was found to be unsuccessful. The sequence in Chart B and consequently Chart C was abandoned.

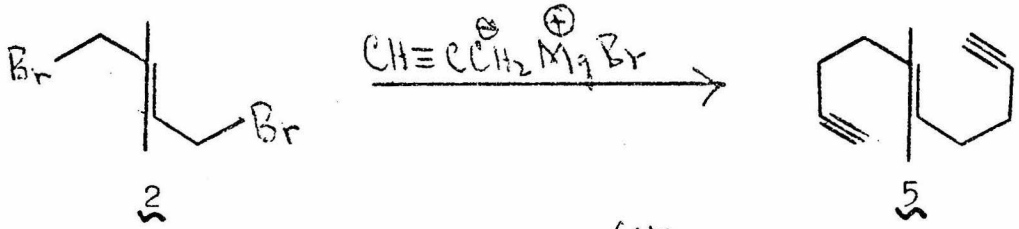
The sequence proposed in Chart B was very attractive because compound (C-1) can, and has been synthesized in our lab by Dr. Chris Lipinski and Dr. Kin Cheng. Their synthesis is shown in Chart D below.

Chart D

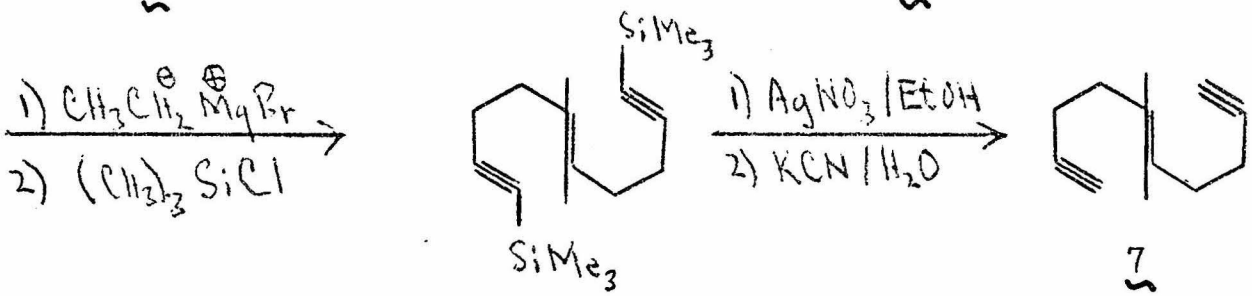
1 2



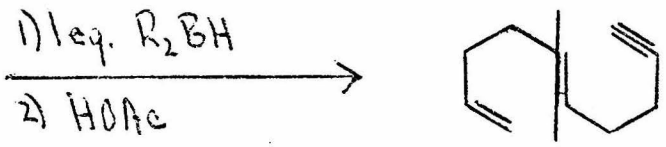
3 4



2 5



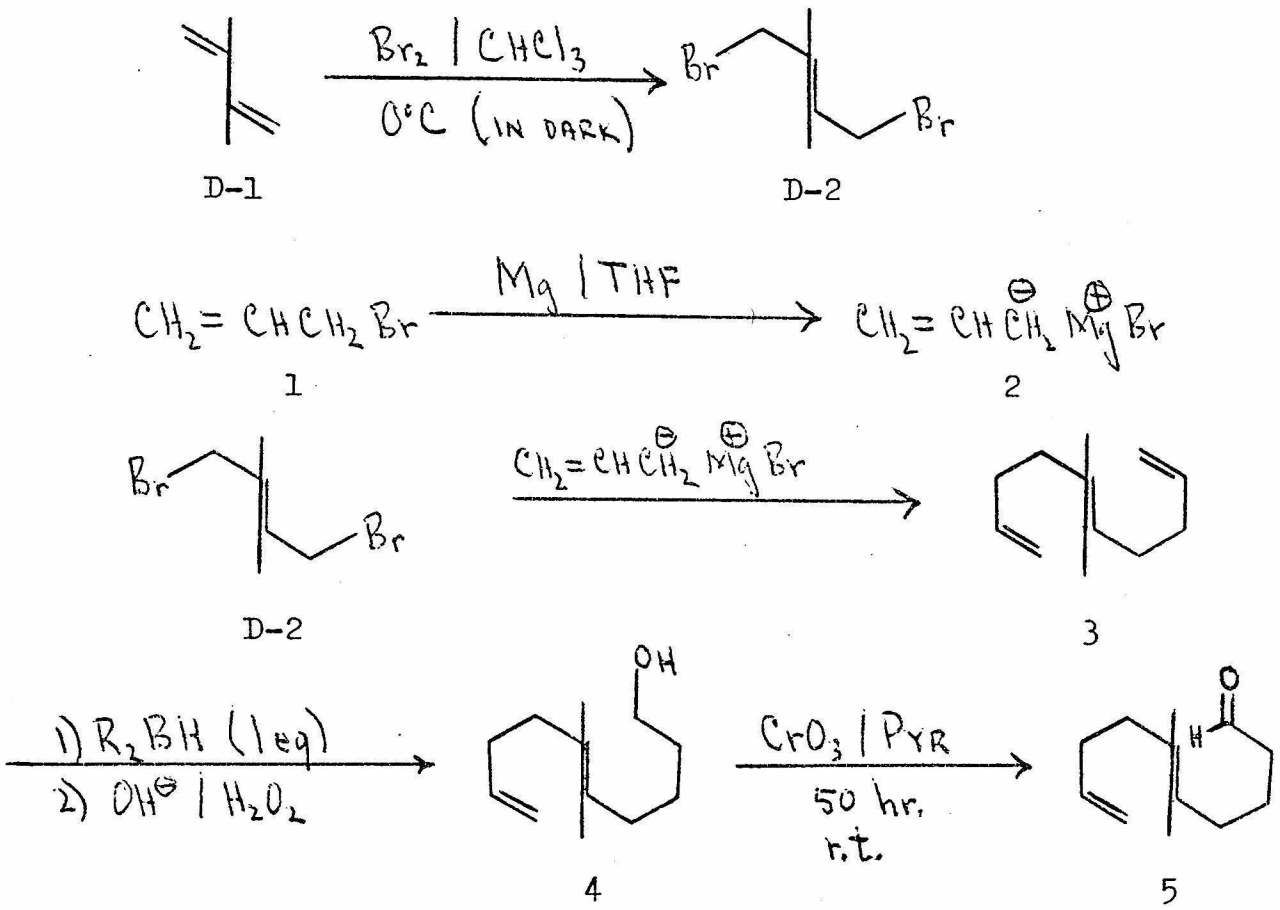
6 7



C-1

An alternate synthetic route was then considered. The first part of this route has been performed before by Ireland and Dawson[7], and to date has been successfully duplicated in this work. The scheme is shown in Chart E below.

Chart E

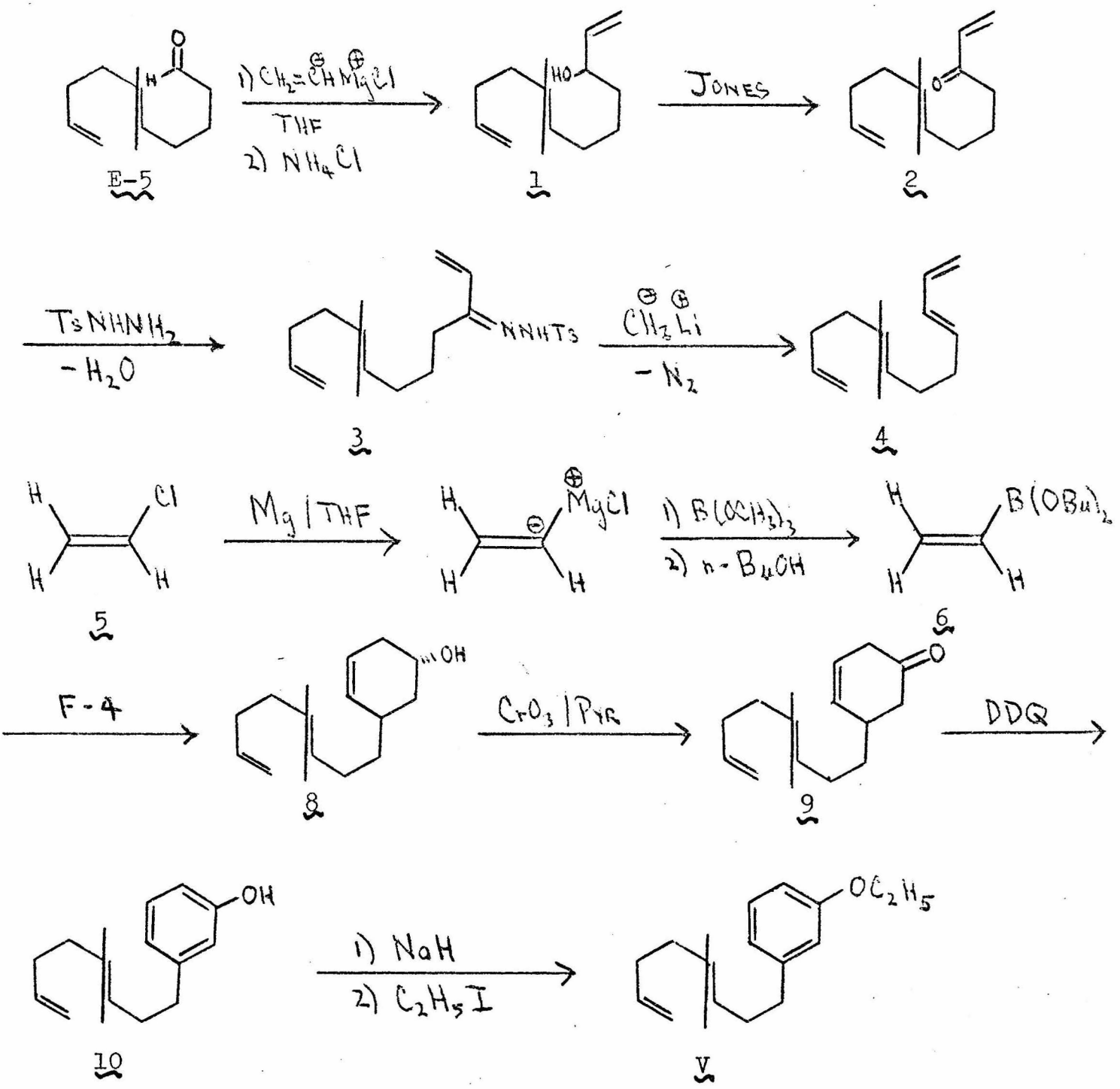


There was no particular problem in any of the steps in Chart E, except for the formation of the alcohol (E-4). The problem arose during the chromatography of the product mixture. The triene (E-3) was eluted with petroleum ether. The column fractions were monitored by VPC. The VPC was not working well at the time, however, and very ambiguous VPC traces were obtained. For example, peaks would appear where none should have appeared, and vice versa. Consequently, after collecting fractions eluted with 20% ether-pet. ether, at which time the VPC was indicating no more "major peaks," it was thought that all of the alcohol had been eluted.

When the solvent was removed, no products were found. It was then decided to elute the column with 100% ether and recover whatever was left on the column. By that time the VPC was fixed, and VPC analysis of the ether fractions showed one major product. This was later confirmed to be the alcohol (E-4).

It will be attempted to complete the sequence for the synthesis of the benzenoid system (V) before June, 1970. The remainder of the sequence appears in Chart F.

Chart F



Experimental

Infrared spectra were taken on a Perkin-Elmer 237B Grating Infrared Spectrophotometer. Nuclear magnetic resonance spectra were taken on a Varian T-60 NMR Spectrometer. All gas chromatographic analysis were run on an F and M Model 810 Gas Chromatograph using a silicon gum rubber (SE-30) column.

The term "dry THF" refers to tetrahydrofuran which has been distilled from lithium aluminum hydride under anhydrous conditions. The term "dry ether" refers to ether which has been distilled from lithium aluminum hydride under anhydrous conditions. Petroleum ether (or pet. ether), unless otherwise stated, is the fraction boiling between 30° and 60°C. Finally, the term "$MgSO_4$" refers to anhydrous powder magnesium sulfate.

trans-1-Iodo-1-heptene (B-2)

This material was prepared according to the general procedure of Zweifel and Whitney[2]. To a solution of 36.76g (0.383 mole) of 1-heptyne in 75ml of heptane was added 51.78 g (0.375 mole) of diisobutyl aluminum hydride in 100 ml of heptane dropwise maintaining the temperature below 40° C. The reaction mixture was heated to 50°C. for two hours. The heptane was removed at reduced pressure, and 150 ml of dry THF was added to the crude vinylalane. To this solution cooled to -50°C. was added 92.50 g (0.365 mole) of I_2 in 120 ml of dry THF. The reaction mixture was stirred and allowed to warm to room temperature. Diisobutylalane was decomposed by dropwise addition of 20% H_2SO_4 until evolution of isobutane ceases. The reaction mixture was then poured into ice-20% H_2SO_4, and extracted with pentane. The combined extracts were washed with sodium thiosulfate, followed by saturated sodium bicarbonate until pH 7. Finally, the organic phase was washed three times with brine and dried over $MgSO_4$. Distillation at 40°C./3mm gave 49.2295g (58.6%) of the vinyl iodide.

Infrared: λ_{max}^{film} 6.24(m)(C=C)μ

1-Heptene-1-(trimethyl boronate) (B-3)[5,6]-1st attempt

Attempted to prepare 1-heptenyl magnesium iodide by the classical method of Ramsden[4]. To 1.0074 g (0.0415 mole) of Mg was added dropwise a solution of 6.0147 g (0.0268 mole) of the iodoheptene (B-2) in 10 ml of dry THF with stirring under N_2. The reaction had to be initiated with 2-3 drops of ethyl bromide. Reflux occurs, and the temperature was maintained at 70°C. Large amounts of white precipitate then formed during the reflux. As much of the clear "Grignard" solution as possible was transferred to an addition funnel, and it was added to a stirred solution of 3.1200 g (0.03 mole) of trimethyl borate in 15 ml of dry ether. cooled to -50°C. The reaction mixture was allowed to warm to room temperature and was then cooled to -50°C. again. The reaction was worked up by addition of water followed by 10% NH_4Cl at -50°C. The mixture was then extracted with 1-1 benzene-ether, then

washed with saturated sodium bicarbonate to pH 7, followed by brine, and dried over $MgSO_4$. When the solvent was removed under reduced pressure, no product was found. The aqueous layer was then extracted with 3 x 100 ml portions of n-butanol. The extracts were washed with saturated sodium bicarbonate, brine, and dried over $MgSO_4$. When the solvent was removed under reduced pressure, a cloudy residue remained. Distillation was attempted, but during the distillation, the residue in the flask became solid.

1-Heptene-1-(trimethyl boronate) (B-3)-2nd attempt

The same procedure was used as in the 1st attempt to form the Grignard reagent. To 0.4701 g (0.01933 mole) of Mg was added a solution of 4.1692 g (0.0186 mole) of the iodo-heptene (B-2) in dry THF. Freshly scraped magnesium filings were used. Again, large amounts of the white precipitate formed. The reaction was discontinued.

1-Heptene-1-(tributyl boronate) (B-3)-3rd attempt

To a stirred mixture of 0.7425 g (0.0306 mole) of Mg filings in 20 ml of dry THF, was added dropwise 2.2067 g (0.00985 mole) of the iodo-heptene (B-2) in 10 ml of dry THF. A cloudy solution resulted. A crystal of 1,10-phenanthroline was added to the reaction mixture, which upon turning red indicated the presence of Grignard. A solution of trimethyl borate in dry ether was added to the Grignard solution dropwise. The reaction mixture soon coagulated, but gentle heating seemed to restore the homogeneity of the solution. The reaction mixture was heated to gentle reflux for one hour. The reaction was worked up by addition of water followed by HCl/H_3PO_4. The mixture was extracted with n-butanol three times, the organic extracts washed with saturated sodium bicarbonate to pH 5, the washed three times with brine, and dried over $MgSO_4$. Removal of solvent at reduced pressure afforded no product.

1-Heptene-1-(tributyl boronate) (B-3)-4th attempt

The same procedure was used in this attempt as used in the 3rd attempt to form the boronate. The only difference

was in the step forming the butyl ester. Instead of simply extracting with n-butanol, the reaction mixture was heated with the butanol. Work-up afforded no product.

trans-2,3-Dimethyl-1,4-dibromo-2butene (D-2)

To a stirred solution of 106.47 g (1.296 moles) of trans-2,3-dimethyl-1,3-butadiene (D-1) in 1000ml of chloroform was added 206.74 g (1.295 moles) of bromine in 360 ml of chloroform over a period of 6 hours and 40 minutes under N_2. Stirring was continued for one additional hour, and the reaction mixture was stored in the ice box under N_2 overnight. Removal of chloroform under reduced pressure and recrystallization of the dibromide (D-2) from absolute methanol afforded a 34.7% yield based on the first crop. The dibromide (D-2) is sensitive to light, so it was usually handled in the dark. It is also a strong lachrymator, and should be handled in the hood.

n.m.r.: $\delta^{CDCl_3}_{TMS}$ 1.85 p.p.m. (s), (methyl)
4.00 p.p.m. (s), (methylene)

trans-5,6-Dimethyl-1,5,9-decatriene (E-3)

Allyl magnesium bromide (E-2) was prepared in a conventional manner. Allyl bromide (E-1) was redistilled, and the fraction boiling at 69-71°C was collected and stored over molecular sieves under N_2 for 9 hours. To a stirred mixture of 97.25 g (4 moles) of Mg in 800 ml of dry THF was added a solution of 86.5 ml (1 mole) of redistilled allyl bromide in 120 ml of dry THF dropwise under N_2 over a period of 19 hours. Grignard coupling was a major problem, which requires the long addition time. The reaction mixture was kept at reflux during the addition, and refluxed for one hour and 35 minutes after additon was complete. The Grignard was then cooled to room temperature, and decanted into another flask. To this solution was added under N_2 35.00 g (0.1446 mole) of the dibromide (D-2) in 50 ml of dry THF at a fairly fast rate. The reaction was quite exothermic, and reflux commences within 30 seconds from the

time of addition. After the addition the reaction mixture was then heated to reflux for one hour. The mixture was then cooled in an ice bath to 0°C. and saturated NH_4Cl was added until the reaction mixture turns white. Anhydrous $MgSO_4$ was then added and stirring commences for 30 minutes. The misture was then filtered, and the funnel washed with ether. The filtrate was diluted with ether, washed twice with water, then brine, and dried over $MgSO_4$. The triene (E-3) was volatile, so ether was removed at atmospheric pressure through a Vigeraux column. A nonviscous yellow liquid remained. Vacuum distillation produced a clear colorless liquid boiling at 47-8°C/1mm. There was obtained 21.95 g (92.5%) of the triene (E-3).

Infrared: λ_{max}^{film} 6.09(m)(C=C)μ
11.0 (s)($C=CH_2$)μ

n.m.r.: $\delta_{TMS}^{CDCl_3}$ 1.63 p.p.m. (s), (methyl)
4.95 p.p.m. (complex), ($C=CH_2$)
5.80 p.p.m. (b complex), (int olefin H)

trans-5,6-Dimethyl-5,9-decadiene-1-ol (E-4)

Disiamyl borane was first generated. To a suspension of 0.78 g (0.0206 mole) of sodium borohydride in 30 ml of dry THF cooled to 0°C. was added dropwise a solution of 3.9 g (0.0275 mole) of boron trifluoride etherate, which was redistilled over calcium hydride, in 5 ml of dry THF, over a period of 25 minutes. The reaction mixture was stirred at 0°C. for an additional hour, and finally stored in the freezer overnight to allow $NaBH_4$ and $NaBF_4$ to settle. To a stirred solution of 7.71 g (0.11 mole) of 2-methyl-2-butene in dry THF cooled between -10° and -20°C. was added under N_2 the BH_3·THF solution prepared above, dropwise over a period of one hour. The reaction mixture was stirred for an additional four hours at 0°C. To a stirred solution of 13.53 g (0.0824 mole) of the triene (E-3) in 50 ml of dry THF cooled to 0°C. under N_2, was added dropwise, the disiamylborane solution prepared above. Addition was accomplished in 2 hours. The reaction mixture was then allowed to stir overnight at room temperature. The reaction mixture

was again cooled to 0°C. and then the ice bath was removed. To the cooled reaction mixture was first added dropwise 3 equivalents of NaOH with respect to the disiamylborane, followed by an equivalent amount of H_2O_2. Stirring was continued at room temperature for 90 minutes. The reaction was then worked up by diluting with water, extracting with ether, then washed with water, followed by brine, and dried over $MgSO_4$. The solvent was removed at atmospheric pressure through a Vigeraux column, and the residue chromatographed on 1000g of florisil. The triene (E-3) was eluted with pet. ether, and the alcohol (E-4) was eluted with 100% ether. There was 9.25 g of recovered triene (68.4%) and 0.5278 g (10.5%) of recovered alcohol, after distillation at reduced pressure.

Infrared: λ_{max}^{film} 2.98(s)(OH)μ
6.09(m)(C=C)μ
11.0 (s)($C=CH_2$)μ

n.m.r.: $\delta_{TMS}^{CDCl_3}$ 1.65 p.p.m. (s), (methyl)
3.6 p.p.m. (t), (C-1 CH_2 J=6 Hz)
4.96 p.p.m. (complex), ($C=CH_2$)
5.80 p.p.m. (b complex), (int olefin H)

trans-5,6-Dimethyl-5,9-decadienal (E-5)

To a stirred suspension of 5.0973 g of pyridinium dichromate in dichloromethane distilled from P_2O_5, was added under N_2 0.5278 g (0.00289 mole) of the alcohol (E-4) in 60 ml of CH_2Cl_2 via syringe. The mixture was stirred at room temperature for 50 hours. The reaction mixture was then filtered through 2.5 g of florisil on a sintered glass funnel, and the florisil was washed with CH_2Cl_2. The clear filtrate was distilled through a Vigeraux column to remove the solvent, and the residue was vacuum distilled. There was obtained 0.2301 g (44.2%) of a slightly green colored oil, found to be the desired aldehyde (E-5).

Infrared: λ_{max}^{film} 5.77(s)(aldehyde C=O)μ
6.10(m)(C=C)μ
11.0 (m)($C=CH_2$)μ

Dibutyl vinyl boronate (F-6)

Vinyl magnesium chloride was prepared in the usual way[4]. To 16.67 g (0.685 mole) of Mg in 70 ml of dry THF, was added dropwise under N_2 38.86 g (0.622 mole) of vinyl chloride in dry THF. The reaction was initiated with about 1 ml of bromoethane. After initiation of the reaction, the vinyl chloride-THF solution was added as rapidly as possible to maintain reflux. After the addition, the reaction mixture was heated at 50-60°C. for 4 hours. The reaction mixture was cooled to room temperature. To a solution of 67.9 g (0.654 mole) of trimethyl borate in 300 ml of dry ether cooled to -60°C., was added the Grignard solution dropwise under N_2. At the end of the addition, the reaction mixture was allowed to warm slowly to room temperature. To the reaction mixture was added 300 ml of 3M HCl dropwise with vigorous stirring, maintaining the temperature between 0° and 10°C. The mixture was extracted with three 100 ml portions of n-butanol, the organic layer washed with two 100 ml portions of 10% NaCl, then washed with 50 ml of saturated NaCl, followed by saturated sodium bicarbonate until a pH of 6 was reached. The extract was washed once again with saturated NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was vacuum distilled. There was obtained 42.25 g (36.9%) of a clear colorless oil.

Infrared: λ_{max}^{film}	6.19(s)(C=C)μ
n.m.r.: $\delta_{TMS}^{CDCl_3}$	0.95 p.p.m. (s), (methyl) 3.86 p.p.m. (t), ($-OCH_2-$ J=6 Hz) 6.00 p.p.m. (b s), (Olefin H)

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