2003

Direct approaches to natural product synthesis

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Direct approaches to natural product synthesis

by

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A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

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Ames, Iowa

2003

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has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

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For the Major Program

TABLE OF CONTENTS

GENERAL INTRODUCTION

Over the last decades, organic synthesis has flourished with the discovery and invention of new synthetic strategies and technologies. Especially, these novel methods allow us to access complex natural products in an efficient way. Likewise, the design of direct approaches to complex molecules almost always prompts us to develop new methodologies.

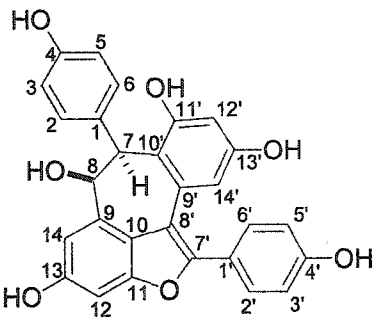
Syntheses of biologically active natural products and their analogs have become an important tool in search of new drugs. Approaches to these molecules in a concise manner are highly desirable.

In this context, we investigated direct routes to several biologically important natural products. During the syntheses, novel synthetic methodologies were developed. These studies will be useful to design approaches to other structurally related natural products.

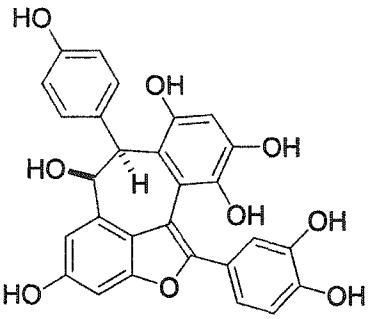
CHAPTER 1. SYNTHETIC APPROACH TO MALIBATOL A

Introduction

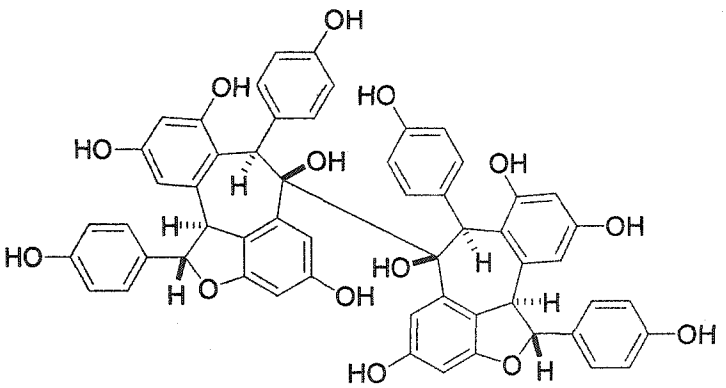
Malibatol A and several other structurally related oligostilbenes were isolated from the organic extract of the leaves of *Hopea malibato* by Boyd and coworkers in 1998.[1]



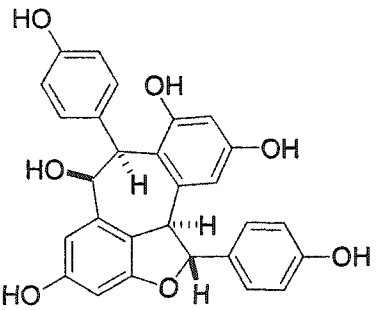
malibatol A



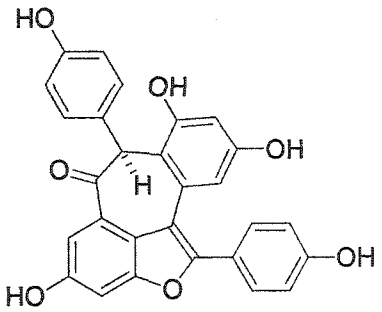
malibatol B



dibalanocarpol



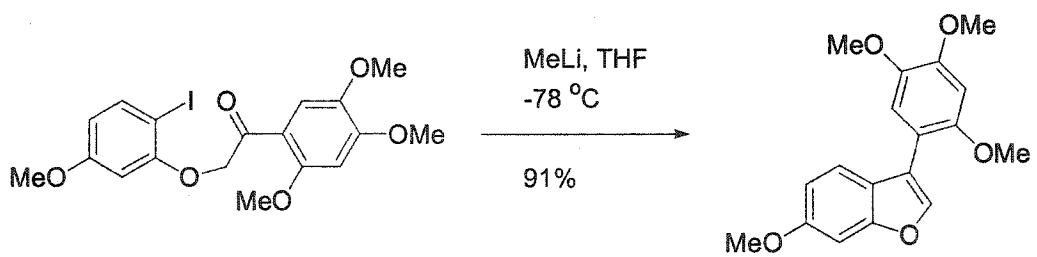
balanocarpol



shoreaphenol
or hopeafuran

While malibatols A and B exhibited cytotoxicity to the host cells (CEM SS) in the antiviral assay, dibalanocarpol and balanocarpol showed very modest HIV-inhibitory activity.[2] Shoreaphenol or hopeafuran was also isolated from the bark of *Shorea robusta* or the stem wood of *Hopea utilis*.[3] In addition, structures of several novel oligostilbenes were determined recently.[4] Despite their interesting biological activities as well as their unique carbon framework, no synthetic approach toward these types of compounds had been reported.

In the course of our synthetic studies towards isoflavanquinones, we observed an interesting reaction in which a metal-halogen exchange using alkyl lithium reagents was faster than the reaction with a carbonyl group.[5] Thus, instead of a product which resulted from a direct addition of methyl lithium to a carbonyl group, benzofuran compound **2** was obtained in good yield from **1**. The mechanism involved the attack of an aryl lithium species (which was formed via fast metal-halogen exchange) to a carbonyl group followed by the loss of water.

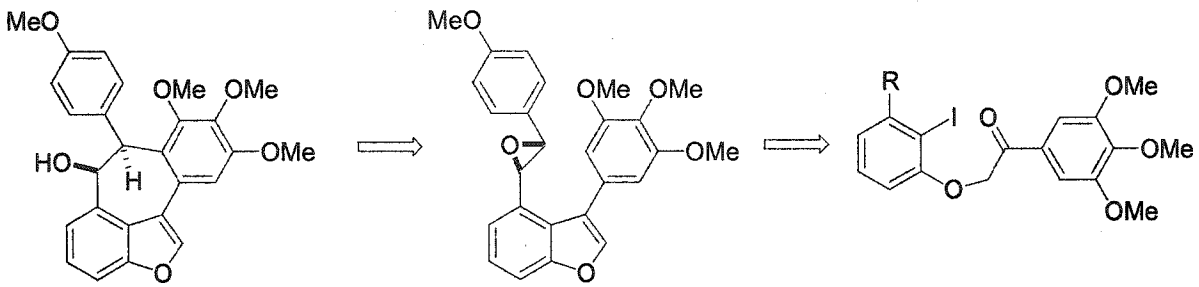


1 **2**

Since many oligostilbenes possess a benzofuran moiety as part of their structures, we decided to apply this new benzofuran preparation method to the synthesis of these natural products.

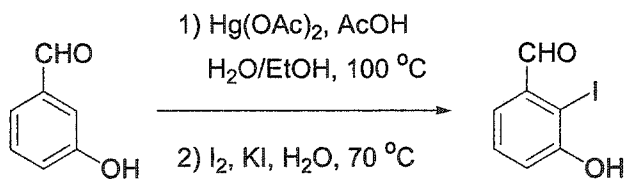
Results and Discussion

Synthetic target **3** was chosen to validate our strategy. We envisioned that a seven-membered ring could be constructed via regioselective epoxide opening, as illustrated in the retrosynthetic scheme. We expected that benzofuran moiety could be produced employing our novel benzofuran formation strategy.



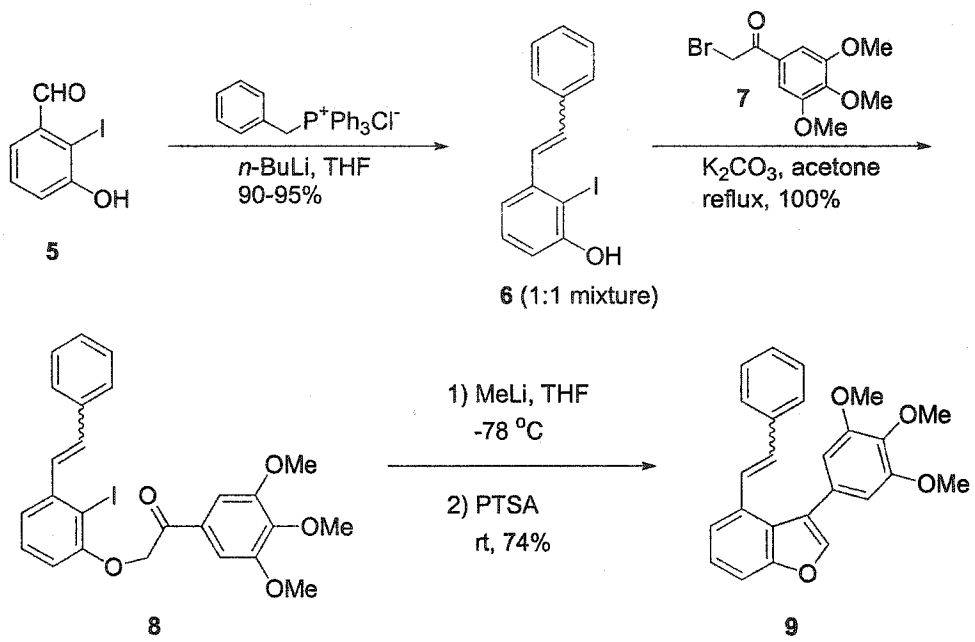
3 **4**

We began our study with iodo aldehyde **5**, which had been prepared by Lock from 3-hydroxybenzaldehyde in one step.[6]

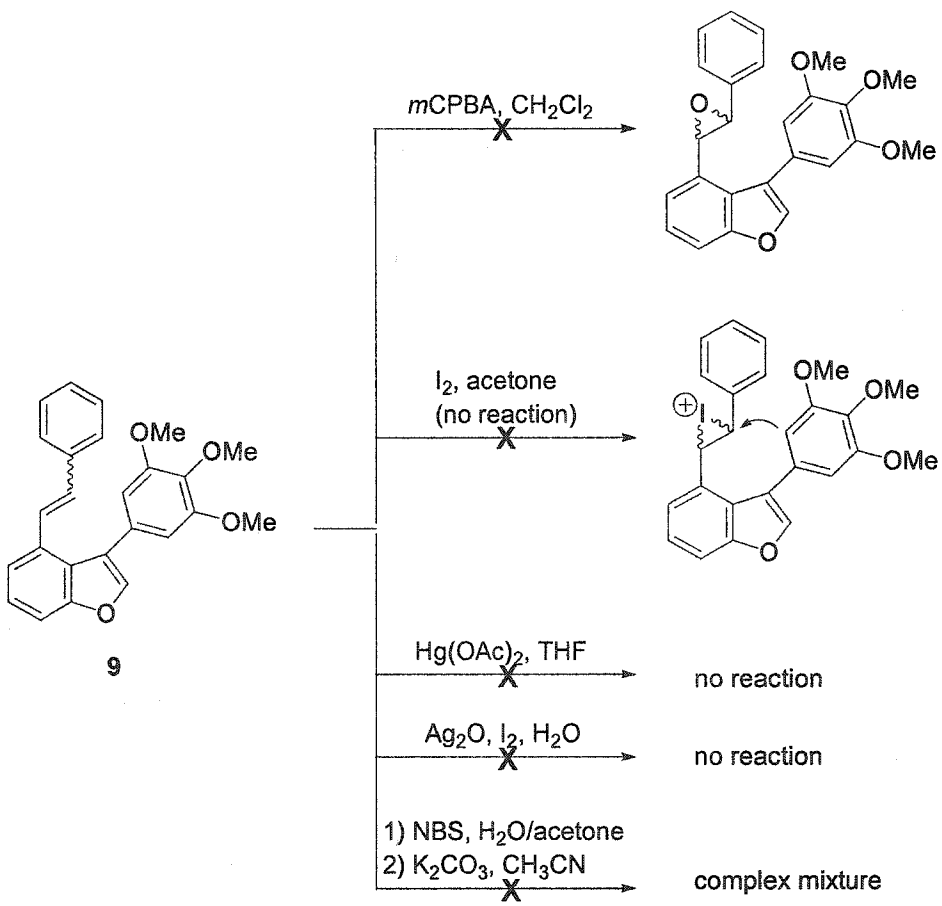


5

Iodo aldehyde **5** was treated with benzyltriphenylphosphonium chloride in the presence of *n*-BuLi to provide compound **6** as a 1:1 E/Z mixture in 90-95% yield. Phenol **6** was then alkylated with bromoketone **7**[7] and potassium carbonate in boiling acetone to give ketone **8** in quantitative yield. Reaction of ketone **8** with 3 equivalents of MeLi at –78 °C followed by the treatment with PTSA at room temperature afforded benzofuran **9** in 74% yield.

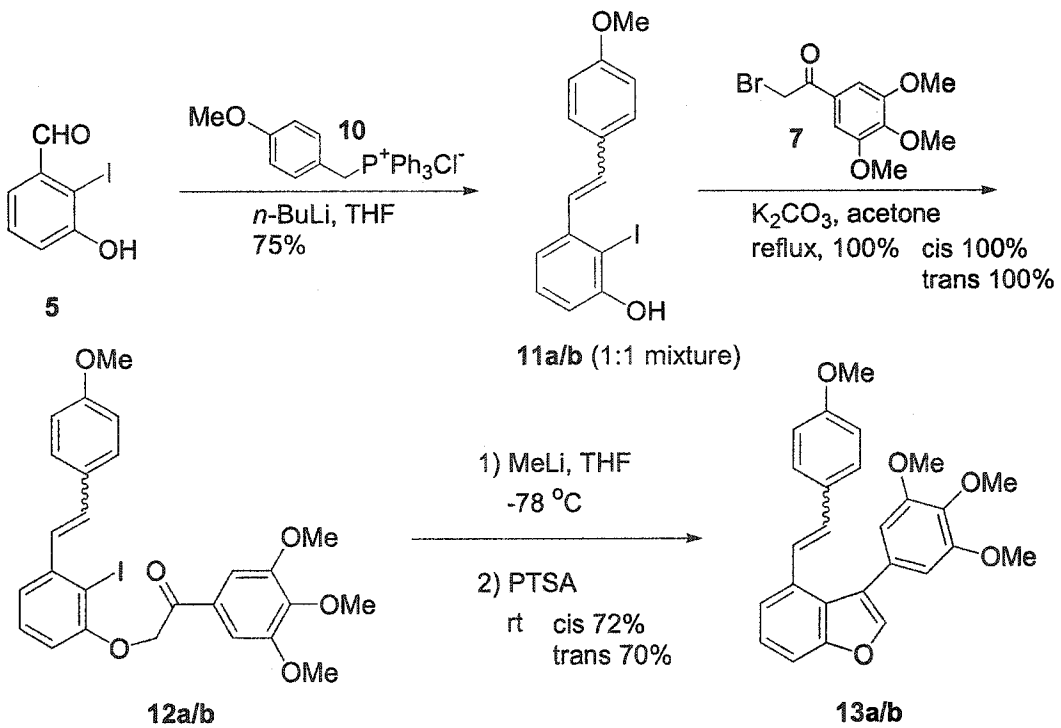


With this benzofuran **9** in hand, we next directed our efforts to make either an epoxide or a

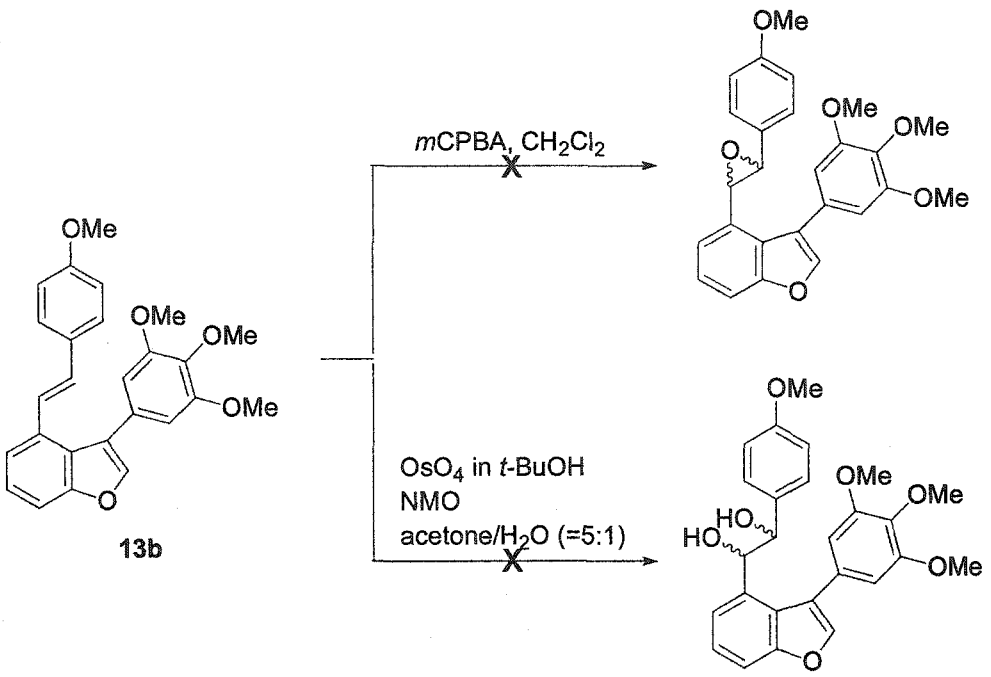


similarly reactive intermediate to initiate seven-membered ring formation. Unfortunately, none of these approaches provided the desired product.

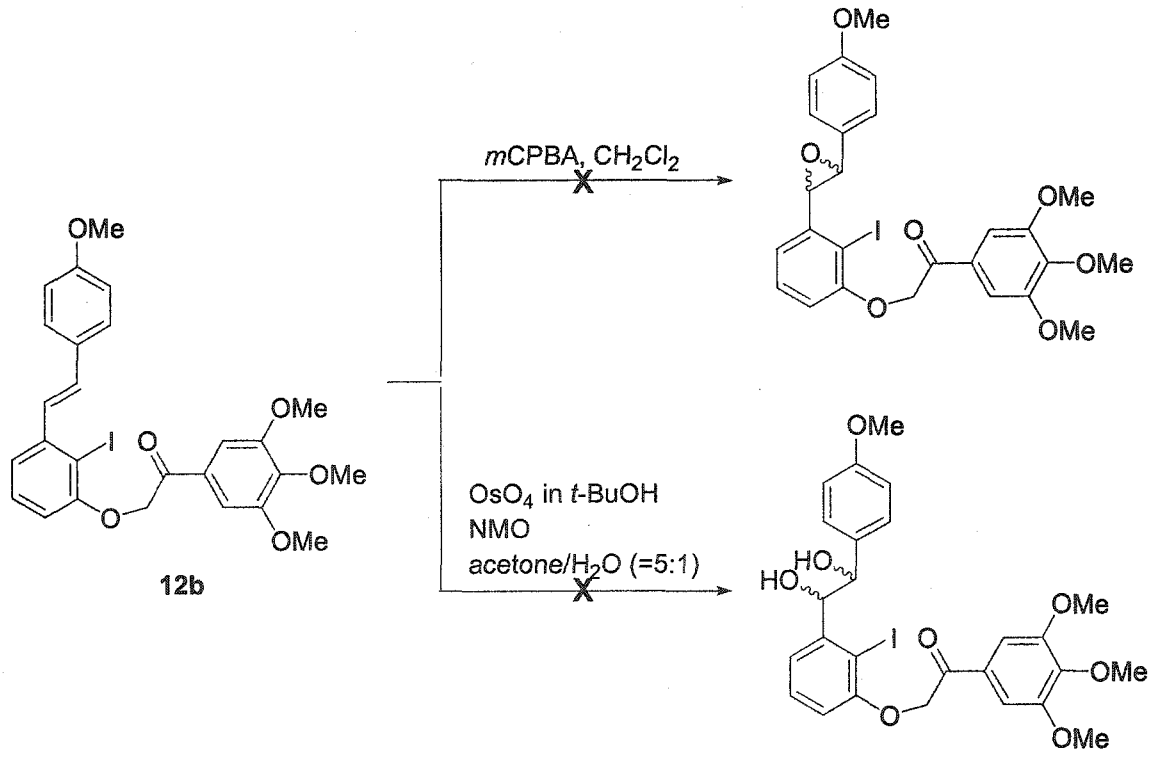
By the same sequence, we also made a *para*-methoxyphenyl analog. Interestingly, cis- and trans-products were separated from the Wittig adduct mixture to a great extent by simply suspending the mixture in *n*-hexane, filtering, and rinsing the solid with *n*-hexane. While the white solid contained the trans isomer as the major product, the liquid contained the cis isomer as the major product. Thus, we reacted the cis isomer **11a** and the trans isomer **11b** separately, with bromoketone **7** and potassium carbonate in boiling acetone. Reaction of adducts **12a** and **12b** with MeLi and subsequent PTSA treatment led to benzofurans **13a** and **13b**, respectively, in good yields.



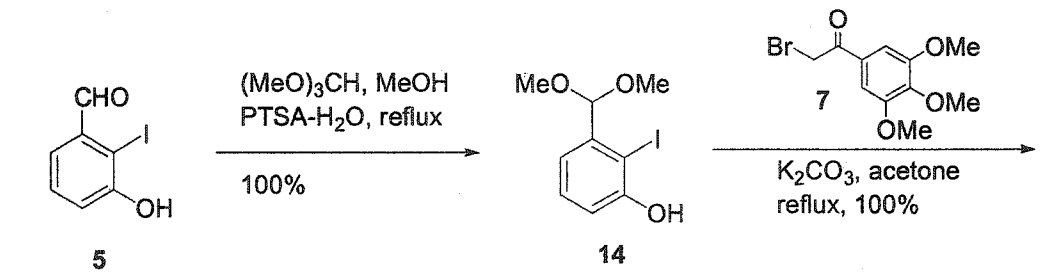
With the trans isomer **13b** in hand, we carried out epoxidation and dihydroxylation. However, both experiments gave a complex mixture.

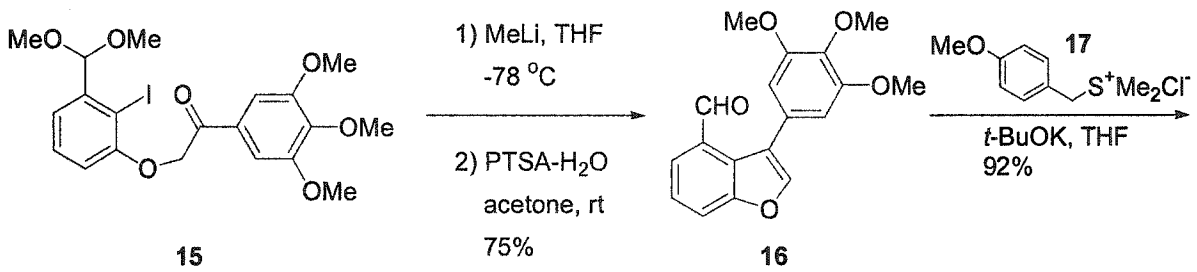


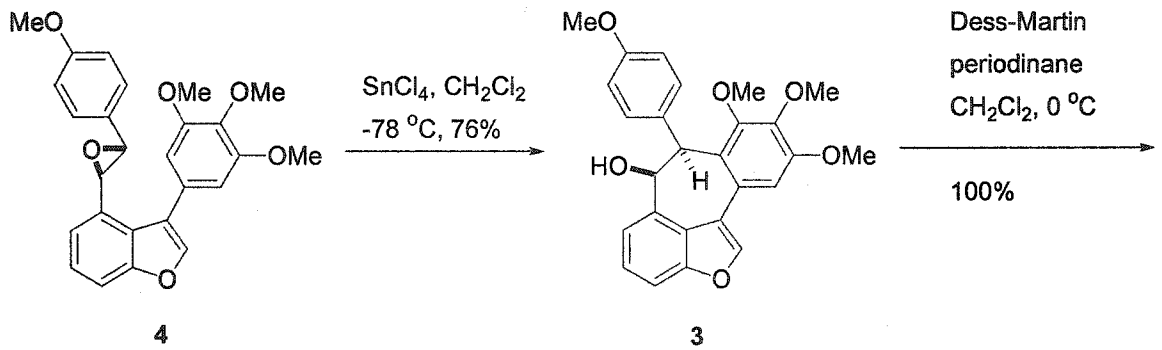
At this stage, we suspected that the benzofuran unit might prevent the desired transformation from occurring. Therefore, we subjected **12b** to the same reaction conditions for **13b**. Unfortunately, this wasn't successful, either.

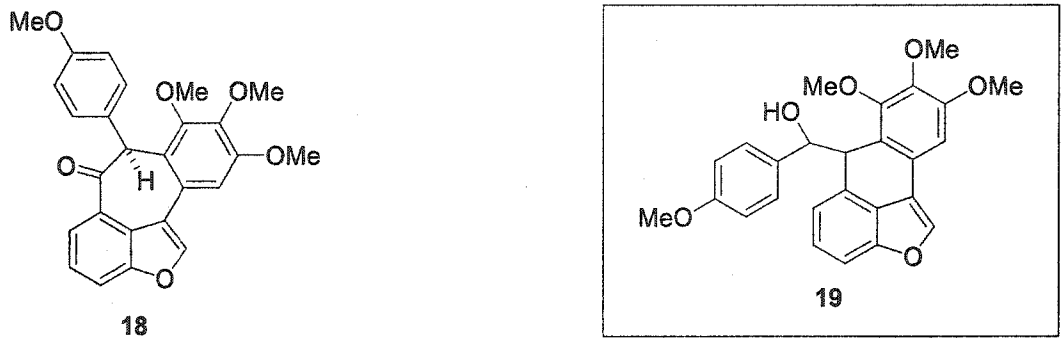


The results described above forced us to modify the original strategy. Thus, we decided to install the epoxide functionality within molecule in a different manner.









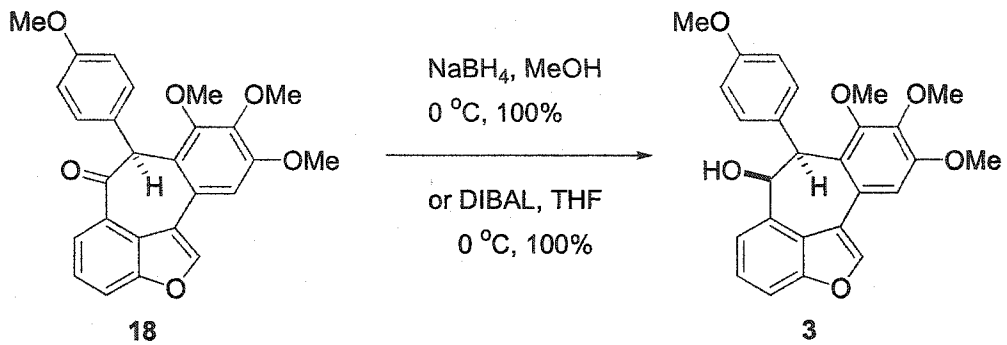
Aldehyde of **5** was protected as the acetal with trimethyl orthoformate and PTSA in boiling methanol. Phenol **14** and bromoketone **7** were coupled in the presence of potassium

carbonate in boiling acetone to afford ketone **15** in quantitative yield. Iodo ketone **15** was treated with MeLi at –78 °C followed by exposure of the resulting mixture to PTSA at ambient temperature to give benzofuran carboxaldehyde **16** in 75% yield. One of the methods to make an epoxide from an aldehyde is the sulfonium chemistry developed by Corey.[8] Thus, treatment of aldehyde **16** with dimethyl *para*-methoxybenzylsulfonium chloride **17**[9] and potassium *tert*-butoxide in THF at room temperature delivered epoxide **4** as a single stereoisomer as evidenced by proton NMR spectroscopy. The small coupling constant (J = 1.8 Hz) of the hydrogens attached to the epoxide ring supported the assigned structure. This epoxide **4** now set the stage for the crucial 7-membered ring formation. Gratifyingly, exposure of epoxide **4** in a catalytic amount of $SnCl_4$ at –78 °C provided benzylic alcohol **3** as a single compound in 76% yield. The coupling constant between the two methine protons in **3** was 2.7 Hz, compared to 2.5 Hz in malibatol A. 2D NMR analysis supported a trans relationship between the methine proton and the hydroxyl group.[10]

We expected that the *para*-methoxyphenyl group would direct the epoxide opening. However, we could not rule out the isomeric alcohol **19**. Oxidation of the alcohol **3** with the Dess-Martin periodinane reagent gave a ketone that we assigned as **18** based on the deshielding of the hydrogen at C-5 of the benzofuran. The chemical shifts of the hydrogens on the *para*-methoxyphenyl group were not deshielded after the oxidation. Moreover, the mass spectra did not exhibit fragmentation that one would expect for alcohol **19** (M^+ - 137) or the ketone derived from oxidation of **19** (M^+ - 135).

Reduction of ketone **18** with either sodium borohydride in methanol or DIBAL in THF provided only alcohol **3**. The tetracyclic ring system in **18** is flat with the *para*-methoxyphenyl group approximately perpendicular to the ring system. Hydride attack

opposite to the *para*-methoxyphenyl group would explain the production of **3**.



In conclusion, we developed a concise synthetic route to the malibatol A ring system and structurally related oligostilbenes, featuring a novel construction of a benzofuran ring and an efficient generation of a seven-membered ring by regio- and stereoselective epoxide opening. This route should enable us to construct malibatol A and several analogs.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used withtout purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

2-(2-Iodo-5-methoxyphenoxy)-1-(2,4,5-trimethoxyphenyl)ethanone (1)

Preparation and characterization data of 1 are described in Chapter 2 of this dissertation.

6-Methoxy-3-(2,4,5-trimethoxyphenyl)benzofuran (2)

To a solution of MeLi (1.4 M solution in THF, 337 μL, 0.471 mmol) in THF (2 mL) was dropwise added a solution of ketone 1 (72 mg, 0.157 mmol) in THF (4 mL + 1 mL for rinse) at –78 °C via cannula. After being stirred at –78 °C for 5 min, the mixture was quenched with saturated NH_4Cl at –78 °C. The mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The resulting residue was purified by sgc (H:EA = 2:1) to give benzofuran 2 (45 mg, 91%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, s), 7.58 (1H, d, J = 8.7 Hz), 7.26 (1H, s), 7.06 (1H, d, J = 2.1 Hz), 6.92 (1H, dd, J = 8.7, 2.4 Hz), 6.68 (1H, s), 3.96 (3H, s), 3.91 (3H, s), 3.87 (3H, s), 3.83 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 158.1, 156.4, 151.6, 149.2, 143.4, 142.6, 121.3, 120.9, 117.5, 114.0, 112.8, 112.0, 98.6, 96.3, 57.0, 56.7, 56.4, 56.0; HRMS *m/z* for $C_{18}H_{18}O_5$ calcd 314.1154, found 314.1160.

3-Hydroxy-2-iodobenzaldehyde (5)

To a solution of 3-hydroxybenzaldehyde (10 g, 81.9 mmol) in EtOH (40 mL) were added $Hg(OAc)_2$ (26 g, 81.9 mmol), H_2O (40 mL), and AcOH (1.2 mL) at rt. The mixture was heated at 100 °C overnight. After being cooled to rt, the mixture was evaporated to remove EtOH. The residue was suction-filtered and the solid was washed with H_2O a couple of times. The solid (not completely dried) was mixed with a solution of KI (47 g, 393.1 mmol) and I_2 (30 g, 163.8 mmol) in H_2O (200 mL). After being heated at 70 °C for 2 h, the mixture was cooled to rt. Excess aqueous $NaHSO_3$ solution was added to it to decolorize. The mixture was extracted with ethyl acetate two times. The organic layer was washed with H_2O

and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The resulting residue was passed through a short silica gel column, eluting with solvent (H:EA = 2:1). The eluted solvent was concentrated and the residue was suspended in benzene. Then, it was filtered and washed with benzene. A yellow solid was obtained. To increase the yield, the filtrate was concentrated, suspended in benzene, and filtered again. 300 MHz ^{1}NMR (acetone-d_6) δ 10.14 (1H, d, J = 1.8 Hz), 9.64 (1H, br s), 7.42-7.30 (2H, m), 7.30-7.20 (1H, m)

2-Iodo-3-styrylphenol (6)

To a suspension of benzyltriphenylphosphonium chloride (3.24 g, 8.34 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M solution in hexanes, 2.78 mL, 6.95 mmol) dropwise at –78 °C. After being stirred for 15 min at rt, the mixture was recooled to –78 °C. To this mixture was transferred a solution of **5** (688 mg, 2.78 mmol) in THF (10 mL + 5 mL for rinse) at –78 °C via cannula. After being stirred at rt for 30 min, the mixture was quenched with saturated NH_4Cl at 0 °C. The organic solvent was evaporated. The residue was diluted with CH_2Cl_2 and washed with 10% HCl. The aqueous layer was extracted with CH_2Cl_2 one more time. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by sgc (H:EA = 3:1) to give **6** (850 mg, 95%) as a 1:1 cis:trans mixture. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.65-6.45 (10H, m), 5.69 and 5.65 (1H, s).

2-Bromo-1-(3,4,5-trimethoxyphenyl)ethanone (7)

To a solution of 3',4',5'-trimethoxyacetophenone (3.57 g, 16.98 mmol) in ethyl acetate (28 mL) and $CHCl_3$ (28 mL) was added $CuBr_2$ (7.59 g, 33.96 mmol) at rt. After being heated at 85 °C for 10 h, the mixture was cooled to rt. The mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated in vacuo. The residue was suspended in

solvent (H:EA = 3:1), filtered, and rinsed with small amount of solvent (H:EA = 3:1). The solid **7** (2.9 g) was dried under reduced pressure. The filtrate was concentrated and the resulting residue was purified by sgc (H:EA = 5:1 to 3:1) to give **7** (780 mg, total yield: 75%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.24 (2H, s), 4.41 (2H, s), 3.94 (3H, s), 3.93 (6H, s).

2-(2-Iodo-3-styrylphenoxy)-1-(3,4,5-trimethoxyphenyl)ethanone (8)

To a solution of **6** (698 mg, 2.168 mmol) and **7** (627 mg, 2.168 mmol) in acetone (7.2 mL) was added K_2CO_3 (300 mg, 2.168 mmol). The reaction mixture was heated to reflux for 2 h. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with H_2O and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford **8** (1.149 g, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.62-6.48 (12H, m), 5.28 and 5.26 (2H, s), 3.94 (6H, s), 3.93 (3H, s).

4-Styryl-3-(3,4,5-trimethoxyphenyl)benzofuran (9)

To a solution of MeLi (1.4 M solution in THF, 6.5 mL, 9.13 mmol) in THF (12 mL) was added a solution of **8** (968 mg, 1.826 mmol) in THF (8 mL + 4 mL for rinse) at –78 °C via cannula. After being stirred at rt for 10 min, the mixture was quenched with saturated NH_4Cl. The organic solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The intermediate benzylic alcohol was purified by sgc (H:EA = 3:1) for NMR data. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-6.14 (12 H, m), 4.61 and 4.55 (2H, d, J = 10.2 Hz), 3.83 (3H, s), 3.80 (3H, s), 3.77 (3H, s).

The crude mixture was dissolved in benzene (10 mL) and MeOH (5 mL). PTSA-H_2O (325 mg, 1.709 mmol) was added to this solution at rt. After being stirred at rt for 3 h, the solvent was evaporated. The residue was diluted with CH_2Cl_2 and washed with brine. The

organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give **9** (520 mg, 74%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-6.40 (13H, m), 3.96 and 3.92 (3H, s), 3.78 and 3.75 (6H, s); HRMS *m/z* for $C_{25}H_{22}O_4$ calcd 386.1518, found 386.1525.

(4-Methoxybenzyl)triphenylphosphonium chloride (10)

A mixture of 4-methoxybenzyl chloride (6.78 g, 43.29 mmol) and triphenylphosphine (11.36 g, 43.29 mmol) in toluene (54 mL) was heated to reflux overnight. After being cooled to rt, the white salt was filtered, washed with toluene a couple of times, and dried under reduced pressure.

2-Iodo-3-[2-(4-methoxyphenyl)vinyl]phenol (11a/b)

To a suspension of 4-methoxybenzyltriphenylphosphonium chloride (7.6 g, 18.153 mmol) in THF (44 mL) was added *n*-BuLi (2.5 M solution in hexanes, 6.051 mL, 15.128 mmol) at 0 °C. After being stirred at rt for 15 min, the mixture was recooled to 0 °C. To this mixture was transferred a solution of **5** (1.5 g, 6.051 mmol) at 0 °C. After being stirred at rt for 20 min, the mixture was quenched with saturated NH_4Cl at 0 °C. The organic solvent was evaporated. The residue was diluted with CH_2Cl_2 and washed with 10% HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 4:1 to 3:1) to afford a cis/trans mixture (1.6 g, 75%). This mixture was suspended in *n*-hexane. The solid was filtered and washed with *n*-hexane. The white solid contained the trans isomer as the major product. The filtrate was evaporated to dryness to give an oil which contained the cis isomer as the major product.

11a (cis): 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.15-7.03 (3H, m), 6.89 (1H, dd, J = 8.1, 0.6 Hz), 6.82 (1H, d, J = 7.5 Hz), 6.74 (2H, d, J = 8.7 Hz), 6.59 (1H, d, J = 12.3 Hz), 6.40 (1H, d, J =

12.0 Hz), 5.69 (1H, br s), 3.77 (3H, s).

11b (trans): 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.49 (2H, d, J = 8.7 Hz), 7.26-7.08 (3H, m), 6.99-6.85 (4H, m), 5.51 (1H, s), 3.85 (3H, s).

2-{2-Iodo-3-[2-(4-methoxyphenyl)vinyl]phenoxy}-1-(3,4,5-trimethoxyphenyl)ethanone (12a) (cis isomer)

To a solution of **11a** (548 mg, 1.557 mmol) and 7 (450 mg, 1.557 mmol) in acetone (5 mL) was added K_2CO_3 (215 mg, 1.557 mmol). The reaction mixture was heated to reflux for 1 h. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with H_2O and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford **12a** (872 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.36 (2H, s), 7.08 (1H, d, J = 7.0 Hz), 7.03 (2H, d, J = 8.4 Hz), 6.84 (1H, d, J = 6.9 Hz), 6.69 (2H, d, J = 9 Hz), 6.61 (1H, d, J = 8.1 Hz), 6.56 (1H, d, J = 12.0 Hz), 6.40 (1H, d, J = 12.0 Hz), 5.27 (2H, s), 3.93 (9H, s), 3.75 (3H, s).

2-{2-Iodo-3-[2-(4-methoxyphenyl)vinyl]phenoxy}-1-(3,4,5-trimethoxyphenyl)ethanone (12b) (trans isomer)

The same procedure for **12a** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.50 (2H, d, J = 9.0 Hz), 7.36 (2H, s), 7.40-6.60 (5H, m), 6.92 (2H, d, J = 9.0 Hz).

4-[2-(4-Methoxyphenyl)vinyl]-3-(3,4,5-trimethoxyphenyl)benzofuran (13a) (cis isomer)

To a solution of MeLi (1.4 M solution in THF, 8.0 mL, 11.24 mmol) in THF (15 mL) was added a solution of **12a** (1.259 g, 2.248 mmol) in THF (10 mL + 3 mL for rinse) at –78 °C via cannula. After being stirred at rt for 10 min, the mixture was quenched with saturated NH_4Cl. The organic solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to

dryness. The crude mixture was dissolved in benzene (10 mL) and MeOH (5 mL). PTSA-H_2O (428 mg, 2.25 mmol) was added to this solution at rt. After being stirred at rt for 3 h, the solvent was evaporated. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give **13a** (674 mg, 72%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.61 (1H, s), 7.42 (1H, dd, J = 6.6, 2.7 Hz), 7.23-7.14 (2H, m), 7.05 (2H, d, J = 8.7 Hz), 6.66 (2H, d, J = 9.0 Hz), 6.61 (2H, s), 6.48 (1H, d, J = 12.3 Hz), 6.37 (1H, d, J = 12.0 Hz), 3.92 (3H, s), 3.77 (6H, s), 3.73 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 158.9, 156.2, 152.8, 142.4. 137.6, 132.1, 130.4, 130.0, 129.7, 127.8, 127.0, 124.8, 124.7, 124.3, 123.9, 113.7, 110.7, 107.2, 61.2, 56.1, 55.3; HRMS *m/z* for $C_{26}H_{24}O_5$ calcd 416.1624, found 416.1629.

4-[2-(4-Methoxyphenyl)vinyl]-3-(3,4,5-trimethoxyphenyl)benzofuran (13b) (trans isomer)

The same procedure for **13a** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.62 (1H, s), 7.52 (1H, d, J = 7.5 Hz), 7.42 (1H, d, J = 8.1 Hz), 7.33 (1H, d, J = 8.1 Hz), 7.19 (1H, d, J = 16.2 Hz), 7.12 (2H, d, J = 8.7 Hz), 6.95 (1H, d, J = 16.5 Hz), 6.79 (2H, d, J = 8.7 Hz), 6.74 (2H, s), 3.94 (3H, s), 3.79 (3H, s), 3.75 (6H, s); HRMS *m/z* for $C_{26}H_{24}O_5$ calcd 416.1624, found 416.1629.

3-Dimethoxymethyl-2-iodophenol (14)

To a solution of **5** (342 mg, 1.38 mmol) in MeOH (5 mL) were added trimethyl orthoformate (377 μL, 3.45 mmol) and PTSA-H_2O (26 mg, 0.14 mmol) at rt. The mixture was heated to reflux overnight. The solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude residue

(405 mg, 100%) was pure enough to run the next step. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.24 (1H, t, J = 7.8 Hz), 7.12 (1H, dd, J = 7.8, 1.8 Hz), 7.00 (1H, dd, J = 7.8, 1.5 Hz), 5.59 (1H, s), 5.34 (1H, s), 3.37 (6H, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 155.2, 140.4, 129.3, 120.2, 115.4, 106.7, 89.7, 60.8, 53.9.

2-(3-Dimethoxymethyl-2-iodophenoxy)-1-(3,4,5-trimethoxyphenyl)ethanone (15)

To a solution of **14** (1.123 g, 3.82 mmol) and **7** (1.1 g, 3.82 mmol) in acetone (13 mL) was added K_2CO_3 (792 mg, 5.73 mmol). The reaction mixture was heated to reflux for 4 h. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with H_2O and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford **15** (1.917 g, 100%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.23 (2H, s), 7.22-7.09 (2H, m), 6.69 (1H, d, J = 7.6 Hz), 5.38 (1H, s), 5.21 (2H, s), 3.84 (9H, s), 3.31 (6H, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 193.3, 156.7, 153.2, 143.3, 141.9, 129.4, 129.0, 121.3, 112.7, 107.0, 106.0, 90.9, 72.5, 60.9, 56.4, 54.2, 53.6.

3-(3,4,5-Trimethoxyphenyl)benzofuran-4-carbaldehyde (16)

To a solution of MeLi (1.4 M solution in THF, 15.0 mL, 21.2 mmol) in THF (25 mL) was added a solution of **15** (2.13 g, 4.24 mmol) in THF (10 mL + 5 mL for rinse) at –78 °C via cannula. After being stirred at rt for 10 min, the mixture was quenched with saturated NH_4Cl. The organic solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to give crude intermediate (1.6 g, 100%). The intermediate benzyl alcohol was identified in crude ^{1}H NMR. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (1H, d, J = 7.8 Hz), 7.07 (1H, dd, J = 7.8, 0.9 Hz), 6.96 (1H, d, J = 8.1 Hz), 6.63 (2H, s), 4.98 (1H, s), 4.69 (1H, d, J = 9.9 Hz), 4.47 (1H, d, J = 1.2 Hz), 4.39 (1H, dd, J = 9.9, 1.5 Hz), 3.84 (3H, s), 3.79 (6H, s), 3.29

(6H, s).

The crude mixture (1.5 g, 3.99 mmol) was dissolved in acetone (22 mL). PTSA-H_2O (759 mg, 3.99 mmol) was added to this solution at rt. After being stirred at rt for 7 h, the solvent was evaporated. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 3:1) to give **16** (934 mg, 75%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 10.24 (1H, d, J = 0.6 Hz), 7.88 (1H, dd, J = 7.5, 0.6 Hz), 7.75 (1H, dd, J = 8.1, 0.6 Hz), 7.74 (1H, s), 7.43 (1H, t, J = 8.1 Hz), 6.68 (2H, s), 3.89 (3H, s), 3.84 (6H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 190.3, 156.2, 153.8, 144.7, 138.3, 130.4, 128.6, 128.2, 124.8, 122.9, 122.5, 117.5, 106.7, 61.2, 56.4; HRMS *m/z* for $C_{18}H_{16}O_5$ calcd 312.0998, found 312.1002.

(4-Methoxybenzyl)dimethylsulfonium chloride (17)

A mixture of 4-methoxybenzyl chloride (1.1 g, 7.02 mmol) and dimethyl sulfide (2.5 mL, 34.04 mmol) in $CHCl_3$ (10 mL) was stirred at rt for 3 days. The solvent was evaporated under reduced pressure. The residue was suspended in ethyl acetate and sonicated for 30 min. The liquid layer was decanted and the solid was suspended in ethyl acetate again. The suspension was suction-filtered rapidly and rinsed with ethyl acetate. White waxy solid was dried under reduced pressure. 300 MHz ^{1}H NMR (D_2O) δ 7.25 (2H, d, J = 8.4 Hz), 6.92 (2H, d, J = 8.4 Hz), 4.39 (2H, s), 3.69 (3H, s), 2.58 (6H, s).

4-[3-(4-Methoxyphenyl)oxiranyl]-3-(3,4,5-trimethoxyphenyl)benzofuran (4)

To a suspension of **17** (1.38 g, 6.32 mmol) in THF (12 mL) was added *t*-BuOK (708 mg, 6.32 mmol) at 0 °C. After being stirred at rt for 1 h, the mixture was recooled to 0 °C. To this mixture was transferred a solution of **16** (492 mg, 1.58 mmol) in THF (12 mL + 5 mL for rinse) at 0 °C via cannula. After being stirred at rt for 3 h, the reaction mixture was quenched

with saturated NH_4Cl at 0 °C. The solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by sgc (H:EA = 7:1) to afford **4** (627 mg, 92%) plus recovered starting material **15** (20 mg, 4%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.58 (1H, s), 7.49 (1H, d, J = 8.4 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.24 (1H, d, J = 7.5 Hz), 6.97 (2H, d, J = 8.7 Hz), 6.81 (2H, d, J = 8.4 Hz), 6.55 (2H, s), 4.09 (1H, d, J = 1.8 Hz), 3.80 (6H, s), 3.74 (1H, d, J = 1.8 Hz), 3.57 (6H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 160.2, 155.3, 153.2, 142.7, 137.9, 131.6, 128.7, 128.1, 127.1, 126.3, 125.2, 122.7, 118.3, 114.3, 111.4, 107.0, 63.5, 61.1, 59.2, 56.0, 55.6; HRMS *m/z* for $C_{26}H_{24}O_6$ calcd 432.1573, found 432.1580.

8,9,10-Trimethoxy-7-(4-methoxyphenyl)-6,7-dihydro-2-oxadibenzo[*cd*,*h*]azulen-6-ol (3)

1) from the reaction of **4** with $SnCl_4$:

To a solution of **4** (41.5 mg, 0.096 mmol) in CH_2Cl_2 (4.8 mL) was added $SnCl_4$ (1 M solution in CH_2Cl_2, 19 μL, 0.019 mmol) at –78 °C. After being stirred at –78 °C for 5 min, the mixture was quenched with saturated NH_4Cl at –78 °C. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA:CH_2Cl_2 = 5:1:1) to give **3** (31.5 mg, 76%).

2) from the reaction of **18** with $NaBH_4$ or DIBAL:

To a solution of **18** (8.9 mg, 0.021 mmol) in MeOH (1 mL) was added $NaBH_4$ (2 mg, 0.053 mmol) at 0 °C. After 5 min, the mixture was quenched with saturated NH_4Cl at 0 °C. After the mixture was concentrated in vacuo, the residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in

vacuo to give **3** (8.9 mg, 100%). Alternatively, to a solution of **18** (10 mg, 0.023 mmol) in THF (1.5 mL) was added DIBAL (1 M solution in THF, 69 μL, 0.069 mmol) at 0 °C. After 5 min, the mixture was quenched with H_2O at 0 °C. The mixture was filtered through Celite and rinsed with CH_2Cl_2. The filtrate was evaporated in vacuo to give **3** (10 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.93 (1H, s), 7.36-7.17 (3H, m), 7.05 (1H, s), 6.94 (2H, d, J = 9.0 Hz), 6.48 (2H, d, J = 8.7 Hz), 5.49 (1H, br s), 5.45 (1H, d, J = 2.7 Hz), 3.96 (3H, s), 3.92 (3H, s), 3.71 (3H, s), 3.60 (3H, s), 2.55 (1H, br s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 158.0, 155.2, 153.0, 152.7, 142.3, 140.6, 137.0, 131.7, 130.1, 127.1, 126.8, 125.0, 123.1, 121.9, 119.0, 113.4, 110.1, 105.8, 73.8, 61.8, 61.2, 56.3, 55.1, 49.8; HRMS *m/z* for $C_{26}H_{24}O_6$ calcd 432.1573, found 432.1580; 300 MHz ^{1}H NMR (acetone-d_6) δ 8.29 (1H, s), 7.48 (1H, dd, J = 6.9, 1.5 Hz), 7.35 (1H, s), 7.27-7.15 (2H, m), 7.03 (2H, d, J = 9.0 Hz), 6.44 (2H, d, J = 9.0 Hz), 5.52 (1H, br s), 5.51(1H, d, J = 4.5 Hz), 5.37 (1H, d, J = 4.5 Hz), 3.97 (3H, s), 3.87 (3H, s), 3.72 (3H, s), 3.55 (3H, s); 75 MHz ^{13}C NMR (acetone-d_6) δ 157.7, 155.0, 152.9, 152.8, 142.3, 141.4, 138.2, 132.9, 129.9, 127.5, 126.9, 124.5, 123.1, 122.1, 119.4, 112.6, 109.2, 106.8, 73.5, 61.1, 60.3, 55.7, 54.3, 49.3.

8,9,10-Trimethoxy-7-(4-methoxyphenyl)-7*H*-2-oxadibenzo[*cd*,*h*]azulen-6-one (18)

To a solution of **3** (9 mg, 0.0208 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (11 mg, 0.025 mmol) at 0 °C. After being stirred at 0 °C for 10 min, the reaction mixture was diluted with Et_2O. The mixture was filtered through Celite and rinsed with Et_2O. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA:CH_2Cl_2 = 3:1:1) to give **17** (9 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (1H, s), 7.79 (1H, d, J = 7.5 Hz), 7.52 (1H, d, J = 8.1 Hz), 7.33 (1H, t, J = 8.1 Hz), 7.03 (1H, s), 6.74 (2H, d, J = 9.0 Hz), 6.51 (2H, d, J = 8.7 Hz), 6.06 (1H, s), 3.98 (3H, s), 3.95 (3H, s), 3.85 (3H, s), 3.60 (3H, s); 75

MHz ^{13}C NMR ($CDCl_3$) δ 196.8, 158.1, 155.2, 153.7, 153.1, 143.0, 141.8, 131.2, 130.5, 128.1, 126.7, 125.2, 124.9, 123.7, 123.0, 121.7, 115.6, 113.8, 106.5, 62.2, 61.3, 56.8, 56.3, 55.2; HRMS *m/z* for $C_{26}H_{22}O_6$ calcd 430.1426, found 430.1424.

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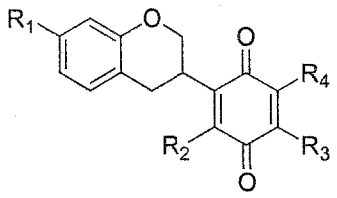
10. In compound **3**, the two-dimensional NOESY spectrum showed a strong interaction between the two methine hydrogens. The benzylic alcohol methine proton showed a NOE interaction only with the adjacent methine proton. If the stereochemistry was reversed, molecular models indicate that there would almost certainly be a strong NOE interaction with the hydrogen on C-5 of the benzofuran.

CHAPTER 2. DIRECT SYNTHESES OF ISOFLAVANQUINONES

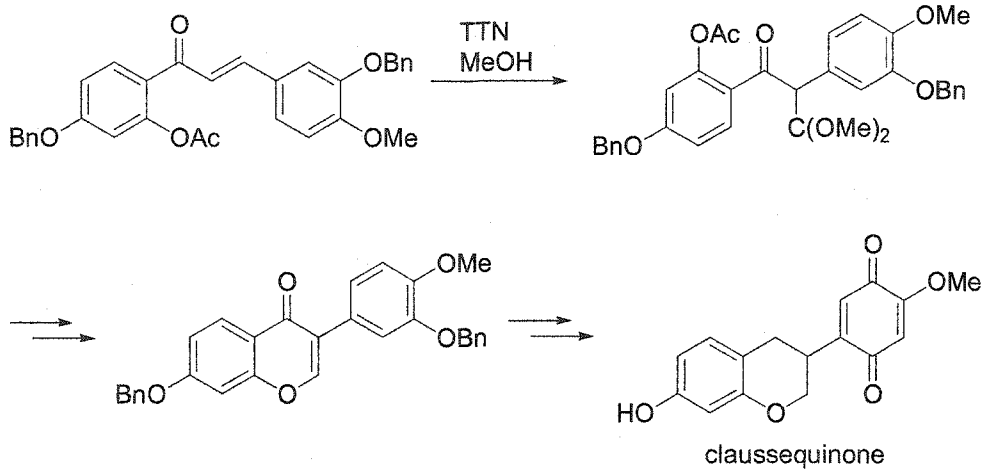
Introduction

Colutequinone A, colutequinone B, and claussequinone are members of a growing family of isoflavanquinones.



$R_1 = R_2 = R_3 = R_4 = H$: **(1)**
$R_1 = OMe$, $R_2 = R_3 = R_4 = H$: **(2)**
$R_1 = R_3 = R_4 = OMe$, $R_2 = H$: **colutequinone A (3)**
$R_1 = R_2 = R_3 = OMe$, $R_4 = H$: **colutequinone B (4)**
$R_1 = OH$, $R_2 = R_4 = H$, $R_3 = OMe$: **claussequinone (5)**
$R_1 = R_3 = OMe$, $R_2 = R_4 = H$: ***O*-methyl claussequinone (6)**

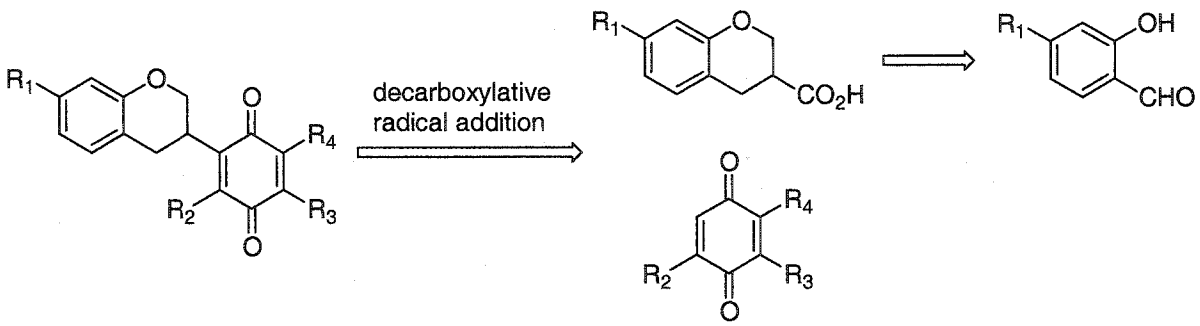
Colutequinones A[1] and B[2] were isolated from the root bark of *Colutea aborescens* and are known to have antimicrobial and antifungal activity. Claussequinone,[3] which was isolated from the heartwood of *Dalbergia odorifera* (Leguminosae),[3c] exhibits anti-inflammatory[4a] and antifertility activity.[4b] It also displays potent activity against bloodstream forms of *Trypanosoma cruzi* (Chagas' disease).[5] Moreover, it is a feeding deterrent for the grass grub *Costelytra zealandica*.[6] While no synthetic approaches to colutequinones A and B have been reported, claussequinone has been synthesized by Farkas and coworkers using thallium



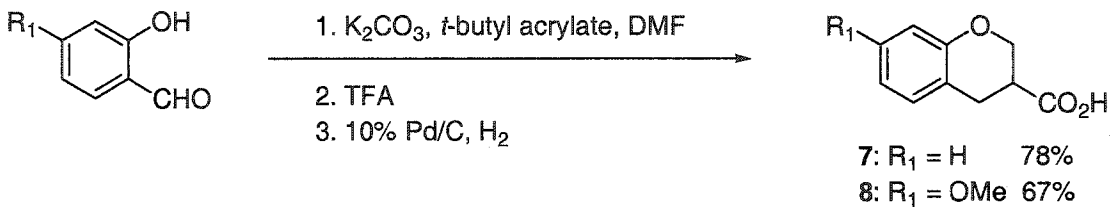
trinitrate (TTN)-mediated rearrangement in the key step.[7] As part of a program to develop environmentally benign radical reactions,[8] we investigated a direct approach to isoflavanquinones.

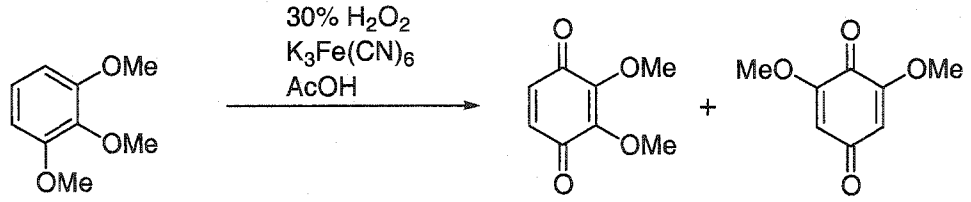
Results and Discussion

As shown in the retrosynthetic analysis, we initially envisioned that these isoflavanquinones could be assembled via decarboxylative radical addition of carboxylic acids to benzoquinones. Carboxylic acids could be derived from 2-hydroxybenzaldehydes.

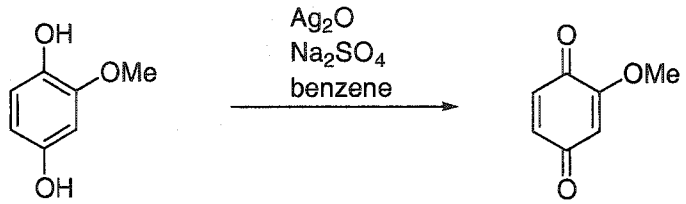


To explore the feasibility of this strategy, we first prepared carboxylic acids and substituted benzoquinones. Thus, chroman-3-carboxylic acid and 7-methoxychroman-3-carboxylic acid were prepared in 78 and 67% yields, respectively, by the procedure of Sato.[9] Synthesis of 2,3-dimethoxybenzoquinone was achieved from 1,2,3-trimethoxybenzene using Matsumoto's protocol.[10] Silver oxide oxidation of 2-methoxyhydroquinone provided 2-methoxybenzoquinone in 99% yield.



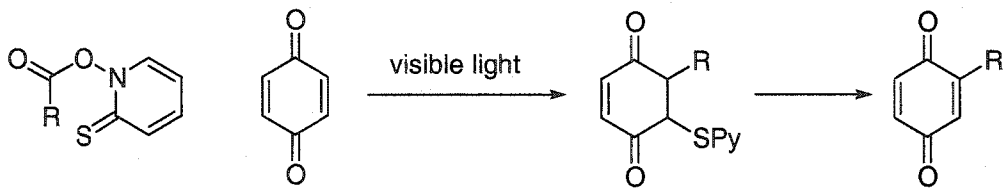


9 (53%)

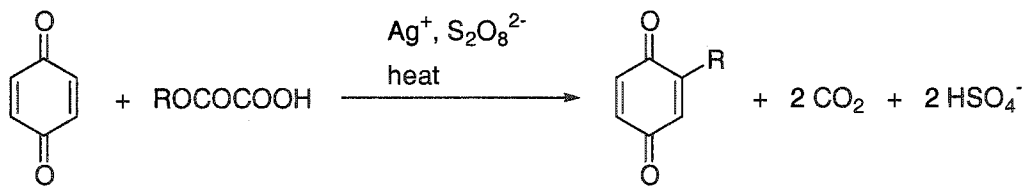


10 (99%)

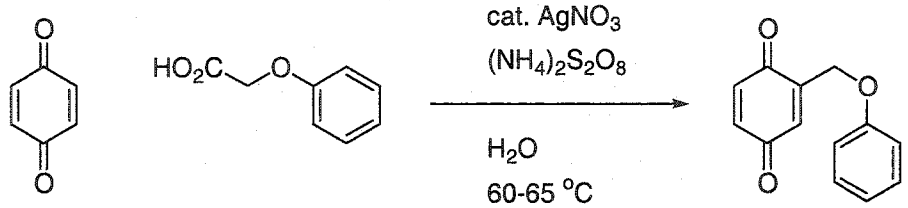
In the literature, there aren't many examples of radical additions to quinones. Barton et al. reported the reaction of acyl thiohydroxamates and benzoquinones under visible light.[11]



Minisci and coworkers used persulfate and a catalytic amount of silver nitrate to generate radical from carboxylic acid or oxalic acid mono ester.[12]



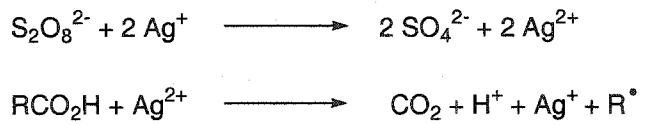
Similarly, Jacobsen added the phenoxymethyl radical to benzoquinone.[13]



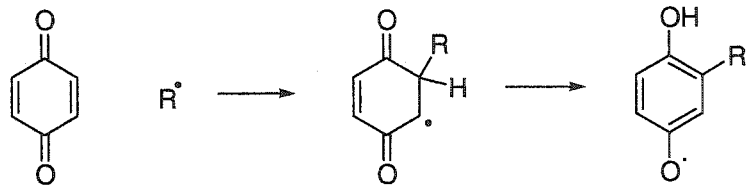
The mechanism of silver (I)-catalyzed persulfate reaction is shown below as proposed

by Minisci.[12a]

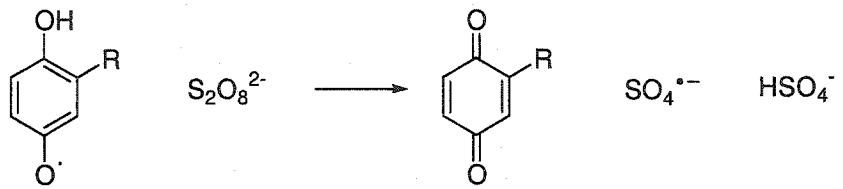
i) generation of the carbon-centered radical



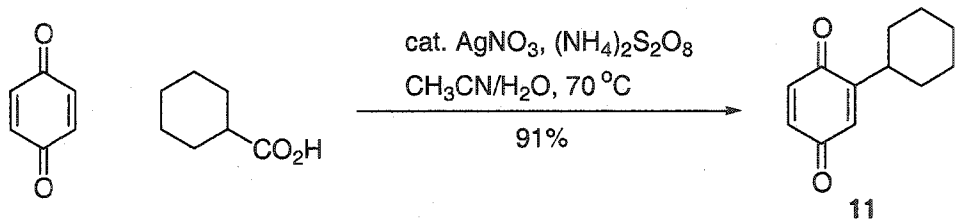
ii) addition to the quinone ring



iii) oxidation of the radical adduct in a redox chain

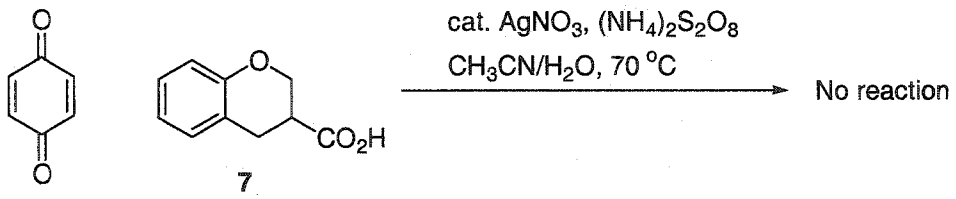


Before we applied persulfate-mediated radical chemistry to the synthesis of isoflavanquinones, we first conducted decarboxylative radical addition of cyclohexanecarboxylic acid to benzoquinone to find the optimal reaction conditions. Thus, a mixture of benzoquinone and cyclohexanecarboxylic acid was treated with a catalytic amount of silver nitrate and 1.5 equivalents of ammonium persulfate to give cyclohexyl benzoquinone **11** in good yield.



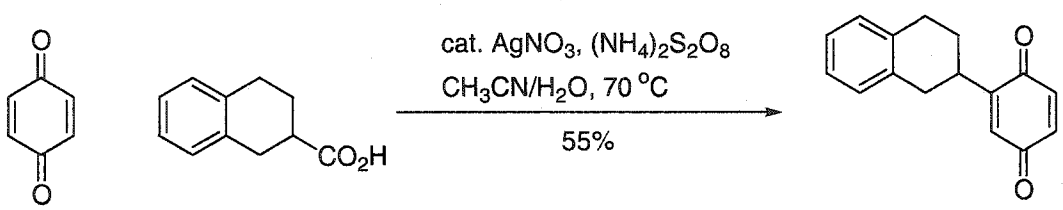
Encouraged by this result, we reacted chroman-3-carboxylic acid with benzoquinone

under the same condition. However, no reaction took place. The starting materials were just recovered with a small amount of decomposed product.



7

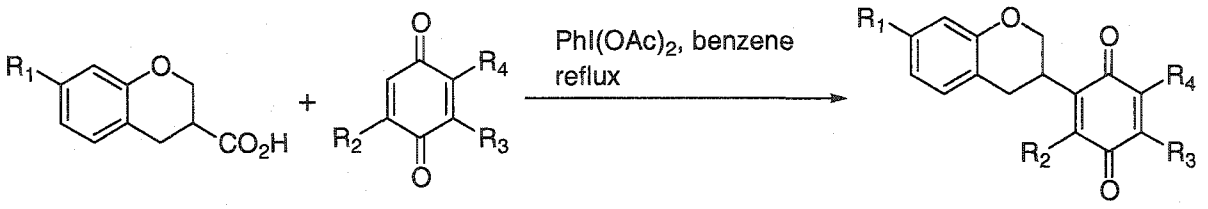
For comparison, we also carried out the reaction with commercially available 1,2,3,4-tetrahydro-2-naphthoic acid. Surprisingly, adduct **12** was obtained in a 55% unoptimized yield.



12

From the observation described above, we came to a tentative conclusion that a subtle electronic issue made a big difference although we were uncertain how the extra oxygen in **7** played a role in this reaction.

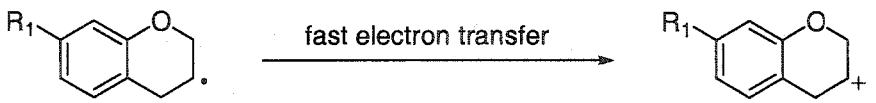
In the meantime, we found that hypervalent iodine reagents, such as iodobenzene diacetate, could generate radicals from the corresponding carboxylic acid precursors.[14] Therefore, we used iodobenzene diacetate as a radical generator. Gratifyingly, colutequinones A and B, as well as unnatural isoflavanquinones, were obtained albeit in low yield. Modification of the reaction conditions by changing the ratio of reagents, temperatures, and solvents did not lead to any improvement in the chemical conversion of this process.



entry		product	yield(%)*	conversion(%)
1	$R_1 = R_2 = R_3 = R_4 = H$	**(1)**	92	27
2	$R_1 = OMe, R_2 = R_3 = R_4 = H$	**(2)**	87	20
3	$R_1 = R_3 = R_4 = OMe, R_2 = H$	**(3)**	85	10
4	$R_1 = R_2 = R_3 = OMe, R_4 = H$	**(4)**	91	23
5	$R_1 = R_3 = OMe, R_2 = R_4 = H$	**(6)**	82	7

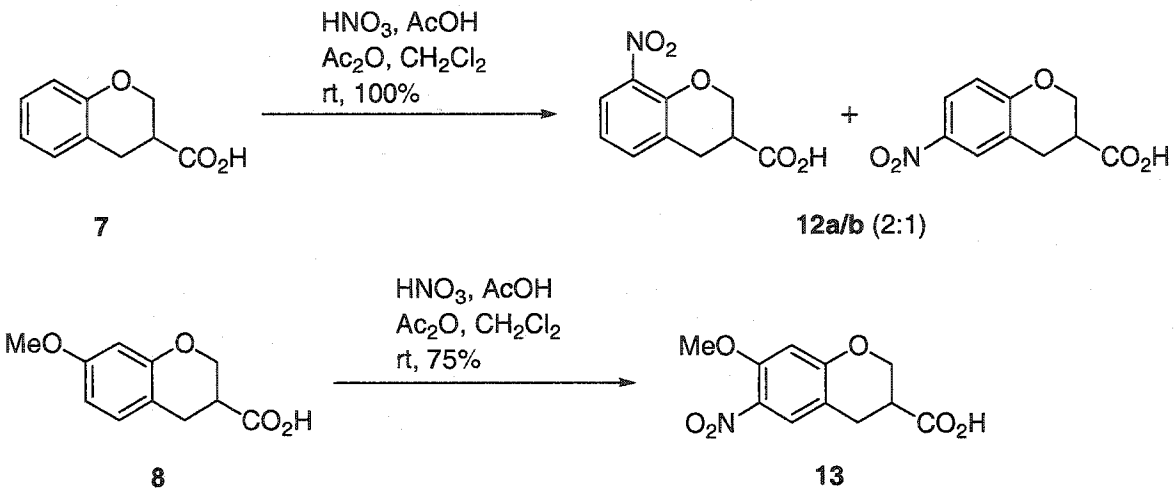
* : yields based on the recovered benzoquinones

At this stage, we went back to the persulfate chemistry. We postulated that fast electron transfer might occur in relatively electron-rich **7** and **8** before radical addition, resulting in the cation species via loss of one electron.

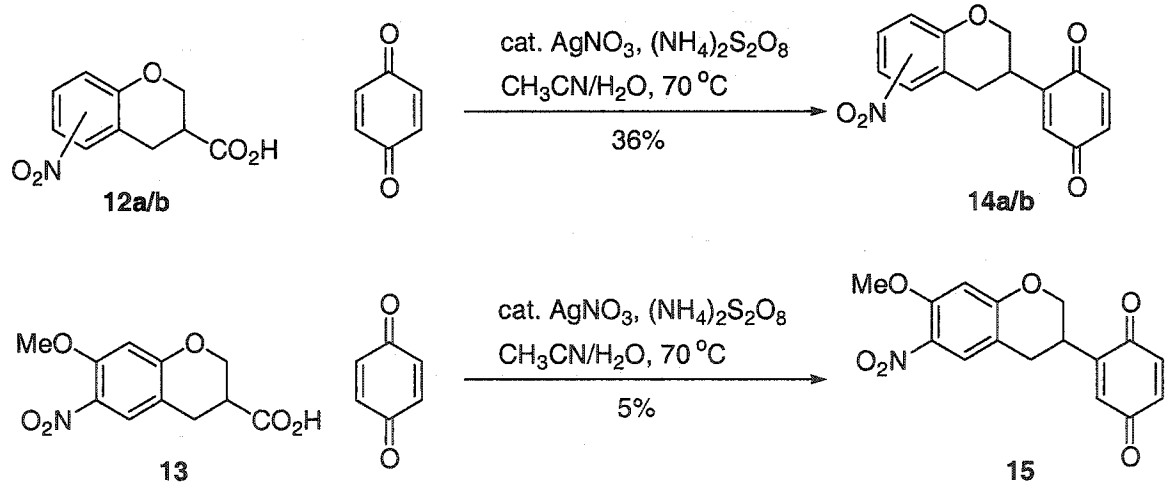


Thus, we decided to introduce the electron-withdrawing group to carboxylic acids to avoid fast electron transfer.

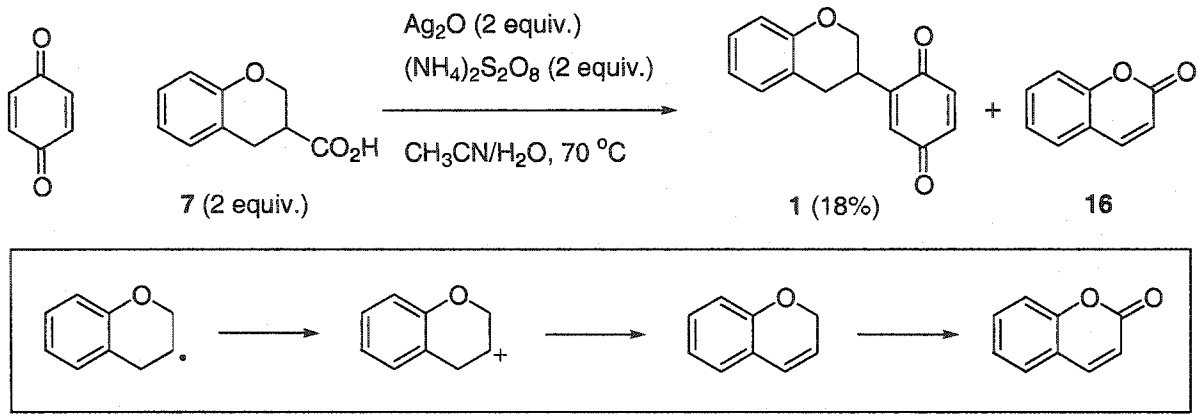
In this regard, compounds **7** and **8** were nitrated. While **7** provided a 2:1 mixture of nitrated products **12a** and **12b**, **8** was nitrated at 6-position to give **13** as a single isomer.



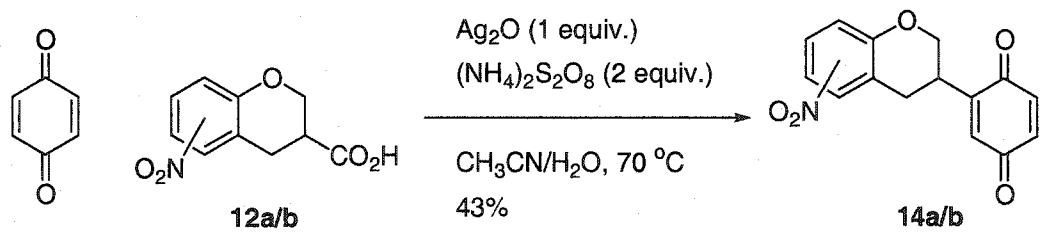
With these compounds in hand, standard persulfate chemistry was undertaken. To our delight, **12a** and **12b** furnished radical adducts **14a** and **14b** as a mixture of regioisomers in 36% yield, although **13** still provided desired product **15** in low yield. We assumed that additional methoxy group in **13** still inhibited the reaction from occuring.



We also employed a stoichiometric amount of silver salt to prevent the possible deactivation of catalytic amount of silver(I) ion in the reaction medium. In this case, an 18% isolated yield of radical adduct **1** was observed along with coumarin **16**. Compound **16** explained our rationale of electron transfer in the reaction mixture.

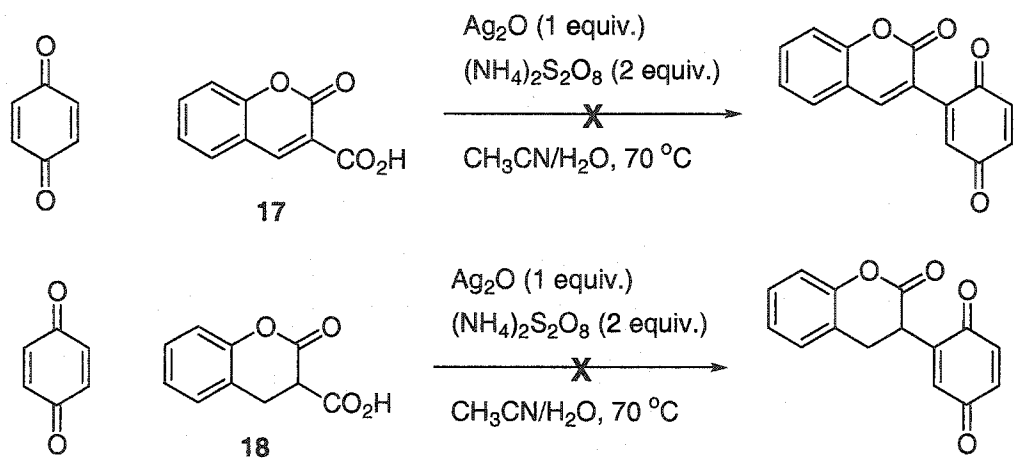


We next used compounds **12a** and **12b** as radical precursors and a stoichiometric amount of silver salt. This combination provided adducts **14a** and **14b** in 43% yield.

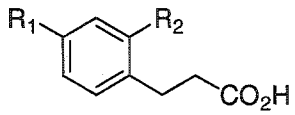


However, these compounds required further manipulation to be transformed into natural products. Therefore, we decided to pursue other routes to these natural products.

In an attempt to generate a vinylic radical from the precursor **17**,[15] we performed the reaction under the modified persulfate conditions. Similarly, carboxylic acid **18** was exposed to the same conditions. But these acids did not provide the desired adducts.

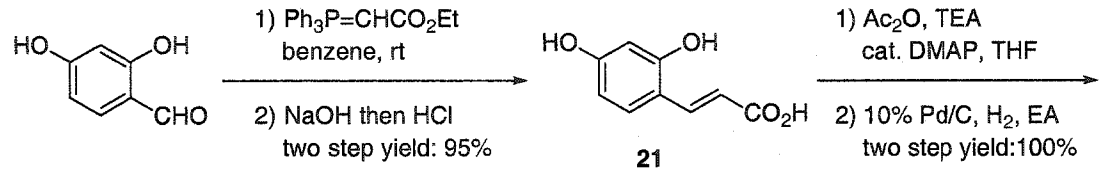


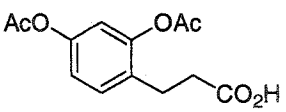
We've learned that electron-rich aromatic ring somehow prevents the radical addition from occurring. In this regard, we designed radical precursors in which two phenol groups were masked by electron withdrawing groups.



$R_1 = R_2 = OAc$: **19**
$R_1 = R_2 = OTf$: **20**

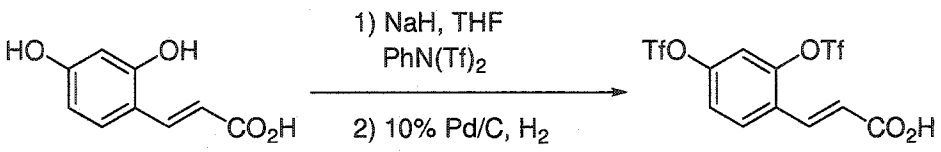
Compounds **19** and **20** were synthesized in a conventional manner from the commercially available 2,4-dihydroxybenzaldehyde. Thus, Wittig olefination, ester hydrolysis, bis O-acetylation,[16] and catalytic hydrogenation provided the radical precursor **19** in good overall yield.



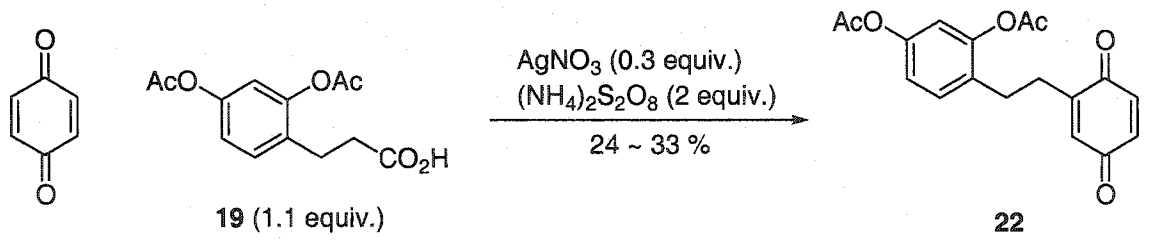


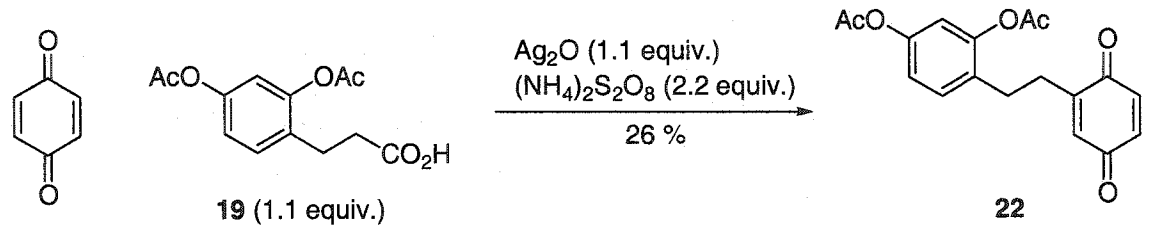
19

In a similar manner, **20** was prepared by bis O-triflation and hydrogenation of **21**.

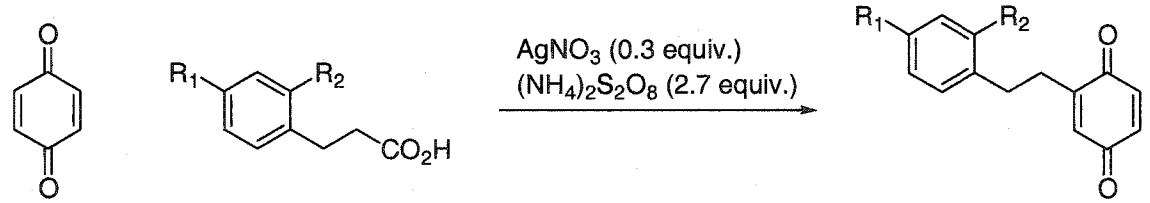


First, we undertook silver(I)-catalyzed persulfate reaction with **19**. It gave a radical adduct **22** in 24-33% yield.[17] Even if we increased the amount of the silver(I) salt to 1.1 equivalents, it did not improve the chemical yield.



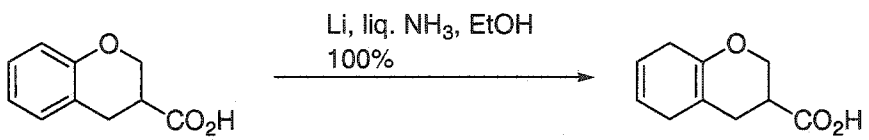


For comparison, other precursors were tested.



entry	R_1	R_2	product	yield(%)
1	OMe	H		0
2	H	H	**23**	21
3	OTf	OTf	**24**	8

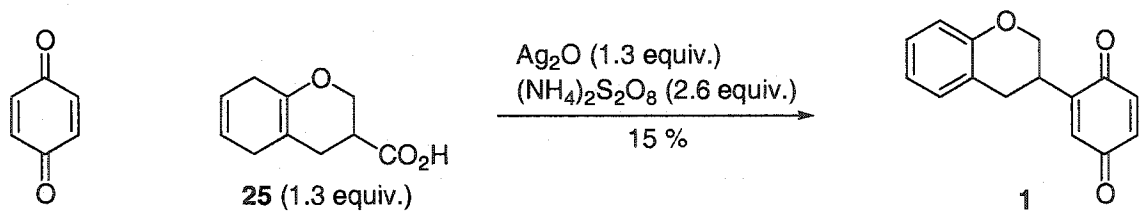
Since triflates in the benzene ring decrease the electron density of the aromatic ring more than acetyloxy groups, we anticipated a better chemical yield. Rather, it gave a poorer result. In line with the effort to decrease the electron density, we also prepared **25** quantitavely from **7** by Birch reduction.[18]



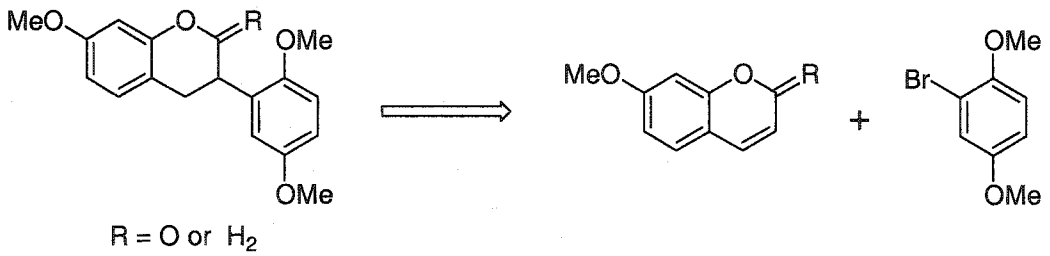
7 **25**

However, subjection of **25** to radical conditions described above gave only a 15% of

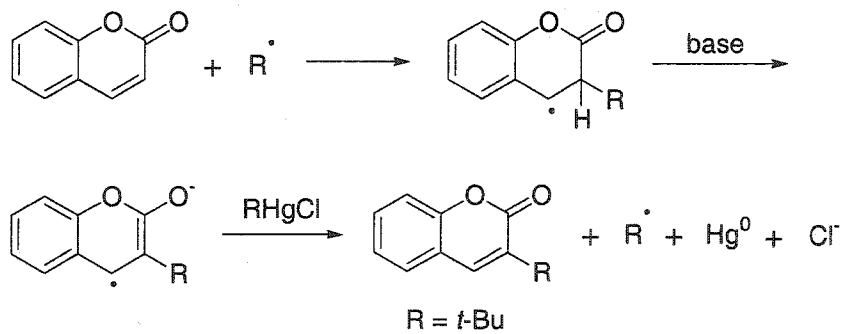
adduct **1**. In the reaction mixture, we observed chroman-3-carboxylic acid **7**, presumably as a consequence of the facile oxidation of **25** under the reaction condition.



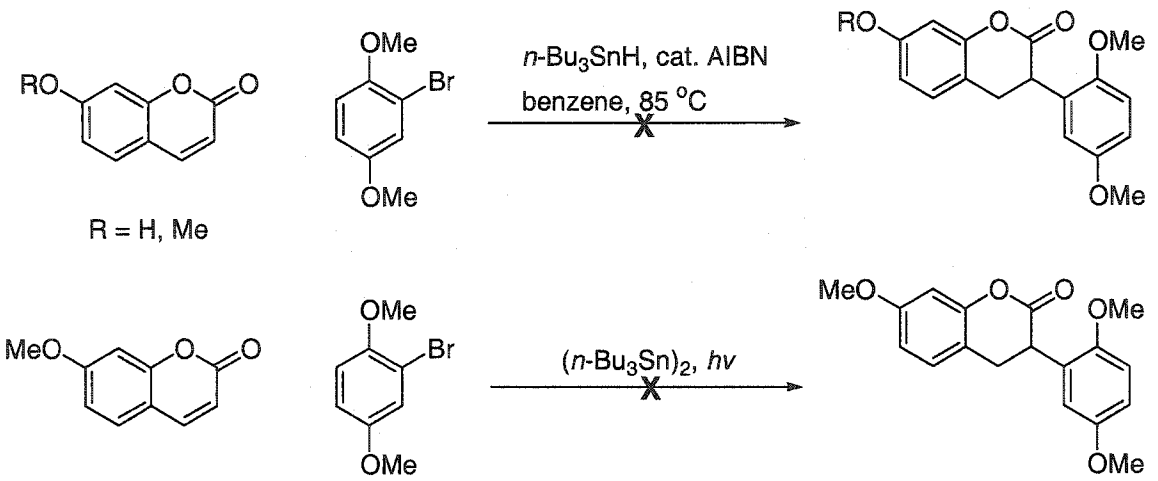
Concurrently, we designed a different approach toward these molecules. Phenyl radical would add preferably to 3-position of chromene or coumarin rather than to 4-position because of the formation of a more stable benzyl radical.



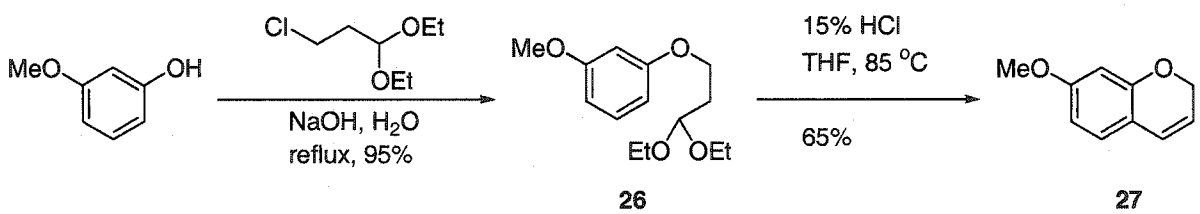
Few radical addition to chromene or coumarin derivatives have been studied.[19] For example, Russel and coworkers added *t*-butyl radical to coumarin in the presence of base.[19d]



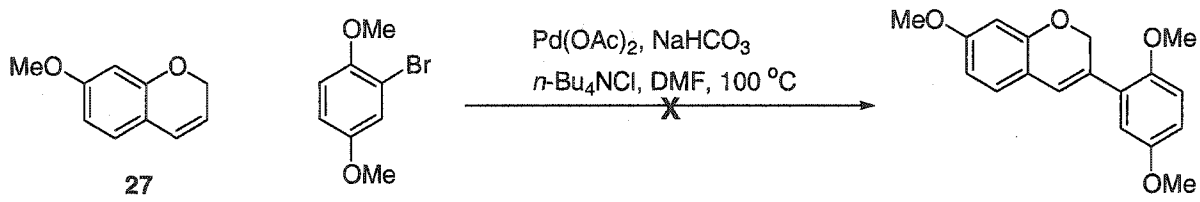
Thus, we employed several different radical or palladium reaction conditions to effect this strategy. Unfortunately, none of them afforded a desirable result. Only debrominated benzene was observed.



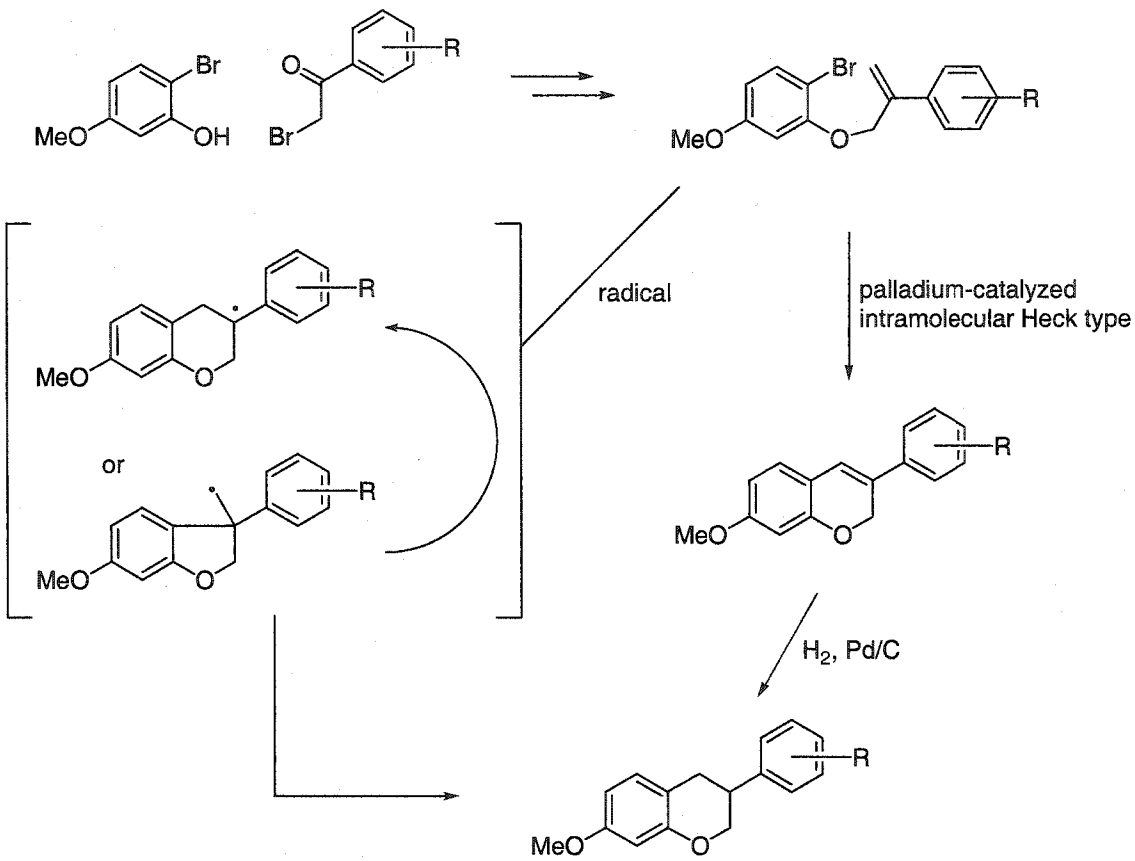
Chromene **27** was also prepared by the slight modification of the known procedure.[20]



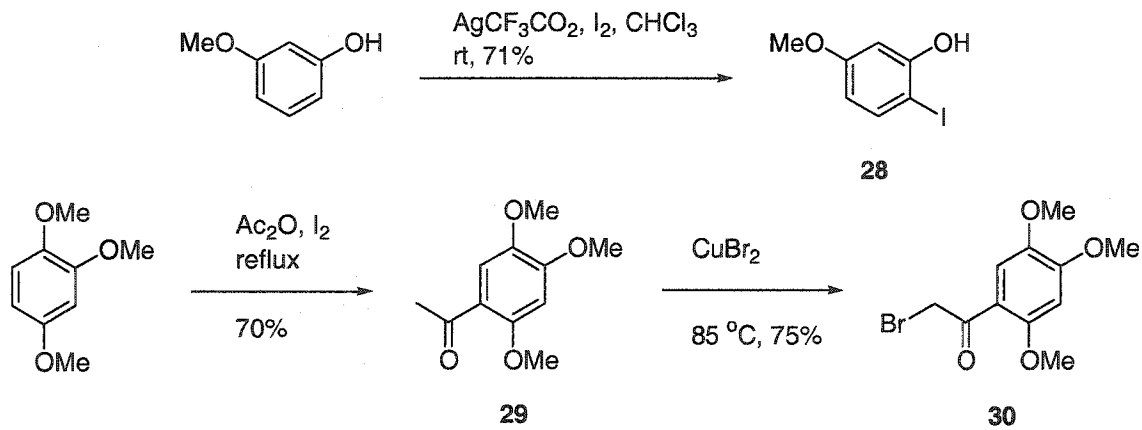
With **27** in hand, a palladium catalyzed Heck reaction[21] was carried out. It failed to give the desired product.



At this point, we came up with a different strategy in which an intramolecular radical or Heck type process would lead to the desired transformation.

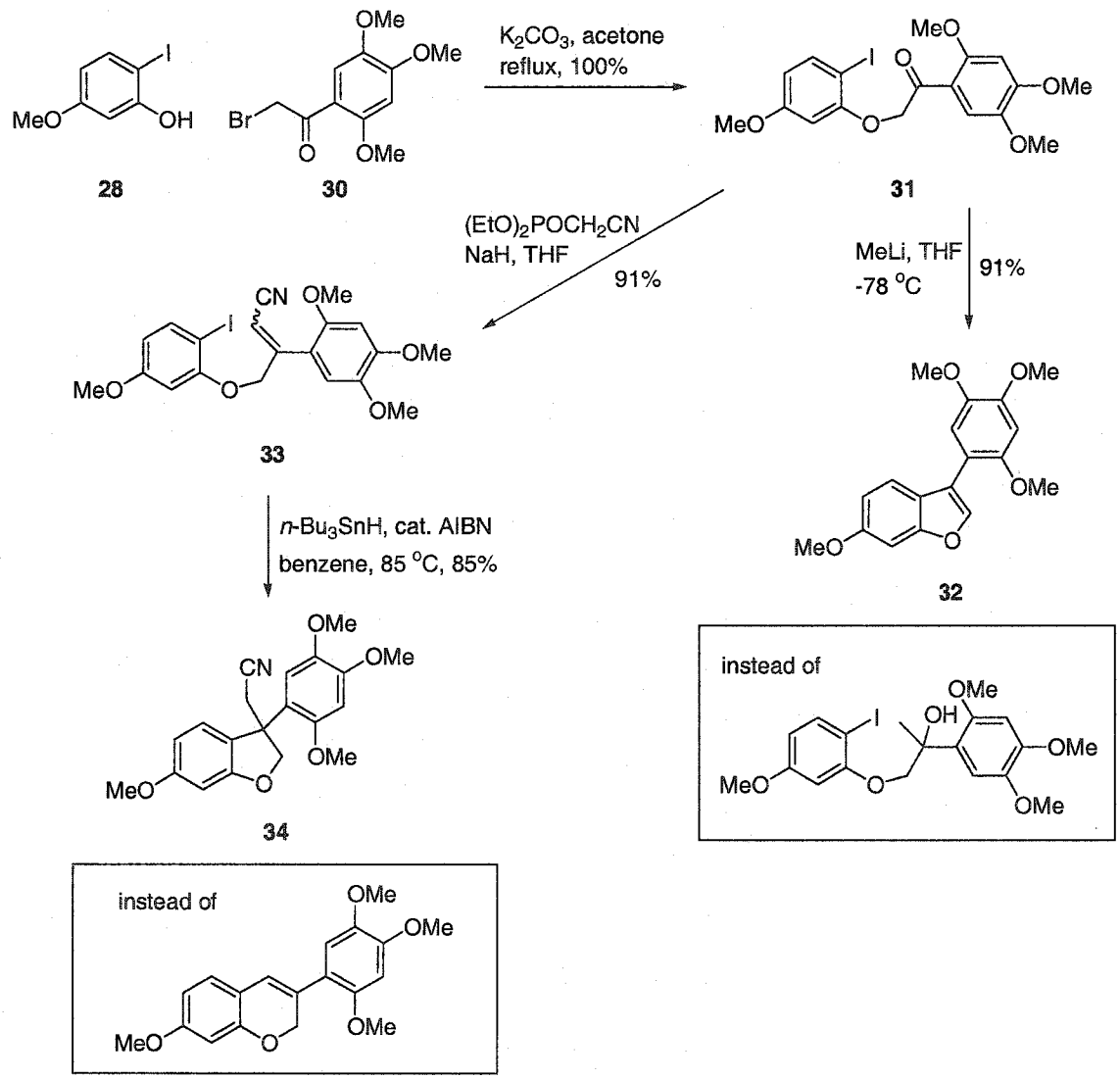


Toward this end, 2-iodophenol **28**[22] and bromoketone **30**[23] were prepared by known procedures.



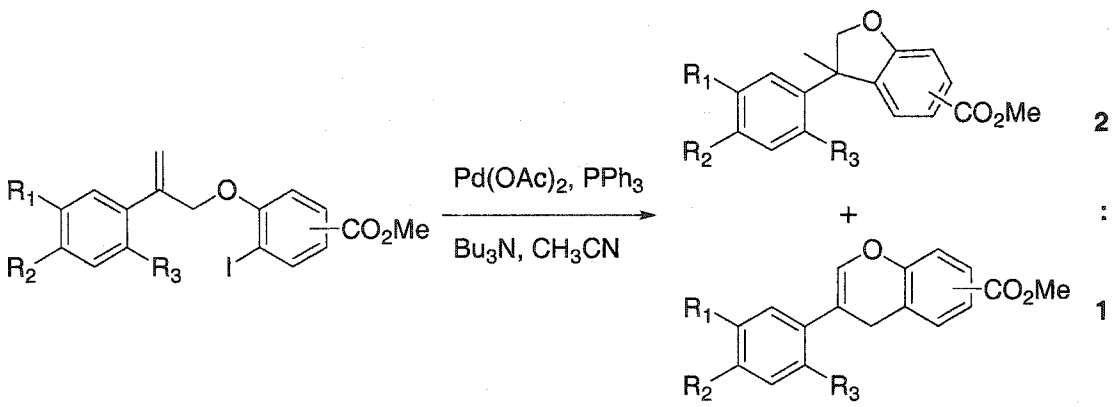
Iodophenol **28** was alkylated with bromoketone **30** and potassium carbonate in boiling acetone in quantitative yield to give ketone **31**. We reacted **31** with excess MeLi at –78 °C to

introduce the exo methylene group on the carbonyl group. To our surprise, instead of the tertiary alcohol as a result of the carbonyl attack, we obtained benzofuran **32** in very good yield. This observation led us to investigate the synthetic approach to the natural products possessing a benzofuran unit, which was discussed in the first part of this dissertation.

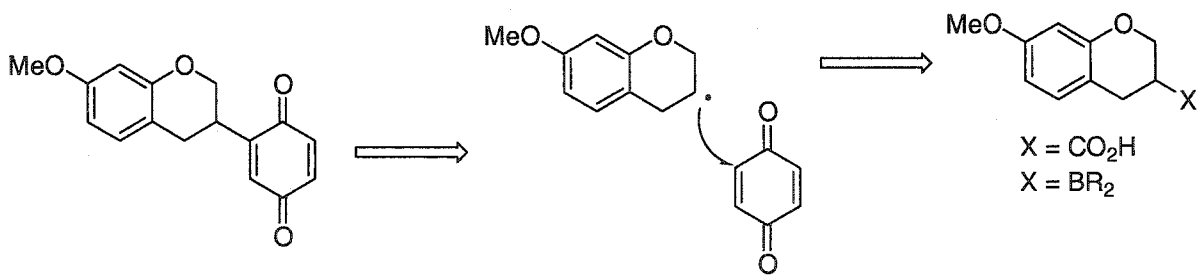


Treatment of **31** with Horner-Wadsworth-Emmons reagent afforded **33** as an E/Z mixture. Exposure of **33** to standard *n*-Bu_3SnH condition gave rise to **34** via a 5-exo radical attack in 85% yield.[24] We expected a 6-endo attack followed by the removal of CN radical,

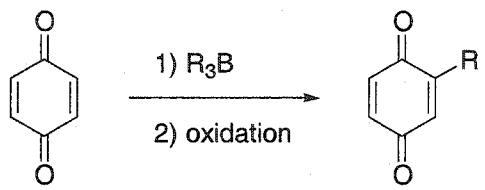
but it did not happen. A similar approach was studied using a palladium-catalyzed intramolecular Heck reaction.[25] They reported that five-membered ring formation was favored over six-membered ring formation despite the conditions in which a true hydride source was not added.



Thus, we sought another approach. Boranes are useful radical precursors and might be good candidates for radical addition to benzoquinones.[26]

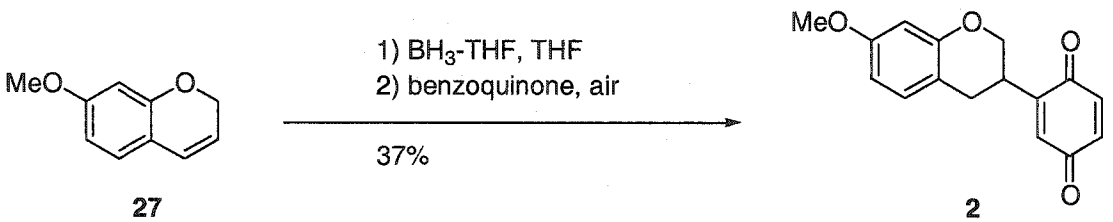


There are literature precedents in which simple alkylboranes add to benzoquinones to give substituted benzoquinones after oxidation of the resulting hydroquinones.[27]



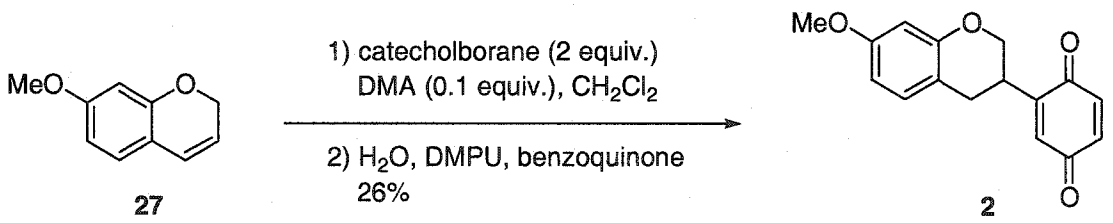
To test this protol, chromene **27** was reacted with BH_3 followed by the treatment of

benzoquinone and air. To our delight, this sequence provided the quinone **2**[28] in 37% yield. Notably, the benzoquinone was obtained from the reaction mixture without need for a subsequent oxidation step.



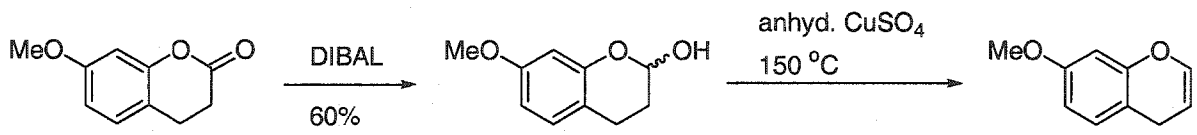
27 **2**

For comparison, we employed a different borane reagent, catecholborane, for hydroboration. Renaud and coworkers reported radical addition to α,β-unsaturated carbonyl compounds using catecholborane.[29] We adopt this method to effect our desired transformation.

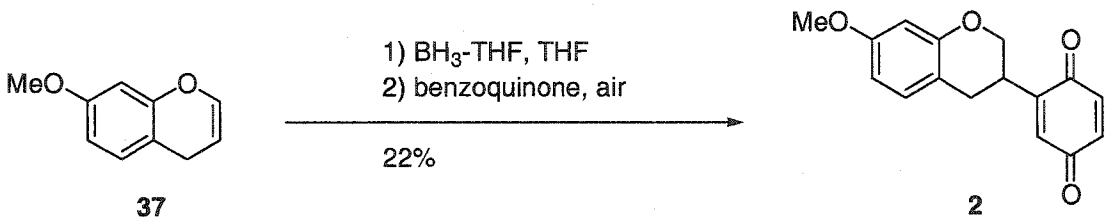


27 **2**

The yield was a little lower than that of BH_3 case. Moreover, it was sometimes more difficult to isolate product from the reaction mixture because of the resulting catechol. Thus, we decided to use BH_3 for other transformations. We also used 2-chromene **37** to see if this gave a better result. 2-Chromene **37** was available in two steps from **35**.[30] However, it did not have an advantage over 3-chromene.

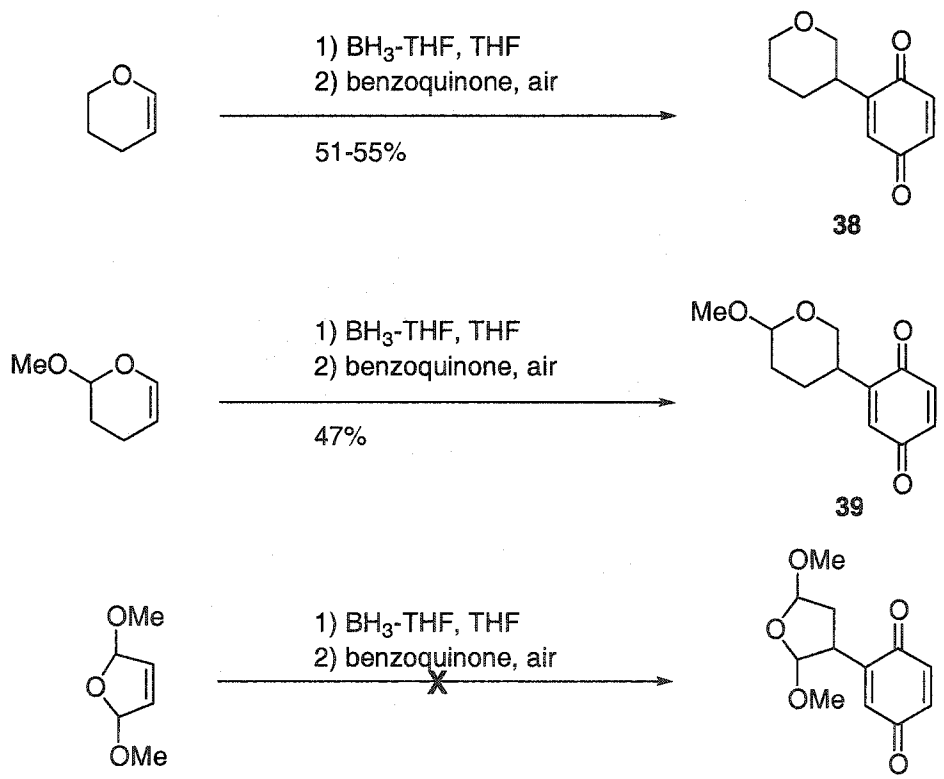


35 **36** **37**



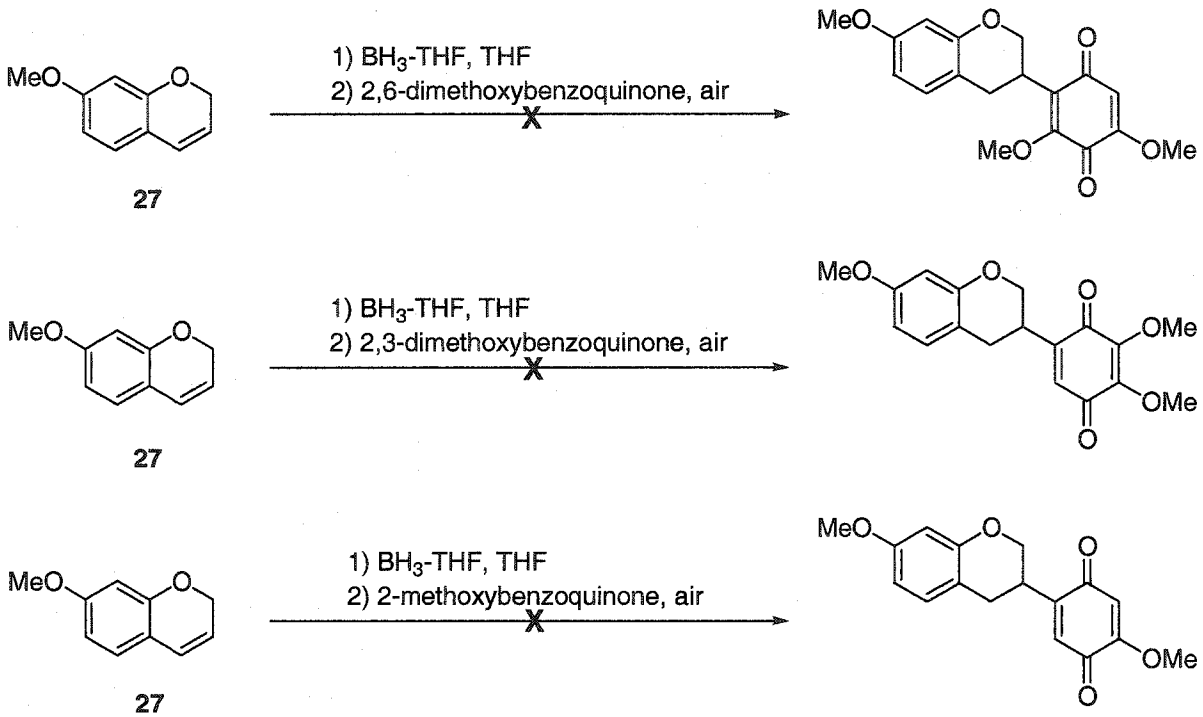
37 2

Three commercially available alkenes were examined with BH_3 and benzoquinone. While the first two alkenes gave good yields of the corresponding products, the third alkene provided only a trace amount of the product.

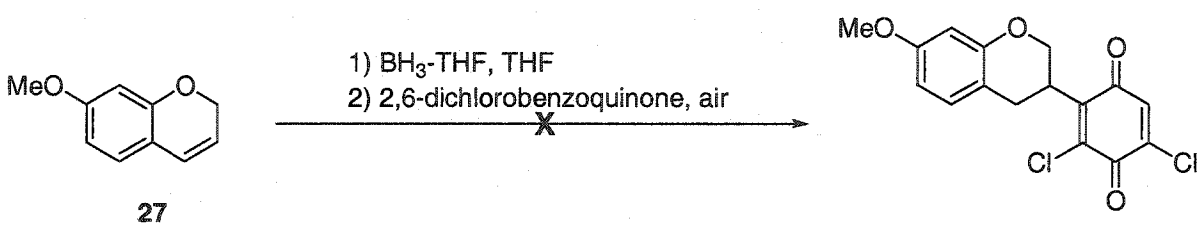


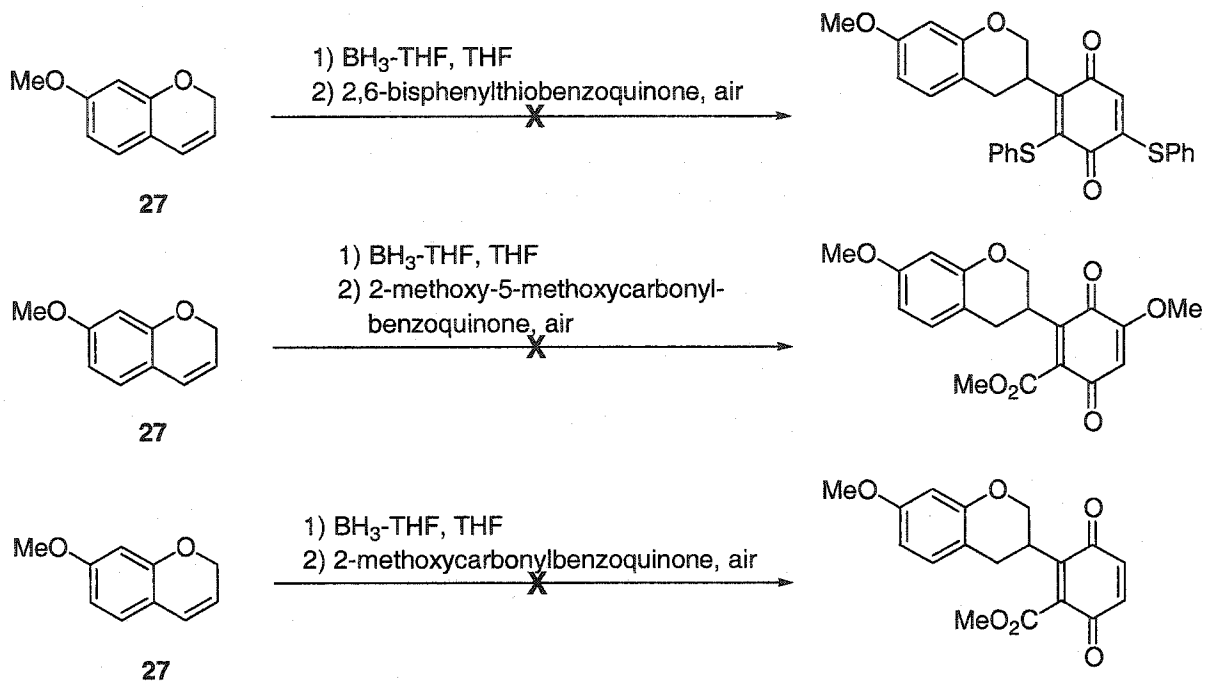
For some reason, large amount of unreacted chromene **27** was recovered after the reaction. We resubmitted the recovered chromene **27** to the same condition to increase the yield up to 65% yield. With this promising result in hand, our attention was next directed to

produce the appropriately substituted benzoquinone natural products in one step. Thus, we reacted the boranes with substituted benzoquinones.

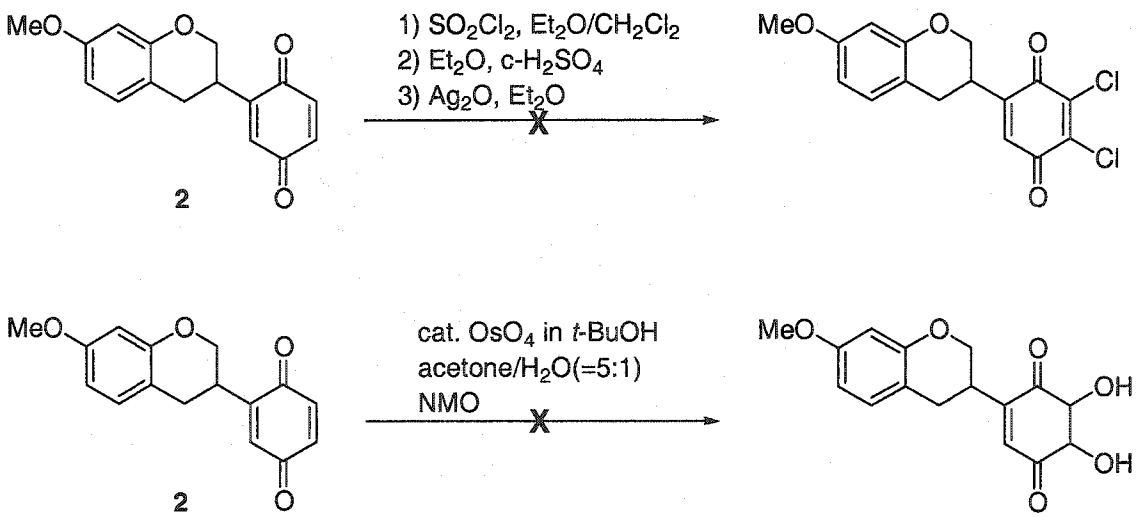


To our surprise, no desired adducts were formed. The major product was the chromanol derived from oxidation of the borane with oxygen. This result was unexpected in light of a recent report on the successful regioselective addition of alkyl radicals to methoxybenzoquinone.[27e] We also tested other functionalized benzoquinones for this reaction. No adducts were obtained, either.



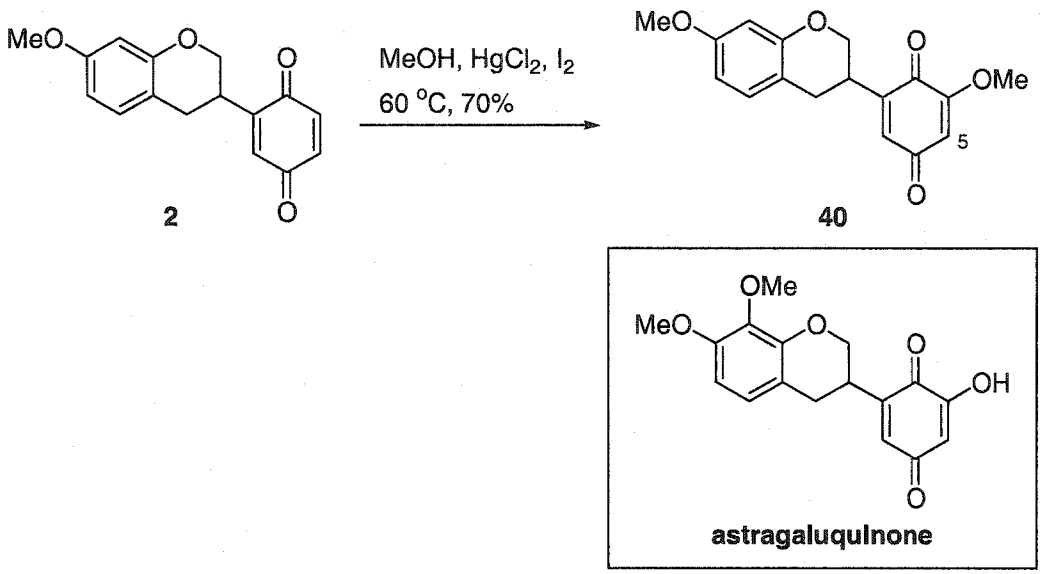


Thus, we decided to manipulate the quinone **2** to add the required functionality onto the benzoquinone. To incorporate the dichloro[31] or dihydroxy[32] functionality onto the benzoquinone, we tried two procedures, but failed to get the desired products.



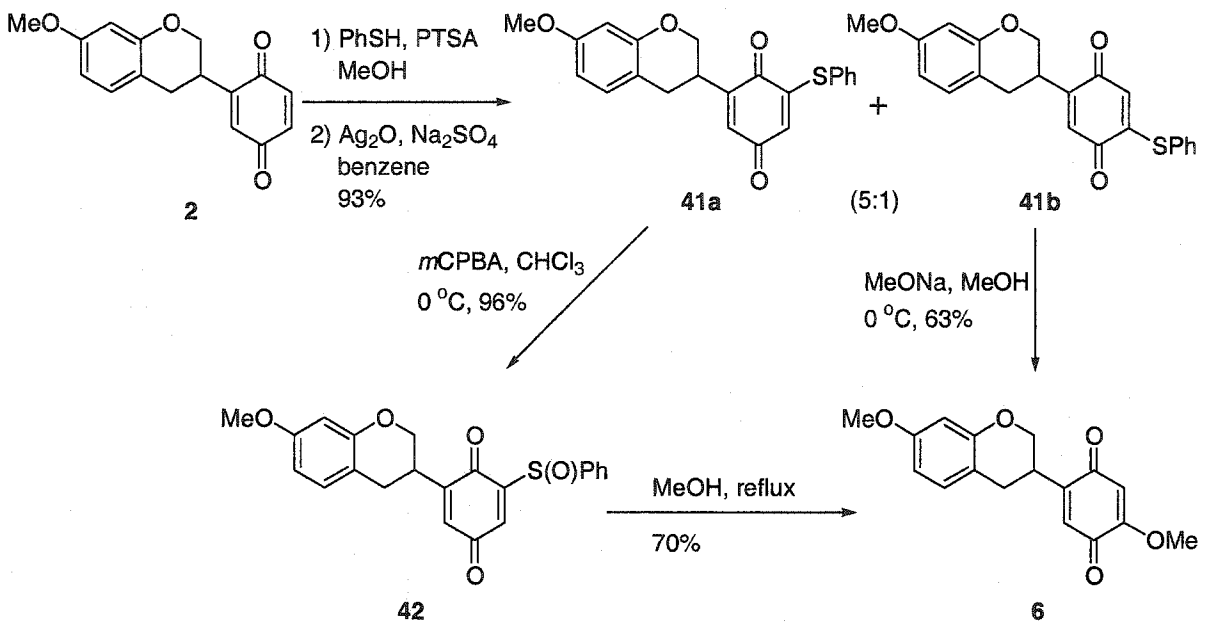
The regioselective addition of alcohols to benzoquinones has little precedent.[33] Our

group recently published the regioselective addition of methanol to a phenanthrenequinone using a Lewis acid catalyst.[34] Employing these conditions with **2** we obtained **40** in 70% yield. In **40**, the proton at C-5 of the quinone (ortho to the methoxy group) has a chemical shift of 5.89 with a coupling constant of 2.4 Hz. The corresponding hydrogen in astragaluquinone[35] has a coupling constant of 2.5 Hz.



The reaction of **2** with thiophenol and PTSA in methanol at 25 °C followed by oxidation with silver oxide produced adducts **41a** and **41b** in a 5:1 ratio in 93% combined yield. Although no precedent was found for the directed addition of thiophenol to substituted benzoquinones, the regiochemistry of thiophenol addition is in accord with our observation for the acid catalyzed addition of methanol to quinones. Oxidation of **41a** with *m*CPBA[36] in chloroform at 0 °C afforded a sulfoxide that was treated with methanol at reflux to afford *O*-methyl analog **6** of claussequinone in 70% yield. Its proton and carbon NMR were consistent with the structure of **6**. Presumably, this transformation occurs by way of methanol addition to the activated benzoquinone followed by sulfoxide elimination. Compound **41b**, the minor

product of thiol addition, was treated with sodium methoxide to afford compound **6** in 63% yield.



In summary, direct approaches to isoflavanquinones have been made utilizing three different radical generation methodologies - persulfate chemistry, hypervalent iodine chemistry, and borane chemistry. Synthetic scope and limitation of each strategy have been presented. Moreover, convenient procedures for the regiospecific addition of thiophenol and methanol to substituted benzoquinones have been developed during the study with boranes. These routes will be useful for the synthesis of quinone natural products with useful biological activity.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used

withtout purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

Chroman-3-carboxylic acid (7)

To a solution of 2-hydroxybenzaldehyde (5.0 g, 40.943 mmol) and *t*-butyl acrylate (9.0 mL, 61.415 mmol) in DMF (82 mL) was added K_2CO_3 (5.66 g, 40.943 mmol) at rt. After being heated at 100 °C for 1 h, the mixture was heated at 135 °C for 14h. Then, additional *t*-butyl acrylate (9.0 mL, 61.415 mmol) was added to the reaction mixture. The mixture was heated at 135 °C for additional 24 h. After being cooled to rt, the mixture was diluted with ethyl acetate and acidified with 10% HCl. The organic layer was washed with H_2O three times and with brine one time, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. *t*-Butyl ester was identified in the crude ^1H NMR. 300 MHz ^1H NMR ($CDCl_3$) δ 7.33 (1H, s), 7.22 (1H, t, *J* = 8.7 Hz), 7.13 (1H, d, *J* = 7.5 Hz), 6.91 (1H, t, *J* = 7.5 Hz), 6.83 (1H, d, *J* = 8.1 Hz), 4.95 (2H, s), 1.52 (9H, s).

The crude residue was diluted with trifluoroacetic acid (20 mL) and stirred at rt for 1 h. The solvent was evaporated under reduced pressure. To this residue was added large amount

of cold H_2O. The resulting precipitate was suction-filtered off and washed with H_2O several times. The solid was air-dried. The acid was identified in the crude ^1H NMR. 300 MHz ^1H NMR ($CDCl_3$) δ 7.57 (1H, s), 7.26 (1H, t, J = 8.7 Hz), 7.17 (1H, d, J = 7.5 Hz), 6.95 (1H, t, J = 7.5 Hz), 6.87 (1H, d, J = 8.1 Hz), 5.01 (2H, s).

The crude residue was dissolved in ethyl acetate and 10% Pd/C was added with care. After being stirred under H_2 balloon pressure for 6 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was transferred to the separatory funnel. The organic layer was washed with saturated $NaHCO_3$ solution. The separated aqueous layer was then acidified with 10% HCl. The aqueous layer was extracted with ethyl acetate two times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 2:1) to give **7** (5.684 g, 78%). 300 MHz ^1H NMR ($CDCl_3$) δ 7.30-7.03 (2H, m), 7.03-6.70 (2H, m), 4.46 (1H, d, J = 11.1 Hz), 4.32-4.08 (1H, m), 3.30-2.82 (3H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 179.1, 154.2, 130.0, 127.9, 121.2, 120.2, 117.0, 66.3, 38.6, 27.4, 16.6.

7-Methoxychroman-3-carboxylic acid (8)

The same procedure for **7** was applied.

***t*-Butyl ester**: 300 MHz ^1H NMR ($CDCl_3$) δ 7.30 (1H, d, J = 0.6 Hz), 7.03 (1H, d, J = 8.4 Hz), 6.47 (1H, dd, J = 8.4, 2.4 Hz), 6.39 (1H, d, J = 2.4 Hz), 4.92 (2H, d, J = 1.2 Hz), 3.85 (3H, s), 1.52 (9H, s).

Acid: 300 MHz ^1H NMR (acetone-d_6) δ 7.45 (1H, s), 7.24(1H, d, J = 8.4 Hz), 6.57 (1H, dd, J = 8.4, 2.4 Hz), 6.45 (1H, d, J = 2.4 Hz), 4.93 (2H, s).

8: 300 MHz ^1H NMR (acetone-d_6) δ 6.99 (1H, d, J = 8.4 Hz), 6.45 (1H, dd, J = 8.4, 2.4 Hz), 6.32 (1H, d, J = 2.4 Hz), 4.38 (1H, dd, J = 10.5, 2.4 Hz), 4.12 (1H, dd, J = 10.5, 7.5 Hz), 3.72

(3H, s), 3.13-2.85 (3H, m); 75 MHz ^{13}C NMR (acetone-d_6) δ 173.0, 159.5, 155.2, 130.4, 113.0, 107.6, 101.5, 66.7, 54.8, 38.2, 26.7.

2,3-Dimethoxy-1,4-benzoquinone (9)

To a solution of 1,2,3-trimethoxybenzene (5.0 g, 29.7 mmol) in AcOH (29.7 mL) were successively added $K_3Fe(CN)_6$ (1.2 g, 3.64 mmol) and H_2O_2 (30% solution, 7.4 mL, 65.34 mmol) at rt. After being stirred at rt for 1 h (exothermic reaction), the mixture was diluted with CH_2Cl_2 and washed with H_2O, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give **9** (2.65 g, 53%). 300 MHz ^1H NMR ($CDCl_3$) δ 6.60 (2H, s), 4.02 (6H, s).

Methoxy-1,4-benzoquinone (10)

To a solution of methoxyhydroquinone (500 mg, 3.568 mmol) in benzene (36 mL) were added Na_2SO_4 (1.06 g, 7.493 mmol) and Ag_2O (1.65 g, 7.136 mmol) at rt. The reaction flask was covered with aluminum foil and stirred overnight. The mixture was suction-filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give **10** (488 mg, 99%). 300 MHz ^1H NMR ($CDCl_3$) δ 6.71 (2H, s), 5.95 (1H, s), 3.83 (3H, s).

Cyclohexyl-1,4-benzoquinone (11)

To a mixture of 1,4-benzoquinone (300 mg, 2.78 mmol) and cyclohexanecarboxylic acid (517 μL, 4.17 mmol) in CH_3CN (5 mL)/H_2O (5 mL) were added $AgNO_3$ (94 mg, 0.556 mmol) and $(NH_4)_2S_2O_8$ (698 mg, 3.058 mmol) at rt. After being heated at 70 °C for 6 h, the mixture was cooled to rt. The solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H_2O and saturated $NaHCO_3$ solution, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The

residue was purified by sgc (H:EA = 20:1) to give **11** (480 mg, 91%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.69 (1H, d, J = 9.9 Hz), 6.63 (1H, dd, J = 9.9, 2.4 Hz), 6.44 (1H, dd, J = 2.1, 0.9 Hz), 2.62 (1H, t, J = 11.7 Hz), 1.84-1.60 (5H, m), 1.45-1.24 (2H, m), 1.24-1.02 (3H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 188.3, 187.2, 154.1, 137.2, 136.1, 130.9, 36.5, 32.2, 26.5, 26.1.

(1,2,3,4-Tetrahydronaphthalen-2-yl)-1,4-benzoquinone (12)

The same procedure for **11** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.20-7.02 (4H, m), 6.80 (1H, d, J = 9.9 Hz), 6.74 (1H, dd, J = 9.9, 2.1 Hz), 6.58 (1H, dd, J = 2.4, 1.2 Hz), 3.26-3.13 (1H, m), 3.07-2.84 (3H, m), 2.70 (1H, dd, J = 15.9, 11.1 Hz), 2.10-1.97 (1H, m), 1.82-1.65 (1H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 188.1, 187.2, 153.0, 137.3, 136.3, 135.8, 135.3, 131.4, 129.2, 129.16, 126.3, 126.1, 35.1, 33.3, 29.1, 28.3; HRMS *m/z* for $C_{16}H_{14}O_2$ calcd 238.0994, found 238.0996.

(3,4-Dihydrobenzopyran-3-yl)-1,4-benzoquinone (1)

To a mixture of 1,4-benzoquinone (10 mg, 0.093 mmol) and **7** (49.7 mg, 0.279 mmol) in benzene (2 mL) was added $PhI(OAc)_2$ (30 mg, 0.093 mmol) at rt. After being heated to reflux overnight, the mixture was cooled to rt. The solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (H:EA = 5:1) to give **1** (6.0 mg, 27%, 92% based on the recovered 1,4-benzoquinone). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.13 (1H, t, J = 7.5 Hz), 7.07 (1H, d, J = 7.5 Hz), 6.89 (1H, t, J = 7.5 Hz), 6.83 (1H, d, J = 7.5 Hz), 6.82 (1H, dd, J = 10.2, 0.6 Hz), 6.74 (1H, ddd, J = 9.9, 2.4, 0.6 Hz), 6.56 (1H, dd, J = 2.4, 1.2 Hz), 4.29 (1H, ddd, J = 10.5, 3.0, 1.2 Hz), 4.08 (1H, ddd, J = 10.8, 6.6, 0.9 Hz), 3.54-3.42 (1H, m), 3.12 (1H, dd, J = 16.5, 5.7 Hz), 2.82 (1H, dd, J = 16.2, 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.5, 186.9, 154.2, 148.6,

137.1, 136.6, 133.0, 129.9, 128.1, 121.3, 120.2, 117.1, 68.3, 31.2, 29.7; HRMS *m/z* for $C_{15}H_{12}O_3$ calcd 240.0786, found 240.0791.

(3,4-Dihydro-7-methoxybenzopyran-3-yl)-1,4-benzoquinone (2)

1) from the reaction of **8** and 1,4-benzoquinone using iodobenzene diacetate:

The same procedure for **1** was applied.

2) from **27**:

To a solution of 7-methoxy-3-chromene **27** (800 mg, 4.94 mmol) in THF (4 mL) was added 1 M BH_3-THF (1.65 mL, 1.65 mmol) at 0 °C. After being stirred at rt for 5 h, H_2O (89 μL, 4.94 mmol) was added at 0 °C. Then benzoquinone (178 mg, 1.65 mmol) was added at rt in one portion. After being stirred at rt for 2 h, the mixture was evaporated in vacuo. The residue was purified by sgc (H:EA = 7:1) to give **2** (165 mg, 37%). 300 MHz ^{1}NMR ($CDCl_3$) δ 6.95 (1H, d, *J* = 8.4 Hz), 6.81 (1H, d, *J* = 10.2 Hz), 6.73 (1H, dd, *J* = 10.2, 2.1 Hz), 6.55 (1H, dd, *J* = 2.1, 1.2 Hz), 6.49 (1H, dd, *J* = 8.4, 2.7 Hz), 6.38 (1H, d, *J* = 2.7 Hz), 4.27 (1H, dd, *J* = 10.8, 3.0 Hz), 4.07 (1H, dd, *J* = 10.8, 6.6 Hz), 3.76 (3H, s), 3.50-3.39 (1H, m), 3.06 (1H, dd, *J* = 15.9, 5.7 Hz), 2.75 (1H, dd, *J* = 15.9, 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.6, 186.9, 159.6, 154.9, 148.6, 137.1, 136.5, 133.0, 130.3, 112.2, 108.3, 101.8, 68.3, 55.6, 31.2, 29.0; HRMS *m/z* for $C_{16}H_{14}O_4$ calcd 270.0892, found 270.0895; Mp 120-123 °C (lit.[28] mp 125 °C); TLC (3:1 H:EA) R_f = 0.25.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5,6-dimethoxy-1,4-benzoquinone (3)

The same procedure for **1** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, d, *J* = 8.4 Hz), 6.48 (1H, dd, *J* = 8.7, 2.7 Hz), 6.37 (1H, d, *J* = 2.7 Hz), 6.37 (1H, s), 4.25 (1H, dd, *J* = 10.8, 3.0 Hz), 4.06 (1H, dd, *J* = 10.8, 6.0 Hz), 4.02 (3H, s), 4.01 (3H, s), 3.76 (3H, s), 3.50-3.40 (1H, m), 3.05 (1H, dd, *J* = 16.2, 6.0 Hz), 2.71 (1H, dd, *J* = 15.9, 6.3 Hz); 75 MHz ^{13}C

NMR ($CDCl_3$) δ 184.3, 183.7, 159.6, 154.9, 146.8, 145.3, 144.9, 131.2, 130.3, 112.2, 108.3, 101.8, 68.4, 61.6, 61.5, 55.6, 31.0, 29.1; HRMS *m/z* for $C_{18}H_{18}O_6$ calcd 330.1103, found 330.1109.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-3,5-dimethoxy-1,4-benzoquinone (4)

The same procedure for **1** was applied. 300 MHz ^1H NMR ($CDCl_3$) δ 6.92 (1H, d, *J* = 8.4 Hz), 6.47 (1H, dd, *J* = 8.1, 2.4 Hz), 6.41 (1H, d, *J* = 2.7 Hz), 5.86 (1H, s), 4.44 (1H, dd, *J* = 10.8, 10.2 Hz), 4.13 (1H, ddd, *J* = 10.2, 3.3, 3.0 Hz), 3.97 (3H, s), 3.81 (3H, s), 3.77 (3H, s), 3.70-3.55 (1H, m), 3.13 (1H, dd, *J* = 15.0, 12.0 Hz), 2.66 (1H, ddd, *J* = 15.0, 5.1, 2.1 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 186.9, 178.4, 159.3, 157.4, 155.9, 155.3, 131.6, 130.2, 114.1, 107.7, 107.6, 101.8, 67.9, 61.6, 56.7, 55.6, 31.4, 29.4; HRMS *m/z* for $C_{18}H_{18}O_6$ calcd 330.1103, found 330.1109.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5-methoxy-1,4-benzoquinone (6)

1) from the reaction of **8** and **10** using iodobenzene diacetate:

The same procedure for **1** was applied.

2) from **42**:

The sulfoxide **42** (35 mg, 0.089 mmol) was dissolved in MeOH (3 mL). The solution was heated to reflux overnight. The solvent was evaporated and the residue was purified by sgc (H:EA = 3:1) to afford **6** (18.7 mg, 70%). 300 MHz ^1H NMR ($CDCl_3$) δ 6.95 (1H, d, *J* =8.4 Hz), 6.48 (1H, dd, *J* = 8.4, 2.4 Hz), 6.48 (1H, d, *J* = 1.2 Hz), 6.37 (1H, d, *J* = 2.7 Hz), 5.97 (1H, s), 4.26 (1H, ddd, *J* = 11.1, 3.3, 1.2 Hz), 4.07 (1H, ddd, *J* = 10.8, 6.0, 1.2 Hz), 3.82 (3H, s), 3.76 (3H, s), 3.53-3.42 (1H, m), 3.06 (1H, dd, *J* = 16.5, 6.3 Hz), 2.73 (1H, dd, *J* = 15.9, 6.3 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 186.9, 182.3, 159.6, 158.7, 154.9, 149.5, 131.1, 130.3, 112.3, 108.3, 108.1, 101.8, 68.5, 56.5, 55.5, 31.1, 29.1; HRMS *m/z* for $C_{17}H_{16}O_5$ calcd

300.0998, found 300.1002; TLC (2:1 H:EA) R_f = 0.36.

8-Nitrochroman-3-carboxylic acid (12a) and 5-Nitrochroman-3-carboxylic acid (12b)

To a solution of **7** (256 mg, 1.44 mmol) and Ac_2O (768 μL) in CH_2Cl_2 (2 mL) were added HNO_3 (64 μL, 1.44 mmol) and AcOH (172 μL) at 0 °C. After being stirred at rt overnight, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was diluted with toluene and evaporated in vacuo to give **12a/b** (321 mg, 100%) as a 2:1 mixture. 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.10-6.85 (3H, m), 4.67-4.25 (2H, m), 3.30-3.05 (3H, m).

7-Methoxy-6-nitrochroman-3-carboxylic acid (13)

The same procedure for **12a/b** was applied. 300 MHz ^{1}H NMR (acetone-d_6) δ 7.77 (1H, s), 6.57 (1H, s), 4.48 (1H, dd, *J* = 10.5, 2.7 Hz), 4.32 (1H, dd, *J* = 10.8, 7.5 Hz), 3.89 (3H, s), 3.25-2.95(3H, m).

(3,4-Dihydro-8-nitrobenzopyran-3-yl)-1,4-benzoquinone (14a) and (3,4-Dihydro-6-nitrobenzopyran-3-yl)-1,4-benzoquinone (14b)

The same procedure for **11** was applied.

14a: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.73 (1H, d, *J* = 7.8 Hz), 7.31 (1H, d, *J* = 7.8 Hz), 6.96 (1H, t, *J* = 7.8 Hz), 6.84 (1H, d, *J* = 9.9 Hz), 6.77 (1H, dd, *J* = 9.9, 2.4 Hz), 6.53 (1H, dd, *J* = 2.4, 1.2 Hz), 4.48 (1H, dd, *J* = 11.1, 3.3 Hz), 4.21 (1H, dd, *J* = 11.7, 7.8 Hz), 3.58-3.47 (1H, m), 3.17 (1H, dd, *J* = 16.2, 5.7 Hz), 2.91 (1H, dd, *J* = 17.1, 8.4 Hz).

14b: 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.10-8.00 (2H, m), 6.92 (1H, d, *J* = 9.9 Hz), 6.94 (1H, d, *J* = 10.2 Hz), 6.77 (1H, dd, *J* = 10.2, 2.4 Hz), 6.53 (1H, d, *J* = 2.4 Hz), 4.41 (1H, dd, *J* = 11.1, 3.3 Hz), 4.19 (1H, dd, *J* = 10.8, 6.9 Hz), 3.55-3.45 (1H, m), 3.15 (1H, dd, *J* = 16.2, 5.4 Hz),

2.91 (1H, dd, J = 16.8, 7.8 Hz).

(3,4-Dihydro-7-methoxy-6-nitrobenzopyran-3-yl)-1,4-benzoquinone (15)

The same procedure for **11** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.83 (1H, s), 6.84 (1H, d, J = 9.6 Hz), 6.77 (1H, dd, J = 9.9, 2.4 Hz), 6.55 (1H, dd, J = 2.4, 1.2 Hz), 6.50 (1H, s), 4.38 (1H, dd, J = 10.8, 2.1 Hz), 4.16 (1H, dd, J = 12.0, 6.9 Hz), 3.92 (3H, s), 3.54-3.40 (1H, m), 3.07(1H, dd, J = 16.2, 5.7 Hz), 2.81(1H, dd, J = 15.9, 7.2 Hz).

2-Oxo-2*H*-chromene-3-carboxylic acid (17)

To a mixture of 2-hydroxybenzaldehyde (2.44 g, 20 mmol) and malonic acid (3.12 g, 30 mmol) in H_2O (6.6 mL) was added Montmorillonite KSF (2 g) at rt. After being heated to reflux overnight, the mixture was cooled down to rt. The solid was suction-filtered off and rinsed with H_2O. The solid was suspended in MeOH (120 mL) and heated for 5 min. The suspension was filtered through Celite and washed with MeOH. The filtrate was evaporated in vacuo to give **17**. 300 MHz ^{1}H NMR (acetone-d_6) δ 8.97 (1H, s), 8.04 (1H, dd, J = 8.1, 1.8 Hz), 7.87 (1H, t, J = 7.5 Hz), 7.62-7.50 (2H, m).

2-Oxochroman-3-carboxylic acid (18)

17 (350 mg, 1.842 mmol) was dissolved in ethyl acetate and 10% Pd/C (50 mg) was added with care. After being stirred under H_2 balloon pressure for 8 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. A mixture of **18** and decarboxylated product was identified in the crude ^{1}H NMR. The filtrate was transferred to the separatory funnel. The organic layer was washed with saturated $NaHCO_3$ solution. The separated aqueous layer was then acidified with 10% HCl. The aqueous layer was extracted with ethyl acetate two times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give pure **18**. 300 MHz ^{1}H NMR (acetone-d_6) δ 7.40-7.28 (2H, m),

7.15 (1H, t, J = 7.5 Hz), 7.05 (1H, d, J = 7.8 Hz), 3.97 (1H, t, J = 6.9 Hz), 3.37 (2H, d, J = 6.6 Hz), 2.84 (1H, br s).

3-(2,4-Dihydroxyphenyl)acrylic acid (21)

To a suspension of 2,4-dihydroxybenzaldehyde (5.92 g, 42.86 mmol) in benzene (150 mL) was added (carbethoxymethylene)triphenylphosphorane (19.42 g, 55.74 mmol) at rt. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to give α,β-unsaturated ester (8.469 g, 95%). 300 MHz ^{1}H NMR (acetone-d_6) δ 8.93 (2H, br s), 7.92 (1H, d, J = 16.2 Hz), 7.44 (1H, d, J = 8.7 Hz), 6.52-6.37 (3H, m), 4.17 (2H, q, J = 7.2 Hz), 1.26 (3H, t, J = 7.2 Hz); 75 MHz ^{13}C NMR (acetone-d_6) δ 168.2, 161.0, 158.5, 140.7, 130.8, 114.4, 114.0, 108.5, 103.0, 60.1, 14.1.

The ester (12.875 g, 61.9 mmol) was dissolved in a solution of NaOH (8.67 g, 216.7 mmol) in H_2O (150 mL) at rt. After being heated to reflux for 1 h, the mixture was cooled to rt. The mixture was acidified with c-HCl at 0 °C and extracted with ethyl acetate two times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to afford acid **21** (11.14 g, 100%). 300 MHz ^{1}H NMR (acetone-d_6) δ 9.05 (2H, br s), 7.94 (1H, d, J = 16.2 Hz), 7.46 (1H, d, J = 8.7 Hz), 6.52-6.37 (3H, m).

3-(2,4-Diacetoxyphenyl)propionic acid (19)

To a solution of acid **21** (1.71 g, 9.52 mmol) in THF (78 mL) were successively added Ac_2O (1.98 mL, 20.94 mmol), triethylamine (4.1 mL, 29.51 mmol), and DMAP (116 mg, 0.95 mmol) at 0 °C. After being stirred at rt for 5h, the mixture was concentrated in vacuo. The residue was acidified with 10% HCl and extracted with ethyl acetate two times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give diacetates (2.5 g, 100%). 300 MHz ^{1}H NMR (acetone-d_6) δ 7.88 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 15.9

Hz), 7.12 (1H, dd, J = 8.7, 2.4 Hz), 7.07 (1H, d, J = 2.4 Hz), 6.54 (1H, d, J = 16.2 Hz), 2.37 (3H, s), 2.26 (3H, s).

Diacetates (1 g, 3.79 mmol) was dissolved in ethyl acetate and 10% Pd/C (100 mg) was added with care. After being stirred under H_2 balloon pressure for 8 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give **19** (1g, 100%). 300 MHz ^{1}H NMR (acetone-d_6) δ 7.37 (1H, d, J = 8.1 Hz), 6.98 (1H, dd, J = 8.1, 2.4 Hz), 6.92 (1H, d, J = 2.4 Hz), 2.83 (2H, t, J = 7.2 Hz), 2.58 (2H, t, J = 7.8 Hz), 2.31 (3H, s), 2.24 (3H, s); 75 MHz ^{13}C NMR (acetone-d_6) δ 173.2, 168.9, 168.8, 150.0, 149.6, 130.6, 130.5, 119.5, 116.6, 33.7, 24.9, 20.3, 20.1.

3-(2,4-Bis-trifluoromethanesulfonyloxyphenyl)propionic acid (20)

To a solution of acid **21** (530 mg, 2.94 mmol) in THF (10 mL) was added 60% NaH (471 mg, 11.76 mmol) at 0 °C. After 5 min, $PhN(Tf)_2$ (3.26 g, 9.11 mmol) was added at 0 °C in one portion. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by sgc (H:EA = 2:1 to 1:1 then, CH_2Cl_2:MeOH = 10:1) to give bis-triflates (822 mg, 63%). 300 MHz ^{1}H NMR (acetone-d_6) δ 8.28 (1H, d, J = 8.7 Hz), 7.85 (1H, d, J = 11.1 Hz), 7.83 (1H, d, J = 2.4 Hz), 7.75 (1H, dd, J = 9.0, 2.4 Hz), 6.79 (1H, d, J = 15.9 Hz).

Bis-triflates (822 mg, 1.85 mmol) was dissolved in ethyl acetate and 10% Pd/C (80 mg) was added with care. After being stirred under H_2 balloon pressure for 5 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give **20** (825 mg, 100%). 300 MHz ^{1}H NMR (acetone-d_6) δ 7.83 (1H, d, J = 8.1 Hz), 7.71-7.53 (2H, m), 3.11 (2H, t, J = 7.2 Hz), 2.77 (2H, t, J = 7.3 Hz).

2-(2,4-Diacetoxyphenyl)ethyl-1,4-benzoquinone (22)

The same procedure for **11** was applied. 300 MHz ^{1}H NMR (CDCl3) δ 7.22 (1H, d, *J* = 8.4 Hz), 6.95 (1H, dd, *J* = 8.4, 2.4 Hz), 6.87 (1H, d, *J* = 2.4 Hz), 6.76 (1H, d, *J* = 9.9 Hz), 6.71 (1H, dd, *J* = 10.2, 2.1 Hz), 6.51-6.46 (1H, m), 2.80-2.60 (4H, m), 2.35 (3H, s), 2.27 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.7, 187.5, 169.3, 169.25, 149.8, 149.3, 148.2, 137.0, 136.7, 133.4, 130.6, 129.9, 119.6, 116.5, 30.6, 29.0, 21.3, 21.1; HRMS *m/z* for $C_{18}H_{16}O_6$ calcd 328.0947, found 328.0954.

2-Phenethyl-1,4-benzoquinone (23)

The same procedure for **11** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.34-7.13 (5H, m), 6.77 (1H, d, *J* = 9.9 Hz), 6.70 (1H, dd, *J* = 9.9, 2.1 Hz), 6.52-6.47 (1H, m), 2.90-2.80 (2H, m), 2.80-2.70 (2H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.9, 187.6, 148.6, 140.5, 137.0, 136.6, 133.2, 128.8, 128.6, 126.6, 34.2, 31.2.

2-(2,4-Bis-trifluoromethanesulfonyloxyphenyl)ethyl-1,4-benzoquinone (24)

The same procedure for **11** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.12 (3H, m), 6.76 (1H, d, *J* = 10.2 Hz), 6.70 (1H, dd, *J* = 9.9, 2.4 Hz), 6.52-6.48 (1H, m), 2.90-2.78 (2H, m), 2.78-2.68 (2H, m).

5,8-Dihydrochroman-3-carboxylic acid (25)

To a solution of **7** (53 mg, 0.298 mmol) in EtOH (0.696 mL, 11.92 mmol) was added gaseous NH_3 at –78 °C. Then, small pieces of Li metal (40 mg, 5.96 mmol) was added to this mixture at –78 °C. After being stirred at –50 °C for 10 min (dark blue color disappeared), the excess NH_3 was blown out using argon. The residue was diluted with cold H_2O. To this mixture was added one drop of bromocresol blue (indicator) at 0 °C. Then, 10% HCl was dropwise added to the reaction mixture at 0 °C (up to pH 4 or 5). The mixture was extracted

with ethyl acetate two times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **25** (54 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.65 (2H, br s), 4.23 (1H, ddd, J = 10.5, 3.6, 1.5 Hz), 3.98 (1H, d, J = 10.5, 8.7 Hz), 3.05-2.90 (1H, m), 2.83-2.51 (4H, m), 2.27 (1H, dd, J = 16.5, 8.7 Hz), 2.11 (1H, dd, J = 16.8, 6.3 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 179.3, 144.8, 124.4, 123.6, 101.1, 65.7, 39.2, 31.3, 28.3, 27.2.

3-(3-Methoxyphenoxy)propanal diethyl acetal (26)

To a solution of NaOH (3.6 g, 93.1 mmol) in H_2O (10 mL) was added 3-methoxyphenol (8 mL, 67.3 mmol) at rt. After being stirred at rt for 30 min, 3-chloropropionaldehyde diethyl acetal (6.0 mL, 35.8 mmol) was slowly added to the mixture at rt. After being heated to reflux overnight, the mixture was cooled down to rt. The mixture was diluted with Et_2O and washed with 15% NaOH and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **26** (8.644 g, 95%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.15 (1H, t, J = 8.0 Hz), 6.53-6.40 (3H, m), 4.73 (1H, t, J = 5.6 Hz), 4.02 (2H, t, J = 6.4 Hz), 3.77 (3H, s), 3.74-3.63 (2H, m), 3.57-3.45 (2H, m), 2.07 (2H, q, J = 6.4 Hz), 1.19 (6H, t, J = 7.2 Hz).

7-Methoxy-2*H*-chromene (27)

To a solution of the acetal **26** (9.6766 g, 38.1 mmol) in THF (72 mL) was added 15% HCl (54 mL) at rt. After being heated at 85 °C for 30 min, the organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H_2O, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by sgc (H:EA = 20:1) to afford **27** (4.0226 g, 65%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.89 (1H, d, J = 8.1 Hz), 6.50-6.35 (3H, m), 5.63 (1H, td, J = 9.6, 3.6 Hz), 4.80 (2H, dd, J = 3.6, 1.8 Hz), 3.77 (3H, s); 75 MHz

^{13}C NMR ($CDCl_3$) δ 160.9, 155.6, 127.5, 124.5, 119.1, 116.0, 107.1, 102.0, 65.9, 55.5.

2-Iodo-5-methoxyphenol (28)

To a suspension of 3-methoxyphenol (5 g, 40.28 mmol) and $AgCF_3CO_2$ (8.9 g, 40.28 mmol) in $CHCl_3$ (40 mL) was dropwise added a solution of I_2 (10.22 g, 40.28 mmol) in $CHCl_3$ (322 mL) at rt. After the addition was complete, the mixture was stirred at rt overnight. The mixture was filtered through Celite and washed with $CHCl_3$. The filtrate was washed with saturated $Na_2S_2O_3$ solution and saturated$NaHCO_3$ solution, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (CH_2Cl_2 only) to give **28** (7.179 g, 71%). 300 MHz ^1H NMR ($CDCl_3$) δ 7.48 (1H, d, J = 8.7 Hz), 6.59 (1H, d, J = 2.7 Hz), 6.33 (1H, dd, J = 8.7, 2.7 Hz), 5.41 (1H, br s), 3.77 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 161.9, 155.9, 138.3, 109.6, 101.2, 74.7, 55.7.

2',4',5'-Trimethoxyacetophenone (29)

A mixture of 1,2,4-trimethoxybenzene (5 g, 29.73 mmol) and I_2 (59.5 mg) in Ac_2O (28 mL, 29.73 mmol) was heated to reflux overnight. After being cooled down to rt, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and saturated $Na_2S_2O_3$ solution, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (residue was loaded with benzene and eluted with H:EA = 1:1) to give **29** (4.374 g, 70%). 300 MHz ^1H NMR ($CDCl_3$) δ 7.43 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.92 (3H, s), 3.87 (3H, s).

2-Bromo-1-(2,4,5-trimethoxyphenyl)ethanone (30)

To a solution of **29** (5.3967 g, 25.68 mmol) in ethyl acetate (43 mL) and $CHCl_3$ (43 mL) was added $CuBr_2$ (11.47 g, 51.36 mmol) at rt. After being heated at 85 °C for 10 h, the

mixture was cooled to rt. The mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated in vacuo. The residue was suspended in solvent (H:EA = 2:1), filtered, and rinsed with small amount of solvent (H:EA = 2:1). The solid **30** (4.1 g) was dried under reduced pressure. The filtrate was concentrated and the resulting residue was purified by sgc (H:EA = 3:1 to 1:1) to give **30** (1.464 g, total yield: 75%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.47 (1H, s), 6.50 (1H, s), 4.59 (2H, s), 3.97 (3H, s), 3.96 (3H, s), 3.88 (3H, s).

2-(2-Iodo-5-methoxyphenoxy)-1-(2,4,5-trimethoxyphenyl)ethanone (31)

To a mixture of **28** (3.8 g, 15.23 mmol) and **30** (4.4 g, 15.23 mmol) in acetone (84 mL) was added K_2CO_3 (2.1 g, 15.23 mmol) at rt. After being heated to reflux for 5 h, the mixture was concentrated in vacuo. The residue was diluted in CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue (6.974 g, 100%) was pure enough to carry out the next reaction. For NMR data, the residue was suspended in solvent (H:EA = 2:1), filtered, and rinsed with small amount of solvent (H:EA = 2:1) to give pure **31**. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, d, J = 8.7 Hz), 7.54 (1H, s), 6.51 (1H, s), 6.33 (1H, dd, J = 8.4, 2.4 Hz), 6.26 (1H, d, J = 2.7 Hz), 5.26 (2H, s), 3.98 (3H, s), 3.96 (3H, s), 3.87 (3H, s), 3.74 (3H, s).

6-Methoxy-3-(2,4,5-trimethoxyphenyl)benzofuran (32)

To a solution of MeLi (1.4 M solution in THF, 337 μL, 0.471 mmol) in THF (2 mL) was dropwise added a solution of ketone **31** (72 mg, 0.157 mmol) in THF (4 mL + 1 mL for rinse) at –78 °C via cannula. After being stirred at –78 °C for 5 min, the mixture was quenched with saturated NH_4Cl at –78 °C. The mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2, washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The resulting residue was purified by sgc (H:EA = 2:1) to give

benzofuran **32** (45 mg, 91%). 300 MHz ^{1}NMR ($CDCl_3$) δ 7.82 (1H, s), 7.58 (1H, d, *J* = 8.7 Hz), 7.26 (1H, s), 7.06 (1H, d, *J* = 2.1 Hz), 6.92 (1H, dd, *J* = 8.7, 2.4 Hz), 6.68 (1H, s), 3.96 (3H, s), 3.91 (3H, s), 3.87 (3H, s), 3.83 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 158.1, 156.4, 151.6, 149.2, 143.4, 142.6, 121.3, 120.9, 117.5, 114.0, 112.8, 112.0, 98.6, 96.3, 57.0, 56.7, 56.4, 56.0; HRMS *m/z* for $C_{18}H_{18}O_5$ calcd 314.1154, found 314.1160.

4-(2-Iodo-5-methoxyphenoxy)-3-(2,4,5-trimethoxyphenyl)but-2-enenitrile (33)

To a suspension of 60% NaH (196 mg, 4.91 mmol) in THF (10 mL) was dropwise added diethyl (cyanomethyl)phosphonate (882 μL, 5.45 mmol) at 0 °C. After being stirred at rt for 20 min, a solution of **31** (500 mg, 1.09 mmol) in THF (22 mL + 10 mL for rinse) was transferred to the mixture at 0 °C via cannula. After being stirred at rt for 30 min, the mixture was quenched with saturated NH_4Cl at 0 °C. The organic solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 3:1 to 2:1) to give **33** (480 mg, 91%) as a cis/trans mixture. Two isomers were separated by sgc for NMR data although we did not determine which one is which. Ratio of upper spot to lower spot = 1.4:1

Upper spot: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.52 (1H, d, *J* = 8.7 Hz), 6.76 (1H, s), 6.51 (1H, d, *J* = 2.7 Hz), 6.51 (1H, s), 6.32 (1H, dd, *J* = 8.7, 2.7 Hz), 5.78 (1H, s), 5.29 (2H, s), 3.91 (3H, s), 3.81 (3H, s), 3.80 (3H, s), 3.77 (3H, s).

Lower spot: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, d, *J* = 8.7 Hz), 6.86 (1H, s), 6.46 (1H, s), 6.45 (1H, d, *J* = 2.7 Hz), 6.37 (1H, dd, *J* = 8.4, 2.4 Hz), 6.07 (1H, t, *J* = 1.8 Hz), 4.91 (2H, d, *J* = 2.1 Hz), 3.94 (3H, s), 3.88 (3H, s), 3.86 (3H, s), 3.78 (3H, s).

[6-Methoxy-3-(2,4,5-trimethoxyphenyl)-2,3-dihydrobenzofuran-3-yl]acetonitrile (34)

To a solution of **33** (80 mg, 0.166 mmol) in benzene (8.3 mL) were added *n*-Bu_3SnH (89 μL, 0.332 mmol) and AIBN (5.5 mg, 0.033 mmol) at rt. After being heated at 87 °C overnight, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 3:1 to 1:1) to give **34** (50 mg, 85%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, d, *J* = 8.4 Hz), 6.79 (1H, s), 6.59 (1H, dd, *J* = 8.4, 2.4 Hz), 6.56 (1H, s), 6.45 (1H, d, *J* = 2.1 Hz), 4.74 (1H, d, *J* = 9.9 Hz), 4.61 (1H, d, *J* = 9.9 Hz), 3.88 (3H, s), 3.87 (3H, s), 3.80 (3H, s), 3.68 (3H, s), 3.32 (1H, d, *J* = 16.5 Hz), 3.06 (1H, d, *J* = 16.5 Hz).

7-Methoxychroman-2-one (35)

7-Methoxycoumarin (10.8 g, 66.61 mmol) was dissolved in ethyl acetate and 10% Pd/C (1 g) was added with care. After being stirred under H_2 balloon pressure for 7 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give **35** (11.87 g, 100%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.05 (1H, d, *J* = 8.0 Hz), 6.63 (1H, dd, *J* = 8.4, 2.4 Hz), 6.58 (1H, d, *J* = 2.0 Hz), 3.77 (3H, s), 2.91 (2H, t, *J* = 6.8 Hz), 2.74 (2H, t, *J* = 6.4 Hz).

7-Methoxychroman-2-ol (36)

To a solution of **35** (2.4367 g, 13.68 mmol) in CH_2Cl_2 was dropwise added DIBAL (1 M solution in THF, 20.3 mL, 20.3 mmol) at –78 °C. After being stirred at –78 °C for 20 min, the mixture was quenched with saturated NH_4Cl with care. After being stirred at rt for 1 h, the mixture was suction-filtered through Celite and rinsed with CH_2Cl_2. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to give **36** (1.478 g, 60%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.95 (1H, d, *J* = 8.4 Hz), 6.48 (1H, dd, *J* = 8.4, 2.4 Hz), 6.41 (1H, d, *J* = 2.4 Hz), 5.55 (1H, t, *J* = 2.7 Hz), 3.73 (3H, s), 2.98-2.82 (1H, m), 2.63 (1H, td, *J* = 16.2, 5.4 Hz), 2.05-1.85 (2H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 159.3, 153.1, 130.0, 114.5,

107.6, 102.3, 92.5, 55.5, 27.6, 20.1.

7-Methoxy-4*H*-chromene (37)

A mixture of **36** (4 g, 22.2 mmol) and anhydrous $CuSO_4$ (570 mg, 3.55 mmol) was heated at 150 °C under 10 or 20 mmHg. After 2 h, the mixture was filtered through Celite and washed with ethyl acetate. The filtrate was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give a small amount of **37**. 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.91 (1H, d, J = 8.7 Hz), 6.58 (1H, dd, J = 8.4, 2.7 Hz), 6.47 (1H, dt, J = 6.3, 2.1 Hz), 6.43 (1H, d, J = 2.4 Hz), 4.95 (1H, dt, J = 6.3, 3.6 Hz), 3.78 (3H, s), 3.37-3.30 (2H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 159.2, 152.3, 140.6, 130.1, 112.1, 110.0, 101.8, 101.1, 55.6, 22.6.

Tetrahydropyran-3-yl-1,4-benzoquinone (38)

The same procedure for **2** from **27** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.76 (1H, d, J = 9.9 Hz), 6.71 (1H, dd, J = 10.2, 2.4 Hz), 6.61 (1H, dd, J = 2.1, 0.9 Hz), 3.99-3.84 (2H, m), 3.55-3.39 (1H, m), 3.30 (1H, dd, J = 11.1, 9.3 Hz), 3.10-2.95 (1H, m), 1.99-1.84 (1H, m), 1.83-1.61 (2H, m), 1.61-1.43 (1H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.8, 186.7, 149.7, 137.2, 136.3, 132.7, 71.7, 68.5, 35.1, 28.4, 25.2; HRMS *m/z* for $C_{11}H_{12}O_3$ calcd 192.0786, found 192.0789.

(6-Methoxytetrahydropyran-3-yl)-1,4-benzoquinone (39)

The same procedure for **2** from **27** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.73-6.40 (3H, m), 4.55 and 4.33 (1H, dd, J = 5.7, 3.0 Hz), 3.92 (1H, dd, J = 11.4, 3.6 Hz), 3.34 (1H, dd, J = 11.4, 6.9 Hz), 3.29 and 3.21 (3H, s), 2.90-2.77 (1H, m), 2.03-1.60 (2H, m), 1.52-1.35 (2H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ **major diastereomer**: 187.7, 186.7, 149.4, 137.1, 136.3, 132.8, 100.9, 65.8, 55.6, 33.4, 28.5, 24.7; **minor diastereomer**: 187.7, 186.6, 149.4, 137.1,

136.2, 132.4, 97.6, 62.9, 54.8, 34.4, 29.4, 23.1; HRMS *m/z* for $C_{12}H_{14}O_4$ calcd 222.0892, found 222.0897.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-methoxy-1,4-benzoquinone (40)

To a solution of **2** (34 mg, 0.126 mmol) in MeOH (3 mL) were added $HgCl_2$ (34 mg, 0.126 mmol) and I_2 (3 mg, 0.013 mmol) at rt. After being stirred at 60 °C for 3 h, the reaction mixture was evaporated in vacuo. The resulting residue was diluted with ethyl acetate and washed with brine. The aqueous layer was extracted with ethyl acetate one more time. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by sgc (H:EA = 2:1) to give **40** (26.5 mg, 70%). 300 MHz ^{1}NMR ($CDCl_3$) δ 6.94 (1H, d, *J* = 8.4 Hz), 6.48 (1H, dd, *J* = 8.4, 2.4 Hz), 6.47 (1H, d, *J* = 1.2 Hz), 6.37 (1H, d, *J* = 2.4 Hz), 5.89 (1H, d, *J* = 2.4 Hz), 4.27 (1H, ddd, *J* = 10.8, 2.7, 0.9 Hz), 4.06 (1H, ddd, *J* = 10.5, 6.3, 1.2 Hz), 3.83 (3H, s), 3.75 (3H, s), 3.53-3.40 (1H, m), 3.04 (1H, dd, *J* = 15.9, 5.7 Hz), 2.74 (1H, dd, *J* = 15.6, 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.3, 181.6, 159.6, 159.0, 154.8, 146.5, 133.6, 130.3, 112.2, 108.3, 107.5, 101.8, 68.3, 56.6, 55.5, 31.1, 29.1; HRMS *m/z* for $C_{17}H_{16}O_5$ calcd 300.0998, found 300.1004; TLC (3:1 H:EA) R_f = 0.21.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-phenylthio-1,4-benzoquinone (41a) and 2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5-phenylthio-1,4-benzoquinone (41b)

To a mixture of **2**(83 mg, 0.307 mmol) and PhSH (35 μL, 0.338 mmol) in MeOH (10 mL) was added PTSA-H_2O (117 mg, 0.614 mmol) at rt. After being stirred at rt for 7 h, the reaction mixture was evaporated in vacuo. The resulting residue was diluted with CH_2Cl_2 and washed with brine. The aqueous layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by sgc (H:EA = 3:1) to afford a regioisomeric mixture of hydroquinones (108.8 mg, 93%). The mixture of hydroquinones (108.8 mg, 0.286 mmol) was

dissolved in benzene (10 mL). Then, Na_2SO_4 (81 mg, 0.572 mmol) and Ag_2O (133 mg, 0.572 mmol) were added at rt. After being stirred at rt for 4 h, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated and purified by sgc (H:EA = 10:1) to give minor product (**41b**) and major product (**41a**) (total 108 mg, 100%).

41a: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.49 (5H, br s), 6.95 (1H, d, J = 8.4 Hz), 6.48 (1H, dd, J =8.4, 2.4 Hz), 6.44 (1H, dd, J = 2.1, 0.9 Hz), 6.37 (1H, d, J = 2.7 Hz), 5.84 (1H, d, J = 2.4 Hz), 4.28 (1H, dd, J =10.5, 2.4 Hz), 4.09 (1H, dd, J = 10.8, 6.3 Hz), 3.75 (3H, s), 3.55-3.42 (1H, m), 3.07 (1H, dd, J = 16.2, 6.0 Hz), 2.75 (1H, dd, J = 16.2, 6.6 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 184.6, 183.9, 159.6, 155.0, 154.9, 148.0, 135.9, 133.9, 130.8, 130.6, 130.4, 127.4, 126.1, 112.2, 108.3, 101.8, 68.3, 55.5, 31.4, 29.1; HRMS *m/z* for $C_{22}H_{18}O_4S$ calcd 378.0926, found 378.0931; TLC (3:1 H:EA) R_f = 0.36.

41b: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.50 (5H, br s), 6.94 (1H, d, J =8.4 Hz), 6.74 (1H, d, J = 1.2 Hz), 6.48 (1H, dd, J = 8.4, 2.4 Hz), 6.37 (1H, d, J = 2.4 Hz), 5.89 (1H,s), 4.23 (1H, ddd, J = 10.8, 3.0, 0.9 Hz), 4.04 (1H, ddd, J = 10.8, 6.0, 0.9 Hz), 3.76 (3H, s), 3.45-3.35 (1H, m), 3.02 (1H, dd, J = 15.9, 5.7 Hz), 2.72 (1H, dd, J = 16.2, 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 184.3, 183.9, 159.6, 154.9, 154.6, 149.7, 135.9, 132.4, 130.8, 130.6, 130.3, 127.2, 126.3, 112.2, 108.3, 101.8, 68.4, 55.6, 31.2, 29.1; HRMS *m/z* for $C_{22}H_{18}O_4S$ calcd 378.0926, found 378.0931; TLC (3:1 H:EA) R_f = 0.42.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-phenylsulfinyl-1,4-benzoquinone (42)

To a solution of **41a** (35 mg, 0.093 mmol) in $CHCl_3$ (3 mL) was added 77% *m*CPBA (23 mg, 0.102 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 one more time. The combined organic layers were dried over $MgSO_4$, filtered,

and concentrated. The crude residue was purified by sgc (H:EA = 3:1) to give sulfoxide **42** (35 mg, 96%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.88-7.74 (2H, m), 7.61-7.45 (3H, m), 7.45-7.36 (1H, m), 6.94 and 6.87 (1H, d, *J* = 8.7 Hz), 6.62-6.52 (1H, m), 6.52-6.42 (1H, m), 6.40-6.29 (1H, m), 4.24 and 4.12 (1H, dd, *J* = 10.5, 2.1 Hz), 4.05 and 3.90 (1H, dd, *J* = 10.8, 6.0 Hz), 3.74 (3H, s), 3.40-3.25 (1H, m), 3.06 and 2.96 (1H, dd, *J* = 16.2, 6.3 Hz), 2.70 and 2.61 (1H, dd, *J* = 16.2, 6.3 Hz); HRMS *m/z* for $C_{22}H_{18}O_5S$ calcd 394.0875, found 394.0882.

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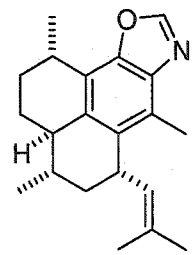
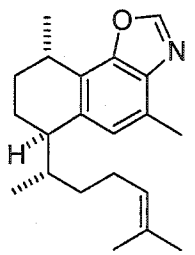
CHAPTER 3. 1,2-DIHALIDES IN ORGANIC SYNTHESIS: A DIRECT SYNTHESIS OF EROGORGIAENE

Introduction

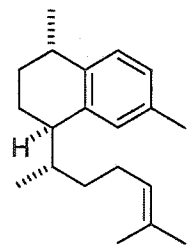
Rodriguez reported in 1999 that pseudopteroxazole and seco-pseudopteroxazole, isolated from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*, exhibited potent and moderate antimycobacterial activity, respectively.[1] More recently, two new serrulatane diterpenes, erogorgiaene and 7-hydroxyerogorgiaene, were also isolated from the same marine source.[2]



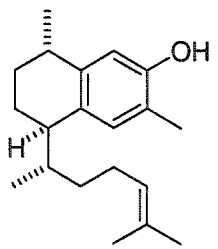
pseudopteroxazole



seco-pseudopteroxazole



erogorgiaene



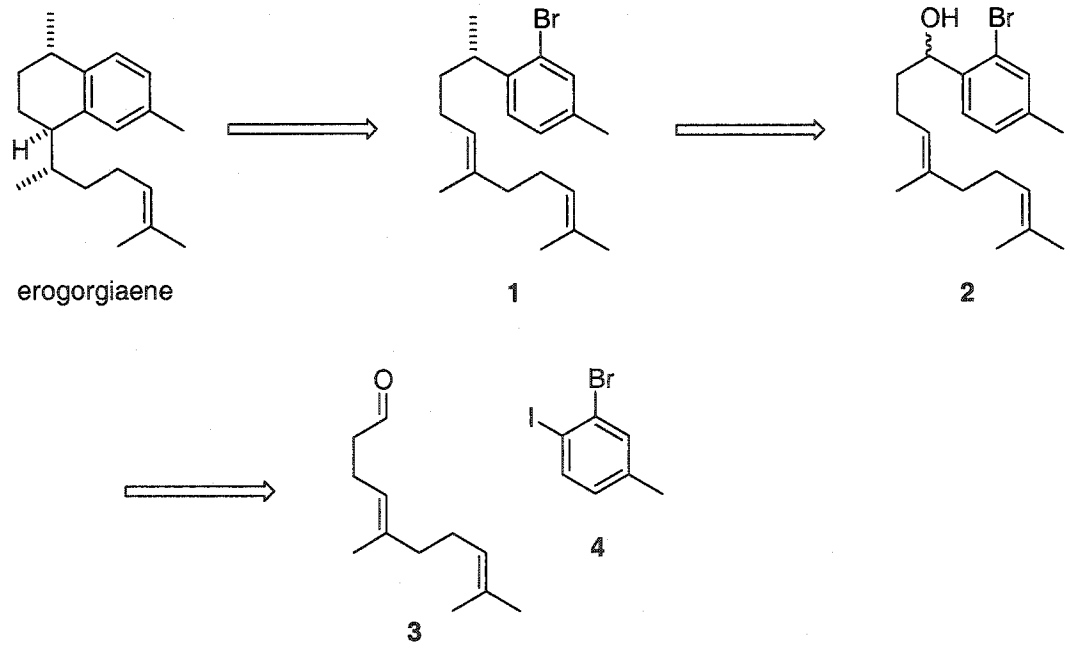
7-hydroxyerogorgiaene

Despite their relatively simple structures, erogorgiaene and 7-hydroxyerogorgiaene showed very strong antitubercular activity. Thus, erogorgiaene induced 96% growth inhibition for *Mycobacterium tuberculosis* H37Rv at the microgram per milliliter level, a level comparable to that of pseudopteroxazole.[2] As part of our continuing synthetic studies on

antitubercular serrulatane diterpenes, we embarked on the synthesis of erogorgiaene and its analogs.

Results and Discussion

As illustrated in the retrosynthetic scheme, erogorgiaene would be accessible from bromobenzene **1** via a 6-exo trig radical cyclization.[3] The methyl group at the benzylic position of the radical precursor **1** could be installed from alcohol **2**, which in turn could be derived from the addition of 2-bromophenyl lithium to aldehyde **3**. 2-Bromophenyl lithium species would be obtainable from 2-bromo-1-iodo-4-methylbenzene **4** by way of a regioselective halogen-metal exchange.[4] This strategy is based on the regioselective 1,2-functionalization of 1,2-dihalobenzene derivatives.

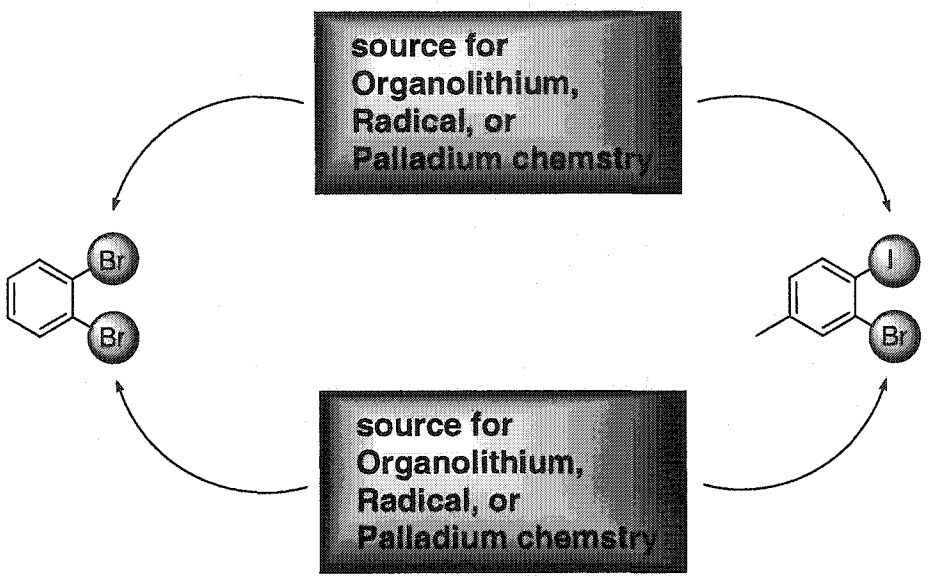


erogorgiaene **1** **2**

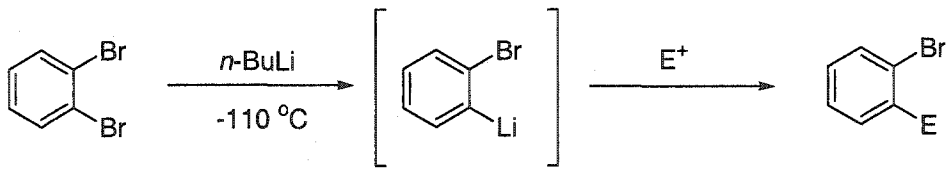
3 **4**

Aromatic halides have been generally considered a useful source for organolithium, radical, or palladium chemistry in organic synthesis. Therefore, if we could selectively functionalize one halogen over the other for symmetrical or unsymmetrical 1,2-

dihalobenzenes, different groups could be introduced at each halogen position.



Since the pioneering work on the *ortho*-halophenyl lithium species by Gilman,[4a] there aren't many synthetic applications of this chemistry, which may be, in part, ascribed to the low temperatures required to generate this species. In 1980, Chen and Tamborski reported the reaction of *ortho*-bromophenyl lithium with several electrophiles to furnish 2-substituted bromobenzenes.[4b]

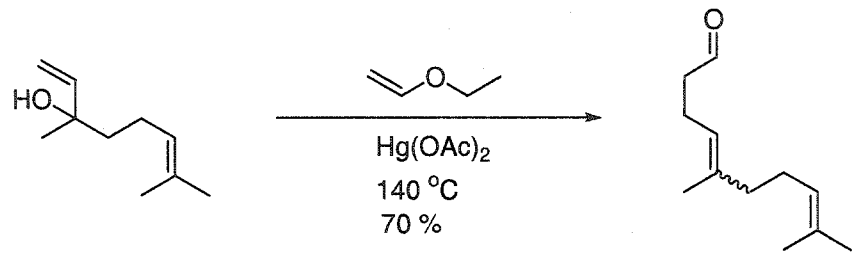


stable at -110 °C
for at least 2 hrs

They prepared *ortho*-bromophenyl lithium by treatment of 1,2-dibromobenzene with *n*-BuLi at –110 °C. They claimed that this species was stable at –110 °C for at least 2 h.[4b]

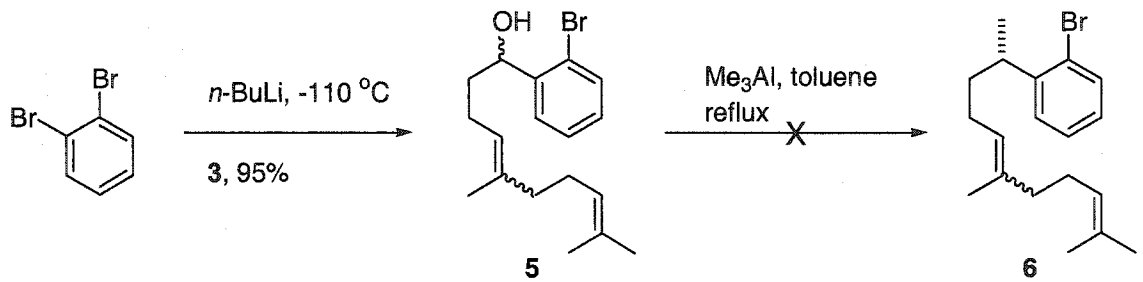
To test the feasibility of our strategy, we first employed the commercially available 1,2-dibromobenzene. Aldehyde **3** was prepared as an E/Z mixture from the Claisen

rearrangement of linalool.[5]



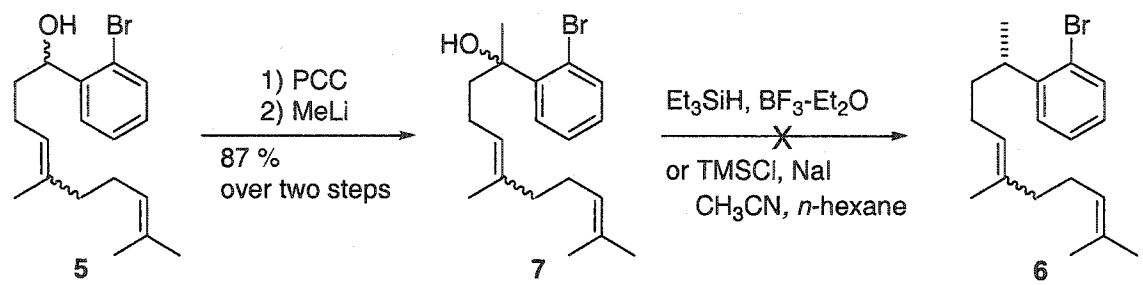
linalool **3**

Treatment of 1,2-dibromobenzene with *n*-BuLi at –110 °C followed by the addition of aldehyde **3** afforded benzyl alcohol **5** in 95% yield.[4b] In order to introduce the methyl group onto the benzylic position of **5**, **5** was directly treated with trimethylaluminum.[6] Surprisingly, no reaction occurred.



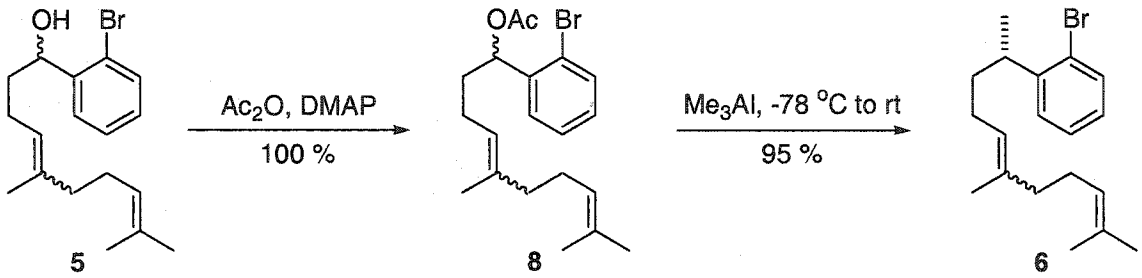
5 **6**

As an another attempt to install the methyl group onto benzylic position, benzyl alcohol **5** was first oxidized to the corresponding ketone using PCC. MeLi addition took place uneventfully to provide **7**. However, tertiary alcohol **7** under ionic hydrogenolysis condition (Et_3SiH, BF_3-Et_2O)[7] did not give rise to **6**, resulting in a complex mixture. Adoption of Sakai's procedure (TMSCl, NaI, and CH_3CN)[8] did not lead to the desired product, either.

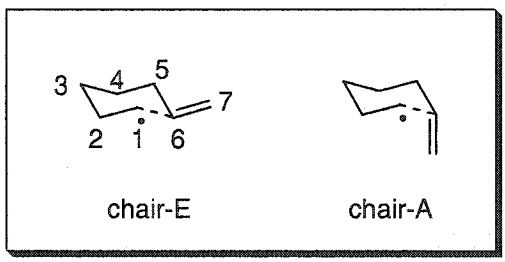


5 **7** **6**

Finally, we resorted to a two-step procedure[9] in which alcohol **5** was acetylated to make a better leaving group. Exposure of the resulting acetate **8** to Me_3Al from –78 °C to rt provided **6** in excellent overall yield.

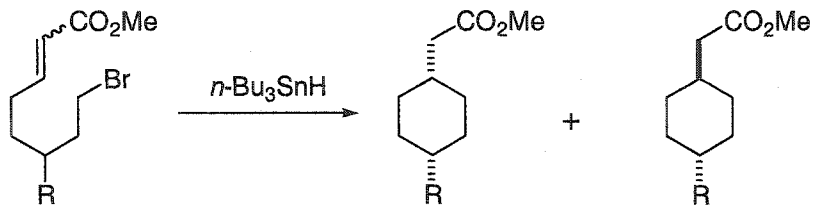


Overall, the three-step sequence supplied the radical precursor **6** without difficulty. Now, the stage is set for the key radical cyclization. The modeling of stereoselective 6-exo cyclizations is not as advanced as that of 5-exo systems. However, chair-like models for 6-exo cyclizations account for many observations.[10]



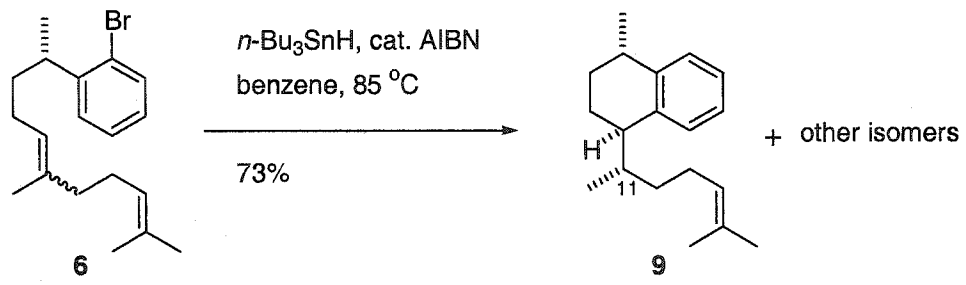
The chair-E transition structure places the radical acceptor in an equatorial-like orientation while this group is axial-like in the chair-A transition state. Introduction of a substituent on a carbon on the chain (C1-C5) then generates two pairs of transition states (chair-E, axial and equatorial, and chair-A, axial and equatorial). Other things being equal, the model predicts that the major product should derive from the transition state where both the acceptor and the substituent are equatorial (chair-E-equatorial). Thus, chair-E-model predicts cis products from 2- and 4-substituted radicals, and trans products from 1-, 3-, and 5-substituted radicals.[10] However, stereoselectivities in many simple carbocyclic systems are

low as demonstrated by Hanessian and coworkers.[11]

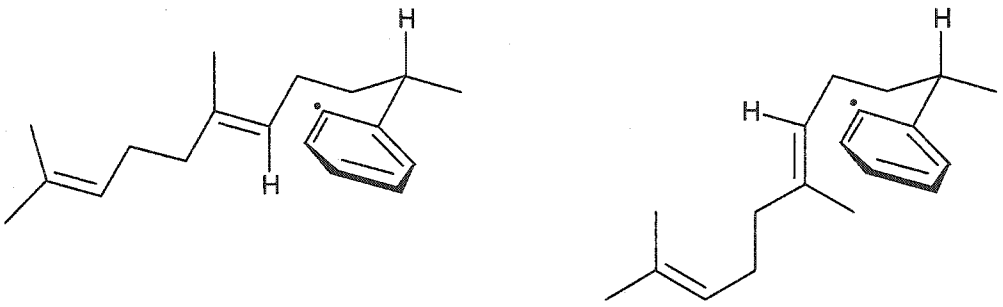


	cis	trans
E, R = Me	35	65
E, R = *t*-Bu	35	65
Z, R = *t*-Bu (*t*-Butyl ester)	10	90

Compound **6** was subjected to the standard *n*-Bu_3SnH-mediated radical conditions to give **9** as well as other isomers in 73% overall yield.

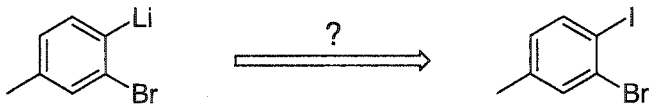


Based on the previous studies on radical cyclizations,[10] the major product would be expected to have a trans relationship between the methyl group and the eight-carbon side chain.

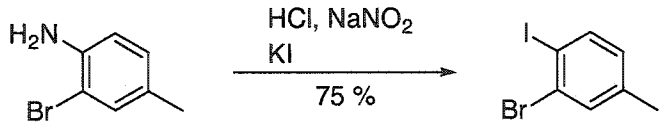


The configuration at C11 was expected to be a mixture. The ratio of trans to cis products was about 1.5 to 1 by crude ^{1}NMR analysis. Other radical initiators such as Et_3B[12] and SmI_2[13] were tested to increase the selectivity. However, they failed to provide better results. With

this information on radical cyclization in hand, attention was paid to regioselective halogen-metal exchange.

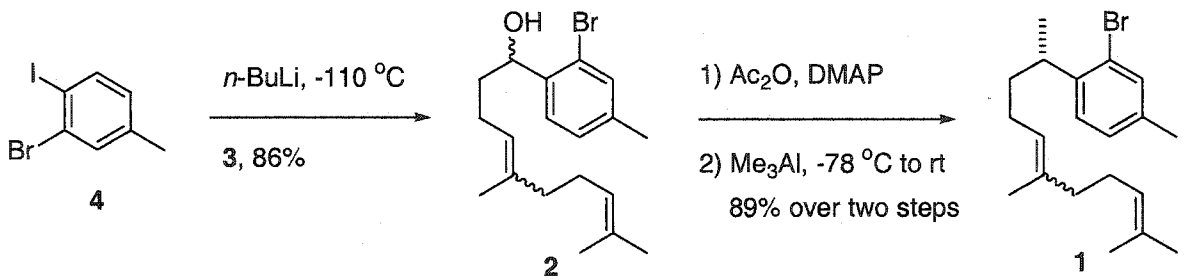


To examine this idea, **4** was prepared from 2-bromo-4-methylaniline in one step.[14]



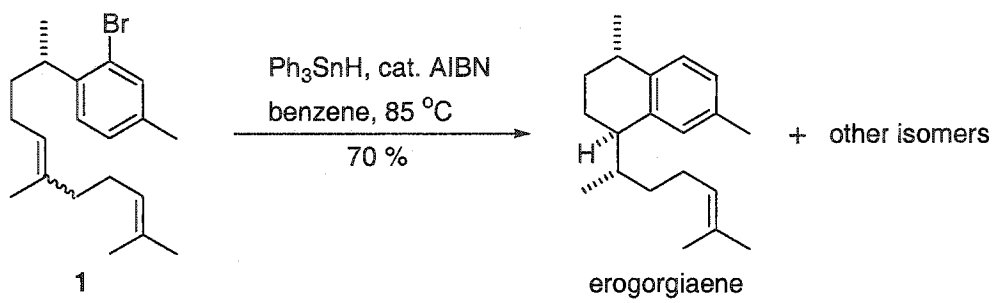
4

Reaction of **4** with *n*-BuLi at –110 °C in 1:1 THF:ether followed by the addition of aldehyde **3** delivered benzyl alcohol **2** in 86% isolated yield. By the similar two-step sequence, **2** was converted to radical precursor **1**.



4 **2** **1**

Again, a 6-exo-trig radical cyclization of bromide **1** with Ph_3SnH and AIBN in boiling benzene led to a mixture of erogorgiaene and its isomers in 70% overall yield.

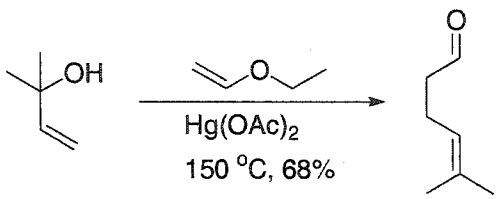


1 erogorgiaene

The ratio of trans to cis products was roughly 1.5 to 1 by crude ^{1}NMR analysis. The separation of erogorgiaene from the product mixture was partially achieved by preparative

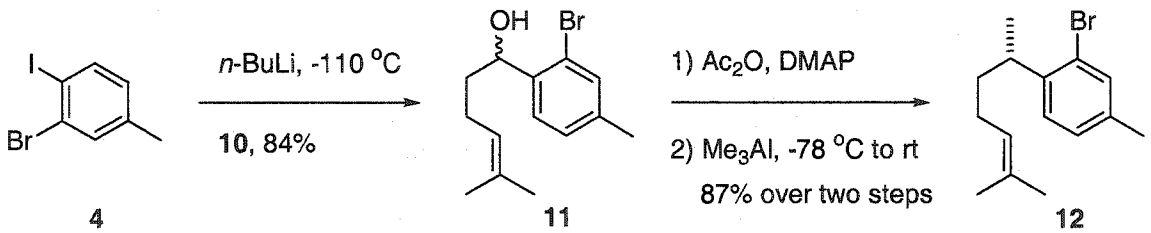
TLC on a $AgNO_3$ impregnated silica gel plate.[15] The NMR of the purified product was identical to the NMR supplied by Professor Rodriguez.

In a similar manner, calamenene[16] was also synthesized. To this end, aldehyde **10** was obtained from the Claisen rearrangement of 2-methyl-3-buten-2-ol.[5]



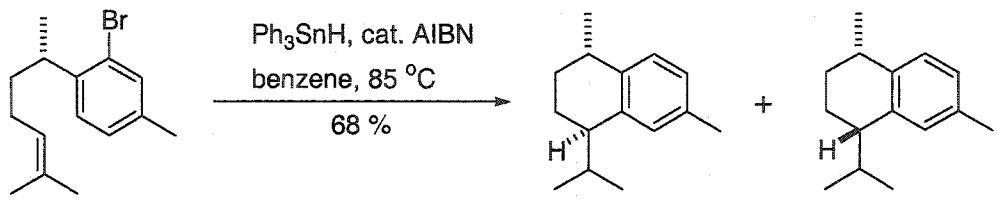
10

With this aldehyde **10** in hand, radical precursor **12** was prepared by following the same sequence we used before.



4 **11** **12**

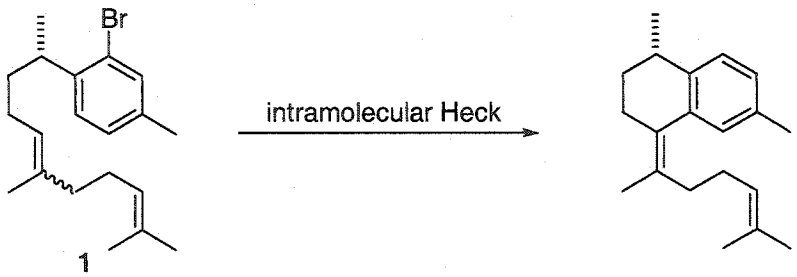
The trans product was again obtained as a major isomer in the radical cyclization. The ratio of trans to cis isomers was about 1.5 to 1 by crude ^1H NMR analysis.



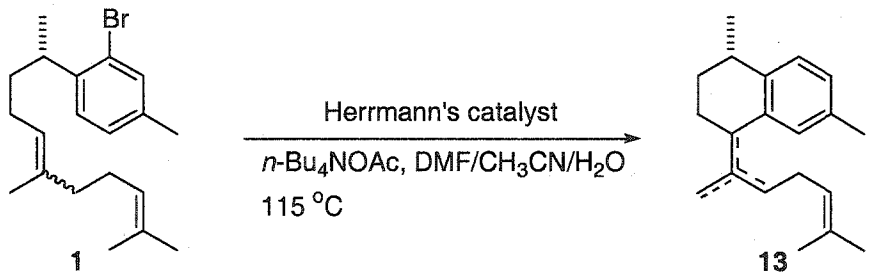
12 *trans*-calamenene *cis*-calamenene

At this point different methodologies were sought to increase the stereoselectivity during cyclization. Thus, an intramolecular Heck reaction[17] of bromide **1** was explored. We anticipated that the benzylic double bond of the product could be later reduced in a stereo-

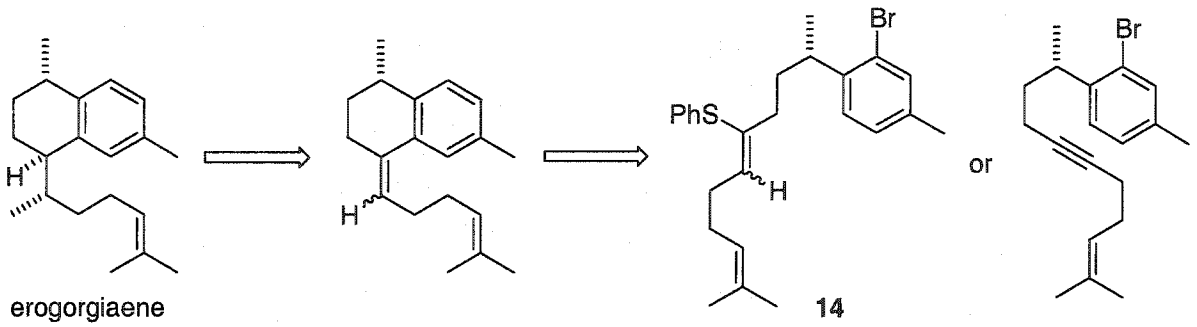
and regioselective way.



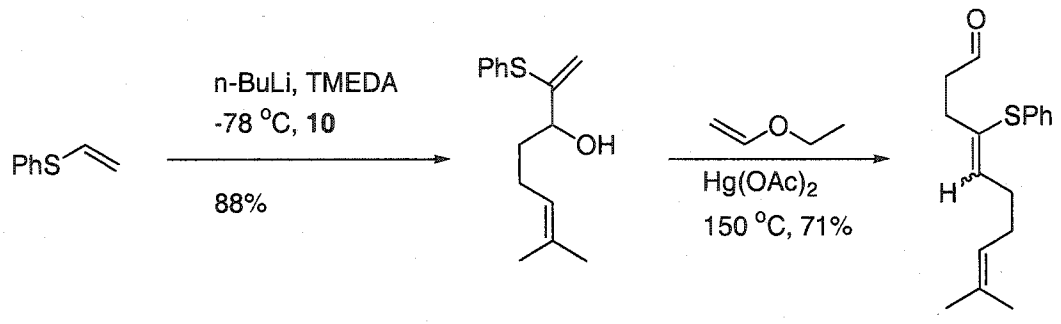
In general, electron-rich aromatic bromides are not good substrates for palladium-catalyzed Heck type process. After several attempts using different palladium catalyst conditions were not fruitful, we found out that cyclization occurred under Herrmann's catalyst condition.[18] However, a mixture of alkenes was produced as a result of nonselective palladium-hydride elimination.



In line with the idea that double bond generation during cyclization and subsequent stereoselective incorporation of methyl group to this double bond could lead to the target compound more effectively, we devised radical precursors, vinyl sulfide **14** or alkynyl precursor.

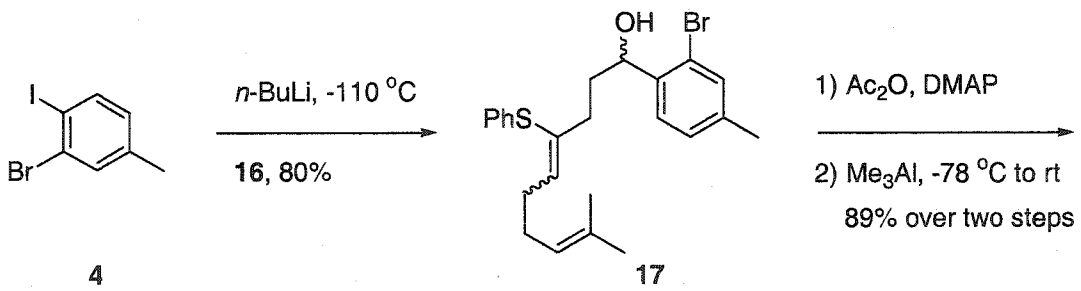


Vinyl sulfide **14** was prepared from phenyl vinyl sulfide in two steps in reasonable yield. Thus, treatment of phenyl vinyl sulfide with *n*-BuLi in the presence of TMEDA and subsequent addition of aldehyde **10** furnished **15** in 88% yield.[19] Claisen rearrangement of **15** in a sealed tube afforded aldehyde **16**.

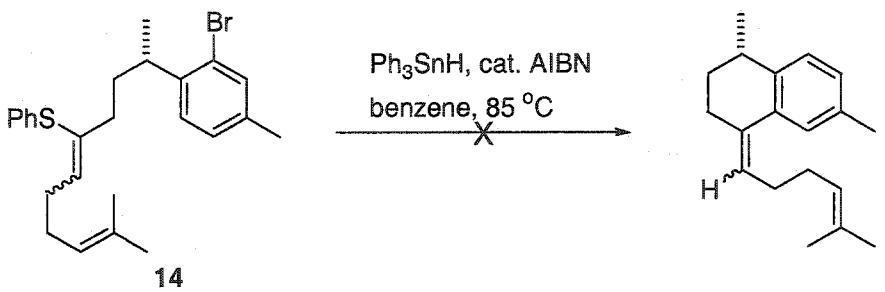


15 **16**

Reaction of **4** with *n*-BuLi and subsequent treatment with **16** provided alcohol **17** which was acetylated and then exposed to Me_3Al to give **14**. Unfortunately, radical cyclization did not occur.

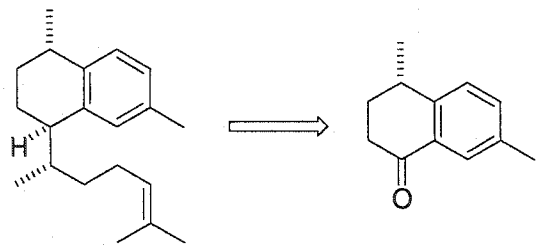


4 **17**

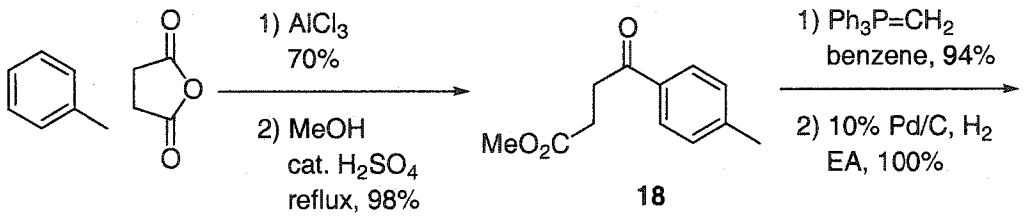


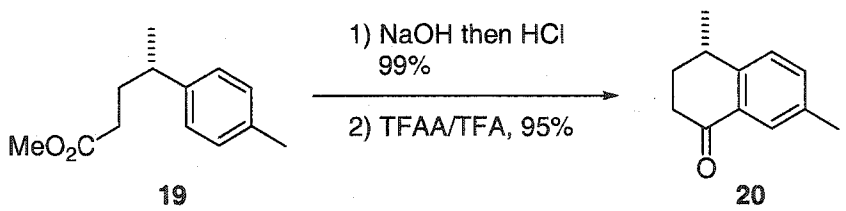
14

Therefore, we decided to form the cyclic ketone first and to elaborate the bottom side chain later.

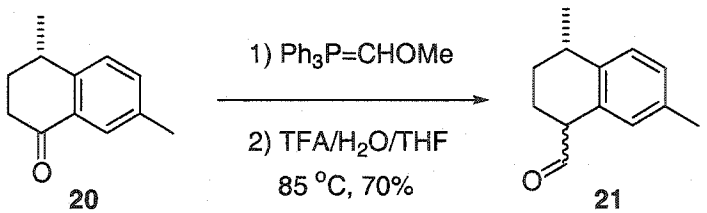


Toward this end, ketoester **18** was obtained from Friedel-Crafts acylation of toluene with succinic anhydride and subsequent esterification.[20] Olefination of **18** followed by reduction of the exomethylene group gave ester **19**.[21] Ester **19** was hydrolyzed to acid which, upon exposure to trifluoroacetic anhydride/trifluoroacetic acid, underwent smooth cyclization to form cyclic ketone **20** in good yield.[22]



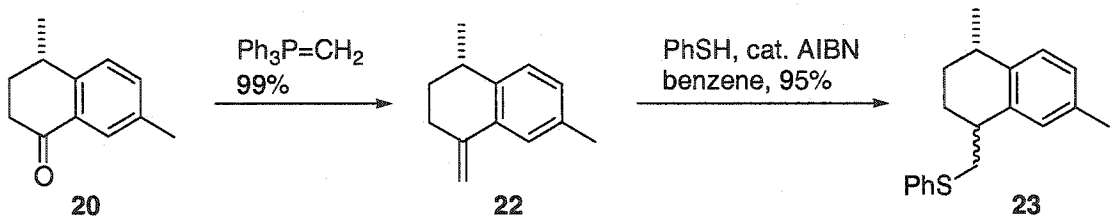


Ketone **20** was subjected to Wittig olefination followed by the hydrolysis of the resulting enol ether to give aldehyde **21** in a 1:1 mixture.[23] This result was in constrast with our expectation that trans product would be favored.



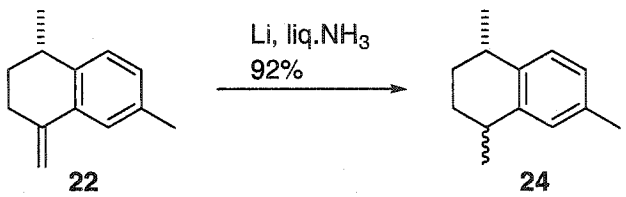
To see the cis/trans ratio of products derived from ketone **20**, ketone **20** was first

methylenated to give **22**. PhSH addition to **22** under radical condition again led to a 1:1 mixture of products.



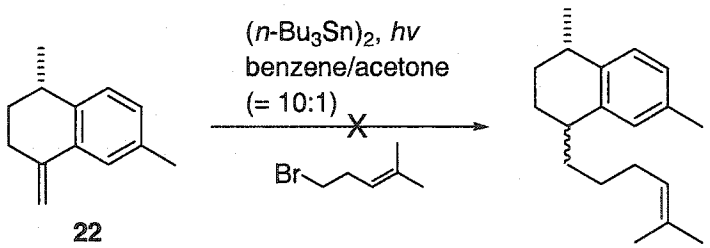
20 **22** **23**

Dissolving metal reduction of **22** provided a 3:1 trans:cis mixture **24**.



22 **24**

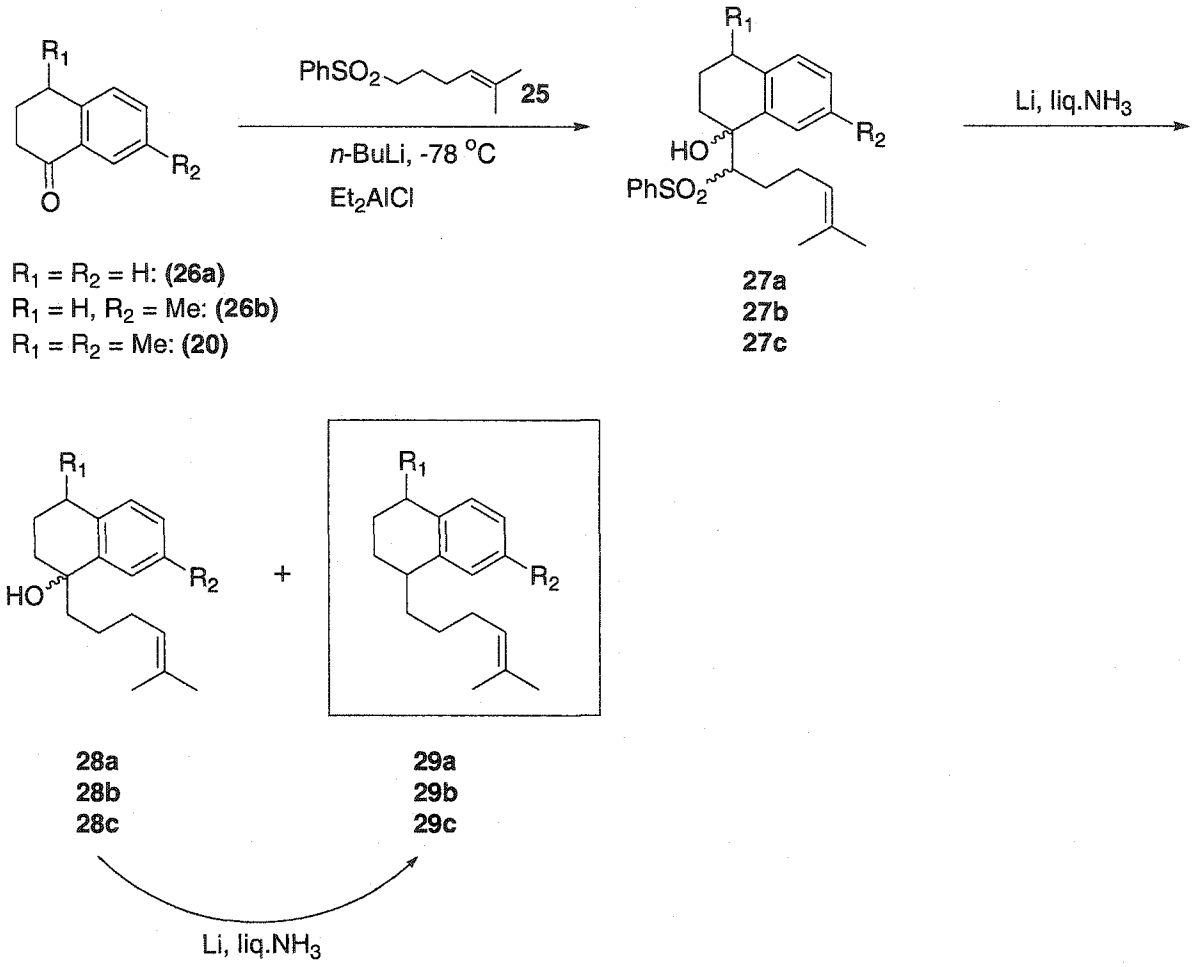
To introduce the alkyl chain, a photochemical reaction was carried out. The intermolecular addition failed to occur.



22

From these series of experimentations, we tentatively concluded that stereoselective introduction of alkyl side chain by nucleophilic or radical addtions to ketone **20** or alkene **22** would be hard to achieve. We decided to make analogs of erogorgiaene to test their biological activity. Thus, ketones **26a**, **26b**, and **20** were reacted with lithiated phenylsulfone in the presence of Et_2AlCl to give hydroxy sulfones **27a**, **27b**, and **27c** in good yields.[24] Dissolving metal reduction of **27a**, **27b**, and **27c** provided analogs of erogorgiaene, **29a**, **29b**, and **29c** along with benzylic alcohols, **28a**, **28b**, and **28c**.[25] These benzylic alcohols were further treated with Li-NH_3 (liq.) to give analogs. Interestingly, the ratio of isomers is 2:1 with the

trans product as the major when R_1 is CH_3. These analogs as well as stereomixture of erogorgiaene were submitted for biological testing.



In summary, a direct synthesis of erogorgiaene was achieved employing a regioselective halogen-metal exchange and a 6-exo-trig radical cyclization as key steps. This strategy could be useful to the synthesis of other benzene-fused natural products. Several other possible routes to this diterpene were also examined. In addition, three analogs of erogorgiaene were prepared for comparison of their antitubercular activity.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used

withtout purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

(4E/Z)-5,9-Dimethyldeca-4,8-dienal (3)

A mixture of linalool (3.00 g, 19.45 mmol) and $Hg(OAc)_2$ (1.24 g, 3.89 mmol) in ethyl vinyl ether (19 mL, 194.5 mmol) was heated in sealed tube at 140 °C overnight. After being cooled to rt, K_2CO_3 (538 mg, 3.89 mmol) was added to this mixture. The mixture was suction-filtered through Celite and washed with *n*-hexane. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give **3** (2.45 g, 70%). 300 MHz ^1H NMR ($CDCl_3$) δ 9.75 (1H, s), 5.17-5.02 (2H, m), 2.53-2.40 (2H, m), 2.40-2.26 (2H, m), 2.18-1.88 (5H, m), 1.76-1.50 (8H, m).

(4E/Z)-1-(2-Bromophenyl)-5,9-dimethyldeca-4,8-dien-1-ol (5)

To a solution of 1,2-dibromobenzene (1.23 g, 5.2 mmol) in THF (86 mL)/Et_2O (86 mL) was slowly added *n*-BuLi (2.5 M solution in hexanes, 2 mL, 5.2 mmol) at –110 °C (EtOH/liq. N_2 bath was used). After 30 min at –110 °C, a solution of **3** (1.2 g, 6.76 mmol) in THF (3 mL) was dropwise added to this mixture at –110 °C. After being stirred at –110 °C for 20 min, the

reaction mixture was allowed to warm to rt. The mixture was quenched with saturated NH_4Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by sgc (H:EA = 30:1 to 20:1) to give **5** (1.67 g, 95%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.54 (1H, d, J = 7.8 Hz), 7.49 (1H, d, J = 8.1 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.10 (1H, t, J = 8.1 Hz), 5.28-5.00 (3H, m), 2.26-2.15 (2H, m), 2.15-1.75 (6H, m), 1.75-1.51 (9H, m); HRMS *m/z* for $C_{18}H_{25}OBr$ calcd 336.1089, found 336.1093.

(5E/Z)-2-(2-Bromophenyl)-6,10-dimethylundeca-5,9-dien-2-ol (7)

To a solution of **5** (157 mg, 0.466 mmol) in CH_2Cl_2 (2 mL) was added PCC (121 mg, 0.559 mmol) at 0 °C. After being stirred at rt for 2 h, PCC (50 mg, 0.233 mmol) and Celite (160 mg) were added to this mixture. After being stirred at rt for additional 1 h, the mixture was diluted with Et_2O. The mixture was filtered through Celite and rinsed with Et_2O. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to afford ketone (135 mg, 87%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.58 (1H, d, J = 7.8 Hz), 7.40-7.18 (3H, m), 5.14 (1H, t, J = 7.2 Hz), 5.13-5.01 (1H, m), 2.93 (2H, q, J = 7.2 Hz), 2.40 (2H, q, J = 7.2 Hz), 2.12-1.90 (4H, m), 1.73-1.50 (9H, m).

To a solution of MeLi (1.4 M solution in THF, 864 μL, 1.209 mmol) in THF (1 mL) was dropwise added a solution of ketone (135 mg, 0.403 mmol) in THF (1 mL + 1 mL for rinse) at –78 °C. After 5 min, the mixture was quenched with saturated NH_4Cl at –78 °C. The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **7** (141 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.73 and 7.71 (1H, dd, J = 7.8, 1.8 Hz), 7.57 and 7.56 (1H, d, J = 8.1 Hz), 7.31 and 7.30 (1H, t, J = 7.8 Hz), 7.09 and 7.08 (1H, t, J =

7.8 Hz), 5.21-5.00 (3H, m), 2.62-2.38 (2H, m), 2.15-1.36 (18H, m).

(4E/Z)-1-(2-Bromophenyl)-5,9-dimethyldeca-4,8-dienyl acetate (8)

To a solution of **5** (1.527 g, 4.53 mmol) in CH_2Cl_2 (15 mL) were added DMAP (664 mg, 5.436 mmol) and Ac_2O (513 μL, 5.436 mmol) at 0 °C. After being stirred at rt for 2 h, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl and saturated $NaHCO_3$ solution, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1 to 20:1) to give **8** (1.716 g, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.53 (1H, d, J = 7.2 Hz), 7.40-7.24 (2H, m), 7.12 (1H, t, J = 7.5 Hz), 6.05 (1H, t, J = 6.6 Hz), 5.20-5.10 (2H, m), 2.10 (3H, s), 2.15-1.90 (6H, m), 1.90-1.75 (2H, m), 1.73-1.50 (9H, m); HRMS *m/z* for $C_{20}H_{27}O_2Br$ calcd 378.1194, found 378.1202.

1-Bromo-2-(1,5,9-trimethyldeca-4,8-dienyl)benzene (6)

To a solution of **8** (1.538 g, 4.06 mmol) in CH_2Cl_2 (46 mL) was dropwise added Me_3Al (2 M solution in hexanes, 7.1 mL, 14.21 mmol) at –78 °C. Then, the mixture was slowly warmed up to rt for 4 h. The mixture was quenched with saturated NH_4Cl at 0 °C. The mixture was suction-filtered through Celite and washed with CH_2Cl_2. The filtrate was evaporated in vacuo. The residue was purified by sgc (*n*-hexane only) to give **6** (1.29 g, 95%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.53 (1H, d, J = 7.2 Hz), 7.36-7.15 (2H, m), 7.02 (1H, t, J = 8.4 Hz), 5.21-5.02 (2H, m), 3.37-3.20 (1H, m), 2.18-1.10 (20H, m); HRMS *m/z* for $C_{19}H_{27}Br$ calcd 334.1296, found 334.1301.

1-(1,5-Dimethylhex-4-enyl)-4-methyl-1,2,3,4-tetrahydronaphthalene (9)

To a solution of **6** (81 mg, 0.242 mmol) in benzene (24.2 mL) were added *n*-Bu_3SnH (130 μL, 0.484 mmol) and AIBN (8 mg, 0.048 mmol) at rt. After being heated at 85 °C

overnight, the solvent was evaporated in vacuo. The residue was suspended in *n*-hexane, filtered through a short pad of silica gel, and washed with *n*-hexane. The filtrate was evaporated in vacuo. The residue was purified by prep TLC (H:EA = 100:1) to give a mixture of **9** and its isomers (46.8 mg, 75%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.05 (4H, m), 5.30-4.93 (1H, m), 3.00-2.60 (2H, m), 2.30-0.60 (21H, m).

2-Bromo-1-iodo-4-methylbenzene (4)

To an emulsion of 2-bromo-4-methylaniline (3 g, 16.12 mmol) in H_2O (4.1 mL) was slowly added c-HCl (4.1 mL) at rt. Then, a solution of $NaNO_2$ (1.22 g, 17.73 mmol) in H_2O (5.6 mL) was slowly added to the mixture at 0 °C. To the almost clear solution was slowly added a solution of KI (2.94 g, 17.73 mmol) in H_2O (3 mL) at 0 °C. After being stirred at rt for 4 h, the dark-colored reaction mixture was heated at 80 °C for 30 min. After being cooled to rt, the mixture was diluted with Et_2O and washed with 15% NaOH and saturated Na_2SO_3 solution, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (*n*-hexane only) to afford **4** (3.59 g, 75%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.70 (1H, d, J = 8.1 Hz), 7.45 (1H, d, J = 1.8 Hz), 6.80 (1H, dd, J = 8.1, 2.1 Hz), 2.28 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 140.1, 133.6, 129.8, 129.7, 97.2, 21.0.

(4E/Z)-1-(2-Bromo-4-methylphenyl)-5,9-dimethyldeca-4,8-dien-1-ol (2)

The same procedure for **5** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.41 (1H, d, J = 7.8 Hz), 7.34 (1H, s), 7.12 (1H, d, J = 7.5 Hz), 5.26-4.98 (3H, m), 2.31 (3H, s), 2.50-1.50 (17H, m); HRMS *m/z* for $C_{19}H_{27}OBr$ calcd 350.1245, found 350.1251.

2-Bromo-4-methyl-1-(1,5,9-trimethyldeca-4,8-dienyl)benzene (1)

The same procedures for **8** and **6** were applied.

Acetate: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.38 (1H, d, J = 2.1 Hz), 7.23 (1H, dd, J = 8.1, 2.1

Hz), 7.09 (1H, d, J = 8.1 Hz), 6.01 (1H, t, J = 6.6 Hz), 5.20-5.00 (2H, m), 2.30 (3H, s), 2.50-1.50 (20H, m).

1: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, d, J = 2.4 Hz), 7.19 (1H, dd, J = 7.8 Hz), 7.13 (1H, d, J = 8.1 Hz), 5.30-5.10 (2H, m), 3.42-3.24 (1H, m), 2.35 (3H, s), 2.20-1.50 (17H, m), 1.28 (3H, d, J = 6.9 Hz); HRMS *m/z* for $C_{20}H_{29}Br$ calcd 348.1453, found 348.1460.

4-(1,5-Dimethylhex-4-enyl)-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene (erogorgiaene) and its isomers

The same procedure for **9** was applied except the use of Ph_3SnH instead of n-Bu_3SnH. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.20-6.83 (3H, m), 5.21-4.90 (1H, m), 2.95-2.60 (2H, m), 2.30 (3H, s), 2.25-0.60 (21H, m).

5-Methylhex-4-enal (10)

The same procedure for **3** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.68 (1H, s), 5.02 (1H, t, J = 6.9 Hz), 2.45-2.32 (2H, m), 2.32-2.16 (2H, m), 1.61 (3H, s), 1.56 (3H, s).

1-(2-Bromo-4-methylphenyl)-5-methylhex-4-en-1-ol (11)

The same procedure for **5** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.38 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 0.9 Hz), 7.10 (1H, dd, J = 8.1, 1.2 Hz), 5.16 (1H, t, J = 7.2 Hz), 5.00 (1H, dd, J = 8.4, 4.2 Hz), 2.55 (1H, br s), 2.30 (3H, s), 2.14 (2H, q, J = 8.4 Hz), 1.87-1.56 (2H, m), 1.72 (3H, s), 1.62 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 141.0, 138.9, 133.2, 132.5, 128.7, 127.3, 124.1, 122.0, 72.7, 37.9, 26.0, 24.8, 20.9, 18.0; HRMS *m/z* for $C_{14}H_{19}OBr$ calcd 282.0619, found 282.0624.

2-Bromo-1-(1,5-dimethylhex-4-enyl)-4-methylbenzene (12)

The same procedures for **8** and **6** were applied.

Acetate: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35 (1H, d, J = 0.9 Hz), 7.24 (1H, d, J = 7.8 Hz),

7.10 (1H, dd, J = 7.8, 0.9 Hz), 6.03 (1H, t, J = 6.3 Hz), 5.13 (1H, t, J = 6.9 Hz), 2.30 (3H, s), 2.09 (3H, s), 2.18-2.02 (2H, m), 1.90-1.76 (2H, m), 1.69 (3H, s), 1.58 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.2, 139.3, 137.7, 133.5, 132.7, 128.7, 127.0, 123.4, 122.2, 74.7, 35.8, 25.9, 24.4, 21.3, 20.9, 17.9.

12: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.40 (1H, d, J = 0.3 Hz), 7.15 (1H, d, J = 7.8 Hz), 7.10 (1H, dd, J = 8.1, 0.9 Hz), 5.15 (1H, t, J = 7.2 Hz), 3.35-3.20 (1H, m), 2.32 (3H, s), 2.10-1.85 (2H, m), 1.71 (3H, s), 1.79-1.50 (2H, m), 1.56 (3H, s), 1.22 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 143.4, 137.3, 133.4, 131.8, 128.7, 127.1, 124.9, 124.6, 37.6, 37.5, 26.3, 26.0, 21.6, 20.8, 17.9; HRMS *m/z* for $C_{15}H_{21}Br$ calcd 280.0827, found 280.0832.

(1S, 4R)-4-Isopropyl-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene (*trans*-calamenene) and *cis*-calamenene

The same procedure for **9** was applied except the use of Ph_3SnH instead of n-Bu_3SnH. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.23-6.90 (3H, m), 3.00-2.60 (2H, m), 2.36 (3H, s), 2.40-0.70 (14H, m).

Mixture of alkenes (13)

To a solution of **1** (130 mg, 0.373 mmol) and n-Bu_4OAc (281 mg, 0.933 mmol) in DMF (2 mL), CH_3CN (2 mL), and H_2O (0.4 mL) was added Herrmann's catalyst at 50 °C. After being heated at 115 °C overnight, the mixture was cooled down to rt. The mixture was diluted with Et_2O and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give a mixture of alkenes. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-6.90 (3H, m), 5.35-5.13 (1H, m), 5.10-0.85 (24H, m).

7-Methyl-2-phenylthioocta-1,6-dien-3-ol (15)

To a solution of n-BuLi (2.5 M solution in hexanes, 3.5 mL, 8.81 mmol) and TMEDA

(1.1 mL, 7.34 mmol) in THF (24 mL) was added phenyl vinyl sulfide (960 μL, 7.34 mmol) at –78 °C. After being stirred at rt for 30 min, a solution of **10** (986 mg, 8.81 mmol) in THF (1 mL) was added to this mixture at –78 °C. After 5 min, the mixture was quenched with H_2O. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give **15** (1.603 g, 88%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.53-7.43 (2H, m), 7.38-7.23 (3H, m), 5.46 (1H, s), 5.13 (1H, t, J = 7.2 Hz), 4.92 (1H, s), 4.22 (1H, br s), 2.78 (1H, br s), 2.10 (2H, q, J = 7.5 Hz), 1.93-1.64 (2H, m), 1.69 (3H, s), 1.61 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 149.5, 133.7, 132.8, 132.4, 129.5, 128.2, 124.1, 112.9, 74.4, 36.4, 26.0, 24.5, 18.0.

(4E/Z)-9-Methyl-4-phenylthiodeca-4,8-dienal (16)

The same procedure for **3** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.66 (1H, s), 7.30-7.10 (5H, m), 5.98 (1H, t, J = 6.9 Hz), 5.13 (1H, t, J = 7.2 Hz), 2.65-2.55 (2H, m), 2.55-2.45 (2H, m), 2,40 (2H, q, J = 7.2 Hz), 2.11 (2H, q, J = 6.9 Hz), 1.70 (3H, s), 1.61 (3H, s).

(4E/Z)-1-(2-Bromo-4-methylphenyl)-9-methyl-4-phenylthiodeca-4,8-dien-1-ol (17)

The same procedure for **5** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.45-7.00 (8H, m), 5.99 (1H, t, J = 6.9 Hz), 5.19 (1H, t, J = 6.9 Hz), 5.03-4.90 (1H, m), 2.50-1.10 (8H, m), 2.32 (3H, s), 1.73 (3H, s), 1.64 (3H, s).

(6E/Z)-10-(2-Bromo-4-methylphenyl)-2-methyl-7-phenylthioundeca-2,6-diene (14)

The same procedures for **8** and **6** were applied.

Acetate: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.42-7.00 (8H, m), 6.07-5.85 (2H, m), 5.19 (1H, t, J = 6.9 Hz), 2.50-2.37 (2H, m), 2.37-1.90 (6H, m), 2.30 (3H, s), 2.20 (3H, s), 1.73 (3H, s), 1.64 (3H, s).

14: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.45-6.95 (8H, m), 6.20-5.75 (1H, m), 5.25-5.05 (1H, m), 3.20-1.76 (9H, m), 2.30 (3H, s), 1.72 (3H, s), 1.62 (3H, s), 1.14 (3H, d, J = 6.9 Hz).

Methyl 4-oxo-4-*p*-tolylbutyrate (18)

To a mixture of toluene (50 mL, 469 mmol) and succinic anhydride (6.8 g, 68 mmol) was carefully added $AlCl_3$ (20 g, 150 mmol) at rt. After being heated to reflux for 1 h, the mixture was cooled down to rt. H_2O (50 mL) was added slowly over 10 min with care. After HCl gas evolution has ceased, the mixture was evaporated to remove toluene. The remaining residue was poured into cold H_2O in beaker. The solid formed was suction-filtered and rinsed with H_2O. The solid was dissolved in aqueous Na_2CO_3 solution. The mixture was filtered through Celite and washed with H_2O. The filtrate was acidified with c-HCl at 0 °C. The white solid formed was filtered, rinsed with H_2O, and dried under reduced pressure to afford acid (9.133 g, 70%). 300 MHz ^{1}H NMR (acetone-d_6) δ 7.93 (2H, dd, J = 8.1, 1.8 Hz), 7.33 (2H, d, J = 8.4 Hz), 3.30 (2H, t, J = 6.3 Hz), 3.24 (1H, br s), 2.70 (2H, t, J = 6.6 Hz), 2.40 (3H, s),

A solution of the acid (16.7 g, 86.98 mmol) and c-H_2SO_4 (1 mL) in MeOH was heated to reflux with the occasional removal of H_2O and MeOH overnight (Dean-Stark trap was used). The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with H_2O and saturated $NaHCO_3$ solution, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **18** (17.56 g, 98%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.1 Hz), 3.70 (3H, s), 3.30 (2H, t, J = 6.6 Hz), 2.75 (2H, t, J = 6.6 Hz), 2.41 (3H, s).

Methyl 4-*p*-tolylpentanoate (19)

A suspension of methyltriphenylphosphonium bromide (17.5 g, 48.86 mmol) and *t*-BuOK (5.48 g, 48.86 mmol) in benzene (210 mL) was stirred under argon atmosphere at rt

for 4h. Then, a solution of 18 (8.388 g, 40.72 mmol) in benzene (80 mL + 4 mL for rinse) was transferred to this mixture at rt via cannula. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was suspended in solvent (H:EA = 10:1), filtered through Celite, and washed with solvent (H:EA = 10:1). The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 100:1) to give alkene (7.808 g, 94%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.4 Hz), 5.29 (1H, s), 5.05 (1H, s), 3.67 (3H, s), 2.90-2.76 (2H, m), 2.55-2.43 (2H, m), 2.35 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 173.8, 146.9, 137.8, 137.6, 129.3, 126.2, 112.2, 51.7, 33.3, 30.7, 21.3.

To a solution of the alkene (12.213 g, 59.87 mmol) in ethyl acetate was carefully added 10% Pd/C (1.2 g) at rt. After being stirred under H_2 balloon at rt for 7 h, the mixture was suction-filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to give **19** (12.333 g, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.14 (2H, d, J = 8.4 Hz), 7.10 (2H, dd, J = 8.4, 2.1 Hz), 3.65 (3H, s), 2.82-2.65 (1H, m), 2.35 (3H, s), 2.30-2.16 (2H, m), 2.05-1.83 (2H, m), 1.29 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 174.3, 143.4, 135.8, 129.4, 127.1, 51.6, 39.2, 33.5, 32.5, 22.5, 21.2.

4,7-Dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (20)

A mixture of **19** (9.953 g, 48.3 mmol) and NaOH (3.9 g, 96.6 mmol) in H_2O (100 mL) and MeOH (25 mL) was heated to reflux for 30 min. After being cooled down to rt, MeOH was evaporated in vacuo. The mixture was acidified with c-HCl at 0 °C. The mixture was extracted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to afford acid (9.2 g, 99%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.19 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.4 Hz), 2.90-2.70 (1H, m), 2.40 (3H, s), 2.38-2.26 (2H, m), 2.10-1.85 (2H, m), 1.34 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 180.9,

143.3, 136.0, 129.5, 127.2, 39.2, 33.3, 32.7, 22.6, 21.3.

To the acid (8.26 g, 43.02 mmol) in TFA (43 mL) was added TFAA (9.1 mL, 64.53 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the mixture was quenched with cold H_2O and saturated $NaHCO_3$ solution at 0 °C. When the aqueous phase was neutral or basic, the mixture was extracted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give **20** (7.11 g, 95%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, s), 7.27 (1H, dd, J = 7.8, 2.1 Hz), 7.17 (1H, d, J = 7.8 Hz), 3.10-2.92 (1H, m), 2.83-2.65 (1H, m), 2.62-2.45 (1H, m), 2.30 (3H, s), 2.26-2.10 (1H, m), 1.90-1.73 (1H, m), 1.33 (3H, d, J = 7.2 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 198.7, 146.3, 136.3, 134.7, 131.8, 127.5, 36.7, 32.7, 31.0, 21.1, 20.9.

4,7-Dimethyl-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (21)

To a suspension of methoxymethyltriphenylphosphonium chloride (2.3 g, 6.792 mmol) in THF (7 mL) was added *n*-BuLi (2.5 M solution in hexanes, 2.3 mL, 5.66 mmol) at 0 °C. After 5 min at 0 °C, a solution of **20** (394 mg, 2.264 mmol) in THF (3 mL + 1 mL for rinse) to this mixture at 0 °C via cannula. After being stirred at rt for 4 h, the mixture was quenched with saturated NH_4Cl and evaporated in vacuo. The residue was dissolved in THF (5 mL) and TFA (500 μL) was added at 0 °C. After being heated at 85 °C for 8 h, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give **21** (298 mg, 70%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.67 and 9.64 (1H, d, J = 2.1 Hz), 7.21 and 7.18 (1H, d, J = 8.1 Hz), 7.07 (1H, d, J = 7.8 Hz), 6.95 (1H, s), 3.60-3.50 (1H, m), 2.99-2.82 (1H, m), 2.33 (3H, s), 2.32-1.45 (4H, m), 1.29 and 1.27 (3H, d, J = 6.9 Hz).

1,6-Dimethyl-4-methylene-1,2,3,4-tetrahydronaphthalene (22)

The same procedure for **19** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.70 (1H, s), 7.36 (1H, dd, J = 7.8, 2.7 Hz), 7.27 (1H, d, J = 7.8 Hz), 5.70 (1H, s), 5.18 (1H, s), 3.26-3.10 (1H, m), 2.97-2.80 (1H, m), 2.78-2.62 (1H, m), 2.56 (3H, s), 2.32-2.16 (1H, m), 1.95-1.78 (1H, m), 1.54 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 144.4, 139.7, 135.5, 134.6, 129.3, 128.5, 125.2, 108.0, 33.5, 32.3, 30.8, 22.8, 21.6.

1,6-Dimethyl-4-phenylthiomethyl-1,2,3,4-tetrahydronaphthalene (23)

To a solution of **22** (103 mg, 0.599 mmol) were added AIBN (20 mg, 0.12 mmol) and PhSH (68 μL, 0.659 mmol) at rt. After being heated at 85 °C for 2 h, the mixture was concentrated in vacuo to give crude **23** (160 mg, 95%) as a 1:1 mixture. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.57-6.90 (3H, m), 3.42-3.26 (1H, m), 3.17-3.05 (1H, m), 3.05-2.75 (2H, m), 2.31 (3H, s), 2.17-1.37 (4H, m), 1.32 and 1.24 (3H, d, J = 6.9 Hz).

1,4,6-Trimethyl-1,2,3,4-tetrahydronaphthalene (24)

To a solution of **22** (68.7 mg, 0.399 mmol) in THF (2 mL) was added gaseous NH_3 at –78 °C. Then, small pieces of Li metal (28 mg, 3.99 mmol) was added to this mixture at –78 °C. After being stirred at –78 °C for 30 min, the mixture was quenched with saturated NH_4Cl at –78 °C. The excess NH_3 was blown out using argon. The residue was diluted with Et_2O and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (*n*-hexane only) to give **24** (64 mg, 92%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.18 (1H, d, J = 7.8 Hz), 7.10 (1H, s), 7.03 (1H, dd, J = 7.8, 1.8 Hz), 3.05-2.85 (1H, m), 2.30 (3H, s), 2.15-1.46 (4H, m), 1.34-1.28 (6H, m)

(5-Methylhex-4-ene-1-sulfonyl)benzene (25)

To a solution of **10** (6.145 g, 54.87 mmol) in MeOH (100 mL) was added $NaBH_4$ (2 g,

54.87 mmol) at 0 °C. After being stirred at rt for 30 min, the mixture was quenched with saturated NH_4Cl at 0 °C. The organic solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give alcohol (5.4 g, 86%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.20-5.05 (1H, m), 3.64 (2H, t, J = 6.3 Hz), 2.06 (2H, q, J = 7.2 Hz), 1.69 (3H, s), 1.63 (3H, s), 1.78-1.55 (2H, m), 1.40 (1H, br s).

To a solution of the alcohol (5.4 g, 47.4 mmol) in CH_2Cl_2 (100 mL) were added PPh_3 (13.7 g, 52.1 mmol) and CBr_4 (17.3 g, 52.1 mmol) at 0 °C (exothermic). After 10 min at 0 °C, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give bromide (7.54 g, 90%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.08 (1H, t, J = 7.2 Hz), 3.40 (2H, t, J = 6.9 Hz), 2.13 (2H, q, J = 6.9 Hz), 1.97-1.83 (2H, m), 1.70 (3H, s), 1.63 (3H, s).

To a solution of bromide (2.63 g, 14.89 mmol) in DMF (15 mL) was added $PhSO_2Na$ (2.9 g, 17.87 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give sulfone **25** (3.01 g, 85%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.96-7.85 (2H, m), 7.72-7.62 (1H, m), 7.62-7.51 (2H, m), 4.98 (1H, t, J = 7.2 Hz), 3.15-3.02 (2H, m), 2.13-1.96 (2H, m), 1.85-1.70 (2H, m), 1.66 (3H, s), 1.55 (3H, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 139.2, 133.7, 133.67, 129.3, 128.1, 122.2, 55.7, 26.5, 25.7, 22.9, 17.8.

7-Methyl-3,4-dihydro-2*H*-naphthalen-1-one (26b)

To a solution of 4-oxo-4-*p*-tolylbutyric acid (2.6 g, 13.54 mmol) and c-HCl (0.6 mL) in MeOH (45 mL) was carefully added 10% Pd/C (1.3 g) at rt. After being stirred at rt for 7 h, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was

evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give methyl 4-*p*-tolylbutyrate (2.6 g, 100%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.11 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 3.67 (3H, s), 2.63 (2H, t, J = 7.6 Hz), 2.34 (3H, s), 2.38-2.27 (2H, m), 2.03-1.88 (2H, m); 100 MHz ^{13}C NMR ($CDCl_3$) δ 174.0, 138.4, 135.5, 129.1, 128.4, 51.5, 34.8, 33.4, 26.7, 21.1.

A mixture of methyl ester (3 g, 15.63 mmol) and NaOH (1.3 g, 31.26 mmol) in H_2O (45 mL) and MeOH (5 mL) was heated to reflux for 30 min. After being cooled to rt, the MeOH was evaporated in vacuo. The residue was acidified with c-HCl at 0 °C. The white solid formed was filtered, rinsed with H_2O, and dried under reduced pressure to provide 4-*p*-tolylbutyric acid (2.75 g, 99%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.12 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 2.61 (2H, t, J = 7.2 Hz), 2.37 (3H, s), 2.33 (2H, t, J = 7.2 Hz), 2.00-1.85 (2H, m); 100 MHz ^{13}C NMR ($CDCl_3$) δ 180.5, 138.6, 135.4, 129.2, 128.5, 34.9, 34.5, 26.8, 21.1.

To a solution of acid (1.83 g, 10.28 mmol) in TFA (10.28 mL) was added TFAA (2.2 mL, 15.42 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the mixture was quenched with cold H_2O and saturated $NaHCO_3$ solution at 0 °C. The basic reaction mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to afford **26b** (1.62 g, 98%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, s), 7.23 (1H, dd, J = 7.6, 1.2 Hz), 7.09 (1H, d, J = 7.6 Hz), 2.87 (2H, t, J = 6.0 Hz), 2.59 (2H, t, J = 6.4 Hz), 2.31 (3H, s), 2.15-2.02 (2H, m); 100 MHz ^{13}C NMR ($CDCl_3$) δ 199.0, 141.7, 136.3, 134.4, 132.4, 128.7, 127.3, 39.3, 29.3, 23.5, 21.0.

1-(1-Benzenesulfonyl-5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalen-1-ol (27a)

To a solution of sulfone **25** (210 mg, 0.882 mmol) in THF (3 mL) was added *n*-BuLi (2.5 M solution in hexanes, 353 μL, 0.882 mmol) at –78 °C. After 5 min at –78 °C, a solution of α-tetralone **26a** (117 μL, 0.882 mmol) in THF (1 mL + 0.5 mL for rinse) was transferred to this mixture at –78 °C via cannula. Then, Et_2AlCl (1.8 M solution in toluene, 490 μL, 0.882 mmol) was slowly added at –78 °C. After being stirred at –78 °C for 15 min, the mixture was quenched with saturated NH_4Cl, diluted with CH_2Cl_2, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **27a** (319 mg, 94%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.10-7.00 (9H, m), 4.40-4.25 (1H, m), 3.76-0.98 (17H, m); HRMS *m/z* for $C_{23}H_{28}O_3S$ calcd 384.1759, found 384.1766.

1-(5-Methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalen-1-ol (28a) and 1-(5-Methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (29a)

To a solution of **27a** (297 mg, 0.773 mmol) in Et_2O (3 mL) was added gaseous NH_3 at –78 °C. Then, small pieces of Li metal (54 mg, 7.73 mmol) was added to this mixture at –78 °C. After being stirred at –78 °C for 30 min, the mixture was quenched with saturated NH_4Cl at –78 °C. The excess NH_3 was blown out using argon. The residue was diluted with *n*-hexane and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (*n*-hexane only to H:EA = 15:1) to give **29a** along with **28a**. Benzyl alcohol **28a** was further treated with Li/NH_3 at –30 °C for 30 min before quenching to give **29a**.

28a: 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.51 (1H, d, J = 7.6 Hz), 7.19 (1H, t, J = 7.2 Hz), 7.15 (1H, dt, J = 7.2, 1.6 Hz), 7.06 (1H, d, J = 7.2 Hz), 5.08 (1H, t, J = 7.2 Hz), 2.77-2.66 (2H, m),

2.09-1.15 (10H, m), 1.66 (3H, s), 1.57 (3H, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 142.4, 136.8, 131.7, 128.9, 127.1, 126.3, 124.5, 72.5, 42.2, 36.1, 30.0, 28.4, 25.8, 24.5, 19.8, 17.8.

29a: 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.21-7.00 (4H, m), 5.15 (1H, t, J = 7.2 Hz), 2.76 (3H, br s), 2.13-1.94 (2H, m), 1.94-1.80 (2H, m), 1.77-1.30 (6H, m), 1.71 (3H, s), 1.62 (3H, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 141.7, 137.1, 131.5, 129.1, 128.7, 125.5, 125.4, 124.8, 37.6, 36.7, 29.8, 28.3, 27.7, 27.5, 25.8, 19.9, 17.8; HRMS *m/z* for $C_{17}H_{24}$ calcd 228.1878, found 228.1882.

1-(1-Benzenesulfonyl-5-methylhex-4-enyl)-7-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (27b)

The same procedure for **27a** was applied. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.05-6.85 (8H, m), 4.48-4.27 (1H, m), 3.68-0.80 (20H, m).

7-Methyl-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphtalen-1-ol (28b) and 7-Methyl-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (29b)

The same procedure for **29a** was applied.

28b: 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (1H, s), 6.97 (2H, s), 5.17 and 5.12 (1H, t, J = 7.2 Hz), 2.87-2.62 (2H, m), 2.31 (3H, s), 2.10-1.19 (10H, m), 1.67 (3H, s), 1.58 (3H, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 142.3, 135.7, 133.7, 131.7, 128.8, 128.0, 126.7, 124.6, 72.5, 42.1, 36.2, 29.6, 28.4, 25.8, 24.5, 21.3, 19.9, 17.8

29b: 400 MHz ^{1}H NMR ($CDCl_3$) δ 6.98 (1H, s), 6.95 (1H, d, J = 7.6 Hz), 6.90 (1H, d, J = 7.6 Hz), 5.14 (1H, t, J = 7.2 Hz), 2.71 (3H, br s), 2.30 (3H, s), 2.11-1.93 (2H, m), 1.90-1.75 (2H, m), 1.75-1.31 (6H, m), 1.68 (3H, s), 1.62 (3H, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 141.5, 134.8, 134.0, 131.4, 129.2, 129.0, 126.3, 124.8, 37.5, 36.7, 29.4, 28.3, 27.8, 27.5, 25.8, 21.2, 19.9, 17.8; HRMS *m/z* for $C_{18}H_{26}$ calcd 242.2035, found 242.2038.

1-(1-Benzenesulfonyl-5-methylhex-4-enyl)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (27c)

The same procedure for **27a** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.12-6.93 (8H, m), 4.58-4.25 (1H, m), 3.79-0.80 (22H, m).

4,7-Dimethyl-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalen-1-ol (28c) and 1,6-Dimethyl-4-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (29c)

The same procedure for **29a** was applied.

28c: 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.34 (1H, s), 7.17-6.98 (2H, m), 5.12 (1H, br s), 2.99-2.71 (1H, m), 2.33 (3H, s), 2.19-1.37 (10H, m), 1.70 (3H, s), 1.60 (3H, s), 1.30 and 1.26 (3H, d, J = 6.9 Hz).

29c: 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.22-6.94 (3H, m), 5.22 (1H, br s), 3.00-2.83 (1H, m), 2.83-2.70 (1H, m), 2.37 (3H, s), 2.19-1.39 (10H, m), 1.77 (3H, s), 1.69 (3H, s), 1.34 and 1.31 (3H, d, J = 6.9 Hz); HRMS *m/z* for $C_{19}H_{28}$ calcd 256.2191, found 256.2194.

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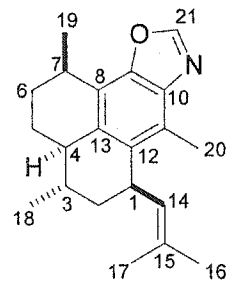
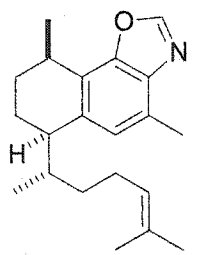
CHAPTER 4. SYNTHETIC STUDIES TOWARDS ANTITUBERCULAR BENZOXAZOLE ALKALOIDS

Introduction

In 1999, Rodriguez and coworkers isolated pseudopteroxazole and seco-pseudopteroxazole from the hexane extracts of the West Indian gorgonian coral *Pseudopterogorgia elibethae* (Bayer) collected near San Andres Island, Colombia.[1] While pseudopteroxazole exhibits potent inhibitory activity (97%) against *M. tuberculosis* H37Rv at a concentration of 12.5 μg/mL, seco-pseudopteroxazole inhibits 66% of mycobacterial growth.[1] Initially, the structures of these two alkaloids were assigned as shown below.



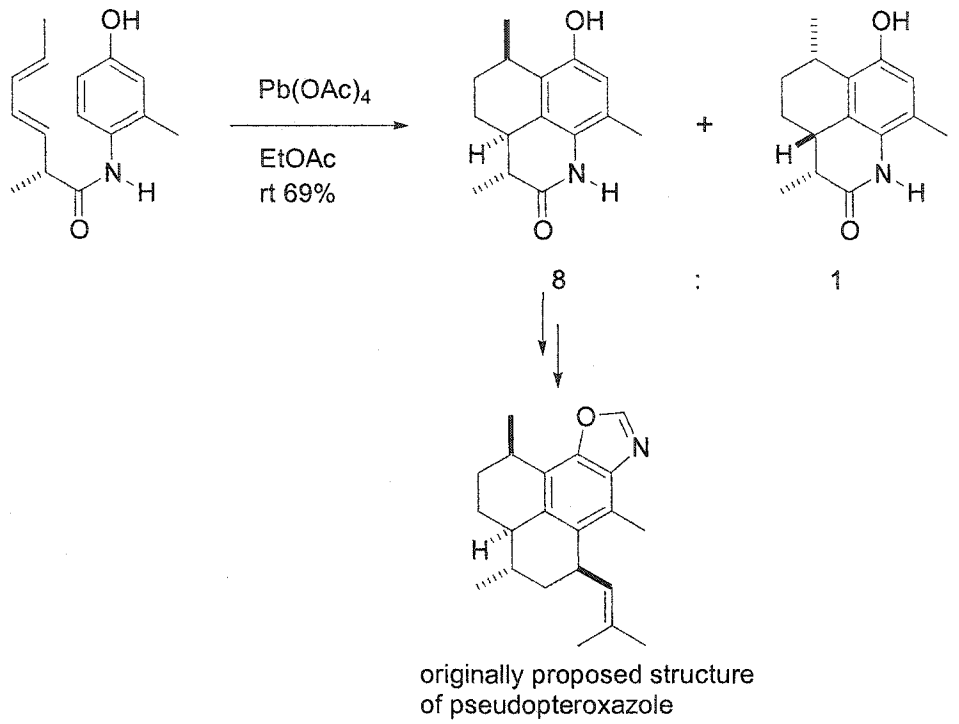
pseudopteroxazole

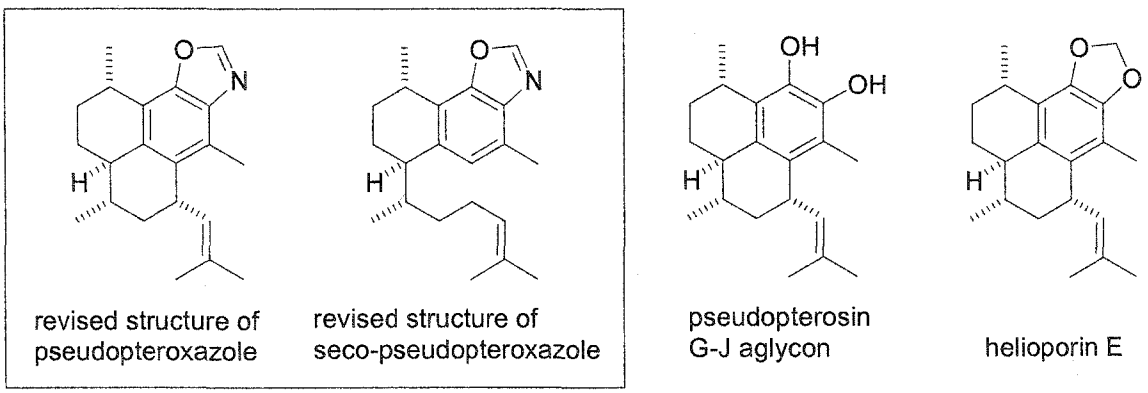


seco-pseudopteroxazole

During the course of our synthetic investigations on the original structures of these natural products, Corey reported the enantiospecific total synthesis of pseudopteroxazole utilizing an intramolecular Diels-Alder reaction as a key step.[2]

But NMR spectra of synthetic sample were inconsistent with the ones of natural product. Therefore, he proposed the revised structure of pseudopteroxazole based on his previous work on this family of diterpenes such as pseudopterosin[3] and helioporin E.[4]





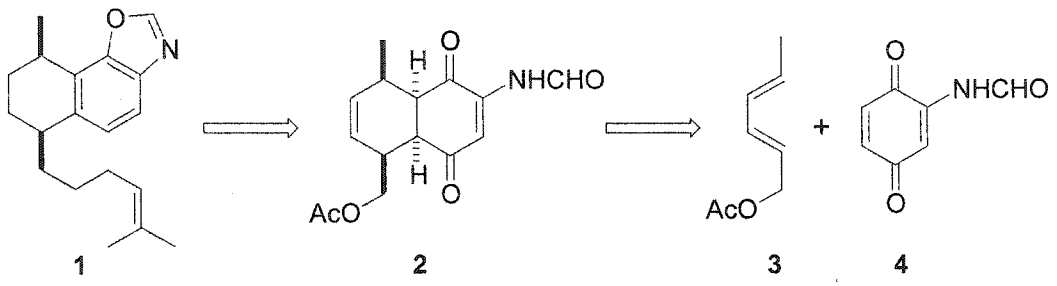
To date no total synthesis of these two new structures has been reported.

Part of this section will describe our synthetic efforts towards the originally proposed structures of two antitubercular benzoxazole alkaloids.

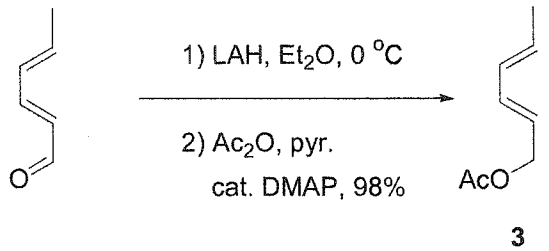
Results and Discussion

Cis orientation of two alkyl chains at C4 and C7 positions of these natural products

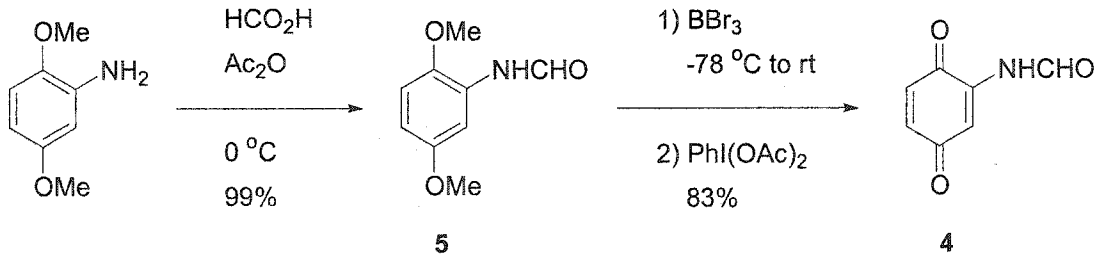
inspired us to employ the Diels-Alder reaction of the diene with benzoquinone dienophile to construct the bicyclic core. To validate the feasibility of this strategy, compound **1** was chosen as a synthetic target. Synthetic analog **1** of seco-pseudopteroxazole would be elaborated from acetate **2** which, in turn, would be assembled from the known diene **3** and dienophile **4** by utilizing an intermolecular Diels-Alder cycloaddition.



In this context, diene **3** and dienophile **4** were prepared from the commercially available source, respectively. Thus, LAH reduction of 2,4-hexadienal provided dienol, which was acetylated to give **3** in good overall yield.[5]

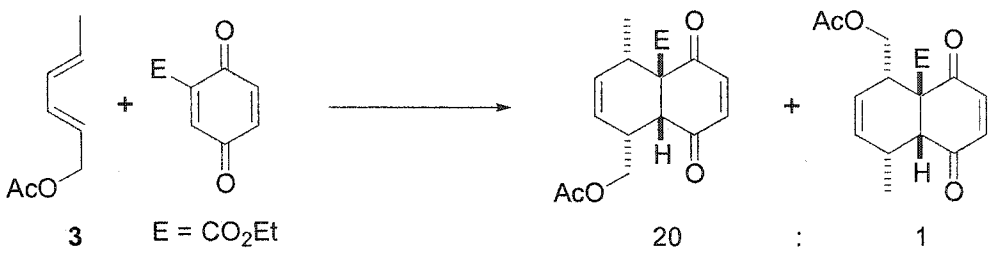


Formylation[6] of 2,5-dimethoxyaniline gave formamide **5**. Exposure of **5** to BBr_3 afforded hydroquinone which was then oxidized to benzoquinone **4** in good yield.[7]

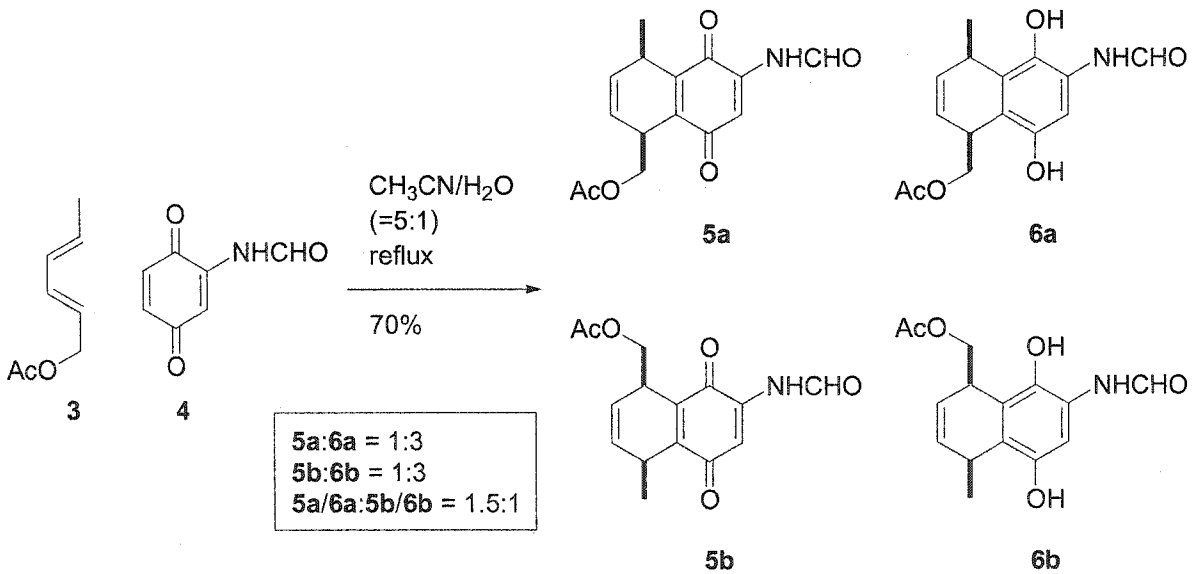


Now, these two coupling partners set the stage for the key Diels-Alder transformation.

In 1985, our group reported the highly regioselective Diels-Alder reaction with the same diene **3**.[5]

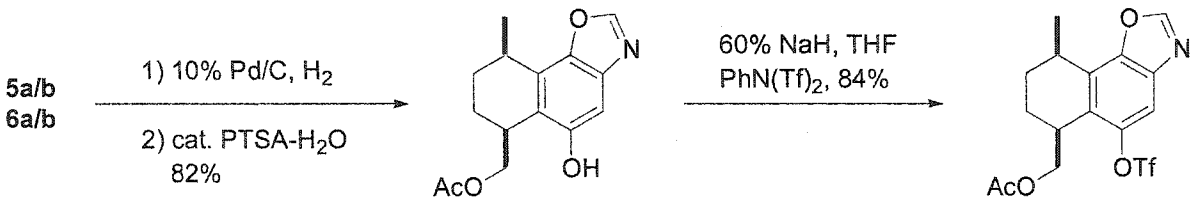


Based on this observation, we expected the similar or higher regioselectivity with diene **3** and dienophile **4**. However, thermal Diels-Alder reaction of **3** and **4** provided an approximately 1.5:1 mixture of inseparable regioisomers in which the desired product was major. Hydroquinones **6a** and **6b** were also obtained along with the corresponding benzoquinones **5a** and **5b** from the reaction mixture in a 3:1 ratio, respectively.



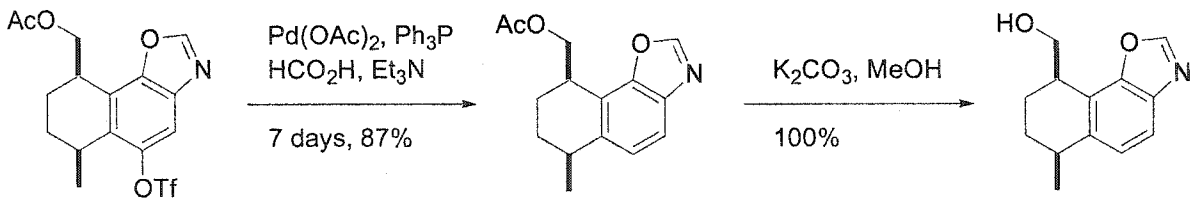
Various attempts to improve the regioselectivity were unsuccessful. With this result in hand, we decided to transform the cycloadducts into the final target molecule. Thus, catalytic hydrogenation of the mixture **5a/b** and **6a/b** and subsequent treatment with PTSA-H_2O in boiling benzene/ethyl acetate gave rise to an inseparable mixture of benzoxazoles **7a** and **7b**.

Triflation of the phenol group of **7a/b** provided **8a** and **8b**.[8]



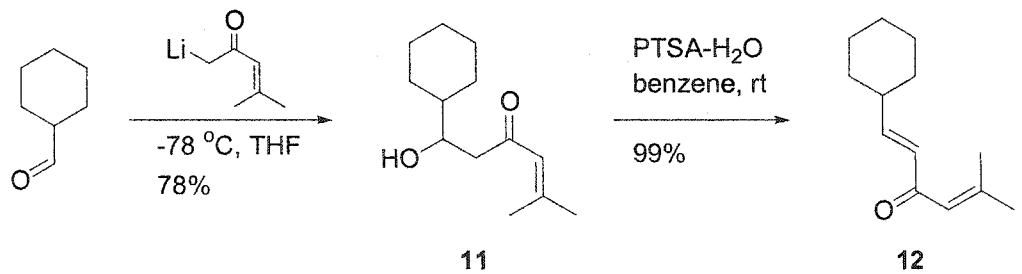
7a/b **8a/b**

At this stage, these two regioisomers were separated by column chromatography. However, we were still not sure which one was our desired product. Unfortunately, the wrong isomer was first considered to be our desired product. A number of reactions had been carried out with the wrong isomer before the structure was unambiguously confirmed by X-ray crystallography. Although the results were not successful, I think that the reactions with isomer **8b** are worthwhile to describe. The triflate group was removed under palladium catalyzed conditions[9] to give **9** which was treated with K_2CO_3 in methanol to furnish alcohol **10**.

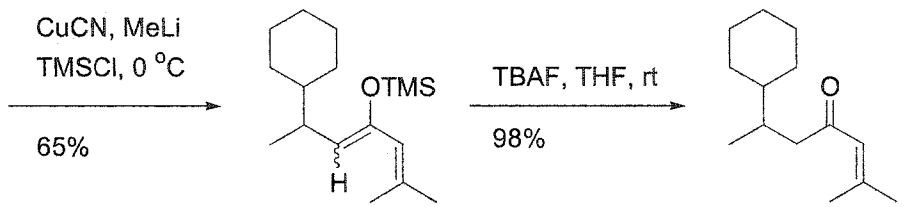


8b **9** **10**

At this point, we carried out a model study to establish the method to install the alkyl side chain. Thus, cyclohexanecarboxaldehyde was treated with the lithium enolate of mesityl oxide at –78 °C to give β-hydroxy ketone **11** which, upon exposure to PTSA-H_2O in benzene at rt, was converted to unsaturated ketone **12**. Regioselective Michael addition[10] of cuprate to **12** in the presence of TMSCl at 0 °C produced enol ether **13** which was subsequently treated with TBAF to give enone **14**.

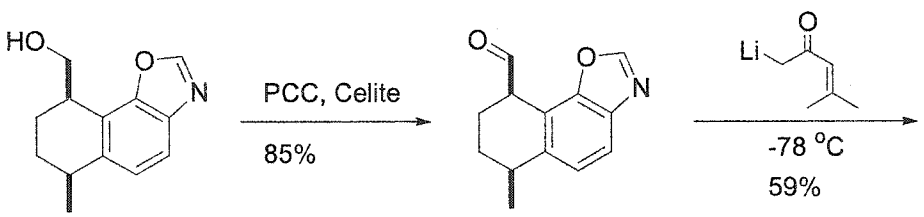


11 12

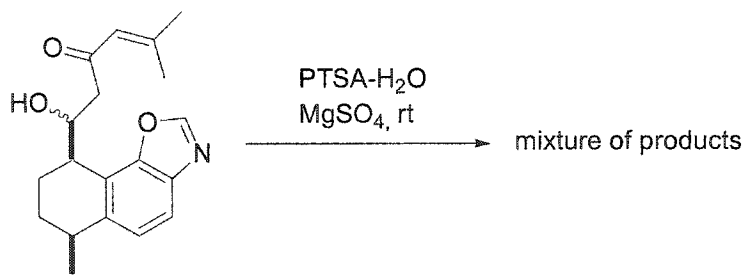


13 14

With this successful result in hand, alcohol **10** was converted to the corresponding aldehyde **15** using PCC. Aldehyde **15** was reacted with the lithium enolate of mesityl oxide to provide aldol product **16** in modest yield. Acid treatment of **16** gave a complex mixture of products. This is probably due to the acidity of benzylic hydrogen which would cause epimerization and/or elimination of H_2O.



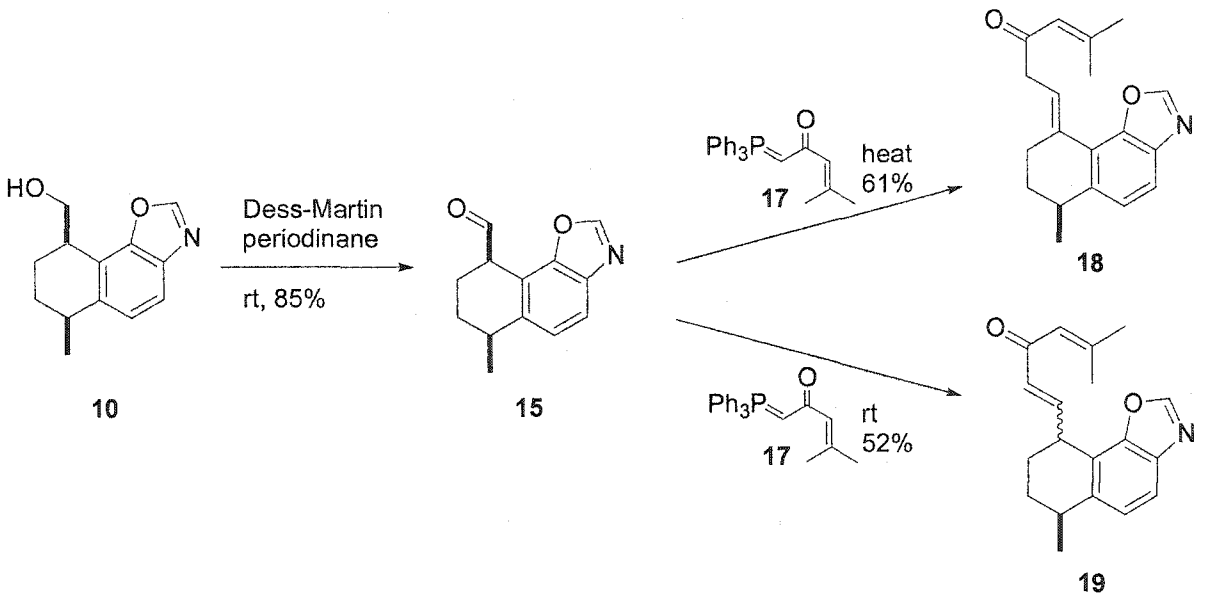
10 15



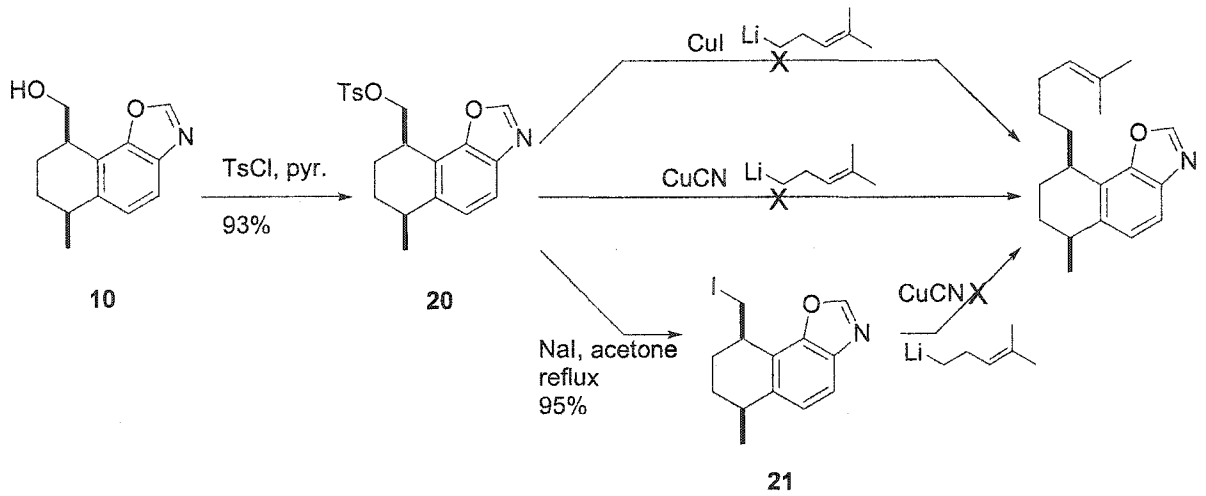
16

A different strategy was also tried to incorporate the alkyl side chain. Thus, Dess-Martin

oxidation of **10** gave aldehyde **15** which was treated with Wittig reagent **17**[11] in boiling methylene chloride to deliver **18**. This compound would be prepared from aldehyde **15** by Wittig reaction followed by the isomerization of the double bond. Conducting the Wittig reaction at room temperature to avoid double bond migration also led to a mixture of diastereomers as a consequence of epimerization.



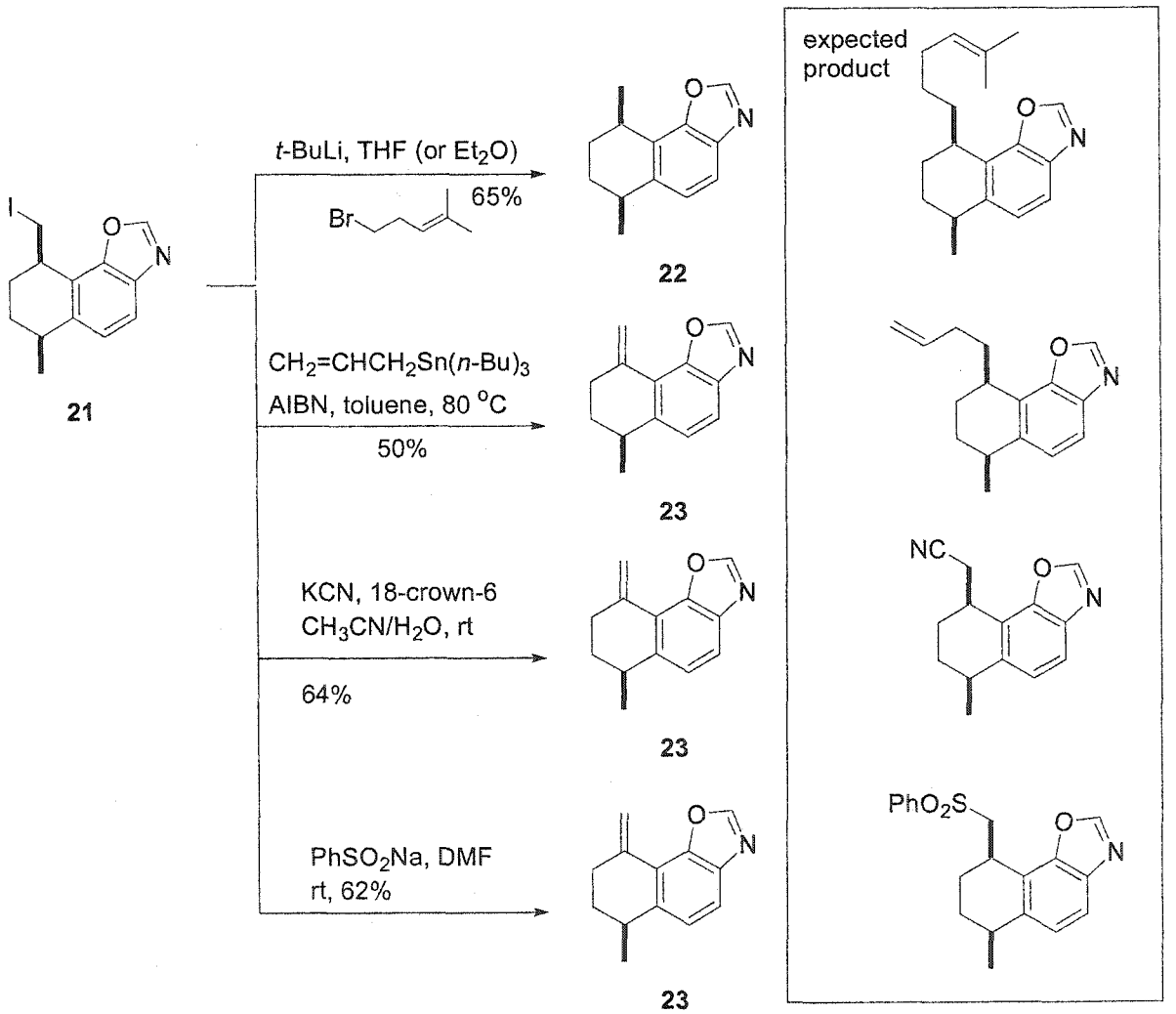
Thus, we sought to introduce the alkyl side chain by nucleophilic displacement.



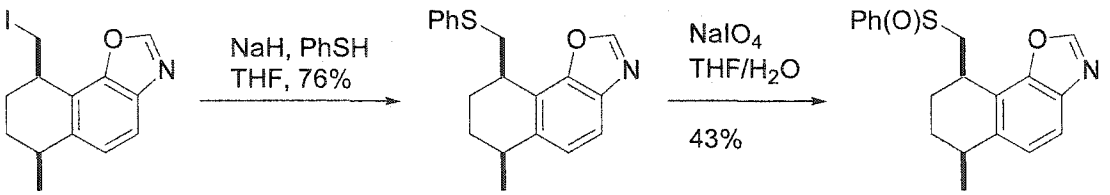
Tosylation of **10** provided **20**. However, many attempts to couple **20** with nucleophiles

under a variety of conditions were unsuccessful. Replacement of the tosyl group in **20** by iodide and the reaction of **21** with a cuprate did not afford the desired product.

Interestingly, a halogen-metal exchange of **21** followed by the addition of 4-methyl-3-pentenyl bromide gave the reduced product. Efforts to introduce the allyl,[12] cyano, or phenylsulfonyl group on the iodide position led to the same alkene product **23** presumably because of the high acidity of the benzylic hydrogen.

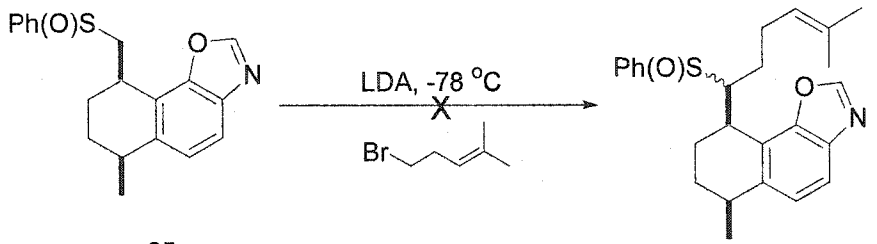


The reaction of **21** with thiophenoxide afforded sulfide **24** which was oxidized to sulfoxide **25** using $NaIO_4$.



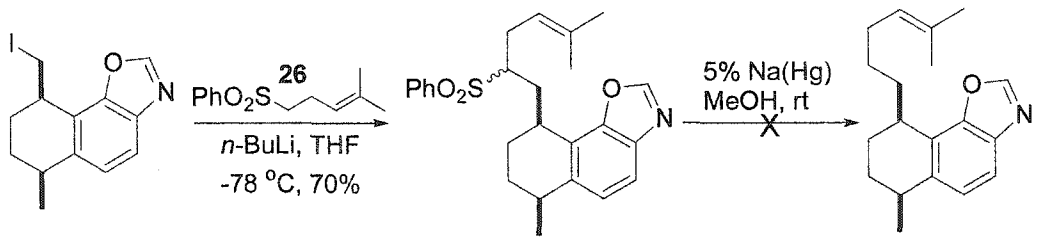
21 **24** **25**

Unfortunately, the reaction of **25** with bromide did not furnish the desired product.



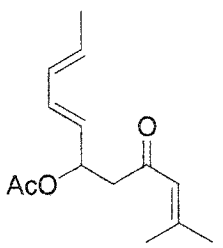
25

Finally, the reaction of lithium anion of sulfone **26** with iodide **21** at –78 °C led to a sulfone **27** as a mixture of diastereomers. However, subjection of **27** to 5% Na amalgam in MeOH provided a complex mixture.



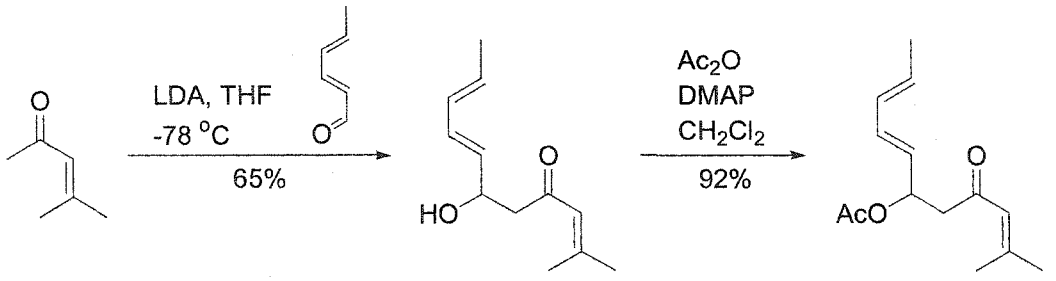
21 **27**

While we were trying to resolve this problem, we envisaged that the side chain could be introduced at the cycloaddition stage. To this end, we designed diene **28**.



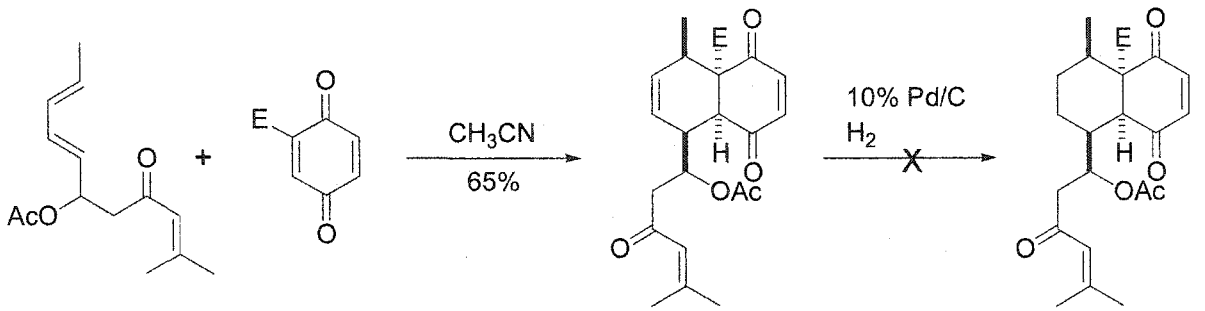
28

This diene was prepared in two steps from mesityl oxide.



29 **28**

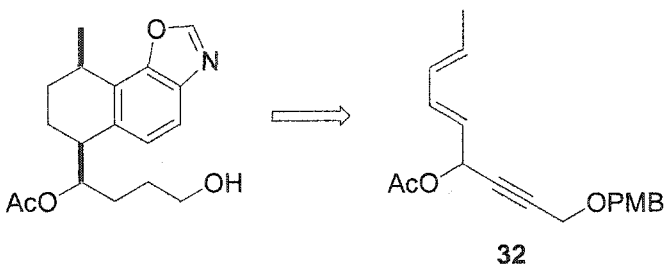
At this time, we used more reactive dienophile **30** for cycloaddition with this diene **28**.



28 **30** **31**

E = CO_2Me

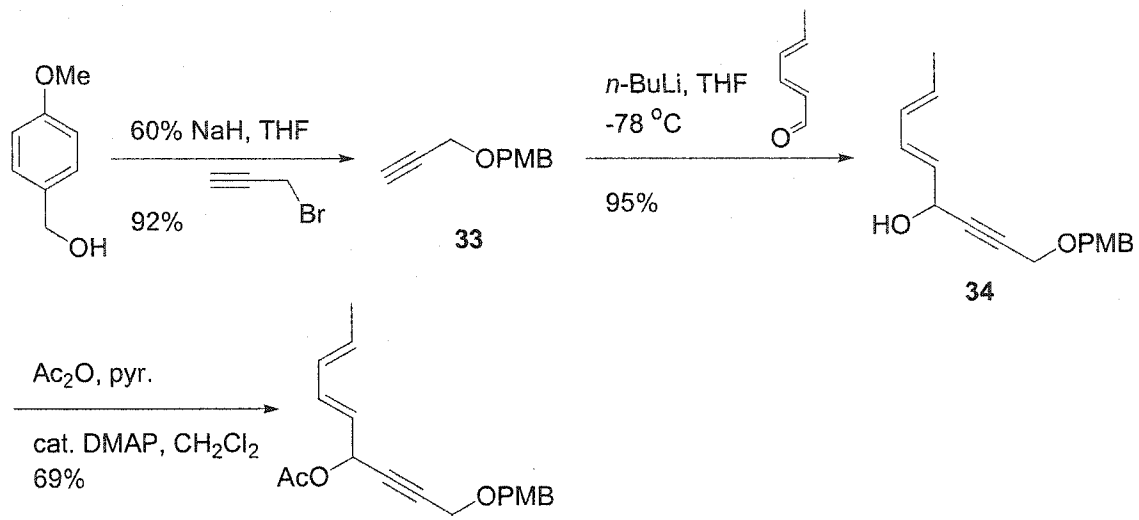
A Diels-Alder reaction of **28** and **30** gave adduct **31** in 65% yield. With the intent of reducing the unconjugated double bond selectively in the presence of double bonds conjugated to the carbonyl group, **31** was subjected to catalytic hydrogenation. However, this resulted in reduction of all of the double bonds. Next, another diene **32** bearing an alkynyl side chain was designed.



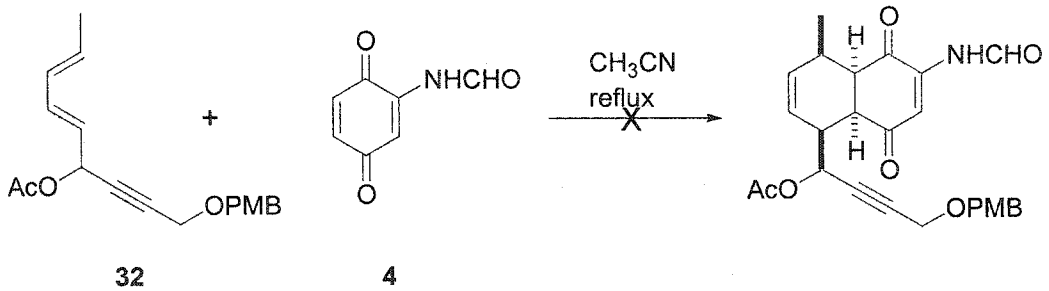
32

p-Methoxybenzyl alcohol was alkylated with propargyl bromide in the presence of NaH to give ether **33**. Nucleophilic attack of lithium acetylide to 2,4-hexadienal led to propargyl

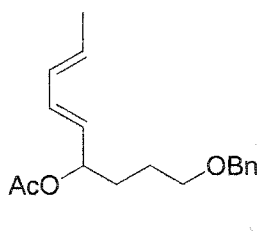
alcohol **34** in good yield. Acetylation of alcohol **34** provided diene **32**.



With this diene **32** in hand, a thermal Diels-Alder reaction was carried out. Unfortunately, the desired cycloadduct was not observed. Lewis acid catalyzed reaction destroyed the diene **32**.

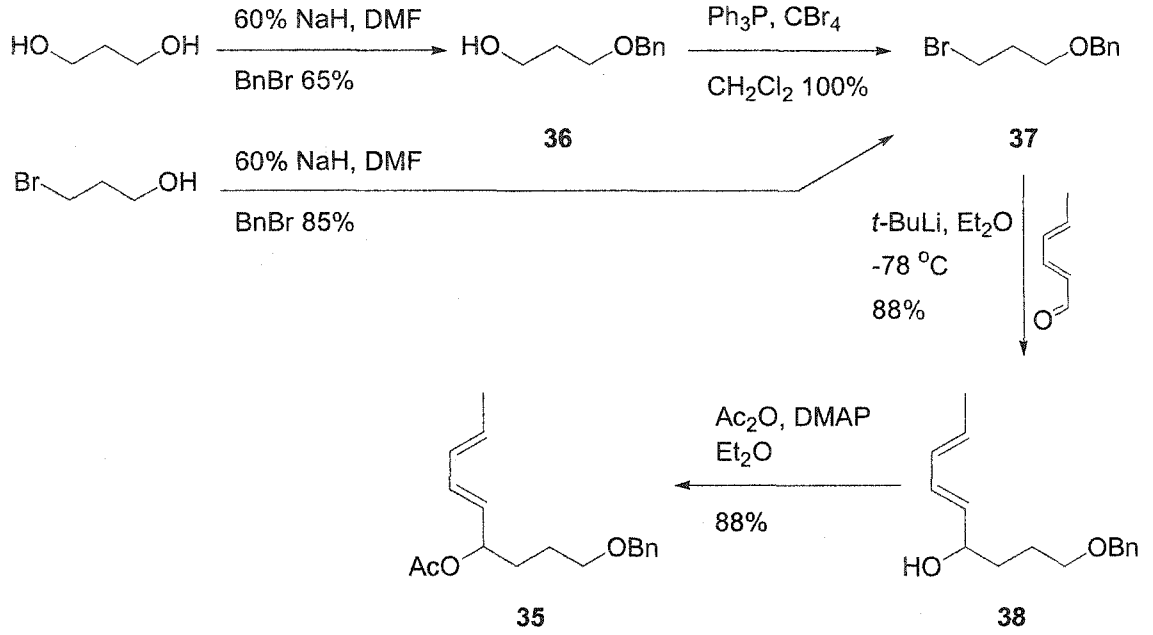


Thus, we designed the more stable diene **35**.

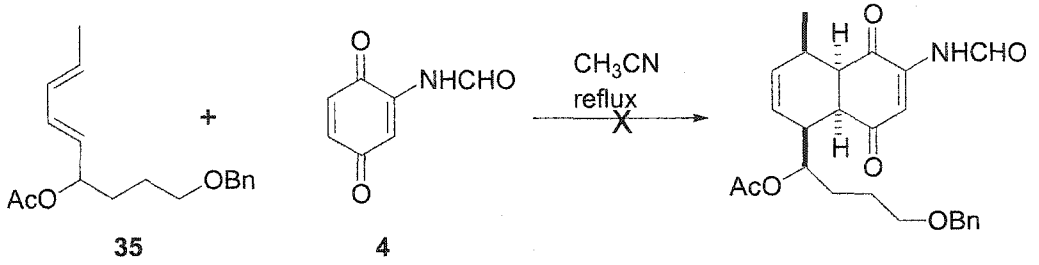


Monobenzylation of 1,3-propanediol gave alcohol **36**[13] which was transformed to the bromide **37** in good yield. Alternatively, benzyl protection of the hydroxyl group on 3-bromo-

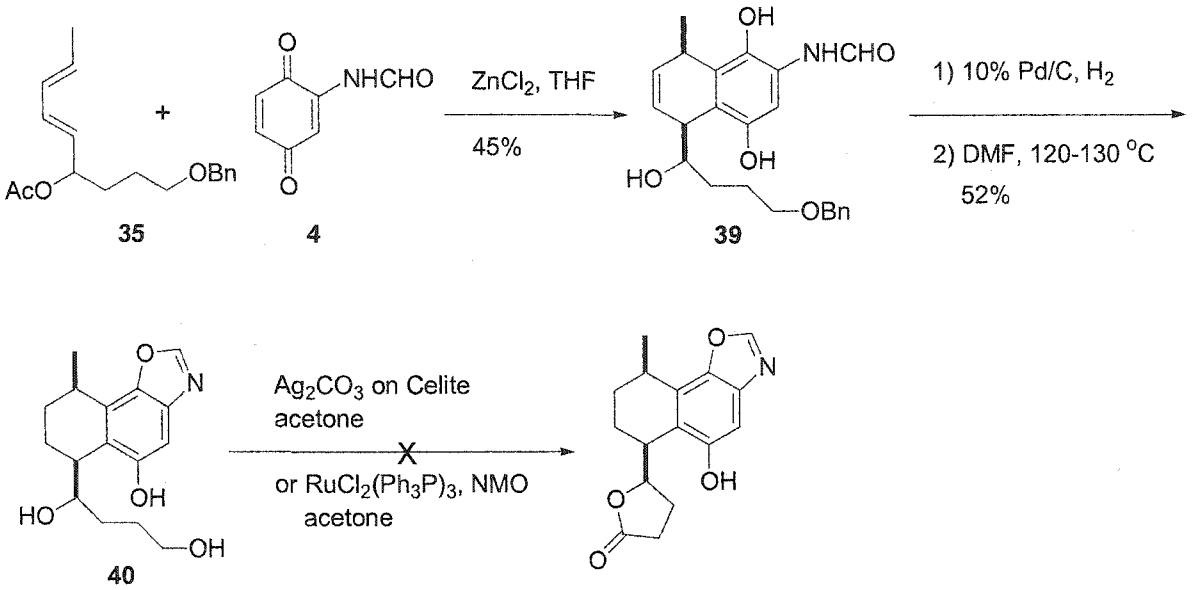
1-propanol directly led to **37**.[14] Lithium-halogen exchange of **37** followed by the addition of 2,4-hexadienal led to dienol **38** which was acetylated to provide **35**.



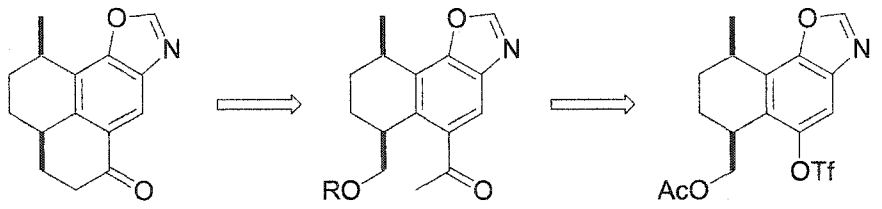
The reaction of **35** and **4** in boiling acetonitrile did not occur.



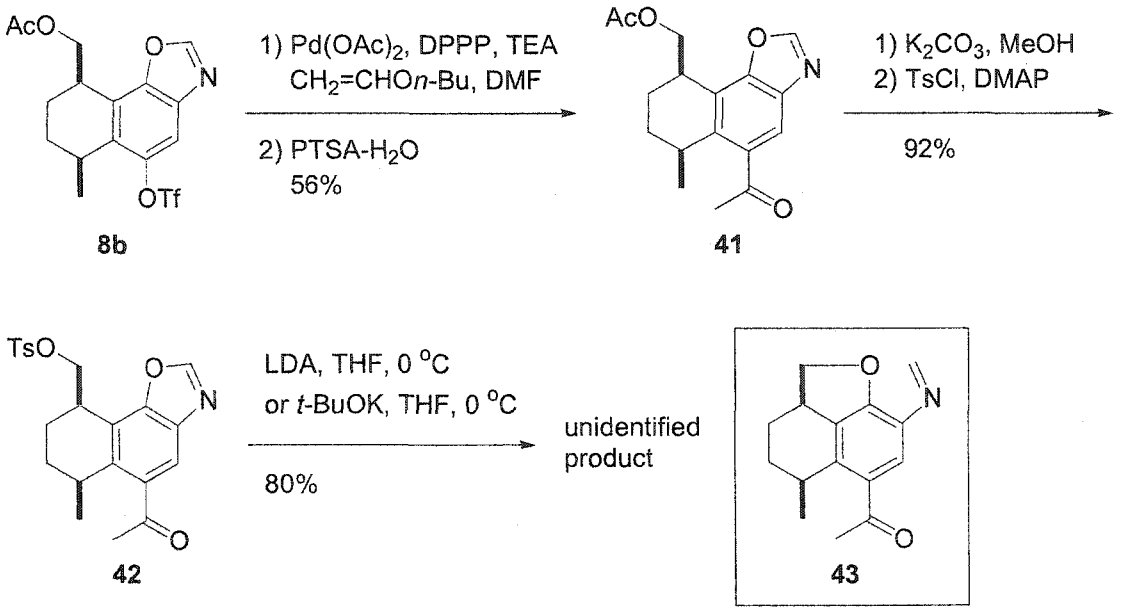
To our delight, $ZnCl_2$ facilitated the cycloaddition albeit in modest yield. The isolated cycloadduct was the triol **39** as a result of deacetylation in the reaction medium. Catalytic hydrogenation not only reduced the double bond but also cleaved the benzyl group. The resulting tetrol was heated in DMF at 120-130 °C to give benzoxazole **40**. To selectively oxidize the primary alcohol in the presence of secondary alcohol, **40** was treated with Fetizon's reagent.[15] However, it did not work. Ruthenium catalyzed oxidation[16] of **40** did not provide the desired lactone.



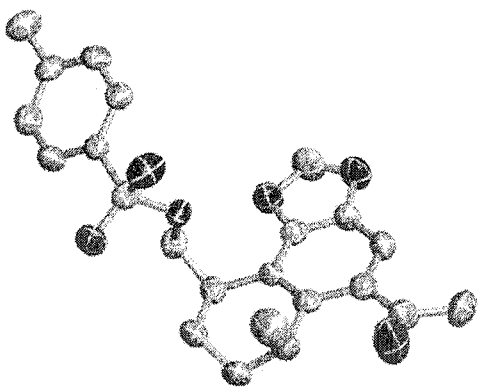
As a means to make the pseudopteroxazole system, we needed to convert triflate group in **8b** to acetyl group.



To test the feasibility of this idea, **8b** was subjected to the Cabri condition[17] followed by acid hydrolysis of the resulting enol ether to give a product with the oxazole ring opened. Acid treatment of this product in boiling benzene recyclized the opened oxazole ring to provide **41**. Methanolysis removed the acetyl group in **41** and tosylation of the resulting alcohol led to **42**. Ketone **42** was treated with LDA or *t*-BuOK in THF at 0 °C to afford a unidentified product which was later assigned as **43**.

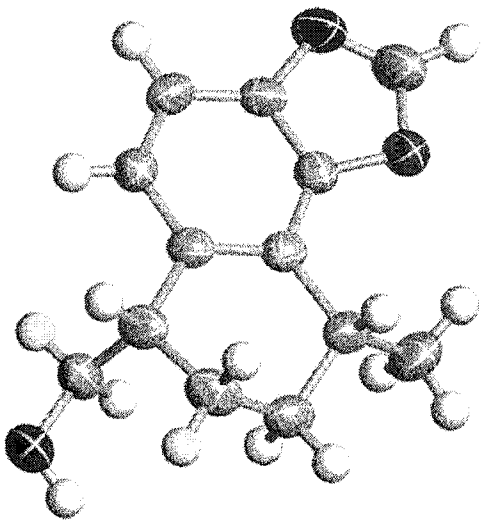


In the meantime we obtained a crystal of **42**. The crystal structure of **42** clearly showed that we chosed the wrong regioisomer from the Diels-Alder reaction.

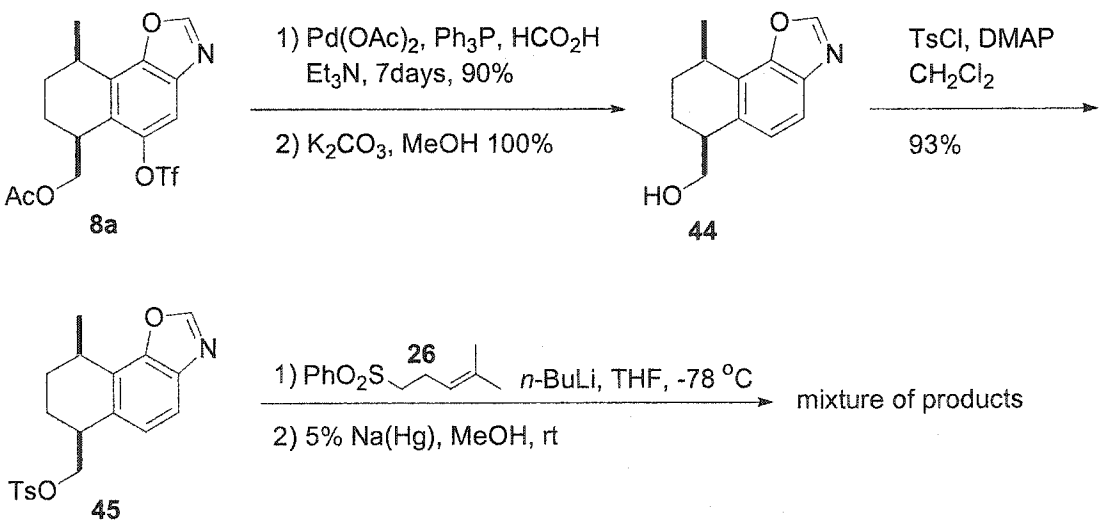


At this stage we went back to the other isomer. By following the same sequence as

described before, triflate **8a** was converted to **44**. A crystal of **44** proved the structure of **44** unambiguously.

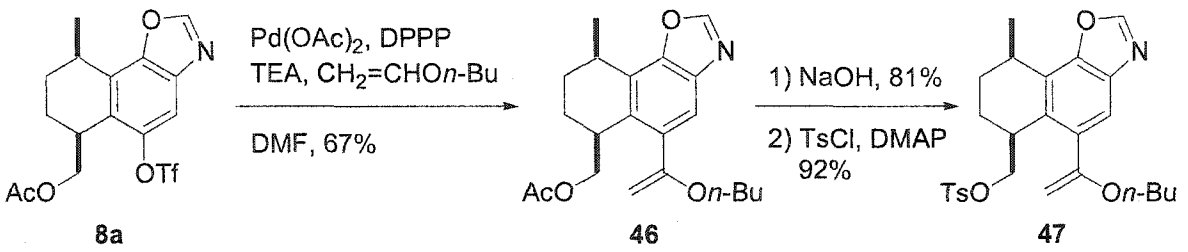


Tosylation of **44** afforded **45**. However, the reaction of **45** with the anion of sulfone **26** and subsequent treatment with Na(Hg) led to a complex mixture of products.



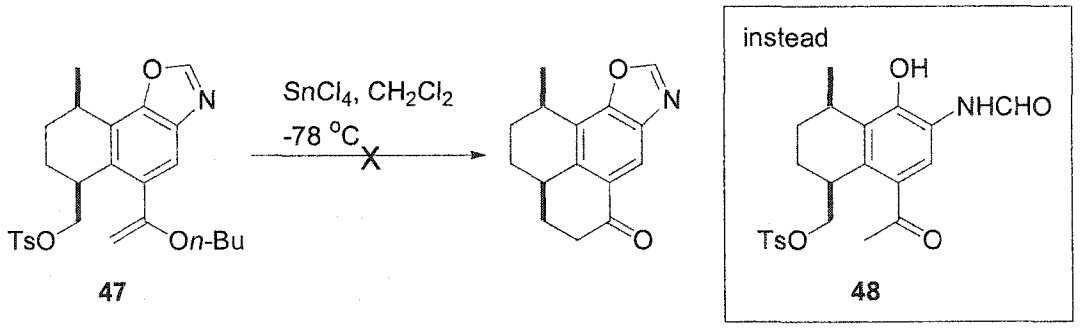
We also applied other approaches we used earlier in case of the wrong isomer **8b** to the

desired isomer **8a**. Thus, triflate **8a** was subjected to Cabri conditions to give enol ether **46**. Ester hydrolysis and subsequent tosylation of **46** provided **47**.



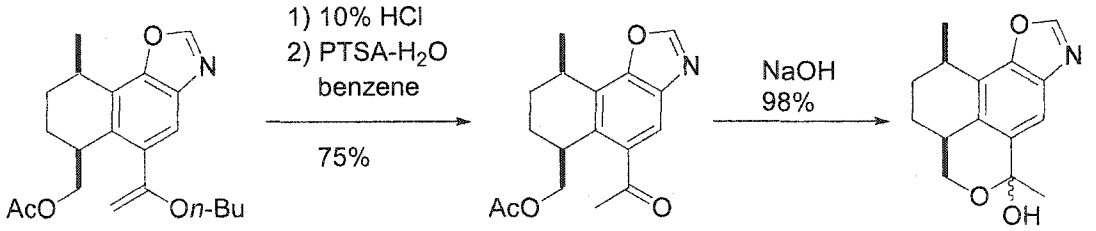
8a **46** **47**

However, exposure of **47** to $SnCl_4$ did not deliver the cyclized product.



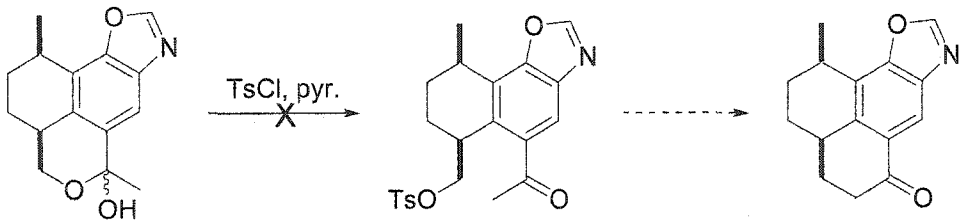
47 **48**

At this time, **46** was converted to **49**. Unmasked alcohol via hydrolysis attacked the neighboring carbonyl group to form hemiketal **50**.



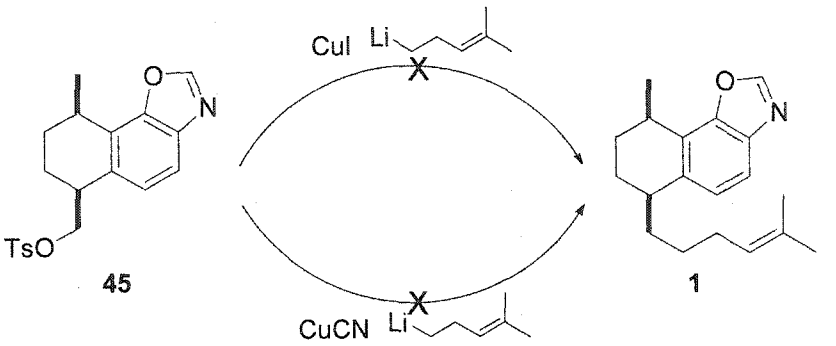
46 **49** **50**

Unfortunately, we were not able to convert **50** to the desired tosylate.

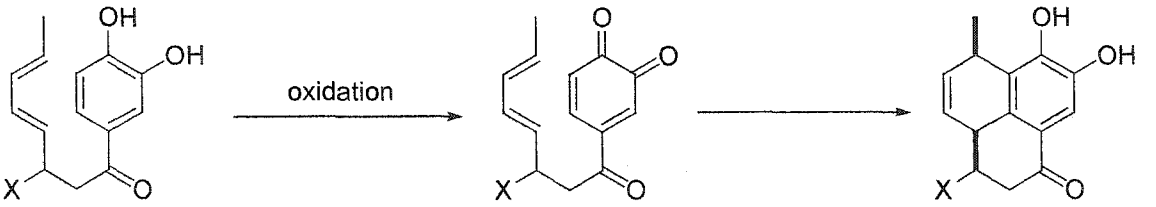


50

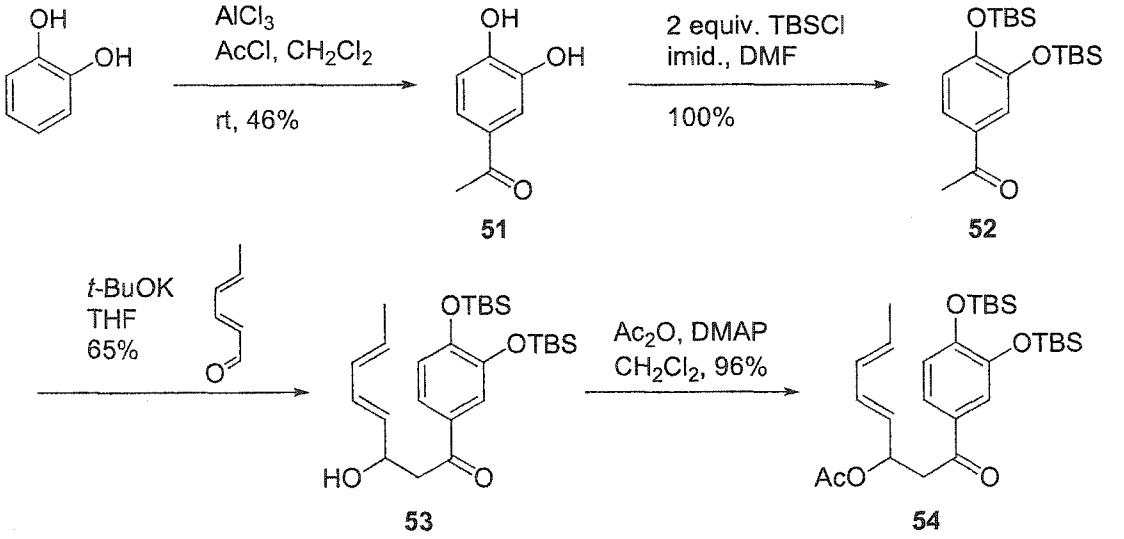
Nucleophilic substitution of tosyl group in **45** by cuprate reagents was not successful, either.



In the meantime, we tried to develop the general route to tricyclic core skeletons using a Diels-Alder cycloaddition of ortho-quinones[18] intramolecularly.

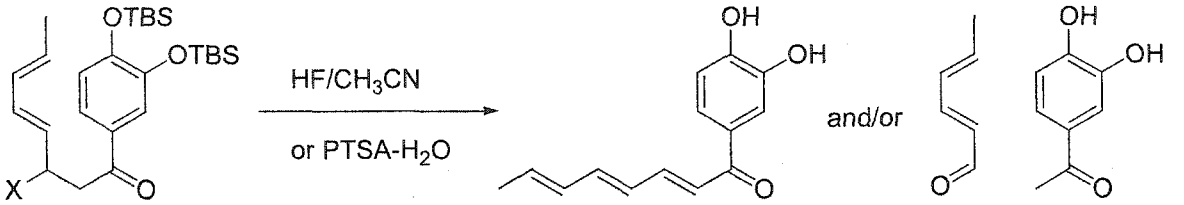


Thus, Friedel-Crafts acetylation of catechol led to **51**[19] which was silylated with TBSCl.



Ketone **52** was reacted with 2,4-hexadienal in the presence of potassium *tert*-butoxide to

give β-hydroxy ketone **53**. Protection of the alcohol in **53** as an acetate produced **54**. Deprotection of TBS groups in **53** or **54** under acidic or basic condition gave **55** or the retroaldol products.

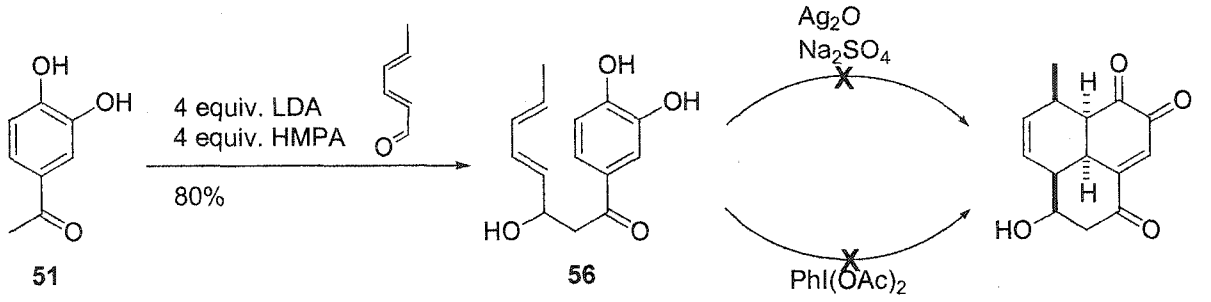


X= OH, OAc
53/54

55

51

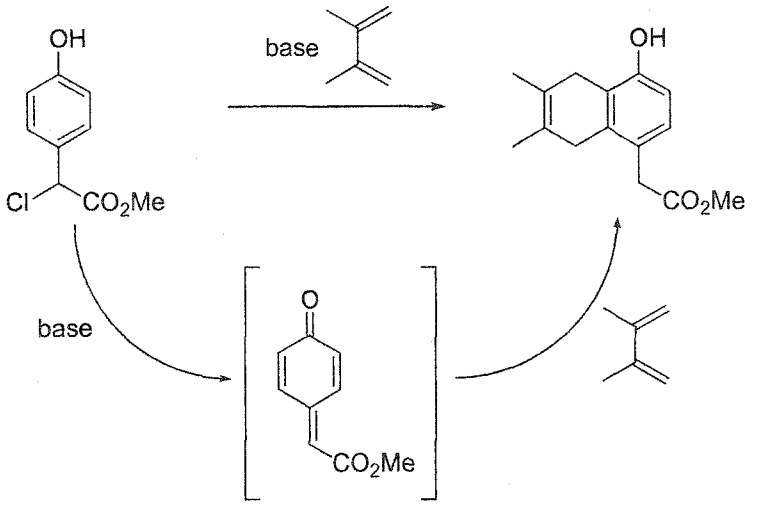
To avoid the deprotection, **51** was directly treated with 4 equivalents of LDA and 4 equivalents of HMPA and subsequent addition of aldehyde to produce **56**. However, oxidation of **56** failed to deliver the cyclized product.



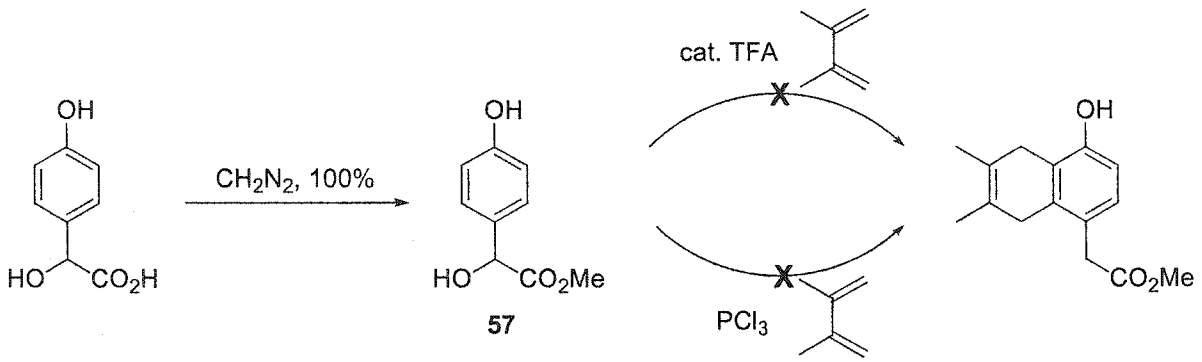
51

56

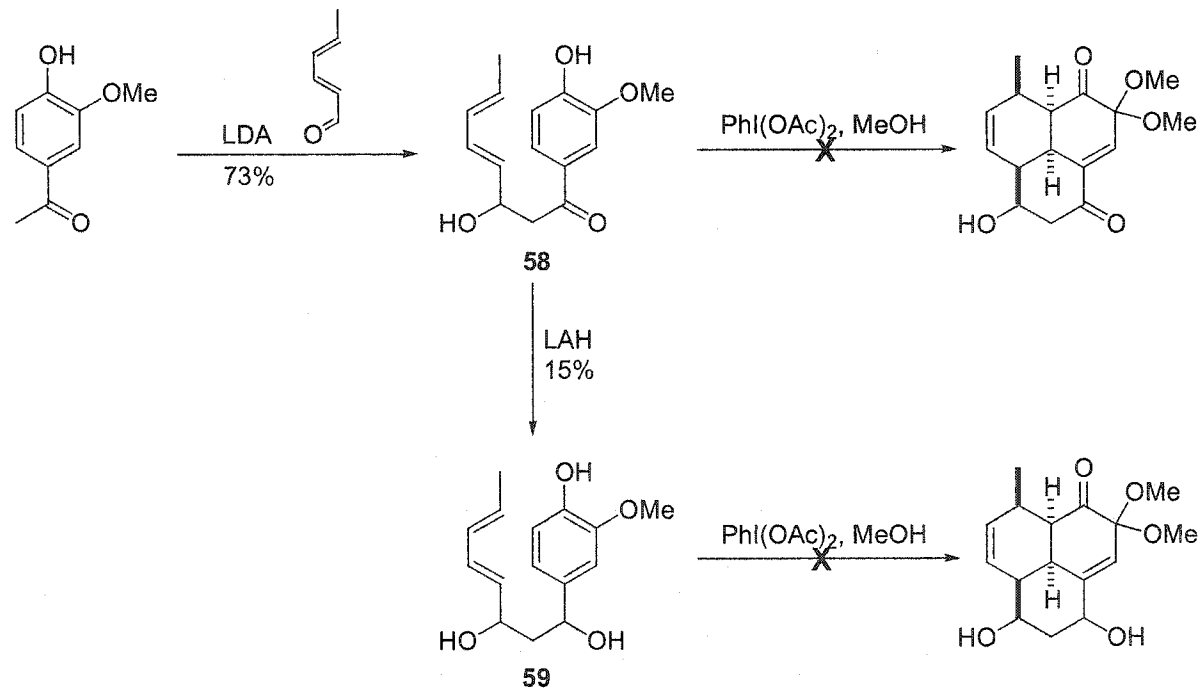
As illustrated below, we also employed quinone methide chemistry to construct the



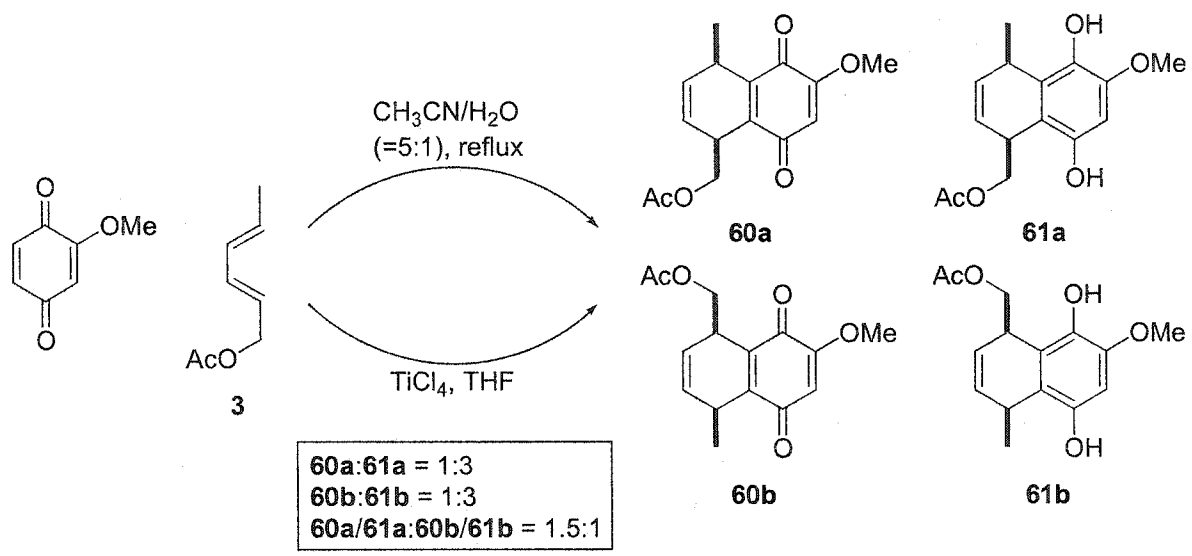
bicyclic structure. To this end, esterification of 4-hydroxymandelic acid was first carried out to give its methyl ester **57**. However, the reaction of **57** with excess diene in the presence of catalytic amount of TFA or a stoichiometric amount of PCl_3 did not give the desired product.



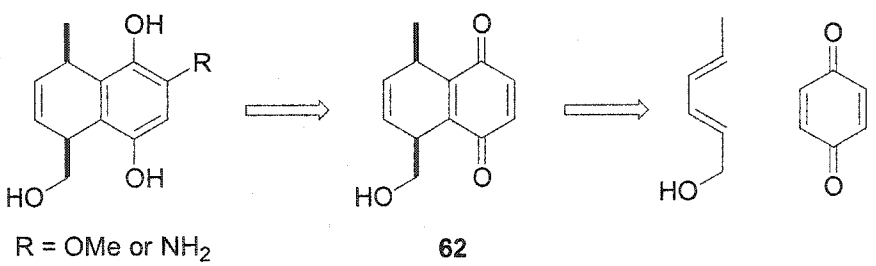
Another intramolecular Diels-Alder reaction was also examined. Thus, reaction of the enolate of acetovanillone with 2,4-hexadienal gave aldol adduct **58**. Exposure of **58** to $PhI(OAc)_2$ in MeOH[20] did not provide the expected product. LAH reduction of **58** led to triol **59** albeit in low yield. However, subjection of **59** to the same condition for **58** failed to afford the desired product, either.



At this stage, we carried out intermolecular Diels-Alder reaction of methoxy-1,4-benzoquinone with diene **3** with a view to comparing the regioselectivity of this case with the one of formamido-1,4-benzoquinone case. Disappointingly, either thermal or $TiCl_4$ catalyzed reaction resulted in about the same ratio that we obtained from the study with formamido-1,4-benzoquinone **4**.

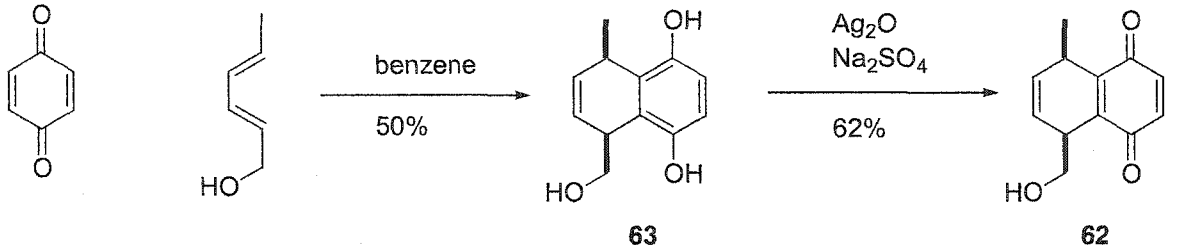


We also came up with an idea that cycloaddition of 2,4-hexadienol with simple benzoquinone would lead to adduct without any regiochemical problems and that regioselective addition of methanol or amine equivalent to the quinone after the oxidation could give the required isomer for subsequent elaboration.

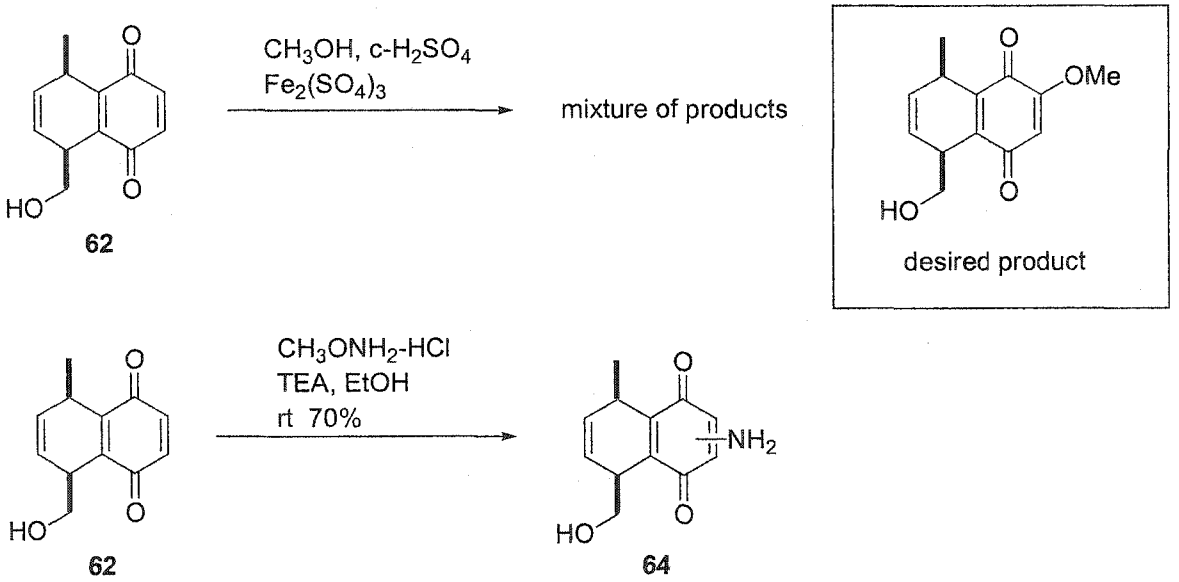


Toward this end, cycloadduct **63** was obtained by reacting the benzoquinone with 2,4-hexadienol in boiling benzene albeit in low yield. Silver oxide treatment of **63** afforded

benzoquinone **62**.



Acid catalyzed methanol addition[21] to **62** gave rise to a mixture of products. Although amino group introduction in benzoquinone moiety was realized by reaction of **62** with methoxylamine,[22] the selectivity of addition was not high.



In conclusion, a direct route to the tricyclic core skeleton of the originally proposed structures of antitubercular benzoxazole alkaloids – pseudopteroxazole and seco-pseudopteroxazole was developed employing an intermolecular Diels-Alder reaction as a key step. In an attempt to directly introduce the alkyl side chain, several dienes were also examined. In addition, two intramolecular Diels-Alder approaches were investigated to construct the core framework as well as a number of other synthetic strategies towards this

family of natural products. The research results delineated above will be useful to the synthesis of these natural products although the elaboration of the tricyclic intermediates to the final molecules and stereochemistry adjustment remain to be accomplished.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used withtout purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

(2E,4E)-Hexa-2,4-dienyl acetate (3)

To a suspension of LAH (3.95 g, 104.026 mmol) in Et_2O (200 mL) was dropwise added a solution of 2,4-hexadienal (10 g, 104.026 mmol) in Et_2O (50 mL) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was quenched with H_2O (5 mL), 1N NaOH (5 mL), and H_2O (15 mL) at 0 °C. The mixture was filtered through Celite and rinsed with Et_2O. The filtrate was evaporated in vacuo to provide alcohol (10.2 g, 100%). 300 MHz ^1H NMR ($CDCl_3$) δ 6.27-6.11 (1H, m), 6.11-5.95 (1H, m), 5.80-5.60 (2H, m), 4.18 and 4.11 (2H, d, *J* =

5.7 Hz), 1.85 (1H, br s), 1.74 (3H, d, J = 6.3 Hz).

To a solution of alcohol (10.2 g, 104.026 mmol) in CH_2Cl_2 (208 mL) were successively added pyridine (12.62 mL, 156.039 mmol), DMAP (1.27 g, 10.4 mmol), and Ac_2O (12.76 mL, 135.234 mmol) at 0 °C. After being stirred at rt overnight, the mixture was washed with 10% HCl, H_2O, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **3** (14.286 g, 98%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.24 (1H, dd, J = 15.3, 10.5 Hz), 6.12-5.97 (1H, m), 5.83-5.68 (1H, m), 5.68-5.54 (1H, m), 4.61 and 4.55 (2H, d, J = 6.6 Hz), 2.07 (3H, s), 1.76 (3H, d, J = 6.6 Hz).

N-(2,5-Dimethoxyphenyl)formamide (5)

A mixture of 96% HCO_2H (50 mL, 1.325 mol) and Ac_2O (21.56 mL, 228.48 mmol) was heated at 50-60 °C for 10 min before being cooled down to rt. Then, 2,5-dimethoxyaniline (10 g, 65.28 mmol) was added in one portion at rt. After being stirred at rt for 10 min, the mixture was concentrated in vacuo. To this residue was added cold H_2O and $NaHCO_3$ to make the mixture basic. The resulting mixture was extracted with ethyl acetate two times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **5** (11.71 g, 99%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.45 (1H, d, J = 1.8 Hz), 8.08 (1H, d, J = 3.0 Hz), 7.80 (1H, br s), 6.80 (1H, d, J = 9.0 Hz), 6.61 (1H, dd, J = 9.0, 3.0 Hz), 3.85 (3H, s), 3.78 (3H, s).

Formamido-1,4-benzoquinone (4)

To a solution of **5** (2 g, 11.04 mmol) in CH_2Cl_2 (80 mL) was added BBr_3 (4.2 mL, 44.16 mmol) at –78 °C. After the dry ice/acetone bath was removed, the mixture was stirred at rt for 40 min. After being carefully poured into cold H_2O, the mixture was extracted with ethyl acetate five or six times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give dihydroquinone. 300 MHz ^{1}H NMR (acetone-d_6) δ 9.11 (1H, br s), 8.40 (2H, br

s), 7.90 (1H, br s), 7.55 (1H, d, J = 2.7 Hz), 6.75 (1H, d, J = 8.4 Hz), 6.48 (1H, dd, J = 8.4, 2.7 Hz).

The resulting dihydroquinone (~1.43 g, 9.31 mmol)) was dissolved in ethyl acetate (40 mL) and CH_2Cl_2 (40 mL). $PhI(OAc)_2$ (3.6 g, 11.18 mmol) was added to this solution at rt. After 5 min, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was suspended in Et_2O and filtered. The yellowish solid (1.38 g, 83%) was obtained. 300 MHz ^{1}H NMR (acetone-d_6) δ 9.51 (1H, br s), 8.68 (1H, br s), 7.49 (1H, br s), 6.89 (1H, d, J = 10.2 Hz), 6.78 (1H, dd, J = 10.2, 2.4 Hz).

(1S, 4R)-6-Formylamino-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (5a), (1R, 4S)-7-Formylamino-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (5b), (1S, 4R)-6-Formylamino-5,8-dihydroxy-4-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (6a), and (1R, 4S)-7-Formylamino-5,8-dihydroxy-4-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (6b)

A mixture of **3** (3.78 g, 27 mmol) and **4** (3.4 g, 22.5 mmol) in CH_3CN (25 mL) and H_2O (5 mL) was stirred ar rt overnight. Then, it was heated to reflux for another 24 h. After being concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was used for the next step without further purification. For NMR data, the residue was purified by sgc (H:EA = 2:1 to 1:2) to give **5a/b** (~1.147 g) first and **6a/b** (~3.441 g) later. Combined yield: 70%

5a/b: 300 MHz ^{1}H NMR (acetone-d_6) δ 9.52 (1H, br s), 8.67 (1H, br s), 7.44 (1H, br s), 5.97 (1H, ddd, J = 9.9, 4.5, 0.9 Hz), 5.79 (1H, dd, J = 9.9, 4.5 Hz), 4.27 (1H, dd, J = 10.8, 4.8 Hz),

4.23-4.10 (1H, m), 3.76-3.64 (1H, m), 3.47-3.31 (1H, m), 1.95 and 1.94 (3H, s), 1.27 and 1.23 (3H, d, J = 6.9 Hz).

6a/b: 300 MHz ^{1}H NMR (acetone-d_6) δ 9.52 (1H, br s), 8.60-7.83 (3H, m), 6.86 (1H, s), 6.03 (1H, dd, J = 9.9, 4.8 Hz), 5.92 (1H, dd, J = 9.9, 4.5 Hz), 4.38 (1H, dd, J = 9.9, 3.9 Hz), 4.15-4.00 (1H, m), 4.00-3.80 (1H, m), 3.75-3.51 (1H, m), 1.98 and 1.96 (3H, s), 1.32 and 1.31 (3H, d, J = 6.6 Hz).

(6S, 9R)-5-Hydroxy-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-ylmethyl acetate (7a) and (6S, 9R)-5-Hydroxy-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-yl methyl acetate (7b)

To a solution of **5a/b** and **6a/b** (4.588 g, 15.75 mmol) in ethyl acetate was carefully added 10% Pd/C (450 mg) at rt. After being stirred under H_2 balloon pressure at rt for 9 h, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to give hydroquinone with the isolated double bond reduced. 300 MHz ^{1}H NMR (acetone-d_6) δ 9.48 (1H, br s), 8.30-8.20 (1H, m), 8.20-7.90 (2H, br s), 6.85 (1H, s), 4.48-4.33 (1H, m), 4.28-4.10 (1H, m), 3.50-3.02 (2H, m), 2.02, 2.00 (3H, s), 1.96-1.50 (4H, m), 1.29 (3H, d, J = 6.9 Hz).

The resulting crude was diluted with benzene (50 mL) and ethyl acetate (10 mL). To this mixture was added PTSA-H_2O (300 mg, 1.58 mmol). Then, it was heated to reflux overnight. After the mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to give **7a/b** (3.5 g, 82%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, s), 7.18 and 7.16 (1H, s), 4.80-4.03 (2H, m), 3.55-3.38 (1H, m), 3.38-3.02 (1H, m), 2.11 and 2.01 (3H, s), 2.15-1.52 (4H, m), 1.47 and 1.27 (3H, d, J

= 6.9 Hz).

(6S, 9R)-9-Methyl-5-trifluoromethanesulfonyloxy-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-ylmethyl acetate (8a) and (6S, 9R)-6-Methyl-5-trifluoromethanesulfonyloxy-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-ylmethyl acetate (8b)

To a solution of **7a/b** (2.4074 g, 8.873 mmol) in THF (30 mL) was added 60% NaH (461 mg, 11.53 mmol) at 0 °C. After 5 min, $PhN(Tf)_2$ (3.49 g, 9.76 mmol) was added at 0 °C in one portion. After being stirred at rt for 4 h, the mixture was quenched with H_2O at 0 °C. The mixture was extracted with ethyl acetate two times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **8a** (~1.804 g) first and **8b** (~1.203 g) later. Combined yield: 84%

8a: 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, s), 7.63 (1H, s), 4.26 (1H, dd, J = 8.4, 6.9 Hz), 4.16 (1H, dd, J = 8.1, 3.6 Hz), 3.55-3.45 (1H, m), 3.33-3.20 (1H, m), 2.15-1.95 (2H, m), 2.03 (3H, s), 1.80-1.58 (2H, m), 1.51 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.9, 154.1, 148.3, 145.1, 139.0, 129.6, 127.7, 120.8, 116.6, 112.2, 111.3, 65.2, 33.0, 29.6, 26.5, 23.4, 21.1, 20.9.

8b: 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, s), 7.61 (1H, s), 4.61 (1H, dd, J = 8.1, 2.7 Hz), 4.52 (1H, dd, J = 8.1, 4.8 Hz), 3.59-3.45 (1H, m), 3.36-3.26 (1H, m), 2.10-1.90 (2H, m), 1.96 (3H, s), 1.90-1.73 (2H, m), 1.30 (3H, d, J = 5.1 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.1, 153.5, 147.9, 145.0, 138.0, 135.1, 123.3, 122.4, 120.2, 117.0, 111.9, 66.1, 34.2, 28.0, 27.9, 20.9, 20.8, 20.6.

(6S, 9R)-6-Methyl-6,7,8,9-tetrahydro-1-oza-3-azacyclopenta[a]naphthalen-9-ylmethyl acetate (9)

To a solution of **8b** (1.272 g, 3.154 mmol) in DMF (43 mL) were added Ph_3P (41 mg, 0.158 mmol), $Pd(OAc)_2$ (14 mg, 0.063 mmol), Et_3N (1.35 mL, 9.65 mmol), and 96% HCO_2H (238 μL, 6.308 mmol) at rt. After being stirred at 70 °C under argon for 7 days, the mixture was diluted with ethyl acetate and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to afford **9** (704 mg, 87%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, s), 7.58 (1H, d, J = 8.4 Hz), 7.26 (1H, d, J = 8.4 Hz), 4.52 (1H, dd, J = 11.1, 4.5 Hz), 4.31 (1H, dd, J = 10.8, 9.3 Hz), 3.65-3.50 (1H, m), 3.10-2.90 (1H, m), 2.05 (3H, s), 2.10-1.97 (1H, m), 1.97-1.80 (2H, m), 1.75-1.68 (1H, m), 1.35 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.3, 152.2, 149.1, 141.2, 137.8, 124.9, 120.0, 118.7, 66.0, 33.6, 33.0, 28.0, 23.0, 22.8, 21.2.

(6S, 9R)-(6-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-yl)methanol (10)

To a solution of **9** (704 mg, 2.76 mmol) in MeOH (9.2 mL) was added K_2CO_3 (419 mg, 3.04 mmol) ar rt. After being stirred at rt for 3 h, the mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **10** (588 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.94 (1H, s), 7.53 (1H, d, J = 8.4 Hz), 7.25 (1H, d, J = 8.4 Hz), 4.05 (1H, dd, J = 10.8, 3.9 Hz), 3.92 (1H, dd, J = 10.5, 7.8 Hz), 3.45-3.30 (1H, m), 3.06-2.88 (1H, m), 2.58 (1H, br s), 2.27-2.05 (1H, m), 1.96-1.79 (2H, m), 1.79-1.60 (1H, m), 1.35 (3H, d, J = 7.2 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 152.0, 149.1, 141.6, 137.5, 125.0, 121.1, 118.2, 64.9, 37.1, 36.4, 33.1, 28.3, 22.9, 22.6.

1-Cyclohexyl-1-hydroxy-5-methylhex-4-en-3-one (11)

To a solution of diisopropylamine (785 μL, 5.6 mmol) in THF (17 mL) was added *n*-

BuLi (2.5 M solution in hexanes, 2.24 mL, 5.6 mmol) at –78 °C. After 15 min at –78 °C, mesityl oxide (500 mg, 5.09 mmol) was slowly added at –78 °C. After 10 min at –78 °C, cyclohexanecarboxaldehyde (555 μL, 4.58 mmol) was dropwise added at –78 °C. After being gradually warmed up to rt, the mixture was quenched with H_2O. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **11** (751 mg, 78%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.06 (1H, s), 3.89-3.73 (1H, m), 2.62 (1H, dd, J = 17.4, 2.7 Hz), 2.49 (1H, dd, J = 17.1, 9.3 Hz), 2.15 (3H, s), 1.90 (3H, s), 1.92-0.90 (11H, m).

(1E)-1-Cyclohexyl-5-methylhexa-1,4-dien-3-one (12)

A mixture of **11** (149 mg, 0.71 mmol) and PTSA-H_2O (40.5 mg, 0.21 mmol) in benzene (3 mL) was stirred at rt for 7 h. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **12** (135.6 mg, 99%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.75 (1H, dd, J = 15.9, 6.6 Hz), 6.22 (1H, s), 6.07 (1H, dd, J = 15.9, 1.5 Hz), 2.42-2.05 (1H, m), 2.14 (3H, s), 1.91 (3H, s), 1.92-1.02 (10H, m).

[(1E/Z)-3-Cyclohexyl-1-(2-methylpropenyl)but-1-enyloxy]trimethylsilane (13)

To a suspension of CuCN (53 mg, 0.59 mmol) in THF (3 mL) was added MeLi (1.4 M solution in THF, 842 μL, 1.18 mmol) at 0 °C. After 5 min, TMSCl (75 μL, 0.59 mmol) was added to this mixture at 0 °C. After 5 min, a solution of **12** (103 mg, 0.536 mmol) in THF (1 mL + 1 mL for rinse) was transferred to this mixture at 0 °C via cannula. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 50:1) to give **13** (94 mg, 65%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.72 and 5.51 (1H,

s), 4.55 and 4.40 (1H, d, J = 6.6 Hz), 2.40 and 2.05 (1H, m), 1.84 and 1.81 (3H, s), 1.76 and 1.75 (3H, s), 1.78-0.80 (11H, m), 0.92 and 0.91 (3H, d, J = 6.9 Hz), 0.18 and 0.15 (9H, s).

6-Cyclohexyl-2-methylhept-2-en-4-one (14)

To a solution of **13** (42 mg, 0.156 mmol) in THF (1 mL) was added TBAF (1 M solution in THF, 187 μL, 0.187 mmol) at rt. After 5 min, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **14** (32 mg, 98%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.04 (1H, t, J = 1.2 Hz), 2.33 (1H, dd, J = 15.0, 4.8 Hz), 2.14 (1H, dd, J = 15.0, 9.0 Hz), 2.11 (3H, s), 1.86 (3H, s), 1.95-0.82 (12H, m), 0.81 (3H, d, J = 6.9 Hz).

(6S, 9R)-6-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene-9-carbaldehyde (15)

1) from PCC oxidation:

To a solution of **10** (32.8 mg, 0.154 mmol) in CH_2Cl_2 (2 mL) were added Celite (36 mg) and PCC (36 mg, 0.169 mmol) at rt. After the mixture was stirred at rt for 1 h, more PCC (10 mg, 0.046 mmol) was added. After additional 1 h, the mixture was diluted with Et_2O, filtered through Celite, and rinsed with Et_2O. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to afford **15** (27.7 mg, 85%).

2) from Dess-Martin periodinane oxidation:

To a solution of **10** (45 mg, 0.211 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (98 mg, 0.231 mmol) at rt. After being stirred at rt for 30 min, the mixture was diluted with Et_2O. The mixture was filtered through Celite and rinsed with Et_2O. The filtrate was evaporated in vacuo to give **15** (38 mg, 85%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.83 (1H, s), 8.06 (1H, s), 7.66 (1H, d, J = 8.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 4.08-3.95 (1H, m), 3.15-2.93 (1H, m), 2.46-2.26 (1H, m), 2.26-1.76 (2H, m), 1.76-1.41 (1H, m), 1.34 (3H, d, J = 7.2 Hz).

1-Hydroxy-5-methyl-1-(6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-yl)hex-4-en-3-one (16)

To a solution of diisopropylamine (13 μL, 0.095 mmol) in THF (1 mL) was added *n*-BuLi (2.5 M solution in hexanes, 38 μL, 0.095 mmol) at –78 °C. After 15 min at –78 °C, mesityl oxide (10 μL, 0.087 mmol) was slowly added at –78 °C. After 10 min at –78 °C, a solution of **15** (16.7 mg, 0.079 mmol) in THF (1 mL) was transferred to the mixture at –78 °C via cannula. After being gradually warmed up to rt, the mixture was quenched with H_2O. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 2:1) to give **16** (14.5 mg, 59%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.26-7.15 (3H, m), 6.12-5.86 (1H, m), 5.05-4.62 (2H, m), 3.60-1.15 (17H, m).

4-Methyl-1-(triphenyl-λ^5-phosphanylidene)pent-3-en-2-one (17)

To a suspension of methyltriphenylphosphonium iodide (10 g, 24.74 mmol) in THF (60 mL) was added *n*-BuLi (2.5 M solution in hexanes, 9.9 mL, 24.74 mmol) at –78 °C. After being stirred at rt for 20 min, the mixture was recooled to –78 °C. Then, a solution of 3,3-dimethylacryloyl chloride (1.5 g, 12.65 mmol) in THF (15 mL) was added to this mixture at –78 °C via cannula. After being stirred at rt for 30 min, the mixture was quenched with H_2O. The mixture was diluted with Et_2O and washed with H_2O and brine. The aqueous layer was extracted with Et_2O two times more. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was triturated with solvent (H:EA = 10:3) and evaporated again to give the yellowish solid **17** (4.3 g, 96%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.82-7.32 (15H, m), 6.03 (1H, s), 3.74 (1H, d, J = 26.1 Hz), 2.13 (3H, s), 1.79 (3H, s).

5-Methyl-1-(6-methyl-7,8-dihydro-6H-1-oxa-3-azacyclopenta[a]naphthalen-9-

ylidene)hex-4-en-3-one (18)

A mixture of **15** (44.6 mg, 0.211 mmol) and **17** (361 mg, 1 mmol) in CH_2Cl_2 (2 mL) was heated to reflux for 5 h. The mixture was concentrated in vacuo and the residue was purified by sgc (H:EA = 10:1) to give **18** (37.9 mg, 61%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, s), 7.56 (1H, d, J = 8.1 Hz), 7.20 (1H, d, J = 8.1 Hz), 7.01 (1H, t, J = 7.2 Hz), 6.17 (1H, s), 3.44 (2H, d, J = 7.2 Hz), 3.15-3.00 (1H, m), 2.70-2.48 (2H, m), 2.18 (3H, s), 2.06-1.86 (1H, m), 1.90 (3H, s), 1.80-1.65 (1H, m), 1.30 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 198.2, 156.6, 152.2, 147.9, 141.1, 138.9, 133.1, 125.0, 123.6, 122.4, 121.0, 118.8, 44.4, 33.9, 30.0, 28.0, 23.6, 22.1, 21.1.

5-Methyl-1-(6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-yl)hexa-1,4-dien-3-one (19)

A mixture of **15** (47.3 mg, 0.224 mmol) and **17** (241 mg, 0.672 mmol) in CH_2Cl_2 (2 mL) was stirred at rt overnight. The solvent was evaporated in vacuo and the residue was purified by sgc (H:EA = 10:1) to give **19** (34.5 mg, 52%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.15-6.85 (4H, m), 6.21-5.85 (2H, m), 4.15-4.00 (1H, m), 3.20-2.93 (1H, m), 2.40-1.20 (13H, m).

(6S, 9R)-6-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-ylmethyl toluene-4-sulfonate (20)

To a solution of **10** (43 mg, 0.202 mmol) in CH_2Cl_2 (2 mL) were added pyridine (25 μL, 0.303 mmol) and TsCl (42 mg, 0.222 mmol) at 0 °C. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1) to give **20** (69 mg, 93%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, s), 7.65 (2H, d, J = 8.1

Hz), 7.55 (1H, d, J = 8.4 Hz), 7.30-7.15 (3H, m), 4.48 (1H, dd, J = 9.9, 3.9 Hz), 4.27 (1H, dd, J = 9.9, 8.7 Hz), 3.58-3.43 (1H, m), 3.00-2.85 (1H, m), 2.42 (3H, s), 2.15-2.00 (1H, m), 1.95-1.75 (2H, m), 1.64-1.45 (1H, m), 1.31 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 151.9, 144.9, 141.6, 133.0, 130.0, 129.9, 128.1, 128.0, 125.0, 119.0, 118.4, 71.3, 33.9, 32.9, 27.9, 22.7, 22.4, 21.9.

(6S, 9R)-9-Iodomethyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (21)

A mixture of **20** (296 mg, 0.806 mmol) and NaI (157 mg, 1.05 mmol) in acetone (3 mL) was heated to reflux for 4 h. After the mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to afford **21** (250 mg, 95%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, s), 7.60 (1H, d, J = 8.4 Hz), 7.22 (1H, d, J = 8.4 Hz), 3.76 (1H, dd, J = 9.6, 3.0 Hz), 3.59 (1H, dd, J = 9.6, 9.6 Hz), 3.45-3.32 (1H, m), 3.05-2.88 (1H, m), 2.22-2.05 (1H, m), 2.05-1.80 (2H, m), 1.70-1.53 (1H, m), 1.36 (3H, d, J = 7.2 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 152.1, 149.0, 140.8, 138.1, 125.2, 122.0, 119.0, 36.3, 33.3, 27.9, 25.9, 23.0, 12.3.

(6S, 9R)-6,9-Dimethyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (22)

To a solution of *t*-BuLi (1.7 M solution in pentane, 88 μL, 0.15 mmol) in THF (1 mL) was slowly added a solution of **21** (24.5 mg, 0.075 mmol) in THF (1 mL) at –78 °C. After 5 min, a solution of 5-bromo-2-methyl-2-pentene (12.2 mg, 0.075 mmol) in THF (0.5 mL) was added to this mixture at –78 °C. After being stirred at –78 °C for 10 min, the mixture was quenched with H_2O at –78 °C, diluted with ethyl acetate, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by

sgc (H:EA = 50:1) to give **22** (9.8 mg, 65%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, s), 7.54 (1H, d, J = 8.1 Hz), 7.25 (1H, d, J = 8.1 Hz), 3.40-3.25 (1H, m), 3.06-2.88 (1H, m), 2.02-1.79 (2H, m), 1.79-1.56 (2H, m), 1.43 (3H, d, J = 7.2 Hz), 1.36 (3H, d, J = 7.2 Hz).

6-Methyl-9-methylene-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (23)

1) from the reaction with allyltributyltin:

To a solution of **21** (15.7 mg, 0.048 mmol) in toluene (2 mL) were added allyltributyltin (30 μL, 0.096 mmol) and AIBN (1.2 mg, 0.007 mmol) at rt. After being heated at 80 °C overnight, the mixture was evaporated in vacuo and the residue was purified by sgc (H:EA = 10:1) to afford **23** (4.8 mg, 50%).

2) from the reaction with KCN:

To a solution of **21** (57 mg, 0.174 mmol) in CH_3CN (1 mL) and H_2O (1 mL) were added KCN (23 mg, 0.348 mmol) and 18-crown-6 (5 mg, 0.017 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **23** (22 mg, 64%).

3) from the reaction with $PhSO_2Na$:

A mixture of **21** (85 mg, 0.26 mmol) and $PhSO_2Na$ (85 mg, 0.52 mmol) in DMF (1 mL) was stirred at rt overnight. The mixture was diluted with ethyl acetate and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **23** (32 mg, 62%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, s), 7.61 (1H, d, J = 8.1 Hz), 7.25 (1H, d, J = 8.1 Hz), 6.17 (1H, s), 5.37 (1H, s), 3.22-3.05 (1H, m), 2.80-2.64 (1H, m), 2.60-2.46 (1H, m), 2.14-1.96 (1H, m), 1.82-1.66 (1H, m), 1.35 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 152.3, 148.1, 141.2,

139.2, 138.7, 125.5, 120.1, 119.5, 114.6, 33.6, 31.1, 30.0, 23.0.

(6S, 9R)-6-Methyl-9-phenylthiomethyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (24)

To a solution of PhSH (96 μL, 0.935 mmol) in THF (2 mL) was added 60% NaH (37 mg, 0.935 mmol) at 0 °C. After 10 min, a solution of **21** (61 mg, 0.187 mmol) in THF (1 mL) was added to this mixture at 0 °C. After being stirred at rt for 30 min, the mixture was quenched with saturated NH_4Cl, diluted with ethyl acetate, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **24** (45 mg, 76%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.01 (1H, s), 7.58 (1H, d, J = 8.1 Hz), 7.49-7.37 (2H, m), 7.37-7.11 (4H, m), 3.67 (1H, dd, J = 12.9, 3.0 Hz), 3.55-3.40 (1H, m), 3.12 (1H, dd, J = 12.9, 10.5 Hz), 3.06-2.89 (1H, m), 2.35-2.18 (1H, m), 1.99-1.80 (2H, m), 1.73-1.57 (1H, m), 1.39 (3H, d, J = 6.9 Hz).

(6S, 9R)-9-Benzenesulfinylmethyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (25)

To a solution of **24** (45 mg, 0.146 mmol) in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (62 mg, 0.292 mmol) at rt. After 4 h at rt, more $NaIO_4$ (62 mg, 0.292 mmol) was added and stirred at rt for another 5 h. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to give **25** (20 mg, 43%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.06-7.21 (8H, m), 3.99-2.88 (4H, m), 2.40-1.50 (4H, m), 1.40 and 1.36 (3H, d, J = 6.9 Hz).

(4-Methyl-3-pentenyl)phenylsulfone (26)

A mixture of 5-bromo-2-methyl-2-pentene (1.7 g, 10.4 mmol) and $PhSO_2Na$ (2.05 g,

12.48 mmol) in DMF (10 mL) was stirred at rt overnight. Then, the mixture was diluted with ethyl acetate and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give **26** (1.4 g, 60%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.96-7.85 (2H, m), 7.70-7.60 (1H, m), 7.60-7.50 (2H, m), 4.95 (1H, t, J = 7.2 Hz), 3.14-3.01 (2H, m), 2.38 (2H, q, J = 7.5 Hz), 1.61 (3H, s), 1.53 (3H, s).

9-(2-Benzenesulfonyl-5-methylhex-4-enyl)-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (27)

To a solution of **26** (101 mg, 0.45 mmol) in THF (1 mL) was added *n*-BuLi (2.5 M solution in hexanes, 150 μL, 0.375 mmol) at –78 °C. After 10 min, a solution of **21** (49 mg, 0.15 mmol) in THF (1 mL) was dropwise added to this mixture at –78 °C. After being stirred at –78 °C for 20 min, the mixture was quenched with H_2O, diluted with ethyl acetate, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 2:1) to give **27** (44 mg, 70%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.10-6.72 (8H, m), 5.10-4.70 (1H, m), 3.40-1.10 (20H, m).

6-Hydroxy-2-methylundeca-2,7,9-trien-4-one (29)

To a solution of diisopropylamine (1.57 mL, 11.2 mmol) in THF (30 mL) was slowly added *n*-BuLi (2.5 M solution in hexanes, 4.48 mL, 11.2 mmol) at -78 °C. After 20 min, mesityl oxide (1 g, 10.188 mmol) was dropwise added to this mixture at -78 °C. After 20 min, a solution of 2,4-hexadienal (1.124 mL, 10.188 mmol) in THF (4 mL) was slowly added to this mixture at -78 °C. After being slowly warmed up to -40 ~ -50 °C, the mixture was quenched with AcOH (642 μL, 11.2 mmol) in THF (3 mL). The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and

evaporated in vacuo. The residue was purified by sgc (H:EA = 6:1) to give **29** (1.29 g, 65%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.23 (1H, dd, J = 15.3, 10.5 Hz), 6.10-5.92 (2H, m), 5.79 (1H, dd, J = 15.0, 6.9 Hz), 5.55 (1H, dd, J = 15.3, 6.9 Hz), 4.67-4.52 (1H, m), 3.36 (1H, br s), 2.74-2.55 (2H, m), 2.15 (3H, s), 1.89 (3H, s), 1.73 (3H, d, J = 6.6 Hz).

1-(4-Methyl-2-oxopent-3-enyl)hexa-2,4-dienyl acetate (28)

To a solution of **29** (1.1864 g, 6.11 mmol) in CH_2Cl_2 (12 mL) were added DMAP (1.12 g, 9.165 mmol) and Ac_2O (691 μL, 7.332 mmol) at 0 °C. After being stirred at rt for 4 h, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give **28** (1.324 g, 92%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.23 (1H, dd, J = 15.3, 10.5 Hz), 6.09-5.90 (2H, m), 5.80-5.61 (2H, m), 5.50 (1H, dd, J = 15.3, 6.9 Hz), 2.81 (1H, dd, J = 15.6, 7.8 Hz), 2.63 (1H, dd, J = 15.6, 5.7 Hz), 2.11 (3H, s), 2.00 (3H, s), 1.88 (3H, s), 1.73 (3H, d, J = 6.6 Hz).

Methoxycarbonyl-1,4-benzoquinone (30)

A mixture of 2,5-dihydroxybenzoic acid (5.24 g, 34 mmol) and c-H_2SO_4 (0.5 mL) in MeOH (100 mL) was heated to reflux overnight with the occasional removal of H_2O and MeOH (Dean-Stark trap was used). After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give methyl ester (5.72 g, 100%) as a white solid. 300 MHz ^{1}H NMR ($CDCl_3$) δ 10.3 (1H, s), 7.27 (1H, d, J = 3.3 Hz), 7.01 (1H, dd, J = 8.7, 3.3 Hz), 6.88 (1H, d, J = 8.7 Hz), 4.52 (2H, br s), 3.93 (3H, s).

To a solution of dihydroquinone (3.1 g, 18.44 mmol) in benzene (184 mL) were added

Na_2SO_4 (5.5 g, 38.72 mmol) and Ag_2O (8.55 g, 36.88 mmol) at rt. The reaction flask was covered with aluminum foil. After being stirred at rt overnight, the mixture was filtered through Celite, rinsed with ethyl acetate, and the filtrate was evaporated in vacuo to give benzoquinone **30** (3.06 g, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.07 (1H, s), 6.80 (2H, s), 3.87 (3H, s).

Methyl 1-(1-acetoxy-5-methyl-3-oxohex-4-enyl)-4,8a-dimethyl-5,8-dioxo-1,3,4,5,8,8a-hexahydro-2H-naphthalene-4a-carboxylate (31)

A mixture of **28** (273 mg, 1.156 mmol) and **30** (160 mg, 0.963 mmol) in CH_3CN (3.2 mL) was heated to reflux overnight. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 3:1 to 1:1) to give **31** (252 mg, 65%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.79 (1H, d, J = 10.5 Hz), 6.65 (1H, d, J = 10.5 Hz), 6.11 (1H, s), 5.80-5.51 (3H, m), 4.05 (1H, d, J = 4.8 Hz), 3.80 (3H, s), 3.35-3.20 (1H, m), 3.01 (1H, dd, J = 15.6, 3.9 Hz), 2.67 (1H, dd, J = 15.6, 7.2 Hz), 2.47-2.32 (1H, m), 2.13 (3H, s), 1.95 (3H, s), 1.90 (3H, s), 0.88 (3H, d, J = 6.9 Hz).

(4-Methoxybenzyl)propargylether (33)

To a suspension of 60% NaH (1,74 g, 43.44 mmol) in THF (70 mL) was slowly added a solution of *p*-methoxybenzyl alcohol (5 g, 36.2 mmol) in THF (5 mL) at 0 °C. After being stirred at for 30 min, the mixture was recooled down to 0 °C. Then, a solution of propargyl bromide (80% in toluene, 4.84 mL, 43.44 mmol) in THF (5 mL) was added to this mixture at 0 °C. After being stirred at rt for 4 h, the mixture was quenched with saturated NH_4Cl. After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1) to afford **33** (5.85 g, 92%). 300 MHz ^{1}H NMR

($CDCl_3$) δ 7.29 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 4.55 (2H, s), 4.14 (2H, d, J = 2.4 Hz), 3.81 (3H, s), 2.46 (1H, t, J = 2.4 Hz).

1-(4-Methoxybenzyloxy)nona-5,7-dien-2-yn-4-ol (34)

To a solution of **33** (4.584 g, 26.05 mmol) in THF (56 mL) was slowly added *n*-BuLi (2.5 M solution in hexanes, 10.4 mL, 26.05 mmol) at -78 °C. After 10 min, a solution of 2,4-hexadienal (2.9 mL, 26.05 mmol) in THF (10 mL) was added to this mixture at -78 °C. After being stirred at -78 °C for 10 min, the mixture was quenched with saturated NH_4Cl. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 5:1 to 2:1) to provide **34** (6.735 g, 95%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.28 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 6.37 (1H, dd, J = 15.3, 10.5 Hz), 6.06 (1H, dd, J = 15.3, 10.5 Hz), 5.87-5.72 (1H, m), 5.65 (1H, dd, J = 15.3, 6.9 Hz), 4.96 (1H, t, J = 6.9 Hz), 4.53 (2H, s), 4.20 (2H, d, J = 1.8 Hz), 3.80 (3H, s), 2.00 (1H, d, J = 6.9 Hz), 1.77 (3H, d, J = 6.9 Hz).

1-[3-(4-Methoxybenzyloxy)prop-1-ynyl]hexa-2,4-dienyl acetate (32)

To a solution of **34** (1.325 g, 4.87 mmol) in CH_2Cl_2 (9.7 mL) were added pyridine (591 μL, 7.31 mmol), DMAP (59 mg, 0.49 mmol), and Ac_2O (597 μL, 6.33 mmol) at 0 °C. After being stirred at rt for 5 h, the mixture was diluted with CH_2Cl_2 and washed with 10% HCl, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give **32** (1.056 g, 69%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.28 (2H, d, J = 8.7 Hz), 6.87 (2H, d, J = 8.7 Hz), 6.46 (1H, dd, J = 15.3, 10.5 Hz), 6.06 (1H, dd, J = 15.3, 10.6 Hz), 5.96 (1H, d, J = 6.9 Hz), 5.90-5.73 (1H, m), 5.60 (1H, dd, J = 15.3, 6.9 Hz), 4.53 (2H, s), 4.19 (2H, d, J = 1.8 Hz), 3.80 (3H, s), 2.09 (3H, s), 1.78 (3H, d, J = 6.9 Hz).

3-Benzyloxypropan-1-ol (36)

To a solution of 1,3-propanediol (1 g, 13.14 mmol) in DMF (20 mL) was added 60% NaH (631 mg, 15.77 mmol) at 0 °C. After being stirred at rt for 30 min, a solution of benzyl bromide (1.41 mL, 11.83 mmol) in DMF (5 mL) was slowly added to this mixture at 0 °C. After being stirred at rt overnight, the mixture was quenched with H_2O, diluted with ethyl acetate, and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **36** (1.276 g, 65%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.23 (5H, m), 4.53 (2H, s), 3.79 (2H, t, J = 5.7 Hz), 3.67 (2H, t, J = 5.7 Hz), 2.23 (1H, br s), 1.95-1.81 (2H, m).

3-Benzyloxypropyl bromide (37)

1) from **36**:

To a solution of **36** (980 mg, 5.9 mmol) in CH_2Cl_2 (12 mL) were added Ph_3P (1.7 g, 6.49 mmol) and CBr_4 (2.15 g, 6.49 mmol) at 0 °C. After being stirred at rt for 10 min, the solvent was evaporated in vacuo and the residue was purified by sgc (H:EA = 20:1) to give **37** (1.35 g, 100%).

2) from 3-bromo-1-propanol:

To a vigorously stirred mixture of 60% NaH (3.72 g, 92.88 mmol) and benzyl bromide (8.6 mL, 72 mmol) in DMF (304 mL) was dropwise added 3-bromo-1-propanol (10 g, 72 mmol) at -78 °C over 30 min. Then, dry ice/acetone bath was removed and the mixture was stirred at rt overnight. The mixture was quenched with H_2O, diluted with *n*-hexane, and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give **37** (14.015 g, 85%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.43-7.23 (5H, m), 4.53 (2H, s), 3.61 (2H, t, J = 5.7 Hz), 3.54 (2H, t, J = 5.7 Hz), 2.23-2.10 (2H, m).

1-Benzyloxynona-5,7-dien-4-ol (38)

To a solution of **37** (522 mg, 2.28 mmol) in Et_2O (12 mL) was slowly added *t*-BuLi (1.7 M solution in pentane, 2.7 mL, 4.56 mmol) at -78 °C. After 20 min, a solution of 2,4-hexadienal (252 μL, 2.28 mmol) in Et_2O (9 mL) was slowly added to this mixture at -78 °C. After being stirred at –78 °C for 15 min, the mixture was quenched with saturated NH_4Cl at -78 °C. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give **38** (492 mg, 88%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.45-7.23 (5H, m), 6.17 (1H, dd, J = 15.6, 10.5 Hz), 6.02 (1H, dd, J = 15.6, 10.5 Hz), 5.77-5.62 (1H, m), 5.56 (1H, dd, J = 15.0, 6.6 Hz), 4.51 (2H, s), 4.14 (1H, q, J = 6.3 Hz), 3.60-3.43 (2H, m), 2.18 (1H, br s), 1.75 (3H, d, J = 6.6 Hz), 1.80-1.50 (4H, m).

1-(3-Benzyloxypropyl)hexa-2,4-dienyl acetate (35)

To a solution of **38** (492 mg, 2 mmol) in Et_2O were added DMAP (269 mg, 2.2 mmol) and Ac_2O (208 μL, 2.2 mmol) at rt. After being stirred at rt for 10 min, the mixture was diluted with ethyl acetate and washed with 10% HCl, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **35** (508 mg, 88%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.23 (5H, m), 6.20 (1H, dd, J = 15.6, 10.5 Hz), 6.00 (1H, dd, J = 15.6, 10.5 Hz), 5.81-5.64 (1H, m), 5.45 (1H, dd, J = 15.0, 6.6 Hz), 5.25 (1H, q, J = 6.3 Hz), 4.49 (2H, s), 3.47 (2H, t, J = 6.3 Hz), 2.03 (3H, s), 1.75 (3H, d, J = 6.9 Hz), 1.80-1.51 (4H, m).

N-[5-(4-Benzyloxy-1-hydroxybutyl)-1,4-dihydroxy-8-methyl-5,6,7,8-tetrahydronaphthalen-2-yl]formamide (39)

To a solution of **4** (500 mg, 3.31 mmol) in THF (10 mL) was added $ZnCl_2$ (496 mg, 3.64

mmol) at 0 °C. After being stirred at 0 °C for 30 min, a solution of **35** (1.14 g, 3.97 mmol) in THF (2 mL + 2 mL for rinse) was added to this mixture at 0 °C. After the mixture was stirred at rt for 4 days, more $ZnCl_2$ (496 mg, 3.64 mmol) was added to this mixture at rt and the mixture was stirred at rt for another 7 days. After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give **39** (592 mg, 45%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.59 (1H, br s), 8.12 (1H, br s), 7.53 (1H, br s), 7.42-7.20 (5H, m), 6.58-6.50 (1H, m), 6.15-5.90 (2H, m), 5.71-5.31 (2H, m), 4.55-4.42 (2H, m), 3.78-3.35 (2H, m), 2.25-2.06 (1H, m), 1.80-1.40 (4H, m), 1.24 (3H, d, J = 6.9 Hz).

1-(5-Hydroxy-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-yl)butane-1,4-diol (40)

To a solution of **39** (145 mg, 0.365 mmol) in ethyl acetate (5 mL) was carefully added 10% Pd/C (39 mg) at rt. After being stirred under H_2 balloon pressure at rt overnight, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to give debenzylated product with the double bond reduced (113 mg, 100%). 300 MHz ^{1}H NMR (acetone-d_6) d 9.08 (1H, br s), 8.33 (2H, br s), 7.80 (1H, br s), 7.43 (1H, s), 6.80-6.62 (1H, m), 3.80-3.40 (3H, m), 3.23-2.95 (2H, m), 1.90-0.70 (11H, m).

A solution of reduced product (101 mg, 0.327 mmol) in DMF (2 mL) was heated at 120 ~ 130 °C overnight. After the solvent was removed by evaporation, the residue was purified by sgc (H:EA = 2:1) to give **40** (49 mg, 52%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.59 (1H, br s), 8.35 (1H, br s), 7.53 (1H, br s), 6.60-6.45 (1H, m), 3.75-3.50 (3H, m), 3.03-2.80 (2H, m), 1.95-0.70 (11H, m).

5-Acetyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-ylmethyl acetate (41)

To a solution of **8b** (341 mg, 0.845 mmol) in DMF (2.3 mL) were added Et_3N (236 μL, 1.69 mmol), *n*-butyl vinyl ether (547 μL, 4.23 mmol), DPPP (19 mg, 0.046 mmol), and $Pd(OAc)_2$ (9.5 mg, 0.042 mmol) at rt. After being purged with argon for 5 min, the mixture was stirred at 80 °C for 6 h. After the mixture was cooled down to 0 °C, 10% HCl (3.5 mL) was added at 0 °C. After being stirred at rt for 30 min, the mixture was diluted with ethyl acetate and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was diluted in benzene (10 mL). PTSA-H_2O (16 mg, 0.08 mmol) was added and the mixture was heated to reflux for 6 h. After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give **41** (142 mg, 56%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, s), 7.86 (1H, s), 4.56 (1H, dd, J = 10.8, 3.9 Hz), 4.44 (1H, dd, J = 10.8, 7.2 Hz), 3.77-3.64 (1H, m), 3.64-3.50 (1H, m), 2.62 (3H, s), 1.98 (3H, s), 2.06-1.90 (2H, m), 1.85-1.68 (2H, m), 1.22 (3H, d, J = 6.9 Hz).

5-Acetyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-ylmethyl toluene-4-sulfonate (42)

To a solution of **41** (68 mg, 0.226 mmol) in MeOH (2 mL) was added K_2CO_3 (34 mg, 0.249 mmol) at rt. After being stirred at rt for 1 h, the mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give alcohol (58.4 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.75 (1H, s), 4.10 (1H, dd, J = 11.1, 6.6 Hz), 4.03 (1H, dd, J =

10.8, 3.6 Hz), 3.70-3.56 (1H, m), 3.50-3.35 (1H, m), 2.60 (3H, s), 2.22-2.02 (1H, m), 2.02-1.86 (1H, m), 1.85-1.68 (2H, m), 1.25 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 203.2, 152.9, 150.5, 142.5, 137.0, 136.8, 122.6, 118.8, 65.4, 37.4, 31.2, 29.3, 28.8, 23.0, 20.7.

To a solution of alcohol (58.4 mg, 0.225 mmol) in CH_2Cl_2 (2 mL) were added DMAP (41 mg, 0.338 mmol) and TsCl (51 mg, 0.27 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with CH_2Cl_2 and washed with 10% HCl, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1) to give **42** (85.7 mg, 92%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.90 (1H, s), 7.80 (1H, s), 7.54 (2H, d, J = 8.4 Hz), 7.17 (2H, d, J = 8.4 Hz), 4.58-4.42 (2H, m), 3.72-3.59 (1H, m), 3.59-3.45 (1H, m), 2.61 (3H, s), 2.40 (3H, s), 2.10-1.80 (2H, m), 1.78-1.63 (2H, m), 1.19 (3H, d, J = 6.9 Hz).

1-(5-Methyl-8-methyleneamino-2a,3,4,5-tetrahydro-2H-naphtho[1,8-bc]furan-6-yl)ethanone (43)

To a solution of **42** (15.6 mg, 0.038 mmol) in THF (1 mL) was added *t*-BuOK (4.7 mg, 0.042 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was quenched with saturated NH_4Cl, diluted with ethyl acetate, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give **43** (7.3 mg, 80%). Alternatively, **42** was treated with LDA at 0 °C to provide **43**. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, s), 4.99 (1H, t, J = 8.7 Hz), 4.21 (1H, dd, J = 12.6, 8.4 Hz), 4.00-3.86 (1H, m), 3.50-3.31 (1H, m), 2.54 (3H, s), 2.07-1.45 (4H, m), 1.06 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 197.7, 167.8, 156.8, 144.4, 131.4, 130.6, 129.6, 81.7, 40.3, 30.8, 29.2, 29.1, 23.9, 20.7.

(9-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-yl)methanol (44)

The same procedures for **9** and **10** were applied.

Acetate: 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, s), 7.54 (1H, d, J = 8.1 Hz), 7.24 (1H, d, J = 8.1 Hz), 4.35 (1H, dd, J = 11.1, 5.1 Hz), 4.23 (1H, dd, J = 10.5, 8.4 Hz), 3.36-3.12 (2H, m), 2.06 (3H, s), 2.02-1.60 (4H, m), 1.44 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.3, 152.3, 149.2, 138.6, 134.2, 127.3, 125.6, 117.9, 68.1, 37.7, 29.0, 27.8, 23.3, 21.24, 21.2.

44: 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, s), 7.44 (1H, d, J = 8.4 Hz), 7.20 (1H, d, J = 8.4 Hz), 3.93-3.72 (2H, m), 3.30-3.12 (1H, m), 3.08-2.93 (1H, m), 2.10-1.94 (1H, m), 1.94-1.71 (2H, m), 1.71-1.55 (1H, m), 1.36 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 152.3, 149.2, 137.9, 135..4, 127.4, 125.6, 117.5, 66.7, 40.9, 28.9, 28.0, 22.8, 21.3.

9-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-ylmethyl toluene-4-sulfonate (45)

The same procedure for **20** was applied. 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.75 (2H, d, J = 8.4 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.06 (1H, d, J = 8.4 Hz), 4.27 (1H, dd, J = 9.9, 4.8 Hz), 4.15 (1H, dd, J = 9.9, 8.7 Hz), 3.33-3.17 (2H, m), 2.44 (3H, s), 2.05-1.75 (3H, m), 1.65-1.47 (1H, m), 1.39 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 152.5, 149.2, 145.1, 138.9, 133.1, 132.6, 130.1, 128.1, 127.5, 125.6, 118.1, 73.4, 37.9, 28.9, 27.5, 22.8, 21.9, 21.2.

5-(1-Butoxyvinyl)-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene-6-ylmethyl acetate (46)

To a solution of **8a** (2.854 g, 7.075 mmol) in DMF (21 mL) were added TEA (2 mL, 14.15 mmol), *n*-butyl vinyl ether (4.6 mL, 35.375 mmol), DPPP (160 mg, 0.389 mmol), and $Pd(OAc)_2$ (79 mg, 0.354 mmol) at rt. After being purged with argon for 5 min, the mixture was stirred at 80 °C for 3 h. After being cooled down to rt, the mixture was diluted with ethyl

acetate and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give **46** (1.704 g, 67%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, s), 7.57 (1H, s), 4.46-4.33 (2H, m), 4.23-4.10 (2H, m), 3.92-3.78 (2H, m), 3.72-3.60 (1H, m), 3.36-3.20 (1H, m), 2.06 (3H, s), 2.10-1.93 (2H, m), 1.80-1.60 (4H, m), 1.49 (3H, d, J = 6.9 Hz), 1.54-1.34 (2H, m), 0.92 (3H, t, J = 7.5 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.1, 162.2, 152.6, 149.5, 138.2, 136.1, 133.1, 127.3, 120.1, 86.9, 68.0, 66.2, 34.6, 31.2, 29.4, 26.5, 23.6, 22.0, 21.2, 19.6, 14.0.

5-(1-Butoxyvinyl)-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene-6-ylmethyl toluene-4-sulfonate (47)

To a solution of **46** (78 mg, 0.218 mmol) in MeOH (1 mL) was added 10% NaOH (2 mL) at rt. After being stirred at rt for 30 min, the mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give alcohol (55.4 mg, 81%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, s), 7.56 (1H, s), 4.36 (1H, d, J = 2.1 Hz), 4.17 (1H, d, J = 1.8 Hz), 4.00-3.61 (4H, m), 3.55-3.40 (1H, m), 3.40-3.21 (1H, m), 2.35-1.93 (2H, m), 1.90-1.60 (4H, m), 1.48 (3H, d, J = 6.9 Hz), 1.59-1.25 (2H, m), 0.92 (3H, t, J = 7.5 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 162.4, 152.5, 149.5, 137.9, 135.8, 134.4, 127.2, 119.9, 86.8, 68.1, 65.7, 38.1, 31.2, 29.3, 26.7, 23.8, 22.1, 19.6, 14.0.

To a solution of alcohol (203 mg, 0.644 mmol) in CH_2Cl_2 (2 mL) were added DMAP (118 mg, 0.966 mmol) and TsCl (147 mg, 0.773 mmol) at rt. After being stirred at rt for 2 h, the mixture was diluted with CH_2Cl_2 and washed with aqueous citric acid solution. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 7:1) to give **47** (279 mg, 92%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.04 (1H, s), 7.73 (2H, d, J = 8.4 Hz), 7.51 (1H, s), 7.29 (2H, d, J = 8.4 Hz), 4.36 (1H, dd, J

= 9.6, 4.2 Hz), 4.23 (1H, d, J = 2.1 Hz), 4.02 (1H, d, J = 2.1 Hz), 3.98 (1H, dd, J = 11.1, 9.9 Hz), 3.90-3.60 (3H, m), 3.33-3.12 (1H, m), 2.41 (3H, s), 2.20-1.83 (2H, m), 1.80-1.55 (4H, m), 1.55-1.25 (2H, m), 1.38 (3H, d, J = 6.9 Hz), 0.92 (3H, t, J = 7.5 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 161.8, 152.7, 149.4, 144.9, 138.6, 136.0, 133.3, 131.5, 130.0, 128.2, 127.5, 120.1, 86.9, 71.5, 68.1, 34.8, 31.1, 29.2, 26.0, 23.1, 21.9, 21.8, 19.6, 14.0.

8-Acetyl-6-formylamino-5-hydroxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-ylmethyl toluene-4-sulfonate (48)

To a solution of **47** (10 mg, 0.021 mmol) in CH_2Cl_2 (1 mL) was added $SnCl_4$ (1 M solution in CH_2Cl_2, 21 μL, 0.021 mmol) at –78 °C. After being stirred at –78 °C for 5 min, the mixture was quenched with saturated $NaHCO_3$ solution. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **48** (8 mg, 89%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.42 (1H, s), 8.83 (1H, s), 7.67 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 4.21 (1H, dd, J = 9.3, 5.4 Hz), 4.12 (1H, dd, J = 9.3, 9.0 Hz), 4.05 (1H, br s), 3.75 (1H, br s), 3.46-3.26 (1H, m), 2.62 (3H, s), 2.42 (3H, s), 2.20-1.35 (4H, m), 1.45 (3H, d, J = 6.9 Hz).

5-Acetyl-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-ylmethyl acetate (49)

A solution of **46** (1 g, 2.8 mmol) in 10% HCl (20 mL) and 1,4-dioxane (10 mL) was stirred at rt for 30 min. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give intermediate, 8-acetyl-6-formylamino-5-hydroxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-ylmethyl acetate which was dissolved in benzene and PTSA-H_2O (53 mg, 0.28 mmol) was added at rt. The mixture was heated to reflux overnight with the azeotropic removal of H_2O

using a Dean-Stark trap. The mixture was concentrated in vacuo and the residue was purified by sgc (H:EA = 2:1) to give **49** (632 mg, 75%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, s), 7.88 (1H, s), 4.16 (1H, dd, J = 10.8, 9.3 Hz), 4.08 (1H, dd, J = 10.8, 4.5 Hz), 4.03-3.92 (1H, m), 3.32-3.16 (1H, m), 2.60 (3H, s), 1.97 (3H, s), 2.02-1.86 (2H, m), 1.72-1.52 (2H, m), 1.48 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 202.2, 171.0, 153.4, 150.8, 138.0, 136.5, 134.6, 128.7, 119.6, 67.1, 33.4, 30.8, 29.4, 26.3, 23.8, 21.9, 21.2.

1,6-Dimethyl-2,3,3a,4-tetrahydro-1*H*,6*H*-5,10-dioxa-8-azacyclopenta[a]phenalen-6-ol (50)

To a solution of **49** (110 mg, 0.365 mmol) in MeOH (1 mL) was added 10% NaOH (3 mL) was added at rt. After being stirred at rt for 10 min, the mixture was acidified with aqueous citric acid solution at 0 °C. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **50** (93 mg, 98%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, s), 7.60 (1H, s), 3.83 (1H, dd, J = 10.5, 4.8 Hz), 3.62 (1H, dd, J = 11.1, 10.8 Hz), 3.50-3.35 (1H, m), 2.96-2.81 (1H, m), 2.10-1.30 (4H, m), 1.66 (3H, s), 1.30 (3H, d, J = 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 152.7, 148.3, 138.3, 134,8, 132.0, 124.3, 116.4, 99.8, 65.3, 36.7, 29.1, 28.1, 26.7, 22.0, 20.0.

3',4'-Dihydroxyacetophenone (51)

To a suspension of $AlCl_3$ (18 g, 136.2 mmol) in CH_2Cl_2 (100 mL) was added catechol (5 g, 45.4 mmol) in one portion at rt. After 5 min, acetyl chloride (3.3 mL, 46.3 mmol) was added to this mixture at rt. After being stirred at rt overnight, the mixture was quenched with cold H_2O at 0 °C. The mixture was diluted with Et_2O and washed with brine. The first extract contained unreacted starting material (catechol) and product **51**. The aqueous layer was extracted with Et_2O several times because the product was soluble in H_2O. The latter extracts

contained almost pure product **51** (3.2 g, 46%). 300 MHz ^{1}H NMR (acetone-d_6) δ 8.51 (2H, br s), 7.47 (1H, d, J = 2.1 Hz), 7.44 (1H, dd, J = 8.1, 2.1 Hz), 6.89 (1H, d, J = 8.1 Hz), 2.46 (3H, s).

3',4'-Bis(*tert*-butyldimethylsilyloxy)acetophenone (52)

To a solution of **51** (118 mg, 0.776 mmol) in DMF (2 mL) were added imidazole (116 mg, 1.71 mmol) and TBSCl (257 mg, 1.71 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with H_2O three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 50:1) to give **52** (295 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.50-7.42 (2H, m), 6.85 (1H, d, J = 9.0 Hz), 2.52 (3H, s), 1.00 (9H, s), 0.99 (9H, s), 0.24 (6H, s), 0.23 (6H, s).

1-[3,4-Bis(*tert*-butyldimethylsilanyloxy)phenyl]-3-hydroxyocta-4,6-dien-1-one (53)

To a solution of **52** (746 mg, 1.96 mmol) in THF (6.5 mL) was added *t*-BuOK (264 mg, 2.35 mmol) at 0 °C. After 5 min, 2,4-hexadienal (216 μL, 1.96 mmol) was added to this mixture at 0 °C. After being stirred at 0 °C for 5 min, the mixture was quenched with 10% HCl at 0 °C. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give **53** (607 mg, 65%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.50-7.42 (2H, m), 6.85 (1H, d, J = 9.0 Hz), 6.29 (1H, dd, J = 15.0, 10.5 Hz), 6.05 (1H, dd, J = 15.0, 10.5 Hz), 5.82-5.70 (1H, m), 5.64 (1H, dd, J = 15.3, 6.3 Hz), 4.74 (1H, t, J = 8.1 Hz), 3.41 (1H, br s), 3.22-2.98 (2H, m), 1.75 (3H, d, J = 6.9 Hz), 1.00 (9H, s), 0.99 (9H, s), 0.24 (6H, s), 0.23 (6H, s).

1-{2-[3,4-Bis(*tert*-butyldimethylsilanyloxy)phenyl]-2-oxoethyl}hexa-2,4-dienyl acetate (54)

To a solution of **53** (65 mg, 0.136 mmol) in CH_2Cl_2 (1 mL) were added DMAP (18 mg, 0.15 mmol) and Ac_2O (14 μL, 0.15 mmol) at rt. After being stirred at rt for 2 h, the mixture was diluted with ethyl acetate and washed with aqueous citric acid solution, saturated $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **54** (67.6 mg, 96%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.50-7.42 (2H, m), 6.85 (1H, d, J = 9.0 Hz), 6.27 (1H, dd, J = 15.0, 10.5 Hz), 6.00 (1H, dd, J = 15.0, 10.5 Hz), 5.94-5.64 (2H, m), 5.58 (1H, dd, J = 15.3, 6.3 Hz), 3.35 (1H, dd, J = 16.5, 7.5 Hz), 3.05 (1H, dd, J = 16.5, 6.0 Hz), 2.01 (3H, s), 1.74 (3H, d, J = 6.9 Hz), 1.00 (9H, s), 0.99 (9H, s), 0.24 (6H, s), 0.23 (6H, s).

1-(3,4-Dihydroxyphenyl)octa-2,4,6-trien-1-one (55)

To a solution of **53** or **54** in CH_3CN was added 49% HF (2 equivalent) at 0 °C. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 2:1) to give **55** and/or **51**. Alternatively, **53** was treated with PTSA-H_2O in benzene to give **55**. 300 MHz ^{1}H NMR (acetone-d_6) δ 8.55 (2H, br s), 7.53 (1H, d, J = 2.1 Hz), 7.50 (1H, dd, J = 8.1, 2.1 Hz), 7.36 (1H, dd, J = 14.7, 11.1 Hz), 7.14 (1H, d, J = 14.7 Hz), 6.91 (1H, d, J = 8.1 Hz), 6.73 (1H, dd, J = 14.7, 10.2 Hz), 6.45 (1H, dd, J = 15.0, 11.4 Hz), 6.26 (1H, dd, J = 15.0, 10.5 Hz), 6.10-5.95 (1H, m), 1.81 (3H, d, J = 6.9 Hz).

1-(3,4-Dihydroxyphenyl)-3-hydroxyocta-4,6-dien-1-one (56)

To a solution of diisopropylamine (3.7 mL, 26.28 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M solution in hexanes, 10.5 mL, 26.28 mmol) at 0 °C. After 5 min, HMPA (4.6 mL, 26.28 mmol) was added to this mixture at 0 °C. After 5 min, a solution of **51** (1 g, 6.57 mmol) in THF (5 mL + 5 mL for rinse) was transferred to this mixture at 0 °C via cannula. After 5 min, a solution of 2,4-hexadienal (725 μL, 6.57 mmol) in THF (3 mL) was added to

this at 0 °C via cannula. After 10 min, the mixture was quenched with aqueous citric acid solution (pH was adjusted to 5 or 6). The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to afford **56** (1.305 g, 80%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.83 (1H, br s), 7.62 (1H, br s), 7.43 (1H, s), 7.30 (1H, d, J = 8.4 Hz), 6.78 (1H, d, J = 8.4 Hz), 6.19 (1H, dd, J = 15.2, 10.4 Hz), 5.93 (1H, dd, J = 15.2, 10.4 Hz), 5.72-5.60 (1H, m), 5.57 (1H, dd, J = 15.2, 6.8 Hz), 4.77 (1H, br s), 4.32 (1H, br s), 3.12 (1H, dd, J = 17.2, 8.8 Hz), 3.01 (1H, dd, J = 17.2, 2.8 Hz), 1.68 (3H, d, J = 6.9 Hz).

Methyl 4-hydroxymandelate (57)

To a solution of 4-hydroxymandelic acid monohydrate (820 mg, 4.4 mmol) in THF (8 mL) was added a solution of diazomethane in Et_2O at 0 °C until the color of the reaction mixture maintained yellow. After the mixture was stirred at 0 °C for 5 min, the excess diazomethane was quenched with AcOH at 0 °C. The mixture was concentrated in vacuo to give ester **57** (802 mg, 100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.28 (2H, d, J = 8.4 Hz), 6.82 (2H, d, J = 8.4 Hz), 5.12 (1H, d, J = 5.7 Hz), 4.88 (1H, br s), 3.76 (3H, s), 3.35 (1H, d, J = 5.7 Hz).

3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)octa-4,6-dien-1-one (58)

To a solution of diisopropylamine (422 μL, 3 mmol) in THF (1.5 mL) was added *n*-BuLi (2.5 M solution in hexanes, 1.2 mL, 3 mmol) at –78 °C. After 5 min at rt, the mixture was recooled to –78 °C. To this mixture was transferred a solution of acetovanillone (200 mg, 1.2 mmol) in THF (1 mL + 1 mL for rinse) at –78 °C. After 5 min, a solution of 2,4-hexadienal (132 μL, 1.2 mmol) in THF (1 mL) was added to this at –78 °C via cannula. After being stirred at –78 °C for 10 min, the mixture was quenched with AcOH at –78 °C. The mixture

was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 3:1) to give **58** (230 mg, 73%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.59-7.47 (2H, m), 6.95 (1H, d, J = 8.4 Hz), 6.29 (1H, dd, J = 15.3, 10.5 Hz), 6.23 (1H, br s), 6.05 (1H, dd, J = 15.3, 10.5 Hz), 5.82-5.68 (1H, m), 5.64 (1H, dd, J = 15.3, 6.3 Hz), 4.83-4.70 (1H, m), 3.94 (3H, s), 3.23-3.03 (2H, m), 1.73 (3H, d, J = 6.9 Hz), 1.70 (1H, br s).

1-(4-Hydroxy-3-methoxyphenyl)octa-4,6-diene-1,3-diol (59)

To a solution of **58** (56.3 mg, 0.215 mmol) in THF (2 mL) was added LAH (24 mg, 0.645 mmol) at 0 °C. After being stirred at 0 °C for 5 min, the mixture was quenched with H_2O and stirred for 30 min. The mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to afford **59** (8.5 mg, 15%). 300 MHz ^{1}H NMR (acetone-d_6) δ 6.95 (1H, d, J = 2.1 Hz), 6.78 (1H, dd, J = 8.4, 2.1 Hz), 6.71 (1H, d, J = 8.4 Hz), 6.25-6.11 (1H, m), 6.11-5.95 (1H, m), 5.73-5.51 (2H, m), 4.90-4.72 (1H, m), 4.40-4.28 (1H, m), 3.79 (3H, s), 3.20-2.60 (5H, br s), 1.71 (3H, d, J = 6.9 Hz).

6-Methoxy-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (60a), 7-Methoxy-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (60b), 5,8-Dihydroxy-6-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (61a), and 5,8-Dihydroxy-7-methoxy-4-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (61b)

A mixture of methoxy-1,4-benzoquinone (66 mg, 0.476 mmol) and **3** (80 mg, 0.571 mmol) in CH_3CN (2 mL) and H_2O (0.4 mL) was heated to reflux overnight. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 2:1) to give **60a/b** and **61a/b**.

60a/b: 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.78-5.33 (3H, m), 4.46-3.95 (2H, m), 3.95-3.35 (5H,

m), 2.12-1.92 (3H, m), 1.35-1.15 (3H, m).

61a/b: 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.50-5.25 (5H, m), 4.49-3.90 (2H, m), 3.89-2.58 (5H, m), 2.17-1.92 (3H, m), 1.35-0.70 (3H, m).

5-Hydroxymethyl-8-methyl-5,8-dihydronaphthalene-1,4-diol (63)

A mixture of 1,4-benzoquinone (1 g, 9.25 mmol) and 2,4-hexadienol (999 mg, 10.18 mmol) in benzene (20 mL) was heated to reflux overnight. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 5:1 to 2:1) to give **63** (954 mg, 50%). 300 MHz ^{1}H NMR (acetone-d_6) δ 8.19 (1H, br s), 7.71 (2H, br s), 6.60 (1H, d, J = 8.7 Hz), 6.55 (1H, d, J = 8.7 Hz), 6.03 (1H, dd, J = 9.9, 5.1 Hz), 5.90 (1H, dd, J = 9.9, 4.5 Hz), 3.85-3.70 (2H, m), 3.70-3.55 (2H, m), 1.23 (3H, d, J = 6.9 Hz).

5-Hydroxymethyl-8-methyl-5,8-dihydro[1,4]naphthoquinone (62)

To a solution of **63** (928 mg, 4.5 mmol) in benzene (10 mL) and ethyl acetate (10 mL) were added Na_2SO_4 (1.34 g, 9.45 mmol) and Ag_2O (2.1 g, 9 mmol) at rt. The reaction flask was covered with aluminum foil. After being stirred at rt overnight, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo and the residue was purified by sgc (H:EA = 3:1 to 2:1) to give **62** (569 mg, 62%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.71 (2H, s), 5.97 (1H, dd, J = 9.6, 4.2 Hz), 5.73 (1H, dd, J = 9.6, 4.2 Hz), 3.71 (1H, dd, J = 10.5, 4.5 Hz), 3.63 (1H, dd, J = 10.8, 4.5 Hz), 3.59-3.48 (1H, m), 3.48-3.33 (1H, m), 2.14 (1H, br s), 1.21 (3H, d, J = 6.9 Hz).

2-Amino-5-hydroxymethyl-8-methyl-5,8-dihydro[1,4]naphthoquinone and 2-Amino-8-hydroxymethyl-5-methyl-5,8-dihydro[1,4]naphthoquinone (64)

To a solution of $MeONH_2$-HCl (38 mg, 0.451 mmol) in EtOH (1 mL) was added Et_3N (63 μL, 0.451 mmol) at 0 °C. To this mixture was dropwise added a solution of **62** (92 mg,

0.451 mmol) in EtOH (1 mL + 1 mL for rinse) at 0 °C. After being stirred at rt overnight, the mixture was concentrated in vacuo, the residue was diluted with ethyl acetate, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to give **64** (69.2 mg, 70%) as a mixture of 3:1 regioisomers. 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.05-5.90 (1H, m), 5.80-5.65 (2H, m), 5.13 and 5.02 (2H, br s), 3.82-3.31 (4H, m), 2.75 (1H, br s), 1.24 and 1.23 (3H, d, J = 6.9 Hz).

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GENERAL CONCLUSIONS

In this dissertation, we have investigated direct routes to several biologically active natural products.

Chapter 1 described a concise construction of core skeleton of malibatol A, employing a novel benzofuran formation methodology and a regio- and stereoselective 7-membered ring formation via Lewis acid catalyzed epoxide ring opening as crucial steps.

Chapter 2 described direct approaches to isoflavanquinones utilizing radical addition to quinones. Three main strategies were presented and were compared to generate radicals from the corresponding precursors.

Chapter 3 described a direct entry to erogorgiaene, naturally occurring potent antitubercular agent, featuring a regioselective metal-halogen exchange and a 6-exo-trig radical cyclization as key transformations.

Chapter 4 described synthetic studies towards antitubercular benzoxazole alkaloids. The core tricyclic skeleton of the originally proposed structures of these natural products was synthesized using an intermolecular Diels-Alder reaction as a key step.

ACKNOWLEDGEMENTS

First, I would like to express my sincere gratitude to my advisor, Dr. George A. Kraus for his invaluable guidance and constant encouragement for the projects in which I've been involved. Without his advice and support, this Ph.D. work would have been impossible.

Thanks are also extended to Dr. Richard C. Larock, Dr. Nicola L. Pohl, Dr. Jacob W. Petrich, and Dr. Earl G. Hammond, members of my study committee for their help and guidance during my study at Iowa State University.

My appreciation goes to the past and present Kraus group members with whom I have worked for the last three and a half years.

I am also grateful to my parents-in-law for their continuing support and encouragement. I am deeply indebted to my two sisters and their families for their love and trust. My special and heartfelt thanks go to my wife, Minyoung for her love, patience, sacrifice, and understanding. I would like to thank my son, Joowan for providing me the reason to smile all the time. I give my deepest appreciation and thanks to my late parents for making me who I am. Without their unyielding love and sacrifice, my life would not have come here.

Finally, I would like to thank my God who always guides me in the right direction.