UNIVERSITY OF ILLINOIS

May 13 1987

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Linda Hu

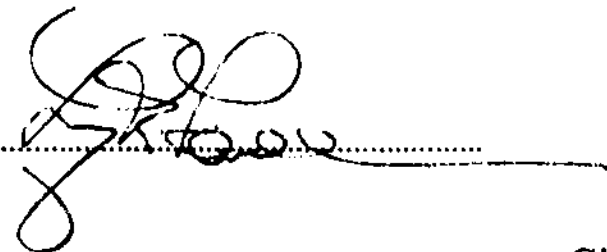ENTITLED A Partial Synthesis of Thyrsiferol

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemistry

C.A. BROKA

Instructor in Charge

APPROVED:

HEAD OF DEPARTMENT OF Chemistry

O-1364

A Partial Synthesis
of
Thyrsiferol

by
Linda Hu

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Thesis

for the
Degree of Bachelor of Science
in
Chemistry

College of Liberal Arts and Sciences
University of Illinois
Urbana, Illinois

1987

# TABLE OF CONTENTS

INTRODUCTION

Thyrsiferol is a tetracyclic ether with cytotoxic[1] and antiviral properties. More specifically, it has potential against lymphocytic leukemia cells.[2] When thyrsiferol was combined with venustatriol and thyrsiferol 23-acetate, it had activity against vesicular stomatitis virus and herpes simplex virus type I. All three components were extracted from marine red algae belonging to the genus Laurencia.[3]

The structures of thyrsiferol determined by Sakemi, et. al.[4] and Suzuki, et. al.[5] were not entirely accurate. The correct structure is given below.[6]
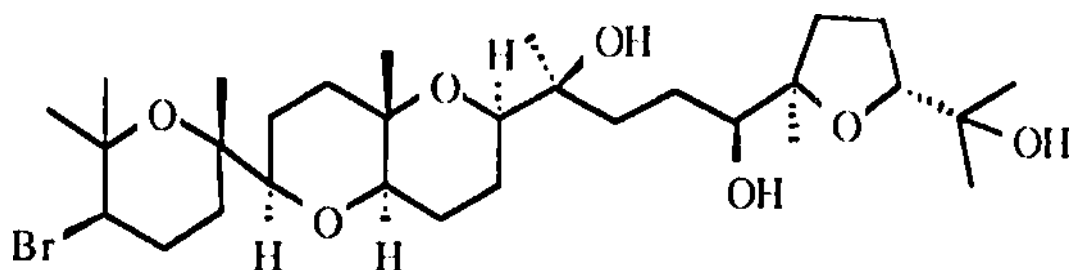
The synthesis of the left half of thyrsiferol and venustatriol is now being attempted.
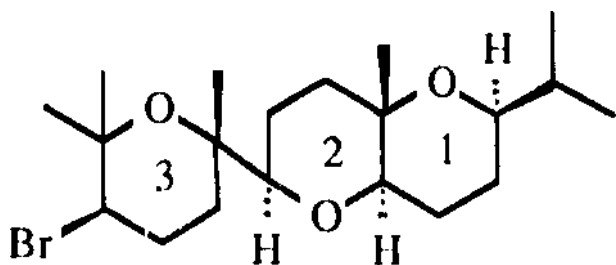
How ring 1 was made will be dealt with here.

All the reactions in the synthesis of ring 1 were conducted under argon atmosphere. Reaction flasks were first filled with argon and stopped by rubber septums. Then argon-filled balloons attached to plastic syringe tubes with metal needles were inserted into the septums, replenishing the supply of argon in the flasks. All the distillations were done under house vacuum, with a pressure of roughly 300 mm Hg. All column chromatography were done using SiO_2 flash columns. NMR spectrums were taken on the EM-390, XL-200, or QE-300 using TMS as a reference, and IR spectrums were taken on the IBM IR/32 spectrometer. Lastly, all ^{1}H- and ^{13}C-NMR spectrums were done using $CDCl_3$ as the solvent.
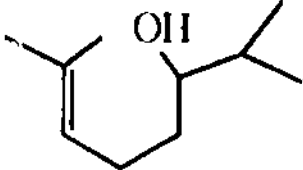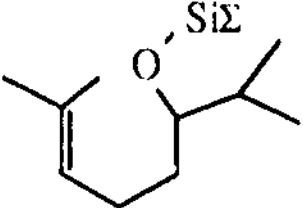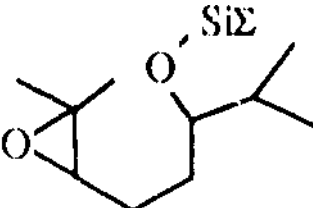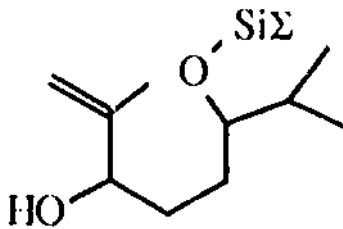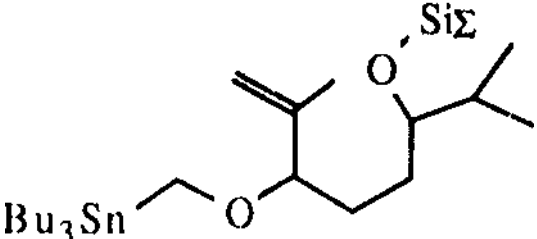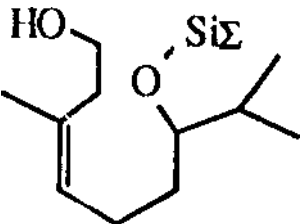
On the next two pages, new intermediate structures and their molecular formulas and weights were shown.

EXPERIMENTAL PROCEDURES

Claisen Rearrangement to an Aldehyde
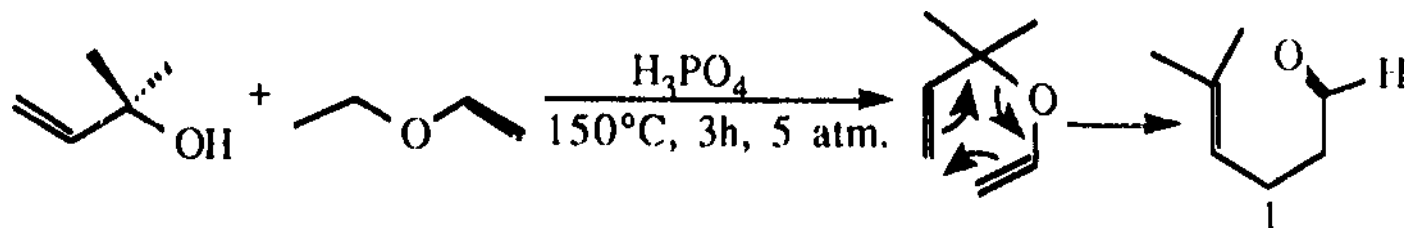
The procedure for this reaction was taken from a paper by Marbet and

Structure	Molecular Formula
	$C_{10}H_{20}O$ (156.27)
	$C_{16}H_{34}OSi$ (270.54)
	$C_{16}H_{34}O_2Si$ (286.54)
	$C_{16}H_{34}O_2Si$ (286.54)
	$C_{29}H_{62}O_2SiSn$ (589.60)
	$C_{17}H_{36}O_2Si$ (300.57)

Structure	Molecular Formula
	$C_{18}H_{37}O_4SSi$ (378.65)
	$C_{18}H_{34}NOSi$ (309.57)
	$C_{12}H_{21}NO$ (195.31)
	$C_{14}H_{20}HgF_3NO_3$ (513.30)
	$C_{12}H_{20}HgClNO$ (430.34)
	$C_{12}H_{21}NO_2$ (211.31)
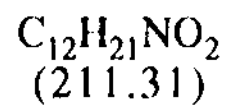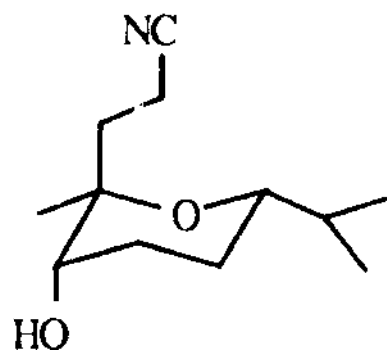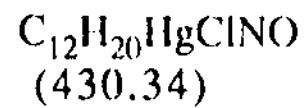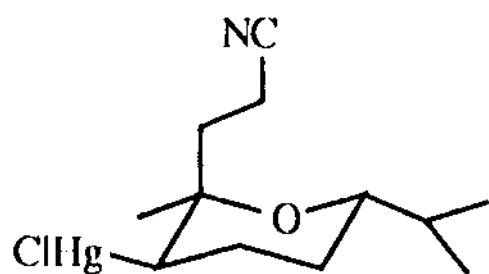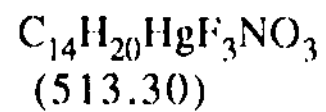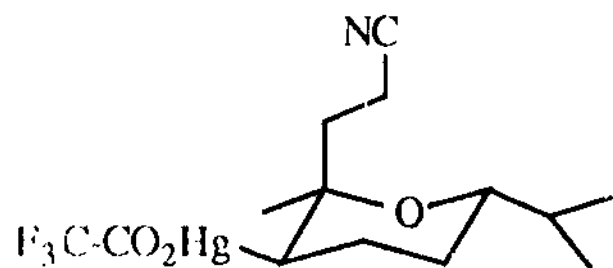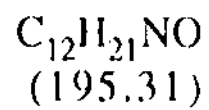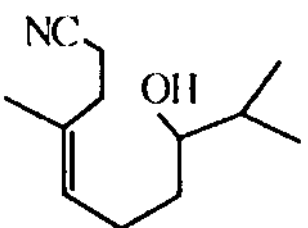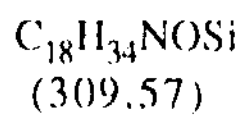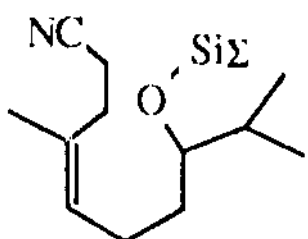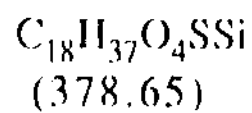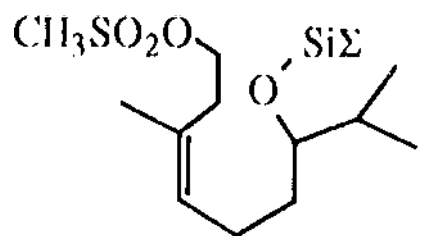
Saucy. 2-methyl-3-buten-2-ol (30.0g, 36.4mL, 350mmol), vinyl ethyl

ether (52.3g, 69.4mL, 730mmol), and 85% phosphoric acid (61mg, 0.12mL)

were combined in an argon-filled pressurized container. The mixture was

heated to 150°C in an oil bath for about 1.5h. The resulting golden brown

solution was then allowed to cool to room temperature and neutralized

with triethylamine (0.70mL, 511mg). Distillation using a vigreaux column

gave the unreacted ether at 27-34°C, the biproduct acetaldehyde at

40-45°C, and the product 5-methyl-4-hexen-1-al 1 at 95-110°C.[7]

The aldehyde 1 was characterized by ^{1}H- NMR: 1.60 (d, J=5Hz, 5H),

2.2-2.4 (m, 4H), 4.9-5.2 (s, 1H), and 9.63 (s, 1H). The spectrum was taken

on the 390.

Grignard Reaction to an Alcohol
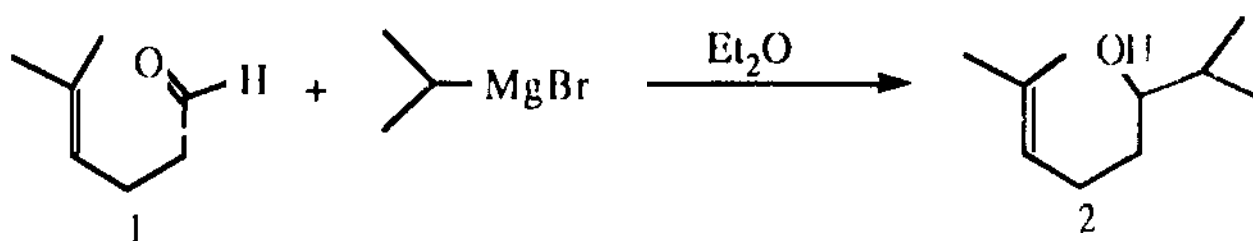
A dry, argon-filled, 500-mL three-necked flask was equipped with an

addition funnel, stirring bar, reflux condensor, and drying tube.

Magnesium turnings (2.49g, 102mmol) and dry ether (135mL) were added

to the flask and stirred for about 5 min. at room temperature until the mixture had become cloudy. Then it was treated with a solution of 2-bromopropane (12.60g, 9.62mL, 102mmol) in dry ether (66mL) dropwise for about 1 h. The Grignard reagent was stirred for 0.5 h after the addition, then it was cooled in a dry ice-acetone bath.

The aldehyde 1 (6.76g, 60mmol) was added to the cooled solution over a 20 min. period, and the reaction mixture was allowed to warm to room temperature gradually. After stirring for 1.5 h, the reaction was quenched with saturated ammonium chloride solution. In a 1-L separatory funnel, the ether and aqueous layers were isolated. The aqueous layer was washed with ether, then the combined ether layers were washed twice with saturated NH_4Cl, $NaHCO_3$, and brine each. The organic solution was dried over $MgSO_4$ then filtered through glass wool. Ether was evaporated to give the alcohol 2. The crude product was then purified by distillation with a vigreaux column, and the resulting clear liquid 2 had a boiling range of 135-175°C and a 71.98% yield (6.78g, 43mmol).

The ^{1}H-NMR spectrum of the alcohol 2 on the 390 was as follows:

0.90 (d, J=8Hz, 6H), 1.40 (s, 1H), 1.50 (s, 4H), 1.67 (d, J=6Hz, 6H), 2.09 (q, J=6Hz, 1H), 3.31 (m, J=4Hz, 1H), and 5.13 (t, J=7Hz, 1H).

Protection of the Alcohol to a Silyl Ether
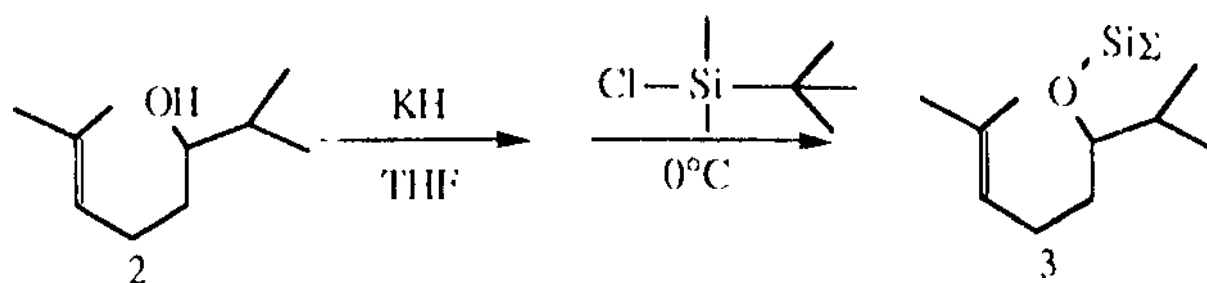
Potassium hydride (2.35g, 59mmol) was added to a dry, round-bottomed flask containing tetrahydrofuran (THF) (40mL). A solution of THF (20mL) and the alcohol 2 (6.15g, 39mmol) was added to the flask dropwise. An open syringe was inserted in the septum in the neck of the flask to let out H_2 gas, which was formed by the reaction of potassium hydride and the hydrogen in the alcohol group. Total addition time was around 0.5 h, with the latter half of the alcohol added at 0°C. Then the rust-colored mixture was stirred for 15 min. at room temperature.

The mixture was treated to t-butyldimethylchlorosilane (9.19g, 61mmol), turning it cloudy yellow. The flask was returned to the ice bath

when it was growing warmer. The contents were stirred for 1 h and then

quenched with water. The solution was worked up with ether/water and

washed with brine. Then it was dried over $MgSO_4$ and filtered using a

Buchner funnel. After evaporation and distillation with a vigreaux column,

the yellow silyl ether **3** had a boiling range of 99-105°C and a 54.18% yield

(5.77g, 21mmol).

^{1}H-NMR on the 300: 0.87 (m, J=6Hz, 15H), 1.39 (q, J=8Hz, 2H), 1.60 (s,

6H), 1.68 (s, 8H), 1.97 (m, J=9Hz, 1H), 3.42 (q, J=5Hz, 1H), and 5.01 (t, J=6Hz,

1H). IR (neat) (cm^{-1}): 1076 (C-O stretch), 1360 (CH_2, CH_3 bend) , 1385

(CH_2, CH_3 bend), 1472 (CH_2, CH_3 bend), and 2938 (C-H stretch).

Epoxidation of the Olefinic Group
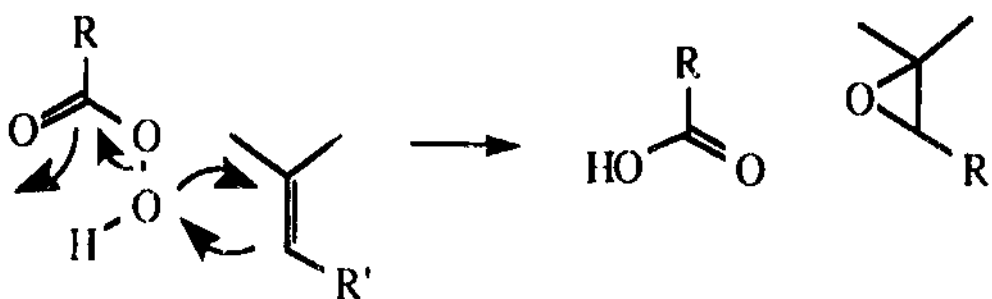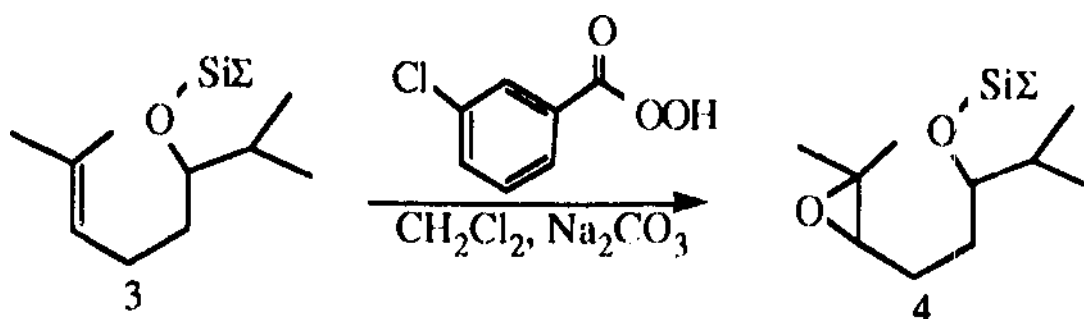
Dichloromethane (120mL), 85% 3-chloroperoxybenzoic acid (6.07g, 35mmol), sodium carbonate (3.7g, 35mmol), and the olefin 3 (5.70g, 21mmol) were added into a dry round-bottomed flask. The sodium carbonate served to neutralize the 3-chlorobenzoic acid that would be forming. After 2 h or when a drop of the reaction mixture would not blacken starch paper, drops of dimethyl sulfide were added to destroy the remaining acid. The finished reaction was treated to a $CH_2Cl_2/NaHCO_3$ work-up. Then it was dissolved in ether and washed with water, and the solvents were removed *in vacuo*. The weight of the epoxide 4 (6.09g, 21mmol) was a little more than the calculated value (6.04g), so 100% yield was assumed.

^{1}H-NMR on the 390: 0.8-1.0 (d, 18H), 1.33 (d, J=3Hz, 9H), 1.4-1.8 (s, 5H), 2.6-2.8 (s, 1H), and 3.3-3.5 (s, 1H).

Dehydrogenation to an Allylic Alcohol

BuLi + HNEt$_2$ → Li$^+$ $^-$NEt$_2$
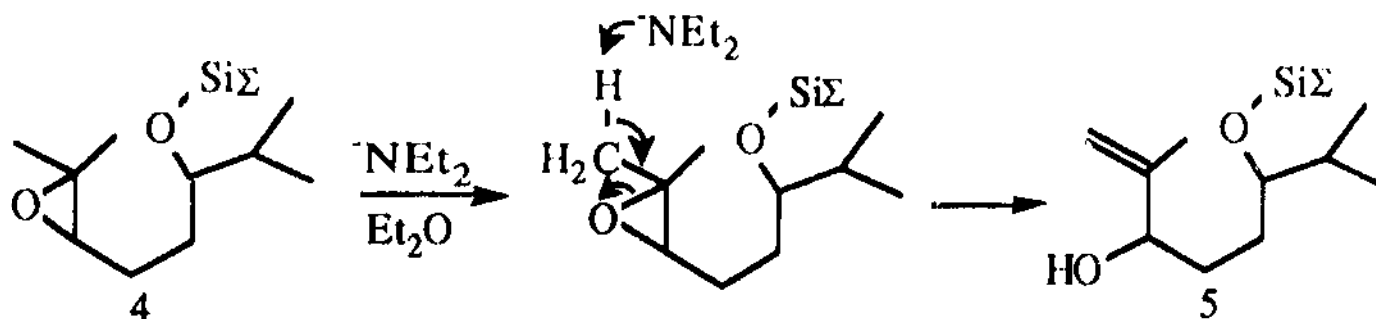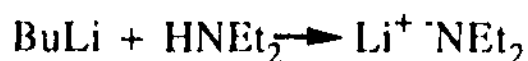
A dry, three-necked flask was equipped with a reflux condensor and an addition funnel. Diethylamine (10.0g, 14.2mL, 137mmol) and ether (130mL) were added to the flask at 0°C, then 1.5M n-butyllithium (90mL, 135mmol) followed. After stirring for 0.5 h, the solution was treated to the epoxide 4 (9.80g, 34mmol). The $^-NEt_2$ in the solution attacked one of the acidic hydrogens on the methyl group nearest to the epoxide group, causing the formation of an olefin and breakage of a C-O bond. This left the anionic oxygen to take a hydrogen from the solvent. The reaction mixture was refluxed for 4 h.

The mixture was treated to an ether/water work-up then washed with brine. Na_2SO_4 served as the drying agent. Ether was removed, and the alcohol 5 was subjected to a SiO_2 flash column (0-3% EtOAc/hexane). The purified product (9.20g, 32mmol) was in 93.88% yield.

The alcohol 5 was characterized by ^{1}H-NMR on the 390: 0.8-1.0 (m, 15H), 1.20 (q, J=4Hz, 3H), 1.47 (q, J=5Hz, 4H), 1.67 (s, 6H), 1.83 (s, 2H), 3.33 (q, J=6Hz, 1H), 3.92 (t, J=6Hz, 1H), 4.70 (s, 1H), and 4.80 (s, 1H).

Deprotonation and Alkylation to an Tributylstannylmethyl Ether

1. Synthesis of Iodomethyltributyltin

$$Zn(s) \xrightarrow{Cu^{2+}} couple \xrightarrow{ICH_2I} ICH_2ZnI \xrightarrow{Bu_3SnCl} Bu_3SnCH_2I$$
$$5a$$
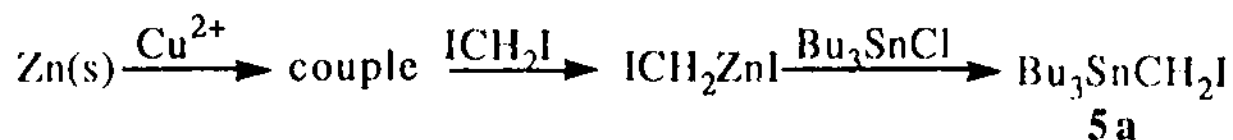
In order to change the alcohol **5** into the tributylstannate **6**, Still's

reagent, iodomethyltributyltin **5a**, must be made first[8,9]. Cupric acetate

monohydrate (50mg, 0.25mmol) was dissolved in glacial acetic acid (4mL)

in a 100-mL three-necked flask, and the solution was heated and stirred.

Granular zinc (2.67g, 41mmol) was stirred in and the mixture was heated

for 2 min. After that, excess acetic acid was decanted, and fresh acetic acid

(4mL) was added and stirred hot for 2 min. The resulting couple was

washed with dry ether (3 8-mL portions).

The reaction flask was then equipped with a reflux condensor and an

addition funnel. The couple was treated to THF (7mL) and diiodomethane

(roughly 830mg, 0.25mL, 3mmol) until the solution turned light purple.

More THF (13mL) was added, darkening the solution to purplish-brown. In

the funnel, a solution of diiodomethane (10.76g, 3.24mL, 40mmol) in THF

(7mL) was added dropwise. The temperature of the flask was kept

lukewarm near 40°C. The total addition time was 50 min., and all the

couple was dissolved in 70 min. The solution was stirred and refluxed

gently for a total of 2.5 h, adding a little heat in the last h. It was then

cooled in an ice bath, turning to a dark olive green solution with some

residue.

The mixture was filtered using a Schlenk tube previously evacuated

with argon. The resulting light yellow solution was transferred to another

flask and underwent a reaction with 96% tributyltin chloride (8.76g,

7.30mL, 27mmol). The contents were stirred overnight at room

temperature. Afterwards, the mixture was poured into petroleum ether

(100mL) and washed with water (2 100-mL portions). The ether layer was

dried over Na_2SO_4 and the solvents were removed to yield the golden

yellow oil **5a** (11.64g, 27mmol) in virtually 100%.

Still's reagent **5a** was characterized on the 390 by ^{1}H-NMR: 0.93 (q,

J=6Hz, 12H), 1.1-1.7 (m, 15H), and 1.93 (s, 2H).

2. Addition of Iodomethyltributyltin

Bu₃SnCH₂I
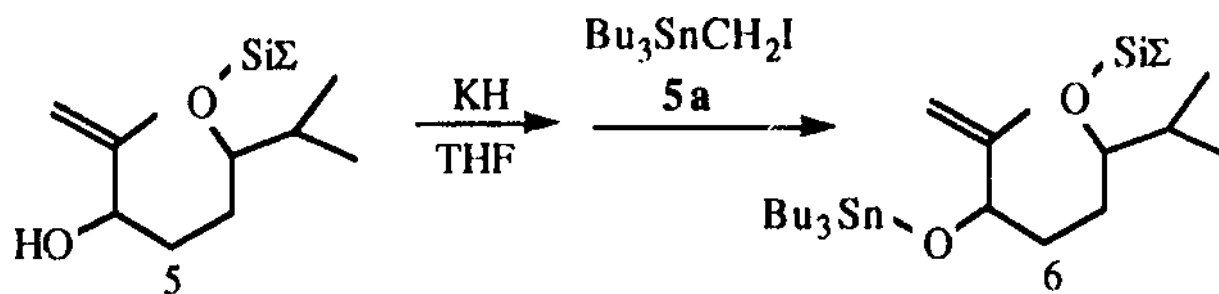
The general procedure was found in two other Still papers.[10,11] THF

(40mL) and KH (820mg, 20mmol) were placed in a 250-mL flask. A

solution of the alcohol **5** (2.89g, 10mmol) in THF (20mL) was added

dropwise in 10 min. The reaction mixture turned from white to yellow.

Then the flask was cooled to 0°C for 20 min., and Still's reagent **5a** (6.52g,

3.33mL, 15mmol) was added. After stirring at room temperature for 1 h,

more KH (200mg, 5mmol) and the reagent **5a** (780mg,, 0.40mL, 2mmol)

were added. The mixture was allowed to stir for 1.75 h. When the

reaction was done, water was added dropwise to destroy the unused KH.

The solution was treated to an Et_2O/H_2O work-up and washed with

brine. The solvents were removed. Either flash column chromatography or

medium pressure liquid chromatography (0-2% EtOAc/hexane) was used

for purification. The reaction gave the tributylstannate **6** (4.90g, 8mmol)

in 82.40% yield.

^{1}H-NMR on the 390 characterized the product 6 as follows: 0.7-1.1

(m, 30H), 1.1-1.8 (m, 27H), 3.2-3.5 (m, 2H), 3.60 (d, J=8Hz, 1H), and 4.7-4.9

(q, 2H)

2,3-Sigmatropic Rearrangement to a Homoallylic Alcohol
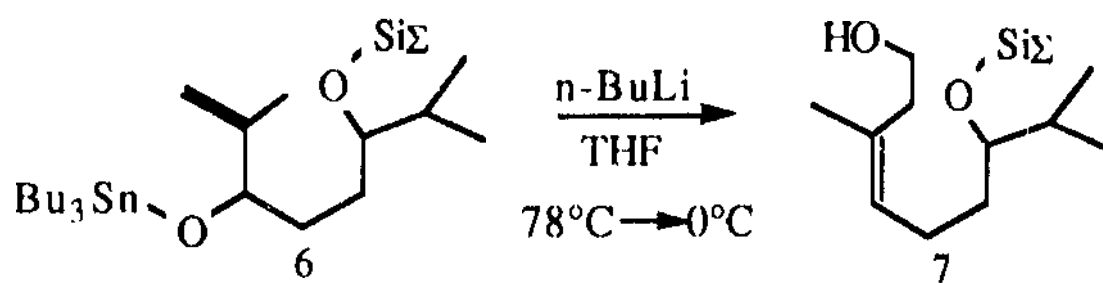
The procedure for this rearrangement was also found in the two Still

papers mentioned earlier.[10,11] The temperature change from -78°C to 0°C

as written in the more recent paper gave better results than the constant

temperature of -78°C in the first. Addition of excess n-butyllithium

prompted an exchange between tin and lithium, causing the rearrangement

and forming the by-product tetrabutyltin.

The starting material 6 (1.3315g, 2.3mmol) was first dried with

toluene then added to THF (55mL) in a dry flask. The solution was cooled

to -78°C and treated with 1.5M n-BuLi (6.025mL, 9mmol). Bipyridine

turned the solution red at this point, indicating the presence of

butyllithium. The flask was kept at -78°C for 1.25 h, then it was

transferred to a 0°C ice water bath for 0.5 h. The finished reaction was

treated to an ether/water work-up and dried with brine. Purification was

done by flash column chromatography (0-10% EtOAc/hexane). The alcohol

7 (627mg, 2mmol) had a yield of 92.38%.

Characterizations of the homoallylic alcohol **7** were as follows.

^{1}H-NMR on the 300: 0.83 (m, J=6Hz, 15H), 1.40 (m, J=7Hz, 3H), 1.69 (s,

6H), 1.97 (m, J=6Hz, 1H), 2.29(t, J=6Hz, 4H), 2.43 (s, 1H), 3.42 (q, J=3Hz, 1H),

3.62 (t, J=6Hz, 4H), and 5.28(t, J=6Hz, 1H). IR (neat) (cm^{-1}): 1076 (C-O

stretch), 1385 (CH$_2$, CH$_3$ bend), 1472 (CH$_2$, CH$_3$ bend), 2856-2957 (C-H

stretch), and 3314 (bonded O-H stretch). ^{13}C-NMR on the 300: 17.40,

17.62, 17.87, 17.99, 18.08, 23.38, 23.43, 23.89, 25.47, 25.69, 25.90, 26.12,

32.45, 33.33, 34.98, 60.43, 76.35, 76.55, 77.00, 77.42, 128.00, and 130.98.

Addition of a Leaving Group to a Mesylate
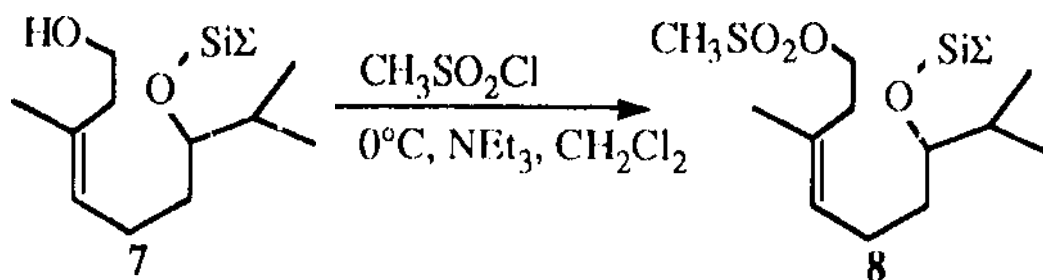
The alcohol **7** (1.2570g, 4mmol) was dried with toluene in a tared flask,

then dichloromethane (10mL) and triethylamine (849mg, 1.17mL, 8mmol) were added to it. The amine was used to take up the H in the alcohol group in the displacement reaction. The clear yellow solution was cooled to 0°C and then underwent a reaction with methanesulfonyl chloride (673mg, 0.46mL, 6mmol). It turned cloudy upon addition. After 0.5 h, thin-layer chromatography indicated that the spots of **7** and the product **8** had the same RF but differ in color. The reaction mixture was worked up with ether and water then dried with $NaHCO_3$ and brine. The mesylate **8** (1.3380g, 3.5mmol) was given in 84.50% yield.

^{1}H-NMR on the 390 characterized the mesylate: 0.6-0.9 (s, 15H), 1.23 (q, J=7Hz, 4H), 1.57 (s, 6H), 1.80 (q, J=7Hz, 1H), 2.28 (t, J=6Hz, 3H), 2.78 (s, 4H), 3.25 (q, J=5Hz, 1H), 4.01 (t, J=8Hz, 3H), and 5.10 (t, J=6Hz, 1H).

Nucleophilic Substitution to a Nitrile
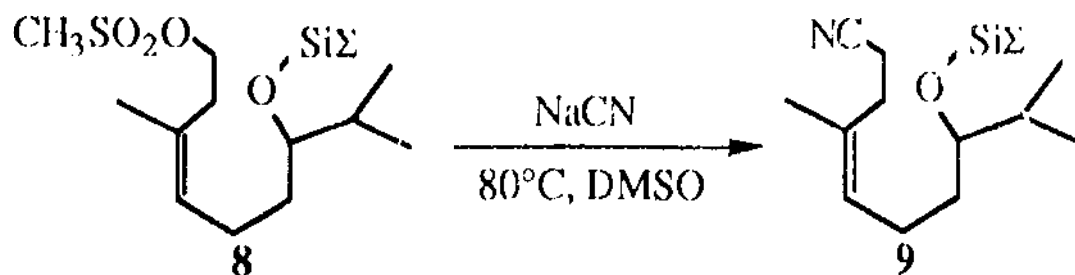
The mesylate **8** (2.20g, 6mmol) was added to dimethylsulfoxide

(20mL) and sodium cyanide (420mg, 9mmol). The solution was warmed to

80°C in an oil bath for 1.25 h. Then it was treated to an ether/water

work-up and dried with brine. The nitrile **9** was purified by flash column

chromatography (0-10% EtOAc/hexane) with a yield of 80.56% (1.45g,

5mmol).

The product **9** was characterized as follows. ^{1}H NMR on the 300:

0.8-1.0 (m, J=6Hz, 15H), 1.27 (m, J=6Hz, 3H), 1.43 (q, J=6Hz, 4H), 1.66 (s,

4H), 2.00 (m, J=8Hz, 1H), 2.40 (s, 6H), 3.42 (q, J=3Hz, 1H), and 5.31 (t, J=6Hz,

1H). IR (neat) (cm^{-1}): 1075 (C-O stretch), 1464 (CH$_2$, CH$_3$ bend),

2351 (C≡N stretch), and 2857-2957 (C-H stretch). ^{13}C-NMR on the 300:

15.87, 17.80, 18.10, 22.65, 23.99, 25.87, 27.50, 32.69, 33.09, 76.48, 76.56,

76.99, 77.41, 128.90, and 130.68.

Deprotection to an Alcohol
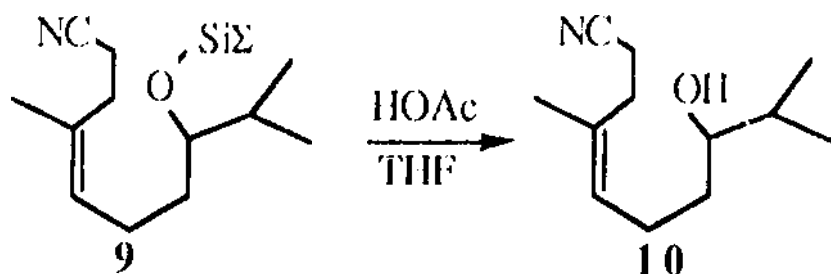
Deprotection was achieved through a mild acidic medium. The nitrile **9**

(2.89g, 9mmol) was added to a solution of 80% acetic acid (30mL) and THF

(10mL). The reaction mixture was stirred for 9 h at 60°C, refrigerated overnight, and stirred again for 5 h at 60°C. Tetrabutylammonium fluoride in THF at 70°C for 3.5 h was the former procedure used, but acetic acid was the better and cheaper reagent. Then it was poured on ice and NH_4OH, extracted with CH_2Cl_2, and washed with brine. Purification was done by flash column chromatography (0-10% EtOAc/hexane). The product 10 (1.67g, 8.6mmol) was yielded in 91.76%.

Characterizations of the nitrile-alcohol 10 were done as listed. ^{1}H-NMR on the 300:   0.90 (m, J=6Hz, 6H), 1.22 (s, 1H), 1.43 (m, J=6Hz, 2H), 1.71 (s, 3H), 2.13 (m, J=6Hz, 2H), 2.40 (d, J=3Hz, 4H), 3.22 (m, J=3Hz, 1H), 5.28 (t, J=8Hz, 1H), and 7.26 (s, 1H). IR (KBr) (cm^{-1}):   1057 (C-O stretch), 1383 (CH_2, CH_3 bend), 1458 (CH_2, CH_3 bend), 2247 (C≡N stretch), 2874-2959 (C-H stretch), and 3451 (bonded O-H stretch). ^{13}C-NMR on the 300: 15.41, 16.98, 18.36, 22.26, 24.04, 26.96, 33.26, 33.57, 75.24, 76.56, 77.00, 77.41, 119.33, 128.31, and 130.69.

Mercuricyclization to a Chloromercuric Pyran
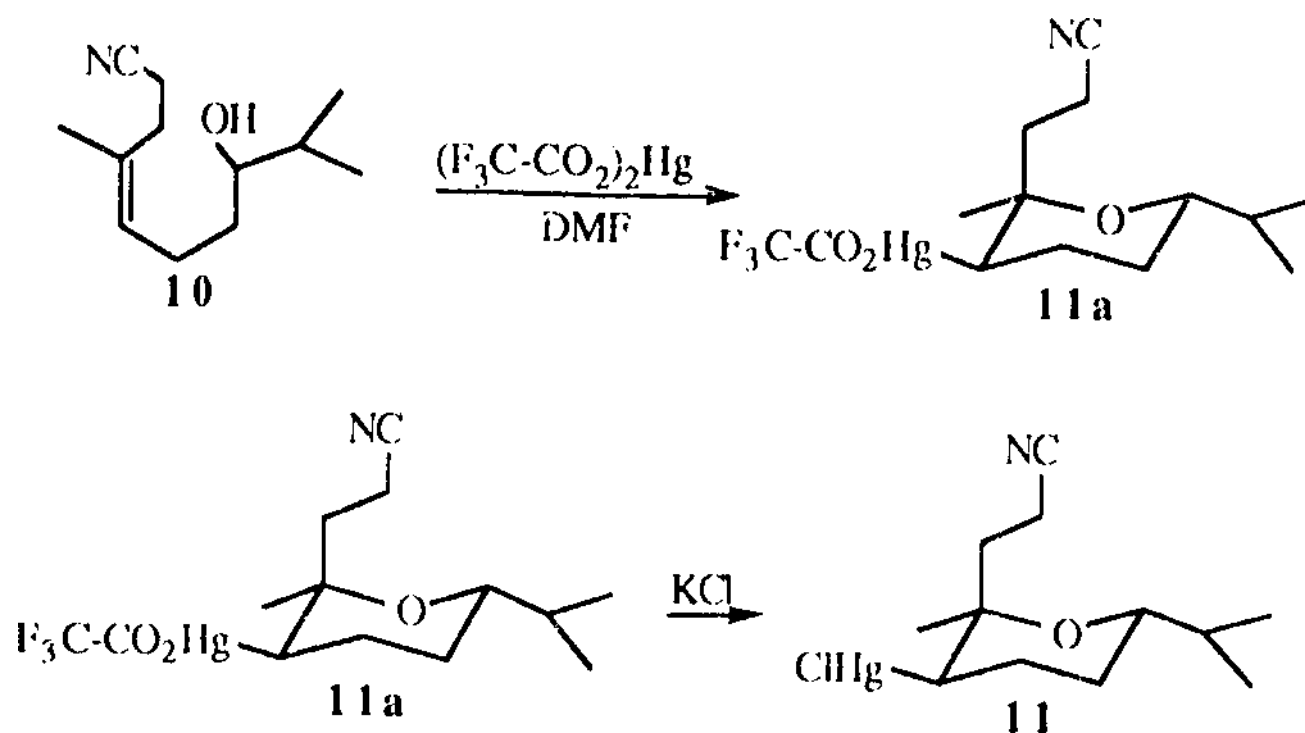
This step was crucial in the partial synthesis of thyrsiferol. The above

procedure resulted after much trial and error with different solvent

systems and mercuric reagents. The standard treatment of mercuric

acetate in THF/H$_2$O gave both the pyran 11 and the furan 11b.[12,13]
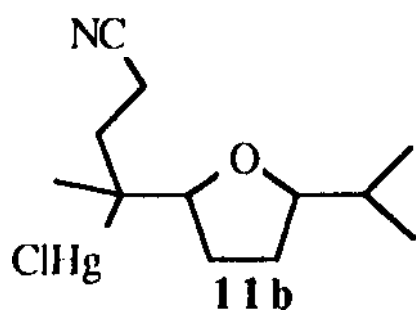
Bentham[14] found that mercuric triflouroacetate, being a stronger acid than

the acetate, yielded much more of the pyran than the furan. Brown[15] stated that HgTFA had a higher selectivity and more activity for Markovnikov ethers than HgOAc. The mercuricyclization underwent a carbocation transition state 11c when the mercury cation attacked the double bond.[16]

11c
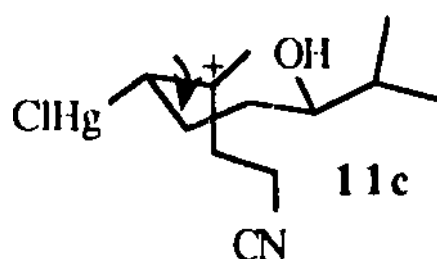
The alcohol 10 (1.17g, 6mmol) in dimethylformamide (20mL) was treated to mercuric trifluoroacetate anhydride (3.25g, 10mmol) in DMF (25mL), and the mixture was allowed to stir overnight. Then the mercurial 11a was poured into saturated KCl (200mL) and $NaHCO_3$ (100mL) solutions and extracted with excess ether. After removal of the solvents, the impure product was dissolved in CH_2Cl_2 and filtered through Celite. The chloromercurial 11 was crystallized from hexane (25mL). Flash column (0-20% EtOAc/hexane) was also used sometimes. The pink crystalline solid 11 had a mp of 151-153°C and a 95.35% yield (2.46g, 6mmol).

The mercurial **11a** was characterized by ^{1}H-NMR on the 200: 0.88 (q, J=7Hz, 6H), 1.28 (s, 4H), 1.55 (q, J=6Hz, 1H), 1.70 (m, J=2Hz, 2H), 2.14 (t, J=2Hz, 2H), 2.40 (m, J=1Hz, 3H), 2.79 (m, J=6Hz, 1H), and 2.98-3.06 (m, 1H).

The chloromericur al **11** had the following identifications. ^{1}H-NMR on the 300: 0.87 (q, J=6Hz, 6H), 1.25 (s, 4H), 1.53 (q, J=6Hz, 1H), 1.66 (m, J=6Hz, 2H), 2.09 (q, J=6Hz, 2H), 2.38 (m, J=3Hz, 3H), 2.75 (m, J=6Hz, 1H), and 3.20 (q, J=6Hz, 1H). IR (CDCl$_3$) (cm^{-1}): 1215 (C-O stretch), 1383 (CH$_2$, CH$_3$ bend), 1474 (CH$_2$, CH$_3$ bend), 2249 (C≡N stretch), and 2975-3023 (C-H stretch). ^{13}C-NMR on the 300: 10.86, 18.33, 18.42, 26.82, 29.90, 30.52, 32.39, 33.29, 62.05, 74.77, 75.30, 76.57, 76.99, 77.42, and 120.18.

Oxidation Demericurization to a Pyran with an Axial Alcohol Group
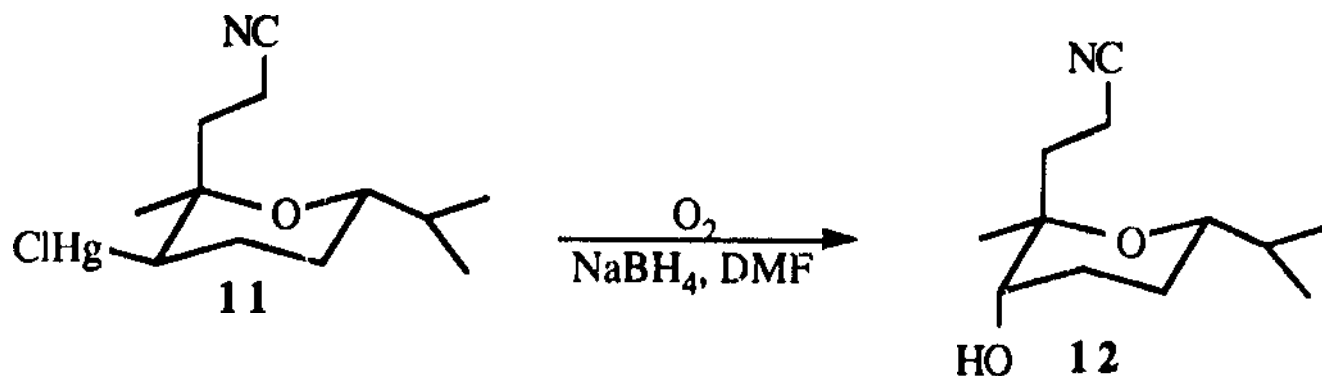
The mechanism of the oxidative demercuration was deduced by Hill and Whitesides.[17]

$$RHgCl \xrightarrow{\text{NaBH}_4} RHgH$$

$$RHgH \longrightarrow R\cdot + \cdot HgH$$

$$R\cdot + O_2 \longrightarrow R\text{-}O\text{-}O\cdot$$

$$ROO\cdot + RHgH \longrightarrow ROOH + R\cdot + Hg(0)$$

$$ROO\cdot \xrightarrow{\text{NaBH}_4} ROOH$$

$$R\text{-}O\text{-}OH \xrightarrow{\text{NaBH}_4} R\text{-}OH$$
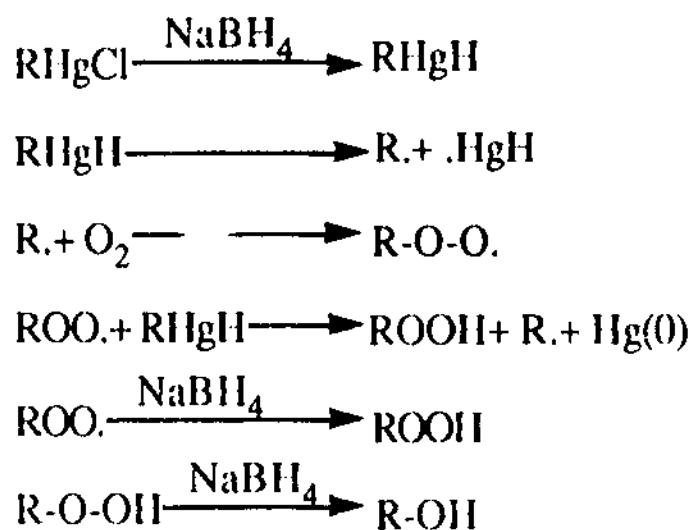
The rapid radical-chain reactions accounted for the fast completion time of the oxidation.

Sodium borohydride (200mg, 53mmol) and DMF (5mL) were placed in a three-necked 100-mL flask. Excess oxygen flowed through the solution, bubbling vigorously. In a second flask, a solution of the mercurial 11 (457mg, 1mmol) and DMF (3mL) was made, and the contents were added dropwise to the first flask. The reaction mixture turned gray due to the formation of mercury. The second flask was rinsed with DMF (two 3-mL portions) and the wash solutions were added to the first flask. More DMF (3mL) was used to replenish the solution in the middle of the reaction. The total reaction time was 30 min. Water (15mL) was then injected in to destroy excess sodium borohydride, and the solution was allowed to stir for

15 min. more. The reaction mixture was worked up with ether/water,

giving the axial and equatorial alcohols in 90.86% yield (204mg, 0.96mmol).

Only the axial isomer **12** was desired, so medium-plate liquid chroma-

tography (0-33% EtOAc/hexane) separated the alcohols in roughly

2:1 in favor of the axial.

^{1}H-NMR on the 300: 0.85 (m, J=6Hz, 6H), 1.13 (s, 4H), 1.23 (s, 1H), 1.46

(m, J=3Hz, 2H), 1.57 (m, J=6Hz, 2H), 1.84 (m, J=3Hz, 1H), 2.35 (m, J=3Hz, 3H),

3.02 (m, J=6Hz, 1H), and 3.35 (t, J=3Hz, 1H).

FURTHER DEVELOPMENTS AND CONCLUSION

There is still a long way to go in terms of experimentation and total

synthesis of thyrsiferol. The Marbet reaction in the beginning step of this

synthesis may be replaced by the following:
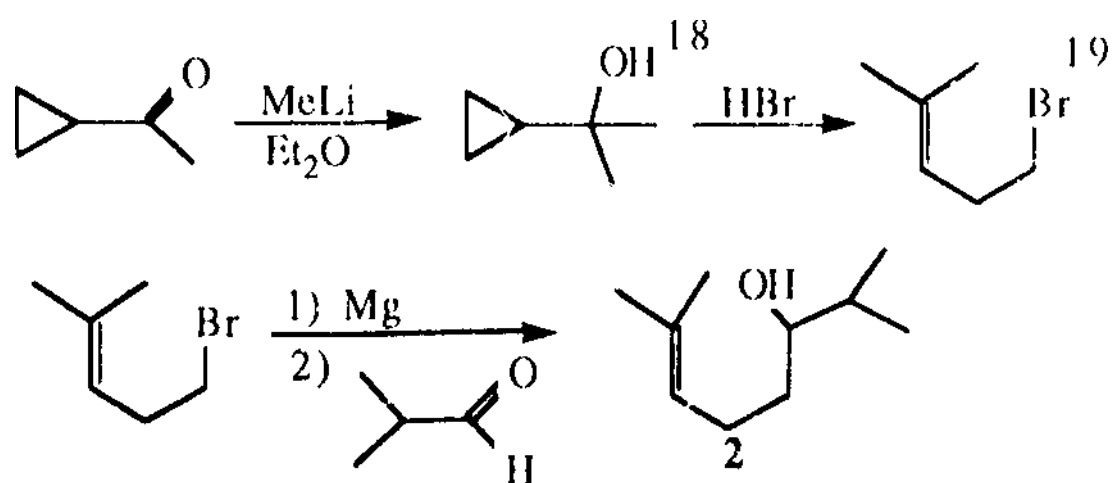
The Whitesides reaction is being tested with dimethylsulfoxide as a

substitute for dimethylformamide. The new solvent is said to give better

results. Lastly, the second ring of thyrsiferol was recently completed via

Corey-Nicoleau thiolester[20] and Tebbe's reagent.[21,22] Given the potential

use of thyrsiferol, the time and effort in modification and synthesis are not

in vain.

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