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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

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APPROVED:

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A Partial Synthesis
of
Thyrsiferol

by
Linda Hu

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INTRODUCTION

Thrysiferol is a tetracyclic ether with cytotoxic and antiviral properties. More specifically, it has potential against lymphocytic leukemia cells. When thrysiferol was combined with venustatriol and thrysiferol 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.

The structures of thrysiferol determined by Sakemi, et. al. and Suzuki, et. al. were not entirely accurate. The correct structure is given below.

The synthesis of the left half of thrysiferol 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**

\[
\text{OH} + \overset{\text{H}_3\text{PO}_4}{\text{O}} \xrightarrow{150^\circ\text{C}, 3\text{h}, 5\text{ atm.}} \text{O} \quad \text{H} 
\]

The procedure for this reaction was taken from a paper by Marbet and
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<th>Structure</th>
<th>Molecular Formula</th>
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<tr>
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<td>C_{16}H_{34}OSi (270.54)</td>
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<td><img src="image3" alt="Structure 3" /></td>
<td>C_{16}H_{34}O_{2}Si (286.54)</td>
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<td><img src="image4" alt="Structure 4" /></td>
<td>C_{16}H_{34}O_{2}Si (286.54)</td>
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<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>C_{29}H_{62}O_{2}SiSn (589.60)</td>
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<tr>
<td><img src="image6" alt="Structure 6" /></td>
<td>C_{17}H_{36}O_{2}Si (300.57)</td>
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</table>
Structure

Molecular Formula

\[ \text{CH}_2\text{SO}_2\text{O} \]
\[ \text{C}_{18}\text{H}_{37}\text{O}_4\text{SSi} \]
(378.65)

\[ \text{NC} \]
\[ \text{C}_{18}\text{H}_{34}\text{NOSi} \]
(309.57)

\[ \text{OH} \]
\[ \text{C}_{12}\text{H}_{21}\text{NO} \]
(195.31)

\[ \text{F}_3\text{C-CO}_2\text{Hg} \]
\[ \text{C}_{14}\text{H}_{20}\text{HgF}_3\text{NO}_3 \]
(513.30)

\[ \text{ClHg} \]
\[ \text{C}_{12}\text{H}_{20}\text{HgClINO} \]
(430.34)

\[ \text{HO} \]
\[ \text{C}_{12}\text{H}_{21}\text{NO}_2 \]
(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 vigreux 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**

\[
\text{O} \quad \text{H} + \quad \text{MgBr} \quad \underset{\text{Et}_2\text{O}}{\text{\rightarrow}} \quad \text{OH}
\]

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 NH₄Cl, NaHCO₃, and brine each. The organic solution was
dried over MgSO₄ 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 ¹H-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 Ester**

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 H₂ 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 MgSO₄ 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).

¹H-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 (CH₂, CH₃ bend), 1385 (CH₂, CH₃ bend), 1472 (CH₂, CH₃ bend), and 2938 (C-H stretch).

Lipoxidation of the Olefinic Group
Dichloromethane (120mL), 85% 3-chloroperbenzoic 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 CH₂Cl₂/NaHCO₃ 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.

¹H-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 + HNEt₂ ⇌ Li⁺ ·NEt₂
A dry, three-necked flask was equipped with a reflux condenser 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 \( ^{\text{NEt}_2} \) 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. \( \text{Na}_2\text{SO}_4 \) 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 \(^1\text{H-NMR}\) 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 a Tributylstannylmethyl Ether**
1. Synthesis of Iodomethyltributyltin

\[
\begin{align*}
\text{Zn(s)} & \xrightarrow{\text{Cu}^{2+}} \text{couple} & \text{ICH}_2\text{I} & \xrightarrow{\text{Bu}_3\text{SnCl}} \text{Bu}_3\text{SnCH}_2\text{I} \\
& & \text{5a}
\end{align*}
\]

In order to change the alcohol 5 into the tributylstannate 6, Stille'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, 41 mmol) 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$_2$SO$_4$ 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
The general procedure was found in two other Still papers.\textsuperscript{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 $\text{Et}_2\text{O}/\text{H}_2\text{O}$ 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, 21H), 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, 1H), 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 NaHCO₃ and brine. The mesylate 8 (1.3380g, 3.5mmol) was given in 84.50% yield.

*H-NMR on the 390 characterized the mesylate: 0.6-0.9 (s, 1H), 1.23 (q, J=7 Hz, 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, 111).

**Nucleophilic Substitution to a Nitrile**

![Chemical Reaction](image)

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, 1H), 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-$^1$H 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 reaction](attachment:image.png)

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.
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 NH₄OH, extracted with CH₂Cl₂, 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. ¹H-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 (CH₂, CH₃ bend), 1458 (CH₂, CH₃ bend), 2247 (C≡N stretch), 2874-2959 (C-H stretch), and 3451 (bonded O-H stretch). ¹³C-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/H₂O gave both the pyran 11 and the furan 11b.¹²,¹³

Bentham⁴ found that mercuric trifluoroacetate, being a stronger acid than
the acetate, yielded much more of the pyran than the furan. Brown 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.

\[ \text{ClHg} \quad \text{OH} \quad \text{CN} \quad \text{11c} \]

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 NaHCO₃ (100mL) solutions and extracted with excess ether. After removal of the solvents, the impure product was dissolved in CH₂Cl₂ 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, 111).

The chloromericurial 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 Demercurization to a Pyran with an Axial Alcohol Group**

The mechanism of the oxidative demercuration was deduced by Hill and Whitesides.
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 chromatography (0-33% EtOAc/hexane) separated the alcohols in roughly 2:1 in favor of the axial.

$^1\text{H-NMR}$ 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:

\[
\begin{align*}
\text{O} & \xrightarrow{\text{MeLi, Et} \text{O}} \text{O} \\
& \xrightarrow{\text{HBr}} \text{Br}
\end{align*}
\]

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\textsuperscript{20} and Tebbe's reagent\textsuperscript{21,22}. Given the potential use of thyrsiferol, the time and effort in modification and synthesis are not in vain.
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