New synthetic strategies for the synthesis of benzo[b]fluorene skeleton of kinobscurinone, 2,3-diaryl benzo[b] furans and 3-alkenyl salicylic acids

Divya Chaudhary
Iowa State University

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New synthetic strategies for the synthesis of benzo[b]fluorene skeleton of 
kinobscurinone, 2,3-diaryl benzo[b] furans and 3-alkenyl salicylic acids 

by 

Divya Chaudhary 

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Program of Study Committee: 
George A. Kraus, Major Professor 
William S. Jenks 
Yan Zhao 
Young-Jin Lee 
Olga Zabotina 

Iowa State University 
Ames, Iowa 
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GENERAL INTRODUCTION

An important aspect of synthetic organic chemistry is the creation of complex molecules for use in materials science, pharmaceuticals, and molecular biology. The invention of new methods, strategies, and reactions is of great importance to the progress of organic synthesis. In this thesis we explore total syntheses as well as methodologies that we used to synthesize various biologically active molecules and/or intermediates that can be used to synthesize important classes of molecules.

Chapter 1 describes our construction of the benzo[b]fluorene core of kinobscurinone. Kinobscurinone has been found to be an important intermediate in the synthesis of stealthins and kinamycins that have potent antioxidant and antitumor properties, respectively. We used a two-step sequence of Michael addition and an LDA mediated cyclization to construct the tetracyclic core. This work has been published in *Tetrahedron Letters* in 2012 (Kraus G. A.; Chaudhary, D.; Yuan, Y.; Schuster, A. *Tet. lett.* 2012, 53(33), 4444-4446).

Chapter 2 describes our recent study of the rearrangement of benzyl phenyl ethers to the corresponding *ortho*-benzyl phenols in the presence of boron trifluoride. The utility of this methodology was demonstrated in the synthesis of biologically active 2,3-diarylbenzo[b]furans using a two-step sequence of benzylation followed by a base-mediated cyclization. This work was published in 2012 in *Tetrahedron letters* (Kraus G. A.; Chaudhary D. *Tet. lett.* 2012, 53(52), 7072-7074).

Chapter 3 describes the first total synthesis of biologically active 3-farnesyl salicylic acid and its analogues. These analogues were tested for their antibacterial activity against two strains of bacteria. This work was conducted in collaboration with veterinary medicine
scientists at Iowa State University and has been published in *Natural Product Communications* (Kraus G. A; Chaudhary D.; Riley S.; Liu F.; Schlapkohl A.; Weems M.; Phillips G. J. *Nat. Prod. Comm.* **2013**, *8*(7), 911-913).
CHAPTER 1. Construction of tetracyclic framework of kinobscurinone

Introduction:

Many diseases, such as atherosclerosis, inflammation, Parkinson’s disease and ischemic injuries to the central nervous system (CNS) and cardiovascular system have been proven to be caused by oxygen-derived free radicals. Free radicals are highly reactive species which can easily capture an atom from another molecule, starting a chain reaction. The cellular zone where oxygen is more active is the mitochondria, endoplasmic reticulum and membranes. During the normal metabolic processes, free radicals form and damage the mitochondria and cellular membranes, which are generally renewed every 5-6 days. In cancer and ischemia the oxidative damage is so high that the repairing processes are insufficient, and the membranes are damaged beyond repair. The diseases caused by free radicals have been reported to be ameliorated by free radical scavengers such as superoxide dismutase (SOD). SOD is a naturally occurring extremely potent antioxidant enzyme that can help protect against cell destruction. It has the distinct ability to neutralize superoxide, one of the most damaging free radical substances in the body. Like so many other protective compounds that naturally occur in the body, it decreases with age, making cells more vulnerable to the oxidants which cause aging and diseases.

During 1990-1991, in the course of screening for free radical scavengers of microbial origin to overcome these diseases, Seto and coworkers isolated Stealthins A and B from Streptomyces viridochromogenes 2220-SV2, which were shown to possess an unprecedented benzo[b]fluoren-10-one skeleton (Figure 1). They exhibited a potent in vitro free radical scavenging activity in a rat liver microsome system with IC₅₀ values 0.04 µg/mL.
and 0.07 µg/mL, respectively. These values are approximately 20-30 times stronger than that for vitamin E (10.8 mg/mL)\(^3\).

An interesting structural feature of these compounds is the NMR silent nature. No signals are observed in the \(^1\)H- and \(^{13}\)C-NMR of these compounds. Seto attributed the failure of observation of any signals to the extensive line broadening caused by many tautomeric forms of this unique chromophore including various keto forms and imine form.

**Figure 1.** The general structure of Stealthins

The strong biological activities as well as the identification of structurally similar natural products, stealthin C (3, Figure 1), kinafluorenone, prekinamycin, and kinamycin antibiotics have resulted in the growing interest in this group of compounds. Their synthesis has become an active area of research since 1996 when Gould and coworkers first synthesized stealthin C (3, Figure 1) and demonstrated its existence in kinamycin biosynthesis.\(^4\)

Various syntheses to put together the tetracyclic core of the stealthins have been reported so far. Strategies that make use of Diels Alder reaction and Friedel-Crafts reaction have been successfully employed towards the synthesis of stealthins and their derivatives. In 1994, Gould and Melville\(^5\) showed the presence of a new important intermediate kinobscurinone (Figure 2) in the biosynthesis of kinamycins.
Kinobscurinone was also found to be NMR silent. To test the rationale put forward by Seto for the “NMR silent” behavior of stealthins, NMR experiments were conducted in deuterated trifluoroacetic acid and deuterated pyridine to disfavor rapid tautomerization. The NMR still failed to show any peaks and the reason for the NMR silent nature has now been ascribed to the existence of polycyclic aromatic quinones at a radical oxidation state under ambient conditions. Presence of a single line in ESR confirmed the presence of an unpaired electron. It was further shown that 6% of kinobscurinone molecules contain an unpaired electron at a given time which should be sufficient to broaden the NMR signals by relaxation to the point where they could not be observed. Kinobscurinone radical is better represented by neutral or anionic species (Figure 3).

Figure 2. Kinobscurinone

Figure 3. Representation of kinobscurinone radical
Kinobscurinone presents an interesting target for synthesis as it has been shown to be present in the synthesis of kinamycins and stealthin C. Since a synthesis of kinobscurinone would constitute the formal synthesis of above class of compounds, a number of syntheses for kinobscurinone have been reported.

**Gould’s synthesis of kinobscurinone**

In the first synthesis approach to kinobscurinone, Gould and co-workers envisioned fashioning the ABD ring through the coupling of cyanopthalide with an appropriately substituted cinnamate (Scheme 1).

![Scheme 1. Gould’s synthesis of kinobscurinone.](image)

While effective in reaching the goal of fashioning kinobscurinone, this route suffered from several mass-limiting steps. The problems were later addressed and subsequently corrected in a revised route to Kinobscurinone (Scheme 2). They capitalized on the versatility of ketone 1 by treating it with hydroxylamine hydrochloride to give the corresponding oxime. Demethylation using BBr₃ followed by the oxidation of the
corresponding hydroquinone with dithionate provided stealthin C. The role of stealthin C was later demonstrated in the biosynthesis of kinamycins.

Scheme 2. Gould’s revised route to kinobscurinone and divergence to stealthin C

Snieckus’ synthesis of kinobscurinone

Snieckus and co-workers formulated an approach to Kinobscurinone based on a key remote-carbamoyl migration reaction\(^6\) (Scheme 3). The construction of the core was envisioned on the basis of a key remote metalation-carbamoyl migration reaction, which necessitates prior silicon protection. The most reactive metalation site in 21 was protected using low temperature metalation-silylation procedure. This step also eliminated any possibility of anionic ortho-Fries rearrangement. The critical O \(\rightarrow\)C ring-to-ring carbamoyl transfer was accomplished with excess LDA to give the corresponding phenol
which was later methylated to give 23 which underwent a second remote metalation-cyclization to furnish fluorenone 24. Treatment of 24 with TFA affords kinobscurinone.

Scheme 3. Snieckus’ synthesis of Kinobscurinone

Jones’ synthesis of benzo[b]fluorenone skeleton

Taking a different approach, Qabaja and Jones utilized a Palladium-mediated Heck cyclization for closure of aryl iodide to secure the ring C of benzo[b]fluorenone core structure. Aldehyde 26 was subjected to 1,2-addition of lithioarene derived from aryl bromide 27. The resulting benzylic alcohol was oxidized with PCC to give ketone 29. In the last step, microwave-assisted closure catalyzed by PdCl₂(PPh₃)₃/NaOAc in DMA effectively secures the target, 30 (Scheme 4).
**Results and Discussion:**

Our incentive for this project was the presence of benzo[\(b\)]fluorenone skeleton in various biologically significant compounds. An entirely different strategy that uses a Michael addition/cyclization reaction sequence has been used towards the construction of the tetracyclic core of kinobscurinone. Although a cyclopentenone or an indenone would be the logical Michael acceptor, annulation reactions involving cyclopentenones and indenones can proceed in low yields due to their sensitivity to strongly basic conditions. Based on the work that nitroalkanes undergo efficient Michael addition to cyclopentenones, we envisaged a route towards the tetracyclic core of kinobscurinone using an indenone, 5 and a Michael donor, 6 to give 4, which can then be cyclized and oxidized to give 2.
Scheme 5. Retrosynthesis of Kinobscurinone, 2, R= SO₂Ph

Our synthesis commenced with the preparation of the Michael donor 6. Michael donor 6 was prepared from ethyl-2-hydroxy-6-methylbenzoate, 31 by the condensation of commercially available crotonaldehyde and ethylacetoacetate in 50% yield over three steps (Scheme 6). The phenol 31 was then protected using benzenesulfonyl chloride to give 32 in 77% yield. Compound 32 was then subjected to radical benzylic bromination to make 33 in 75% yield, followed by nucleophilic substitution of the bromide with the nitro group using silver nitrite to form the Michael donor 34 in 50% yield.

Scheme 6. Synthesis of Michael donor 6
We then turned our attention to the formation of the indenone 5 (Scheme 7). The synthesis starts with the reduction of commercially available dihydrocoumarin\textsuperscript{11} 35. Compound 35 underwent intramolecular Friedel-Crafts acylation\textsuperscript{12} when it was treated with AlCl\textsubscript{3} and NaCl at 210 °C to give hydroxyindanone 37. Hydroxyindanone 37 was protected using benzenesulfonyl chloride to give 38 in 87% yield. Benzenesulfonyl chloride was the reagent of choice as the Michael donor we had previously made was also protected using the same reagent. Having same protecting groups on the molecule will allow for one step deprotection in the later stages of the synthesis. The indanone 38 was subjected to Sageusa oxidation\textsuperscript{13} conditions to afford the desired indenone, 5 in 66% yield.

**Scheme 7.** Synthesis of the indenone 5

Other indenones that were prepared included methyl ether and TBS ether analogues of indenone 40 (Figure 4). These indenones were less stable than 5 and their reactions with the Michael donor were not successful, presumably because of the electron donating nature of these groups which can make the α,β-unsaturated ketone less electrophilic.
Figure 4. Methyl ether and TBS ether analogues

Though the oxidation in the last step shown in Scheme 7 gives the indenone in good yield, it uses stoichiometric amounts of palladium (II) acetate, which makes the use of this reaction impractical on larger scales. So we sought alternate reagents that could achieve this transformation cost effectively. The first thought we had, was to introduce an inexpensive oxidant that could oxidize palladium (0) back to palladium (II), thereby eliminating the use of stoichiometric amounts of palladium (II) acetate. We tried the same reaction with catalytic amounts of palladium (II) acetate, using O₂ as the oxidant. These reaction conditions afforded the desired indenone in only 5% yield. After screening a couple of reaction conditions, we found that the reaction of the indanone with iodic acid, HIO₃ in DMSO afforded the desired indenone cleanly in 87% yield (Scheme 8).

Scheme 8. Improved reaction conditions for the synthesis of indenone 5

After successfully synthesizing the Michael acceptor and donor for the key Michael addition reaction, we decided to try the key reaction with commercially available or easily makeable acceptors and donors. Our first attempt towards Michael addition was a reaction between commercially available nitromethane and indenone 40 (Scheme 9), which can be
synthesized from commercially available coumarin via Friedel-Crafts acylation and oxidation as described before.

Scheme 9. The key Michael addition reaction on Model system 1

Encouraged with the success of the key step we decided to test these reaction conditions on a more complicated system. Subjecting indenone 40 and ethyl 2-(nitromethyl)-benzoate, 41 to same set of conditions afforded the Michael adduct 42 in 68% yield (Scheme 10). Other solvents and bases were also used to affect cyclization but DBU in acetonitrile was found to be the most effective reagent for Michael addition. With two successful examples of Michael addition with our set of reagents, we next worked towards attaching indenone 5 and Michal donor 6 (Scheme 11). The reaction proceeded in 72% yield to give an inseparable mixture of diastereomers of 4.

Scheme 10. Michael addition on Model system 2
Scheme 11. The key Michael addition reaction on the real system.

We then focused our attention to the cyclization of the Michael adduct to put the core of tetracyclic structure in place. Previous work in our group (Scheme 12) had shown the utility of this Michael addition/cyclization protocol towards the syntheses of various tetracyclic and tricyclic ketones in low to modest yields (Figure 5). Sodium methoxide was the base of choice for the cyclization.

Scheme 12. Previous strategy for the Michael addition/cyclization sequence

Figure 5. Various tetracyclic and tricyclic ketones that were synthesized using Scheme 12

Unfortunately, use of sodium methoxide for the cyclization of Michael adduct, 42, did not result in the cyclized product. After screening various bases, LDA was found to be the most effective. The model compound 42 was treated with 2.2 equiv. of LDA to affect
cyclization to give the tetracyclic product 43 (Scheme 13). The use of LDA not only afforded the cyclized product, it also removed the nitro group from the product unlike the work that was done previously using NaOMe.

![Scheme 13. Cyclization of Michael adduct 42](image1)

The same reaction conditions were employed to cyclize the real system, 4 in 23% yield (Scheme 14). The lower yield can be attributed to the presence of a more acidic proton next to the nitro group.

![Scheme 14. LDA assisted cyclization of the real system](image2)

The compound 44 can then be converted into kinobscurinone 2 by oxidation followed by the deprotection of the benzenesulfonyl groups (Scheme 15).
Scheme 15. Pathway to reach kinobscurinone 2, from 44

Various oxidizing agents such as ceric ammonium nitrate, PIFA and Fremy’s salt (Figure 6) have been shown to oxidize a phenol into a quinone. We decided to try these oxidizing agents to get 45 from 44. Unfortunately, none of these oxidizing agents were successful in oxidizing the phenol 44 to quinone 45. The reason could be attributed to the fact that the phenol 44 is flanked by rings that contain electron withdrawing groups, which reduce the ability of the phenol to undergo oxidation. The other strategy could be the removal of the electron withdrawing protecting groups to make the oxidation easier. But as shown in Scheme 16, this strategy will leave open many a sites susceptible to oxidation - this route was not examined further.

Figure 6. Structures of PIFA and Fremy’s salt
Scheme 16. Possible products from deprotection-oxidation strategy

Conclusions:

Since its isolation and characterization in 1994, kinobscurinone has been shown to be an important intermediate in the synthesis of stealthins and kinamycins. The remarkable antioxidant and antibiotic activities of these compounds will continue to inspire many new syntheses in the future. Our work has demonstrated the utility of Michael addition/cyclization sequence to secure the tetracyclic core of benzo[b]fluorenones. Future work on this project will focus on the screening of different oxidizing agents to synthesize the oxidized product from the cyclized phenol. Furthermore, different protecting groups can be used to make the oxidation more effective.

Experimental:

All NMR spectra were obtained on a Varian VXR spectrometer, operating at 300 or 400 MHz for $^1$H NMR and 75 or 100 MHz for $^{13}$C NMR instrument. Chemical shifts in CDCl$_3$ were reported downfield from TMS (= 0 ppm) for $^1$H NMR. For $^{13}$C NMR, chemical
shifts were reported relative to the solvent signal [CDCl$_3$ (77.15 ppm)]. All reactions were carried out under argon unless otherwise noted. Thin-layer chromatography was performed using commercially available 250 micron silica gel plates (Analtech). Commercially available 1000 micron silica gel plates (Analtech) were used for preparative thin-layer chromatography. Visualization of TLC plates was effected with short wavelength ultraviolet light (254 nm). High resolution mass spectra were recorded on an Agilent 6540 QTOF using EI or ESI. All reagents were used directly as obtained commercially unless otherwise noted.

![Chemical Structure](image)

**Ethyl-2-hydroxy-6-methylbenzoate (31).** To a magnetically stirred solution of sodium (0.327 g) dissolved in ethanol (5 mL) was added ethylacetoacetate (3.44g, 49.10 mmol). After the reaction mixture was cooled in an ice bath, purified crotonaldehyde (6.39g, 49.10 mmol) in ethanol (5mL) was added drop-wise and the resultant reaction mixture was stirred at room temperature overnight. Dry HCl gas was passed through the resulting brown solution until the color lightened to pale yellow. It was then stirred at room temperature for a day. It was then concentrated *in vacuo* and dissolved in dry DMF (10 mL). 6.83g of CuCl$_2$ and 2.96 g of LiCl were added and the resulting mixture was then heated at 90 °C overnight. The dark brown mixture, after it was cooled to room temperature, was diluted with ice cold water and poured on a celite® gel bed. After filtration under vacuum the crude solid was washed with water to remove DMF. The crude product was purified using 10% ethyl acetate
in hexanes. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.44 (s, 1H), 7.21 (t, $J = 8.4$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.0$ H, 1H), 4.37 (q, 2H), 2.50 (s, 3H), 1.39 (t, $J = 8.0$ Hz, 3H).

**Ethyl-2-methyl-6-((phenylsulfonyl)oxy)benzoate (32).** A solution of benzenesulfonyl chloride (2.18 mL, 71.03 mmol) in THF (5 mL) was added drop-wise to a solution of 31 (2.05 g, 11.35 mmol) and triethylamine, Et$_3$N (2.38 mL, 17.03 mmol) in THF (20 mL) at room temperature. The reaction mixture was allowed to stir at room temperature overnight and it was then poured into water. The mixture was extracted with ethyl acetate and the organic layer was washed with 10% aqueous HCl three times, saturated aqueous NaHCO$_3$ (twice) and brine and dried over MgSO$_4$ and concentrated *in vacuo*. The product was purified via silica gel chromatography using 20 % ethyl acetate in hexanes to give 32 in 87% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.81 (d, $J = 9.0$ Hz, 2H), 7.61 (t, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.0$ Hz, 2H), 7.16 (t, $J = 6.0$ Hz, 1H), 7.04 (d, $J = 6.0$ Hz, 1H), 6.88 (d, $J = 6.0$ H, 1H), 4.21 (q, 2H), 2.27 (s, 3H), 1.27 (t, $J = 9.0$ Hz, 3H).

**Ethyl-2-(bromomethyl)-6-((phenylsulfonyl)oxy)benzoate (33).** NBS (1.93g, 10.84 mmol) and AIBN (0.081 g, 0.49 mmol) were refluxed in benzene (25 mL). A solution of 32 (3.16 g, 9.86 mmol) in benzene (5 mL) was added drop-wise to the refluxing solution. The reaction mixture was refluxed overnight. After cooling the reaction mixture to room temperature, it
was diluted with ethyl acetate. It was then washed with water, brine and dried over MgSO₄. The product was purified via silica gel chromatography using 15% ethyl acetate in hexanes. 

\[ ^1H \text{NMR (300 MHz, CDCl}_3) : \delta 7.83 (d, J = 6.0 \text{ Hz, 2H}), 7.67 (t, J = 7.5 \text{ Hz, 1H}), 7.53 (t, J = 7.5 \text{ Hz, 2H}), 7.32-7.30 (m, 2H), 7.04 (t, J = 4.5 \text{ Hz, 1H}), 4.58 (s, 2H), 4.29 (q, 2H), 1.34 (t, J = 7.5 \text{ Hz, 3H}) \].

![Chemical Structure](image)

**Ethyl-2-(nitromethyl)-6-((phenylsulfonyl)oxy)benzoate (34).** In a 100 mL flask were placed AgNO₂ (1.84 g, 11.92 mmol) and diethyl ether, Et₂O (20 mL) at 0 °C, and the flask was purged with argon and covered with aluminum foil. Ethyl-2-(bromomethyl)-6-((phenylsulfonyl)oxy)benzoate, 33 (1.19 g, 2.98 mmol) in Et₂O (10 mL) was then added drop-wise using a syringe. The reaction mixture was stirred overnight at room temperature. It was then filtered, washed with H₂O, and dried over MgSO₄. The product was purified via silica gel chromatography using 30% ethyl acetate in hexanes to give pure product in 51% yield. 

\[ ^1H \text{NMR (300 MHz, CDCl}_3) : \delta 7.81 (d, J = 6.0 \text{ Hz, 2H}), 7.70 (t, J = 7.5 \text{ Hz, 1H}), 7.57 (t, J = 7.5 \text{ Hz, 2H}), 7.37-7.35 (m, 2H), 7.19 (t, J = 4.5 \text{ Hz, 1H}), 5.62 (s, 2H), 4.28 (q, 2H), 1.32 (t, J = 7.5 \text{ Hz, 3H}) \].

![Chemical Structure](image)

**7-Methylchroman-2-one (36).** 7-methylcoumarin 35, (1.09 g, 6.8 mmol) in ethyl acetate (20 mL) was added slowly to a three-necked flask containing 10% Pd/C (0.16 g) in ethyl
acetate. The mixture was stirred under a hydrogen atmosphere for 6 h at room temperature. The reaction mixture was filtered through a layer of Celite® in a sintered glass funnel and, after evaporation of the solvent, colorless oil was left, which crystallized on standing. Drying under vacuum overnight left 36 as off-white crystals. $^1$H NMR (400 MHz, CDCl$_3$): δ 6.98 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.73 (s, 1H), 2.85 (t, $J = 10.0$ Hz, 2H), 2.64 (t, $J = 8.0$ Hz, 2H), 2.23 (s, 3H).

4-Hydroxy-6-methyl-2,3-dihydro-1H-inden-1-one (37). AlCl$_3$ (1.51g, 2.22mol) and NaCl (0.30 g, 2.22 mmol) were mixed and heated in an oil bath. When the bath temperature was about 150 °C, 36 (0.33g, 2.02 mmol) was added slowly. The bath temperature was then raised to 210 °C and the mixture was stirred for 1 hour. The mixture was cooled to room temperature and quenched with 100 g crushed ice and 5 mL conc. HCl at 0 ºC. The suspension was stirred at room temperature for 30 minutes and the crude product was obtained as a gray solid upon filtration. The solid was purified via silica gel chromatography using 30% ethyl acetate in hexanes. $^1$H NMR (400 MHz, CD$_3$OD): δ 7.00 (s, 1H), 6.87 (s, 1H), 4.64 (s, 1H of OH), 2.96 (t, 2H), 2.65 (t, $J = 8.0$ Hz, 2H), 2.32 (s, 3H).
6-Methyl-1-oxo-2,3-dihydro-1\textit{H}-inden-4-ylbenzenesulfonate (38). A solution of benzenesulfonyl chloride (0.68 mL, 5.13 mmol) in THF (2 mL) was added drop-wise to a solution of 37 (0.65 g, 4.01 mmol) and triethylamine, Et\textsubscript{3}N (0.84 mL, 6.01 mmol) in THF (10 mL) at room temperature. The reaction mixture was allowed to stir at room temperature for 3.5 h and it was then poured into water. The mixture was extracted with ethyl acetate and the organic layer was washed with 10% aqueous HCl three times, saturated aqueous NaHCO\textsubscript{3} (twice) and brine and dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The product was purified via silica gel chromatography using 25% ethyl acetate in hexanes. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 7.88 (d, \(J = 9.0\) Hz, 2H), 7.72 (t, \(J = 3\) Hz, 1H), 7.56 (t, \(J = 9\) Hz, 2H), 7.46 (s, 1H), 7.04 (s, 1H), 2.78 (t, \(J = 6.0\) Hz, 2H), 2.58 (t, \(J = 6.0\) Hz, 2H), 2.34 (s, 3H).

6-Methyl-1-oxo-1\textit{H}-inden-4-ylbenzenesulfonate (5). 1.7 equivalence of HIO\textsubscript{3}.DMSO complex were prepared by heating HIO\textsubscript{3} (2.46 g, 13.98 mmol) in DMSO (5 mL) at 80 °C for one hour. To this was added 1.74 mL of cyclohexene. To this was added a solution of indanone, 38 (2.11 g, 6.99 mmol) in DMSO (7 mL). The resulting mixture was heated in an aluminum foil wrapped sealed tube at 55°C overnight. The reaction mixture was then concentrated and purified via column chromatography using 15% ethyl acetate in hexanes. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 7.85 (d, \(J = 3.0\) Hz, 2H), 7.70 (t, \(J = 3.0\) Hz, 1H), 7.56 (t, \(J = \)}
6.0 Hz, 2H), 7.23 (d, J = 6.0 Hz, 1H), 7.17 (s, 1H), 6.78 (s, 1H), 5.73 (d, J = 3.0 Hz, 1H), 2.28 (s, 3H).

4-Methoxy-1H-inden-1-one. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.76 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 5.76 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H).

4-((tert-butyldimethylsilyl)oxy)-1H-inden-1-one. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.52 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 5.91 (d, J = 8.0 Hz, 1H), 1.01 (s, 9H), 0.21 (s, 6H).

Ethyl 2-((5-methyl-3-oxo-7-((phenylsulfonyl)oxy)-2,3-dihydro-1H-inden-1-yl)(nitro)methyl)-6-((phenylsulfonyl)oxy)benzoate (4). To a stirred solution of ethyl 2-(nitromethyl)-6-((phenylsulfonyl)oxy)benzoate, 34 (0.97 g, 2.65 mmol) and 6-methyl-1-oxo-
1H-inden-4-yl benzenesulfonate, 5 (0.63 g, 2.10 mmol) in 10 mL acetonitrile was added DBU (0.40 mL, 2.65 mmol) at 0 °C under an Argon atmosphere and stirred at room temperature overnight, where it was worked up with 5 % aqueous HCl and extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over MgSO₄ and evaporated in vacuo. Purification via silica gel chromatography using 40 % ethyl acetate in hexanes yielded the desired Michael adduct as an inseparable mixture of diastereomers in 72% yield.

10-Hydroxy-2-methyl-11-oxo-11H-benzo(b)fluorene-4,9-diyldibenzesulfonate (44).

To a stirred solution of freshly prepared LDA (2.2 eq.) in THF at -78 °C was added a solution of the Michael adduct (0.41 g, 0.61 mmol) in dry THF (10 mL) under an argon atmosphere. The reaction mixture was allowed to warm to room temperature, where it was stirred for 3 hrs. The reaction mixture was then worked-up with aqueous NH₄Cl and extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over MgSO₄ and evaporated in vacuo. Purification via silica gel chromatography using 30 % ethyl acetate in hexanes yielded the desired cyclized product as a yellow compound in 23% yield. ¹H NMR (300 MHz, CDCl₃): δ 7.94 (d, J = 7.2 Hz, 4H), 7.66-7.62 (m, 2H), 7.53-7.51 (m, 6H), 7.46-7.43 (m, 2H), 7.32 (s, 1H), 7.11(d, J = 8.1 Hz, 1H), 7.09 (s, 1H), 2.38 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 21.6, 113.6, 116.4, 119.8, 121.5, 123.7, 128.6, 128.9, 129.2, 129.6, 130.1, 132.7, 134.5, 135.0, 136.2, 138.5, 141.4, 142.0, 145.6,
147.7, 156.7, 194.3. HRMS (ESI) m/z exact mass calculated for C\textsubscript{30}H\textsubscript{21}O\textsubscript{8}S\textsubscript{2} 573.0672; found 573.0677.

References:


CHAPTER 2. Conversion of aryl benzyl ethers to diarylmethanes. A direct synthesis of diarylbenzofurans

Introduction:

The diarylmethane subunit is contained in a variety of natural products. Representative members are shown in Figure 1 and include procyanidin B2 (1), diarylbenzofuran (2) and justicidin H (3). Because many of these compounds exhibit useful biological activities, a number of synthetic approaches to the diarylmethane subunit have been reported. Organometallic-based approaches and Friedel-Crafts based approaches are the most commonly reported strategies. In some cases the former approach is limited by the requirement for regioselective metalation. The latter approach has the disadvantage that after the acylation, a one- to two-step conversion of the benzophenone to the diarylmethane still needs to be accomplished.

Figure 1. Compounds containing the diarylmethane subunit

Due to their unique positional selectivity, o-aryl rearrangements (Scheme 1) significantly increase the synthetic scope of aromatic substitution reactions involving carbon—carbon bonds. Although studies of o-aryl rearrangements by a number of groups have continued to persist, the studies have been limited to only benzyl phenyl ether, with reports focusing on the catalysts and/or the conditions.
Scheme 1. Rearrangement of benzyl phenyl ether

The initial study on this type of rearrangement was done by W. F. Short in 1928, where he observed that benzyl phenyl ether on heating to 225 °C in presence of anhydrous zinc chloride, or to 180 °C in the presence of hydrogen chloride gave phenol, o-hydroxydiphenylmethane and p-hydroxydiphenylmethane (Scheme 2).

Scheme 2. Rearrangement of benzyl phenyl ether by Short

Tarbell and coworkers in 1950 discussed in depth, the aluminum bromide-mediated rearrangement of benzyl phenyl ethers to o-benzyl phenol in chlorobenzene with respect to product distribution and temperature (Scheme 3). They believed the rearrangement to occur by an intramolecular process, supported by the facts that the ratio of phenol to o-benzyl phenol did not change by addition of excess phenol and that p-benzylphenol was not formed in this reaction.
In 1972, Badr and El-Sherief studied the thermal rearrangement of benzyl naphthyl ethers. They observed that benzyl α-naphthyl ether on heating at 260°C for some days gave 2- and 4-benzyl-1-naphthol, toluene, dibenzyl and 9-phenyl-3,4,5,6-dibenzoxanthene (Scheme 4). Benzyl β-naphthyl ether also rearranged under similar conditions to give corresponding rearranged products.

Scheme 3. Rearrangement by Tarbell

Scheme 4. Explanation for the formation of the unexpected products in the thermal rearrangement
Rearrangement of benzyl α-naphthyl ether in quinoline gave the normal products of rearrangement together with 2- and 4- benzylquinolines and 2-quinolyl-1-hydroxynaphthalene (Scheme 5). The products of this thermal reaction differ markedly from the acid-mediated rearrangements, from which neither benzoanthene nor toluene nor dibenzyl have been reported yet. Due to the formation of all these additional products, they concluded that the thermal rearrangement of the benzyl naphthyl ethers depends on a homolytic fission of the ether to benzyl and naphthoxy radicals.

![Scheme 5. Additional products of the rearrangement of benzyl naphthyl ether in quinoline](image)

Luzzio and Chen in 2009 reported a clever camphorsulfonic acid mediated rearrangement of 2-nitroresorcinol ethers (Scheme 6). They observed that the presence of at least one electron releasing-group on the migrating ring allowed them to use a relatively milder camphorsulphonic acid as the mediator. The 2-nitro-1,3-resorcinolic pattern on the non-migrating ring tolerated the rearrangement well and allowed for only monosubstitution. The nitrophenolic diarylmethane products which were isolated in modest yields could be further transformed into heterocycles such as 2-aminobenzoxazoles and 2-arylbenzoxazoles.
This rearrangement has not been investigated extensively with respect to the scope and substrate generality and thus has acquired less synthetic efficacy than its conventional counterpart, the Fries rearrangement. We describe a Lewis acid-mediated rearrangement of a substituted benzyl aryl ether (Scheme 7) that is strategically different from the commonly reported strategies and is flexible with regard to substituent patterns.

Compounds such as 4 are of interest because if the methylene group of the diarylmethane unit could be efficiently deprotonated, a flexible route to these phenols could lead to a direct synthesis of substituted 2,3 diarylbenzo[b]furans by a benzylation/cyclization protocol (Scheme 8).
Scheme 8. Plausible mechanism for the formation of the 2,3-diarylbenzo[b]furan from 4

The possible mechanism for this reaction is based on the assumption that a base successfully deprotonates the benzylic position which bears the most acidic hydrogen. The anion thus generated reacts with the carbonyl carbon giving rise to the intermediate which undergoes dehydration at elevated temperature to give 2,3-diarylbenzo[b]furan.

2,3-Diarylbenzo[b]furans are a class of natural products that are broadly distributed and exhibit diverse biological activities.\textsuperscript{10} Their biological significance is exemplified by resveratrol-derived natural oligomers anigopreissin A (a resveratrol dimer) and amurensins L and M (resveratrol tetramers) inter alia and the pharmacological use of some other derivatives bearing the same framework. Anigopreissin A, 6 (Figure 2) was isolated from root cultures of \textit{Anigozzanthospreissii} and from rhizomes of \textit{Musa cavendish} plants by D. Holscher and B Schneider.\textsuperscript{11} The broad range of biological activities of resveratrol and its derivatives and their significant pharmacological potential have generated extensive and enduring efforts toward the syntheses of these important compounds.\textsuperscript{12} The
structure of viniferifuran (7a), was first identified from *Vitis vinifera* ‘Kyohou’ on the basis of the extensive NMR spectroscopic and chemical analysis by Niwa and coworkers.\(^{13}\) Its congener, gnetuhainin B, \((7b)\) was isolated from the lianas of *Gnetum hainanense* by the Lin group.\(^{14}\) Compounds such as 8 have been found to have favorable in vitro pharmacological properties as highly potent and selective COX-2 inhibitors.\(^{15}\)

![Structures of compounds](image)

**Figure 2.** Compounds containing diaryl benzo[b]furan subunit

**Results and discussion:**

The rearrangement shown below in Scheme 9 was originally discovered when purification of 9 by silica gel chromatography using ethyl acetate in hexanes produced phenol 10 in 72% yield. This selective reaction was mediated by the acidic surface of the silica gel and occurred at ambient temperature.

![Scheme 9](image)

**Scheme 9.** Rearrangement during column chromatography
To further investigate this rearrangement, we synthesized different benzyl phenyl ethers from the corresponding benzyl bromides and phenols using potassium carbonate as a base (Scheme 11).\textsuperscript{16} We used 4-methoxy benzyl bromide, \textbf{11} and 3,4-dimethoxy benzyl bromide, \textbf{12} for the synthesis of benzyl phenyl ethers. They were prepared by the action of phosphorus tribromide on the commercially available 4-methoxy benzyl alcohol and 3,4-dimethoxy benzyl alcohol, respectively (Scheme 10).\textsuperscript{17} Figure 3 shows different ethers that were prepared to study the boron trifluoride mediated rearrangement.

\begin{center}
\textbf{Scheme 10.} Synthesis of the benzyl bromides
\end{center}

\begin{center}
\textbf{Scheme 11.} General Scheme for the synthesis of benzyl phenyl ethers
\end{center}
Figure 3. Various benzyl phenyl ethers that were studied for the rearrangement

We evaluated the ethers shown in Scheme 12 and found that the ethers bearing only one electron-donating substituent required a Lewis acid such as boron trifluoride etherate for rearrangement. Interestingly, a benzyl ether \((X = H)\) did not react under our conditions. This selectivity may be useful in complex systems.

Scheme 12. Rearrangement of pholoroglucinol ethers

Benzyl ethers of sesamol were synthesized and subjected to the rearrangement conditions as shown in Scheme 13. Although two isomeric phenols could have been produced, the rearrangement was regioselective in generating phenols 15 and 16. These regioselectivities parallel the results observed in Friedel-Crafts acylation of sesamol.\textsuperscript{18}
Scheme 13. Rearrangement of sesamol ethers

Substituted benzyl ethers of 2,6-dimethoxyphenol were prepared and were reacted with boron trifluoride etherate as shown in Scheme 14. In these cases the rearrangement produced the 4-benzyl phenols in good yields.

Scheme 14. Rearrangement of 2,6-disubstituted phenol ethers

To show the synthetic utility of this rearrangement, we decided to use the previously described benzoylation/cyclization strategy (Scheme 8) towards the synthesis of 2,3-diarylbenzo[b]furans. When our initial attempts with LDA as a base did not seem to yield any product, we turned our attention to P₄-tBu, a phosphazene base (Figure 4) as our group had previously demonstrated that even weakly acidic subunits such as benzyl ethers could be deprotonated by the strong base, P₄-tBu (Scheme 15).
Schwesinger and coworkers developed and arranged members of novel class of kinetically highly active uncharged phosphazene bases in order of strength and steric hindrance, to higher pKa values. Phosphazene bases are strong non-metallic, non-ionic and low nucleophilic bases. They are stronger bases than regular amine or amidine bases such as Hünig’s base or DBU. Among the strongest of these phosphazene bases, P₄-tBu is the most readily available. The P₄-tBu base is an extremely strong nonmetallic organic base with pKₐ BH⁺ = 42.7 in acetonitrile.²⁰

![Phosphazene structure](image)

**Figure 4.** P₄-tBu, Schwesinger base

The strong nonmetallic P₄-tBu base has found a variety of uses, from enolate and peptide alkylations to catalytic aldol reactions, desilylations and alkynyl deprotonations.²¹ Kondo and Imahori in 2003 studied a regio- and chemo- selective strategy for deprotonative functionalization of aromatics with P₄-tBu base (Scheme 16).²² As the base is extremely basic and less nucleophilic, it allows for highly chemoselective reactions. Also, the
nonmetallic P₄-tBu base cannot function as a Lewis acid. Therefore, the reactions using P₄-tBu base proceed without the “coordination mechanism”, and the reactions with unique regioselectivities can be expected.

\[
\begin{align*}
\text{Scheme 16. Deprotonative functionalization with P₄-tBu}
\end{align*}
\]

In an approach towards the synthesis of benzofuran, the ether 19 was regioselectively rearranged as shown in Scheme 17. Benzoylation\(^{23}\) of the resulting phenol 20 followed by reaction with P₄-tBu in benzene at 80 °C afforded benzofuran 21 in 47% yield after flash column chromatography.

\[
\begin{align*}
\text{Scheme 17. Synthesis of the diarylbenzofuran, 21}
\end{align*}
\]

**Conclusions:**

In conclusion the Lewis-acid mediated rearrangement of benzyl ethers into diarylmethanes can provide a facile entry into a 2,3-diarylbenzo[b]furan subunit via a benzoylation/ intramolecular cyclization using P₄-tBu as a base. In terms of functionalized diarylmethane synthesis, the benzyl phenyl ether rearrangement of a suitable phenolic ether
substrate would beat the conventional $\alpha$-fries rearrangement as the required one- or two-step carbonyl to methylene conversion can now be circumvented.

**Experimental:**

All NMR spectra were obtained on a Varian VXR spectrometer, operating at 300 or 400 MHz for $^1$H NMR and 75 or 100 MHz for $^{13}$C NMR instrument. Chemical shifts in CDCl$_3$ were reported downfield from TMS (= 0 ppm) for $^1$H NMR. For $^{13}$C NMR, chemical shifts were reported relative to the solvent signal [CDCl$_3$ (77.15 ppm)]. All reactions were carried out under argon unless otherwise noted. Thin-layer chromatography was performed using commercially available 250 micron silica gel plates (Analtech). Commercially available 1000 micron silica gel plates (Analtech) were used for preparative thin-layer chromatography. Visualization of TLC plates was effected with short wavelength ultraviolet light (254 nm). High resolution mass spectra were recorded on an Agilent 6540 QTOF using EI or ESI. All reagents were used directly as obtained commercially unless otherwise noted.

**General procedure for the preparation of aryl bromides.** To a solution of the benzyl alcohol (1.0 equiv.) in diethyl ether were added pyridine (0.05 equiv.) and phosphorus tribromide (1.1 equiv.) sequentially at room temperature under argon. The reaction mixture was then refluxed for 1 hour. After the completion of the reaction, it was quenched with water. The reaction mixture was then extracted with diethyl ether (3x). The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude benzyl bromide was not purified and used as such.
1-(Bromomethyl)-4-methoxybenzene (11). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34 (d, $J = 9.0$ Hz, 2H), 6.88 (d, $J = 9.0$ Hz, 2H), 4.52 (s, 2H), 3.81 (s, 3H).

4-(Bromomethyl)-1,2-dimethoxybenzene (12). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.93-6.89 (m, 2H), 6.78 (d, $J = 6.0$ Hz, 1H), 4.97 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H).

**General Procedure for the Preparation of Aryl Ethers.** To a solution of phenol (1.0 equiv.) in acetone was added anhydrous potassium carbonate (1.5 equiv.) at room temperature under argon. Benzyl bromide (1.2 equiv.) was then added drop wise and the reaction mixture was refluxed till the TLC indicated the completion of the reaction. After the completion of the reaction, water was added to it. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The aryl ethers were not purified and were used as such for the rearrangement reaction.

**General Procedure for the rearrangement reaction.** To a solution of benzyl phenyl ether (1.0 equiv.) in dichloromethane was added BF$_3$.Et$_2$O (1.0 equiv.) drop wise at 0 °C under argon atmosphere. Reaction mixture was allowed to stir at room temperature overnight.
After the completion of the reaction, water was added to it. The aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography using ethyl acetate in hexanes as the eluent.

![Chemical Structure](image)

2-(3,4-Dimethoxybenzyl)-3,5-dimethoxyphenol (10). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.82 (s, 1H), 6.75-6.76 (m, 2H), 6.12 (d, $J = 2.0$ Hz, 1H), 6.03 (d, $J = 2.0$ Hz, 1H), 5.50 (s, 1H of OH), 3.91 (s, 2H), 3.81 (s, 6H), 3.79 (s, 3H), 3.71 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.67, 159.27, 155.63, 148.97, 147.33, 133.93, 120.21, 112.07, 111.44, 108.44, 93.99, 91.58, 56.12, 55.95, 55.48, 28.15. HRMS (ESI) m/z exact mass calculated for C$_{17}$H$_{21}$O$_5$ 305.1384; found 305.1388.

![Chemical Structure](image)

3,5-Dimethoxy-2-(4-methoxybenzyl)phenol (13). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.14 (d, $J = 9$Hz, 2H), 6.78 (d, $J = 9$Hz, 2H), 6.13 (d, $J = 2.4$ Hz, 1H), 6.01 (dd, $J = 7.8$ Hz, 2.4 Hz, 1H), 4.81 (s, 1H of OH), 3.90 (s, 2H), 3.79 (s, 3H), 3.76 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.7, 159.3, 157.9, 155.6, 133.2, 129.4, 114.0, 108.5, 94.4, 91.5, 60.8, 55.9, 55.5, 27.6. HRMS (ESI) m/z exact mass calculated for C$_{16}$H$_{19}$O$_4$ 275.1278; found 275.1268.
1-(Benzyl oxy)-3,5-dimethoxybenzene (14). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35-7.46 (m, 5H), 6.22 (d, $J = 2.1$ Hz, 2H), 6.16 (t, $J = 2.1$ Hz, 1H), 5.05 (s, 2H), 3.79 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 161.8, 160.9, 137.1, 128.9, 128.3, 127.9, 94.0, 93.5, 70.3, 55.6. HRMS (ESI) m/z exact mass calculated for C$_{15}$H$_{17}$O$_3$ 245.1172; found 245.1178.

6-(3,4-Dimethoxybenzyl)benzo[d][1,3]dioxol-5-ol (15). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.73-6.80 (m, 3H), 6.58 (s, 1H), 6.41 (s, 1H), 5.87 (s, 2H), 4.79 (s, 1H of OH), 3.84 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.3, 148.5, 147.8, 146.8, 141.6, 132.6, 120.6, 119.2, 112.0, 111.6, 110.1, 101.2, 98.9, 56.14, 56.1, 36.1. HRMS (ESI) m/z exact mass calculated for C$_{16}$H$_{15}$O$_5$ 287.0925; found 287.0923.

6-(4-Methoxybenzyl)benzo[d][1,3]dioxol-5-ol (16). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.12 (d, $J = 8.4$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.59 (s, 1H), 6.40 (s, 1H), 5.88 (s, 2H), 4.61 (s, 1H of OH), 3.83 (s, 2H), 3.78 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.4, 148.4, 146.8, 141.7, 132.1, 129.7, 119.4, 114.3, 110.2, 101.2, 98.9, 55.5, 35.6. HRMS (ESI) m/z exact mass calculated for C$_{15}$H$_{13}$O$_4$ 257.0808; found 257.0797.
4-(3,4-Dimethoxybenzyl)-2,6-dimethoxyphenol (17). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.74-6.79 (m, 3H), 6.58 (s, 2H), 5.56 (s, 1H of OH), 3.89 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.0, 147.4, 146.5, 145.5, 138.8, 134.1, 127.8, 120.9, 120.2, 112.4, 111.3, 106.5, 60.7, 56.4, 56.1, 56.0, 35.4. HRMS (ESI) m/z exact mass calculated for C$_{17}$H$_{19}$O$_5$ 303.1227; found 303.1232.

2,6-Dimethoxy-4-(4-methoxybenzyl)phenol (18). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.10 (d, $J$ = 8.4 Hz, 2H), 6.8 (d, $J$ = 8.8 Hz, 2H), 6.58 (s, 2H), 5.53 (s, 1H of OH), 3.88 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.0, 146.5, 145.5, 138.8, 133.7, 129.9, 128.0, 120.3, 113.9, 106.5, 60.7, 56.4, 55.5, 35.0. HRMS (ESI) m/z exact mass calculated for C$_{16}$H$_{17}$O$_4$ 273.1132; found 273.1135.

5-Methoxy-2-(4-methoxybenzyl)phenol (19). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.13 (d, $J$ = 8.0 Hz, 2H), 7.00 (d, $J$ = 8.0 Hz, 1H), 6.83 (d, $J$ = 8.0 Hz, 2H), 6.46 (dd, $J$ = 8.4 Hz, 2.4 Hz, 1H), 6.39 (d, $J$ = 2.4 Hz, 1H), 4.95 (s, 1H of OH), 3.88 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.7, 158.3, 154.9, 132.3, 131.5, 129.7, 119.7, 114.3,
106.3, 102.3, 55.6, 55.5, 35.2. HRMS (ESI) m/z exact mass calculated for C_{15}H_{17}O_{3} 245.1172; found 245.1174.

![Chemical Structure](image)

5-Methoxy-2-(4-methoxybenzyl)phenyl benzoate (20). A solution of benzoyl chloride (0.40 mL, 3.42 mmol) in dichloromethane (5 mL) was added drop-wise to a solution of 19 (0.83 g, 3.42 mmol) and triethylamine, Et₃N (0.52 mL, 3.75 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature overnight and it was then poured into water. The mixture was extracted with dichloromethane and the organic layer was washed with 10% aqueous HCl three times, saturated aqueous NaHCO₃ (twice) and brine and dried over MgSO₄ and concentrated *in vacuo*. The product was purified via silica gel chromatography using 5% ethyl acetate in hexanes to give the benzyolated product in 70% yield.

$^1$H NMR (300 MHz, CDCl₃): $\delta$ 8.17 (dd, $J = 8.4$ Hz, 1.2 Hz, 2H), 7.65 (t, $J = 6.0$ Hz, 1H), 7.54-7.49 (m, 2H), 7.15 (d, $J = 8.7$ Hz, 1H), 7.08 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 6.6$ Hz, 2H), 6.79 (s, 1H), 3.87 (s, 2H), 3.68 (s, 3H), 3.73 (s, 3H). $^{13}$C NMR (75 MHz, CDCl₃): $\delta$ 165.1, 159.2, 158.2, 150.0, 133.9, 131.5, 130.5, 130.0, 128.8, 125.9, 114.0, 112.5, 108.5, 55.7, 55.5, 35.1.
6-Methoxy-3-(4-methoxyphenyl)-2-phenylbenzofuran (21). To a solution of the benzoyl derivative of phenol (0.27g, 0.76 mmol) in dry benzene (10mL) was added 1M solution of P₄-tBu in hexane (0.84 mL, 0.84 mmol). The reaction mixture was refluxed for 3 hours. After the completion of the reaction, benzene was evaporated in vacuo. The resulting liquid was purified on silica gel by column chromatography using 5% ethyl acetate in hexanes as eluent to get pure compound in 47% yield. ¹H NMR (300 MHz, CDCl₃): δ 7.63 (d, J = 6.6 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.29 -7.37 (m, 4H), 7.09 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.87 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 159.3, 158.6, 155.1, 149.6, 131.0, 128.6, 128.0, 126.7, 125.3, 124.2, 120.4, 117.3, 114.6, 112.1, 95.9, 56.0, 55.5. HRMS (ESI) m/z exact mass calculated for C₂₂H₁₉O₃ 331.1334; found 331.1187.

References:


CHAPTER 3. Syntheses and biological evaluations of 3-alkenyl salicylic acids

Introduction:

The Gram stain test, developed in the 1800s by Hans Christian Gram, is a method for classifying different types of bacteria using a chemical stain and viewing through a microscope the results on the bacteria’s protective cell wall. Most bacteria are classified into two groups—Gram-positive or Gram-negative—depending on whether they retain a specific stain color. Gram-positive bacteria retain a purple-colored stain, while Gram-negative bacteria appear pinkish or red. Some examples of Gram-negative bacteria include *Campylobacter, Enterobacter, Escherichia, Morganella, Proteus, Providencia, Pseudomonas, Salmonella, Shigella*.

A distinctive feature of Gram-negative bacteria is the presence of a double membrane surrounding each bacterial cell. Although all bacteria have an inner cell membrane, Gram-negative bacteria have a unique outer membrane which contains lipopolysaccharide (an endotoxin) which protects the sensitive inner membrane by blocking antibiotics, dyes, and detergents. As opposed to Gram-positive cells, Gram-negative cells are resistant to lysozyme and penicillin attack.

In addition to greater resistance, Gram-negative bacteria have a great facility for exchanging genetic material (DNA) among strains of the same species and even among different species. This means that if a Gram-negative bacterium either undergoes a genetic change (mutation) or acquires genetic material that confers resistance to an antibiotic, the bacterium may later share its DNA with another strain of bacteria and the second strain can become resistant as well.
Gram-negative bacteria can cause many types of infections and are spread to humans in a variety of ways. Several species, including *Escherichia coli*, are common causes of food–borne disease. *Vibrio cholerae*—the bacteria responsible for cholera—is a waterborne pathogen. Gram-negative bacteria can also cause respiratory infections, such as certain types of pneumonia, and sexually transmitted diseases, including gonorrhea. *Yersinia pestis*, the Gram-negative bacterium responsible for plague, is transmitted to people through the bite of an infected insect or handling an infected animal.

Treating Gram-negative bacterial infections can be difficult because of several unique features of these bacteria. For example, the unique nature of their cell wall makes them resistant to several classes of antibiotics. Infections have typically been treated with broad-spectrum antibiotics, such as beta-lactams followed by carbapenems. However, even these drugs have become ineffective against some bacteria, leaving healthcare providers no choice but to use older drugs, such as colistin\(^1\), which can have toxic side effects.

Gupta and coworkers recently isolated 3-farnesyl-2-hydroxybenzoic acid (Figure 1), from the leaves of *Piper multiplinervium* C. DC. (Piperaceae)\(^2\). *Piper multiplinervium* C. DC. is a climbing shrub in tropical rainforests, which grows from Nicaragua to Peru. The Kuna Indians of Panama, who live in the Kuna Yala Archipelago in the north-eastern part of Panama prepare a traditional remedy with the young leaves of *Piper multiplinervium* using a method called “Ina Kuamakalet” in which the plant material is mixed with water to make a dough, which is divided into small balls and dried under the sun. The dried balls of *Piper multiplinervium* are then dissolved in water and the extract is then used to treat stomach aches. During the course of antimicrobial screening using the agar dilution method, the methanolic leaf extract of *Piper multiplinervium* showed significant activity at 2.5 to 5
µg/mL against Staphylococcus *aureus*, Escherichia *coli*, Pseudomonas *aeruginosa*, Mycobacterium *smegmatis*, Klebsiella *pneumoniae* and Candida *albicans*. Moreover, it was active against Helicobacter *pylori* (MIC 12.5 µg/mL). 3-Farnesyl salicylic acid (1, Figure 1) is the only 2-hydroxybenzoic acid prenylated in the *ortho* position that has been isolated from plants until now.

The great biological activity of 3-farnesyl salicylic acid against various gram negative bacteria prompted us to develop a synthesis of members of this class of compounds. Interestingly, with its salicylic acid subunit, it might also exhibit anti-inflammatory activity. Related natural products include O-methylgrifolic acid (2, Figure 1) that was isolated from the lipophilic fraction of fresh *P. dispanssus* and grifolic acid (3, Figure 1) that was isolated from an American *Albatrellus* species.

![Figure 1](image)

**Figure 1.** Natural products containing salicylic acid subunit

Currently, there exist relatively few direct methods for the synthesis of 3-substituted salicylic acids. Some salicylic acid derivatives can be synthesized directly from their corresponding phenols via a Kolbe–Schmitt carboxylation (Scheme 1); however, that reaction requires proper apparatus to work with carbon dioxide at high pressures and temperatures.
Another common route is through Reimer–Tiemann or Duff formylations of the 2-substituted phenols to give the 3-substituted salicaldehydes followed by oxidation to the acid (Scheme 2). The main drawback of this reaction is that the formylation is rarely selective and the aldehyde can be introduced *ortho* and (or) *para* to the phenol.

Lau reported a useful synthesis of 3-alkyl salicylic acids in 2001 using a MOM-protected phenol. We prepared the MOM ether of 2,6-dibromophenol using MOMCl in the presence of diisopropylethylamine. Alkylation of the anion generated from halogen-metal exchange with farnesyl bromide followed by another halogen-metal exchange and reaction with carbon dioxide produced the protected salicylic acid (Scheme 3). Unfortunately, the
deprotection of the MOM group with aqueous acid gave a complex mixture, presumably due
to the reactions of the trisubstituted alkenes.

![Scheme 3. Synthesis of MOM protected farnesyl salicylic acid](image)

To circumvent this difficulty, we generated the MEM ether of 2,6-dibromophenol in
quantitative yield as shown in Scheme 4. Halogen-metal exchange followed by reaction
with farnesyl bromide, afforded the alkylated compound in 67% yield. Another halogen-
metal exchange and carboxylation using gaseous carbon dioxide followed by deprotection of
the MEM ether with zinc bromide gave the natural product 1, albeit in only 10% yield over
the last two steps. The same four step sequence was used to synthesize geranyl salicylic acid
2,6-dibromophenol and geranyl bromide (4, Scheme 4).

![Scheme 4. Synthesis of 3-substituted salicylic acids](image)

The low yield of farnesyl salicylic acid over the last two steps could be attributed to
the low solubility of carbon dioxide gas in THF. The lower yield prompted us to look for a
more soluble electrophile. Substitution of methyl chloroformate for the carbon dioxide gave the corresponding methyl ester in 80% yield. Deprotection of the MEM ether and base-mediated hydrolysis of the ester using sodium hydroxide afforded 1 in 80% yield. The substitution of methyl chloroformate for carbon dioxide gas yielded the desired farnesyl salicylic acid in 40% yield over the last three steps, which is a four times increase. Scheme 5 shows the first synthesis of farnesyl salicylic acid, 1.

Scheme 5. Synthesis of farnesyl salicylic acid, 1

To study the structure activity relationships (SAR) of these types of compounds, different analogues of 3-substituted salicylic acid were synthesized. Prenyl salicylic acid (5) was synthesized (Scheme 6) using the same reaction Scheme as shown in Scheme 3, in 19% yield over 5 steps.

Scheme 6. Synthesis of prenyl salicylic acid
To understand how important the double bonds were in the acyclic chain at the 3-position, we synthesized 3-benzyl salicylic acid where the double bonds were a part of the benzene ring. 3-Benzyl salicylic acid was synthesized from commercially available ortho-benzyl phenol in two steps. The first step is the Reimer-Tiemann reaction\textsuperscript{11} which introduces a –CHO group ortho and para to the hydroxyl group. This reaction, as expected was not selective and produced monosubstituted o- and p- aldehydes along with small amount of o,p- dialdehyde (Scheme 7).

Scheme 7. Products of Reimer-Tiemann reaction on o-benzylphenol

The desired o-aldehyde was separated from the mixture using flash column chromatography over silica gel and was then subjected to oxidation under boiling conditions using silver (I) oxide which was freshly prepared by the reaction of silver (I) nitrate and sodium hydroxide\textsuperscript{12} (Scheme 8).

Scheme 8. Synthesis of 3-benzyl salicylic acid
Biological testing:

Compounds 1, 4, 5, 3-benzylsalicylic acid (9), 3-allylsalicylic acid prepared from salicylic acid\(^{13}\) (10), and commercially available 3-phenylsalicylic acid (11), were tested against two strains of bacteria. We used simple zone of inhibition assays to determine their level of antimicrobial activity.

Figure 2. Analogs

Zone of inhibition assay

Zone of Inhibition testing is a fast, qualitative means to measure the ability of an antimicrobial agent to inhibit the growth of microorganisms.\(^{14}\) The assay is performed by spreading a microbial suspension by a sterile swab, evenly, over the face of a sterile agar plate. The antimicrobial agent is applied to the center of the agar plate (in a fashion such that the antimicrobial doesn't spread out from the center) and incubated. If substantial antimicrobial activity is present, then a zone of inhibition appears around the test product. The zone of inhibition is simply the area on the agar plate that remains free from microbial growth. The size of the zone of inhibition is usually related to the level of antimicrobial activity present in the sample or product - a larger zone of inhibition usually means that the antimicrobial is more potent.
Strengths of Zone of Inhibition Testing: Zone of inhibition testing is fast and inexpensive relative to other laboratory tests for antimicrobial activity. It is especially well suited for qualitatively determining the ability of water-soluble antimicrobials to inhibit the growth of microorganisms. A number of samples can be screened for antimicrobial properties quickly using this test method. A variety of antimicrobial product types can be tested using this method. Liquids, coated antimicrobial surfaces, and antimicrobial-impregnated solid products can all be tested for their ability to produce a "zone of inhibition."

Weaknesses of Zone of Inhibition Testing: Zone of Inhibition tests do not necessarily indicate that microorganisms have been killed by an antimicrobial product - just that they have been prevented from growing. Microbial growth agars themselves may interfere with the function of some antimicrobial agents. The method cannot be used to test the activity of antimicrobial agents against viruses, since viruses don't "grow" on agar plates like bacteria because they don't replicate outside of their host organisms.

Results of zone of inhibition assays

Compounds 1, 4, 5, 3-methylsalicylic acid and 3-benzylsalicylic acid, 9 (~50 mg/mL), along with solvent (DMSO) alone, were applied to a 10 mm filter paper disc and positioned at the center of an agar plate that had been inoculated with a wild type E. coli (strain K12). Following incubation at 37 °C for 24 hours, the zone of inhibition (ZOI) was measured. We observed that 3-methylsalicylic acid, as well as solvent alone failed to inhibit bacterial growth (ZOI = 0).

Zone of inhibition assays of the various salicylic acid analogues yielded the following results. The control consisted of salicylic acid and DMSO. With strain MG1655,
compound 1 and 4 gave ZOI values of 5.5 mm and 7 mm respectively whereas the salicylic acid and DMSO solvent control was found to have a ZOI = 5 mm. With another strain NR688, compound 1 and 4 were found to have ZOI = 8 mm and 14 mm respectively. The salicylic acid and DMSO control had the same ZOI value as it did with strain MG 1655. In contrast, the antibiotic tetracycline gave zones of inhibition of 10 mm (MG1655) and 12 mm (NR688). Prenyl salicylic acid, 5 did not show any activity against these strains.

Effect of EDTA on cell membranes

As mentioned earlier, Gram-negative bacteria are resistant to a large number of noxious agents as a result of the effective permeability barrier function of their outer membrane (OM). Such permeability barriers have been thought to be responsible for the resistance of Escherichia coli and other Gram negative organisms to chloramphenicol, actinomycin D, benzyl penicillin and vancomycin. The molecular basis of the integrity of the OM lies in its lipopolysaccharide (LPS)-covered surface. Because of the presence of a number of negative charges in its lipid and inner-core parts, LPS is polyanionic and therefore, can bind cations. Adjacent polyanionic LPS molecules are linked electrostatically by divalent cations (Mg$^{2+}$, Ca$^{2+}$), inherent in the OM, to each other to form a stable “covering” on the surface of the OM. These cation-binding sites of LPS are therefore essential for the integrity of the OM. From studies done on the naturally occurring polycationic antibiotics of the polymyxin group, it has been known that they complex strongly with LPS and upset the entire OM, which helps them to penetrate the OM to reach their final target, the cytoplasmic membrane.
A chelating agent, such as ethylenediamine tetraacetic acid (EDTA)\textsuperscript{20} can also bind Ca\textsuperscript{2+} and Mg\textsuperscript{2+} ions. Its OM-disorganizing and permeabilizing action is well known. EDTA has a profound effect on the OM permeability barrier of Gram-negative enteric bacteria and \textit{P. aeruginosa}.\textsuperscript{21} By chelation, it removes stabilizing divalent cations from their binding sites in lipopolysacchride. This results in the release of a significant proportion of lipopolysacchride from the cells, as first shown by Leive\textsuperscript{22} in 1965. The permeability-increasing effect is at least partly facilitated by the activation of the detergent-resistant phospholipase A1. Under certain conditions, the OM becomes ruptured and permeable to macromolecules.

The molecular mechanism by which the EDTA-treated OM allows the penetration of hydrophobic compounds is not known, but it is very logical to suggest that the loss of LPS will secondarily lead to the appearance of phospholipids in the outer leaflet of the OM. The formed phospholipid bilayer patches would then act as channels through which hydrophobic compounds, such as antibiotics can diffuse.

As EDTA helps in the penetration of lipophilic compounds by rupturing the OM, we decided to synthesize \textbf{14} and study the effect of EDTA, if any, on its biological activity. Compound \textbf{14} was synthesized from commercially available 5-chlorosalicylic acid and the di-anhydride of EDTA (Scheme 9)\textsuperscript{23}. 

This EDTA conjugate did not show any antibacterial activity against MG1655 and NR688, as indicated by its zone of inhibition assay.

Conclusions:

While compounds 1 and 4 showed low levels of antimicrobial activity against both *E. coli* strains, these results indicate that the antimicrobial activity reported by Rüegg *et al.* cannot be explained solely by the presence of salicylic-acid derivatives. Evaluation of 3-methyl salicylic acid, 1 and 4 showed that the alkene is important for biological activity. Further testing on 3-benzyl salicylic acid, 9 and 3-phenyl salicylic acid, 11 showed that the double bonds need to be present in an acyclic chain form and not as a part of the benzene ring. The synthesis of salicylic acid 1 in five steps from commercially available 2,6-dibromophenol makes available a novel antibiotic for further biological evaluation.

Experimental:

All NMR spectra were obtained on a Varian VXR spectrometer, operating at 300 or 400 MHz for $^1$H NMR and 75 or 100 MHz for $^{13}$C NMR instrument. Chemical shifts in
CDCl\textsubscript{3} were reported downfield from TMS (\(\approx 0\) ppm) for \(^1\)H NMR. For \(^{13}\)C NMR, chemical shifts were reported relative to the solvent signal [CDCl\textsubscript{3} (77.15 ppm)]. Chemical shifts in (CD\textsubscript{3})\textsubscript{2}SO were reported relative to the solvent signal [(CD\textsubscript{3})\textsubscript{2}SO (2.50 ppm)]. All reactions were carried out under argon unless otherwise noted. Thin-layer chromatography was performed using commercially available 250 micron silica gel plates (Analtech). Preparative thin-layer chromatography was performed using commercially available 1000 micron silica gel plates (Analtech). Visualization of TLC plates was effected with short wavelength ultra violet light (254 nm). High resolution mass spectra were recorded on an Agilent 6540 QTOF using EI or ESI. All reagents were used directly as obtained commercially unless otherwise noted.

**Antimicrobial activity assays:** We tested the antimicrobial activity of the compound using a standard disc diffusion assay. For this we inoculated 10 cm LB agar plates with overnight cultures of wild-type *Escherichia coli* K-12 along with a K-12 mutant (strain NR688) with impaired LPS biosynthesis showing heightened sensitivity to hydrophobic drugs.\(^{24}\) Sterile filter paper disks (5 mm) were positioned at the center of the plates and impregnated with either 2 mg of each compound, or antibiotic control (tetracycline, 15 mg). The diameter of the zone of inhibition of growth around each disk was recorded in mm after overnight incubation at 37 °C.

![structure](image)

1,3-Dibromo-2-((2-methoxyethoxy)methoxy)benzene. In an oven-dried flask under argon, 2,6-dibromophenol (2.04 g, 8.09 mmol) was dissolved in 20 mL dry
dichloromethane. To this were added diisopropylethylamine (7.05 mL, 40.46 mmol) and MEMCl (2.84 mL, 25.08 mmol). The mixture was allowed to stir at room temperature overnight, where it was worked up with saturated NaHCO₃, extracted with dichloromethane, and dried over MgSO₄. Purification by silica gel chromatography using 10% ethyl acetate in hexanes yielded the protected phenol in 95% yield. ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, J = 7.8 Hz, 2H), 6.82 (t, J = 7.95 Hz, 1H), 5.23 (s, 2H), 4.07 (t, J = 4.65 Hz, 2H), 3.59 (t, J = 4.65 Hz, 2H), 3.35 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 151.7, 133.1, 126.8, 118.8, 98.6, 71.9, 70.1, 59.3. HRMS (EI) m/z exact mass calculated for C₁₀H₁₂Br₂O₃ 337.9153; found 337.9160.

1-Bromo-3-methylbut-2-ene. To a solution of 3-methylbut-2-en-1-ol (2.06 g, 23.97 mmol) in diethyl ether (25 mL) was added phosphorus tribromide (2.73 mL, 28.76 mmol) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 1 h. After the completion of the reaction, it was diluted with diethyl ether and washed with an aqueous solution of NaHCO₃. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude prenyl bromide was not purified and used as such. ¹H NMR (300 MHz, CDCl₃): δ 5.51 (t, J = 5.55 Hz, 1H), 4.00 (d, J = 8.4 Hz, 2H), 1.77 (s, 3H), 1.72 (s, 3H).

1-Bromo-2-((2-methoxyethoxy)methoxy)-3-(3-methylbut-2-en-1-yl)benzene. The MEM protected phenol (1.18 g, 3.48 mmol) in dry THF (10 mL) was treated with 2.5 M n-BuLi
(1.39 mL, 3.47 mmol) at -78 °C under argon. The reaction mixture was stirred at this temperature for 30 minutes. The resultant mixture was treated with a solution of freshly prepared prenyl bromide (0.62 g, 4.16 mmol) in THF (2 mL). The reaction mixture was allowed to warm to room temperature and allowed to stir overnight, where it was worked up with aqueous NH₄Cl, extracted with diethyl ether, dried over MgSO₄ and concentrated in vacuo. Purification via silica gel chromatography using 5% ethyl acetate in hexanes yielded pure compound in 67 % yield. 

1H NMR (300 MHz, CDCl₃): δ 7.38 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 5.30-5.25 (m, 1H), 5.18 (s, 2H), 4.01 (t, J = 4.65 Hz, 2H), 3.61 (t, J = 4.65 Hz, 2H), 3.44 (d, J = 7.2 Hz, 2H), 3.40 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H). 13C NMR (75 MHz, CDCl₃): δ 18.0, 25.9, 29.2, 59.2, 69.7, 71.9, 98.8, 117.5, 122.4, 125.8, 129.3, 131.3, 133.3, 137.6, 152.7.

Methyl-2-((2-methoxyethoxy)methoxy)-3-(3-methyl-2-en-1-yl)benzoate. The prenyl adduct (0.32 g, 0.97 mmol) in dry THF (10 mL) was treated with 2.5 M n-BuLi (0.43 mL, 1.07 mmol) at -78 °C under argon. The reaction mixture was stirred at this temperature for 30 minutes. A solution of methyl chloroformate (0.11 mL, 1.46 mmol) in THF (2mL) was added to the reaction mixture, which was then warmed to room temperature for 3 hr, where it was quenched with HCl. The reaction mixture was extracted with ethyl acetate, dried over MgSO₄ and concentrated in vacuo. Purification via silica gel chromatography using 15 % ethyl acetate in hexanes yielded pure compound in 59 % yield. 

1H NMR (300 MHz, CDCl₃): δ 7.65 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 7.34 (dd, J = 7.5 Hz, 1.5Hz, 1H), 7.09 (t, J = 7.65 Hz,
1H), 5.31-5.26 (m, 1H), 5.14 (s, 2H), 3.92 (t, J = 4.65 Hz, 2H) 3.88 (s, 3H), 3.57 (t, J = 4.65 Hz, 2H), 3.45 (d, J = 7.2 Hz, 2H), 3.38 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 18.1, 26.0, 28.6, 52.4, 59.3, 69.4, 71.9, 100.3, 122.4, 124.2, 124.7, 129.4, 133.5, 134.2, 136.8, 155.7, 167.0.

**Methyl 2-hydroxy-3-(3-methylbut-2-en-1-yl)benzoate**. The MEM protecting group was removed using ZnBr\(_2\). The ZnBr\(_2\) was freshly prepared by suspending oven-dried zinc powder (0.70 g) in 5 mL dry THF. To this was added 1,2-dibromoethane (0.99 mL) and the solution was heated to reflux overnight, during which time the color turned cloudy white. The MEM protected phenol from the previous step (0.29 g, 0.97 mmol) was added to this freshly prepared ZnBr\(_2\) solution. The reaction mixture was then stirred overnight at room temperature. The reaction was worked up with H\(_2\)O, extracted with ether, dried over MgSO\(_4\) and concentrated *in vacuo*. Purification via silica gel chromatography using 5 % ethyl acetate in hexanes yielded pure compound in 70 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 11.09 (s, 1H), 7.70 (dd, J = 7.95 Hz, 1.65 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 6.81 (t, J = 7.5 Hz, 1H), 5.38-5.32 (m, 1H), 3.94 (s, 3H), 3.39 (d, J = 7.2 Hz, 2H), 1.78 (s, 3H), 1.74 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 18.0, 26.0, 28.1, 52.4, 112.0, 118.8, 122.0, 127.7, 130.3, 133.4, 135.4, 159.9, 171.3.
2-Hydroxy-3-(3-methylbut-2-en-1-yl)benzoic acid (5). To a solution of methyl ester (0.095 g, 0.43 mmol) from the previous step in methanol (5mL) was added a solution of NaOH (0.069 g, 1.72 mol) in H$_2$O (2.5 mL) and the resulting suspension was heated at 55 °C for 3 hours. After the reaction was done, it was cooled to room temperature and washed with diethyl ether. The aqueous layer was acidified (1N HCl) and the suspension was extracted with ethyl acetate, dried over MgSO$_4$ and concentrated in vacuo to give the prenyl salicyclic acid as an off-white solid in 67 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 10.66 (s, 1 H), 7.79 (dd, $J = 7.95$ Hz, 1.65 Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 6.86 (t, $J = 7.5$ Hz, 1H), 5.35-5.29 (m, 1H), 3.37 (d, $J = 7.2$ Hz, 2H), 1.77 (s, 3H), 1.73 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 18.0, 26.0, 28.1, 110.9, 119.3, 121.7, 128.7, 130.6, 133.7, 136.8, 160.5, 175.6. HRMS (EI) m/z exact mass calculated for C$_{12}$H$_{14}$O$_3$ 206.0943; found 206.0947.

1-Bromo-2-((2-methoxyethoxy)methoxy)-3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene. The MEM protected phenol (1.02 g, 2.99 mmol) was dissolved in dry THF (10 mL) under argon at -78 °C. To this was carefully added a solution of 2.5 M n-BuLi (1.2 mL, 2.99 mmol) and the reaction was stirred at -78 °C for 30 minutes. The reaction mixture was then treated with a solution of freshly prepared farnesyl bromide (0.94 g, 3.29 mmol) in 5 mL THF. The reaction was allowed to warm to room temperature and allowed to stir overnight, where it was worked-up with aqueous NH$_4$Cl, extracted with ether, and
dried over MgSO₄. Purification via silica gel chromatography using 5% ethyl acetate in hexanes yielded the desired compound in 67% yield. $^1$H NMR (300 MHz, CDCl₃): $\delta$ 7.38 (d, $J = 6.0$ Hz, 1H), 7.12 (d, $J = 5.7$ Hz, 1H), 6.92 (t, $J = 5.85$ Hz, 1H), 5.31-5.28 (m, 1H), 5.18 (s, 2H), 5.14-5.07 (m, 2H), 4.01 (t, $J = 3.5$ Hz, 2H), 3.61 (t, $J = 3.6$ Hz, 2H), 3.46 (d, $J = 5.4$ Hz), 3.40 (s, 3H), 2.13-1.95 (m, 8H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 6H). $^{13}$C NMR (75 MHz, CDCl₃): $\delta$ 152.6, 137.6, 135.4, 133.6, 131.3, 129.3, 128.7, 125.9, 124.5, 123.3, 118.4, 116.4, 98.8, 71.9, 69.7, 59.3, 39.9, 39.5, 29.0, 27.0, 26.7, 26.0, 18.0, 16.4, 16.3. HRMS (ESI) m/z exact mass calculated for C$_{25}$H$_{37}$BrO$_3$ 464.1926; found 464.1938.

Methyl 2-((2-methoxyethoxy)methoxy)-3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoate. Farnesyl adduct (0.61 g, 1.13 mmol) was dissolved in 10 mL dry THF at -78 °C, where it was treated with 2.5 M $n$-BuLi (0.50 mL, 1.25 mmol) for 30 minutes. A solution of methyl chloroformate (0.13 mL, 1.69 mmol) in THF (2 mL) was added to the reaction mixture, which was then warmed to room temperature and allowed to stir overnight, where it was quenched with HCl. The reaction mixture was extracted with ethyl acetate, dried over MgSO₄ and concentrated in vacuo. Purification via silica gel chromatography using 15% ethyl acetate in hexanes yielded pure compound in 80% yield. $^1$H NMR (300 MHz, CDCl₃): $\delta$ 7.64 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 7.34 (d, $J = 7.5$ Hz, 1H), 7.07 (t, $J = 7.65$ Hz, 1H), 5.32-5.27 (m, 1H), 5.13 (s, 2H), 5.13-5.05 (m, 2H), 3.92 (t, $J = 4.65$ Hz, 2H), 3.87 (s, 3H), 3.57 (t, $J = 4.65$ Hz, 2H), 3.46 (d, $J = 7.2$ Hz, 2H), 3.37 (s, 3H), 2.12-1.96 (m, 8H), 1.67 (s, 3H), 1.66 (s, 3H), 1.58 (s, 6H). $^{13}$C NMR (100 MHz, CDCl₃): $\delta$ 167.0, 155.7, 137.3,
136.7, 135.5, 134.1, 129.4, 125.1, 124.6, 124.2, 122.2, 100.3, 71.9, 69.4, 59.3, 52.3, 39.9, 32.2, 28.3, 26.9, 25.9, 23.6, 17.9, 16.4, 16.3. HRMS (ESI) m/z exact mass calculated for C_{27}H_{41}O_{5} 445.2949; found 445.2954.

**Methyl-2-hydroxy-3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoate.** The MEM protecting group was removed using ZnBr\(_2\). The ZnBr\(_2\) was freshly prepared by suspending oven-dried zinc powder (0.16 g, 2.55 mmol) in 10 mL dry THF. To this was added 1,2-dibromoethane (0.24 mL, 2.81 mmol) and the solution was heated to reflux overnight, during which time the color turned cloudy white. Methyl ester from the previous step (0.10 g, 0.23 mmol) was added to this freshly prepared ZnBr\(_2\) solution. The reaction mixture was stirred overnight at room temperature. The reaction was worked up with H\(_2\)O, extracted with ether, dried over MgSO\(_4\) and concentrated in vacuo. Purification via silica gel chromatography with 5 % ethyl acetate in hexanes yielded pure compound in 70 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 11.05 (s, OH), 7.69 (d, \(J = 8.1\) Hz, 1H), 7.32 (d, \(J = 7.5\) Hz, 1H), 6.80 (t, \(J = 7.65\) Hz, 1H), 5.36-5.31 (m, 1H), 5.14-5.07 (m, 2H), 3.93 (s, 3H), 3.38 (d, \(J = 7.5\) Hz, 2H), 2.12-1.99 (m, 8H), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 171.3, 159.9, 137.2, 135.4, 130.2, 127.6, 125.2, 124.6, 124.3, 121.8, 118.8, 111.9, 52.4, 39.9, 32.2, 27.8, 26.9, 26.7, 26.6, 26.0, 17.9, 16.3. HRMS (ESI) m/z exact mass calculated for C\(_{23}\)H\(_{33}\)O\(_3\) 357.2424; found 357.2430.
2-Hydroxy-3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoic acid (1). To a solution of the phenolic compound (0.047 g, 0.13 mmol) from the previous step in MeOH (5 mL) was added a solution of NaOH (0.02 g, 0.53 mmol) in H₂O (0.7 mL) and the resulting suspension was heated at 55 °C for 3 hours. After the reaction was done, it was cooled to room temperature and washed with diethyl ether. The aqueous layer was acidified with 1N HCl and the suspension was extracted with ethyl acetate, dried over MgSO₄ and concentrated in vacuo to give the farnesyl salicylic acid in 72 % yield. ¹H NMR (300 MHz, CDCl₃): δ 10.68 (s, OH), 7.80 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.2 Hz, 1H), 6.86 (t, J = 7.2 Hz, 1H), 5.36-5.32 (m, 1H), 5.13-5.07 (m, 2H), 3.39 (d, J = 7.5 Hz, 2H), 2.15-1.98 (m, 8H), 1.72 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 175.4, 160.6, 137.3, 136.6, 135.3, 130.5, 128.7, 125.2, 124.6, 124.3, 121.6, 119.2, 110.8, 40.2, 40.0, 32.2, 27.9, 26.7, 25.9, 17.9, 16.4, 16.3. HRMS (ESI) m/z exact mass calculated for C₂₂H₂₉O₃ 341.2122; found 341.2129.

(E)-1-Bromo-3-(3,7-dimethylocta-2,6-dien-1-yl)-2-((2methoxyethoxy)methoxy)benzene.

The MEM-protected phenol (0.37 g, 0.93 mmol) in THF (10 mL) was treated with 2.5 M n-BuLi (0.37 mL, 0.93 mmol) at -78 °C for 30 min under argon. The resultant mixture was treated with a solution of freshly prepared geranyl bromide (0.24 g, 1.1 mmol) in THF (2 mL). The reaction mixture was allowed to warm to room temperature where it was stirred
overnight. The reaction was worked up with aqueous NH₄Cl, extracted with diethyl ether, dried over MgSO₄ and concentrated in vacuo. Purification via silica gel chromatography using 5% ethyl acetate in hexanes yielded the geranyl adduct in 83% yield. ¹H NMR (300 MHz, CDCl₃): δ 7.49 (d, J = 6.0 Hz, 1H), 7.11 (d, J = 6.0 Hz, 1H), 6.93 (t, J = 6.0 Hz, 1H), 5.28 (t, J = 6.0 Hz, 1H), 5.18 (s, 2H), 5.10 (t, J = 6.0 Hz, 1H), 4.02 (t, J = 6.0 Hz, 2H), 3.62 (t, J = 6.0 Hz, 2H), 3.46 (d, J = 6.0 Hz, 1H), 3.40 (s, 3H), 2.10-2.05 (m, 4H),1.68 (s, 6H), 1.60 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 152.6, 137.3, 133.6, 131.8, 131.3, 129.3, 125.9, 124.4, 122.2, 117.6, 98.8, 71.9, 69.7, 59.3, 39.9, 29.0, 26.8, 26.0, 18.0, 16.4. HRMS (ESI) m/z exact mass calculated for C₂₀H₂₉BrO₃ 396.1300; found 396.1308.

(E)-3-(3,7-Dimethylocta-2,6-dien-1-yl)-2-hydroxybenzoic acid (4). Geranyl adduct (0.21 g, 0.77 mmol) was dissolved in 10 mL dry THF at -78 °C, where it was treated with 2.5 M n-BuLi (0.31 mL, 0.77 mmol) for 30 min. Carbon dioxide gas was bubbled through the solution and warmed to room temp for 2 h. The reaction was worked up with acetic acid and concentrated. The crude product was used in the next step without further purification. Zinc bromide was prepared on the same scale as in the synthesis of 1. The starting material was added to the zinc bromide solution in THF and stirred overnight. The reaction was worked up with H₂O, extracted with diethyl ether, dried over MgSO₄ and concentrated in vacuo. Purification via silica gel chromatography using 15% ethyl acetate in hexanes yielded 4 as an off-white solid in 74% yield over 2 steps. ¹H NMR (300 MHz, CDCl₃): δ 10.72 (s, OH), 8.02 (d, J = 6.0 Hz, 1H), 7.38 (d, J = 6.0 Hz), 7.03 (t, J = 6.0, 1H), 5.32 (t, J = 6.0 Hz,
1H), 5.10 (t, J = 6.0 Hz, 1H), 3.51 (d, J = 6.0 Hz, 1H), 2.03-1.96 (m, 4H), 1.68 (s, 6H), 1.60 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 169.5, 153.1, 136.8, 136.0, 132.0, 131.2, 124.2, 121.6, 119.7, 116.0, 47.8, 41.2, 39.8, 32.0, 23.1, 19.9. HRMS (ESI) m/z exact mass calculated for C$_{17}$H$_{22}$O$_3$ 274.1569; found 274.1575.

3-Benzyl-2-hydroxybenzaldehyde (6). In a three-necked flask fitted with a reflux condenser was placed 2-benzyl phenol (1.00 g, 5.43 mmol) in 10 mL 95% ethanol. It was stirred before a solution of NaOH in H$_2$O (1.57 g in 3.3 mL H$_2$O) was rapidly added. The reaction mixture was then heated to 80 °C and chloroform (0.70 mL, 8.65 mmol) was added drop-wise to maintain gentle refluxing. Near the end of the addition, the sodium salt of the aldehyde separated out. Stirring was continued for an additional 1 h after all the chloroform was added. Ethanol and excess chloroform were then removed on a rotary evaporator. HCl was added to the residue with stirring until the contents of the flask were acidic. Ethyl acetate was then added to the solution to extract the organic compound. The organic layer was washed with water twice, dried over MgSO$_4$ and concentrated on rotary evaporator. The crude was purified via silica gel column chromatography using 10% ethyl acetate in hexanes to separate the desired o-aldehyde from the undesired p- aldehyde and o,p- disubstituted aldehyde. $^1$H NMR (300 MHz, CDCl$_3$): δ 11.38 (s, OH), 9.89 (s, 1H), 7.45 (d, J = 1.8 Hz, 1H), 7.43-7.22 (m, 6H), 6.96 (t, J = 7.5 Hz, 1H), 4.04 (s, 2H).
3-Benzyl-4-hydroxybenzaldehyde (7). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.78 (s, 1H), 7.70-7.67 (m, 2H), 7.30-7.22 (m, 5H), 6.96 (d, $J = 9$ Hz, 1H), 4.05 (s, 2H).

5-Benzyl-4-hydroxyisophthalaldehyde (8). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 11.93 (s, OH), 9.99 (s, 1H), 9.88 (s, 1H), 8.01 (d, $J = 2.1$ Hz, 1H), 7.89 (d, $J = 2.1$ Hz, 1H), 7.32-7.23 (m, 5H), 4.07 (s, 2H).

3-Benzyl-2-hydroxybenzoic acid (9). Fresh was prepared by treating a solution of AgNO$_3$ (0.157g, 0.92 mmol) with 1M aq. NaOH solution (0.93 mL) at room temperature for 30 minutes. A solution of 3-benzyl-2-hydroxybenzaldehyde (0.098g, 0.462 mmol) in 3mL 1M aq. NaOH solution was added to the suspension of silver (I) oxide and the mixture was refluxed for 2 h. After cooling, the mixture was filtered to remove metallic silver and the aq. alkaline filtrate was washed once with diethyl ether, acidified with 10% HCl and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO$_4$ and concentrated in vacuo. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.69 (s, OH), 7.83 (dd, $J = 7.95$ Hz,
1.65 Hz), 7.36-7.21 (m, 6H), 6.87 (t, J = 7.8 Hz, 1H), 4.03 (s, 2H). HRMS (ESI) m/z exact mass calculated for C_{14}H_{11}O_{3} 227.0714; found 227.0717.

5-Chloro-3-((2-chloroacetamido)methyl)-2-hydroxybenzoic acid (12). A finely pulverized mixture of 5-chlorosalicylic acid (0.68 g, 3.93 mmol) and 2-chloro-N-(hydroxymethyl)acetamide (0.49 g, 3.93 mmol) was added portion-wise with stirring to a conc. H_{2}SO_{4} (4.0 mL) at 10 °C. After the mixture was stirred at room temperature for 16 h, it was poured into ice. The crude amide precipitated out as a cream colored powder. ¹H NMR (300 MHz, d-DMSO): δ 8.66 (t, J = 5.9 Hz, 1H), 7.64 (d, J = 2.7 Hz, 1H), 7.38 (d, J = 2.7 Hz, 1H), 4.28 (d, J = 6 Hz, 2H), 4.13 (s, 2H). HRMS (ESI) m/z exact mass calculated for C_{10}H_{10}Cl_{2}NO_{4} 277.9981; found 277.9975.

(3-Carboxy-5-chloro-2-hydroxyphenyl)methanaminium chloride (13). The crude amide from the previous step was hydrolyzed in EtOH- conc. HCl (10:3; v:v) 10mL at reflux for 1.5 h. After cooling to room temperature, the crude product as a white solid precipitated out. The solid product was filtered out and air dried before using for the next step. HRMS (ESI) m/z exact mass calculated for C_{8}H_{9}ClNO_{3} 202.0265; found 202.0725.
3,3’-(5,8-Bis(carboxymethyl)-3,10-dioxo-2,5,8,11-tetraazadodecane-1,12-diyl)bis(5-chloro-2-hydroxybenzoic acid) (14). EDTA di-anhydride (0.03 g, 0.13 mmol) was added portion wise to a solution of the methanaminium chloride from the previous step (0.06 g, 0.27 mmol) and triethylamine, Et₃N (0.29 mmol, 0.04 mL) in dry DMF (5 mL) under argon at room temperature. After stirring the reaction mixture at room temperature overnight, it was concentrated on rotary evaporator. Chloroform was added to the concentrated solution to give the product as a white solid. The supernatant liquid was removed and the residue was trititated twice with chloroform. The solid product was filtered and dried under vacuum. ¹H NMR (300 MHz, d-DMSO): δ 8.55 (t, J = 5.7 Hz, 2H), 7.58 (d, J = 2.7 Hz, 2H), 7.29 (d, J = 2.7 Hz, 2H), 4.26 (d, J = 5.4 Hz, 4H), 3.64 (s, 4H), 3.58 (s, 4H), 3.00 (s, 4H). ¹³C NMR (75 MHz, d-DMSO): δ 171.9, 171.5, 170.0, 163.0, 158.9, 132.7, 129.4, 128.2, 121.9, 116.3, 57.1, 55.4, 52.4, 46.4. HRMS (ESI) m/z exact mass calculated for C₂₆H₂₇Cl₂N₄O₁₂ 657.1008; found 657.1002.

References:


GENERAL CONCLUSIONS

The synthesis and study of some biologically active compounds have been shown in this dissertation. Chapter 1 describes the synthetic efforts towards the tetracyclic core of kinobscurinone. A novel Michael addition/ cyclization strategy has been used towards the construction of the tetracyclic skeleton. The use of LDA for the cyclization not only affects the cyclization but also aids in the removal of the nitro group from the Michael adduct. Various novel indenones (Michael acceptors) and Michael donors were synthesized for this study. Though our efforts with oxidation did not meet with the success we would have liked, this strategy, nevertheless, presents an efficient way of synthesizing molecules with benzo[b]fluorene skeleton.

Chapter 2 describes our recent studies in the benzyl phenyl rearrangement chemistry. Boron trifluoride was successfully used for the rearrangement of a number of substituted benzyl phenyl ethers to their corresponding benzyl phenols in good yields. The study also showed that for rearrangement to occur, it was absolutely crucial to have a methoxy group at para-position in the migrating benzyl ring. The synthetic utility of this type of rearrangement was further shown by the conversion of one of the rearranged products to a 2,3-diarylbenzo[b]furan using P₄-tBu as a base.

Chapter 3 describes the syntheses and determination of biological activities of 3-farnesyl salicyclic acid and its analogues. Three 3-alkenyl salicylic acids namely, 3-farnesyl, 3-geranyl and 3-prenyl salicylic acids, were synthesized in five steps from commercially available 2,6-dibromophenol. This five-step sequence represents the first total synthesis of biologically active 3-farnesyl salicylic acid. Other analogues which were synthesized for
biological evaluations include 3-benzyl salicylic acid and 3,3’-(5,8-bis(carboxymethyl)-3,10-dioxo-2,5,8,11-tetraazadodecane-1,12-diyl)bis(5-chloro-2-hydroxybenzoic acid). While 3-farnesyl salicylic acid and 3-geranyl salicylic acid showed low levels of antimicrobial activity against *E. coli* strains, the EDTA-5-chlorosalicylic acid hybrid molecule did not show any. Further evaluation of various analogues showed that the alkene is important for the biological activity and that the double bonds are required to be present in an acyclic chain form and not as a part of the benzene ring.
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