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Synthetic Approaches to a Thysanone Analog

Herbert Ogutu
Iowa State University

Synthetic Approaches to

A Thysanone Analog

by

Herbert Ogutu

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Dr. George A. Kraus, Major professor
Dr. Dennis C. Johnson
Dr. Valerie V. Sheares

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Graduate College

Iowa State University

This is to certify that the Master's thesis of

Herbert Ogutu

has met the thesis requirements of Iowa State University

Signatures have been redacted for privacy

To my wife Felicina, for her constant encouragement and support.

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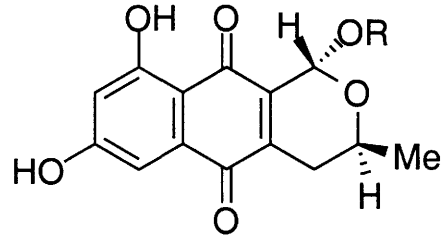
INTRODUCTION

I. General and biological background

Thysanone **(1)** is a novel naphthoquinone with a lactol ring that was isolated[1] from the solid state fermentations of the fungus *Thysanophora penicilloides.* In 1991, Singh and coworkers at Merck, Sharp and Dohme research laboratories were screening microbial extracts for lead compounds that would be developed into chemotherapeutic agents for eventual control/cure of the common cold. It was during this process that thysanone was isolated. They proposed structure **1** from spectroscopic data. They also determined the relative stereochemistry (but *not* the absolute configuration) between the C-1 and C-3 stereogenic centers from single crystal x-ray analysis of the methyl acetal **2**. Treatment of thysanone with methanol in the presence of concentrated sulfuric acid gave the acetal **2**.

Figure 1



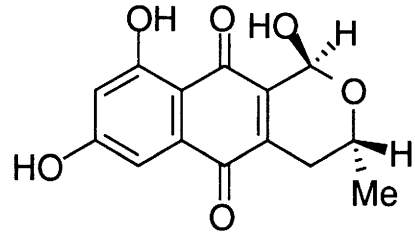
1 R = H
2 R = Me

Thysanone is an effective inhibitor (IC_{50} 13μg/mL) of human rhinovirus 3C-protease. Human rhinoviruses (HRVs) are piconarviruses and are responsible for causing the common cold in humans.[2] The picornavirus family of viruses is comprised of members that are human pathogens, e.g. enteroviruses (polioviruses, coxsackieviruses, echoviruses, and hepatitis A viruses), aphthoviruses (foot-and-mouth disease virus), and cardioviruses (mengo virus and encephalomyocarditis virus). A common feature of all piconarviruses is that the positive strand RNA genome of HRVs is translated directly into a large viral polyprotein (200 kD) precursor which undergoes a series of controlled proteolytic cleavages to generate functional viral gene products. Proteolytic processing is critical to the replication of many animal and plant viruses. There are several functions in which proteolytic enzymes are involved. These functions include; the separation of structural and non-structural proteins, generation of specific enzymes (RNA polymerases), coordinated assembly of the virus particle (virion), and maturation. Processing of the polyprotein is dependent upon two virally encoded proteases ("3C-protease" and "2A- protease") which have no known cellular homologues. These enzymes therefore represent attractive targets for the development of antiviral chemotherapeutic agents. The aforementioned proteases are thought to be cysteine proteases but with significant differences to other cysteine proteases. The enzyme 3C-protease cleaves the polyprotein between glutamine and glycine (Q-G), while the 2A-protease cleaves it between tyrosine and glycine (Y-G). The piconarviruses that have been studied produce a 3C-protease, which is required for the virus maturation. Thysanone effectively inhibits HRV-3C protease, thus curtailing viral replication.

II. Recent synthetic work

To date, there is only one published total synthesis of thysanone. It was done by Gill and co-workers.[3] They synthesized (*1R, 3S*)-thysanone **1** in 16 steps, and established its hitherto undocumented absolute stereochemistry. When they compared the ^{1}H and ^{13}C NMR data for the synthetic sample of **1** and the corresponding published data for the natural product, they concluded that natural and synthetic thysanone possess the same substitution pattern, and *trans* relative configuration in the lactol ring. Comparison of the chirotopical data obtained for the synthetic material with the data published for the natural product demonstrated that the two substances are enantiomers. Hence, the absolute configuration of natural thysanone **3** as it occurs in *Thysanophora penicilloides* must be (*1S, 3R*) as shown in Figure 2.

Figure 2



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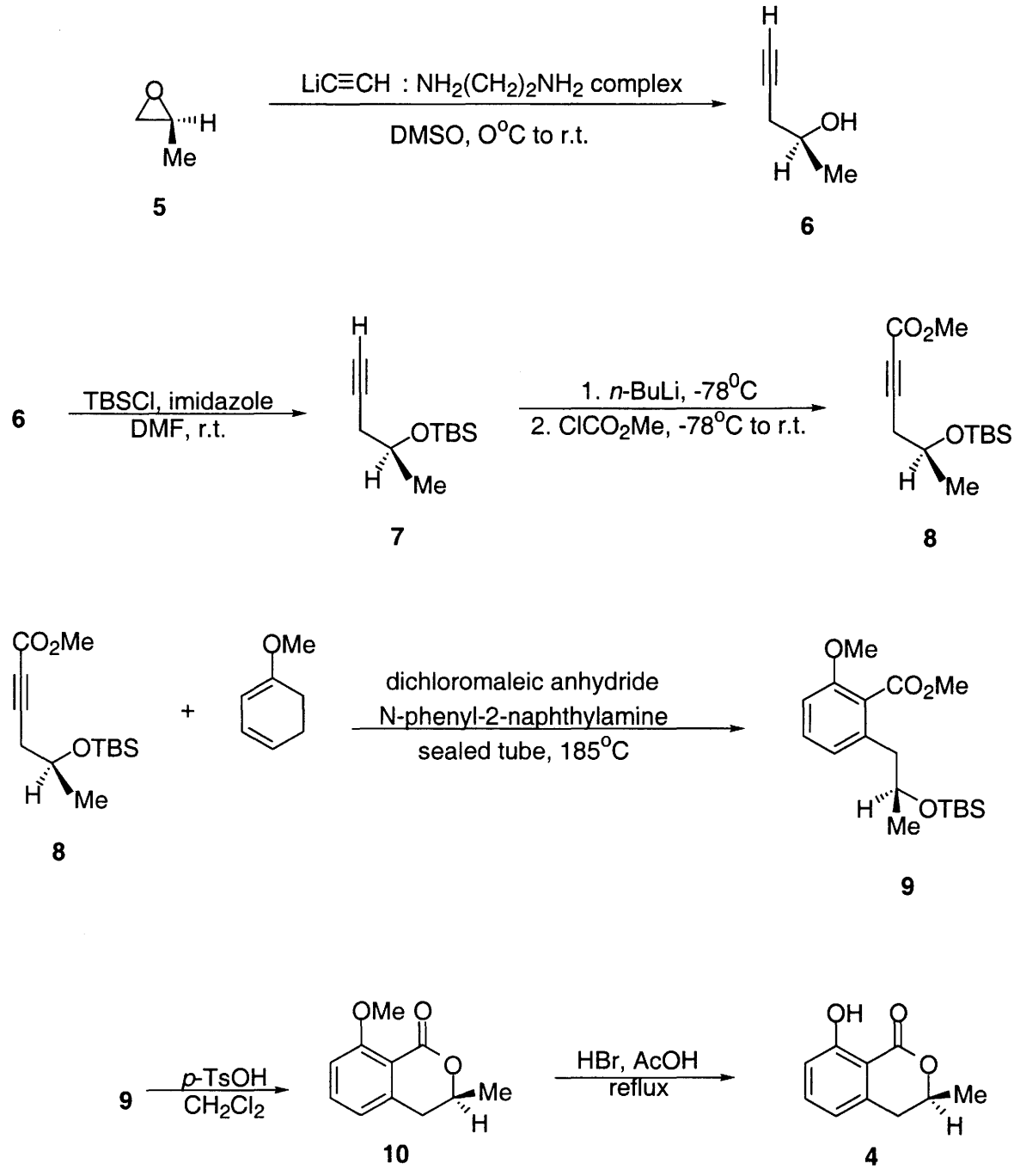
The key intermediate in their synthesis is the (*S*)-enantiomer of the natural product mellein **(4)**. In an earlier paper, Gill and co-workers reported the first stereospecific

synthesis of both isomers of mellein.[4] Scheme 1 outlines Gill's synthesis of (*S*)-(+)-mellein **(4)**.

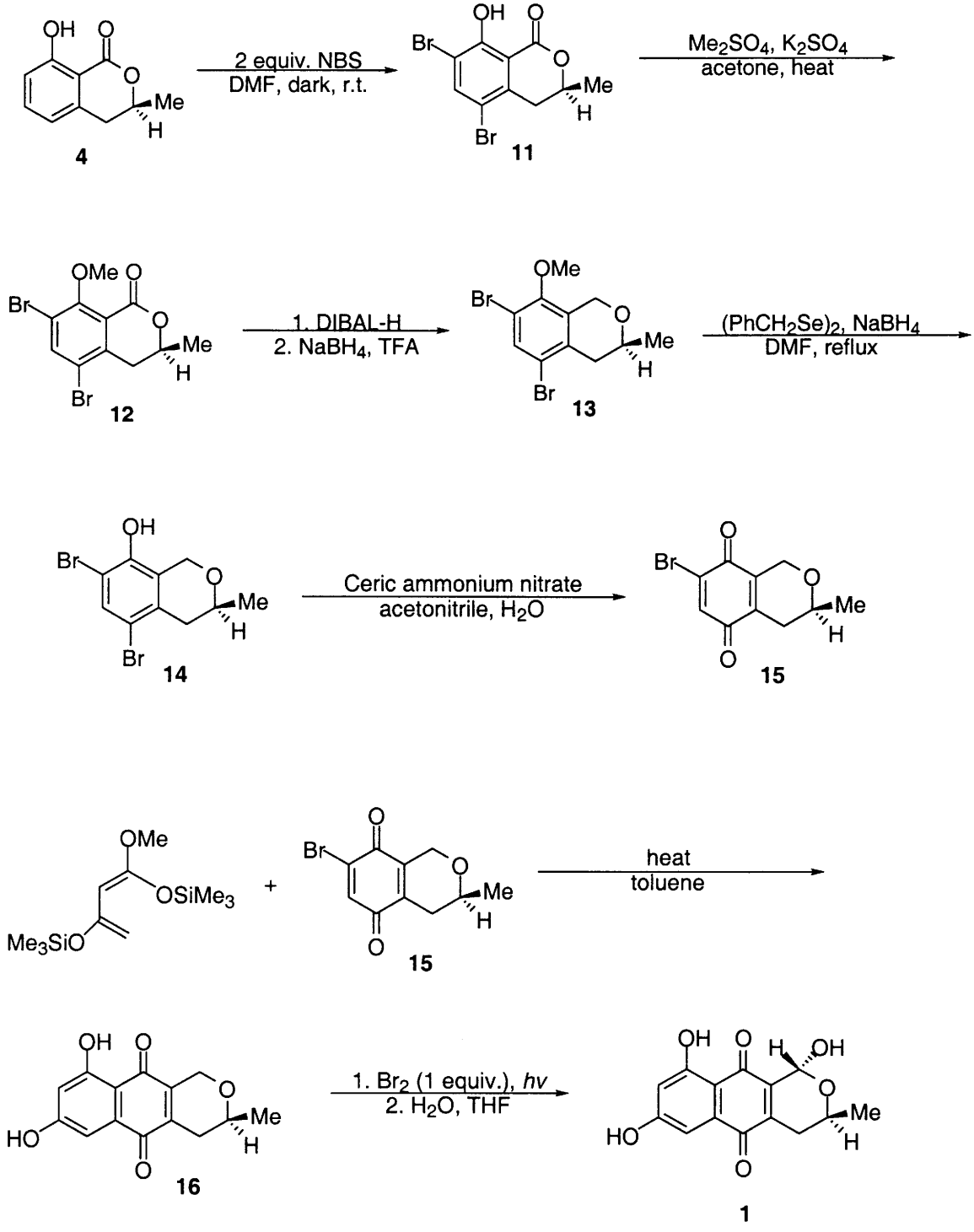
The synthesis of **4** begins by treatment of the commercially available (*S*)-propylene oxide **(5)** with the ethylenediamine complex of lithium acetylide to afford (*S*)-pent-4-yn-2-ol, which was subsequently protected under standard conditions to give the silyl ether **7** in 58% yield from **5**. Reaction of **7** with *n*-butyl lithium followed by exposure of the resulting acetylide anion to methyl chloroformate resulted in the formation of the (*S*)-hexynoate **8** in 81% yield over the two steps.

Hexynoate **8** and 1-methoxy-1,3-cyclohexadiene underwent a regioselective Diels-Alder reaction in the presence of a trace of 2,3-dichloromaleic anhydride and *N*-phenyl-β-naphthylamine giving benzoate **9** in 79% yield based on the quantity of alkynoate used. The addition of 2,3-dichloromaleic anhydride to this reaction mixture promotes *in situ* conjugation of the 1,4-diene. The hydrolysis of the silyl ether group of the benzoate **9** with subsequent lactonization of the secondary hydroxyl group afforded (*S*)-8-*O*-methylmellein **10** which is itself a natural product isolated from the phytopathogen *Septoria nodorum*. Demethylation of (*S*)-8-*O*-methylmellein **10** under acidic conditions gave (*S*)-(+)-mellein **4** in 32% yield from (*S*)-propylene oxide **(5)**. They could then use both enantiomers of mellein to synthesize compounds **1** and **3.**

Scheme 1


LiC≡CH : NH2(CH2)2NH2 complex
DMSO, O°C to r.t.
TBSCl, imidazole
DMF, r.t.
1. n-BuLi, -78°C
2. ClCO2Me, -78°C to r.t.
dichloromaleic anhydride
N-phenyl-2-naphthylamine
sealed tube, 185°C
p-TsOH
CH2Cl2
HBr, AcOH
reflux
5
6
7
8
9
10
4

Scheme 2

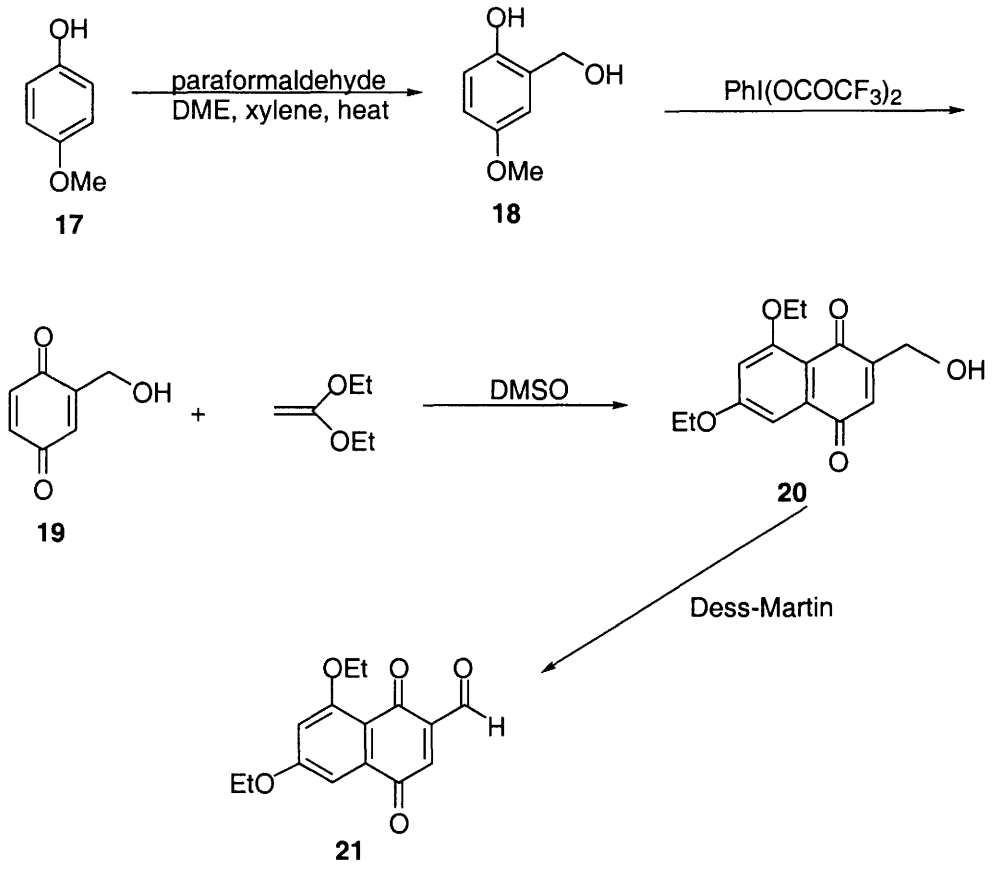

OH
O
Me
H
4
2 equiv. NBS
DMF, dark, r.t.
Br
11
Me2SO4, K2SO4
acetone, heat
OMe
12
1. DIBAL-H
2. NaBH4, TFA
13
(PhCH2Se)2, NaBH4
DMF, reflux
14
Ceric ammonium nitrate
acetonitrile, H2O
15
OSiMe3
Me3SiO
heat
toluene
16
1. Br2 (1 equiv.), hv
2. H2O, THF
HO
1

The formal total synthesis of thysanone began with the bromination of **4** with two equivalents of N-bromosuccinimide in the dark (Scheme 2). The resulting dibromophenol **11** was methylated with dimethylsulfate and potassium carbonate in boiling acetone to give **12**. Reduction of the benzoisocoumarin **12** to the corresponding lactol with diisobutyl aluminum hydride followed by reaction with sodium borohydride in the presence of trifluoroacetic acid afforded the benzopyran **13**. The ether group in benzopyran **13** was cleaved by application of benzylselenide anion to give phenol **14** in 86% yield. Ceric ammonium nitrate oxidation of **14** afforded the unique chiral bromopryranobenzoquinone **15** in 82% yield.

Heating 1-methoxy-1,3-bis(trimethyl silyloxy)-1,3-butadiene and quinone **15** in toluene for three hours resulted in a Diels-Alder cycloaddition reaction that gave quinone **16** in 73% yield. Molecular bromine was then utilized to carry out a benzylic bromination of **16**. *In situ* treatment of the intermediate bromide with aqueous tetrahydrofuran afforded (*1R, 3S*)-thysanone **1** in 35% overall yield from (*S*)-mellein **4**.

Recently, work in our laboratory led to the synthesis of 5,7-diethoxy-1,4-naphthoquinone-2-carbaldehyde **(21)**, a key intermediate to thysanone.[5] Scheme 3 gives a summary of this work. This approach utilized a regioselective 1,2-addition of 1,1-dialkoxyethenes with quinones. The most prominent feature of this route was the simplicity of the starting materials, and the high atom efficiency of the reaction. The reaction was found to be greatly dependent on reaction conditions; for example, using benzene as a solvent inhibited the reaction. Pure dimethyl sulfoxide was found to be the best solvent.

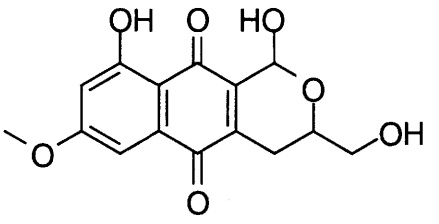
Scheme 3



Heating a mixture of 4-methoxyphenol **17** and paraformaldehyde at 135 °C in a sealed tube resulted in the formation of compound **18** in 60% yield. Phenyl iodo-*di*-trifluoroacetate oxidation of **18** proceeded in almost quantitative yield to give quinone **19**. A regioselective 1,2-addition between **19** and 1,1-diethoxyethene in dimethylsulfoxide, and subsequent oxidation with silver (I) oxide gave compound **20** in 55% yield. Dess-Martin oxidation of quinone **20** resulted in compound **21** that might be converted to thysanone.

The most recent work focused on an analog of thysanone **22** shown in Figure 3. The main feature of our analog is the hydroxymethyl group at the 3-position.

Figure 3



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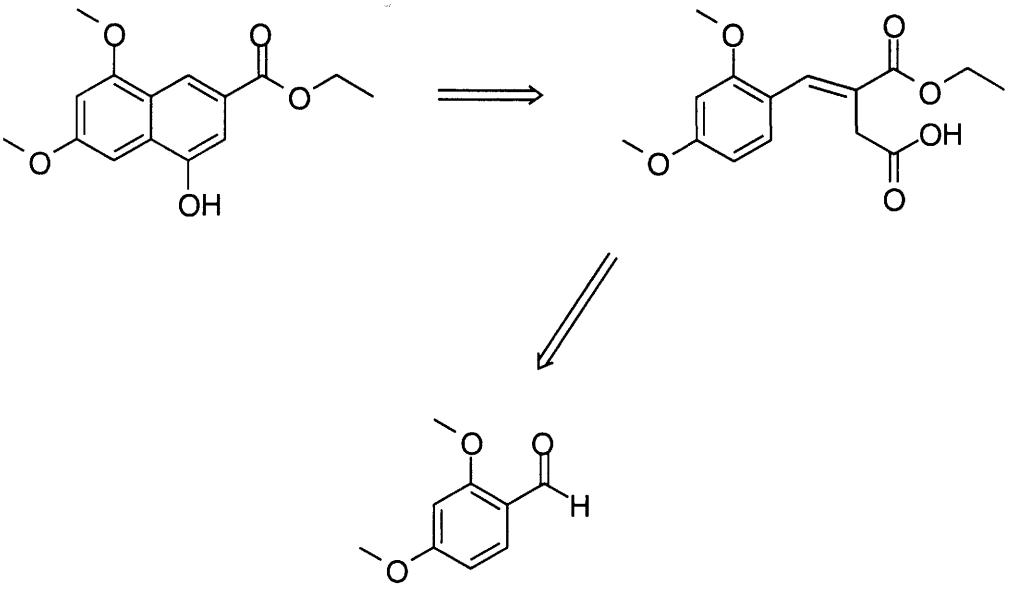
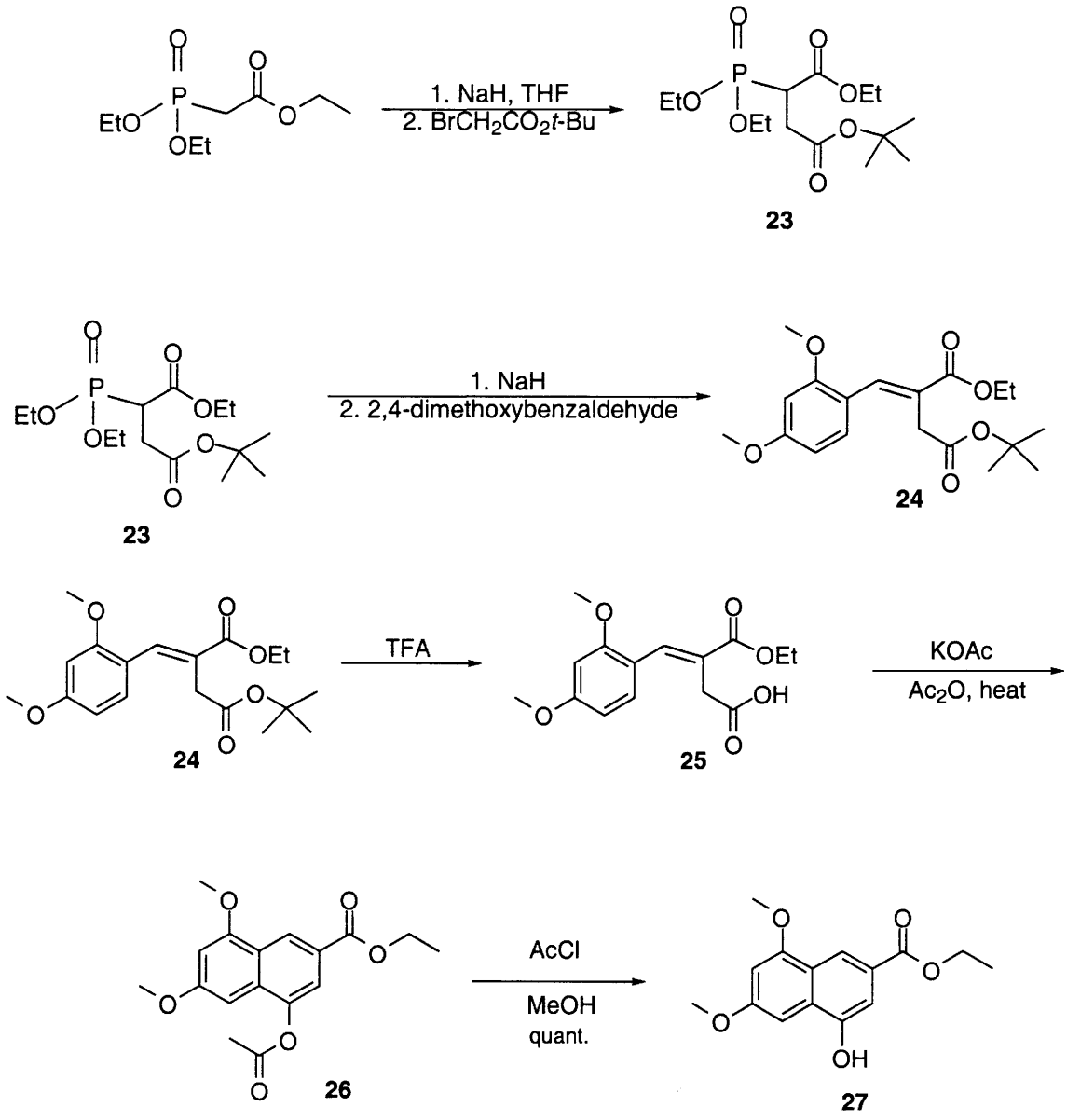
RESULTS AND DISCUSSION

We attempted the synthesis of **22** using two different routes. A common intermediate in both routes is a 5,7-substituted naphthol that can be synthesized via an intramolecular Friedel-Crafts reaction. The precursor to the compound that undergoes the Friedel-Crafts reaction could be easily prepared via a Wadsworth-Horner-Emmons condensation involving 2,4-dimethoxybenzaldehyde. The retrosynthetic analysis of this procedure is shown in scheme 4.

Scheme 4



Scheme 5

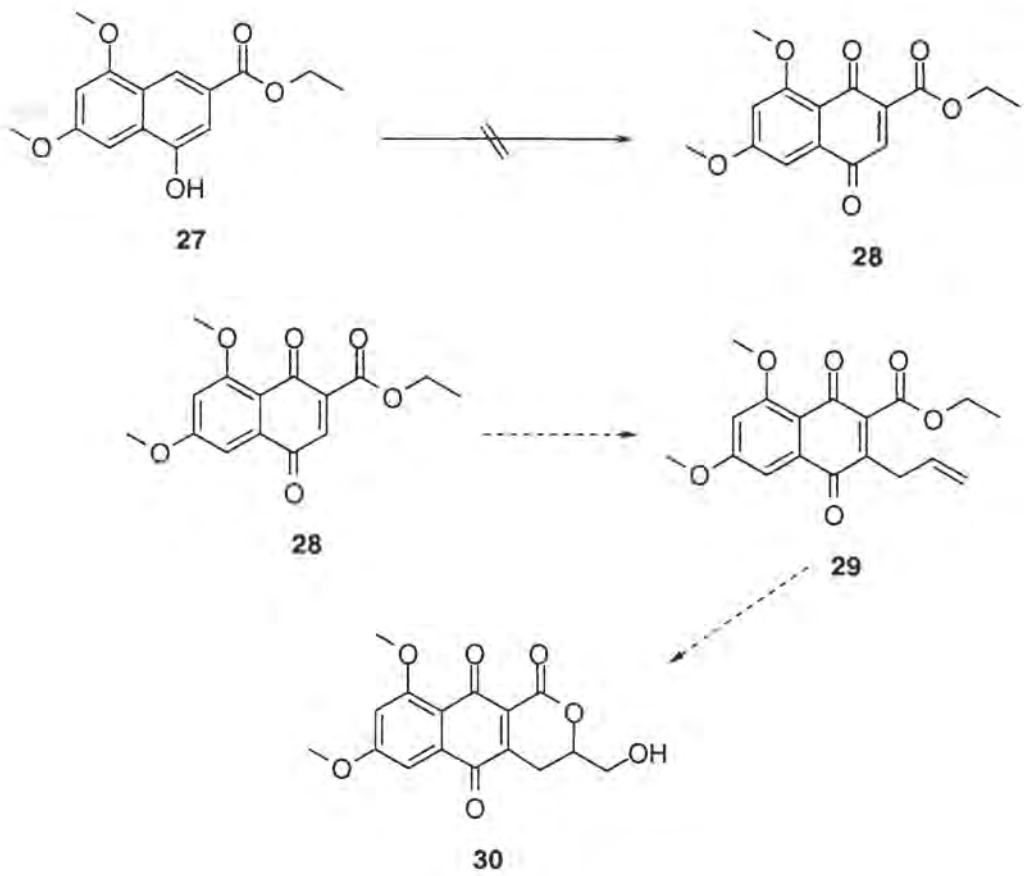


Our synthesis of the 5,7-substituted naphthol **27** (Scheme 5) began with the condensation of 2,4-dimethoxybenzaldehyde to give an ethyl *t*-butyl itaconate that would eventually be hydrolyzed to an itaconate half-ester.[6] This is akin to the classical Stobbe

reaction that involves the condensation of succinate esters with aldehydes or ketones to directly give itaconate half-esters.

The main drawback to the Stobbe reaction is that the yields obtained are variable and a number of undesirable side products can arise.[7] The alternative method we chose gives improved selectivity and better yields, a consequence of using *tert*-butyl 3-carboxyethyl-3-phosphonodiethylpropionate (**23**)-which is essentially an activated succinate ester. Commercially available triethylphosphonoacetate dissolved in tetrahydrofuran (THF) is reacted with sodium hydride after which *tert*-butyl bromoacetate is added to afford **23** in 75%

Scheme 6



yield. The anion of **23** was made by addition of one equivalent of sodium hydride to THF dissolved **23** at 0 °C. The anion solution was then added to 2,4-dimethoxybenzaldehyde resulting in a Wadsworth-Horner-Emmons reaction that furnished **24**, the preferred *E*-isomer (10:1). The *tert*-butyl ester was selectively cleaved with 90% aqueous trifluoroacetic acid to

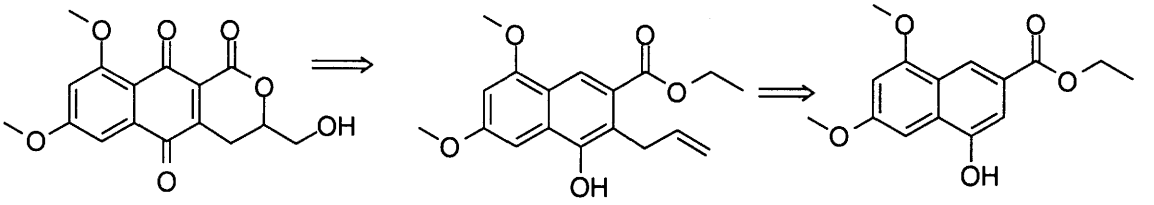
The acid **25**, potassium acetate, and acetic anhydride were heated for three hours and **26** was produced in 75% yield.[8] To hydrolyze **26** to the desired naphthol, we generated HCl *in situ* by adding acetyl chloride to a methanol solution of **26** at 0 °C and allowing the temperature to rise to 25 °C. Using this method, we were able to obtain naphthol **27** in almost quantitative yield.

With **27** in hand, we embarked on the first route that we had planned (Scheme 6). The first step in this sequence of reactions was the oxidation of naphthol **27** to the corresponding naphthoquinone **28**. In our attempts to effect this oxidation, we applied the following oxidizing agents: potassium dinitrodisulfonate (Fremy's salt),[9] phenyl iodo-*di*-trifluoroacetate,[10] salcomine (Cobalt-salen),[11] and ceric ammonium nitrate.[12] All these reagents failed to give us the product that we desired. We hypothesized that the electron-withdrawing effect of the carbonyl at the 3-position of **27** rendered the B-ring of the naphthol electron deficient, and consequently made the oxidation difficult. If we had been successful in synthesizing **28**, we had planned to introduce the allyl group at the 2-position of **27** via a Lewis acid assisted Michael addition with allyl tributyltin. We then would have functionalized the double bond, and subsequently constructed the

C-ring to give **30**.

Since our original plan did not work as we had hoped, we decided to modify our synthesis to the retrosynthetic pathway shown in Scheme 7. The lactone **30** could be obtained from ring closure of naphthol **32** that is derived from **27**.

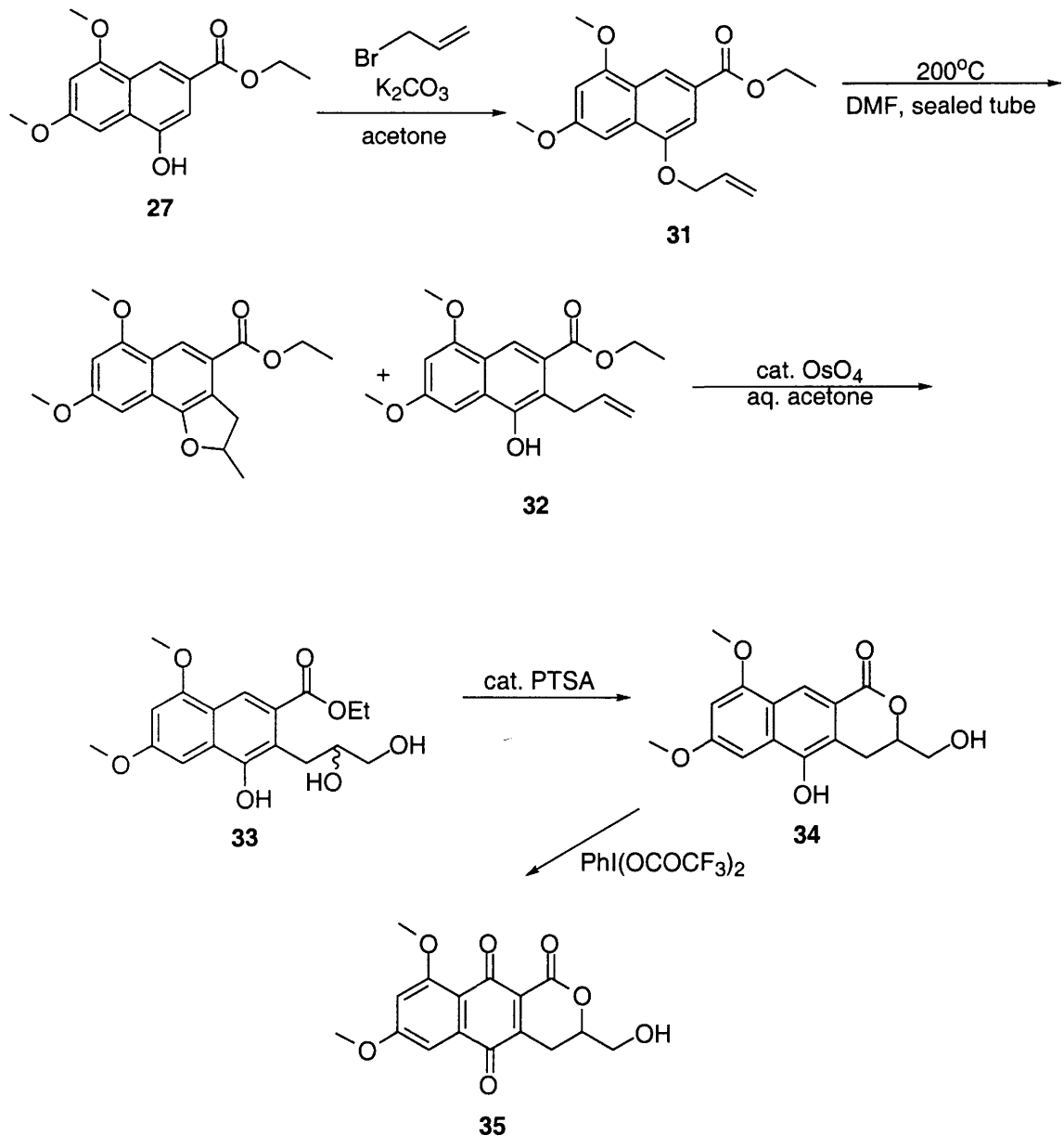
Scheme 7



30 **32** **27**

The *O*-alkylation of the naphthol **27** (Scheme 8) was accomplished by heating **27**, allyl bromide, and potassium carbonate in acetone.[13] The reaction gave ether **31** in 90% yield. We then carried out a Claisen rearrangement that initially gave low yields. After considering several solvents, we decided to use dimethylformamide (DMF), and carried out the reaction in a sealed tube. Compound **31** was dissolved in DMF, purged with argon to remove dissolved oxygen, and the tube was then sealed and heated to over 200 °C. After several attempts, the optimal conditions were established which resulted in naphthol **32** being produced in yields exceeding 75%. One of the side products of this reaction was compound **32a**. This side-product was most likely due to trace amounts of acid that may have been present in the reaction vessel. We therefore made sure that the tube was rinsed in aqueous base before carrying out the Claisen rearrangement.

Scheme 8

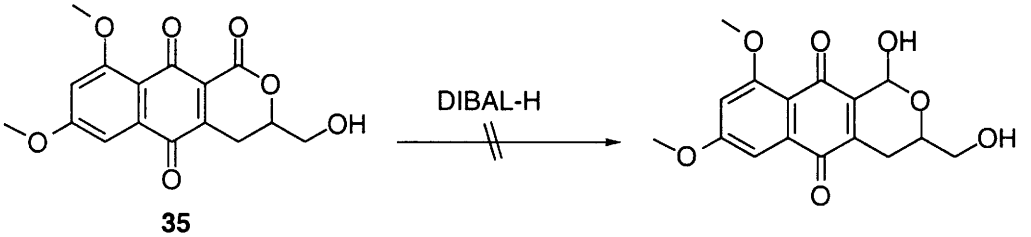


We next embarked on the functionalization of the allylic double bond in anticipation of cyclization to form the C-ring of thysanone. To this end, we employed a catalytic amount of osmium tetroxide (10 mol %), in the presence of *N*-methyl-morpholine-N-oxide (NMO).[14] The reaction proved to be quite sluggish but nonetheless proceeded in 74% yield. The

resulting highly polar compound **33** was then dissolved in 1,2-dichloroethane and treated with a catalytic amount of *p*-toluenesulfonic acid. Lactone **34** was isolated in almost quantitative yield.

On obtaining **34** we explored ways of oxidizing it to its corresponding naphthoquinone. We essentially tried all the oxidizing agents that we had used earlier. Phenyl iodo-*di*-trifluoroacetate was the only oxidizing agent that gave napthoquinone **35**, albeit in only 40% yield.[15] Having succeeded in constructing the tricyclic napthoquinone, the next challenge was the conversion of the lactone to the lactol. To accomplish this, we reacted **35** with DIBAL-H (Scheme 9) under the following conditions: at –78 °C, -40 °C, 0 °C in methylene chloride; at –78 °C, -40 °C, 0 °C in toluene.[16] Our efforts were fruitless as no reaction seemed to occur as was evidenced by recovery of starting material in all the cases. This development compelled us to seek another route to our target molecule. The goal of our new route would be to get to the lactol by bypassing the lactone. This would mean reduction of the ester group of naphthol **32** to the corresponding alcohol, followed by oxidation to the aldehyde. The oxidation would then be followed by dihydroxylation to give the lactol.

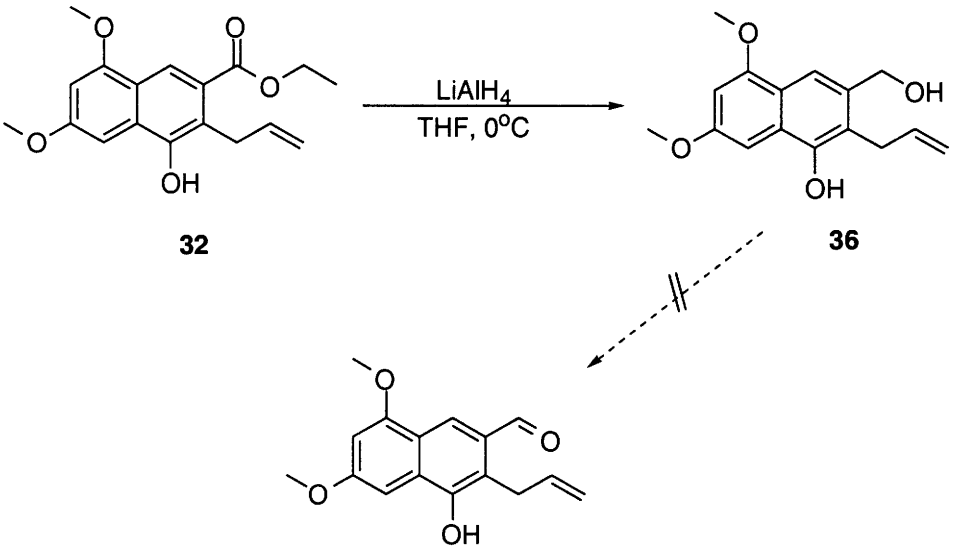
Scheme 9



35

We started on the new route by reducing naphthol **32** with lithium aluminumhydride (LAH) to the corresponding alcohol[17] (Scheme 10). This reaction proceeded in 90% yield to give compound **36**.

Scheme 10



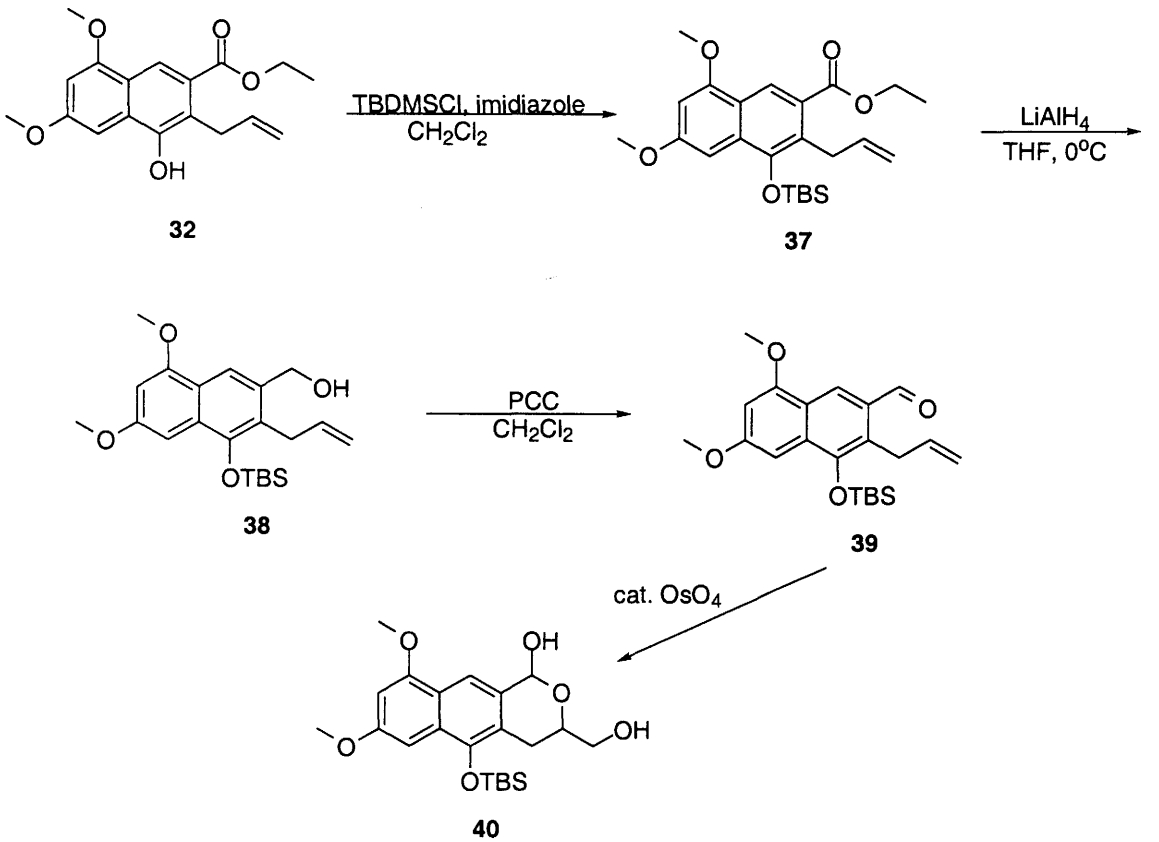
The next step was to oxidize the primary alcohol to the corresponding aldehyde. The use of activated manganese dioxide or pyridinium chlorochromate (PCC) did not afford the desired product. We consequently decided to protect **32** prior to proceeding with the sequence of reactions in Scheme 10.

The naphthol **32** underwent *O*-silyl protection[18] when it was dissolved in methylene chloride and reacted with *tert*-butyldimethylsilyl chloride, in the presence of imidazole. The protected napthol **37** was obtained in 92% yield over two steps. LAH reduction of **37**

occurred in 95% yield to give **38**. PCC oxidation[19] proceeded smoothly in 90% yield to give aldehyde **39** (Scheme 11).

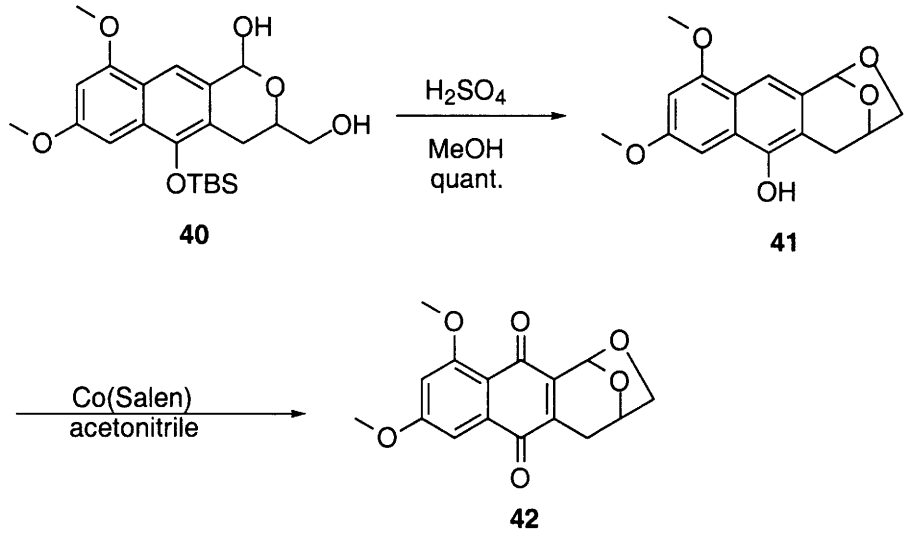
When we obtained **39**, we carried out a dihydroxylation reaction using a catalytic amount of osmium tetroxide with NMO as the oxidant. This reaction directly afforded the TBS-protected lactol **40** as a racemic mixture in 75 % yield.

Scheme 11



We decided to oxidize the deprotected naphthol to the corresponding naphthoquinone at this point. We expected the reaction to proceed smoothly since there would be no electron-withdrawing effect on the B-ring. Lactol **40** was dissolved in methanol, followed by addition of a catalytic amount of concentrated sulfuric acid (Scheme 12). Instead of replacing the hydroxy group at C-1 with a methoxy group, an acetal was formed. Additionally, the *O*-silyl linkage was broken to give naphthol **41**.

Scheme 12



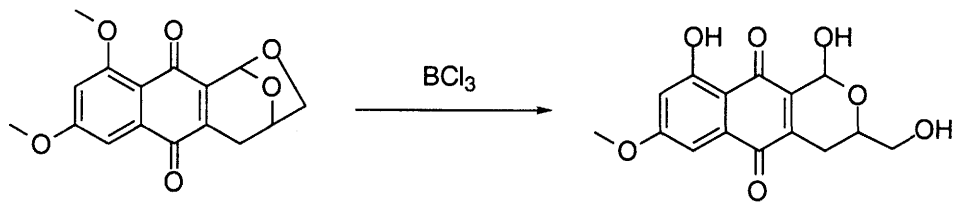
40 **41** **42**

We then carried out a series of reactions to find the best oxidizing agent that would give us naphthoquinone **42** (Scheme 13). Fremy's salt, ceric ammonium nitrate, and phenyl iodo-*di*-trifluoroacetate did not react with **41**. However, when naphthol **41** was reacted with a

catalytic amount of salcomine in the presence of oxygen, naphthoquinone **42** was given in 60% yield.

With the naphthoquinone **42** in hand, we purposed to selectively demethylate at C-9 *peri* to the carbonyl C-10 (Scheme 13). This was achieved by utilizing 1.1 equivalents of boron trichloride,[20] at 0 °C in methylene chloride. The choice of BCl_3 over BBr_3 was that BBr_3 is an extremely reactive demethylating reagent. The reaction occurred as we had anticipated. In addition to the demethylation, the acetal opened resulting in hemiacetal **22**, our target molecule.

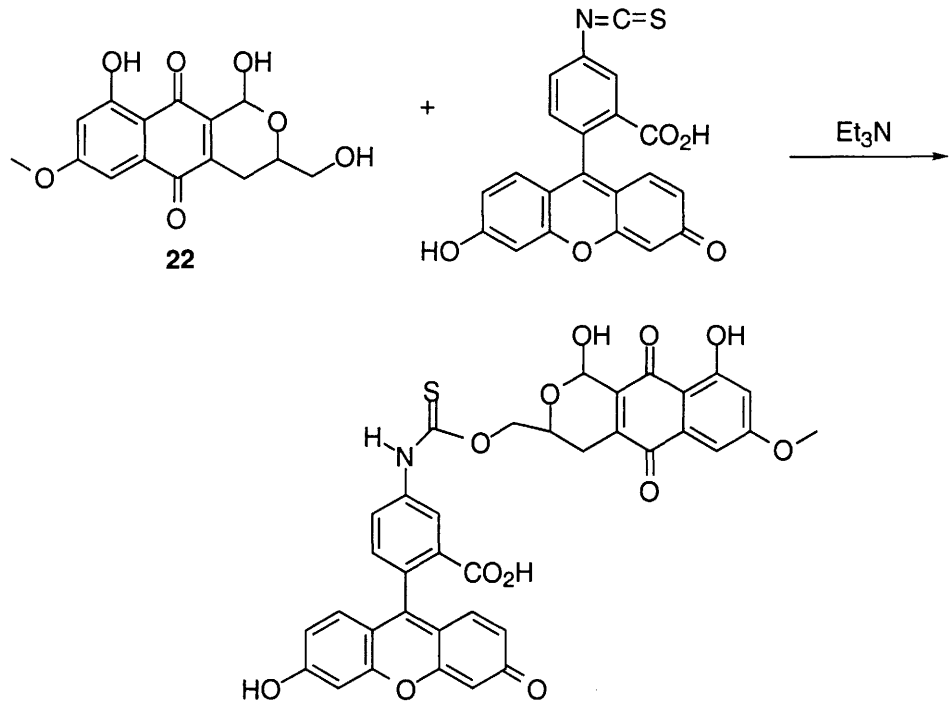
Scheme 13



42 **22**

We then attached compound **22** to Flourescein isothiocyanate in the presence of triethylamine (Scheme 14). The product of this reaction would then be useful in the biological testing of the thysanone analog that we synthesized.

Scheme 14



CONCLUSIONS

We successfully synthesized an analog of thysanone in 14 steps from 2,4-dimethoxybenzaldehyde. The hydroxymethyl is a unique feature of the analog that can be used to tether another biologically active molecule. The biological properties of the analog will be investigated, and the properties compared to thysanone.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercially available suppliers and were used without further purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. Methylene chloride and acetonitrile were purified by distillation from calcium hydride. All reactions were conducted under an argon atmosphere except where noted. All extracts were dried over anhydrous sodium sulfate except where otherwise noted. Apparatus for experiments requiring anhydrous conditions were flame-dried under argon, or dried in a 150 ^{o}C oven for 12 hours and cooled under a stream of argon. Silica gel chromatography (sgc) was performed on Scientific Absorbance Silica gel 60 (mesh 230-400). Thin layer chromatography (tlc) was performed using glass backed silica gel plates, thickness of 0.250 mm, purchased from Aldrich Chemical Company. The solvent systems for both (sgc) and (tlc) were suitable mixtures of hexane (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-Elmer 1320 Spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Varian 300 Spectrometer. All chemical shifts are reported in δ relative to $CDCl_3$ (7.26 ppm) as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), ABQ (AB quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet). The addition of br is indicative of a broadened pattern. Carbon-13 nuclear magnetic resonance spectra (75.46 MHz) were obtained on a Varian 300 Spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm) as an internal standard. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution

mass spectra (MS) were obtained on a Finnigan 4123 mass spectometer. The purity of all titled compounds was found to be >95% by ^{1}H NMR spectral determination.

2-(Diethoxy-phosphoryl)-succinic acid 4-*tert*-butyl ester 1-ethyl ester (23)

To a suspension of 5.538 g (115.5 mmol) of pentane-washed sodium hydride (50% dispersion) in 150 mL of dry THF at 0 °C was added dropwise (over 30 minutes) a solution of 24.64 g (110 mmol in 75 mL of THF) of triethylphosphonoacetate. The reaction mixture was stirred and allowed to warm to room temperature overnight. *Tert*-butyl bromoacetate (22.5 g, 115.5 mmol) was added dropwise at 0 °C over 30 minutes and the reaction mixture was stirred and allowed to warm to room temperature. After 24 hours the reaction mixture was concentrated under reduced pressure and partitioned between water and ethyl acetate. The organic phase was collected, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a pale yellow liquid (37.5 g). This crude product was vacuum distilled to give fraction 1 (120-132 °C, 0.08 mm Hg, 8.15 g) then fraction 2 (132 °C, 0.08 mm Hg, 16.24 g). Both fractions were the required product giving an overall yield of **23** in 66% yield (24.39 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 6H), 1.43 (s, 9H), 2.73 (ddd, J = 12.3 Hz, 9.0Hz, 3.3 Hz, 1H), 2.99 (ddd, J = 15 Hz, 11.7 Hz, 4.5 Hz, 1H), 3.40 (ddd, J = 15 Hz, 11.7 Hz, 3.6 Hz, 1H), 4.06 – 4.12 (m, 4H), 4.10 - 4.23 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.0, 167.9, 81.1, 62.8, 61.5, 42.1, 40.4, 32.4, 28.0, 27.7, 16.2, 14.0. IR 2982, 1733, 1258, 1151cm^{-1}. HRMS calcd for $C_{14}H_{27}O_7P$ 339.1573, found 339.1559.

2-(2,4-Dimethoxy-benzylidene)-succinic acid 4-*tert*-butyl ester 1-ethyl ester (24)

To a suspension of 1.46 g (36.5 mmol) sodium hydride (60% dispersion, hexane washed) in 50 mL of dry THF was added phosphonate **23** (12.2 g, 36 mmol) dropwise. The reaction mixture was stirred for two hours at 0 °C under argon. A solution of 2,4-dimethoxybenzaldehyde (5.82 g, 35.0 mmol) in 30 mL THF was prepared in a 250 mL flask. The anion solution was added dropwise with stirring to the aldehyde solution at 0 °C under argon. The cooling bath was removed and the reaction mixture was stirred and allowed to warm to room temperature overnight. After 18 hours, water (20 mL) was added and the solvent was removed under reduced pressure. The residue was partitioned between water and methylene chloride. The organic phase was collected, dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by flash column chromatography using hexanes and ethyl acetate (30:1). The pure product was obtained in 75% yield as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 3H), 1.46 (s, 9H), 3.40 (s, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.50 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.91 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.4, 28.2, 35.5, 55.5, 55.6, 60.9, 80.9, 98.5, 104.4, 117.2, 125.2, 130.6, 137.2, 159.1, 161.9, 167.9, 170.9. MS (m/z) 350 (M+), 294, 249, 166, 148, 89, 61, 43. HRMS calcd for $C_{19}H_{26}O_6$ 350.1729, found 350.1735.

2-(2,4-Dimethoxy-benzylidene)-succinic acid 1-ethyl ester (25)

Compound **24** (5.2 g, 14.86 mmol) was dissolved in 20 mL of trifluoroacetic acid/water (9/1) at room temperature. The mixture was stirred, and the progress of the reaction monitored by tlc. When the reaction was complete, the solvent was removed under

reduced pressure to give crude compound **25**. The crude product was partitioned between 10% aqueous sodium hydrogen carbonate (100 mL) and ethyl acetate (50 mL). The aqueous phase was separated, acidified with concentrated hydrochloric acid to pH 2, and extracted with ethyl acetate (3 × 30 mL). The organic extract was dried and evaporated under reduced pressure to give pure **25**, a white solid, in almost quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 3.52 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.34 (q, J = 7.2 Hz, 2H), 6.47 (d, J = 2.4 Hz, 1H), 6.55 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H). ^{13}C NMR (300MHz, $CDCl_3$) δ 14.3, 34.3, 55.7, 55.8, 62.0, 98.8, 104.9, 116.6, 123.3, 130.9, 139.6, 159.2, 164.5, 168.9, 178.3. MS (m/z) 294 (M+), 294, 249, 166, 148, 89, 61, 43. HRMS calcd for $C_{15}H_{18}O_6$ 294.2998, found 294.2986.

4-Acetoxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (26)

The acid **25** (4.2 g, 14.3 mmol) and anhydrous potassium acetate (1.54 g, 15.7 mmol) were dissolved in acetic anhydride (50 mL). The solution was heated at reflux for 2 hours. The solvent was removed under reduced pressure, and the product was purified by recrystallization from ethanol to give a pale yellow crystalline solid in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 2.46 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 4.44 (q, J = 7.2 Hz, 2H), 6.54 (d, J = 2.1 Hz, 1H), 6.67 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 1.5 Hz, 1H), 8.80 (s, 1H). ^{13}C NMR (300MHz, $CDCl_3$) δ 14.7, 21.3, 29.9, 55.6, 56.0, 61.3, 91.8, 98.8, 119.4, 122.5, 123.5, 124.6, 131.4, 145.6, 158.2, 161.2, 166.5, 169.5.

MS (m/z) 294 (M+), 294, 249, 166, 148, 89, 61, 43. HRMS calcd for $C_{17}H_{18}O_6$ 318.1103, found 318.1112.

4-Hydroxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (27)

To a solution of 1.84 g (5.79 mmol) of **26** in 10 mL of methanol was added 94.2 mg (1.2 mmol) of acetyl chloride at 0 °C. The mixture was stirred at 0 °C and allowed to warm to room temperature. After 12 hours, the solvent was removed under reduced pressure, and the product was purified by recrystallization from ethanol to give a grayish-white solid in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, J = 7.2 Hz, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.46 (q, J = 7.2 Hz, 2H), 6.55 (d, J = 2.1 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 8.50 (s, 1H). ^{13}C NMR (300MHz, $CDCl_3$) δ 14.7, 21.3, 29.9, 55.6, 56.0, 61.3, 91.8, 98.8, 119.4, 122.5, 123.5, 124.6, 131.4, 145.6, 158.2, 161.2, 166.5, 169.5.

4-Allyloxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (31)

To a stirred solution of 3.71 g (13.4 mmol) of **27** in 50 mL of acetone was added 3.73 g (27 mmol) of potassium carbonate and 3.3 g (27 mmol) of allyl bromide. The resulting mixture was heated under reflux and the reaction was monitored by tlc. After 18 hours, the reaction mixture was cooled, and then suction filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the product was purified by flash column chromatography using hexanes and ethyl acetate (15 : 1), to give **31**, a pale yellow solid, in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, J = 7.2 Hz, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 4.78 (d, J_1 = 4.8 Hz, 2H), 5.35 (dd, J_1 = 10.1 Hz, J_2 = 1.5Hz, 1H), 5.52 (dd, J_1 = 17.1 Hz, J_2 = 1.5Hz, 1H), 6.13 – 6.26 (m, 1H), 6.55 (d, J = 2.1 Hz, 1H), 7.17

(d, J = 2.1 Hz, 1H), 7.43 (d, J = 1.5 Hz, 1H), 8.52 (s, 1H). ^{13}C NMR (300MHz, $CDCl_3$) δ 14.7, 52.3, 55.6, 55.8, 69.3, 92.9, 98.7, 105.7, 117.3, 118.4, 121.8, 124.3, 130.1, 133.4, 153.3, 157.7, 160.3, 167.8. MS (m/z) 316 (M+), 271, 243, 227, 199, 139, 128. HRMS calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1314.

3-Allyl-4-hydoxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (32)

A flame-dried pressure tube, cooled under a stream of argon, was charged with 1.58 g (5 mmol) of ether **31** and dissolved in 5 mL of dimethylformamide. The solution was degassed with argon for 10 minutes. The pressure tube was sealed and placed in an oil bath. The temperature of the oil bath was raised to 210 °C, and the solution stirred at this temperature for 6 hours. The tube was cooled to room temperature and the solvent removed under reduced pressure. The resulting crude product was purified by flash column chromatography using hexanes and ethyl acetate (10 : 1) to afford naphthol **32** in 78% yield as the major product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 3.88 (d, J = 1.8), 3.92 (s, 3H), 3.99 (s, 3H), 4.43 (q, J = 7.2 Hz, 2H), 5.19 (dd, J_1 = 4.2 Hz, J_2 = 1.5Hz, 1H), 5.24 (dd, J_1 = 17.1 Hz, J_2 = 1.5Hz, 1H), 6.07 – 6.20 (m, 1H), 6.50 (d, J = 2.1 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 8.37 (s, 1H). ^{13}C NMR (300MHz, $CDCl_3$) δ 14.6, 32.0, 55.6, 55.8, 61.1, 92.2, 98.4, 116.4, 118.7, 119.0, 120.5, 125.8, 128.5, 136.6, 149.9, 157.4, 160.2, 168.3. MS (m/z) 316 (M+), 269, 255, 243, 227, 211, 199, 139, 128. HRMS calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1314.

6,8-Dimethoxy-2-methyl-2,3-dihydro-naphthol[1,2-*b*]furan-4-carboxylic acid ethyl ester

15% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 1.56 (d, J = 6.3 Hz), 3.27 (dd, J_1 = 16.8 Hz, J_2= 7.5 Hz, 1H), 3.81 (dd, J_1 = 16.8 Hz, J_2= 9.3 Hz, 1H), 3.93 (s, 3H), 3.97 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 5.09 – 5.13 (m, 1H), 6.45 (d, J = 2.1 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 8.41 (s, 1H). ^{13}C NMR (300MHz, $CDCl_3$) δ 14.7, 16.6, 22.4, 39.5, 55.6, 55.8, 60.8, 80.7, 91.9, 98.3, 117.9, 121.7, 122.0, 124.3, 154.9, 157.9, 160.3, 167.3.

3-(2,3-Dihydroxy-propyl)-4-hydroxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (33)

To a magnetically stirred solution of **32** (105 mg, 0.30 mmol) and *N*-methylmorpholine *N*-oxide (54 mg, 0.46 mmol) in 20 mL of 10% water in acetone (v/v) was added a solution of osmium tetroxide (850 μL, 0.017 mmol) in *tert*-butyl alcohol (0.02 M, 1.0 g of osmium tetroxide in 196 mL of *tert*-butyl alcohol containing 0.5% *tert*-butyl hydroperoxide). The reaction progress was monitored by tlc analysis. After 36 hours of stirring at room temperature, tlc analysis indicated the complete disappearance of **32** and the appearance of a new, more polar spot. A 1:1 (w/w) mixture of sodium hydrosulfite and sodium sulfite (600 mg) was then added to the reaction mixture and stirring continued for 10 minutes. The mixture was then filtered through a short pad of Celite on a 150 mL sintered-glass funnel. The Celite pad was washed with three 15 mL portions of acetone. The filtrate, combined with the acetone wash, was dried over sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by flash column chromatography using hexanes and ethyl acetate (1: 1) to afford **33** in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ

1.49 (t, J = 7.2 Hz, 3H), 3.18 (br dd, J_1 = 14.4 Hz, J_2= 7.2 Hz, 1H), 3.32 (br dd, J_1 = 14.7 Hz, J_2= 3.3 Hz, 1H), 3.59 (br dd, J_1 = 11.1 Hz, J_2= 6.9 Hz, 1H), 3.88 (br dd, J_1 = 11.1 Hz, J_2= 4.5 Hz, 1H), 4.29 – 4.33 (m, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 6.50 (d, J = 2.1 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 8.39 (s, 1H).

5-Hydroxy-3-hdroxymethyl-7,9-dimethoxy-3,4-dihydro-benzo[*g*]isochromen-1-one (34)

To a solution of 237 mg (68 mmol) of **33** in 15 mL of 1,2-dichloroethane was added 10 mg (5 mmol) of *p*-toluenesulfonic acid. The mixture was stirred for 18 hours at room temperature. After removal of the solvent, the crude product was purified by flash column chromatography using hexanes and ethyl acetate (10 :1) to afford **34** in 59% yield. ^{1}H NMR (300 MHz, d_6 – acetone) 3.00 (br dd, J_1 = 17.1 Hz, J_2= 11.4 Hz, 1H), 3.35 (br dd, J_1 = 16.8 Hz, J_2= 3.6 Hz, 1H), 3.84 (t, J = 5.4 Hz, 2H), 3.93 (s, 3H), 4.06 (s, 3H), 4.52 – 4.60 (m, 1H), 6.62 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 2.1 Hz, 1H), 8.55 (s, 1H). MS (m/z) 304 (M+), 286, 245, 216, 201, 159, 115, 77. HRMS calcd for $C_{16}H_{16}O_6$ 304.0947, found 304.0953.

3-Hydroxymethyl-7,9-dimethoxy-3,4-dihydro-benzo[*g*]isochromene-1,5,10-trione (35)

To a solution of **34** (280 mg, 921 mmol) in 20 mL of 33% water in acetonitrile (v/v) was added a solution of *bis*[trifluoroacetoxy]iodobenzene (396 mg, 921 mmol) in 30mL of 33% water in acetonitrile (v/v). The mixture was stirred at room temperature for 1 hour, neutralized with aqueous sodium bicarbonate solution, and extracted with methylene chloride (2 × 20ml). The combined organic layer was washed with brine, dried with magnesium sulfate, and evaporated to give the crude naphthoquinone. The crude sample was purified by

flash column chromatography using hexanes and ethyl acetate (gradient of 10:1 → 1:1) to give **35** in 48% yield. ^{1}H NMR (300 MHz, d_6 – acetone) 3.00 (br dd, J_1 = 16.8 Hz, J_2= 11.4 Hz, 1H), 3.35 (br dd, J_1 = 16.5 Hz, J_2= 3.6 Hz, 1H), 3.86 (t, J = 4.5 Hz, 2H), 3.93 (s, 3H), 3.96 (s, 3H), 4.56 – 4.63 (m, 1H), 6.57 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H).

2-Allyl-3-hydroxymethyl-5,7-dimethoxy-nahthalen-1-ol (36)

A solution of **32** (772 mg, 2.44 mmol) dissolved in 30 mL of THF was added dropwise to a stirred suspension of lithium aluminum hydride (310 mg, 8.13 mmol) and 20 mL THF at 5 °C under argon. The reaction was stirred under these conditions for 1.5 hours and then quenched with the sequential dropwise addition of the following: water (0.3 mL), 15% sodium hydroxide solution (0.3 mL), and water (0.9 mL). This mixture was stirred for 16 hours at 25 °C and then suction filtered through a short pad of Celite and silica gel. The filtering pad was washed with three 5 mL portions of ethyl acetate. The filtrate was combined with the ethyl acetate wash, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give impure **36**. The residue was purified by flash column chromatography using hexanes and ethyl acetate (10: 1), to afford **36** in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (br d, J = 6Hz, 2H), 3.93 (s, 3H), 3.97 (s, 3H), 4.78 (s, 2H), 5.11 (br dd, J_1 = 17.1 Hz, J_2= 1.5 Hz, 1H), 5.22 (br dd, J_1 = 10.2 Hz, J_2= 1.5 Hz, 1H), 6.03 – 6.15 (m, 1H), 6.50 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 2.1 Hz, 1H), 7.73 (s, 1H).

3-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (37)

Naphthol **32** (377 mg, 1.2 mmol) was dissolved in methylene chloride (20 mL) and treated with *tert*-butyl dimethylsilylchloride (270 mg, 1.8 mmol), imidazole (123 mg, 1.8 mmol), and dimethylaminopyridine (20 mg). The mixture was stirred for 18 hours at room temperature after which the solvent was removed under reduced pressure. The residue was directly subjected to flash column chromatography (hexane-ethyl acetate 25:1) to give the desired silyl ether **37** in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 6H), 1.13 (s, 9H), 1.44 (t, J = 7.2 Hz, 3H), 3.88 (d, J = 6.6 Hz, 2H), 3.92 (s, 3H), 3.96 (s, 3H), 4.37 (q, J = 7.2 Hz, 2H), 4.89 (dd, J_1 = 5.1 Hz, J_2 = 1.5Hz, 1H), 4.97 (dd, J_1 = 15.1 Hz, J_2 = 1.5Hz, 1H), 5.86 – 5.97 (m, 1H), 6.50 (d, J = 2.1 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 8.40 (s, 1H). ^{13}C NMR (300MHz, $CDCl_3$) δ -2.7, 14.6, 19.0, 26.0, 26.3, 30.0, 32.2, 55.6, 55.8, 61.0, 94.3, 98.0, 115.0, 119.7, 120.6, 126.2, 127.1, 131.7, 148.4, 157.5, 159.7, 168.7. MS (m/z) 316 (M+), 269, 255, 243, 227, 211, 199, 139, 128. HRMS calcd for $C_{24}H_{34}O_5Si$ 430.6093, found 430.6085.

[3-Allyl-4-(*tert*-butyl-dimethylsilanyloxy)-6,8-dimethoxy-naphthalen-2-yl]-methanol (38)

A solution of **37** (570 mg, 1.32 mmol) dissolved in 20 mL of THF was added dropwise to a stirred suspension of lithium aluminum hydride (150 mg, 3.96 mmol) and 20 mL THF at 5 °C under argon. The reaction was stirred under these conditions for 1.5 hours and then quenched with the sequential dropwise addition of the following: water (0.15 mL), 15% sodium hydroxide solution (0.15 mL), and water (0.45 mL). This mixture was stirred

for 6 hours at 25 °C and then suction filtered through a short pad of Celite and silica gel. The filtering pad was washed with three 5 mL portions of ethyl acetate. The filtrate was combined with the ethyl acetate wash, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude mixture of **38**. The residue was purified by flash column chromatography using hexanes and ethyl acetate (10: 1), to afford **38** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.11 (s, 9H), 3.68 (br d, J = 5.7 Hz, 2H), 3.91 (s, 3H), 3.95 (s, 3H), 4.78 (s, 2H), 4.90 (br dd, J_1 = 17.1 Hz, J_2= 1.8 Hz, 1H), 5.00 (br dd, J_1 = 10.2 Hz, J_2= 1.8 Hz, 1H), 5.90 - 6.03 (m, 1H), 6.47 (d, J = 2.1 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 7.85 (s, 1H).

^{13}C NMR (300MHz, $CDCl_3$) δ -2.6, 19.0, 26.3, 30.9, 55.5, 55.7, 64.4, 94.2, 97.5, 115.2, 115.6, 121.5, 125.1, 129.2, 135.5, 137.3, 148.3, 156.7, 157.8. MS (m/z) 388 (M+), 370, 312. HRMS calcd for $C_{22}H_{32}O_4Si$ 388.2070, found 388.2076.

3-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-6,8-dimethoxy-naphthalene-2-carbaldehyde (39)

To a solution of **38** (0.53 g, 1.36 mmol) in methylene chloride (20 mL) was added a finely ground portions of a mixture of pyridinium chlorochromate (0.52 g, 2.72 mmol) and Celite (1.18 g) over a period of 30 minutes at room temperature. The reaction mixture was stirred for 18 hours at 25 °C, after which it was diluted with methylene chloride and filtered through a short pad of Celite. The Celite pad was washed with two 10 mL portions of methylene chloride which were combined with the filtrate, dried over sodium sulfate, and

evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane – ethyl acetate 10:1) giving **39** in 90% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.12 (s, 9H), 3.96 (br d, J = 5.7 Hz, 2H), 3.91 (s, 3H), 3.98 (s, 3H), 4.90 (br dd, J_1 = 17.1 Hz, J_2= 1.8 Hz, 1H), 4.97 (br dd, J_1 = 10.2 Hz, J_2= 1.8 Hz, 1H), 5.90 - 6.03 (m, 1H), 6.49 (d, J = 2.1 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 7.85 (s, 1H), 10.16 (s, 1H).

^{13}C NMR (300MHz, $CDCl_3$) δ -3.6, 14.4, 22.9, 26.3, 29.3, 30.3, 55.7, 55.9, 94.8, 98.2, 115.5, 125.3, 125.9, 129.2, 130.7, 137.5, 148.5, 158.1, 160.9, 193.1. MS (m/z) 386 (M+), 369, 329, 301, 296, 260. HRMS calcd for $C_{22}H_{30}O_4Si$ 386.1913, found 386.1919.

5-(*tert*-Butyl-dimethyl-silanyloxy)-3-hydroxymethyl-7,9-dimethoxy-3,4-dihydro-1*H*-benzo[*g*]isochromen-1-ol (40)

To a magnetically stirred solution of **39** (364 mg, 0.94 mmol) and *N*-methylmorpholine *N*-oxide (165 mg, 1.41 mmol) in 25 mL of 10% water in acetone (v/v) was added a solution of osmium tetroxide (4.7 mL, 0.094 mmol) in *tert*-butyl alcohol (0.02 M, 1.0 g of osmium tetroxide in 196 mL of *tert*-butyl alcohol containing 0.5% *tert*-butyl hydroperoxide). The reaction progress was monitored by tlc analysis. After 42 hours of stirring at room temperature, tlc analysis indicated the complete disappearance of **39** and the appearance of a new, more polar spot. A 1:1 (w/w) mixture of sodium hydrosulfite and sodium sulfite (700 mg) was then added to the reaction mixture and stirring continued for 30 minutes. The mixture was then filtered through a short pad of Celite on a 150 mL sintered-glass funnel. The Celite pad was washed with three 15 mL portions of acetone. The filtrate, combined with the acetone wash, was dried over sodium sulfate. The solvent was removed

under reduced pressure, and the product was purified by flash column chromatography using hexanes and ethyl acetate (1: 1) to afford **40** in 72% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 3H), 0.26 (s, 3H), 1.11 (s, 9H), 2.79 (br d, J = 17.1 Hz, 1H), 3.32 (br dd, J_1 = 17.1 Hz, J_2= 1.5 Hz, 1H), 3.69 (br dd, J_1 = 7.2 Hz, J_2= 1.8 Hz, 1H), 3.89 (s, 3H), 3.94 (s, 3H), 4.00 (td, J_1 = 6.3 Hz, J_2= 1.8 Hz, 1H), 4.94 – 4.98 (m, 1H), 6.12 (s, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 7.62 (s, 1H),

^{13}C NMR (300MHz, $CDCl_3$) δ -3.4, -3.1, 19.0, 26.3, 31.8, 55.5, 55.8, 68.2, 72.4, 93.6, 97.7, 101.2, 112.3, 117.7, 121.6, 129.7, 132.0, 148.6, 158.1. MS (m/z) 420 (M+), 402, 345, 315, 273, 228. HRMS calcd for $C_{22}H_{32}O_6Si$ 420.1968, found 420.1973.

8,10-Dimethoxy-1,3,4,5-tetrahydro-1,4-epoxy-2-naphthoxepin-6-ol (41)

To a solution of **40** (340 mg, 0,81 mmol) in 20 mL of methanol was added 2 drops of 6 M sulfuric acid. The mixture was heated at reflux for 1 hour, after which the solvent removed under reduced pressure. The residue was directly subjected to flash column chromatography (hexane – ethyl acetate 1:1), affording **41** in 75% yield as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (br d, J = 16.5 Hz, 1H), 3.31 (br dd, J_1 = 16.2 Hz, J_2= 5.1 Hz, 1H), 3.73 (br dd, J_1 = 7.5 Hz, J_2= 1.5 Hz, 1H), 3.92 (s, 3H), 3.96 (s, 3H), 4.03 (td, J_1 = 7.5 Hz, J_2= 1.5 Hz, 1H), 4.98 – 5.02 (m, 1H), 6.18 (s, 1H), 6.48 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 2.1 Hz, 1H), 7.57 (s, 1H),

^{13}C NMR (300MHz, $CDCl_3$) δ 25.5, 54.9, 55.3, 65.6, 68.6, 76.5, 92.0, 97.4, 108.5, 116.6, 121.2, 125.2, 131.0, 148.9, 156.6, 157.7. MS (m/z) 288 (M+), 258, 230, 215, 187. HRMS calcd for $C_{16}H_{16}O_5$ 288.0998, found 288.1002.

8,10-Dimethoxy-1,3,4,5-tetrahydro-1,4-epoxy-2-naphthoxepin-6,11-dione (42)

To a solution of **41** (124 mg, 0.43 mmol) in 25 mL acetonitrile was added *bis*(salicylidene)ethylenediiminocobalt(II) (salcomine) (5 mg, 0.15 mmol). Oxygen was bubbled into the solution for 2 hours and the mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with 10 mL acetonitrile and filtered through a short pad of Celite. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (ethyl acetate-hexane 2:1) to give **42**, a crystalline yellow solid, in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (br d, J = 19.5 Hz, 1H), 3.05 (br ddd, J_1 = 19.5 Hz, J_2= 4.5 Hz, J_3 = 2.4 Hz 1H), 3.67 (br dd, J_1 = 7.8 Hz, J_2= 1.8 Hz, 1H), 3.92 (s, 3H), 3.96 (s, 3H), 4.02 (td, J_1 = 6.0 Hz, J_2= 2.4 Hz, 1H), 4.89 – 4.92 (m, 1H), 6.39 (s, 1H), 6.73 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H).

^{13}C NMR (300MHz, $CDCl_3$) δ 26.2, 29.6, 56.4, 56.7, 69.1, 71.5, 93.2, 103.6, 104.6, 136.0, 136.6, 143.0, 162.3, 164.9, 180.7, 185.3. MS (m/z) 302 (M+), 303, 284, 271, 255, 227. HRMS calcd for $C_{16}H_{14}O_6$ 302.0790, found 302.0795.

1.9-Dihydroxy-3-hydroxymethyl-7-methoxy-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (22)

To a solution of quinone **42** (24 mg, 0.079 mmol) in dry methylene chloride (10 mL) under argon, 1 M boron trichloride solution in methylene chloride (0.095 ml, 0.095 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour and at room temperature for 2 hours. After the reaction was complete, the reaction mixture was diluted

with methylene chloride, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 2:1 ethyl acetate/hexane) to give **22**, an orange solid, in 58% yield. . ^{1}H NMR (300 MHz, d_6 – acetone) δ 2.38 (br dd, J_1 = 19.5 Hz, J_2= 10.2 Hz, 1H), 2.70 (br dd, J_1 = 19.5 Hz, J_2= 3.6 Hz, 1H), 3.72 (t, J = 5.1 Hz, 2H), 3.98 (s, 3H), 4.26 – 4.34 (m, 1H), 6.00 (s, 1H), 6.76 (d, J = 2.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H).

^{13}C NMR (300MHz, $CDCl_3$) δ 24.4, 56.0, 59.9, 64.6, 66.4, 85.9, 106.0, 107.5, 136.6, 145.8, 156.8, 159.2, 164.6, 175.9, 185.2. MS (m/z) 302 (M+), 303, 284, 271, 255, 227. HRMS calcd for $C_{15}H_{14}O_7$ 306.0740, found 306.0744.

REFERENCES

1. S. B. Singh, M. G. Cordingley, R. G. Ball, J. L. Smith, A.W. Dombrowski, and M. A. Goetz.; *Tetrahedron Lett.,* **1991**, 32, 5279.

2 Gwaltney, J.M.; in *"Viral Infection of Man: Epidemiology and Control"* (Evans E.A., ed.) 2nd Ed., pp. 491-517, Plenum Publishing Corp., New York (**1982**).

3. Gill, M., Donner, C. D.; *Tetrahedron Lett.,* **1999**, 40, 3921.

4. Gill, M., Dimitriadis, C., Harte M. F. *Tetrahedron: Asymmetry,* **1997**, 8, 2153.

5. Lu, Y.; MS thesis, **1999**, Iowa State University, Ames, Iowa.

6. (a) Owton, W. M.; Gallagher, P. T.; Juan-Montesinos, A.; *Synth. Comm.* **1993**, 23, 2119. (b) Kameoka,H., Nishiyama, T.; *Chemistry Express,* **1993**, 8, 397.

7. Johnson, S.W., Guido, H.D.; *"The Stobbe Condensation" Organic reactions*, **6**, 1.

8. (a) Boger, D. L., Turnbull, P.; *J. Org. Chem.* **1998**, 63, 8004. (b) Sargent, M. V., Comber, M. F.; *J.Chem. Soc. Perkin 1*, **1991**, 2783.

9. Achari, B., Bandyopadhyay, S., Basu, K., Pakrashi, S.C.; *Tetrahedron,* **1985**, 41, 107.

10. Tamura, Y., Yakura, T., Tohma, H., Kikuchi, K., Kita, Y.; *Synthesis*, **1989**, 127.

11. (a) Bloomer, J. L., Stagliano, K. W.; *Tetrahedron Lett.*, **1993**, 34, 757. (b) Corey, E.J., Martinez E. J.; *Organic Lett.* **1999**, 1, 75.

12. Hewson, A.T., Sharpe, D. A., Wadsworth, A. H.; *Synth. Comm.* **1989**, 19, 2095.

13 (a) Kaufman, K.D., Hewitt, L.E.; *J.Org.Chem.*, **1980**, 45, 738. (b)Ghosh, C. K., Bhattacharyya, S., Ghosh, C., Patra, A.; *J.Chem. Soc., Perkin 1,* **1999**, 3015.

1. (a) Nemoto, H., Miyata, J., Fukumoto, K.; *Tetrahedron,* **1996**, 52, 103363. (b) Iyer, *J.Org.Chem.*, **1994**, 59, 6042.

15. Couladouros, E. A., Strongilos, A.T.; *Tetrahedron Lett.*, **2000**, 41, 535.

16. Kirmse,W., Kund, K.; *J. Org. Chem.*, **1990**, 55, 2330

17. Kinder, F. R., Bair, K.W.; *J. Org. Chem.*, **1994**, 59, 6965.

18. Pettus, T. R. R., Inoue, M., Chen, X-T., Danishefsky, S. J.; *J. Am .Chem. Soc.*, **2000**, 122, 6160.

19. Zhu, J., Beugelmans, R., Bourdet, S., Chastanet, J., Roussi, G.; *J. Org Chem.*, **1995**, 60, 6389.

20. Demuynck, M., DeClerq. P., Vandewelle, M.; *J. Org. Chem.*, **1979**, 44, 4863.

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