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The synthesis of homoallylic alcohols through diasteriomeric transition states

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THE SYNTHESIS OF HOMOALLYLIC ALCOHOLS THROUGH DIASTERIOMERIC TRANSITION STATES

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ABSTRACT

Theoretically, optically active homoallylic alcohols can be synthesized by reacting an optically active organotin with an aldehyde in the presence of a Lewis acid. It is expected that the chirality of the organotin will induce one diastereomeric transition state which will have a significantly reduced activation energy than the transition state of the other diastereomer. If the difference between the two activation energies is substantial enough, the transition state with the lower activation energy will be preferred over the other transition state. If the preference is absolute one completely pure alcohol enantiomer will be produced. If there is a preference, but it is not absolute, there will be an excess of one enantiomer produced. Various aldehydes were reacted with the synthesized organotin, diallylisopropylmyrtanyltin to produce alcohols. Three aldehydes (benzaldehyde, ortho -chlorobenzaldehyde, and 2-ethylhexanal) were used to determine the correlation, if any, between the optical purity of the reaction product and the reacting aldehyde. The optical rotations measured for each of the alcohols produced revealed no correlation: the products were racemic mixtures, regardless of the aldehyde used.

This thesis is dedicated to Professor Lawrence F. McGahey who has not only helped me to develop an understanding for the interdependence of many aspects of chemistry, but also has taught me how to apply this knowledge logically. Thanks for all of your time and patience, Professor.

I would like to acknowledge the guidence of Professor McGahey; Barry Cohen, my predecessor on this project who layed a significant foundation on which to base this research project; and my family who never quite understood what I was working on but always cared enough to try.

"I am a great believer in luck,
and I find the harder I work
the more I have of it"
-Stephen Leacock

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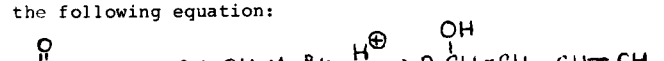
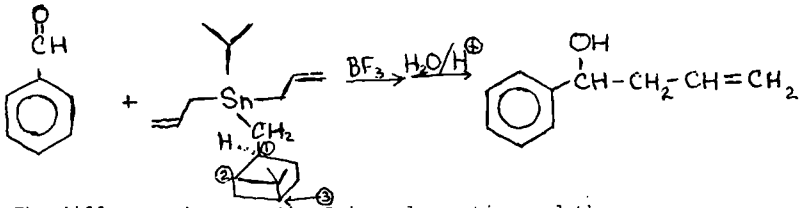
BACKGROUND

Homoallylic alcohols which are not optically active can be produced by reacting an aldehyde with a Grignard in the presence of a Lewis acid. This can be represented by the following equation:



This reaction is not specific for one enantiomer.

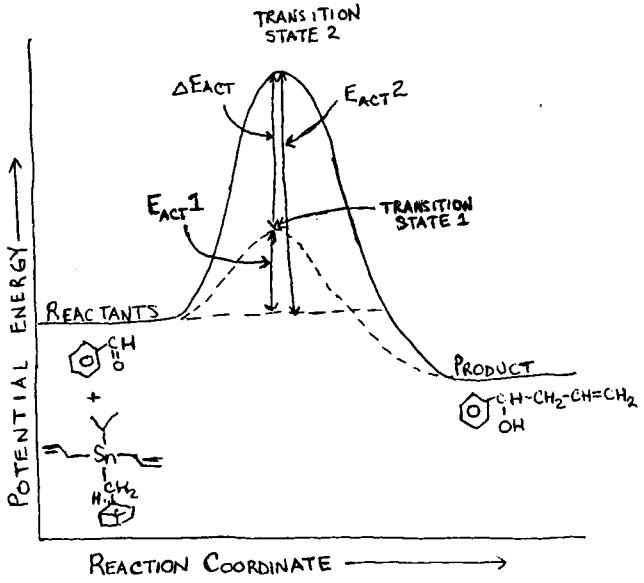
The actual reaction attempted involved the optically active organotin compound diallylisopropylmyrtanyltin reacting with the aldehyde, benzaldehyde, according to the following reaction:



The difference between the Grignard reaction and the above reaction is the organotin which contains the myrtanyl constituent. Myrtanyl contains three chiral carbons, each of which is marked above. The chiral myrtanyl group is not transferred to the resultant alcohol. Because of the excess of one enantiomer of the myrtanyl, the tin compound does rotate the plane of

polarized light.

The transition complex of the Grignard reaction is not specific for either enantiomer since there is no optical rotation of the product. However, it is suspected that if a diasteromeric transition state can be induced there will be two transition states, one of which will be preferred. The preferred transition state will be that one which has the lower activation energy. This reaction profile is illustrated below.



There are many interesting characteristics of this energy diagram which should be carefully analyzed. According to this profile, transition state 1 will be preferred over transition state 2. It is important to note that the reactants and products for each of the paths have the same energies, and that the reaction is exothermic as experimentally determined. The sole difference between the two paths is the value of E_{ACT} which is the difference between the two activation energies. This quantity is marked on the above reaction profile. The absolute configuration of the tin molecule should dictate which alcohol enantiomer will be preferred. The enantiomer which forms through the transition state with the lower E_{ACT} will be the preferred enantiomer and will form at a quicker rate than the other enantiomer since less energy is needed. What is an essential assumption for this research is that the value of E_{ACT} is large enough to exact a substantial, if not absolute, preferrence for one enantiomer. The optical purity of the product can be calculated using a value for the specific rotation for each of the enantiomers which was separated by resolution techniques.

The project has been divided into four parts for convenience. The first section is concerned with

producing a racemic mixture of 1-phenyl-3-buten-1-ol. This was done by a Grignard reaction. The purpose of such a reaction was to characterize the compound for identification so that it would be known later when the same exact compound had been synthesized and purified completely. Once the compound was purified, an optical rotation could be determined to test for a preference for one enantiomer.

Part Two of this project concerns the synthesis of an optically active tin compound which had never been made previously, triphenylmyrtanyltin (TMT). This new compound was synthesized starting from a naturally occuring optically active compound (-)-B-Pinene which was readily available at a reasonable cost.

Part Three of the thesis involves the reactions of the optically active triphenylmyrtanyltin compound to yield the optically active final product, diallylisopropylmyrtanyltin. This transormation involves successive brominations and Grignard reactions to develop the desired product. After purification, the final tin compound was complete and could be used in the last part of the thesis, the Addition Reactions.

Part Four of this thesis focuses on the reactions of various aldehydes with the end product of part three, diallylisopropylmyrtanyltin. In essence this is the

culmination of the whole project. Three aldehydes were used and all were purified prior to the final reaction. The first aldehyde was benzaldehyde. The second aldehyde used was ortho -chloro-benzaldehyde while the final aldehyde was 2-ethylhexanal. The major problem faced during these reactions was formulating a procedure for the purification and isolation of the desired end product. This technique was perfected after several attempts.

If a system is found which can accomplish the goal of this experiment, there are countless applications for this new synthesis. Perhaps most important, the medical field will be able to benefit from utilizing this type of process as it will enable pharmecutical companies to make medicines at a higher purity, greater yield, and lower cost. Hopefully the reduction in cost would be passed down to the consumers.

The process yielded three alcohols, each of which was purified. The optical rotations observed for each of these alcohols were, however, not nearly significant enough to say that one enantiomer is definitely preferred over the other. This indicates that the systems tested do not possess the needed qualities to produce only one enantiomer.

RESULTS AND THEORY

Part One

Preparation of Racemic 1-phenyl-3-buten-1-ol

The alcohol was synthesized by a Grignard reaction. Though the goal is to produce one enantiomer of the alcohol, a racemic mixture could be easily synthesized and characterized by IR and NMR spectra. Except for the way each enantiomer rotates the plane of polarized light, all other characteristics of both enantiomers are the same. Once purified, the spectra of the racemic mixture can be used as a comparison later to verify the compound produced through a diastereomeric transition state. Below is the synthetic scheme:

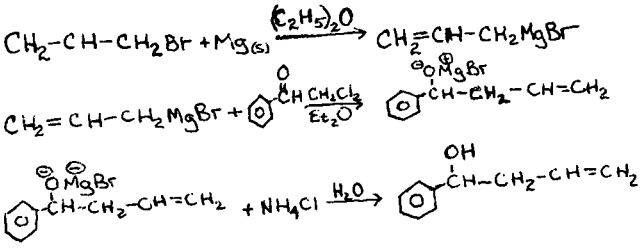


Table 1

Important IR and NMR Bands of Racemic 1-phenyl-3-buten-1-ol

IR (Figure 1)

1645 cm^{-1}	moderate	C-C stretch
3350 cm^{-1}	strong	-O-H stretch
1497, 1453 cm^{-1}	strong	C=C ring stretch
3100-3000 cm^{-1}	moderate	-C-H aromatic stretch
1700 cm^{-1}	no peak	-C=O stretch

NMR (Figure 2)

7.2 ppm	singlet	aromatic hydrogens

The integration is in agreement with the proposed structure.

FIGURE ONE : IR SPECTRUM OF RACEMIC 1-PHENYL-3-BUTEN-1-OL

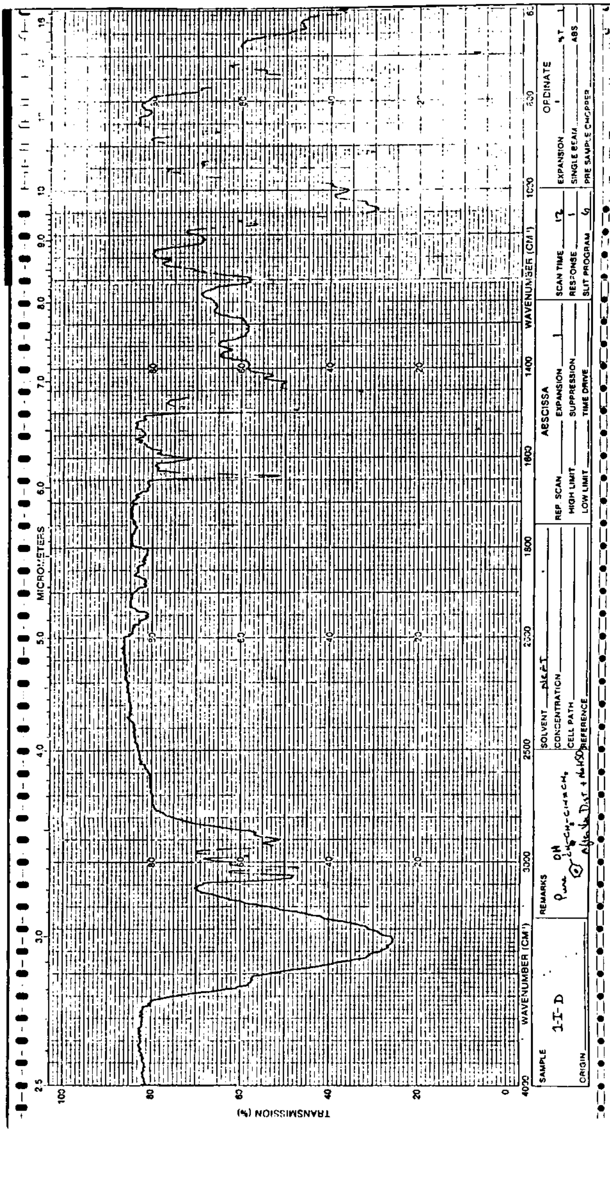
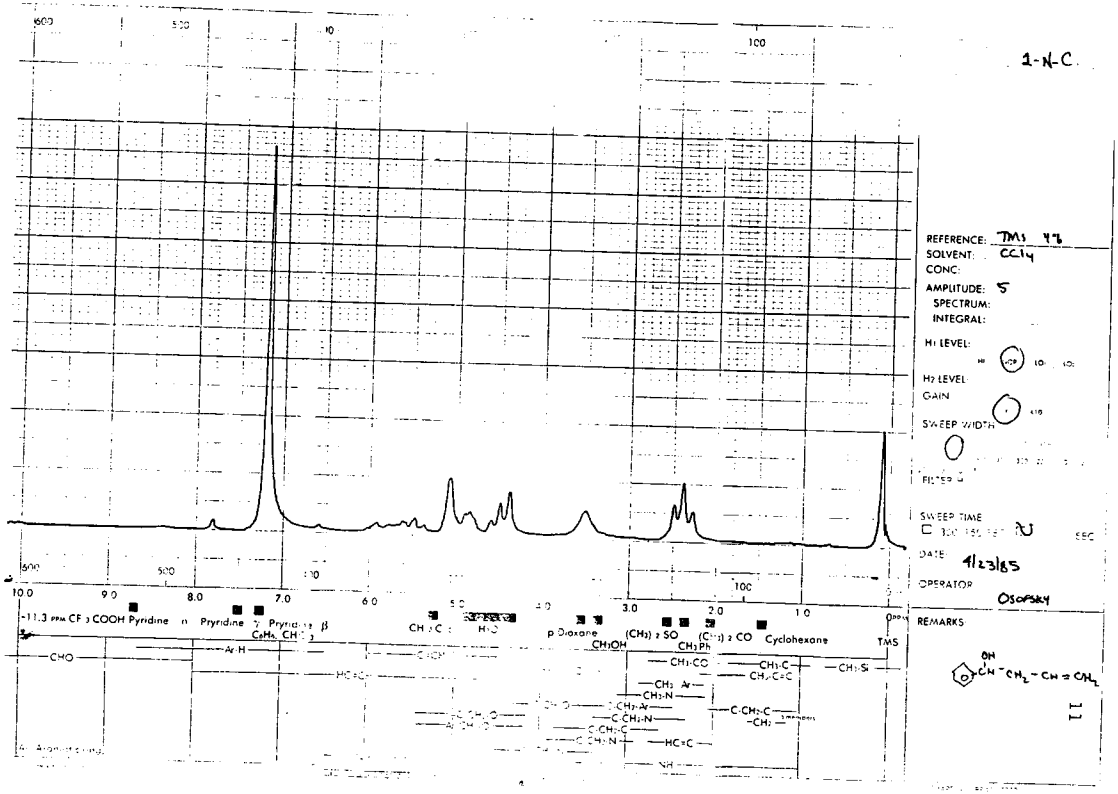

MICROMETERS
WAVENUMBER (CM⁻¹)
TRANSMISSION (%)
SAMPLE 1-I-D
ORIGIN
REMARKS
SOLVENT neat
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP. SCAN
HIGH LIMIT
LOW LIMIT
EXPANSION 1
SUPPRESSION
TIME DRIVE
SCAN TIME 12
RESPONSE 1
SLIT PROGRAM 4
ORDINATE
EXPANSION
SINGLE BEAM
PRE SAMPLE CHOPPER

FIGURE TWO : NMR SPECTRUM OF RACEMIC

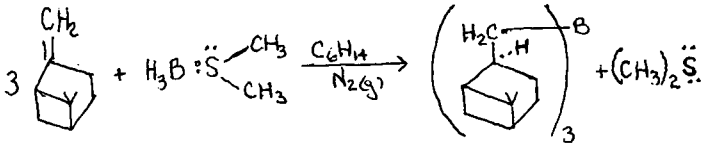
1-PHENYL-3-BUTEN-1-OL


1-N-C
REFERENCE: TMS 4%
SOLVENT: CCl4
CONC:
AMPLITUDE: 5
SPECTRUM:
INTEGRAL:
H1 LEVEL:
H2 LEVEL
GAIN
SWEEP WIDTH
FILTER
SWEEP TIME
DATE 4/23/85
OPERATOR OSORSKY
REMARKS
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM
TMS
Cyclohexane
p Dioxane
Pyridine
CHO
Ar-H
HC=C
NH

Part Two

Preparation of (-)-cis-myrtanol

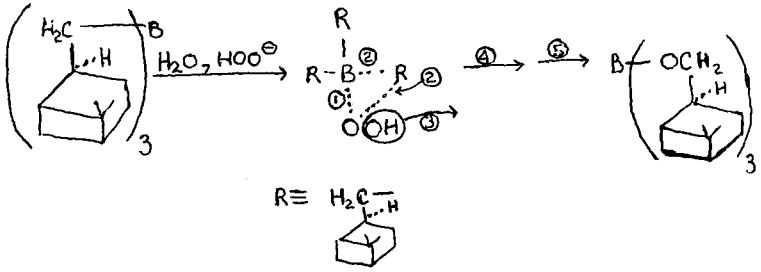
This preparation was completed in several steps. The first step involved the hydroboration of(-)-B-Pinene at a temperature of $0^{o}C$.



The next step involved the oxidation of the trialkylborane to an alcohol. Absolute ethanol was added to accomplish two functions. First, the ethanol destroys the excess BH_3 by the following reaction:

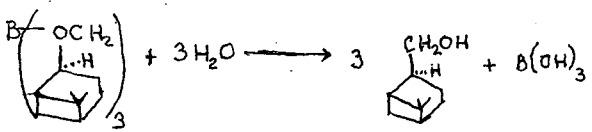
$$BH_3 + C_2H_5OH \longrightarrow 3H_2 + B(OCH_2CH_3)_3$$

Second, the ethanol forms a cosolvent for the H_2O addition later. After the ethanol had been added, NaOH then H_2O_2 were added to the mixture. This caused the following reaction to occur:



1) ^{-}OOH attacks the boron atom and forms a fourth bond to it.
2) Myrtane group breaks its bond with the boron atom and forms a new bond with the oxygen atom.
3) ^{-}OH group leaves
4,5) Steps 1-3 repeat twice more.

The addition of H_2O caused the protonation of the alcohol by the following reaction:



This synthesis was run three times. The specific rotations which were calculated for each preparation's product and the combined products can be found in Table 2 below:

Table 2

Specific Rotations of the (-)- cis -myrtanol

	$[\alpha]_D$
Run 1:	-20.4+/-0.3°
Run 2:	-20.2+/-0.3°
Run 3:	-20.2+/-0.3°
Combined:	-19.5+/-0.3°

Optical purity of combined: 93.3 +/-1.5%1

These results indicate that the compounds produced are exactly the same and the results are reproducible. Therefore, the products were combined. The value for the combined specific rotation does not correlate well with

the independent measurements above. The polarimeter was very erratic and this was probably the reason for the lack of consistence. An optical purity was calculated though the percentage is actually believed to be higher.

IR and NMR spectra (Figures 3 and 4 respectively) were taken to characterize the (-)- cis -myrtanol. Both spectra matched those found in the Aldrich Libraries. The important IR characteristics to note were the strong peak at 3300 cm^{-1} indicative of the -OH stretching, and the lack of any peak at 1645 cm^{-1} which would be the C=C stretching from unreacted (-)-B-Pinene.

IR and NMR spectra were made of the (-)-B-Pinene for reference and are labeled Figures 5 and 6 respectively.

FIGURE THREE : IR SPECTRUM OF (-)- CIS -MYRTANOL

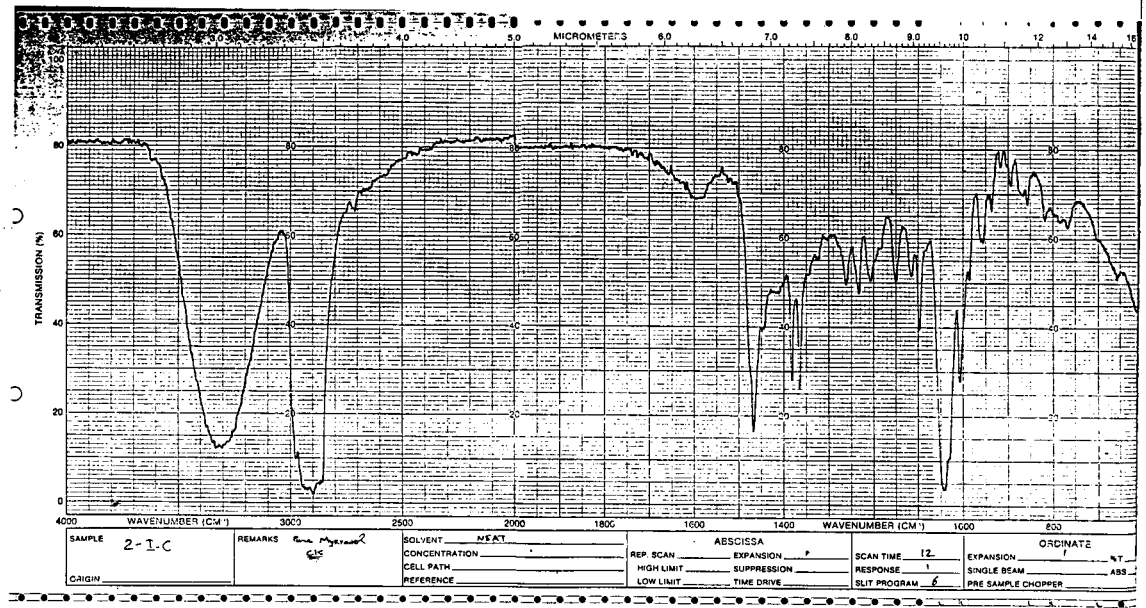

MICROMETERS
4,0
5,0
6,0
7,0
8,0
9,0
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
4000
WAVENUMBER (CM⁻¹)
3000
2500
2000
1800
1600
1400
WAVENUMBER (CM⁻¹)
1000
800
SAMPLE 2-I-C
ORIGIN
REMARKS
SOLVENT NEAT
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP. SCAN
EXPANSION
HIGH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME 12
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION
%T
SINGLE BEAM
ABS
PRE SAMPLE CHOPPER

FIGURE FOUR : NMR SPECTRUM OF (-)- CIS -MYRTANOL

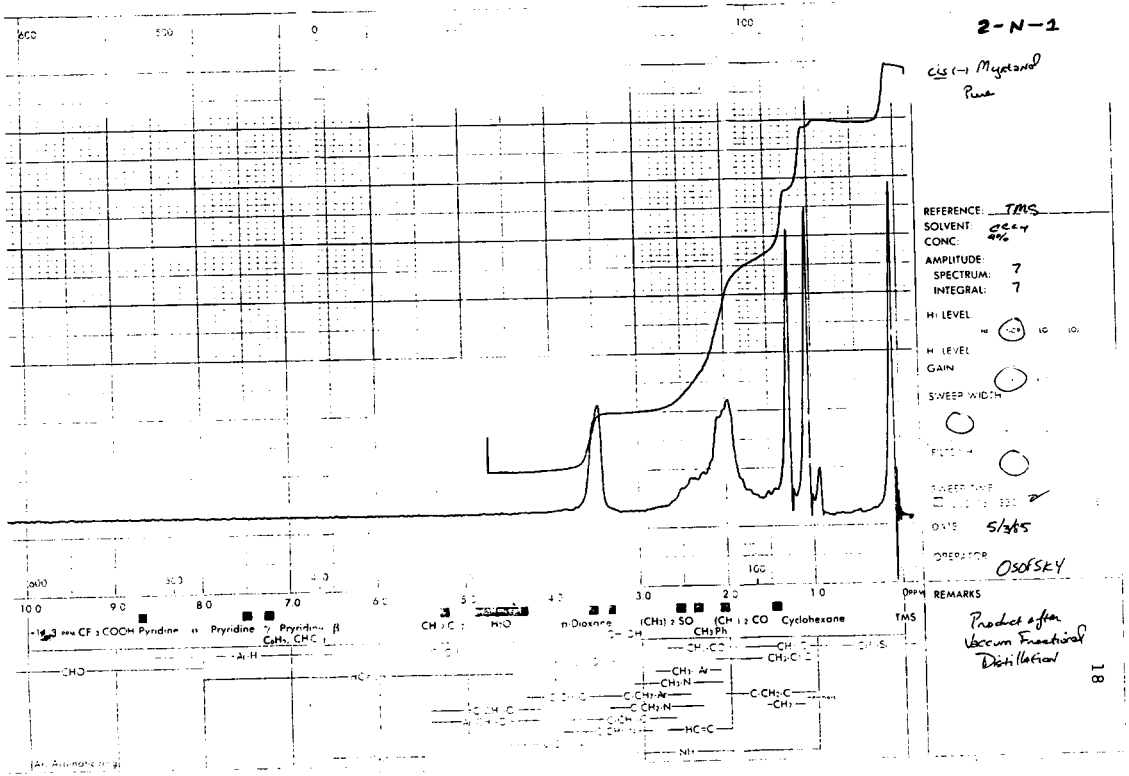

2-N-1
cis (-) Mycaranol
Pure
REFERENCE: TMS
SOLVENT: CCl4
CONC: 4%
AMPLITUDE:
SPECTRUM: 7
INTEGRAL: 7
HI LEVEL
LO LEVEL
GAIN
SWEEP WIDTH
DATE 5/3/65
OPERATOR OSOFSKY
REMARKS
Product after Vacuum Fractional Distillation
18
TMS
CF3COOH Pyridine α Pyridine γ Pyridine β
(CH3)2SO (CH3)2CO Cyclohexane
n-Dioxane
CH3Ph
CH3N
HC≡C
NH

FIGURE FIVE : IR SPECTRUM OF (-)-B-PINENE

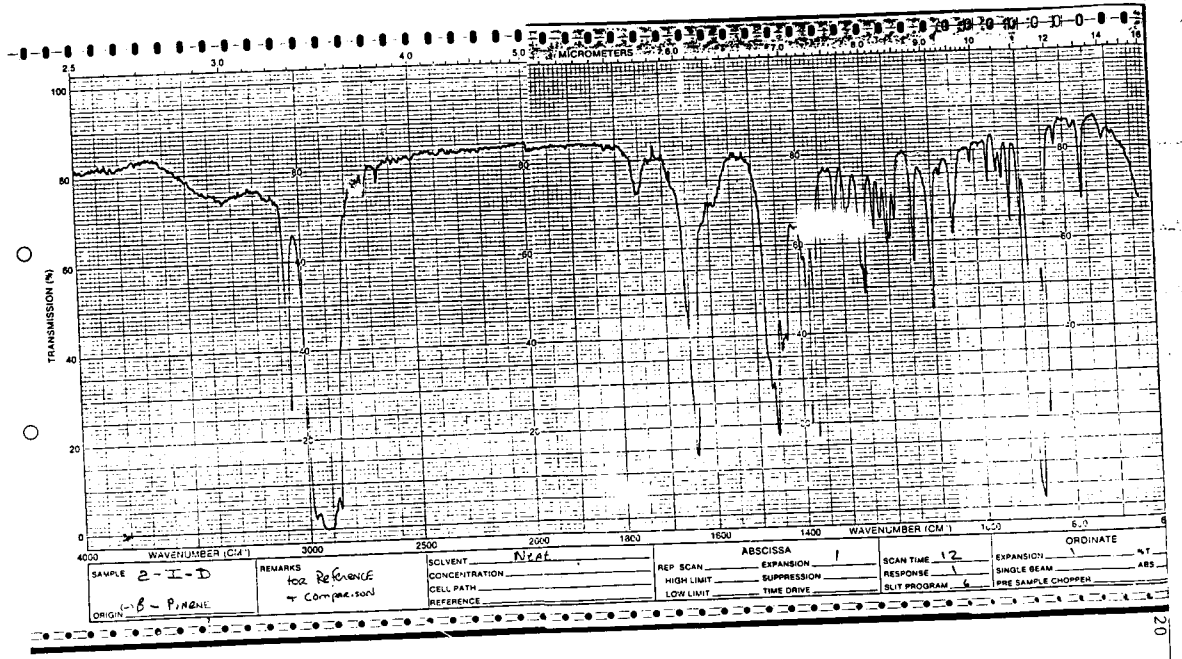
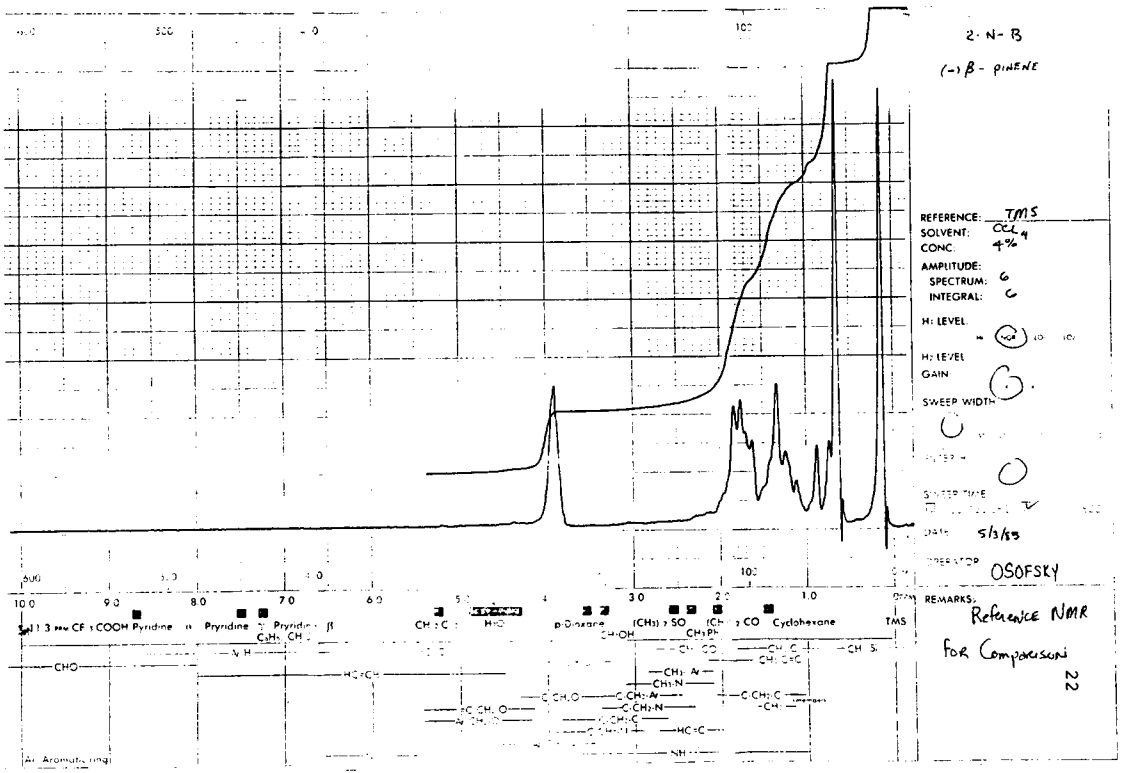

MICROMETERS
TRANSMISSION (%)
WAVENUMBER (CM⁻¹)
SAMPLE 2-I-D
(-)-β-PINENE
REMARKS for Reference + Compare.scan
SOLVENT Neat
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP SCAN
EXPANSION 1
HIGH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME 12
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION
%T
SINGLE BEAM
ABS
PRE SAMPLE CHOPPER

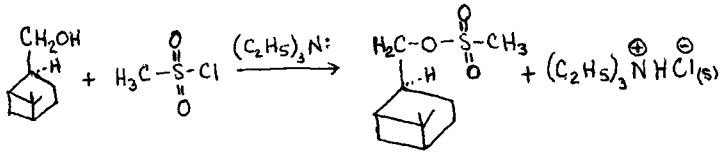
FIGURE SIX : NMR SPECTRUM OF (-)-B-PINENE


2-N-B
(-) β - PINENE
REFERENCE: TMS
SOLVENT: CCl4
CONC: 4%
AMPLITUDE:
SPECTRUM: 6
INTEGRAL: 6
H1 LEVEL
H2 LEVEL
GAIN
SWEEP WIDTH
SWEEP TIME
DATE 5/3/65
OPERATOR OSOFSKY
REMARKS: Reference NMR for Comparison
22
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
TMS
CHO
NH
HC=CH
Ar Aromatic ring

Preparation of Mesylates

Understanding that the goal of this section is to attach the (-)- cis -myrtanol to the tin compound, the -OH group would have to be removed and replaced by a good leaving group. The -OH group is a poor leaving group and would make attachment to the tin molecule extremely hard if not impossible.

Using the (-)- cis -myrtanol from the previous preparation, and combining it with methanesulfonyl chloride, a better leaving group was added to the myrtanol derivative. This reaction is outlined below:



The yield was 92%.

Table 3

Characteristics of the Myrtanyl Methanesulfonate

Specific Rotations of the Myrtanyl Methanesulfonate

Run 1: $[\alpha]_D$= -13.7+/-0.3°
Run 2: $[\alpha]_D$= -13.9+/-0.3°

Important IR and NMR Bands of the Alkyl Methanesulfonate

IR (Figure 7)

3300 cm^{-1}	no peak	-O-H stretch
1372-1335 cm^{-1}	strong	S-O symmetric stretch
1195-1168 cm^{-1}	strong	S-O symmetric stretch
1351 cm^{-1}	strong	O=S=O asymmetric str.
1000-769 cm^{-1}	strong	S-O-C stretches
2900 cm^{-1}	strong	C-H aliphatic stretches

NMR (Figure 8)

3 ppm	singlet	methyl hydrogens attached to the sulfur

FIGURE SEVEN : IR SPECTRUM OF MYRTANYL MESYLATE

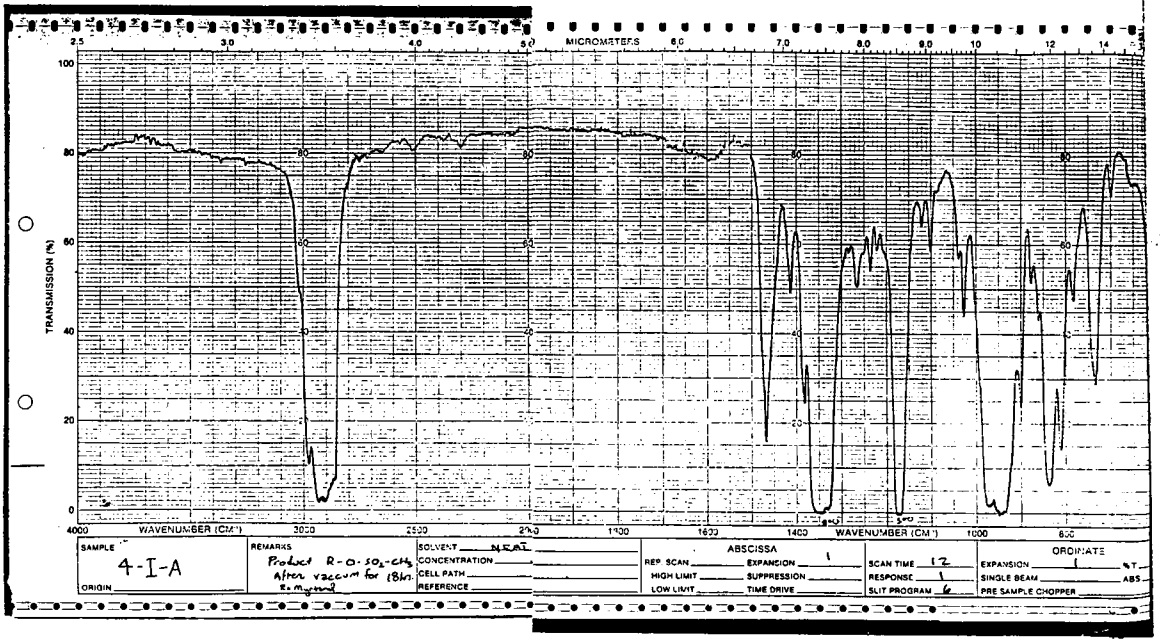
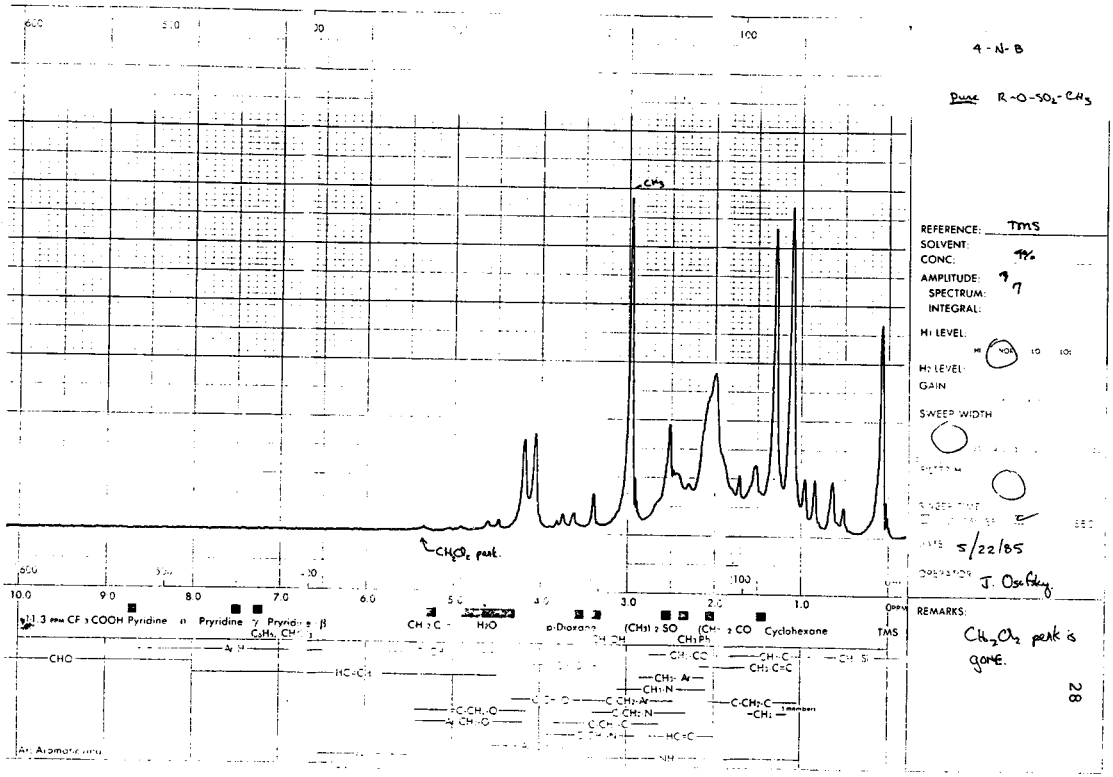
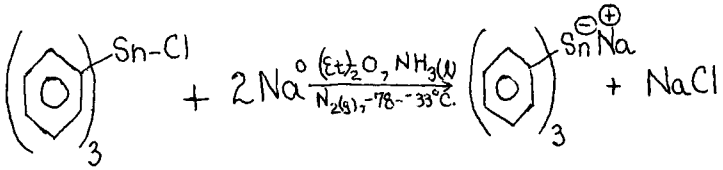

MICROMETERS
2.5
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
12
14
100
80
60
40
20
0
TRANSMISSION (%)
4000
WAVENUMBER (CM⁻¹)
3000
2500
2000
1800
1600
1400
WAVENUMBER (CM⁻¹)
1000
650
SAMPLE
4-I-A
ORIGIN
REMARKS
Product R-O-SO2-CH3
After vacuum for 18hr.
Remained
SOLVENT NEAT
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP SCAN
EXPANCION 1
HIGH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME 12
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION 1 %T
SINGLE BEAM ABS
PRE SAMPLE CHOPPER

FIGURE EIGHT : NMR SPECTRUM OF MYRTANYL MESYLATE

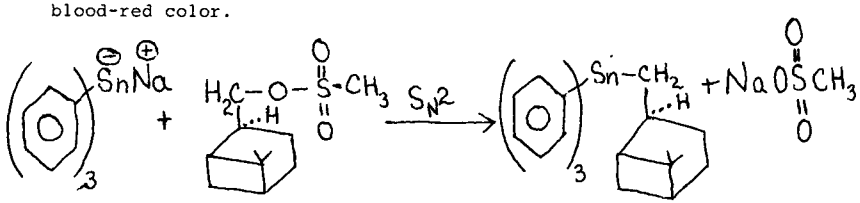

4-N-B
Pure R-O-SO2-CH3
CH3
CH2Cl2 peak.
REFERENCE: TMS
SOLVENT:
CONC:
AMPLITUDE:
SPECTRUM:
INTEGRAL:
HI LEVEL:
H2 LEVEL:
GAIN
SWEEP WIDTH
DATE 5/22/85
OBSERVER J. Osofsky
REMARKS:
CH2Cl2 peak is gone.
28
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
TMS
CHO
HC=CH
CH3 Ar
CH3 C=C
CH3 N
C-CH2-C
HC≡C
NH

Preparation of Triphenylmyrtanyltin (TMT)

This is the final reaction of part two and was extremely complicated. The mesylate produced in the previous preparation was reacted with a triphenylstannyl anion as follows:



The endpoint of the above reaction was signalled by a blood-red color.



The endpoint of this reaction was signalled by a gray color.

Table 4

Characteristics of Triphenylmyrtanyltin (TMT)

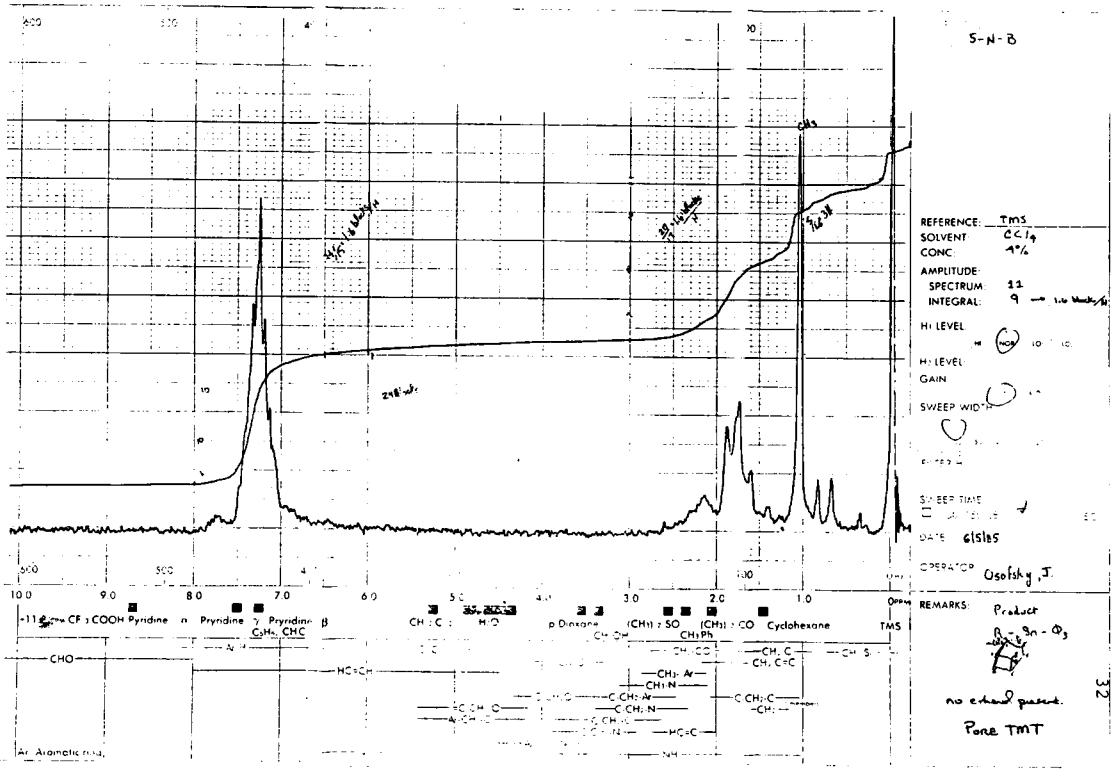
Preparation	Purified Yield	$[\alpha]_D$
1	67%	-14.0+/-0.3%
2	28%	-14.5+/-0.3%

NMR (Figure 9)

1.0 ppm	singlet	$-CH_3$ from myrtane
7.2 ppm	multiplet	hydrogens attached to the aromatic rings

The integration agrees with the proposed structure.

FIGURE NINE : NMR SPECTRUM OF TRIPHENYLMYRTANYLTIN

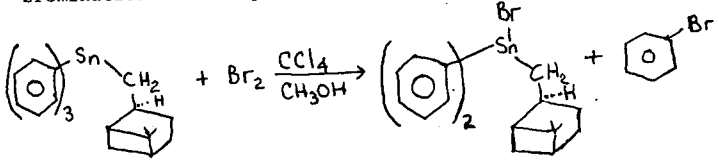

S-N-B
REFERENCE: TMS
SOLVENT CCl4
CONC. 4%
AMPLITUDE:
SPECTRUM 11
INTEGRAL: 9
HI LEVEL
HI LEVEL GAIN
SWEEP WIDTH
SWEEP TIME
DATE 6/5/85
OPERATOR Osofsky, J.
REMARKS: Product
no ethanol present.
Pure TMT
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
TMS
CF3COOH Pyridine α Pyridine γ Pyridine β
C6H6 CHCl3
CH3CN
H2O
p Dioxane
(CH3)2SO
(CH3)2CO
Cyclohexane
CH3OH
CH3Ph
CHO
HC=CH
CH3-Ar
CH3-N
C CH3-Ar
C CH2-N
C CH3-C
CH2-C
CH3-
HC≡C
NH
Ar Aromatic ring

Part Three

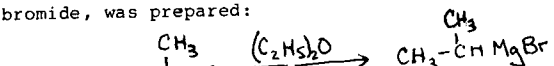
Preparation of Diphenylisopropylmyrtanyltin

The isopropyl group was chosen to be a substituent on the tin atom, because of its physical properties. It is a good group to use because it is modestly bulky and will provide a good amount of steric hinderance but not so much as to inhibit the final reaction with an aldehyde. In addition, the isopropyl group is readily available.

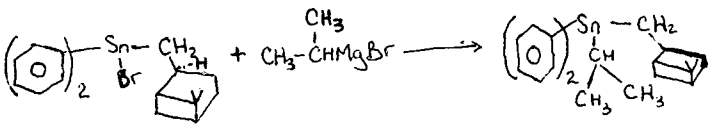
The first step of this substitution was the bromination of the optically active TMT:



After this, the Grignard reagent, isopropylmagnesium bromide, was prepared:

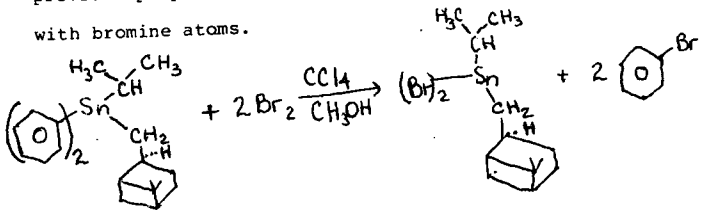


The Grignard was then reacted with the brominated tin compound to yield the desired product:

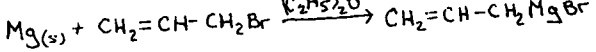


Preparation of Diallylisopropylmyrtanyltin

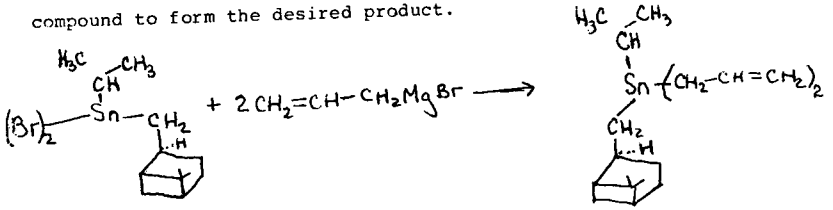
Two allyl groups were added to the tin molecule to replace the last two aromatic rings. This was the last step in the preparation of the tin compound. As in the previous preparation the aromatic rings were replaced with bromine atoms.



The Grignard was prepared as before only the compound prepared was allylmagnesium bromide:



Finally the Grignard was reacted with the tin compound to form the desired product.

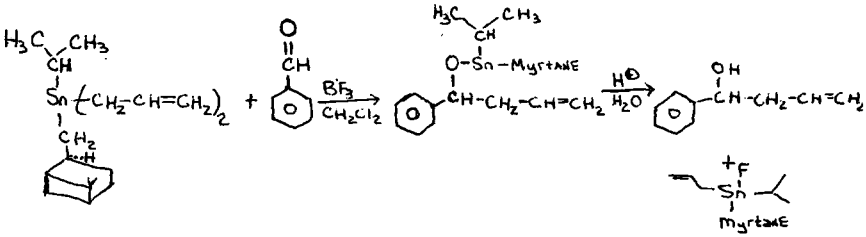


The yield of the final product based on the TMT started with was 22.8%. The product was distilled, collecting

Part Four

Reaction of the Diallylisopropylmyrtanyltin with Benzaldehyde

The reaction to produce the alcohol, 1-phenyl-3-buten-1-ol is simple and can be represented by the reaction equation below:



The main problem faced was in the isolation and purification of the alcohol; it was not easily separated from the tin compounds which were very viscous. For this reason the alcohol was characterized in Part One. This way there was a verification that a correct technique had been established which would separate out the desired compound.

The first preparation was designed assuming that both allyl groups on the tin compound react. Therefore it was also assumed that two moles of alcohol would be produced for every mole of tin reacted.

After the first purification attempt, there was

two fractions, each of which were tested for optical activity.

Table 5

Characterisics of Diallylisopropylmyrtanyltin

	boiling point at 0.5 - 0.3 mm Hg	$[\alpha]_D$
Flask 1	125°C	-23.0+/-0.3°
Flask 2	125°C	-23.2+/-0.3°

The IR and NMR spectra can be found in Figures 10 and 11 respectively. When the percent composition analysis was performed by Galbraith Laboratories the percent of carbon and oxygen actually found was lower than theoretically calculated. As shown by the NMR spectrum there still is present some unreacted tin with a phenyl group attached. This explains the slight discrepency in the percent composition test. This should not affect the results of the reactions with the aldehydes. This is because the phenyl groups stericly hinder any reaction and any unreacted tin compounds will be separated out in the work-up.

FIGURE TEN : IR SPECTRUM OF DIALLYLISOPROPYLMYRTANYLTIN

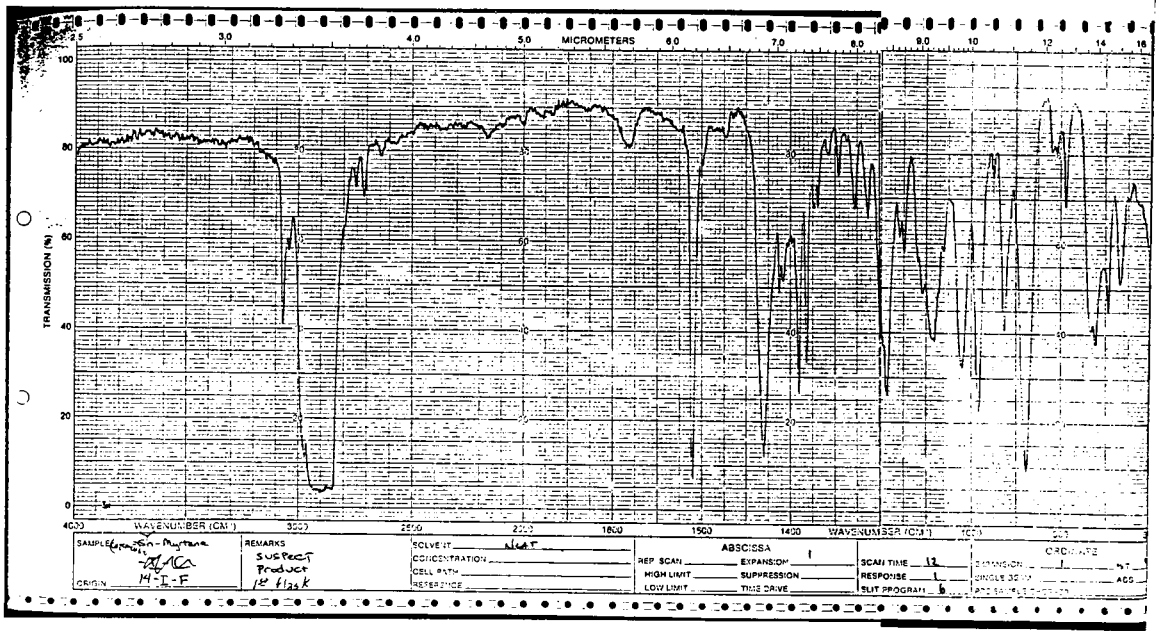
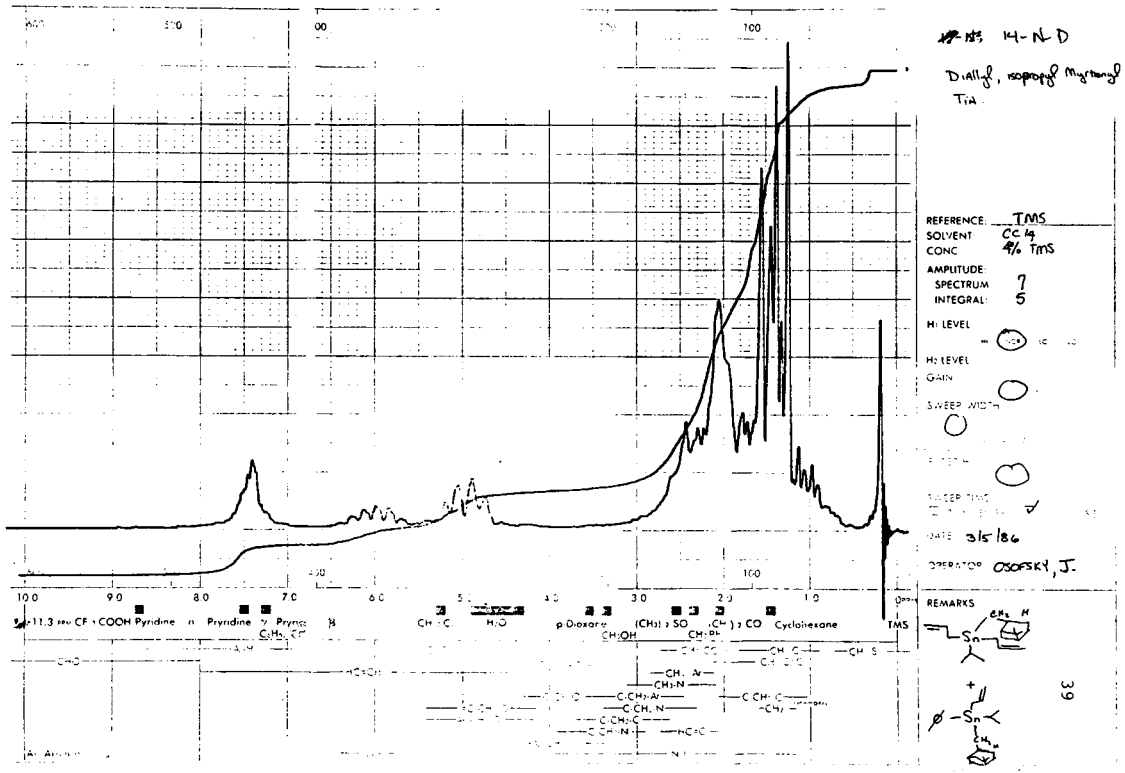

MICROMETERS
TRANSMISSION (%)
WAVENUMBER (CM-1)
SAMPLE
ORIGIN
REMARKS
SUSPECT
SOLVENT
CONCENTRATION
CELL PATH
ABSCISSA
SCAN TIME
RESPONSE

FIGURE ELEVEN : NMR SPECTRUM OF

DIALLYLISOPROPYLMYRTANYLTIN


14-N D
Diallyl, isopropyl Mgbromide
THF
REFERENCE: TMS
SOLVENT CCl4
CONC 4% TMS
AMPLITUDE
SPECTRUM 7
INTEGRAL 5
H1 LEVEL
H2 LEVEL
GAIN
SWEEP WIDTH
SWEEP TIME
DATE 3/5/86
OPERATOR OSOFSKY, J.
REMARKS
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0ppm
TMS
Cyclohexane
p Dioxane
H2O
CH3CN
Pyridine
CF3COOH
CH2OH
CH3OH
CHO
39

still a significant carbonyl peak representative of unreacted benzaldehyde in the IR spectrum of the crude product. This can be observed by the peak at 1700 cm^{-1} in Figure 12. Although the presence of an alcohol peak at 3400 cm^{-1} was detected there did not seem to be any C=C peak at 1645 cm^{-1} in the spectrum, though it may have been masked by the wide C=O band. In order to reduce the carbonyl peak, the product was washed a few more times with $NaHSO_3$. The product was treated with $NaHSO_3$ previously in the first purification attempt. Another IR was taken (Figure 13) and this revealed that the C=O peak had been reduced by half but was still abundant in the sample. It was concluded from this preparation that only one allyl group on the tin compound reacted with the aldehyde, assuming that the reaction went to completion. When a vacuum fractional distillation was attempted to separate the alcohol from the tin residues, the contents in the reaction flask burned and only vapors were observed flowing over the condenser.

The next reaction scaled down the amount of benzaldehyde used. The purification techniques also were altered in order to better isolate the alcohol which had burned in the previous workup. A column chromatography step was incorporated into the procedure as well as a

FIGURE TWELVE : IR SPECTRUM OF CRUDE

1-PHENYL-3-BUTEN-1-OL

(C=O PEAK PRESENT)

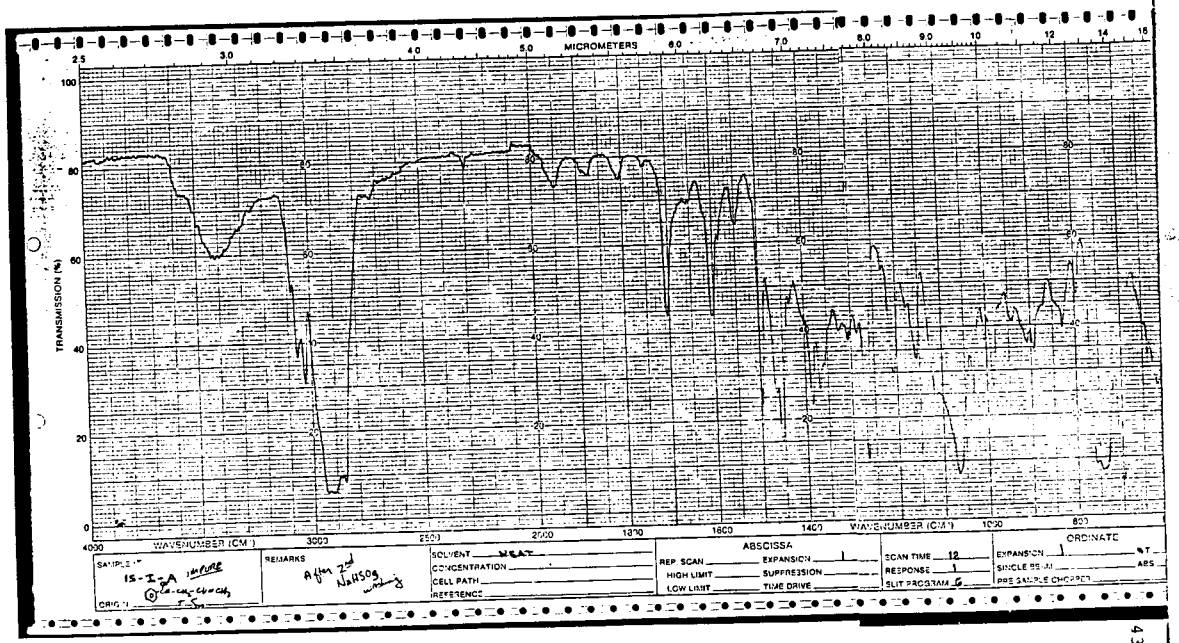
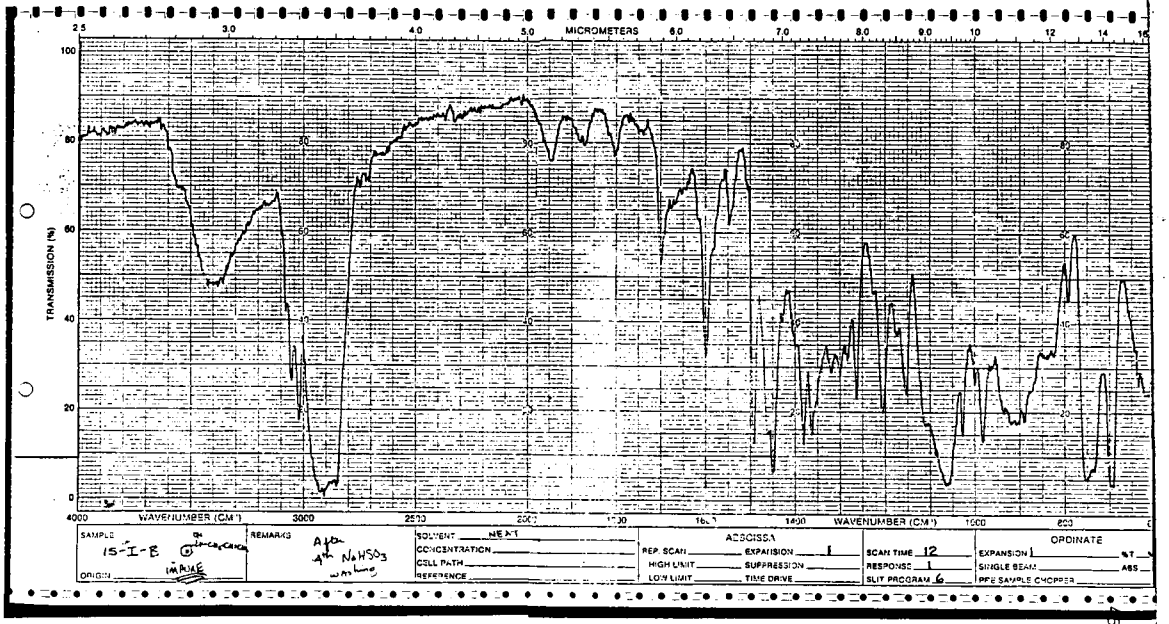

MICROMETERS
2.5
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
12
14
15
TRANSMISSION (%)
100
80
60
40
20
0
WAVENUMBER (CM⁻¹)
4000
3000
2500
2000
1800
1600
1400
1200
1000
800
SAMPLE
15-I-A
IMINE
ORIG
REMARKS
After 2nd
NaHSO3
wash
SOLVENT NEAT
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP. SCAN
EXPANSION 1
HIGH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME 12
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION 1
%T
SINGLE BEAM
ABS
PRE SAMPLE CHOPPER

FIGURE THIRTEEN : IR SPECTRUM OF CRUDE

1-PHENYL-3-BUTEN-1-OL

(C=O PEAK REDUCED)


2.5
3.0
4.0
5.0
MICROMETERS
6.0
7.0
8.0
9.0
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
4000
WAVENUMBER (CM-1)
3000
2500
2000
1500
1400
WAVENUMBER (CM-1)
1000
600
SAMPLE
15-I-B
ORIGIN
REMARKS
After 4th NaHSO3 washing
SOLVENT NEAT
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP. SCAN
EXPANSION 1
HIGH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME 12
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION 1
%T
SINGLE BEAM
ABS
PPE SAMPLE CHOPPER

wash with KF which would precipitate out the reacted tin by forming insoluble tin fluorides. An IR spectrum was taken of the alcohol after the new purification steps had been completed. The spectrum is labeled Figure 14. Although the sample was still impure, the carbonyl peak at 1700 cm^{-1} present in Figure 13 had disappeared. The amount of sample remaining was too little to proc ed with a vacuum fractional distillation.

In the third preparation of the 1-phenyl-3-buten-1-ol, the reaction was run on a double scale. Changes in the work-up included using 10% $NaHCO_3$ to neutralize the acid of the catalyst BF_3. The low pH was altered because an acidic solution is detrimental to an alcohol. In addition, a vacuum fractional distillation was incorporated into the purification process after the mixture had been purified as much as possible using column chromatography and KF washings, like the second preparation, along with treatments with reagents such as $NaHSO_3$ which are described in the Experimental section.

FIGURE FOURTEEN : IR SPECTRUM OF CRUDE

1-PHENYL-3-BUTEN-1-OL

(NO C=O PEAK PRESENT)

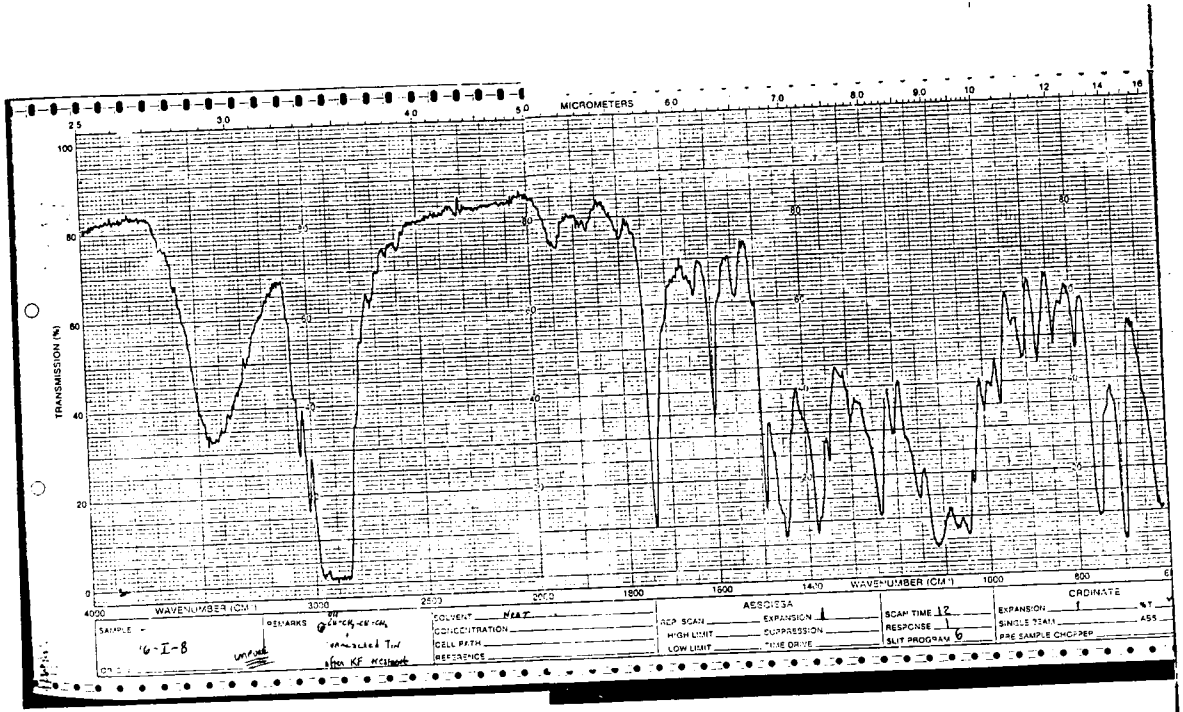

MICROMETERS
2.5
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
12
14
16
TRANSMISSION (%)
100
80
60
40
20
0
4000
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER (CM-1)
SAMPLE
16-I-B
REMARKS
Unknown
Recrystallized THF
from KF treatment
SOLVENT Neat
CONCENTRATION
CELL PATH
REFERENCE
ASSOCIATED
REP. SCAN
HIGH LIMIT
LOW LIMIT
EXPANSION 1
SUPPRESSION
TIME DRIVE
SCAN TIME 12
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION 1
%T
SINGLE BEAM
ABS
PRE SAMPLE CHOPPER

Table 6

Characteristics of 1-phenyl-3-buten-1-ol
From the Third Preparation

boiling point = 67°C at 0.6 mm Hg
yield = 39%

IR (Figure 15)

1645 cm^{-1}	strong	C=C stretch
3350 cm^{-1}	strong	-O-H stretch
1497, 1453 cm^{-1}	strong	C=C ring stretch
3100-3000 cm^{-1}	moderate	-C-H aromatic stretch
1700 cm^{-1}	weak	-C=O stretch

NMR (Figure 16)

7.2 ppm	singlet	aromatic hydrogens
3.4 ppm	doublet	alcohol hydrogen

The integration agrees with the proposed structure.

$[\alpha]_D$=+0.878°

As mentioned in Table VI there is a slight carbonyl peak present in Figure 15. It was not deemed important enough to purify the product further until a specific rotation determination had been executed. The results of the optical rotation test revealed a specific rotation of +0.878°. The observed rotation, $[\alpha]_{obs}$, was viewed skeptically because it was only very slight. In any event, the specific rotation did not indicate that there was a definite preference for either enantiomer. The literature values for the specific rotation of each enantiomer are as follows:

(R) $[\alpha]_D$ = +48.3°, 6.7g/100mL, benzene[1] and
(S) $[\alpha]_D$ = -48.7°, 6.9g/100mL, benzene[2]

FIGURE FIFTEEN : IR SPECTRUM OF PURE

1-PHENYL-3-BUTEN-1-OL

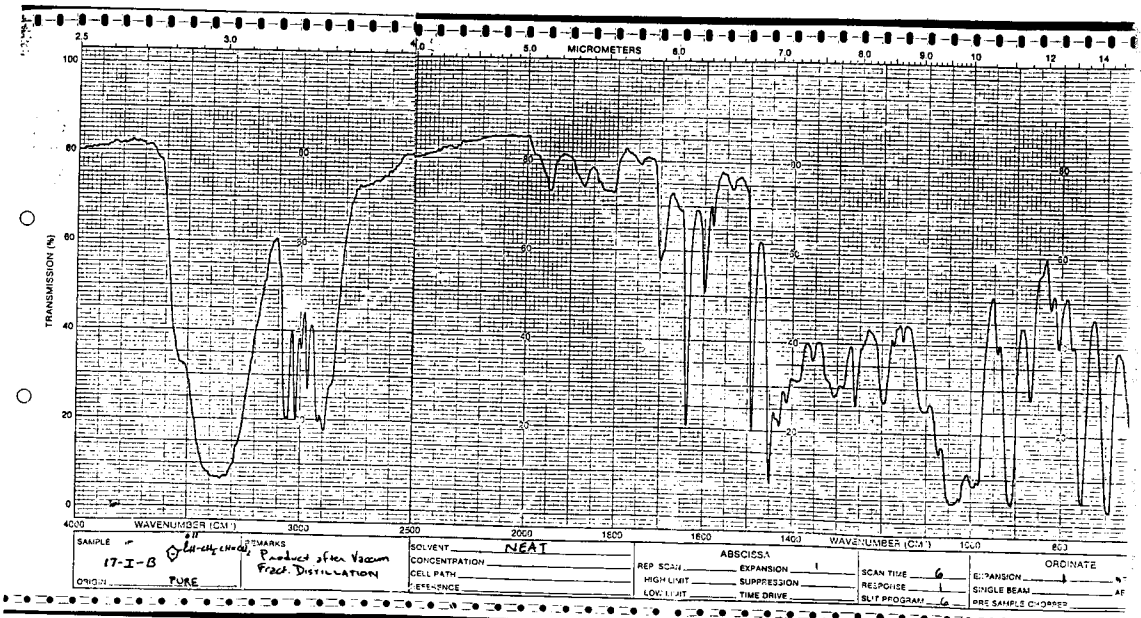
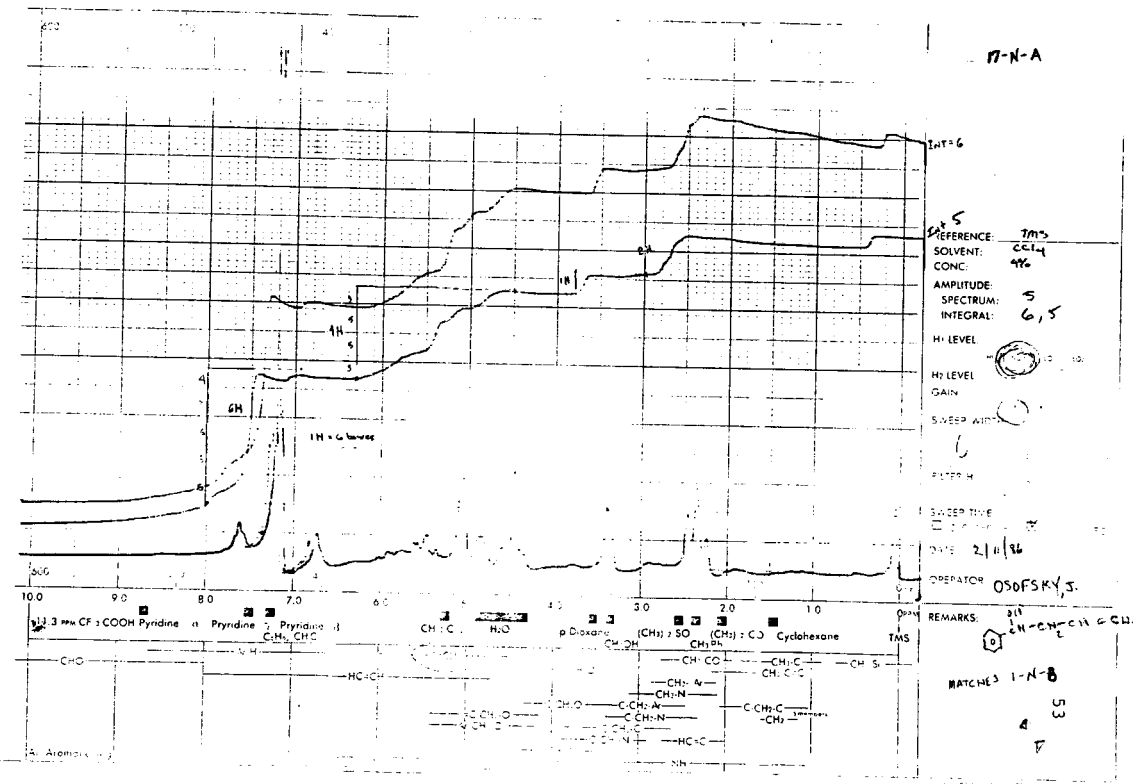

2.5
3.0
4.0
5.0
MICROMETERS
6.0
7.0
8.0
9.0
10
12
14
100
80
60
40
20
0
TRANSMISSION (%)
4000
WAVENUMBER (CM⁻¹)
3000
2500
2000
1800
1600
1400
WAVENUMBER (CM⁻¹)
1000
800
SAMPLE
17-I-B
ORIGIN
PURE
REMARKS
Product after Vacuum Fract. Distillation
SOLVENT
NEAT
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP SCAN
EXPANSION
1
HIGH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME
6
RESPONSE
1
SLIT PROGRAM
6
ORDINATE
EXPANSION
1
SINGLE BEAM
PRE SAMPLE CHOPPER

FIGURE SIXTEEN : NMR SPECTRUM OF PURE

1-PHENYL-3-BUTEN-1-OL


17-N-A
INT=6
REFERENCE: TMS
SOLVENT: CCl4
CONC: 4%
AMPLITUDE:
SPECTRUM: 5
INTEGRAL: 6,5
H1 LEVEL
H2 LEVEL
GAIN
SWEEP WIDTH
FILTER
SWEEP TIME
DATE 2/11/86
OPERATOR OSOFSKY, J.
REMARKS:
MATCHES 1-N-B
6H
1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM
TMS
CHO
HC=CH
Aromatics

Reaction of the Diallylisopropylmyrtanyltin with 2-chlorobenzaldehyde

This preparation was run on the exact scale as the third reaction with benzaldehyde. The purification techniques were also the same. The new aldehyde was used because the chlorine atom at the ortho position on the ring would add steric hinderance. It was hoped that the steric hinderance would favor a diastereomeric transition state in which one transition state would be preferred over the other to yield one enantiomer.

Table 7

Characteristics of 1-(2-chlorophenyl)-3-buten-1-ol

boiling point = 81°C at 0.5 mm Hg
yield = 46.7%

IR (Figure 17)

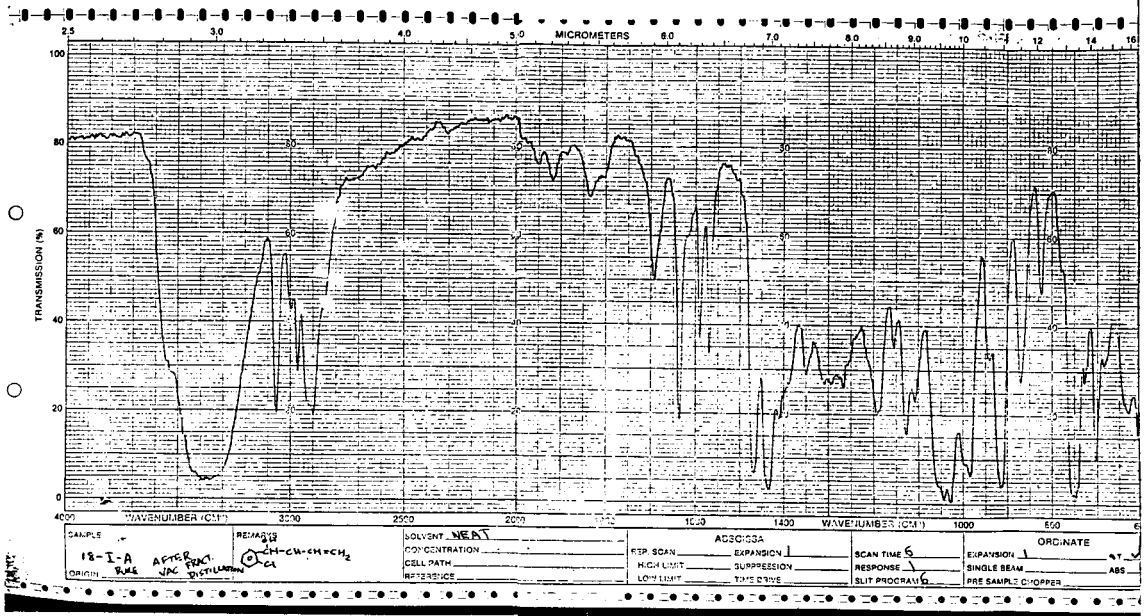
3350 cm^{-1}	strong	-O-H stretch
3100-3000 cm^{-1}	moderate	-C-H stretch
1645 cm^{-1}	strong	C=C stretch
1440, 1470 cm^{-1}	strong	C=C ring stretch
1700 cm^{-1}	weak	C=O stretch

$[\alpha]_D = +0.926^{\circ}$

Once again, the specific rotation was not deemed highly significant as the observed rotation was inconclusive. This indicates that neither transition state was preferred.

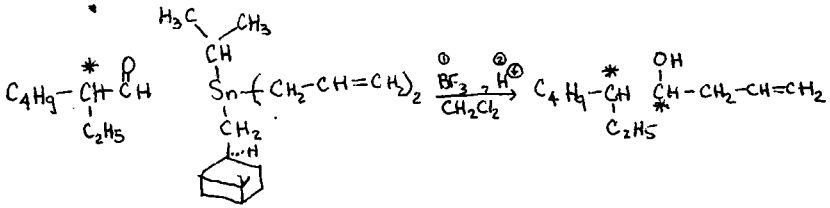
FIGURE SEVENTEEN : IR SPECTRUM OF PURE

1-(2-CHLOROPHENYL)-3-BUTEN-1-OL


MICROMETERS
2.5
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
12
14
16
TRANSMISSION (%)
100
80
60
40
20
0
WAVENUMBER (CM⁻¹)
4000
3500
2500
2000
1800
1600
1400
1200
1000
800
600
SAMPLE
18-I-A
ORIGIN PURE AFTER VAC FRACT. DISTILLATION
REMARKS
SOLVENT NEAT
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
EXP. SCAN
EXPANSION 1
H.CH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME 6
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION 1
%T
SINGLE BEAM
ABS
PRE SAMPLE CHOPPER

Reaction of Diallylisopropylmyrtanyltin with Racemic 2-ethylhexanal

This reaction was prepared on the same scale as the last two preparations. In this case, however, the aldehyde also has a chiral center as indicated below:



The product was purified as before.

Table 8

Characteristics of 5-ethyl-1-nonen-4-ol

boiling point = 53°C at 0.5 mm Hg
yield = 26.3%

IR (Figure 18)

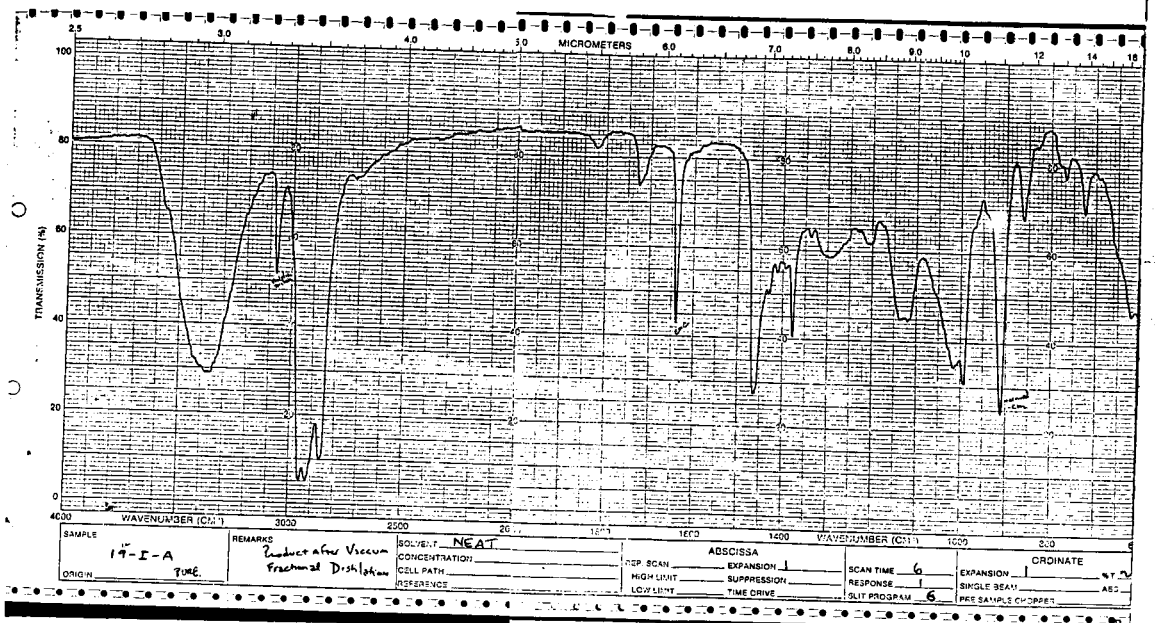
3350 cm^{-1}	strong	-O-H stretch
3070 cm^{-1}	moderate	vinylic stretch
1645 cm^{-1}	moderate	C=C stretch
920 cm^{-1}	moderate	terminal $-CH_2$ stretch

$[\alpha]_D = -0.4°$

The optical rotation was too small to be of any conclusive evidence for any preference of enantiomers.

FIGURE EIGHTEEN : IR SPECTRUM OF PURE

5-ETHYL-1-NONEN-4-OL


2.5
3.0
4.0
5.0
MICROMETERS
6.0
7.0
8.0
9.0
10
12
14
18
100
80
60
40
20
0
TRANSMISSION (%)
4000
WAVENUMBER (CM⁻¹)
3000
2500
2000
1800
1600
1400
WAVENUMBER (CM⁻¹)
1200
1000
800
SAMPLE
19-I-A
ORIGIN
Pure.
REMARKS
Product after Viscous Fractional Distillation
SOLVENT NEAT
CONCENTRATION
CELL PATH
REFERENCE
ABSCISSA
REP. SCAN
EXPANSION 1
HIGH LIMIT
SUPPRESSION
LOW LIMIT
TIME DRIVE
SCAN TIME 6
RESPONSE 1
SLIT PROGRAM 6
ORDINATE
EXPANSION 1
SINGLE BEAM
PRE SAMPLE CHOPPER

EXPERIMENTAL

Part One

Preparation of Racemic 1-phenyl-3-buten-1-ol

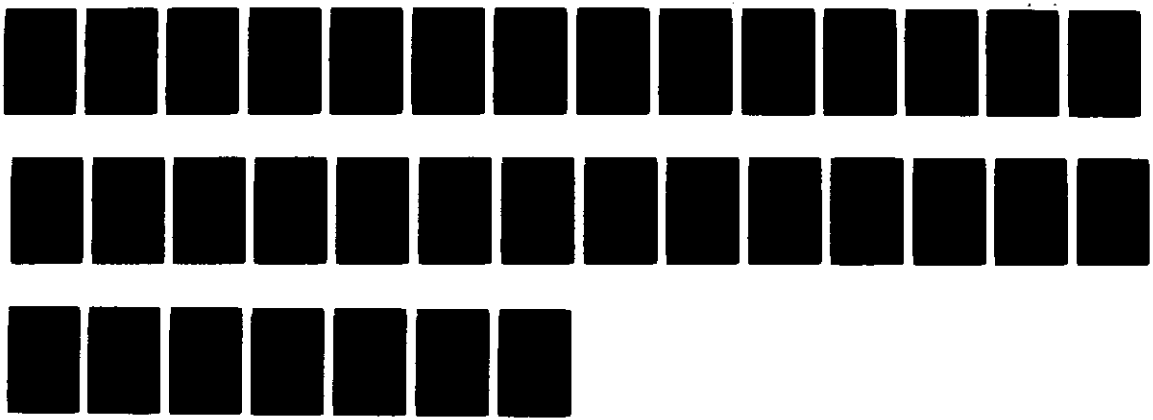
A dry 500-mL round bottom flask was equipped with an addition funnel, reflux condenser, and magnetic stirrer. A N_2 inlet with a bubbler was attached to the top of the reflux condenser. A stir bar, Mg, (8.6 grams, 0.36 moles) and 115 mL of anhydrous Grignard-grade ether were all added to the flask. In addition, a tiny crystal of I_2 was added to the flask. The system was then flushed with a slow stream of N_2 gas.

Thirteen milliliters (0.15 moles) of allyl bromide ($Br-CH_2-CH=CH_2$) and 15 mL of the Grignard-grade ether were added to the addition funnel.

The flask was immersed in an ice bath and the stirrer was turned on. The allyl bromide was added dropwise over a 45 minute period. After the addition funnel had drained, the ice bath was removed, and the solution in the flask was allowed to stir at room temperature for 30 minutes.

The liquid was quickly decanted from the excess Mg into another dry 500-mL flask containing a stir bar. The

UN82 OSOFSKY, J.L. THE SYNTHESIS OF HOMOALLYLIC, etc.
083/1987 Chemistry HRS. 6/87 2 of 2



magnesium was washed with 15 mL of anhydrous ether and this liquid was added to the allyl magnesium bromide. The condenser and addition funnel were reattached to the flask.

Thirteen milliliters (0.12 moles) of benzaldehyde and 20 mL of CH_2Cl_2 were placed in the addition funnel. The flask was immersed in the ice bath and the stirrer turned on. The benzaldehyde was slowly dripped into the Grignar solution. When the addition was complete, the ice bath was removed and the flask was heated with a mantle under reflux for 30 minutes. The mantle was removed and the reaction was allowed to cool to room temperature.

The solution was cooled in an ice bath and the N_2 inlet was removed. Then 25 mL of $NH_4Cl_{(aq)}$ was added to the addition funnel and dripped in slowly with stirring. The ice bath was removed. The layers were separated, the ether phase dried with Na_2CO_3, filtered into a 250-mL flask, and then rotavapped off. An IR was taken to test for excess benzaldehyde. The result was positive. The impure product was vacuum distilled. The product was characterized by IR and NMR. Since the IR contained a C=O peak, the product was dissolved in a solution of 25 mL ether and 25 mL of a saturated $NaHSO_{3(aq)}$ solution

which was separated off. The ether was dried over $MgSO_4$ (anhydrous) which was filtered off. The ether was then rotavapped off. Another IR and NMR were taken to test for the removal of the C=O peak. The pure product was characterized by IR and NMR, Figures 1 and 2 respectively. Later the spectra will be compared to the alcohol produced through an addition of an allyltin reagent to benzaldehyde.

Part Two

Preparation of (-)-cis-myrtanol

A 500-mL round-bottom, 3-neck flask and a 125-mL "self equalizing" addition funnel were heated for 2 hours in an oven at approximately 110°C. They were assembled in the hood. A serum cap was placed over the top of the addition funnel and a N_2 inlet and bubbler was attached to the top of the condenser. A magnetic stirrer was added to the flask and a thermometer was inserted in the third neck. The flask was placed in an ice bath. Forty-eight milliliters (0.30 moles) of (-)-B-Pinene and 100 mL of hexane were added to the round bottommed flask and the system was flushed with N_2. The stirrer was turned on. Borane-methyl Sulfide (BMS) (10.5 mL, 0.12 moles) was added all at once to the addition funnel by way of a syringe and then the BMS was added dropwise over 20 minutes. After the addition, the flask was magnetically stirred for 3 hours at room temperature. One hundred milliliters of absolute ethanol was then added slowly to the mixture followed by 37 mL of 3M NaOH which was added dropwise tc the solution by way of the separatory funnel. The flask was immersed in an ice bath and cooled to 5-10°C internal temperature. At this temperature, H_2O_2

(37 mL, 0.36 moles) was added at a rate so as not to raise the intenal temperature beyond 40°C. When the addition was complete, the solution was allowed to stir for 30 minutes in the ice bath. The ice bath was then removed and the flask was heated in a water bath at 50°C for 1 hour. A precipitate was present at this time, so in order to dissolve it, the flask was heated by the mantle for 30 minutes at 50V.

Once a solution had been obtained, the mixture was poured onto 1 L of ice water in a 2-L flask. Ether, 400 mL, was added and stirred to mix the layers. The layers were separated, the ether layer was washed twice with 200 mL of H_2O per wash and the H_2O discarded after each washing. The ether was then washed with 200 mL of brine, separated, dried over anhydrous K_2CO_3, and filtered. The ether was rotavapped off. An IR was taken of the crude product.

A vacuum fractional distillation was assembled with the pump pulling a pressure between 1.9 and 2.2 mm Hg. An IR (Figure 3) and a NMR (Figure 4) were taken of the distilled product. The actual yield was 68%. A test for optical rotation revealed the following:

$[\alpha]_{obs}$ = -0.82 +/- 0.01°

concentration = 0.0401 +/- 0.0001g/mL

solvent = $CHCl_3$

$[\alpha]_D$= -20.4 +/- 0.3°

The literature value for $[\alpha]_D$= -20.9° [3].

Preparation of (-)-cis-myrtanol (II)

Since this preparation is essentially the same as the previous preparation, only the differences in procedure will be discussed. This preparation entailed doubling the starting materials.

When the rotation measurements, IR and NMR spectra were compared to those of the previous preparation they were identical.

solvent = $CHCl_3$

concentration = 0.0401 +/- 0.0001g/mL

$[\alpha]_D$= -20.2 +/- 0.3°

Because the $[\alpha]_D$ measurements were equal, the products were combined. An optical rotation of the combined product was measured.

solvent = $CHCl_3$

concentration = 0.0401 +/- 0.0001g/mL

$[\alpha]_D$= -20.2 +/- 0.3°

Preparation of the (-)-cis-myrtanol (III)

The (-)- cis -myrtanol was synthesized on the same scale as the last time it was prepared. The NMR and IR verified the product's structure. The yield was 90.1%. The optical rotation determination revealed the following:

solvent = $CHCl_3$

concentration = 0.0484 +/- 0.0001 g/mL

$[\alpha]_D$= 20.2 +/- 0.3°

The myrtanol preparations were combined and the optical rotation taken.

solvent = $CHCl_3$

concentration = 0.0405 +/- 0.0001 g/mL

$[\alpha]_D$= -19.5 +/- 0.8°

The optical purity is equal to (-19.5/20.90) X 100 = 93.3%.

*Polarimeter was erratic. $[\alpha]_{obs}$ may be in error up to 0.03°.

Preparation of the Alkyl Methanesulfonate ("Mesylate") (I)

In the hood a 1-L, round-bottom, two-neck flask was equipped with a thermometer and an addition funnel. A rubber serum cap was placed on the top of the addition funnel and a $CaCl_2$ drying tube was inserted into the serum cap.

A stir bar, myrtanol (38.6g, 0.25 moles), $(C_2H_5)_3N$: (45.2 mL 0.325 moles), and 540 mL of CH_2Cl_2 (the amount of solvent needed to make the alcohol concentration equal to 0.4M) were added to the flask. Methane sulfonyl chloride, $CH_3SO_2Cl_2$ (22.0 mL 0.284 moles) and 45 mL of CH_2Cl_2 were added to the addition funnel.

The flask was immersed in an ice bath and stirred until the internal temperature was 5^{o} +/- 2^{o}. When this temperature range had been reached the CH_3SO_2Cl/CH_2Cl_2 in the addition funnel was slowly added into the flask with rapid stirring so that the internal temperature did not exceed $10^{o}C$. When the addition was completed, 25 mL of CH_2Cl_2 was used to rinse the addition funnel, and then drained into the reaction mixture. The reaction mixture was allowed to stir in the ice bath for 30 minutes. After this time had elapsed, the ice bath was removed and the solution was allowed to stir at room

temperature for 3.5 hours.

The solution was poured over a 50:50 ice:water mixture with the volume of the mixture approximately the same as the volume of CH_2Cl_2 (650 mL). The solution was stirred until the white $(C_2H_5)_3NHCl$ precipitate dissolved and the ice melted. The phases were separated in a funnel and the CH_2Cl_2 layer was saved.

The CH_2Cl_2 phase was washed with 2 150-mL portions of 10% HCl, a 150-mL portion of saturated $NaHCO_3$, and a 150-mL portion of brine.

After being isolated the CH_2Cl_2 phase was dried over 4A molecular sieves, and rotavapped off leaving the crude product. Using a liquid nitrogen trap a high vacuum was pulled on the product over night to remove trace volatiles.

IR (Figure 7) and NMR spectra were taken. There were still traces of CH_2Cl_2 indicated by the NMR so the high vacuum was pulled for 6 more hours while stirring this time. The NMR (Figure 8) confirmed the absence of CH_2Cl_2. An optical rotation was measured:

solvent = $CHCl_3$
concentration = 0.0402 +/- 0.0001 g/mL
$[\alpha]_D$ = -13.7 +/- 0.3°

An actual yield of 92% was calculated.

Preparaton of the Alkyl Mesylates (II)

The same procedure was employed here as previously only the scale of the reaction was doubled. When the high vacuum was pulled overnight, the trap was cooled by a dry ice/acetone slush bath instead of liquid nitrogen, and a stirrer was utilized. An IR was run and it matched Figure 7. The same correspondence held for this NMR and Figure 8. An optical rotation was determined as follows:

solvent = $CHCl_3$

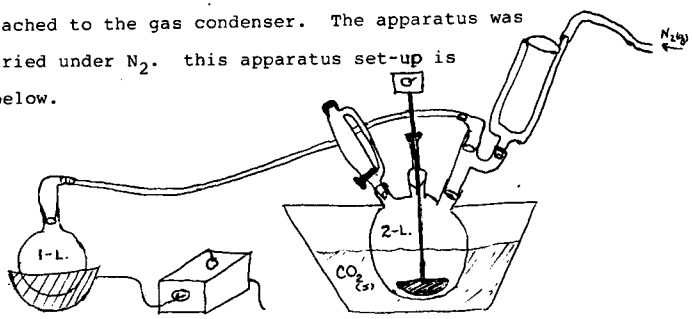
concentration = 0.0402 +/- 0.0001g/mL

$[\alpha]_D$= -13.9 +/- 0.3°

This specific rotation matched that of the previous preparation. The product was stored in the refrigerator under N_2.

Preparation of Triphenylmyrtanyltin (TMT)

A 2-L, 3-neck, round-bottom flask was equipped with a self-equalizing addition funnel, a gas condenser, and a mechanical stirrer. The 2-L flask was set in a styrofoam container. A one-neck, 1-L round-bottom flask was connected by a Tygon® tube to the 2-L flask. A heating mantle was placed under the 1-L flask and attached to a rheostat. A N_2 inlet and bubbler was attached to the gas condenser. The apparatus was flame-dried under N_2. this apparatus set-up is shown below.



Triphenyltin chloride, (95.61g, 0.248 moles), was added to the 2-L flask along with 500 mL of ether. The gas condenser and styrofoam container were stocked with dry ice. Liquid ammonia, 500 mL, was poured into the 1-L flask and a small piece of sodium metal, Na^0, was added to the NH_3. Whenever the NH_3 turned back to colorless, another fragment of Na^0 was added.

The Na^0 dries the NH_3. The rheostat was turned to 70V to distill the liquid NH_3 into the reaction flask. When most of the NH_3 had distilled over, the adapter was stoppered and the mantle turned off.

Sodium metal, (12.3g, 0.533 moles), was cut into small fragments after the oxide coat was removed. The fragments were dunked in ligroin then placed into a cyclohexane solution before being added to the NH_3 ether solution.

In small fragments, sodium was added to the 2-L flask until the solution reached its endpoint -- a blood red color. When this color had been reached, the CO_2 bath was removed, but the CO_2 condenser was kept filled.

After 45 minutes, 53.58g (0.23 moles) of the myrtane mesylate and an equal volume of ether were placed in an addition funnel, and were added to the reaction mixture all at once. The CO_2 was kept packed in the condenser. The solution turned to a final gray color, and the N_2 inlet was taken off. The remaining NH_3 was let evaporate over night.

Ether, 190 mL, and 500 mL of distilled water, were added to the mixture and the phases were stirred. The solution was transferred to a separatory funnel and the

organic layer saved. The ether layer was washed once again with one third its volume of water. After separating the layers, the ether layer was dried with anhydrous Na_2CO_3, then the Na_2CO_3 was separated by filtering the mixture through fluted filter paper, and the ether was rotavapped off (60°C water bath temperature). The residue was cooled in ice. A NMR was taken to verify that all the mesylate had been reacted. This was confirmed because there was no peak at 3 ppm where the $-SO_2CH_3$ hydrogens would be located. The product was left to stand open in the hood over night to let any trace volatiles evaporate.

A recrystalization in absolute ethanol was performed and from this a solubility was calculated equal to 0.144g/mL at 78.5°C. When crystallization had occurred the crystals were filtered (Buchner funnel). In order to get a maximum yield the ethanol volume was reduced and another recrystalization was performed. Masses and melting points were recorded for both crops.

Table 9

Triphenylmyrtanyltin Crop Data (I)

	Mass	Melting Point	Yield
Crop 1	74.58g	74 - 75°C	66.6%
Crop 2	20.45g	58 - 74°C	18.2%

optical rotation of Crop #1

solvent = $CHCl_3$
concentration = 0.0400 +/- 0.0001g/mL
$[\alpha]_D$ = -14.0 +/- 0.3°

Using the percent optical purity of the myrtanol, the maximum possible rotation of the TMT equaled 14.5°.[1]

The NMR spectrum of the pure product is labelled Figure 9.

Preparation of TMT (II)

This procedure is the same as the first time only double the scale. A total of 30.0g (more than double the previous amount) of Na^0 was added to the reaction mixture. In addition all the mesylate was added without any ether. The workup was the same as before. Five crops were recovered from the recrystalization process. Yields and melting points were calculated and can be found in the table below. Blank spaces indicate data which was not collected because the crops contained

impurities and therefore had no distinct melting ranges.

Table 10

Triphenylmyrtanyltin Crop Data (II)

	Mass	Melting Range	Yield
Crop 1	69.10	69 - 71°C	35%
Crop 2	28.95	70 - 72°C	15%
Crop 3	47.97		
Crop 4	25.39		
Crop 5	14.68	70 - 71°C	8%

The three pure crops (#1,2,5) were recrystalized in absolute ethanol together and two crops of crystals were collected. The recrystalized crops had melting ranges between 70-73°C. It was therefore decided to combine the crystals. The total mass equalled 61.7g (0.13 moles), which is a yield of 28.3%.

$[\alpha]_D$= -14.5 +/- 0.6°
solvent = $CHCl_3$
concentration = 0.0401 +/- 0.0001g/mL

This value is equal to the specific rotation taken of the first TMT preparation.

The following is the result from the elemental composition test of the TMT done at Galbraith Laboratories Inc., Knoxville, TN.

	Theoretical	Actual
C%	68.88	68.85
O%	6.81	6.77

This correlation is excellent.

Part Three

Bromination of TMT

A 2-neck, 2-L round-bottom flask with a stir bar was placed in an ice bath, which could be removed. The stirrer was placed under the ice bath. The center neck was occupied by a 250-mL self-equalizing addition funnel while the side neck was stoppered with a glass stopper.

The TMT (136.42g, 0.28 moles) was added to the flask; 450 mL of CCl_4 was added before all the TMT dissolved. The flask was cooled in ice and 150 mL of CH_3OH was added to the solution, along with 100 mL more of CCl_4. The lights in the hood were shut to minimize bromine free radical reactions.

In four equal additions 44.74g (0.28 moles) of bromine was added to the reaction mixture at a slow drip with rapid stirring. Each 11g portion was diluted with 10 mL of CCl_4 in the addition funnel. After all four additions the funnel was rinsed with 50 mL of CCl_4. The total time for the addition was 4 hours.

The mixture was rotavapped down (temperature of water bath 50°C). A high vacuum was drawn on the product for 5 hours while stirring to remove volatiles (bromobenzene and CCl_4). A dry ice trap was used.

Preparation of Isopropylmagnesium Bromide

A 500-mL, 3-neck round-bottom flask was set in a heating mantle and equipped with a mechanical stirrer, a 250-mL addition funnel, and a reflux condenser.

Magnesium (17.017g, 0.70 moles) was added to the flask with 25 mL of Grignard-grade ether. The stirrer was started. Five milliliters of 2-bromopropane was added to 10 mL of ether in the separatory funnel and both were added to the flask all at once. Four additions, each containing 17.5 mL of 2-Bromopropane (0.805 moles total) and 54 mL of ether, were added to the flask at a rate slow enough to prevent the ether from boiling out, but fast enough to cause reflux. The total addition time was 1.5 hours. After the additions were complete, the mantle was turned on to cause refluxing for 30 minutes. The flask was allowed to cool to room temperature and the top of the reflux condenser was stoppered.

Preparation of Diallylisopropylmyrtanyltin

The Grignard from the previous preparation was transferred to a 3-neck, round-bottom flask which had a mechanical stirrer in the center neck and rubber stopples over the side necks. The transfer was executed with a double-tipped transfer needle which was inserted in the left neck of the 500-mL flask from the previous preparation (on which a stopple was placed) and in the right neck of the 1-L flask. Pressurized nitrogen pumped the Grignard solution from the 500-mL flask to the 1-L flask. When most all of the Grignard had been transferred, a 20-mL portion of ether rinsed the Mg then was transferred. This was done twice more. The needle and two serum caps were removed and the 1-L flask was equipped with a 125-mL addition funnel and a condenser.

The solution was placed in an ice bath. When the Grignard was cold the brominated organotin was added dropwise, neat, at a rate so as not to cause boiling over. Two 20-mL portions of ether were used to wash the original tin flask and the addition funnel. The ether was drained into the reaction mixture.

The ice bath was removed and the heating mantle was attached. The solution was refluxed for 45 minutes. The ice bath was then replaced after the 45 minutes had elapsed. Deionized water, 100 mL, was added to the

reaction mixture slowly so as to neutralize any extra Grignard, and to prevent boiling over.

The supernatant was poured into a 1-L Erlenmeyer flask. Ether, 100 mL, was added to the solid white precipitate to remove any trapped product. The solid was broken-up with glass rods. The mixture was swirled and filtered through fluted paper. The funnel drained into the 1-L Erlenmeyer. This was repeated with a second 100 mL of ether.

The solution was dried with anhydrous $MgSO_4$, and filtered. The $MgSO_4$ was washed with two 50-mL portions of ether, and the solution was rotavapped. A high vacuum was pulled for 4 hours to remove last trace volatiles. An IR was taken of the crude product.

Preparation of Dibromoisopropylmyrtanyltin

This preparation was run exactly like the first bromination. The crude product from the previous preparation was used unpurified. Both remaining phenyl groups were replaced by bromine atoms. The solvent was 350 mL CCl_4, and 150 mL of CH_3OH. The bromine (75.0g, 0.47 moles) was added in 11g portions, as before. Any extra Br_2 was let evaporate overnight while stirring. The product was rotavapped down then placed on a high vacuum for 5 hours.

Preparation of Allylmagnesium Bromide

A 2-L, 3-neck, round-bottom flask was equipped with a reflux condenser, a mechanical stirrer, and a 125-mL separatory funnel. The flask was immersed in an ice bath.

Magnesium (58.3g, 2.4 moles), was added to the flask with 767 mL of Grignard-grade ether. Allyl bromide (87 mL, 1.00 mole) was added to the addition funnel. A rubber serum cap was placed over the top of the addition funnel. A small hole was pierced in it so there would be no pressure build-up and not much would evaporate. A tiny I_2 crystal was added to the flask and prior to the addition, the flask was allowed to cool with the stirrer on.

The allyl bromide was added slowly over 1.5 hours with rapid stirring. The funnel was then washed with two 25-mL portions of ether and then the ether was added to the flask. The ice bath was removed and the solution was allowed to stir for 45 minutes. The Grignard was transferred to another 2-neck, 2-L flask by way of a double-tipped needle as described earlier.

Preparation of Diallylisopropylmyrtanyltin

The 2-L flask was placed in an ice bucket. In one-neck a reflux condenser was attached with a N_2 inlet and bubbler in the top of the condenser. A three-neck adapter was placed in the remaining neck of the flask. The mechanical stirrer was placed in one arm while a 125-mL addition funnel was placed in the other.

The ice bucket was filled with ice and the stirrer started. The diallylisopropylmyrtanyltin prepared earlier was placed in the addition funnel. A serum cap with a small hole in the top was placed over the addition funnel. The addition was made so there would be minimal condensation in the condenser. The funnel was washed with 20 mL of ether after the addition was completed. The ice bath was then removed and a heating mantle was placed under the flask. The solution was heated at reflux for 45 minutes. The mantle was removed and the ice bath replaced. Deionized H_2O, 120 mL, was added to the flask slowly with stirring so there would be no condensation in the condenser. The N_2 inlet was removed and a stopper put in place.

The ether layer was poured off into a 1-L Erlenmeyer flask. One hundred milliliters of wet ether was added to the solid left behind to release any trapped product. This involved breaking up the solid. The solid salts

were washed twice more with 50-mL portions of ether. The ether was then rotavapped off.

A vacuum fractional distillation apparatus with a liquid nitrogen trap was assembled. The major product was collected at 125°C at a pressure of 0.3 to 0.5 mm Hg. The IR spectrum of the pure product is Figure 10. The NMR spectrum is Figure 11. The mass of the pure product was 86.79g total, a yield of 22.8% assuming all the previous Grignard reactions went to completion.

Two optical rotation determinations were executed since the product was collected in two flasks. Results are as follows:

solvent = $CHCl_3$.

	Concentration	$[\alpha]_D$
Flask 1	0.0400+/-0.0001	-23.0+/-0.3°
Flask 2	0.0401+/-0.0001	-23.2+/-0.3°

These rotations are equivalent.

An elemental analysis of the product was performed by Galbraith Laboratories. Results are as follows.

	Actual	Theoretical
%C	53.35	59.87
%O	8.13	8.99

The agreement is relatively good. The agreement is not excellent because of some impurities which show up in Figure 11, such as unreacted phenyl groups. These impurities should not affect later reactions, as discussed in the Results and Theory section.

Part Four

Addition Reactions

Reaction of Diallylisopropylmyrtanyltin with Benzaldehyde

Preparation of 1-phenyl-3-buten-1-ol (I)

Distilled benzaldehyde, 5.0-6.0 mL (0.05 moles) was added to a 250-mL, 19/22 round-bottom flask. A stir bar and 50 mL of CH_2Cl_2 were also added to the flask. The flask was flushed with nitrogen gas and was sealed with a serum cap and wired shut. The flask was immersed in a dry ice bath for 15 minutes with the stirrer on. After the 15 minutes 6.1 mL (0.05 moles) of distilled $BF_3{\cdot}O(C_2H_5)_2$ was added to the solution with a syringe. The solution was vented when any solution was being added and then flushed with nitrogen. This mixture was stirred for ten minutes in the dry ice. Then, using proper venting techniques, 7.71g (0.02 moles) of the diallylisopropylmyrtanyltin was added to the flask. The mixture was stirred in the dry ice for 15 minutes, then in an ice bath for 4.25 hours. The ice bath was removed and the mixture stirred for 2-3 days at room temperature.

The flask was again immersed in ice. The serum cap was removed once the mixture had cooled. Deionized water, 25.0-30.0 mL, was added to the mixture slowly with just enough stirring to mix phases but not so much as to cause it to foam out of the flask. After the bubbling had ceased, the two phases were separated and the organic phase saved, washed with two 25-mL portions of saturated $NaHSO_3$, and a 25-mL portion of deionized water.

The organic phase was dried with anhydrous $MgSO_4$ and filtered through fluted paper. The CH_2Cl_2 was rotavapped off (water bath temperature of $35^{\circ}C$).

An IR (Figure 12) was run. This spectrum showed a carbonyl peak at 1700 cm^{-1}, so the procedure was repeated from the washings with the $NaHSO_3$. An IR (Figure 13) after this showed the same peak reduced by half.

A micro vacuum fractional distillation apparatus was set up with a dry ice trap. The reaction mixture did not distill: it burned. The few drops of liquid which did flow over were not what was wanted, as determined by a NMR spectrum.

Preparation of 1-phenyl-3-buten-1-ol: (II)

The procedure for this experiment was exactly as the

previous preparation except for the amounts of reagents used. There were only 25 mL of CH_2Cl_2 used, 3.1 mL (0.03 moles) of benzaldehyde used, 3.7 mL (0.03 moles) of $BF_3 \cdot O(C_2H_5)_2$ and 7.60g (0.02 moles) of the tin compound used. It was assumed that only one allyl group per diallylisopropylmyrtanyltin reacted. This was the reason for the downscale. The reaction was carried out in a 100-mL flask.

The work-up was quite different from the previous preparation. Until the $NaHSO_3$ addition everything was done as before. Then 25 mL of CH_2Cl_2 was added. After this the $NaHSO_3$ was added in four separate 25-mL portions, separating it out between washings. Deionized water, 25 mL, was added then separated. The organics were dried with anhydrous $MgSO_4$ and filtered. The CH_2Cl_2 was rotavapped off.

A column chromatograph was set up in a cylindrical funnel. It had cotton at the bottom, 0.5 inches of sand, 30-40g of silica gel, then another 0.5 inches of sand (vertical order). The product was poured onto the column. A 300-mL mixture of 250 mL hexanes and 50 mL ether was made to flush the column. Two 100-mL portions

of eluant were collected and rotavapped down yielding a more purified product.

Potassium fluoride, 100g, was dissolved in 225 mL of water. The rotavapped product was dissolved in 25 mL of ether in a 250-mL Erlenmeyer and an equal volume of KF solution was added and stirred for 30 minutes. Then 10 mL of ethyl acetate and 50 mL of ether were added to the mixture to separate the layers. Three phases were seen: the KF, R_3SnF (reacted tin salts), and the top organic layer. The KF layer was discarded and the remaining phases were filtered through fluted paper. The ether layer was dried with anhydrous $MgSO_4$, filtered, then rotavapped off.

An IR (Figure 14) was taken. In addition to the alcohol peak at 3450cm^{-1}, a peak at 1745 cm^{-1} was present which was determined to be from the ethyl acetate. It was decided to perform the reaction on a larger scale as there was not enough product at the present time to proceed with a vacuum fractional distillation.

Preparation of 1-phenyl-3-buten-1-ol: (III)

This preparation was run exactly like the previous two except on a different scale. Benzaldehyde, 4.6 mL (0.045 moles), was used along with 5.5 mL (0.045 moles)

of $BF_3 \cdot O(C_2H_5)_2$, 15.21g (0.040 moles) of the tin compound, and 75 mL of CH_2Cl_2.

The workup had some minor changes from the last time. The serum cap was removed and instead of adding water, 25 mL of 10% $NaHCO_3$ was added with stirring. The pH of the solution was checked. In order to reach a pH of 8 (indicator paper) an additional 25 mL of $NaHCO_3$ was added. After separating the aqueous phase, the organic layer was washed with two 50-mL portions of $NaHSO_3$. After rotavapping the CH_2Cl_2 off, the organics were mixed with the ether and KF solution and, as before, stirred, and separated. The ether was dried and rotavapped off. An IR showed no carbonyl at 1700 cm^{-1}. A column was prepared as before and the eluting solvent was changed to 250 mL hexanes and 50 mL ethyl acetate. Two 100-mL portions were collected. An additional 50 mL was collected to make sure most of the product had flowed through the column. The 250 mL of solution was rotavapped down with a water bath temperature of 60°C to make sure all the ethyl acetate was removed. The product was combined in one flask and the flask was placed under a high vacuum for four hours to remove any volatiles.

A vacuum fractional distillation was set-up. At

67°C and a pressure of 0.5 mm Hg, 2 mL of clear, colorless liquid was collected. The mass of the liquid was 2.05g, a 39% yield of 1-phenyl-3-buten-1-ol. An IR (Figure 15) was taken and matched that of the Grignard-produced alcohol (Figure 1) except for a peak at 1700 cm^{-1}.

Thin layer chromatography was performed. Spottings of the reacting tin compound were made as well as the alcohol produced by the Grignard and the alcohol just purified. The results of the chromatographs were inconclusive.

Rather than trying to purify the alcohol further, it was decided to try an optical rotation determination. Results are as follows:

concentration = 0.0683 +/- 0.0001g/mL

$[\alpha]_{obs} = +0.06^{\circ}$

solvent: C_6H_6

$[\alpha]_D = +0.876^{\circ}$

The $[\alpha]_{obs}$ was not believed to be of any significance. Therefore the same holds true for the specific rotation. Literature values for each enantiomer are R $[\alpha]_D = +48.3^{\circ}$ [4], S $[\alpha]_D = -48.7^{\circ}$ [5].

An NMR (Figure 16) of the product matched that of Figure 2, the NMR of the Grignard produced alcohol.

Reaction of Diallylisopropylmyrtanyltin with ortho -chloro Benzaldehyde

Preparation of 1-(2-chlorophenyl)-3-buten-1-ol:

The procedure was run exactly like the previous preparation with benzaldehyde except o-chlorobenzaldehyde, 3.4 mL (0.045 moles), was substituted for the benzaldehyde. The product distilled over at 81°C at a pressure of 0.5 mm Hg. A yield of 46.7% was achieved. The product was characterized by an IR spectrum (Figure 17).

An optical rotation was determined prior to any other tests.

concentration = 0.0756g/mL

solvent = $CHCl_3$

$[\alpha]_{obs} = +0.07^{\circ}$

$[\alpha]_D = +0.926^{\circ}$

Once again this result was judged to be insignificant. No other tests were initiated.

Reaction of Diallylisopropylmyrtanyltin with 2-ethylhexanal

Preparation of 5-ethyl-1-nonen-4-ol

The same procedure was employed as in the past two preparations. Distille 2-ethylhexanal (b.p.=53°C, 0.5 mm Hg, 0.045 moles) was used in the addition reaction. Two milliliters of 5-ethyl-1-nonen-4-ol was collected, a yield of 26.3%. The product was characterized by an IR spectrum (Figure 18). An optical rotation test was performed.

concentration = 0.0747 +/- 0.0001g/mL

solvent = $CHCl_3$

$[\alpha]_{obs}$ = -0.03 +/- 0.01°

$[\alpha]_D$ = -0.40°

Once again this measurement was deemed to be insignificant. No further tests were performed.

CONCLUSION:

(-)-B-Pinene will rotate the plane of polarized light because there is an excess of one enantiomer and there are three chiral centers. The compound is bulky and therefore will contribute some steric hinderance to an organotin molecule once it is attached to the tin atom. The attachment to the tin atom can be made once the Pinene has been converted to the alkyl methanesulfonate by way of an alcohol, intermediate myrtanol. Through a tin anion preparation, a new optically active compound, triphenylmyrtanyltin (TMT), was synthesized.

Through successive brominations and Grignard reactions, the phenyl rings were replaced since the rings are large and would stericly inhibit any reaction. The end product of these reactions was the optically active diallylisopropylmyrtanyltin. Because the isopropyl group is moderately bulky and stericly hindered, any reactions must involve the allyl groups.

In theory the organotin should react with the aldehyde in the presence of a Lewis acid to form the alcohol. What was not clear was whether or not the system could be altered so that a diastereomeric transition state would be formed. This transition

complex was described in detail in the background section. The "system" is composed of two independent entities -- the organotin and the aldehyde. It was suspected, though, that the more important component was the optically active organotin, as the absolute configuration and steric hinderance theoretically dictate the mechanism of the reaction.

The alcohol was formed in all three systems tested. The formations were confirmed by IR spectra. The alcohols were also isolated from the reacted and unreacted diallylisopropylmyrtanyltin in every case. The results of the individual polarimetry measurements, however, tend to indicate that none of the three systems tested proceeded through a diastereomeric transition state which would have selectively produced only one enantiomer. In all cases $[\alpha]_{obs}$ was very small. Once again the assumption being made is that there is a large enough energy difference between the two transition states for one state to be preferred. This result confirmed the suspicion that the aldehyde involved does not alone significantly change the results of the polarimetry test. Therefore if the system does react to yield one enantiomer the organotin must be involved directly. The tin compound used for this series of experiments may not have had a large enough difference

between the activation energies which is probably a result of the amount of steric hinderance the molecule posesses.

Logically, the next step in this quest to obtain a system which has a diastereomeric transition state with a large enough energy difference, is to vary the sidegroups on the tin atom and test the new molecule by reacting it with various aldehydes in the presence of a Lewis Acid. The delicate balance to be achieved is to find an organotin with enough steric hinderance to affect the reaction but not so much that the reaction will be inhibited.

Endnotes

1. Holding and Ross, Journal of American Chemical Society, 145 , pages 383-387 (1954)
2. Ibid. , pages 383-387
3. Zurefel and Brown, Journal of American Chemical Society, 86 , pages 363-397, (1964)
4. Holding and Ross, pages 383-387
5. Ibid. , pages 383-387

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