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Synthesis of polyphenols and azafluorenones

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Synthesis of polyphenols and azafluorenones

by

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GENERAL INTRODUCTION

The total synthesis of natural products continues to be a valuable tool for the development of new pharmaceuticals. Important classes of natural products towards this end include alkaloids, terpenoids, polyketides, polyphenols and others, which have inspired countless synthetic efforts based on their array of biological activity and remarkable scaffolds. Skilled synthetic chemists need to be mindful of not only completing their target but doing so that in a way that is elegant and insightful to those in the synthetic community. The interface between organic and medicinal chemistry provides an avenue for synthetic chemists to do creative, thought-provoking work that is also biologically relevant. In this context, we have investigated the synthesis of polyphenols (±)-1,3,4,5-tetragalloylapiitol, ellagitannins and flavonols and the construction of the alkaloid azafluorenones.

Chapter one describes the total synthesis of (±)-1,3,4,5-tetragalloylapiitol. Our synthesis provides the shortest route to this polyphenolic compound.

The synthesis of natural and unnatural ellagitannins is discussed in chapter two. A key oxidative C-C bond between gallic acid moieties is explored.

The third chapter focuses on a base-mediated cyclization step towards the synthesis of flavonols. This method is vastly different than the current methods for their synthesis.

The synthesis of azafluorenones is examined in chapter four. An intramolecular Heck reaction is used to close the core of these 6-5-6 tricyclic alkaloids.

CHAPTER 1. Total synthesis of (±)-1,3,4,5-tetragalloylapiitol

Introduction:

Human Immunodeficiency virus (HIV) is responsible for the development of acquired immunodeficiency syndrome (AIDS).[1] The World Health Organization (WHO) has classified AIDS as a pandemic, meaning that the disease is not only widespread, but also actively spreading. Two types of HIV have been characterized; HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV-1 has been found to be more prevalent because of its ability to invade the host's genome without being detected. In 2007, AIDS is estimated to have killed 2.1 million people, largely in the underdeveloped countries which have limited access to current antiretroviral treatments (WHO 2007). Particularly affected by this pandemic is Sub-Saharan Africa, which has just over 12% of the world's population but accounts for two-thirds of the population infected with HIV (UN AIDS Report 2011). Without treatment, the average patient with HIV develops AIDS in 9 to 10 years. The average survival rate after acquiring AIDS is only 9 months.[2] Although the disease can be controlled with proper treatment, the high costs associated with the current drug treatments severely limits this option in underdeveloped countries.

HIV is a lentivirus, a retrovirus that uses the reverse transcriptase enzyme to make a genetic DNA copy from its RNA genome. Retroviruses, as the name would indicate, replicate in the opposite fashion of most viruses, which produce RNA from DNA. Once infected, HIV attaches to the glycoproteins that reside on the outside of $CD4^+$ T cells. Eventually the viral envelope fuses with the cell membrane causing the release of the virus into the cell.[3] After penetrating the cell, HIV reverse transcriptase copies the viral RNA into complementary DNA (cDNA).[4] cDNA proceeds to make a genetic copy and then integrates itself into the host cell's DNA via the integrase enzyme. When the proper transcription

factors are present, the virus begins to replicate itself into messenger RNA (mRNA),[5] and fragments of this mRNA are released into the cytoplasm for the production of proteins.[6] Regulatory proteins synthesized from the mRNA, Tat and Rev, are instrumental in allowing the unspliced RNA to leave the nucleus intact.[6] If splicing of the RNA in the nucleus were to occur, it would destroy the viral RNA copy needed for replication, thereby ending the lifecycle of the virus. However, if splicing does not occur, the structural proteins Gag and Env are produced. The Gag protein provides the structural elements of the virus, while the Env protein is responsible for the formation of the viral envelope of the new virus. These newly created proteins help shuttle the virus out of the cell through the plasma membrane and allow it to infect another $CD4^+$ T cell.

Although the replication cycle of HIV has numerous intricate pathways, researchers have not found a way to completely inhibit any of these pathways. The HIV virus replicates about 10^{10} times each day, and coupled with a high mutation rate, the virus's genome changes significantly, which allows HIV to quickly develop resistances to antiviral pharmaceuticals.[7] Another challenge of the disease is that most patients with HIV are unaware they are infected with the disease.[8] Initially, people suffer from an acute infection and experience many of the same symptoms of the common cold, including, fever, sore throat and muscle pain among others. This is followed by the latency period or the incubation period, where few, if any, symptoms are present. This period can last for weeks up until years, allowing the infected patient plenty of time to unknowingly spread the disease. After this incubation period, the patient contracts AIDS which is dictated by the $CD4^+$ T cell counts.

While no cure exists for HIV/AIDS, there are treatment options available to slow the development of AIDS from HIV. Currently, patients take a cocktail of different drugs in

conjunction, referred to as Highly Active Antiretroviral Therapy (HAART). These drugs target an array of enzymatic pathways, including entry inhibitors, CCR5 receptor antagonists, nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, integrase inhibitors, and maturation inhibitors. Multiple targets are necessary; if any of these drugs were taken independently, rapid mutation rates would lead to drug resistance. Combination therapy slows replication on many enzymatic fronts to minimize drug resistance. Unfortunately, not all these drugs work together effectively, so drug makers are constantly improving the combinations to be more advantageous. Overall, treatment of HIV is limited by drug intolerance[9] and virus resistance.[10]

Many different enzymatic pathways have been exploited for drugs against HIV, but inhibition of ribonuclease H (RNase H) has been left unexplored as a treatment option.[11] During reverse transcription, RNase H is needed to cleave the RNA strand from the RNA/DNA heteroduplex.[12] Inhibition of this enzyme would hamper or shut down the ability of the virus to replicate.[13,14] Gustafson and coworkers at the NIH created a screening campaign of over 82,000 compounds and isolated 1,3,4,5-tetragalloylapiitol (**1**, Figure 1) from the plant *Hylodendron gabuunensi*. The compound inhibited HIV-1, HIV-2 and human RNase H with IC_{50} values of 0.24, 0.13 and 1.5 μM respectively.[15] They were able to elucidate the gallic acid moieties of **1** by ^{1}H NMR and ^{13}C NMR. Gallic acid (**3**) has been widely used for medicinal purposes because of its anti-fungal and anti-viral properties.[16] It is also prevalent in tannins, which have been extensively characterized and studied. Further examination of **1** using heteronuclear multiple bond correlation (HMBC) revealed an apiitol core (**2**).[15] This is the first example of apiitol being isolated as a secondary metabolite in nature. Apiitol is the reduced form of D-apiose which is found in plant cell wall polysaccharides.[17]

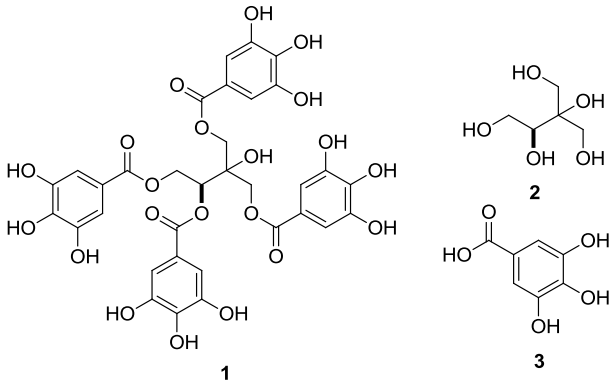
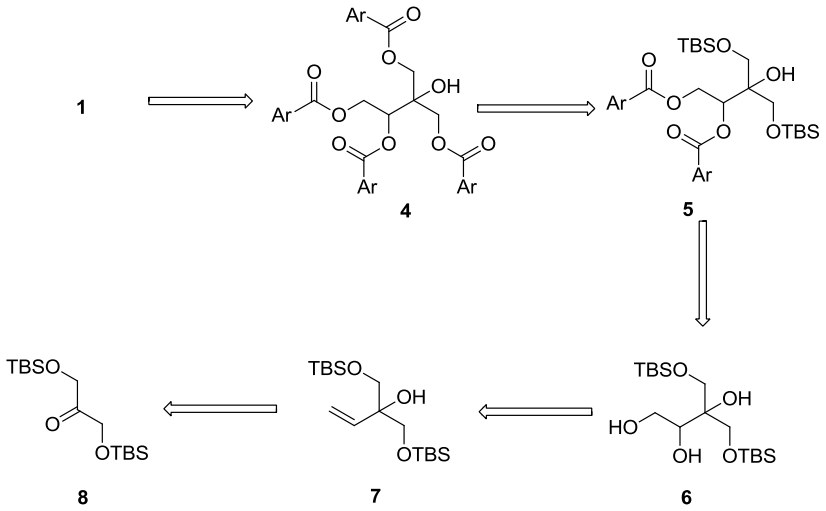


Figure 1. The structures of (-)-1,3,4,5-tetragalloylapiitol (**1**), apiitol (**2**) and gallic acid (**3**)

Results and Discussion:

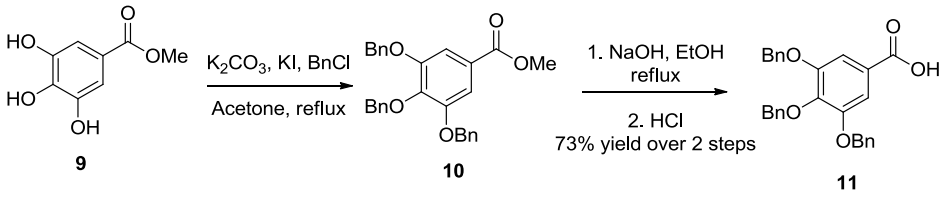
Our impetus for this project was the significant biological activity of (-)-1,3,4,5-tetragalloylapiitol (**1**) and its unusual structure. Our initial retrosynthesis analysis of the compound was cognizant of the polar nature of this molecule. We wanted to protect the 12 gallic acid phenols as benzyl ethers to prohibit protecting group translocation, which is known for other phenol protecting groups, and allow for facile global deprotection. In addition, we also wanted to add the protected gallic acid moieties two at a time to maintain organic solubility throughout the synthesis. With this in mind, we envisioned the benzyl



Scheme 1. The retrosynthesis of 1,3,4,5-tetragalloylapiitol (**1**). Ar = 3,4,5-*O*-benzylgalloyl

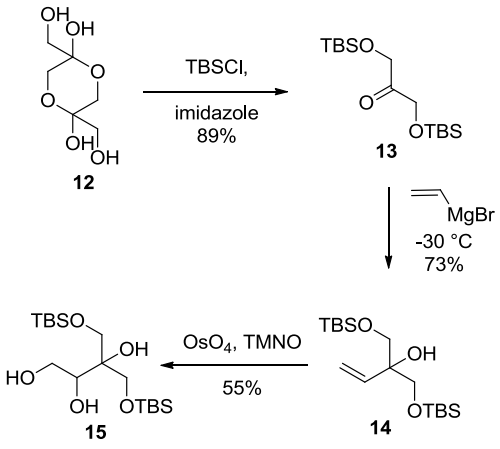
protected intermediate **4** coming from bis-acylated product **5** (Scheme 1). This compound would derive from bis-TBS-protected apiitol **6**. The core of the sugar would be generated from dihydroxylation of **7**, which in turn, would be obtained by vinyl addition to the known TBS ether **8**.

The extensive use of gallates in the synthesis of tannins provided an efficient route to the 3,4,5-O-benzylgallic acid (**11**).[18] Readily known methyl gallate **9** was benzyl protected to afford intermediate **10** (Scheme 2). The compound was hydrolyzed to give **11**.[18]



Scheme 2. The synthesis of trisbenzyl protected gallic acid **11**.

Our synthesis commenced with the formation of the bis-TBS ether **13** from commercially available 1,3-dihydroxyacetone dimer (**12**, Scheme 3).[19] Addition of vinylgrignard at sub-ambient temperatures afforded the terminal olefin **14**, which was

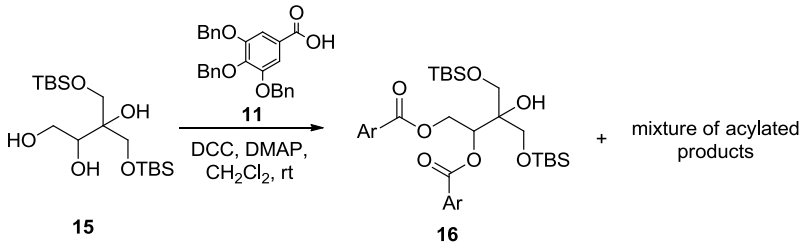


Scheme 3. Synthesis of **15** from commercially available dihydroxyacetone dimer (**12**).

dihydroxylated with catalytic osmium tetraoxide (OsO_4) and trimethylamine N-oxide dihydrate (TMNO) in 55% yield to furnish the protected apiitol intermediate **15**.

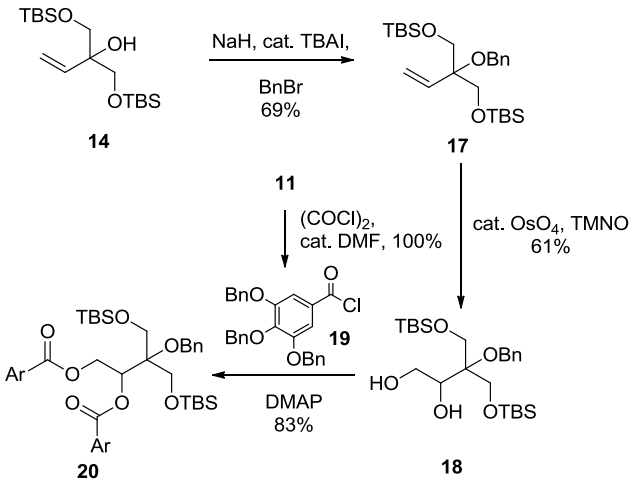
Steglich esterification of triol **15** with acid **11** rendered the desired diacylated product **16** along with a complex mixture of acylated materials (Scheme 4). Difficulty in purification and characterization made proper identification of the acylated products challenging. We postulated that we were generating a mixture of mono-, di- or triacylated compounds. To alleviate this problem, we decided to make two changes to our synthesis:

1. Protection of the tertiary alcohol: The tertiary alcohol would be selectively protected as a benzyl ether to eliminate the potential acylation of the tertiary alcohol.
2. Use of the tribenzylgallic acid chloride rather than acid **11**: The more electrophilic acid chloride will provide a more reactive material to drive the reaction to completion.



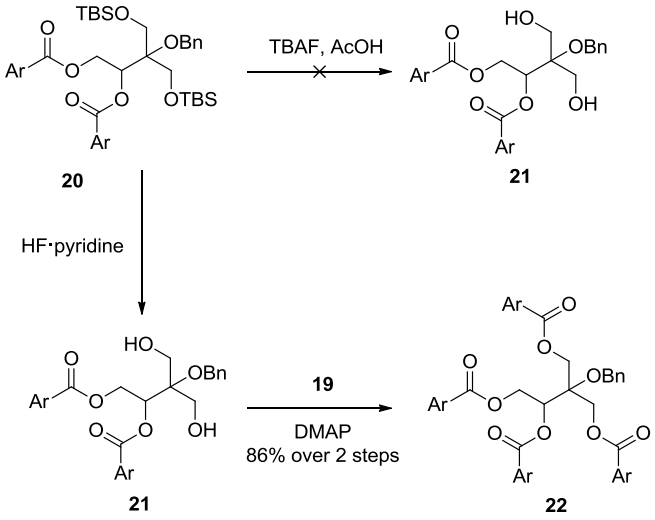
Scheme 4. Steglich esterification of **15** with acid **11**. Ar = 3,4,5-*O*-benzylgalloyl

We protected the tertiary alcohol **14** by the action of sodium hydride, catalytic tetrabutylammonium iodide (TBAI) and benzyl bromide (BnBr) to give olefin **17** (Scheme 5). If TBAI was not included, the reaction yield was less than 10%. Dihydroxylation with catalytic OsO_4 gave diol **18**. Acid **11** was converted to the corresponding acid chloride **19** under mild conditions with oxalyl chloride.[18] Gratifyingly, treating diol **18** with acid chloride **19** afforded the desired digallate **20** cleanly and in 83% yield.



Scheme 5. Synthesis of intermediate **20** through dihydroxylation and benzyl protection of **14**. Ar = 3,4,5-*O*-benzylgalloyl

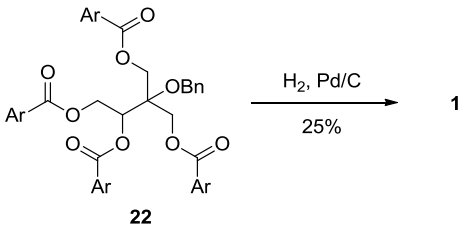
After obtaining **20**, we focused our attention toward the removal of the TBS ethers. Initial attempts with tetrabutylammonium fluoride (TBAF) buffered with acetic acid proved unsuccessful. Either we recovered the starting material or under more rigorous conditions the esters were cleaved. Deprotection of the silyl ethers was achieved using HF·pyridine, which was selective for the deprotection of the silyl groups (Scheme 6).[20] Without further



Scheme 6. Synthesis of protected intermediate **22**. Ar = 3,4,5-*O*-benzylgalloyl

purification, crude diol **21** was coupled with acid chloride **19** to generate benzyl protected intermediate **22** in excellent yield.

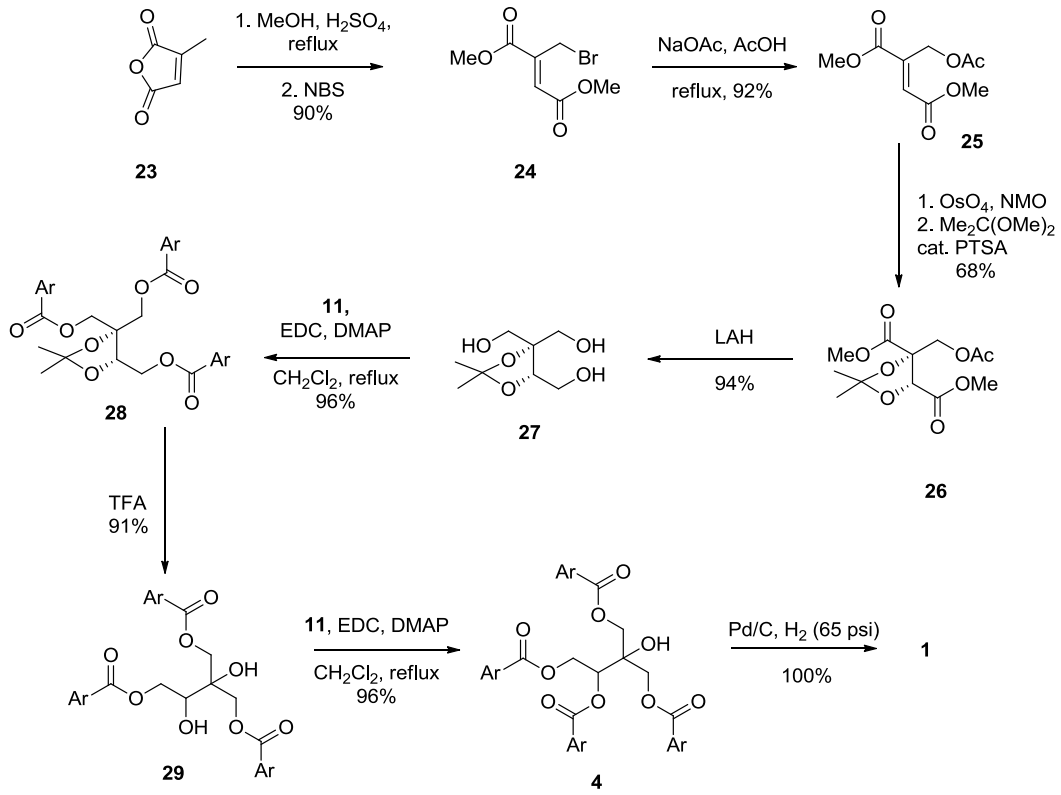
Global deprotection of the benzyl groups was carried out with palladium on carbon under a hydrogen atmosphere to furnish the racemic natural product **1** in 25% yield (Scheme 7). The low yield was the result of recrystallizing on a 30 mg scale. Overall, the natural product was formed in 8 steps and 5% overall yield.[21] Characterization data of product **1** was in excellent agreement with that literature values.[15]



Scheme 7. Completion of the total synthesis of **1**. Ar = 3,4,5-*O*-benzylgalloyl

Upon completion of **1**, we became aware of another synthesis of this molecule by Argade's group.[22] Their synthesis had similarities including the use of the 3,4,5-O-benzylgallic acid **11** and the generation of the esters in iterations to maintain organic solubility. However, their synthesis used a different route to construct the apiitol core. Their synthesis began with methanolysis of commercially available citriconic anhydride (**23**, Scheme 8). Subsequent allylic bromination with N-Bromosuccinimide (NBS) gave allylic bromide **24**, and nucleophilic substitution of **24** with sodium acetate formed the allylic acetate **25**. Dihydroxylation with catalytic OsO_4 produced a diol, which was protected with 2,2-dimethoxypropane and catalytic *para*-toluenesulfonic acid (PTSA) to produce cyclic ketal **26**. Triol **27** was formed from reduction of the esters using lithium aluminum hydride (LAH). Steglich esterification with acid **11** rendered **28**, which followed by ketal deprotection with trifluoroacetic acid (TFA) and a second Steglich esterification produced protected

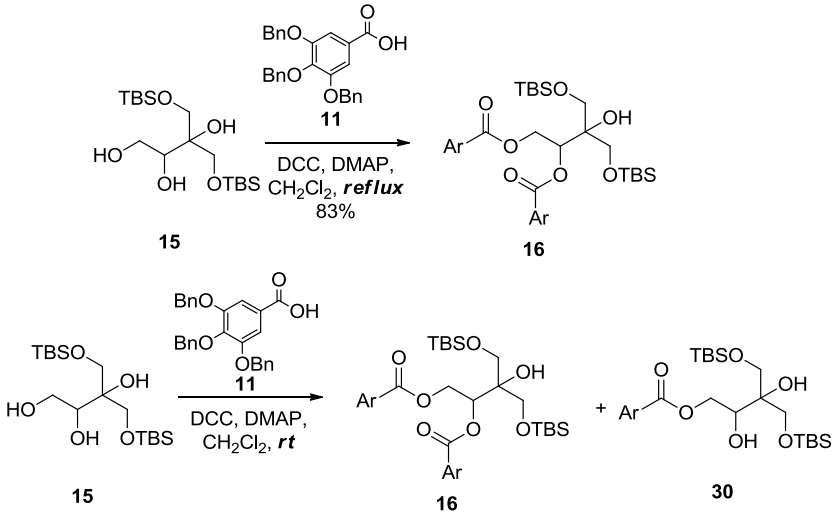
intermediate **29**. Hydrogenolysis at 65 psi of hydrogen and purification by column chromatography afforded racemic **1** in quantitative yield. They accomplished the total synthesis in 10 steps with 44% overall yield.



Scheme 8. Argade's synthesis of **1**. Ar = 3,4,5-*O*-benzylgalloyl

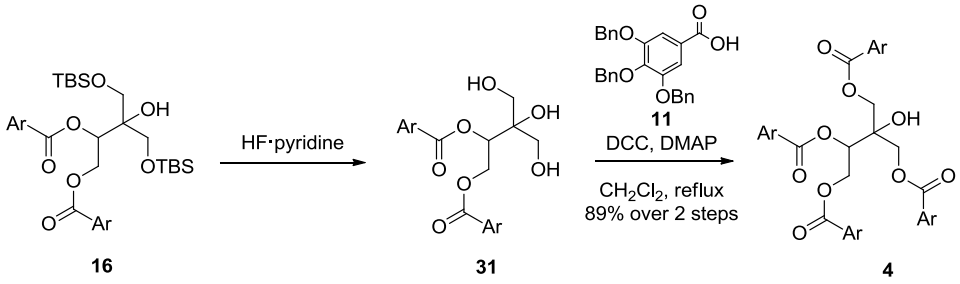
Argade's synthesis provided some valuable information to improve our previous synthesis. They were able to selectively use the Steglich esterification conditions to go from **29** to **4** without protection of the tertiary alcohol. Furthermore, esterification of **27** to **28** was complete and did not lead to a mixture of different acylated products. With this in mind, we decided to reexamine our previous reaction from **15** to **16** using Argade's conditions. The amount of carbodiimide was doubled and the temperature of the reaction was increased to boiling dichloromethane, these conditions afforded compound **16** as a single product (Scheme 9). For comparison, this reaction was also attempted using the conditions we had

used previously, which had resulted in a complex mixture of products (Scheme 4). After exhaustive preparative TLC separations, we were able to separate **16** and monoacylated **30**. This result validated that it was unnecessary to protect the tertiary alcohol and our previous mixture had been the result of incomplete coupling.



Scheme 9. Studies of the Steglich Esterification with triol **15**. Ar = 3,4,5-*O*-benzylgalloyl

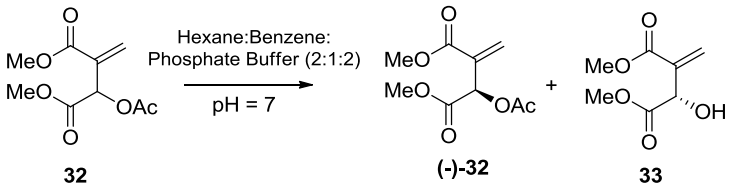
Deprotection of diester **16** with HF·pyridine yielded **31** (Scheme 10). The polarity of **31** made it difficult to purify, so the crude material was taken to the next step without further purification. Esterification of this crude material gave us the protected intermediate **4**. A subsequent and quantitative global deprotection, as shown in Argade's synthesis (Scheme 8), would afford the target molecule **1** in quantitative yield, which constituted a formal



Scheme 10. Synthesis of protected intermediate **4**. Ar = 3,4,5-*O*-benzylgalloyl

synthesis of compound **1**. We accomplished the advanced intermediate **4** in 6 steps in 23% overall yield.[21] This second generation synthesis accomplished the synthesis in one fewer step and avoided the use of the acid chloride **19**.

Since our completion of this synthesis, further research has been done on this intriguing molecule. Argade and co-workers continued their pursuit of **1** by accomplishing the first asymmetric synthesis of the compound.[23] They utilized a key chemoenzymatic resolution that made enatiopure **(-)-32** (Scheme 11). This intermediate was carried through a similar sequence of reactions as their previous synthesis to generate **(-)-1**. Overall, their synthesis was accomplished in 9 steps with an overall yield of 5%.[23]

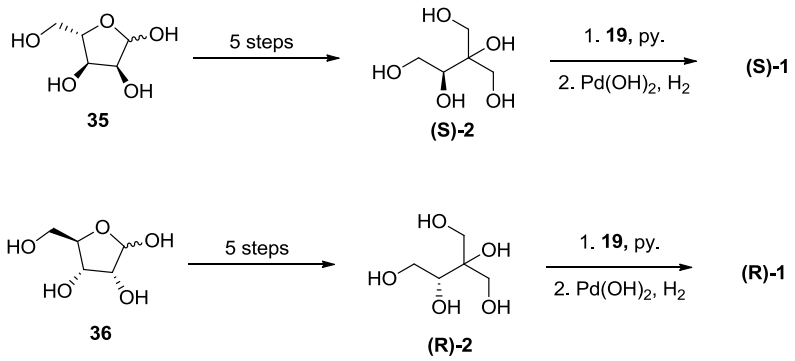


32 **(-)-32** **33**

Entry	Enzyme	Temp/Time	Yield (%) (-)-32/ee
a	PPL	25 °C, 48 h	NR
b	PPL	35 °C, 48 h	NR
c	CCL	25 °C, 48 h	NR
d	CCL	35 °C, 48 h	57/25
e	Amano PS	25 °C, 96 h	83/N/A
f	Amano PS	35 °C, 8 days	44/95
g	Amano PS	50 °C, 84 h	42/97

Scheme 11. Chemoenzymatic resolution of compound **32**. *Pig pancreas* lipase (PPL), *Candida cylindracea* lipase (CCL), *Pseudomonas cepacia* lipase (Amano PS).

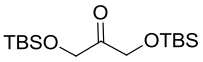
Kojima and coworkers group also accomplished an asymmetric synthesis of **(-)-1** by starting with commercially available L-ribose (**35**).[24] In 5 steps, they were able to synthesize L-apiitol **(S)-2**. Coupling of **(S)-2** with acid chloride **19**, followed by global deprotection, generated **(S)-1** (Scheme 12). However, when they compared optical rotations of this compound to those of the natural product, they were opposite in direction. To further understand this discrepancy, they synthesized **(R)-2** from D-Ribose (**36**). Esterificaiton with **19** and hydrogenolysis produced **(R)-1**. This compound had excellent agreement with the optical rotations reported by Gustafson, which indicated that their synthesis generated the **(R)-1** enantiomer rather than **(S)-1** as reported previously by Argade and coworkers.[15]



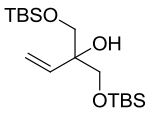
Scheme 12. Synthesis of **(S)-1**, however they proposed the absolute configuration is **(R)-1** based on optical rotation of the extracted natural product.

Since its isolation 5 years ago, **1** has inspired four synthetic efforts. It is a popular synthetic target due to its encouraging biological activity and unique structure. Despite these newer syntheses, our 7-step synthesis is still tied for the shortest route toward the natural product. In addition, our synthesis is amendable to different derivatives including different mono-, di- and triacylated galloylapiitols for future biological studies.

Experimental:

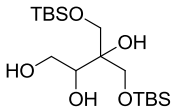


1,3-Bis[(tert-butyldimethylsilyl)oxy]-2-propanone (13). To a stirred solution of dihydroxyacetone dimer (**12**) (4.000 g, 22.20 mmol) in DMF (30 mL) were added imidazole (7.558 g, 111.0 mmol) and *tert*-butyldimethylsilyl chloride (16.73 g, 111.0 mmol) at 0 °C. The mixture was stirred at rt for 1 h and then water (30 mL) was added at 0 °C. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography (hexanes) to give **13** (12.56 g, 89% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.10 (s, 12 H), 0.93 (s, 18 H), 4.42 (s, 4 H).

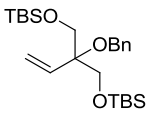


4-tert-Butyldimethylsilyloxy-3-tert-Butyldimethylsilyloxymethyl-1-buten-3-ol. (14). To a stirred solution of vinylmagnesium bromide solution (1M in THF) (9.41 mL, 9.41 mmol) in 15 mL of THF at -30 °C, a solution of the protected ketone **13** (1.000 g, 3.138 mmol) in THF (10 mL) was added dropwise. The mixture was then stirred at -30 °C for 3 h and then saturated aqueous NH_4Cl (20 mL) was added to the mixture. The reaction mixture was extracted with EtOAc (3×10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (hexanes-ethyl acetate, 10:1) to give **14** (0.794 g, 73% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.06 (s, 12 H), 0.90 (s, 18 H), 2.71 (s, 1 H), 3.54 (dd, J = 29.7 and 9.3 Hz, 4 H), 5.19 (dd, J = 11.1 and 1.8 Hz, 1 H), 5.42 (dd, J = 17.4 and 1.8 Hz, 1 H), 5.96 (dd, J = 17.5 and 10.8

Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): -5.24, 18.5, 26.1, 65.9, 75.0, 114.9, 138.7; MS m/z 347 (M^+).

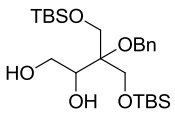


4-tert-Butyldimethylsilyloxy-3-tert-butyldimethylsilyloxymethyl-3-hydroxybutane-1,2-diolbis3,4,5-tris(benzyloxy)benzoate (15). To a solution of olefin **14** (1.500 g, 4.326 mmol), trimethylamine N-oxide dihydrate (0.962 g, 8.65 mmol), and osmium tetraoxide solution (10 mg/1.0 mL) (4.40 mL 0.216 mmol) in acetone (80 mL) and water (40 mL) was stirred at rt for 7 hours. The reaction was quenched with saturated sodium sulfite solution (100 mL) and stirred for 0.5 h, concentrated, and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (hexanes, ethyl acetate) to give **15** (0.9052 g, 55% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.10 (s, 12 H), 0.90 (s, 18 H), 2.86 (t, J = 6.9 Hz, 1 H), 3.05 (d, J = 5.4 Hz, 1 H), 3.35 (s, 1 H), 3.57 – 3.90 (m, 7 H)

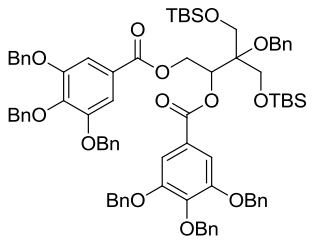


3-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-3-(tert-butyldimethylsilyloxymethyl) butane-1,2-diol (17). To a suspension of NaH (0.243 g 60% dispersion in mineral oil, 6.07 mmol) in THF (20 mL) was added a solution of alcohol **14** (1.915 g, 5.522 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 20 minutes. Tetrabutylammonium iodide (204 mg, 0.552 mmol) and benzyl bromide (0.72 mL, 6.1 mmol) were added. The mixture was allowed to warm to rt and was stirred for 18 h. The reaction was quenched with a

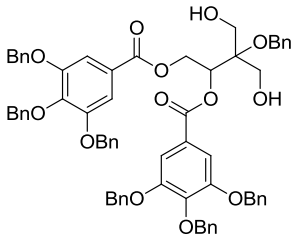
saturated aqueous solution of NH_4Cl (20 mL) and diluted with ethyl acetate (20 mL). After extraction with ethyl acetate (3×10 mL), the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (hexanes) to give the benzyl ether **17** (1.665 g, 69% yield) as a colorless oil. : ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.06 (s, 12 H), 0.90 (s, 18 H), 3.67 (d, J = 9.9 Hz, 2 H), 3.85 (d, J = 9.6 Hz, 2 H), 4.55 (s, 2 H), 5.29 (dd, J = 8.1 Hz, J = 1.6 Hz, 1 H), 5.34 (dd, J = 14.9 Hz, J = 1.6 Hz, 1 H), 5.84 (dd, J = 18.0 Hz, J = 11.1 Hz, 1 H), 7.39-7.25 (m, 5 H)



3-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-butane-1,2-diol (15). A solution of benzyl ether **17** (1.401 g, 3.207 mmol), trimethylamine N-oxide dihydrate (0.713 g, 6.41 mmol), and osmium tetroxide solution (10.0 mg/1.0 mL) (0.160 mmol, 4.07 mL) in acetone (90 mL) and water (45 mL) was stirred at rt for 7 h. The reaction was quenched with a saturated sodium sulfite solution (100 mL), stirred for 0.5 h, concentrated, and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (hexanes, ethyl acetate 5:1) to give **15** (0.911 g, 61% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.10 (s, 12 H), 0.92 (s, 18 H), 2.87 (m, 1 H), 3.27 (d, J = 29.7 and 9.3 Hz, 4 H), 3.91 (m, 7 H), 4.71 (dd, J = 17.4 and 1.8 Hz, 2 H), 7.32 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): -5.44, 18.3, 26.0, 62.6, 63.0, 63.1, 66.1, 72.9, 80.0, 127.6, 128.5, 139.1; MS m/z 493 (M^+ + Na).

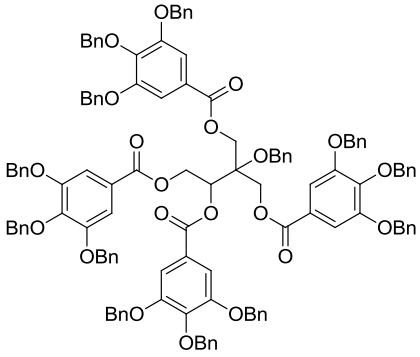


3-benzyloxy-4-tert-butyldimethylsilyloxy-3-(tert-butyldimethylsilyloxymethyl) butane-1,2-diol bis-3,4,5-tris(benzyloxy)benzoate (**20**). To a solution of diol **18** (0.456 g, 0.972 mmol), DMAP (0.475 g, 3.89 mmol) in CH_2Cl_2 (40 mL) was added 3,4,5-tris(benzyloxy)benzoyl chloride (**19**) (1.784 g, 3.886 mmol). The reaction was stirred at rt for 8 h. The solvent was evaporated and chromatography of the residue (hexanes, ethyl acetate 10:1) to give **20** (1.094 g, 83% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.10 (s, 12 H), 0.94 (s, 18 H), 3.83-4.08 (m, 4 H), 4.81-5.13 (m, 15 H), 6.05 (dd, J = 8.6, and 3.6 Hz, 1 H), 7.27-7.39 (m, 39 H); ^{13}C NMR (100 MHz, $CDCl_3$): -5.4, 18.4, 26.1, 61.6, 62.5, 66.3, 71.1, 71.2, 72.7, 75.2, 75.3, 80.6, 109.0, 109.3, 109.3, 125.2, 125.3, 127.5, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 136.6, 136.8, 137.6, 137.7, 139.1, 142.3, 142.8, 152.6, 152.7, 165.4, 166.1; MS m/z 1339 (M^+ + Na).

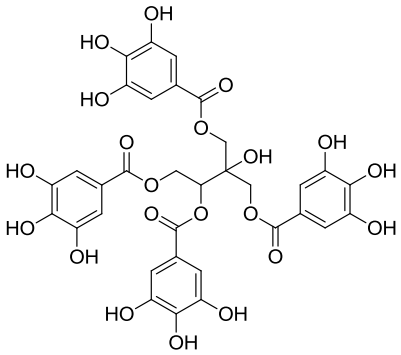


3-Benzyloxy-3-3,4,5-tris(benzyloxy)benzoyloxymethylbutane-1,2,4-trioltris(3,4,5-tris(benzyloxy)benzoate) (21). To a solution of protected alcohol **20** (0.459 g, 0.350 mmol) in dry THF (6 mL) and pyridine (6 mL) cooled to 0°C was added HF·pyridine (2.0 mL). The reaction mixture was warmed to rt and stirred for 18 h. The mixture was then diluted with EtOAc (5 mL) and washed with 10% aqueous $CuSO_4$ (5 mL). The aqueous phase was

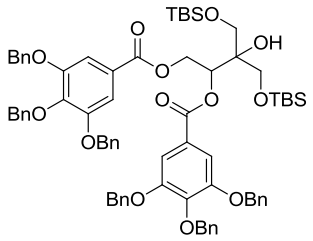
extracted with EtOAc (3 × 5 mL) and then combined organics washed with saturated aqueous $NaHCO_3$ (10mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford **21** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.47 (br, 1 H), 2.71 (br, 1 H), 3.96-3.81 (m, 4 H), 4.72-5.92 (m, 16 H), 5.94 (d, J = 9.0 Hz, 1 H), 7.22 – 7.39 (m, 39 H).



3-(benzyloxy)-3-(((3,4,5-tris(benzyloxy)benzoyl)oxy)methyl)butane-1,2,4-triyltris(3,4,5-tris(benzyloxy)benzoate) (22). To a solution of crude diol **21** (0.350 mmol) and DMAP (0.228g, 1.86 mmol) in CH_2Cl_2 (20mL) was added 3,4,5-tris(benzyloxy)benzoyl chloride(**19**) (0.855 g, 1.86 mmol). The reaction was stirred at rt for 8 hours. The solvent was evaporated and chromatography of the residue (CH_2Cl_2, ethyl acetate 10:1) gave **22** (0.554 g 86% yield over 2 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.39-5.16 (m, 33 H), 6.17 (dd, J = 7.0 and 3.0 Hz, 1 H), 7.26-7.43 (m, 73 H); ^{13}C NMR (100 MHz, $CDCl_3$): 62.1, 63.1, 63.3, 66.5, 71.2, 71.3, 71.7, 75.3, 78.6, 109.0, 109.1, 109.3, 124.3, 124.4, 124.7, 127.5, 127.6, 127.7, 127.9, 128.2, 128.3, 128.4, 128.6, 128.7, 136.5, 136.6, 136.7, 136.8, 137.5, 137.6, 137.7, 137.8, 142.7, 142.8, 143.0, 143.2, 151.0, 152.7, 152.8, 165.2, 165.4, 165.6, 165.9; MS m/z 1933 (M^+).

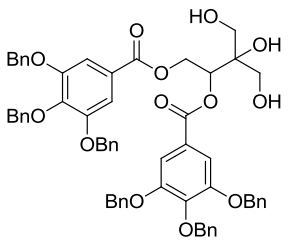


1,3,4,5-Tetragalloylapiitol (1). A suspension of benzylprotected tetragalloylapiitol (0.249 g, 0.129 mmol), 10% Pd/C (25 mg) in 15 mL of dry THF was stirred at 40 °C under a hydrogen gas atmosphere for 16 h. The reaction mixture was cooled and filtered through Celite, and the filtrate was evaporated. The residue was crystallized from toluene/ethyl acetate. Compound **1** (26 mg, 26% yield) was obtained as colorless crystals. Spectral data is in complete agreement with literature values.

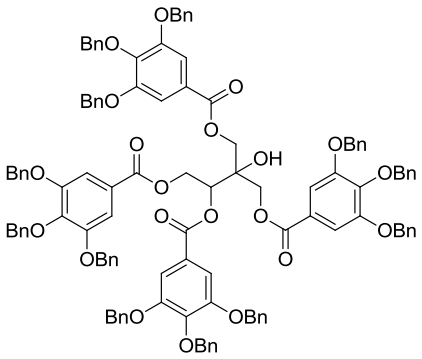


4-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-3-hydroxybutane-1,2-diyl bis(3,4,5-tris(benzyloxy)benzoate) (16). To a solution of triol **15** (0.401 g, 1.053 mmol) was added 3,4,5-tris(benzyloxy)benzoic acid (**11**) (0.401 g, 1.053 mmol), DCC (0.861 g, 4.21 mmol) DMAP (0.283 g, 2.32 mmol) in CH_2Cl_2 (20 mL). The solution was refluxed for 2 h. The solvent was evaporated and chromatography of the residue (5:1 hexanes, ethyl acetate) furnished **16** (1.035 g, 80.20% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.11 (s, 12 H), 0.89 (s, 18 H), 3.62-4.74 (m, 4 H), 4.98-5.10 (m, 13 H), 6.05 (dd, J = 96, and 2.4 Hz, 1 H), 7.269-7.382 (m, 34 H); ^{13}C NMR (100 MHz,

$CDCl_3$): -5.3, 18.4, 26.0, 60.6, 63.4, 63.3, 64.2, 71.2, 71.3, 73.2, 75.3, 75.3, 109.1, 109.4, 125.1, 125.3, 127.7, 127.9, 128.1, 128.3, 128.6, 128.7, 136.7, 136.8, 137.6, 137.7, 142.5, 142.9, 152.6, 152.7, 165.6, 166.1; MS m/z 1248 (M^+ + Na).



3-Hydroxy-3-(3,4,5-tris-benzyloxy)benzoyloxymethylbutane-1,2,4-trioltris-3,4,5-tris-benzyloxy)benzoate (31). A solution **16** (0.160 g, 0.130 mmol) in dry THF (2.0 mL) and pyridine (2.0 mL) was cooled to 0°C and HF·pyridine (0.67 mL) was added. The reaction mixture was warmed to rt and stirred for 18 h. The mixture was then diluted with EtOAc (2 mL) and washed with 10% aqueous $CuSO_4$ (2 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL) and the combined organics washed with saturated aqueous $NaHCO_3$ (10mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford **31** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.60-3.80 (m, 4 H), 4.96-5.07 (m, 14 H), 5.58 (dd, J = 8.7, and 2.7 Hz, 1 H), 7.21-7.37 (m, 34 H)



3-hydroxy-3-(((3,4,5-tris(benzyloxy)benzoyl)oxy)methyl)butane-1,2,4-triyl-tris(3,4,5-tris(benzyloxy)benzoate) (4). To crude **31** (0.130 mmol) was added 3,4,5-

tris(benzyloxy)benzoic acid (**11**) (0.172 g, 0.391 mmol), DCC (0.106 g, 0.521 mmol), and DMAP (0.035 g, 0.286 mmol) in CH_2Cl_2 (5 mL). The solution was boiled for 2 h. The solvent was evaporated and chromatography of the residue (10:1 CH_2Cl_2, ethyl acetate) furnished **4** (0.213 g, 89% yield over 2 steps) as a colorless oil.

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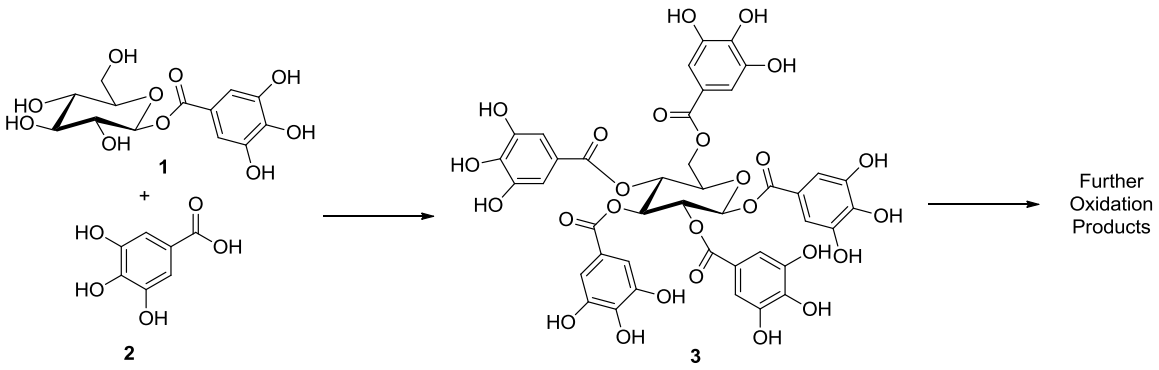
CHAPTER 2. Synthesis of ellagitannins

Introduction:

Tannins are defined as any polyphenolic compound that can bind and precipitate proteins and alkaloids.[1] They are derived from plants where they play an important role in protection from predators and providing functional support.[2] There are three main classes of tannins: hydrolyzable tannins, condensed tannins and phlorotannins.[3] With nearly 1000 different hydrolyzable tannins isolated and characterized, it constitutes the largest group of tannins found in nature.[4,5]

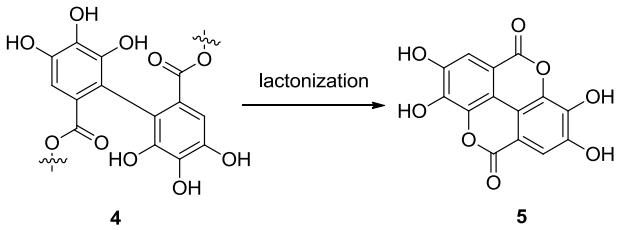
The biosynthetic pathway of hydrolyzable tannins is believed to originate from β-glucogallin (**1**) and gallic acid (**2**, Scheme 1).[6] The acids couple to the hydroxy groups of **1** to synthesize a polygallated glucose, in this case penta-O-galloyl-β-D-glucopyranose β-PGG (**3**). Hydrolyzable tannins similar to **3** can have further derivatives made *via* intra- or intermolecular oxidative C-C biaryl and C-O diaryl ether bond couplings.[7,8,9]



Scheme 1. Proposed biosynthetic pathway of hydrolyzable tannins.

There are two classes of hydrolyzable tannins: gallotannins and ellagitannins. Ellagitannins possess a 6,6'-dicarbonyl-2,2',3,3',4,4'-hexahydroxylbiphenyl moiety (**4**), or

simply hexahydroxydiphenoyl (HHDP), which when hydrolyzed, forms ellagic acid (**5**), the namesake of ellagitannins (Scheme 2).



4 **5**

Scheme 2. Rapid lactonization of HHDP (**4**) to form ellagic acid (**5**).

Since this initial classificiation, ellagitannins have been further classified by Haslam and later Okuda.[6,10] Okuda's classification system is based on the level of oxidation of the gallic acid moieties (Figure 1). Thus, ellagitannins can be classified into four classes:

Type I: Gallotannins, which feature a glucose core with a varying degree of galloyl esters attached to either the sugar or through depside bonds (**6**).[11]

Type II: Contain the HHDP moiety with no further oxidation products (**7**).

Type III: Posses the dehydrohexahydroxydiphenoyl (DHHDP) subunit which is derived from oxidation of the HHDP unit (**8**).

Type IV: Oxidation of DHHPD to further oxidized subunits (**9**).

In addition, due to structural differences beyond oxidation, Okuda's classification system was quickly amended to include a fifth class:

Type II-IV (+): The roman numeral classifies the oxidation state of the gallic acids and a (+) indicates if any additional chemical transformations in the molecule have taken place (**10** and **11**).

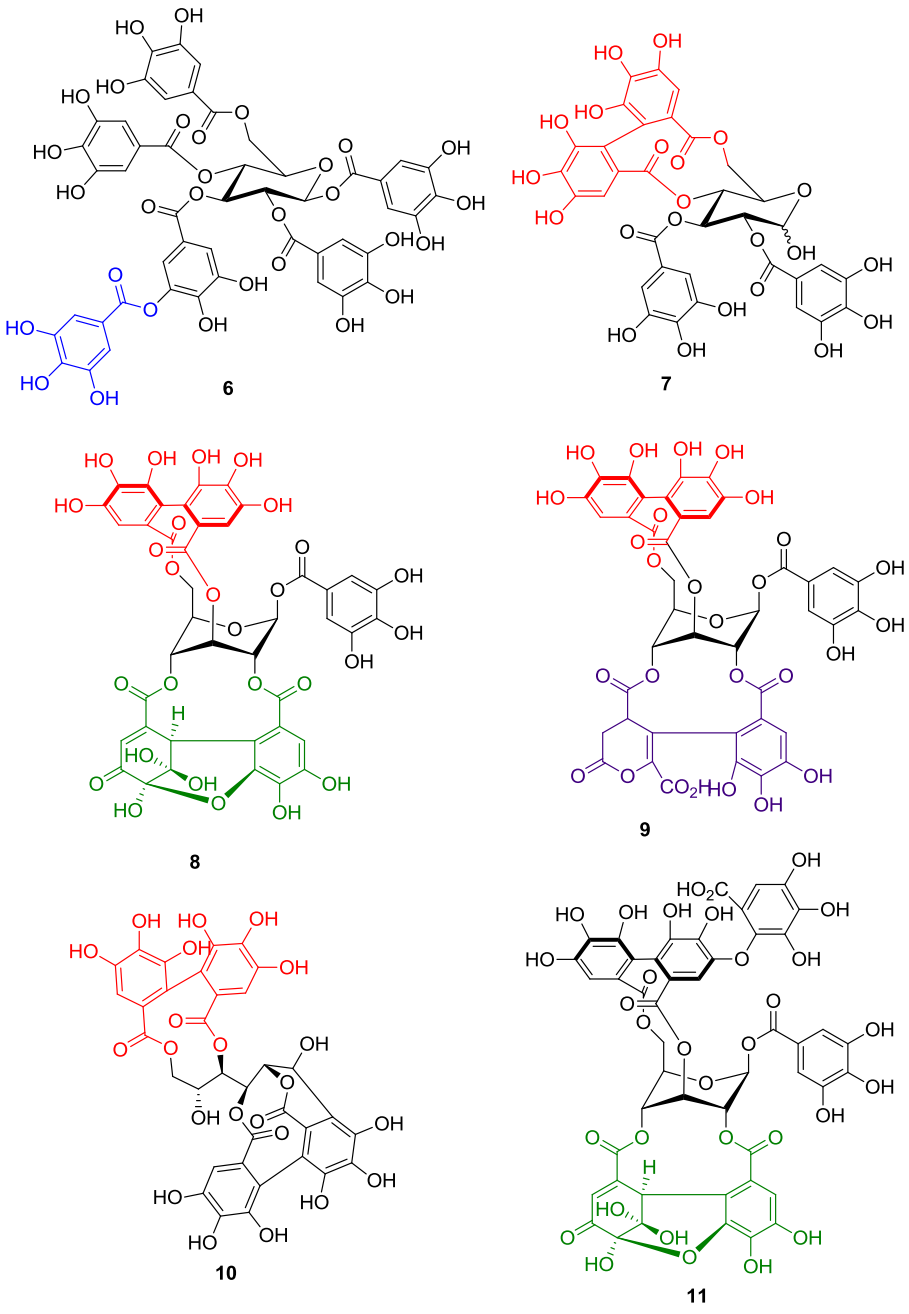
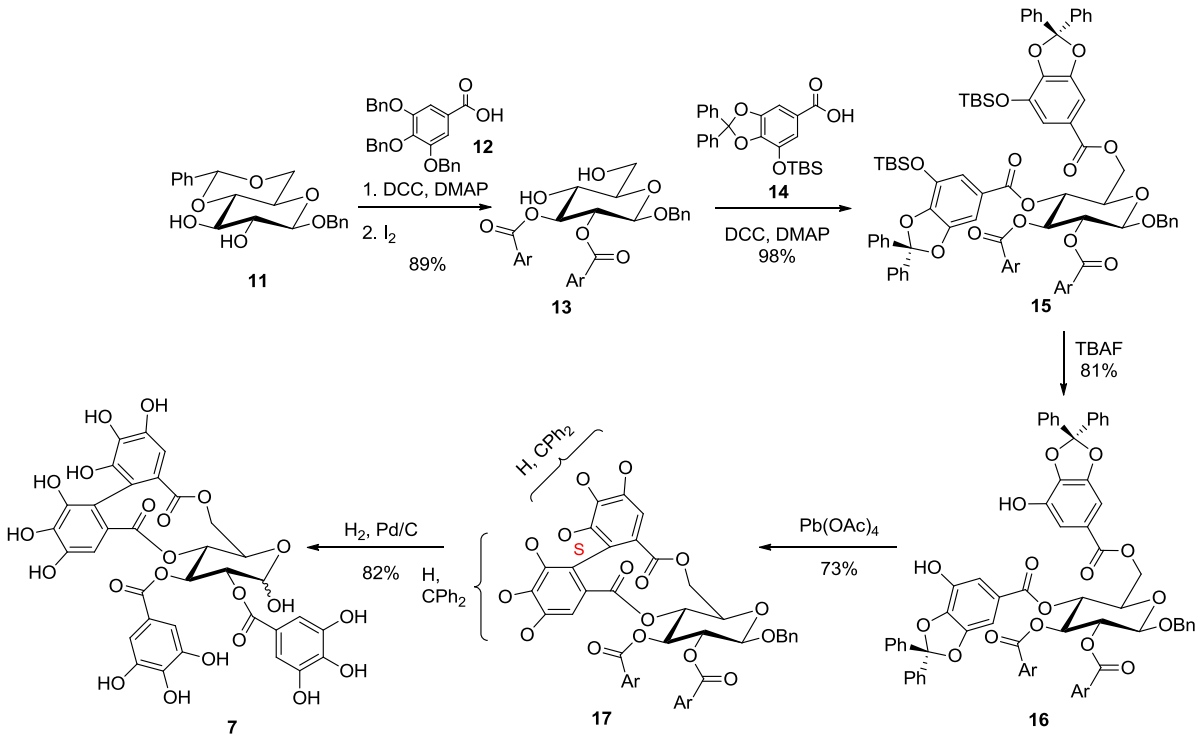


Figure 1. Structures of type I (**6**, depside bond in blue), type II tellimagrandin I (**7**, HHDP in red), type III geraniin (**8**, DHHDP in green), type IV phyllanthusiin A (**9**, DHHDP oxidation in purple), type II+ stachyurin (**10**), and type III+ mallotusinic acid (**11**).

The presence of the HHDP or further oxidized subunits have a dramatic effect on the molecular recognition differences between gallotannins and ellagitannins.[12] Gallotannins

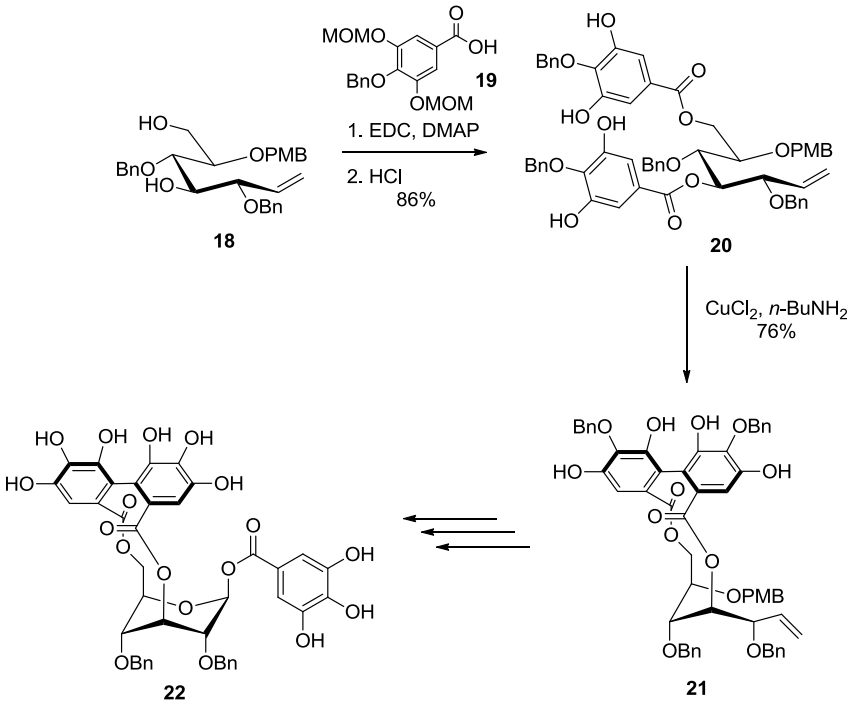
are flexible and can orient to many conformations to adapt to their surroundings,[13] whereas ellagitannins are rigid and have well defined three-dimensional structures.[14] The organization of ellagitannins is believed to aid precise recognition and facilitate H-bonding and hydrophobic bonding to target proteins.[8] Ellagitannins biological profile includes anticancer, antiviral and RNase H activity, whereas gallotannins have a more limited profile.[8,15] Unfortunately, because ellagitannins are difficult to isolate from nature, synthetic efforts are required to further explore the biological activity of these compounds.[16] Difficulties in controlling the regio- and stereochemistry of appended gallic acids make these complex molecules synthetically challenging. Moreover, controlling the atropisomers of the HHDP is vital to any synthetic effort on these molecules.[8]

Early synthetic efforts on ellagitannis were pioneered by Feldman and co-workers. Their synthesis of tellimagrandin I (**7**) started with the acylation of diol **11** with 3,4,5-*O*-benzyl



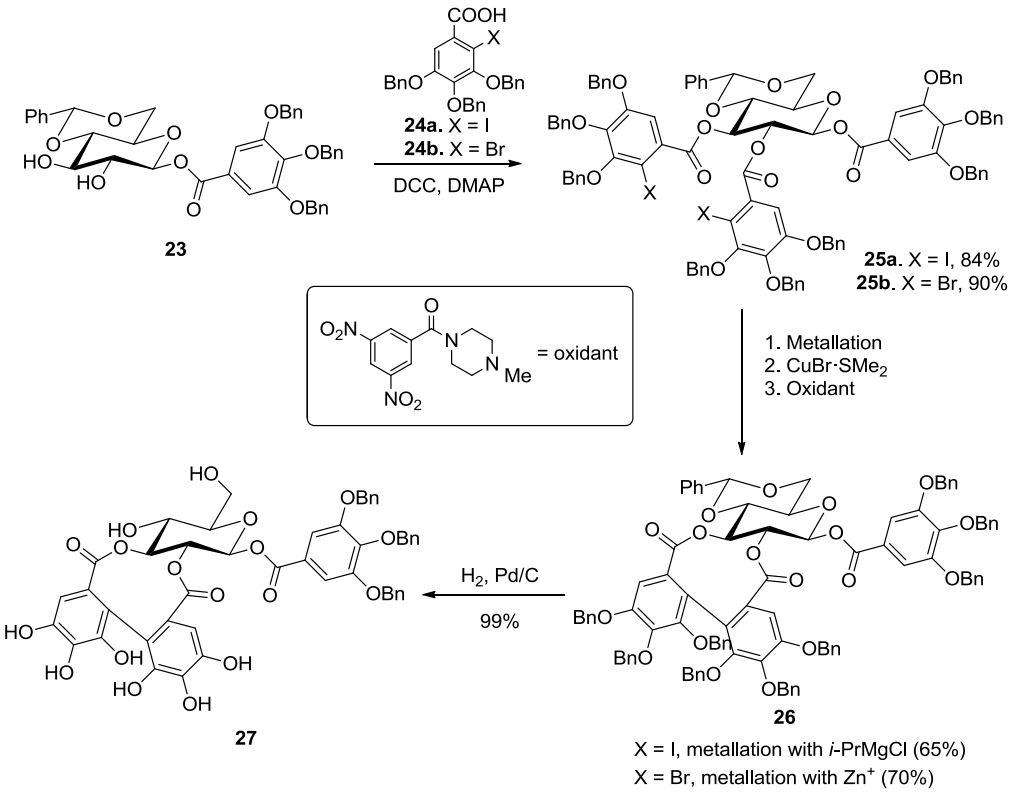
Scheme 3. Synthesis of tellmagrandin I (**7**). Ar = 3,4,5-*O*-benzylgalloyl

protected acid **12** (Scheme 3).[17] Deprotection of the benzylidene with iodine afforded diol **13**. This compound was coupled with benzoic acid **14** *via* a Steglich esterificaiton, which after silyl ether deprotection with TBAF gave intermediate **16**. Lead tetraaceteate ($Pb(OAc)_4$) was their optimal oxidizing agent to give a mixture of diastereomeric HHDP compounds **17**. The diastereomers were formed from different diphenyl ketal regioisomers, but this regiomisomeric mixture was later resolved after deprotection. In addition, **17** was formed as the S atropisomer only, which is the proper orientation of the natural product. This result is consistent with the Schmidt-Haslam postulate that either the S or the R conformer is energetically favored depending on the natural product.[4,11] Okuda type II ellagitannins are almost always the S orientation in nature.[18] Hydrogenolysis of **17** deprotected the benzyl groups to yield tellmagrandin I (**7**) in 82% yield. Feldman's group used similar lead tetraacetate strategies toward the synthesis of tellimagrandin II,[19] dimeric coriariin A[20] and sanguiin H-5.[21]



Scheme 4. Synthesis of corilagin (**22**).

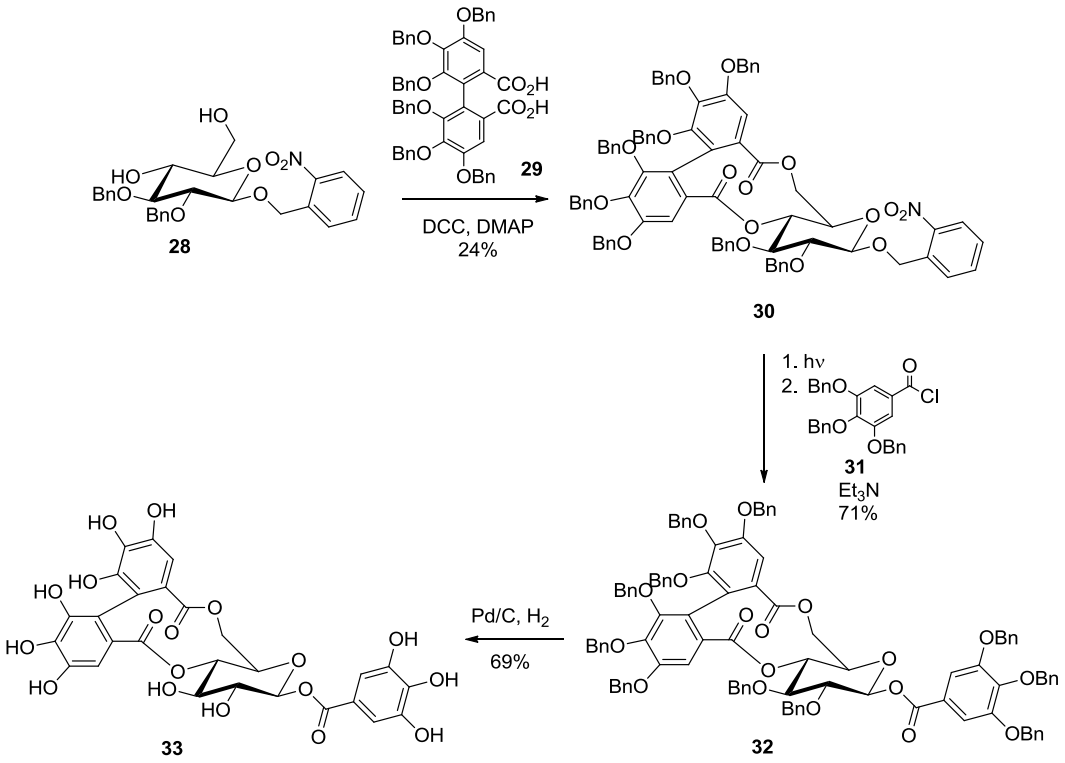
An alternative oxidative coupling strategy was developed by Yamada and co-workers toward the synthesis of corilagin (**22**, Scheme 4).[22] Instead of using the diphenyl ketal group of acid **14**, they synthesized the 4-*O*-benzylgallic acid derivative **19**. This acid was attached to diol **18** under standard Steglich esterification conditions. After MOM-ether deprotection with HCl at 40 °C, compound **20** was formed in 86% yield. The gallic acid moieties were oxidatively coupled with a $CuCl_2$·$BuNH_2$ complex to form 3,6-HHDP bridged compound **21** as the R atropisomer only, which is consistent with atropisomeric formation of the HHDP at the 3,6-position. This intermediate was used to complete the synthesis of **22**. Interestingly, the rigidity of the HHDP moiety at the 3,6-positions made the glucose core adopt an all axial orientation, and this served as the only known synthesis of an all axial oriented glucose natural product.



Scheme 5. Synthesis of sanguiin H-5 (**27**).

Spring and co-workers developed a strategy to synthesize the key biaryl bond of sanguiin H-5 (**27**, Scheme 5) with the aid of aryl halides, which limited the protection and deprotection steps of the two previous strategies. Diol **23** was esterified with halogenated gallic acids **24a** and **24b** under Steglich esterification reaction conditions.[23] The halogens underwent metal-halogen exchange, transmetallation with $CuBr{\cdot}SMe_2$ and organocuprate oxidation to form compound **26** in the S configuration. Compound **26** was deprotected to give the natural product **27**.

A non-biomimetic pathway was accomplished by Khanbabaee and co-workers towards the synthesis of strictinin (**33**). They utilized a previously synthesized perbenzylated HHDP unit **29** to significantly shorten their synthetic route (Scheme 6).[24] Diacid **29** was coupled to diol **28** to make 4,6-HHDP compound **30**. Unfortunately, this reaction gave a

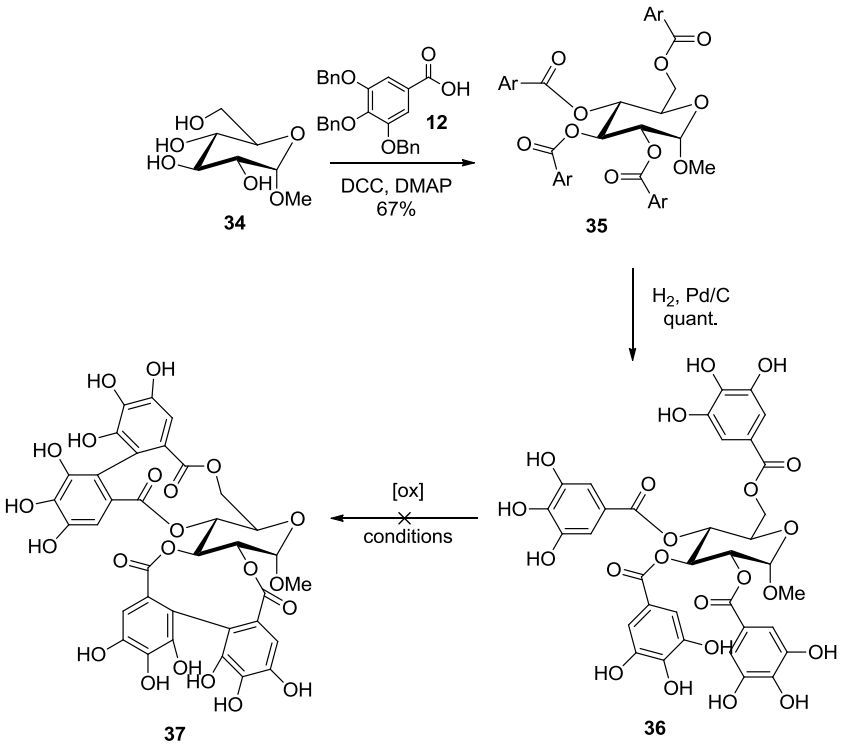


Scheme 6. Synthesis of strictinin (**33**).

mixture of atropisomers that needed to be separated by column chromatography. The S configuration was isolated, and under light irradiation, the *ortho*-nitrobenzyl ether was removed. The resulting alcohol was acylated by the addition of 3,4,5-*O*-benzylgallic acid chloride (**31**) to give protected intermediate **32**. Global deprotection with hydrogenolysis gave strictinin (**33**). Although this route was more direct than the biomimetric pathways, the formation of atropisomers led to a poor overall yield of 12% from diol **28**.

Results and Discussion:

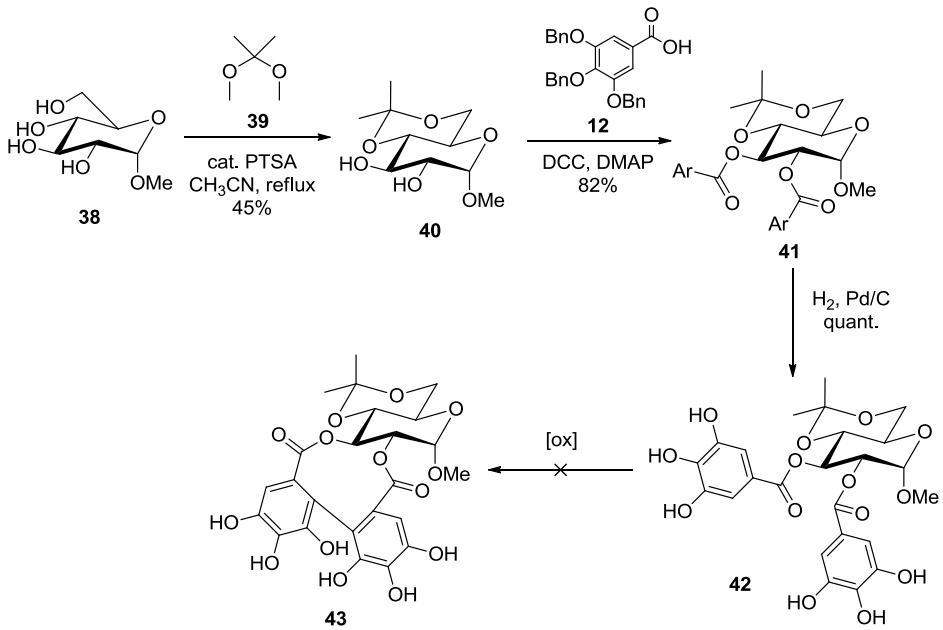
We were intrigued by the complexity of these molecules and their close resemblance to 1,3,4,5-tetragalloylapiitol.[25] Our plan was to synthesize the ellagitannins in a biomimetic process with minimal use of protecting groups. Our initial effort started by coupling previously prepared 3,4,5-(tribenzyloxy)benzoic acid (Chapter 1) to methyl-α-D-gluco-pyranoside (**34**, Scheme 7). Hydrogenonlysis cleaved the benzyl ethers to give tetragallate



Scheme 7. Attempts at oxidative of coupling to form compound **37**. Ar = 3,4,5-*O*-benzylgalloyl

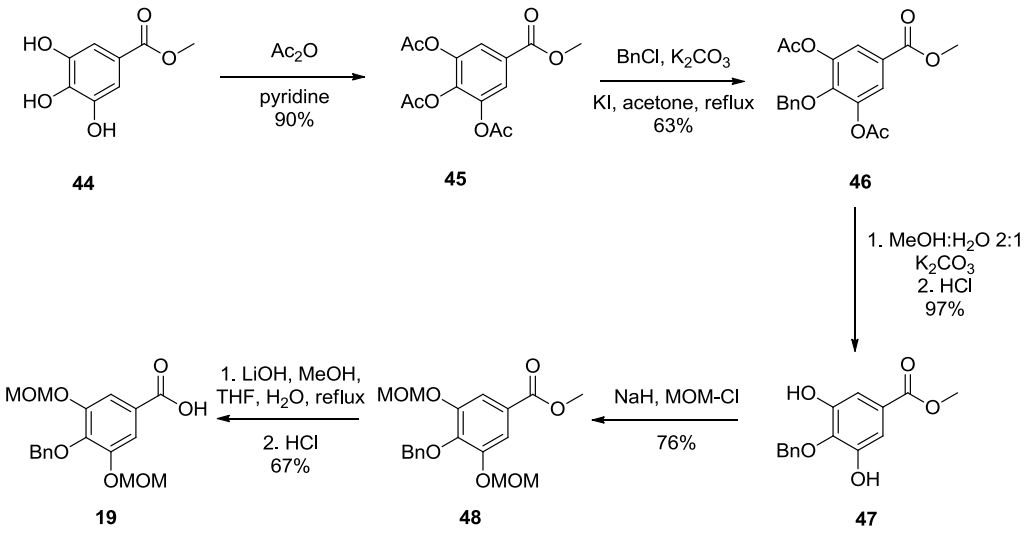
36. Unfortunately, attempts to generate the HHDP-containing molecule, **37**, using Feldman's conditions with $Pb(OAc)_4$ were unsuccessful. Alternative oxidative methods using CuCl(OH)·TMEDA,[26] AIBN[27] and DDQ[28] also failed.

We decided that trying to form two HHDP groups at the same time might be forming too many side reactions, so we focused on protecting the 4,6-positions and attempt the oxidative HHDP coupling at the 2,3-positions. The dimethyl ketal of **34** was formed with 2,2-dimethoxypropane (**39**) and catalytic amount of *para*-toluenesulfonic acid (PTSA) at 60 °C (Scheme 8). Acid **12** was coupled to the remaining diol **40** to give intermediate **41**, which was subsequently deprotected to give HHDP precursor **42.** Once again, attempts to form the HHDP moiety with $Pb(OAc)_4$ failed. Different oxidation conditions known for phenol biphenyl couplings were attempted, including $CuSO_4$ in O_2,[29] $FeCl_3·6H_2O$,[30] $K_3[Fe(CN)_6]$,[31] $CuCl_2·BuNH_2$,[22] and $VO(acac)_2$,[32] but none of these conditions showed any promise of affording the desired product **43**.



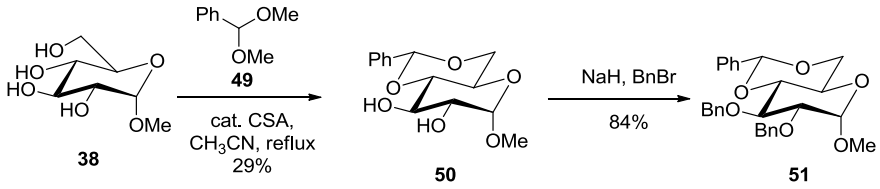
Scheme 8. Attempts at oxidation of compound **42**. Ar = 3,4,5-*O*-benzylgalloyl

After reexamining Feldman and Yamada's strategies we concluded that protection of the *para*-phenol of the gallic acid is paramount to the success of these oxidative couplings. We decided to synthesize acid **19** and pursue Yamada's conditions for oxidative coupling due to copper's low toxicity and the regiochemical control of this reaction. The synthesis of acid **19** began with the construction of the triacetate of gallic acid methyl ester (**44**, Scheme 9). Selective protection of the *para*-phenol was accomplished with benzyl chloride, potassium carbonate, and potassium iodide in refluxing acetone.[33] Interestingly, compound **44** cannot be selectively protected with these same conditions. We believe selective protection at the p*ara*-position of compound **46** is preferential due to the *para*-acetate having to orient itself out of the plane making it more susceptible to deprotection. The acetates were removed to give dihydroxy compound **47**. Free hydroxys were subsequently protectedas methoxymethyl (MOM)-ethers to give compound **48**. The methyl ester was hydrolyzed and acidified to give acid **19**.



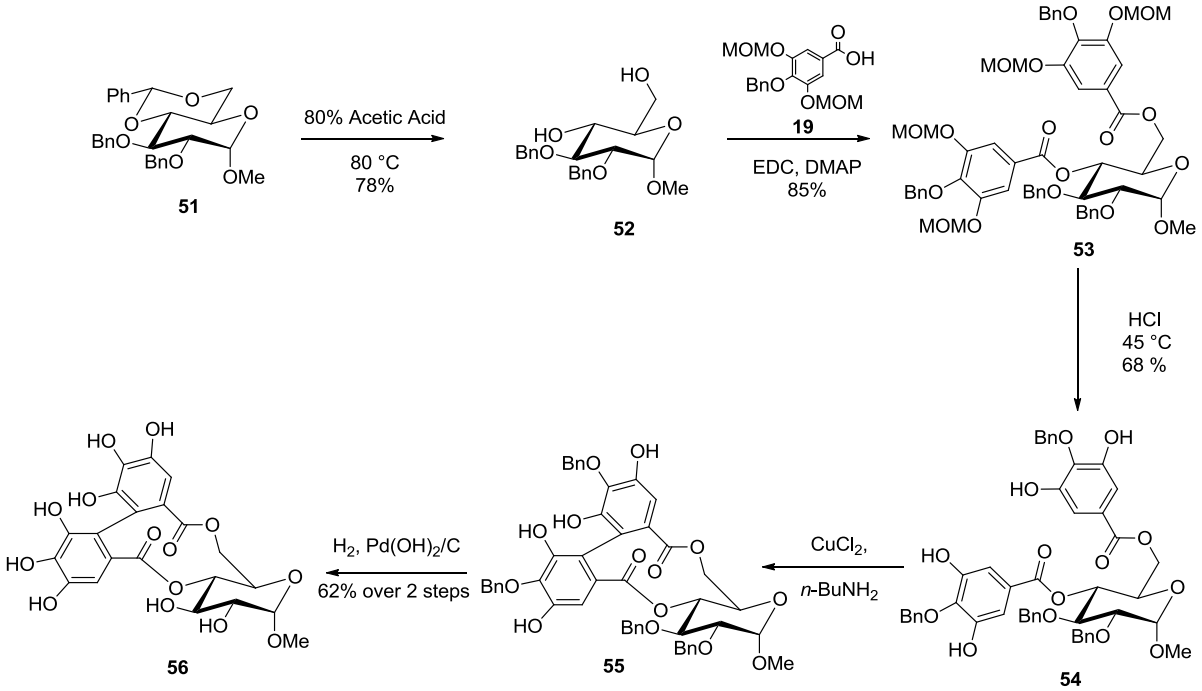
Scheme 9. Synthesis of acid **19**.

Due to the steric challenges of HHDP formation at the 2,3-positions of the glucose core, we decided to focus on its formation at the 4,6-position of glucose.[21] The benzylidene was formed on compound **38** with benzaldehyde dimethyl acetal (**49**) and catalytic camphorsulfonic acid (CSA, Scheme 10). Diol **50** was protected as benzyl ethers to give compound **51** in 84% yield.



Scheme 10. Synthesis of intermediate **51**.

The benzylidene was removed in an 80% acetic acid solution in water at 80 °C to give diol **52**, which was esterified with acid **19** under Steglich esterification conditions to give



Scheme 11. Synthesis of ellagitannin **56** *via* Yamada's oxidative coupling conditions.

diester **53** (Scheme 11). The coupling precursor **54** was made from MOM deprotection with HCl at 45 °C. Gratifyingly the key oxidative coupling with $CuCl_2$·$BuNH_2$ was successful at generating the desired product **55**. The compound was afforded as a single product and was easily distinguishable based on its identifiable upfield singlets at δ 6.46 and 6.84 in the ^{1}HNMR. After hydrogenolysis, ellagitannin **56** was collected in 62% yield in two steps from compound **54**.

With the successful synthesis of ellagitannin **56**, we were interested in using this synthetic scheme to make a variety of ellagitannins derivatives with substitutents at the C-1, C-2 and C-3 positions of the glucose core. Our targets included the deprotected anomeric compound **56b**, strictinin (**33a** and **33b**) and ellagitannin **56c** (Figure 2). Initially we had hoped to hydrolyze the methyl ether of compound **56** to generate **56b**, however, these attempts were unsuccessful with a variety of different reagents, including AcOH/1M H_2SO_4 at 110 °C,[34] Ac_2O/AcOH, H_2SO_4 then N_2H_2·AcOH 50 °C.[35] The reactions returned starting material, or upon more vigorous conditions, cleaved the HHDP moiety.

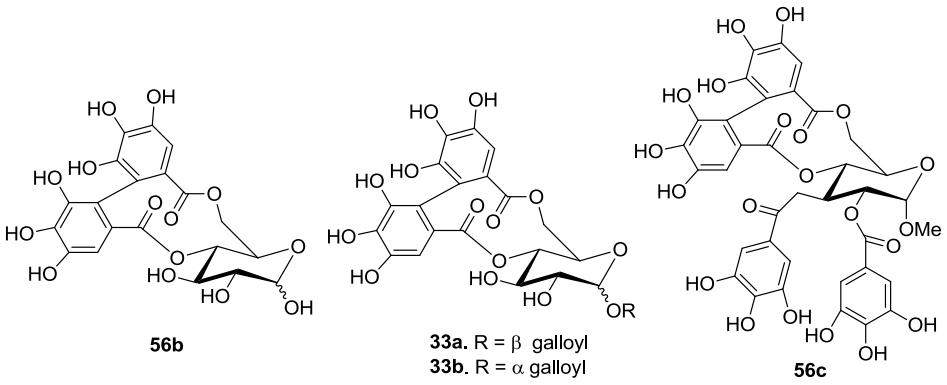
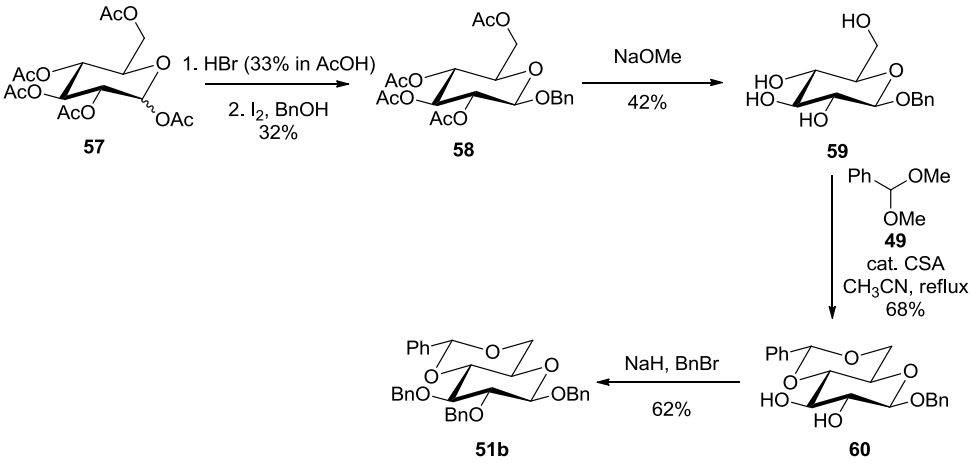


Figure 2. Ellagitannin **56b**, **33a**, **33b**, and **56c** which posses the 4,6-HDDP and differing substituents at C-1, C-2 and C-3 of the glucose core.

It was postulated that a more labile group would have to be introduced at the anomeric position from the beginning of the synthesis. Accordingly, we sought to replace

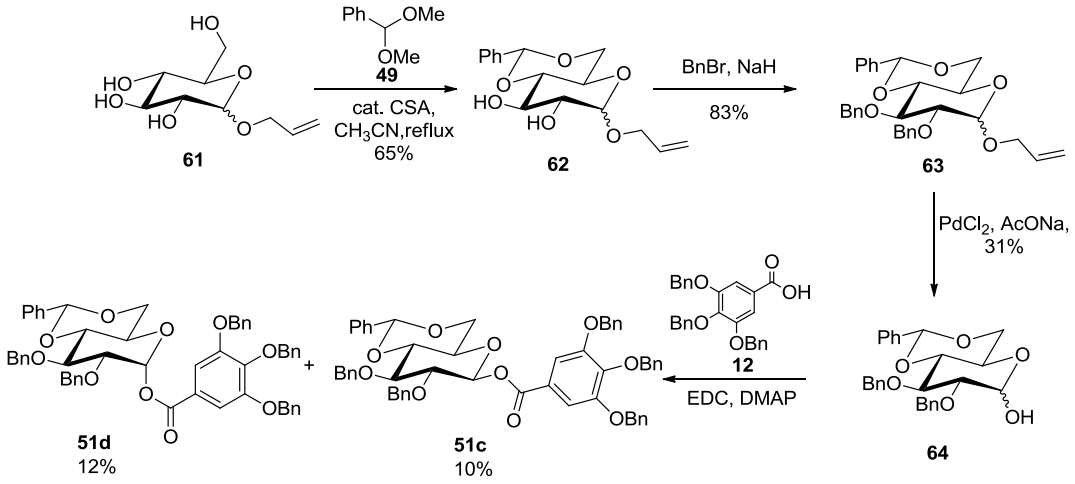
the methoxy group with a benzyl ether. Starting with α,β-D-glucose pentaacetate (**57**), bromo substitution at the anomeric position with HBr in AcOH, followed by nucleophilic displacement with benzyl alcohol afforded β-compound **58** (Scheme 12).[36] The acetate groups were deprotected with sodium methoxide to give tetraol **59**, which upon treatment with **49** was converted to compound **60**. The hydroxyl groups were protected as benzyl ethers under standard conditions of sodium hydride and benzyl bromide to yield **51b** in 62% yield.



Scheme 12. Synthesis of diol **51b**.

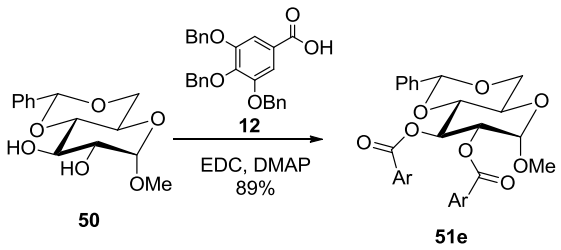
Next, we targeted the derivate with a galloyl group at the anomeric position. Starting with allyl gluco-pyranoside **61**, benzylidene **64** was synthesized using **49** and catalytic amounts of CSA (Scheme 13). Protection of the remaining alcohols as benzyl ethers afforded dibenzyl protected **63**. The *O*-allyl group was removed under stoichiometric $PdCl_2$ and sodium acetate in acetic acid. An alternative condition with *t*-BuOK was attempted but that procedure led to the removal of the benzylidene protecting group. The hydroxy group on compound **64** was esterified with acid **12** to give a mixture of α,β-diastereomers **51c** and **51d**. The two diastereomers were separated by column chromatography to yield pure **51c**

and **51d**. Lower yields are due to the difficulty in separating the diastereomers *via* flash chromatography.



Scheme 13. Synthesis of benzylidene **51c** and **51d**.

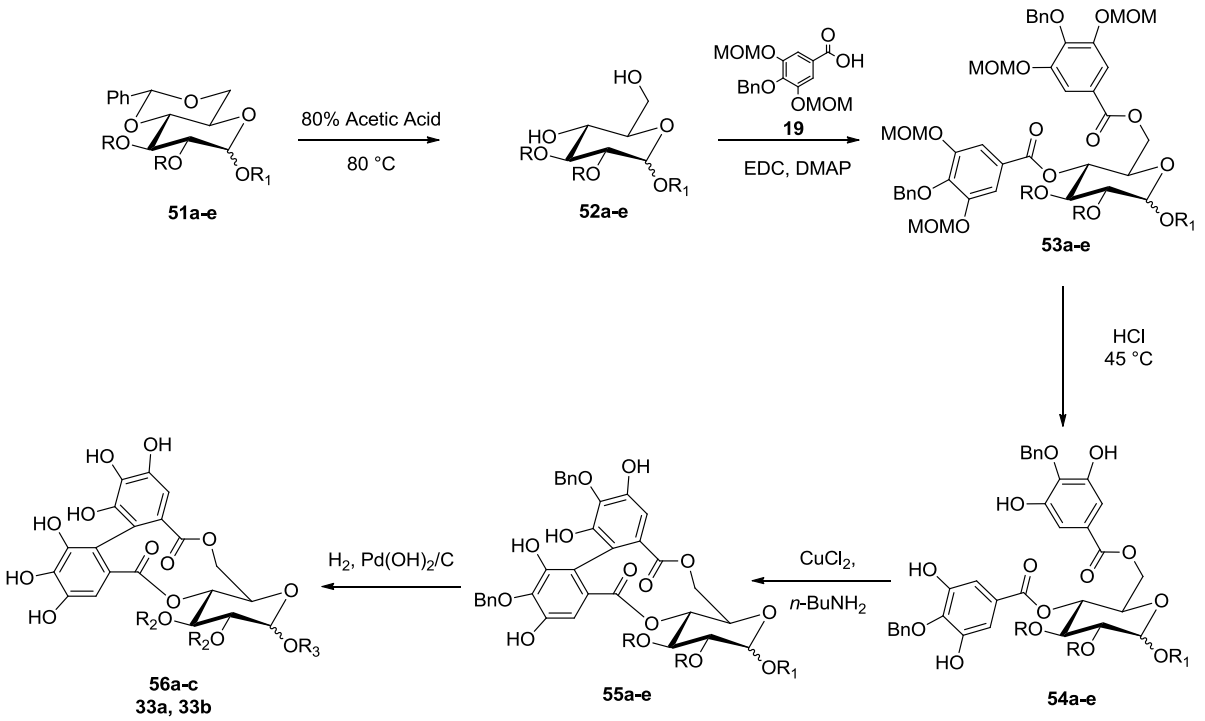
Our next target, compound **51e**, had galloyl substituents at the C-2 and C-3 positions. Starting with previously prepared compound **50**, we made the diester under Steglich esterification conditions with acid **12** to give intermediate **51e** (Scheme 14).



Scheme 14. Esterificaiton of compound **50** to yield benzylidene **51e**. Ar = 3,4,5-*O*-benzylgalloyl

After isolating compounds **51b-e**, we turned our attention toward the installation of the HHDP moiety following the pathway described previously for **56a** (Scheme 15). Benzylidene deprotection with acetic acid at 80 °C proceeded smoothly for **51b**, but compounds **51c-e** required addition of dichloroethane as a cosolvent due to starting material

insolubility. Diols **52b-e** were coupled to compound **19** to form products **53b-e**. Then, the oxidative coupling precursors **54b-e** were generated from deprotection of the MOM-ethers with HCl without incident. Oxidative coupling using Yamada's conditions was effective for **54b**, but compounds **54c-e** were insoluble in the reaction solvent, methanol, and attempts to increase solubility with heating to 40 °C led to decomposition of the starting material.

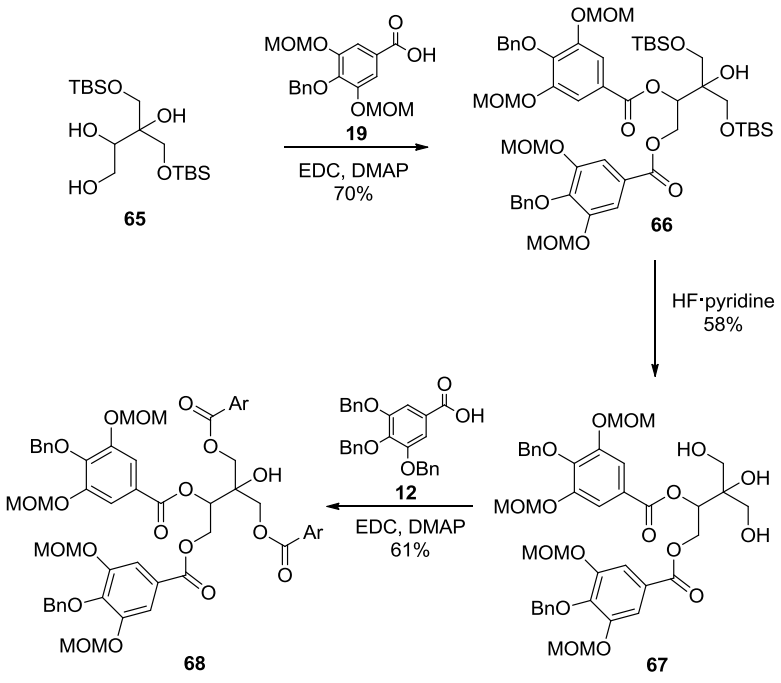


SM	R	R_1	Yield (%) 51	Yield (%) 52	Yield (%) 53	Yield (%) 54	Pdt.	R_2	R_3
51a	OBn	α-OMe	78	85	68	62	**56a**	OH	α-OMe
51b	OBn	β-OBn	76	60	75	44	**56b**	OH	α/ β-OH
51c	OBn	β-OTBG	70	77	85	52	**33a**	OH	β-galloyl
51d	OBn	α-OTBG	73	73	75	64	**33b**	OH	α-galloyl
51e	*O*-galloyl	α-OMe	85	81	70	40	**56c**	*O*-galloyl	α-OMe

Scheme 15. Synthesis of ellagitannins **56a-c**, **33a** and **33b**. OTBG = 3,4,5-*O*-benzylgalloyl

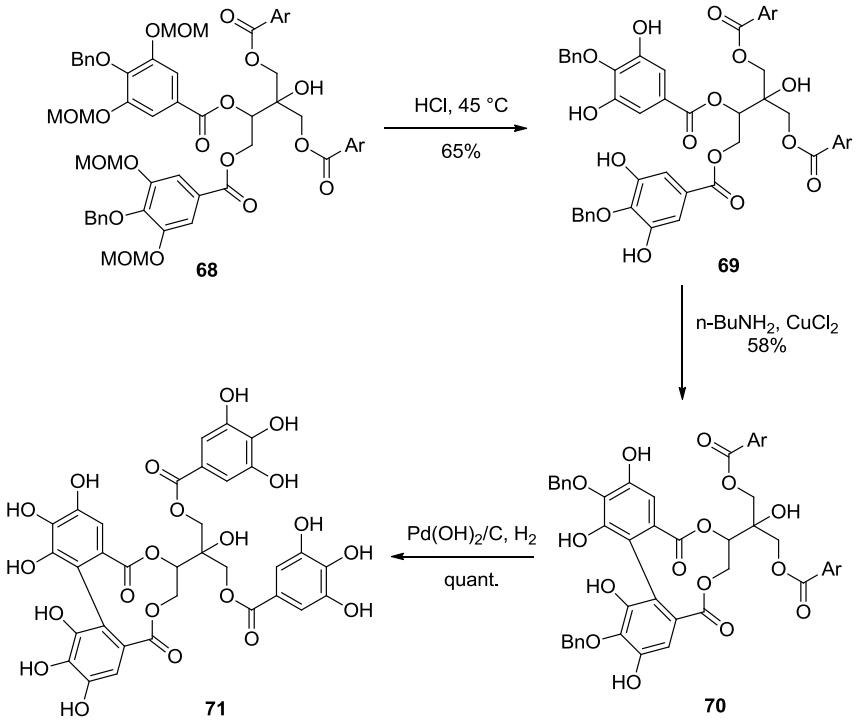
However, addition of dichloromethane as a co-solvent circumvented this problem and afforded the oxidative coupling products **55c-e** in good yields. All of the HHDP-containing compounds were made as a single atropisomer by this method. The compounds were subjected to hydrogenolysis conditions to remove the benzyl ethers to afford ellagitannis **56b**, **56c**, **33a** and **33b**.

So far, we have only synthesized ellagitannins with a cyclic glucose core, but we wanted to extend our testing to acyclic sugars, in particular, our previously synthesized apiitol. Starting with the partially protected apiitol **65** (Chapter 1), coupling with acid **19** afforded diester **66** (Scheme 16). The silyl ethers were deprotected to give triol **67** with no observed decomposition of the MOM-ethers. Acid **12** was attached *via* the Steglich esterification to give tetragallate **68**.



Scheme 16. Synthesis of tetragallate **68**. Ar = 3,4,5-*O*-benzylgalloyl

Deprotection of the MOM groups with HCl was successful in affording compound **69** without eliminating the tertiary alcohol (Scheme 17). We believe that intramolecular hydrogen bonding between the tertiary alcohol and carbonyl moieties stabilizes the tertiary alcohol with respect to elimination. Compound **69** was oxidatively coupled with $CuCl_2 \cdot BuNH_2$ to give the HHDP apiitol **70** as a single atropisomer in 58% yield. Global deprotection with $Pd(OH)_2/C$ under a hydrogen atmosphere gave us ellagitannin **71**. Biological testing with this compound is currently underway.



Scheme 17. Completion of the synthesis of apiitol ellagitannin **71**. Ar = 3,4,5-*O*-benzylgalloyl

So far, efforts toward the synthesis of ellagitannins have only reached the tip of the iceberg. The structural diversity and recently discovered biological activity of these compounds will continue to inspire many new syntheses in the future. Our work has demonstrated the importance of the protection of the *para*-phenol of gallic acid for oxidative coupling. In addition, our collaborators demonstrated that many of these compounds exhibit

significant anti-HIV activity. Future work on this project will focus on the synthesis of more derivatives, including type III and IV ellagitannins, to gain an insight into the origin of their anti-HIV activity.

Experimental:

Steglich esterification:

In a round bottom flask, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3 equiv), *N,N*-4-dimethylaminopyridine (3.5 equiv), and acid (1.25 equiv) were added to the alcohol in methylene chloride. The reaction was stirred at rt for 3 h. When the reaction was complete 1 M phosphoric acid was added and the organic layer was extracted with methylene chloride. The organic layer was washed with 1 M phosphoric acid, water and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was then purified by column chromatography.

Benzylidene deprotection:

In a round bottom flask, the benzylidene compound was heated in 80% acetic acid to 80 °C for 2 h. (Dichloroethane was added if the compound was insoluble at 80 °C.) Upon completion the reaction was evaporated *in vacuo*. The crude material was taken up in EtOAc, washed with $NaHCO_3$ (sat.) until neutral pH, water and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography.

MOM deprotection:

To a stirred solution of methoxymethyl-protected phenol in 2-propanol (80% volume) and THF (20% volume), was added conc. HCl (0.01 M). The mixture was stirred for 12 h at

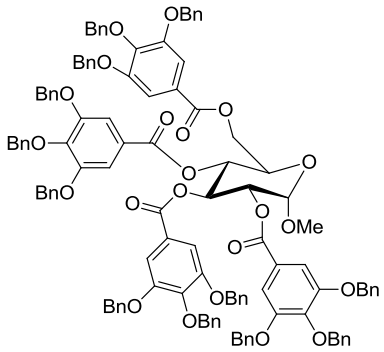
45 °C. Sat. $NaHCO_3$ was added until the reaction reached neutral pH. Evaporated *in vacuo*. The mixture was extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was then purified by column chromatography.

Oxidative copper coupling:

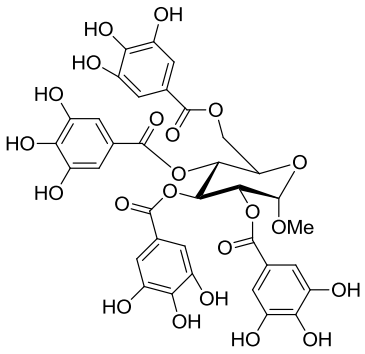
To a stirred solution of $CuCl_2$ (5 equiv) in methanol was added n-butylamine (20 equiv) at rt. The mixture was stirred for 30 min at this temperature. The phenol in methanol (unless insoluble then CH_2Cl_2) was added and the reaction mixture was stirred at rt for 20 min. The reaction was quenched with 4 M HCl and extracted with ethyl acetate. Washed with 1 M HCl, sat. $NaHCO_3$, and then brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was then purified by column chromatography.

Hydrogenolysis:

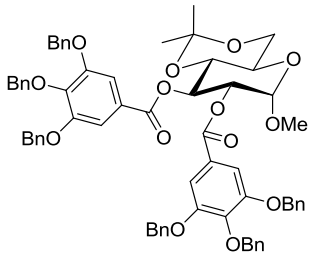
To a stirred solution of 1 in methanol and THF was added 10% $Pd(OH)_2/C$ (10% by weight). The flask was evacuated and filled with H_2, this process was repeated three times. The reaction was stirred under a H_2 atmosphere for 6 h. Upon competition, the reaction mixture was filtered through a pad of celite and evaporated *in vacuo* to furnish the desired product.



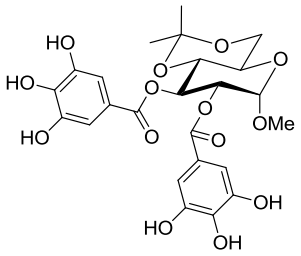
(2S,3R,4S,5R,6R)-2-methoxy-6-(((3,4,5-tris(benzyloxy)benzoyl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(3,4,5-tris(benzyloxy)benzoate) (35). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3 H), 4.13 (br, 1 H), 4.49 (t, J = 12.9 Hz, 2 H), 4.90-5.21 (m, 24 H), 5.42 (t, 3 Hz, 1 H), 5.77 (dt, J = 9.6 Hz, 3.3 Hz, 1 H), 6.07 (d, J = 6.6 Hz, 1 H), 6.27 (dt, J = 10.2 Hz, J = 3.3 Hz 1 H), 6.96-7.52 (m, 68 H).



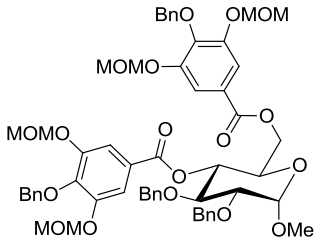
(2S,3R,4S,5R,6R)-2-methoxy-6-(((3,4,5-trihydroxybenzoyl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(3,4,5-trihydroxybenzoate) (36). ^{1}H NMR (300 MHz, $COCD_6$) δ 3.50 (s, 3 H), 4.21 (br, 1 H), 4.37 (m, 2 H), 4.50 (d, J = 12.9 Hz, 1 H), 5.20 (m, 1 H), 5.55 (t, J = 9.3 Hz, 1 H), 6.02 (t, J = 9.6 Hz, 1 H), 6.70 (s, 2 H), 7.00 (s, 2 H), 7.07 (s, 2 H), 7.21 (s, 2 H)



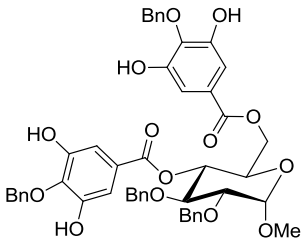
(4aR,6S,7R,8S,8aR)-6-methoxy-2,2-dimethylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl bis(3,4,5-tris(benzyloxy)benzoate) (41). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.50 (s, 3 H), 3.43 (s, 3 H), 3.86-4.00 (m, 4 H), 3.89 (m, 13 H), 5.21 (d, J = 3.0 Hz, 1 H), 5.85 (t, J = 10.2 Hz, 1 H), 7.18-7.45 (m, 34 H).



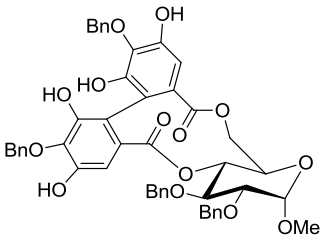
(4aR,6S,7R,8S,8aR)-6-methoxy-2,2-dimethylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl bis(3,4,5-trihydroxybenzoate) (42). ^{1}H NMR (300 MHz, $COCD_6$) δ 1.29 (s, 3 H), 1.51 (s, 3 H), 3.40 (s, 3 H), 3.63 (t, J = 6.6 Hz, 1 H), 3.73-3.90 (m, 3 H), 5.05-5.11 (m, 2 H), 5.69 (t, J = 9.6 H, 1 H), 7.04 (s, 2 H), 7.07 (s, 2 H).



(2R,3R,4S,5R,6S)-4,5-bis(benzyloxy)-2-(((4-(benzyloxy)-3,5-bis(methoxymethoxy) benzoyl)oxy)methyl)-6-methoxytetrahydro-2H-pyran-3-yl4-(benzyloxy)-3,5-bis (methoxymethoxy)benzoate (53). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 9 H), 3.47 (s, 6 H), 3.66 (dd, J = 9.3 Hz, J = 3.6 Hz, 1 H), 4.07-4.31 (m, 4 H), 4.46 (d, 11.7 Hz, 1 H), 4.67 (m, 3 H), 4.83 (d, J = 8.1 Hz, 1 H), 4.87 (d, J = 7.5 Hz, 1 H), 5.13-5.27 (m, 14 H), 7.13-7.53 (m, 22 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.37, 56.30(4), 63.64, 67.75, 71.27, 73.48, 75.14, 75.19, 75.51, 79.20, 79.57, 95.41(4), 98.04, 112.1(4), 122.2(2), 124.9, 125.2, 127.4-128.5(20), 137.2, 137.3, 138.0, 138.2, 150.9(4), 164.7, 164.5.

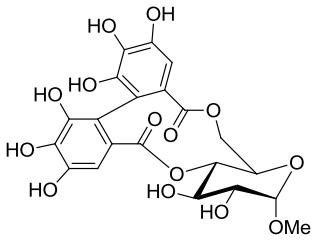


(2R,3R,4S,5R,6S)-4,5-bis(benzyloxy)-2-(((4-(benzyloxy)-3,5-dihydroxybenzoyl)oxy) methyl)-6-methoxytetrahydro-2H-pyran-3-yl 4-(benzyloxy)-3,5-dihydroxybenzoate (54). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 3 H), 3.70 (dd, J = 6.3 Hz, 3.6 Hz, 1 H), 4.06 (m, 2 H), 4.30 (d, J = 7.5 Hz, 1 H), 4.54 (dd, J = 9.3 Hz, J = 3.0 Hz, 1 H), 4.60-4.67 (m, 3 H), 4.79 (d, J = = 5.4 Hz, 1 H), 4.82 (d, J = 5.4 Hz, 1 H), 5.10 (d, J = 8.1 Hz, 4 H), 5.29 (t, J = 7.5 Hz, 1 H), 6.08 (br, 4 H), 7.05-7.36 (m, 24 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.65, 60.82, 63.21, 67.64, 71.02, 73.86, 75.23, 75.29, 75.59, 79.03, 79.91, 99.39, 110.1(4), 124.7, 125.0, 127.6-128.9(20), 136.8(2), 138.0(3), 149.2(4), 165.7, 166.6.

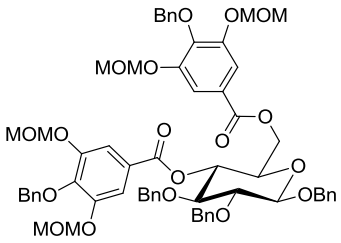


(11aR,13S,14R,15S,15aR)-3,6,14,15-tetrakis(benzyloxy)-2,4,5,7-tetrahydroxy-13-methoxy-11,11a,13,14,15,15a-hexahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacyclo undecine-9,17-dione (55). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (s, 3 H), 3.59 (dd, J = 9.6 Hz, J = 3.6 Hz, 1 H), 3.80 (d, J = 12.6 Hz, 1 H), 3.96 (t, J = 9.3 Hz, 1 H), 4.52 (d, J = 3.9 Hz, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.72 (d, J = 11.4 Hz, 1 H), 4.79 (d, J = 12.0 Hz, 1 H), 4.84 (d, J = 11.4 Hz, 1 H), 4.95 (t, J = 9.9 Hz, 1 H), 5.07-5.20 (m, 6 H), 5.61 (br, 1 H), 5.72 (br, 1 H), 5.77 (br, 2 H), 6.46 (s, 1 H), 6.68 (s, 1 H), 7.25-7.41 (m, 20 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.61, 63.88, 66.79, 72.27, 73.94, 75.12, 75.50, 75.65, 79.36, 79.94, 98.87, 108.1, 108.6, 113.5,

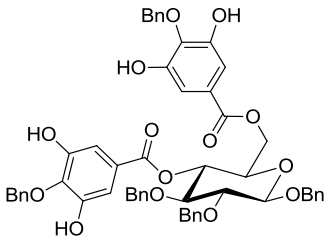
114.7, 127.8-129.0(20), 129.9, 130.4, 135.9, 136.1, 136.7, 136.8, 138.0, 138.4, 147.4(2), 149.1, 149.2, 167.1, 168.2.



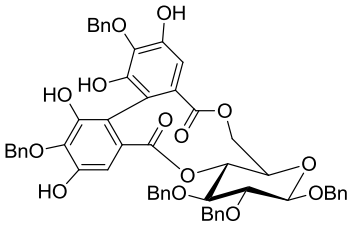
(11aR,13S,14R,15R,15aS)-2,3,4,5,6,7,14,15-octahydroxy-13-methoxy-11,11a,13,14, 15,15a-hexahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacycloundecine-9,17-dione(56). ^{1}H NMR (300 MHz, COCD6) δ 3.38 (s, 3 H), 3.55 (dd, J = 9.9 Hz, J = 3.3 Hz, 1 H), 3.72-3.82 (m, 2 H), 3.94 (s, 1 H), 4.13 (dd, J = 10.5 Hz, J = 7.2 Hz, 1 H), 4.70-4.80 (m, 2 H), 5.14 (dd, J = 12.9 Hz, J = 6.3 Hz, 1 H), 6.59 (s, 1 H), 6.59 (s, 1 H).



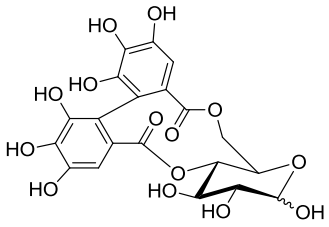
(2R,3R,4S,5R,6R)-4,5,6-tris(benzyloxy)-2-(((4-(benzyloxy)-3,5-bis(methoxymethoxy) benzoyl)oxy)methyl)tetrahydro-2H-pyran-3-yl4-(benzyloxy)-3,5-bis(methoxymethoxy) benzoate (53b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (s, 12 H), 3.64 (t, J = 9.0 Hz, 1 H), 3.78 (t, J = 9.3 Hz, 1 H), 3, 87 (t, J = 6.9 Hz, 1 H), 4.29 (dd, J = 12.3 Hz, J = 7.2 Hz, 1 H), 4.57-4.80 (m, 6 H), 4.93-4.98 (m, 2 H), 5.12-5.18 (m, 12 H), 5.28 (t, J = 9.9, 1 H), 7.08-7.56 (m, 29 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.51(4), 63.97, 71.07, 71.60, 72.25, 75.04, 75.34, 75.37(2), 81.75, 82.10, 95.61(4), 102.1, 112.4(4), 125.0, 125.5, 127.6-128.7(25), 137.1, 137.4, 138.1, 138.4(2), 143.3, 143.4, 151.0(2), 151.1(2), 164.8, 165.7.



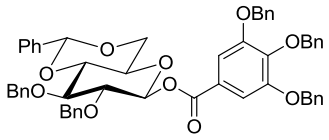
(2R,3R,4S,5R,6R)-4,5,6-tris(benzyloxy)-2-(((4-(benzyloxy)-3,5-dihydroxybenzoyl)oxy) methyl)tetrahydro-2H-pyran-3-yl4-(benzyloxy)-3,5-dihydroxybenzoate (54b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51-3.80 (m, 3 H), 4.50 (t, J = 4.8 Hz, 1 H), 4.57-4.78 (m, 6 H), 4.95-5.00 (m, 2 H), 5.12-5.14 (d, 4 H), 5.39 (t, 9.3 Hz, 1 H), 6.23 (br, 4 H), 7.07-7.38 (m, 29 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.42, 71.36, 71.43, 71.76, 75.20, 75.35(2), 75.56, 81.39, 82.24, 102.5, 110.1(4), 124.7, 125.0, 127.8-129.0(25), 136.8, 136.9, 137.1, 137.8, 137.9, 138.0, 138.3, 149.2(4), 165.8, 166.6.



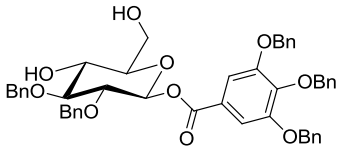
(11aR,13R,14R,15S,15aR)-3,6,13,14,15-pentakis(benzyloxy)-2,4,5,7-tetrahydroxy-11,11a,13,14,15,15a-hexahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacycloundecine-9,17-dione(55b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47-3.78 (m, 3 H), 3.98 (d, J = 12.9 Hz, 1 H), 4.55-5.00 (m, 8 H), 5.09-5.23 (m, 5 H), 5.84-6.19 (br, 4 H), 6.50 (s, 1 H), 6.68 (s, 1 H), 7.17-7.39 (m, 25 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.83, 71.43, 71.64, 72.12, 74.91, 75.38, 75.67, 75.84, 81.35, 82.53, 103.2, 108.0, 108.8, 110.1, 113.2, 114.7, 127.9-129.1(25), 129.9, 130.6, 135.8, 136.1, 136.7, 137.2, 138.2(2), 147.3, 147.4, 149.2(2), 167.0, 168.0.



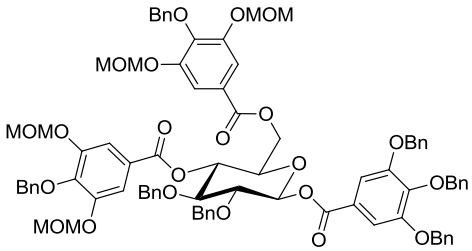
(11aR,14R,15R,15aS)-2,3,4,5,6,7,13,14,15-nonahydroxy-11,11a,13,14,15,15a-hexahydro dibenzo[g,i]pyrano[3,2-b][1,5]dioxacycloundecine-9,17-dione (56b). ^{1}H NMR (300 MHz, $CDCl_3$) mixture of anomers 3:2 δ 3.41-3.94 (m, 4 H), 4.29-4.58 (m, 1 H), 4.82-4.85 (m, 1 H), 5.10-5.23 (m, 1 H), 6.56 (s, 0.6 H), 6.59 (s, 0.4 H), 6.67 (s, 0.6 H), 6.68 (s, 0.4 H).



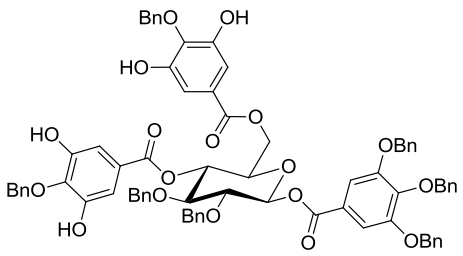
(2R,4aR,6S,7R,8S,8aR)-7,8-bis(benzyloxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl 3,4,5-tris(benzyloxy)benzoate^{1}H (51c). NMR (300 MHz, $CDCl_3$) δ 3.66 (m, 5 H), 4.41 (dd, J = 9.9 Hz, J = 4.8 Hz, 1 H), 4.63 (d, J = 11.1 Hz, 1 H), 4.76 (d, J = 11.4 Hz, 1 H), 4.80 (d, J = 11.4 Hz, 1 H), 4.98 (d, J = 11.1 Hz, 1 H), 5.07 (m, 2 H), 5.11 (d, J = 4.5 Hz, 2 H), 5.17 (s, 2 H), 5.60 (s, 1 H), 5.96 (d, J = 7.8 Hz, 1 H), 7.17-7.53 (m, 32 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.85, 68.72, 71.36(2), 75.26(2), 75.45, 80.80, 81.27, 81.46, 94.89, 101.4, 109.7(2), 124.0, 126.2(2), 129.2-127.5(28), 136.7(2), 137.3, 137.4, 137.8, 138.4, 143.2, 152.7(2), 164.3. m/z: 893 $[M+Na]^+$, 608, 568, 489; HRMS: calcd. for $C_{55}H_{50}NaO_{10}$: 893.3296 $[M+Na]^+$; found 893.3279.



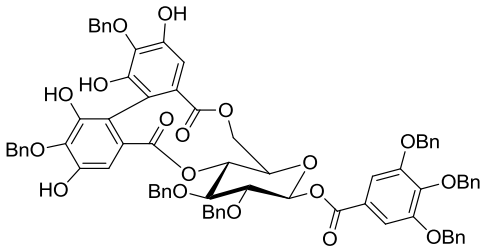
(2S,3R,4S,5R,6R)-3,4-bis(benzyloxy)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl 3,4,5-tris(benzyloxy)benzoate (52c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92-3.53 (m, 6 H), 4.67 (d, J = 2.4 Hz, 2 H), 4.73 (d, J = 11.4 Hz, 1 H), 4.98 (d, J = 11.7 Hz, 1 H), 5.16-5.08 (m, 6 H), 5.89 (d, J = J = 7.8 Hz, 1 H), 7.19-7.42 (m, 27 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.12, 70.05, 71.38(2), 75.16, 75.29, 75.54, 76.19, 81.05, 84.25, 94.94, 109.7(2), 124.1, 128.8-127.5(25), 136.7(2), 137.4, 137.8, 138.5, 143.2, 152.8(2), 164.5. m/z: 805 $[M+Na]^+$, 553, 441; HRMS: calcd. for $C_{48}H_{46}NaO_{10}$: 805.2983 $[M+Na]^+$; found 805.2986.



(2R,3R,4S,5R,6S)-4,5-bis(benzyloxy)-2-(((4-(benzyloxy)-3,5-bis(methoxymethoxy) benzoyl) oxy)methyl)-6-((3,4,5-tris(benzyloxy)benzoyl)oxy)tetrahydro-2H-pyran-3-yl 4-(benzyloxy)-3,5-bis(methoxymethoxy)benzoate (53c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (s, 6 H), 3.47 (s, 6 H), 3.83 (t, J = 8.7 Hz, 1 H), 3.95 (t, J = 9.3 Hz, 1 H), 4.12 (m, 1 H), 4.25 (dd, J = 12.6 Hz, J = 6.9 Hz, 1 H), 4.82-4.57 (m, 6 H), 5.22-5.12 (m, 17 H), 5.43 (t, J = 9.3 Hz, 1 H), 5.99 (d, J = 7.8 Hz, 1 H), 7.13-7.51 (m, 41 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.57(4), 63.48, 70.95, 71.38(2), 73.23, 75.19, 75.29(2), 75.37(2), 75.42, 75.47, 80.88, 81.91, 94.52, 95.65(4), 109.7(2), 112.4(2), 112.6(2), 124.2, 124.8, 125.4, 128.7-127.6(35), 136.7(2), 137.4, 137.5(2), 137.7, 137.8, 143.5, 150.9(2), 151.2(2), 152.8(2), 164.3, 164.8, 165.6. m/z: 1465 $[M+Na]^+$, 922, 859; HRMS: calcd. for $C_{84}H_{82}NaO_{22}$: 1465.5190 $[M+Na]^+$; found 1465.5184.

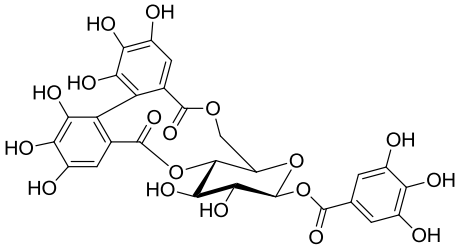


(2R,3R,4S,5R,6S)-4,5-bis(benzyloxy)-2-(((4-(benzyloxy)-3,5-dihydroxybenzoyl)oxy) methyl)-6-((3,4,5-tris(benzyloxy)benzoyl)oxy)tetrahydro-2H-pyran-3-yl 4-(benzyloxy)-3,5-dihydroxybenzoate (54c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05-3.87 (m, 3 H), 4.34 (d, J = 12.9 Hz, 1 H), 4.80-4.63 (m, 5 H), 5.20-5.10 (m, 10 H), 5.46 (t, J = 10.5 Hz, 1 H), 5.99 (d, J = 7.8 Hz, 1 H), 7.10-7.42 (m, 41 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.12, 70.05, 71.40(3), 73.04, 75.25, 75.34, 75.40(2), 80.99, 81.68, 94.82, 109.7(2), 110.1(4), 123.9, 124.5, 124.9, 130.0-127.6(35), 136.7(2), 136.9, 137.0, 137.4, 137.7(2), 138.0, 138.1, 143.3, 149.2(2), 149.3(2), 152.8(2), 164.8, 165.8, 166.7. m/z: 1265 $[M-H]^+$, 971, 615; HRMS: calcd. for $C_{76}H_{65}O_{18}$: 1265.4176 $[M-H]^+$; found 1265.4149.

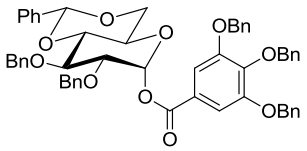


(11aR,13S,14R,15S,15aR)-3,6,14,15-tetrakis(benzyloxy)-2,4,5,7-tetrahydroxy-9,17-dioxo-9,11,11a,13,14,15,15a,17-octahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacyclo undecin-13-yl 3,4,5-tris(benzyloxy)benzoate (55c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (t, J = 5.4 Hz, 1 H), 4.03-3.75 (m, 4 H), 4.77-4.52 (m, 4 H), 5.24-5.08 (m, 11 H), 5.91 (d, J = 7.5 Hz, 1 H), 6.52 (s, 1 H), 6.67 (s, 1 H), 7.10-7.41 (m, 37 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.59, 71.36, 71.48, 71.95, 72.33, 74.94, 75.23, 75.36, 75.74, 75.89, 81.35, 81.59, 94.69, 108.1, 108.8, 109.7(2), 113.1, 114.8, 124.0, 129.1-127.6(35), 129.7, 130.8, 135.8, 136.3, 136.7,

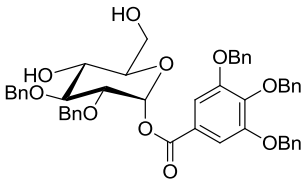
136.8(3), 137.5, 137.6, 138.0, 143.2, 147.4, 147.5, 149.2, 149.3, 152.8(2), 164.5, 167.1, 167.6. m/z: 1263 $[M-H]^+$, 855, 529; HRMS: calcd. for $C_{76}H_{63}O_{18}$: 1263.4020 $[M-H]^+$; found 1263.3999.



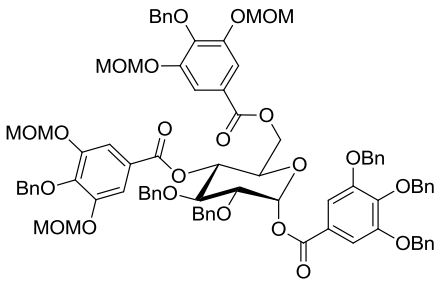
Strictinin (33a).[37] m/z: 633 $[M-H]^+$, 498, 306; HRMS: calcd. for $C_{27}H_{21}O_{18}$: 633.0733 $[M-H]^+$; found 633.0752.



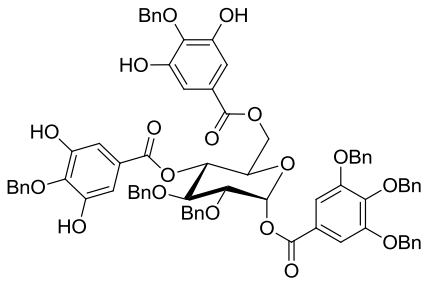
(2R,4aR,6R,7R,8S,8aR)-7,8-bis(benzyloxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin -6-yl 3,4,5-tris(benzyloxy)benzoate (51d). ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (m, 5 H), 4.03 (t, J = 9.3 Hz, 1 H), 4.75 (s, 2 H), 4.90 (d, J = 11.4 Hz, 1 H), 5.00 (d, J = 11.4 Hz, 1 H), 5.11 (m, 2 H), 5.14 (s, 2 H), 5.17 (s, 2 H), 5.63 (s, 1 H), 6.44 (d, J = 3.9 Hz, 1 H), 7.29-7.58 (32 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.15, 68.90, 71.43(2), 73.66, 75.24, 75.34, 78.22, 78.38, 81.68, 91.29, 101.5, 109.8(2), 124.5, 126.2(2), 129.2-127.6(28), 136.8(2), 137.4, 137.5, 137.8, 138.6, 143.2, 152.7(2), 164.7. m/z: 893 $[M+Na]^+$, 589, 489, 441; HRMS: calcd. for $C_{55}H_{50}NaO_{10}$: 893.3296 $[M+Na]^+$; found 893.3293.



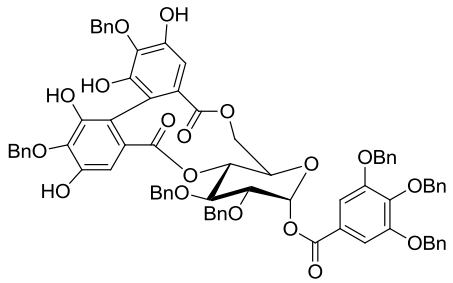
(2R,3R,4S,5R,6R)-3,4-bis(benzyloxy)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl 3,4,5-tris(benzyloxy)benzoate (52d). 1H NMR (300 MHz, $CDCl_3$) δ 3.83-3.69 (m, 6 H), 4.78-4.64 (m, 3 H), 5.03 (d, J = 11.7 Hz, 1 H), 5.21-5.12 (m, 6 H) 6.49 (d, J = 3.3 Hz, 1 H), 7.44-7.27 (m, 27 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.01, 69.58, 71.40(2), 73.00, 73.82, 75.27, 75.35, 78.93, 80.77, 90.74, 109.7(2), 124.6, 128.8-127.5(25), 136.7(2), 137.5, 137.6, 138.6, 143.2, 152.7(2), 164.7. m/z: 805 $[M+Na]^+$, 553, 441; HRMS: calcd. for $C_{48}H_{46}NaO_{10}$: 805.2983 $[M+Na]^+$; found 805.2983.



(2R,3R,4S,5R,6R)-4,5-bis(benzyloxy)-2-(((4-(benzyloxy)-3,5-bis(methoxymethoxy) benzoyl)oxy)methyl)-6-((3,4,5-tris(benzyloxy)benzoyl)oxy)tetrahydro-2H-pyran-3-yl4-(benzyloxy)-3,5-bis (methoxymethoxy)benzoate (53d). ^1H NMR (300 MHz, $CDCl_3$) δ 3.41 (s, 6 H), 3.43 (s, 6 H), 3.89 (dd, J = 9.3 Hz, J = 3.6 Hz, 1 H), 4.13-4.33 (m, 3 H), 4.56 (d, J = 10.5 Hz, 1 H), 4.68-4.90 (m, 4 H), 5.08-5.20 (m, 18 H), 5.42 (t, J = 9.9 Hz, 1 H), 6.56 (d, J = 3.6 Hz, 1 H), 7.13-7.55 (m, 41 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.49(4), 63.03, 70.57, 70.78, 71.33(2), 73.39(2), 75.34(5), 78.69, 78.97, 90.62, 95.55(2), 95.66(2), 109.7(2), 112.3(2), 112.5(2), 124.6, 124.9, 125.3, 128.8-127.5(35), 136.8(2), 137.3, 137.5, 137.6, 138.1, 143.1, 143.4, 150.9(2), 151.2(2), 152.6(2), 164.4, 164.8, 165.6. m/z: 1465 $[M+Na]^+$, 764; HRMS: calcd. for $C_{48}H_{46}NaO_{10}$: 1465.5190 $[M+Na]^+$; found 1465.5190.

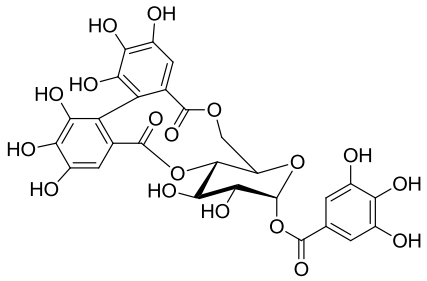


(2R,3R,4S,5R,6R)-4,5-bis(benzyloxy)-2-(((4-(benzyloxy)-3,5-dihydroxybenzoyl)oxy) methyl)-6-((3,4,5-tris(benzyloxy)benzoyl)oxy)tetrahydro-2H-pyran-3-yl 4-(benzyloxy)-3,5-dihydroxybenzoate (54d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03-4.31 (m, 4 H), 4.72-4.88 (m, 5 H), 5.16-5.32 (m, 10 H), 5.44 (t, J = 10.2, 1 H), 6.61 (d, J = 3.6 Hz, 1 H), 7.16-7.53 (41 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.27, 69.91, 70.50, 71.46(2), 73.52, 75.08, 75.20, 75.31, 75.42, 78.05, 78.34, 90.79, 109.8(2), 110.1(4), 124.5(2), 124.7, 130.0-127.6(35), 136.8(2), 136.9, 137.0, 137.5, 137.7, 137.8, 138.0, 138.1, 143.2, 149.2(2), 149.3(2), 152.8(2), 164.6, 165.9, 166.8. m/z: 1265 $[M-H]^+$, 615; HRMS: calcd. for $C_{76}H_{65}O_{18}$: 1265.4176 $[M-H]^+$; found 1265.4155.

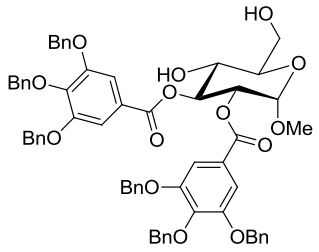


(11aR,13R,14R,15S,15aR)-3,6,14,15-tetrakis(benzyloxy)-2,4,5,7-tetrahydroxy-9,17-dioxo-9,11,11a,13,14,15,15a,17-octahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacyclo undecin-13-yl 3,4,5-tris(benzyloxy)benzoate (55d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71-4.00 (m, 5 H), 4.62-4.88 (m, 5 H), 5.00-5.24 (m, 10 H), 6.39 (d, J = 4.2 Hz, 1 H), 6.59 (s, 1 H), 6.71 (s, 1 H), 7.25-7.43 (m, 37 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.42, 69.95, 71.36,

71.44(2), 73.64, 74.70, 75.40, 75.69, 75.88, 78.48, 79.29, 90.75, 107.7, 108.74, 109.8(2), 113.1, 114.9, 124.4, 129.1-127.4(35), 129.8, 130.8, 135.7, 136.1, 136.6, 136.7, 136.8(2), 137.5(2), 138.2, 143.1, 147.4, 147.5, 149.2, 149.4, 152.7(2), 164.4, 166.9, 167.5. m/z: 1287 $[M+Na]^+$, 922, 688; HRMS: calcd. for $C_{76}H_{64}NaO_{18}$: 1287.3985 $[M+Na]^+$; found 1287.3996.

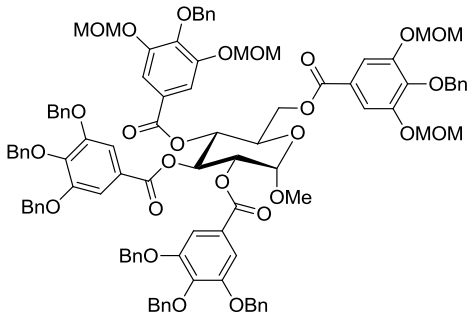


(11aR,13R,14R,15R,15aS)-2,3,4,5,6,7,14,15-octahydroxy-9,17-dioxo-9,11,11a,13,14,15, 15a,17-octahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacycloundecin-13-yl3,4,5-tri hydroxybenzoate (33b). ^{1}H NMR (300 MHz, $COCD_6$) δ 3.72 (d, J = 13.2 Hz, 1 H), 3.88 (dd, J = 9.9 Hz, J = 4.2 Hz, 1 H), 4.08 (t, J = 9.3 Hz, 1 H), 4.41 (dd, J = 9.9 Hz, J = 6 Hz, 1 H), 4.91 (t, J = 9.3 Hz, 1 H), 5.19 (dd, J = 13.4 Hz, J = 6.6 Hz, 1 H), 6.35 (d, J = 4.2 Hz, 1 H), 6.60 (s, 1 H) 6.72 (s, 1 H), 7.19 (s, 2 H). m/z: 657 $[M+Na]^+$, 568, 454, 301; HRMS: calcd. for $C_{27}H_{22}NaO_{18}$: 657.0698 $[M+Na]^+$; found 657.0695.

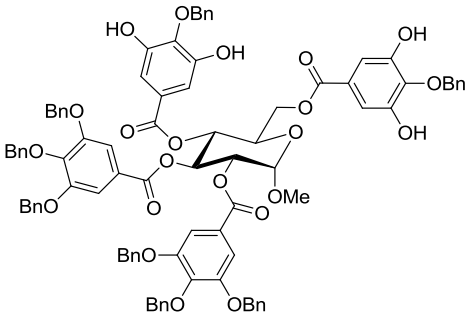


(2S,3R,4S,5R,6R)-5-hydroxy-6-(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-3,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) (52e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 3 H), 3.85-4.00 (m, 4 H), 4.94-5.04 (m, 12 H), 5.13-5.16 (m, 2 H), 5.69 (t, J = 9.9, 1 H), 7.22-7.39 (m, 34 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.52, 62.03, 69.56, 71.10(2), 71.16(2), 71.57, 72.26,

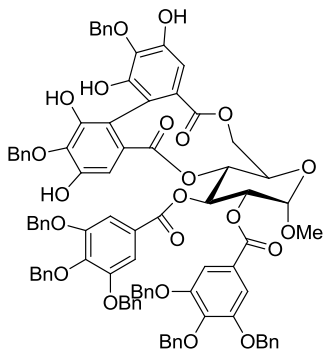
74.68, 75.19(2), 97.23, 109.2(2), 109.3(2), 124.1, 124.3, 127.7-128.6(30), 136.5(2), 136.6(2), 137.4, 137.5, 142.9, 143.0, 152.6(4), 165.8, 167.1. m/z: 1061 $[M+Na]^+$, 715, 559; HRMS: calcd. for $C_{63}H_{58}NaO_{14}$: 1061.3719 $[M+Na]^+$; found 1061.3709.



(2S,3R,4S,5R,6R)-5-((4-(benzyloxy)-3,5-bis(methoxymethoxy)benzoyl)oxy)-6-(((4-(benzyloxy)-3,5-bis(methoxymethoxy)benzoyl)oxy)methyl)-2-methoxytetrahydro-2H-pyran-3,4-diyl-bis(3,4,5-tris(benzyloxy)benzoate) (53e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 6 H), 3.48 (s, 6 H), 3.53 (s, 3 H), 4.43 (m, 2 H), 4.66 (d, J = 10.5 Hz, 1 H), 4.90-5.20 (m, 25 H), 5.32 (d, J = 3.3 Hz, 1 H), 5.63 (t, J = 9.9 Hz, 1 H), 6.13 (t, J = 9.9 Hz, 1 H), 7.19-7.47 (m, 46 H), 7.61 (s, 2 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.66, 56.46(2), 56.53(2), 63.40, 67.50, 69.65, 71.14(3), 71.18(2), 72.78, 75.19, 75.22, 75.33, 75.34, 95.56(2), 95.58(2), 97.01, 109.1(2), 109.3(2), 112.4(2), 112.5(2), 124.2, 124.3, 124.4, 125.3, 127.7-128.7(40), 136.5(2), 136.7(2), 137.4, 137.4, 137.5(2), 142.9(2), 143.3, 143.9, 151.1(4), 152.6(4), 165.0, 165.5, 165.6, 165.7. m/z: 1721 $[M+Na]^+$, 872; HRMS: calcd. for $C_{99}H_{94}NaO_{26}$: 1721.5926 $[M+Na]^+$; found 1721.5916.

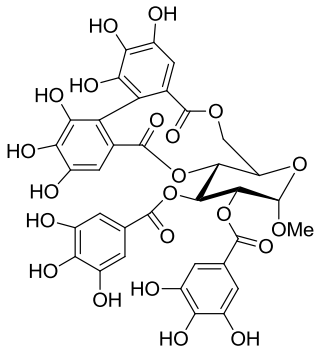


(2S,3R,4S,5R,6R)-5-((4-(benzyloxy)-3,5-dihydroxybenzoyl)oxy)-6-(((4-(benzyloxy)-3,5-dihydroxybenzoyl)oxy)methyl)-2-methoxytetrahydro-2H-pyran-3,4-diyl-bis(3,4,5-tris(benzyloxy)benzoate) (54e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (s, 3 H), 4.40 (br, 2 H), 4.77-5.37 (m, 19 H), 5.65 (t, J = 9.9 Hz, 1 H), 5.87 (br, 4 H), 6.12 (t, J = 9.9 Hz, 1 H), 7.08-7.46 (m, 48 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.91, 62.71, 67.94, 68.98, 71.16(2), 71.21(2), 72.86, 75.18, 75.24(2), 75.28(2), 97.30, 109.0(2), 109.4(2), 110.1(4), 124.1(2), 124.2, 124.6, 128.9-127.8(40), 136.4(2), 136.7(2), 136.8, 136.9, 137.4, 137.5, 138.1, 138.4, 142.9(2), 149.2(4), 152.7(4), 165.7, 165.8, 165.9, 166.6. m/z: 1545 $[M+Na]^+$, 955, 715, 489; HRMS: calcd. for $C_{91}H_{78}NaO_{22}$: 1545.4877 $[M+Na]^+$; found 1545.4832.

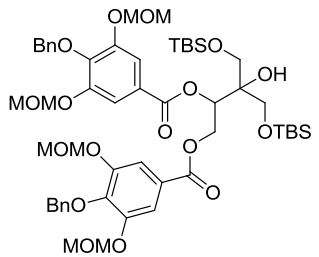


(11aR,13S,14R,15S,15aR)-3,6-bis(benzyloxy)-2,4,5,7-tetrahydroxy-13-methoxy-9,17-dioxo-9,11,11a,13,14,15,15a,17-octahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacyclo undecine-14,15-diyl-bis(3,4,5-tris(benzyloxy)benzoate) (55e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3 H), 3.97 (d, J=12.9 Hz, 1 H), 4.45 (br, 1 H), 4.81-5.38 (m, 20 H), 5.94 (t, J =

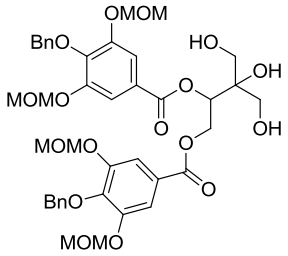
10.2 Hz, 1 H), 6.70 (s, 1 H), 6.80 (s, 1 H), 7.14-7.45 (m, 44 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.89, 63.46, 67.78, 70.49, 71.11, 71.22(2), 71.45, 72.94, 75.18, 75.24, 75.28, 75.65(2), 97.61, 108.2, 108.6, 109.4(4), 113.7, 114.0, 124.1, 124.2, 130.0-127.7(40), 129.7, 130.1, 136.0, 136.1, 136.6(3), 136.7(3), 137.5, 137.6, 142.9(2), 147.3, 147.5, 149.2, 149.3, 152.7(4), 165.7, 166.0, 167.0, 167.8. m/z: 1543 $[M+Na]^+$, 608; HRMS: calcd. for $C_{91}H_{76}NaO_{22}$: 1543.4720 $[M+Na]^+$; found 1545.4731.



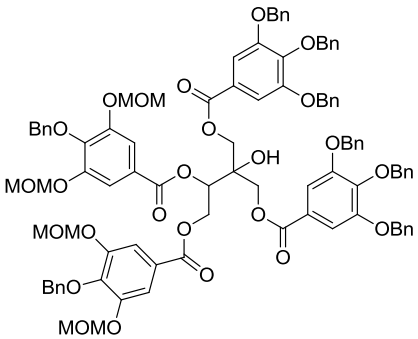
(11aR,13S,14R,15S,15aR)-2,3,4,5,6,7-hexahydroxy-13-methoxy-9,17-dioxo-9,11,11a, 13,14,15,15a,17-octahydrodibenzo[g,i]pyrano[3,2-b][1,5]dioxacycloundecine-14,15-diyl-bis (3,4,5-trihydroxybenzoate) (56e). ^{1}H NMR (300 MHz, $COCD_6$) δ 3.44 (s, 3 H), 3.86 (d, J = 14.7 Hz, 1 H), 4.40-4.47 (br, 1 H), 5.17-5.10 (m, 3 H), 5.33 (dd, J=12.9 Hz, 6.6 Hz, 1 H), 5.82 (t, J = 10.2 Hz, 1 H), 6.44 (s, 1 H), 6.64 (s, 1 H) 6.98 (s, 2 H), 7.05 (s, 2 H). m/z: 823 $[M+Na]^+$, 552, 489, 413; HRMS: calcd. for $C_{35}H_{28}NaO_{22}$: 823.0964 $[M+Na]^+$; found 823.0952.



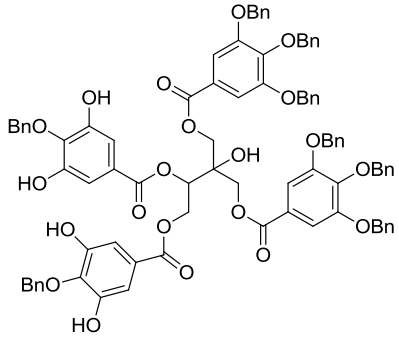
4-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-3-hydroxy butane-1,2-diylbis(4-(benzyloxy)-3,5-bis(methoxymethoxy)benzoate) (66). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.10 (s, 3 H), 0.11 (s, 3 H), 0.89 (s, 9 H), 0.92 (s, 9 H), 2.87 (br, 1 H), 3.43 (s, 6 H), 3.47 (s, 6 H), 3.61-3.80 (m, 4 H), 4.59 (dd, J = 12 Hz, J = 9.3 Hz, 1 H), 4.72 (dd, J = 12.3 Hz, J = 2.7 Hz, 1 H), 5.10-5.21 (m, 12 H), 5.69 (dd, J = 9.0 Hz, J = 2.1 Hz, 1 H), 7.30-7.56 (m, 14 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.48(4), 18.31(2), 25.94(3), 25.96(3), 56.44(2), 56.46(2), 63.22, 63.35, 64.15, 73.35, 75.17, 75.28, 75.34, 95.49(2), 95.69(2), 112.3(2), 112.5(2), 125.5, 125.7, 128.2-128.5(10), 137.4, 137.5, 143.3(2), 150.9(2), 151.0(2), 165.2, 165.8. .



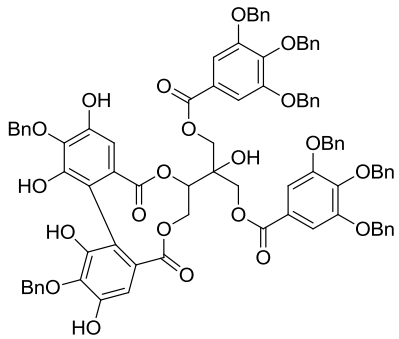
3,4-dihydroxy-3-(hydroxymethyl)butane-1,2-diylbis(4-(benzyloxy)-3,5-bis(methoxy methoxy)benzoate) (67). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 6 H), 3.44 (s, 6 H), 3.71-3.89 (m, 5 H), 4.68 (dd, J = 12.0 Hz, J = 8.1 Hz, 1 H), 4.83 (dd, J = 12.3 Hz, J = 3.0 Hz, 1 H), 5.09-5.18 (m, 12 H), 5.63 (dd, J = 8.1 Hz, J = 2.7 Hz, 1 H), 7.28-7.52 (m, 14 H).



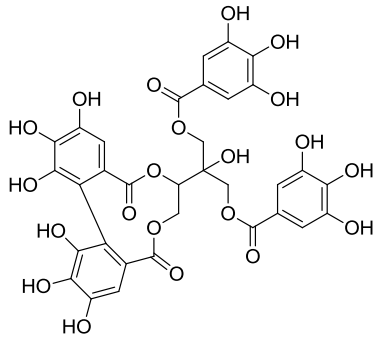
2-(1,2-bis((4-(benzyloxy)-3,5-bis(methoxymethoxy)benzoyl)oxy)ethyl)-2-hydroxy propane-1,3-diylbis(3,4,5-tris(benzyloxy)benzoate) (68). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (br, 1 H), 3.37 (s, 6 H), 3.44 (s, 6 H), 4.50-4.77 (m, 5 H), 4.94-5.21 (m, 25 H), 5.94 (d, J = 7.2 Hz, 1 H), 7.28-7.58 (m, 48 H).



2-(1,2-bis((4-(benzyloxy)-3,5-dihydroxybenzoyl)oxy)ethyl)-2-hydroxypropane-1,3-diyl bis(3,4,5-tris(benzyloxy)benzoate) (69). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (br, 1 H), 4.53-4.91 (m, 6 H), 5.06-5.13 (m, 16 H), 5.90 (br, 5 H), 7.09-7.39 (m, 48 H).



2-(2,13-bis(benzyloxy)-1,3,12,14-tetrahydroxy-5,10-dioxo-5,7,8,10-tetrahydrodibenzo [f,h][1,4]dioxecin-7-yl)-2-hydroxypropane-1,3-diylbis(3,4,5-tris(benzyloxy)benzoate) (70). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (m, 5 H), 4.69 (d, J = 11.1 Hz, 1 H), 5.06-5.14 (m, 16 H), 5.56 (d, J = 10.5 Hz, 1 H), 6.58 (s, 1 H), 6.71 (s, 1 H), 7.15-7.38 (m, 44 H).



2-(1,2,3,12,13,14-hexahydroxy-5,10-dioxo-5,7,8,10-tetrahydrodibenzo[f,h][1,4]dioxecin-7-yl)-2-hydroxypropane-1,3-diyl bis(3,4,5-trihydroxybenzoate) (71). ^{1}H NMR (300 MHz, $COCD_6$) δ 4.33 (dd, J = 10.8 Hz, 3.0 Hz, 1 H), 3.35-4.58 (m, 3 H), 5.13-5.18 (m, 1 H), 5.35 (t, J = 10.5 Hz, 1 H), 5.55 (dd, J = 10.8 Hz, 3.3 Hz, 1 H), 6.54 (s, 1 H), 6.62 (s, J = 1 H), 7.14-7.19 (m, 4 H).

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CHAPTER 3. New approach to flavonols via base mediated cyclization

Introduction:

Flavonols are one of nine different types of flavonoids, which also include: tannins (Chapter 2), flavones, flavanones, isoflavones, aurones, flavanediols, anthocyanidins, chalcones (Figure 1).[1] Flavonols are biosynthesized exclusively in plants and play an important role in floral pigmentation, act as signal molecules and show antimicrobial activity.[2] Unfortunately their isolation can be problematic, as mixtures of products are difficult to separate.[3]

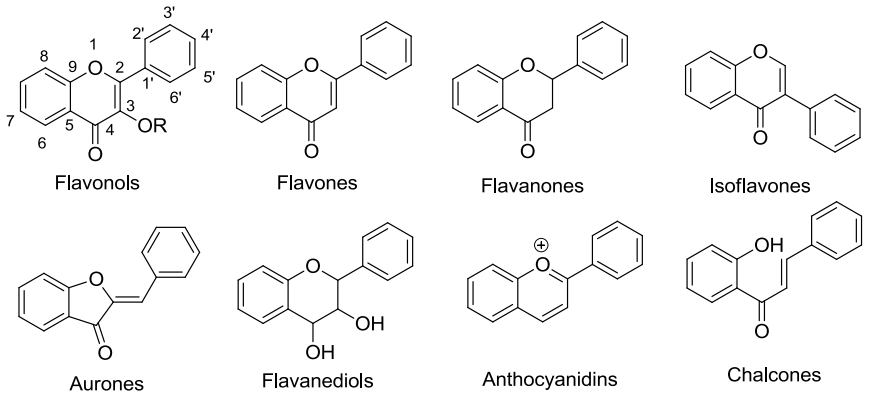


Figure 1. Different flavonoids structures.

Flavonols are found in a variety of different foods including, tomatoes and onions[4] and have been discovered as sugar conjugates in fruits and vegetables.[5] Tea and red wine are also known to possess a variety of different flavonols.[6,7] Quercetin (**1**), which is found in red wine, has shown antiviral,[8] anticancer,[9] and anti-inflammatory behavior (Figure 2).[10,11] Tetramethoxy flavove **2** has shown antimicrobial, antitumor and antifungal activity.[12] Another flavonol, kaempferol (**3**), was reported to reduce the risk of pancreatic cancer.[13] Other flavonols have displayed antioxidant and free radical scavenging activity.[14,15]

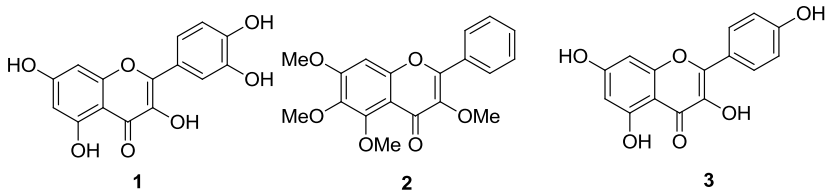
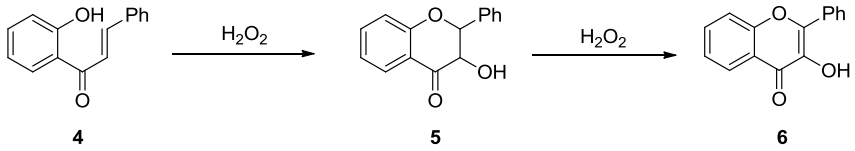


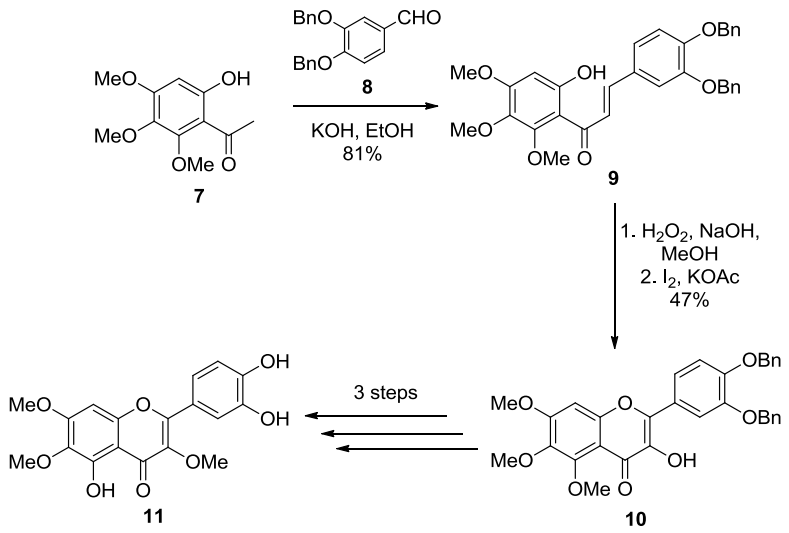
Figure 2. The structure of flavonol natural products Quercetin (**1**), 3,5,6,7-tetramethoxyflavone (**2**), and kaempferol (**3**).

The wealth of biological activity of flavonols has attracted considerable synthetic attention. The Algar-Flynn-Oyamada (AFO) reaction is the most common way to construct the flavonol core (Scheme 1).[16,17] This reaction oxidizes chalcones **4** with hydrogen peroxide to the corresponding flavonol **6**. The exact mechanism of this reaction is currently unclear, but studies have shown that it does not go through an epoxide mechanism.[18]



Scheme 1. The Algar-Flynn-Oyamada (AFO) reaction.

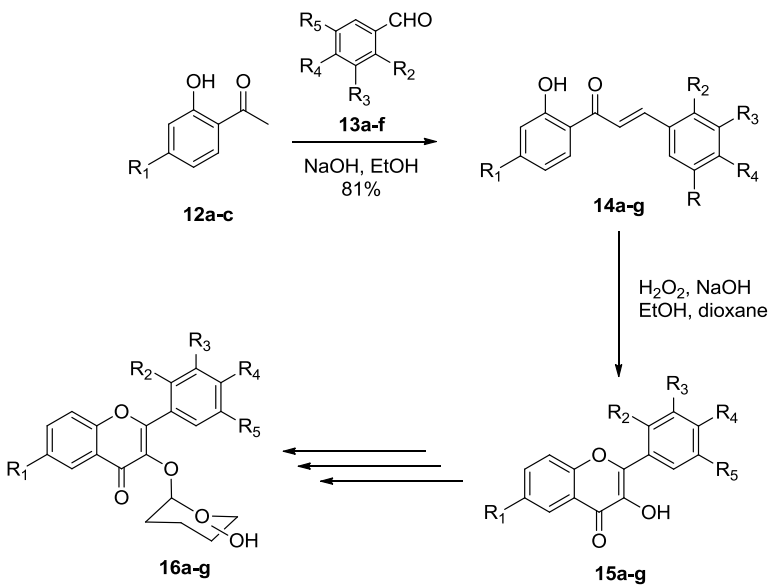
This approach has been used for the synthesis of a variety of different natural flavonols One example is the synthesis of chroysosplenol D (**11**) from the Kraus group (Scheme 2).[19] The synthesis commenced with an aldol condensation of acetephenone **7** and aldehyde **5** to yield chalcone **9** in 81 % yield. Direct oxidation to the flavonol with conventional AFO reaction conditions was unsuccessful, and instead, furnished the partially oxidized product. This intermediate was further oxidized with iodine to afford flavonol **10** in 47% yield over two steps. This compound was elaborated over three steps to accomplish the total synthesis of **11**.



Scheme 2. The synthesis of chroysosplenol D (**11**) utilizing an AFO reaction.

Li and co-workers used a similar approach to synthesize a variety of different glycosylated flavonols **16a-g** (Scheme 3). Their synthesis began with the aldol condensation of 2'-hydroxyacetophenones **12a-c** and benzaldehydes **13a-f** to synthesize chalcones **14a-g**. The chalcones were oxidized with H_2O_2 in accordance with the AFO reaction conditions to provide flavonols **15a-g**. They proceeded to attach different monosaccharides including glucose, galactose, xylose and arabinose to their flavonols to generate glycosylated flavonols **16a-g**.[20]

Trivedi and co-workers utilized an oxidation of the 2-aryl-3-nitrochromene **17a-g** to generate flavonols **18a-g** (Scheme 4). The nitrochromenes **17a-g** were synthesized from the condensation of *O*-hydroxybenzaldehydes with substituted nitrostyrenes. Treatment of **17a-g** with alkaline H_2O_2 lead to flavonols **18a-g** in good yields.[21] Trivedi and co-workers later reported the oxidation of nitrochromenes with light irradiation and aqueous acid.[22]

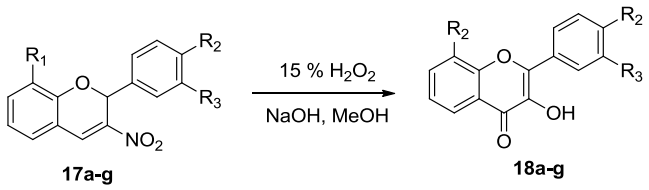


#	R_1	R_2	R_3	R_4	R_5	Yield (%) 14	Yield (%) 15
a	H	H	OMe	OMe	H	50	70
b	H	OMe	H	H	H	46	74
c	H	H	OMe	OMe	OMe	35	38
d	H	H	H	OBn	H	72	71
e	OMe	H	OMe	OMe	H	30	69
f	OMe	OMe	OMe	H	H	72	62
g	OBn	H	H	OMe	H	54	76

Scheme 3. Synthesis of flavonols **15a-g**.

An alternative approach towards the synthesis of flavonols includes the oxidation of organoborane flavones to yield flavonols.[23] Detty was able to synthesize flavone **21** in 63% yield *via* a coupling of 3,4,5-trimethoxyphenol (**19**) and phenylpropiolic acid (**20**) in the presence of Eaton's reagent (10% P_2O_5 in $MeSO_3H$, Scheme 5). The anion was generated

at C-3 with LDA and quenched with trimethylborate to give organoborate **22**. This compound was oxidized with H_2O_2 in acetic acid to give flavonol **23**.



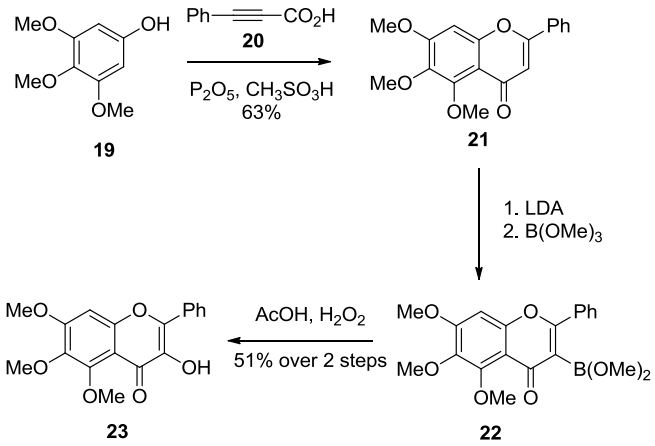
17a-g 18a-g

#	R_1	R_2	R_3	Yield (%)
a	H	H	H	76
b	H	OMe	H	80
c	H	Cl	H	70
d	H	Me	H	72
e	H	OMe	OMe	89
f	OMe	H	H	79
g	OMe	Me	H	83

Scheme 4. Synthesis of flavonols **18a-g** from 2-aryl-3-nitrochromenes **17a-g**.

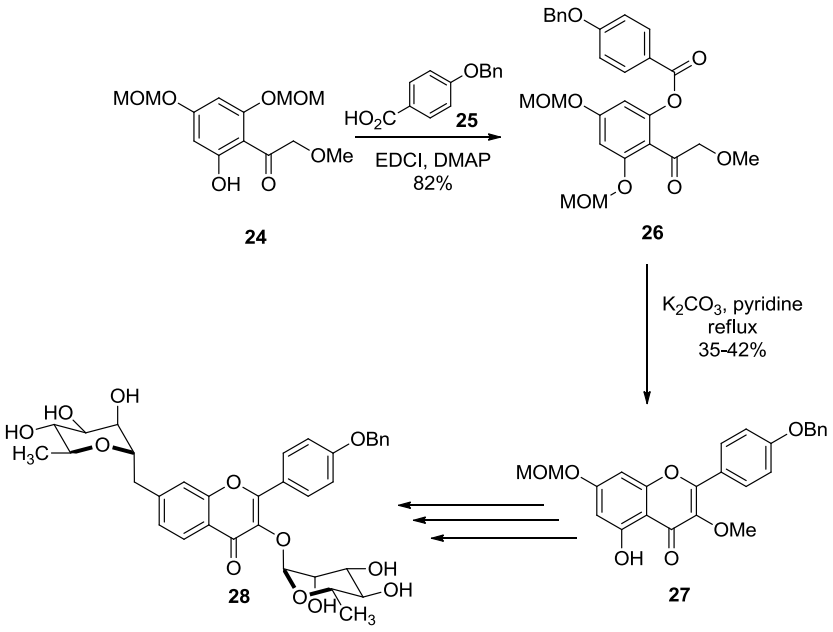
at C-3 with LDA and quenched with trimethylborate to give organoborate **22**. This compound was oxidized with H_2O_2 in acetic acid to give flavonol **23**.

Shaw and Urgaonkar utilized a Baker-Venkataraman-type reaction to synthesize flavonol **27** as a key intermediate towards their total synthesis of Kaemferitin (**28**), which is the 3,7-dirhamoniside of kaempferol (**3**, Scheme 6). Intermediate **24** was made from phloroglucinol undergoing a Houben-Hoesch reaction, followed by selective MOM deprotection.[24] Esterificaiton with acid **25** afforded flavonol precursor **26**. Cyclization with potassium carbonate in boiling pyridine was successful in generating the desired 5-



Scheme 5. Synthesis of flavonol **23**.

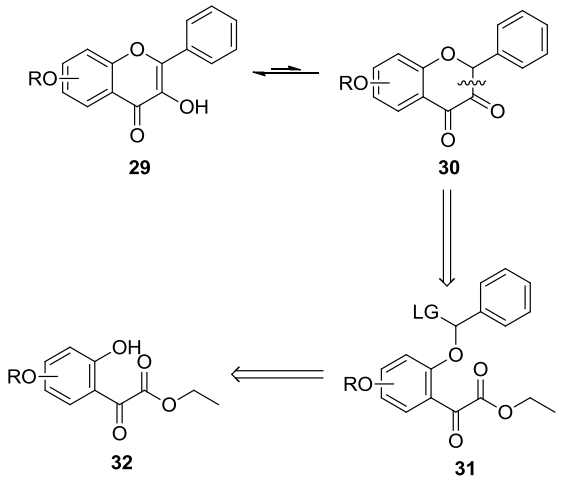
hydroxyflavone **27**. It is worth mentioning that the basic conditions also cleaved the MOM-ether ortho to the carbonyl. In 5 more steps they were able to generate the natural product **28**. This Baker-Venkataraman-type reaction has been used to synthesize pelargonidin 3-O-6”-O-acetyl-β-D-glucopyranoside, a kaempferol glucoside,[25] and glycosylated **1**.[26]



Scheme 6. Synthesis of Kaemferitin (**28**).

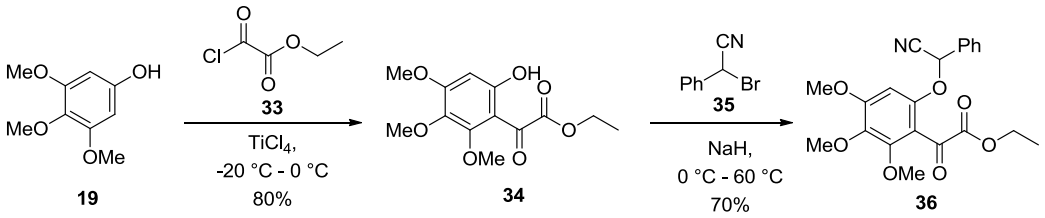
Results and Discussion:

While the encouraging biological profile of flavonols has inspired numerous synthetic efforts, many of these syntheses revolve around a late-stage oxidation of flavones. We were interested in designing a direct synthesis of these molecules conceptually different than the previous syntheses. Our retrosynthetic analysis focused on the disconnection between C-2 – C-3 of compound **30** (Scheme 7). This key C-C bond would originate from intramolecular attack of the benzyl anion on the ethyl ester of the 1,2 dicarbonyl followed by elimination of a leaving group. Precursor **31** could be derived from α-keto ester **32**.



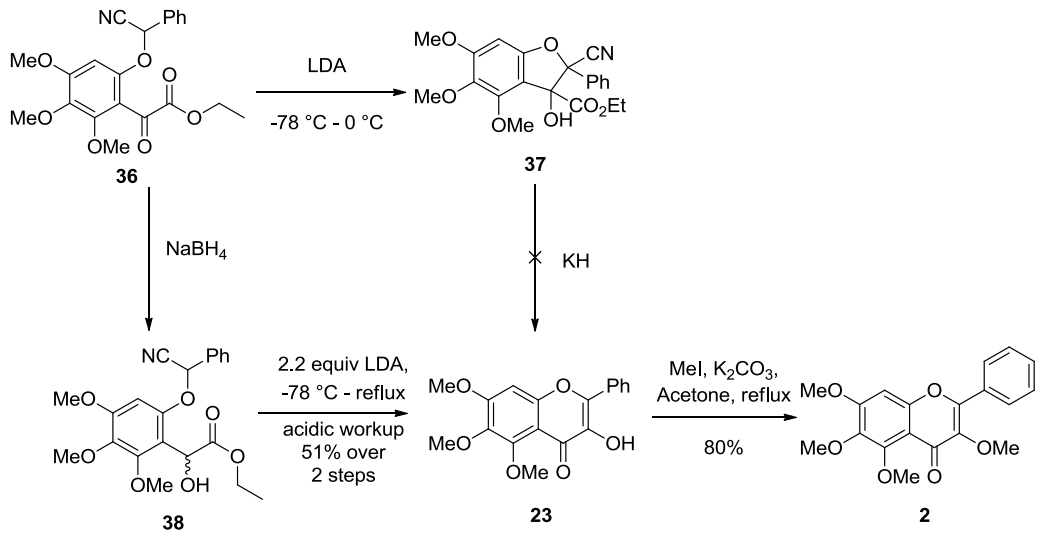
Scheme 7. Retrosynthetic analysis of the construction of flavonols.

Our synthesis began with the titanium tetrachloride ($TiCl_4$) mediated Friedel-Crafts acylation of commercially available 3,4,5-trimethoxyphenol (**19**) with ethyl chlorooxoacetate (**33**) to give α-keto ester **34** (Scheme 8). Due to its inherent nucleophilicity, the nitrile group would serve a dual role in the synthesis – it will act as an activator of benzylic position and leaving group. To this end, α-bromophenylacetonitrile (**34**) was *O*-alklyated to yield benzyl ether **36** in 70% yield.



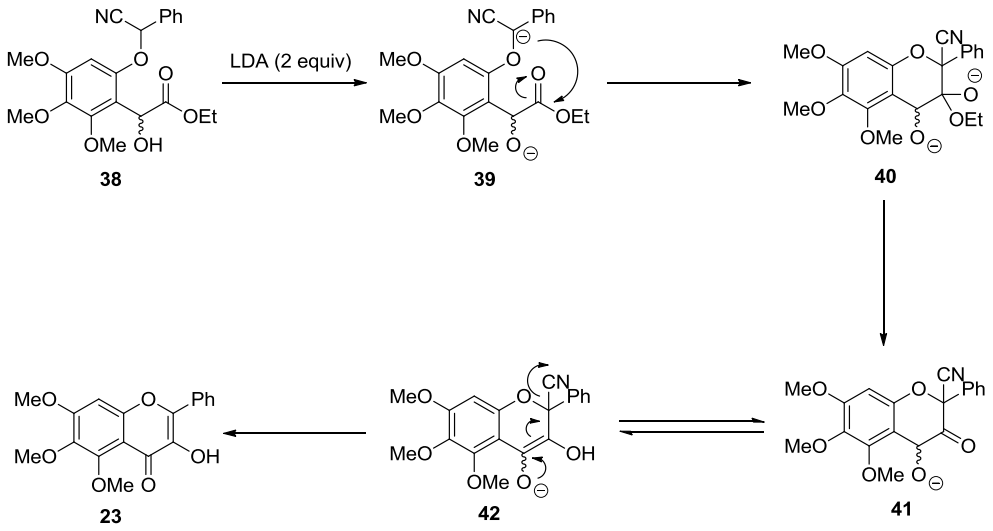
Scheme 8. Synthesis of α-keto ester **36**.

With this intermediate in hand, we attempted our key base mediated cyclization to form the corresponding flavonols; however, instead we recovered the 5-membered cyclization product **37** (Scheme 9). Attempts at converting this intermediate to flavonol **23** with potassium hydride (KH) were unsuccessful. Undeterred, we reduced compound **36** with sodium borohydride ($NaBH_4$) to a diastereomeric mixture of α-hydroxy-esters **38**. Gratifyingly, with two equivalents of LDA and elevated temperatures we were able to generate flavonol **23** as a single product. Using standard methylation reaction conditions, **23** was methylated to yield natural product **2**.[27]



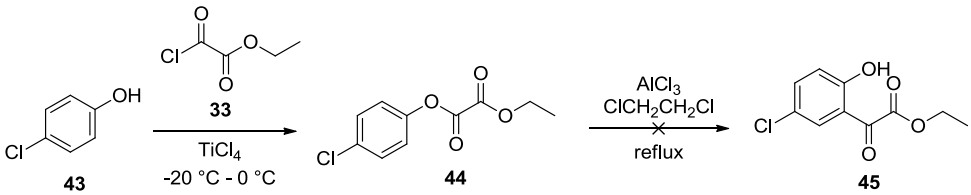
Scheme 9. Completion of the synthesis of natural product **2**.

The proposed mechanism of our key base-mediated cyclization step is depicted in Scheme 10. The first equivalent of base deprotonates the hydroxy group while the second equivalent generates the benzylic anion. This anion attacks the α-keto ester **39**, which in turn eliminates ethoxide. Compound **41** then tautomerizes to form intermediate **42**, which can facilitate the elimantion of the cyanide to form the desired flavonol **23**.



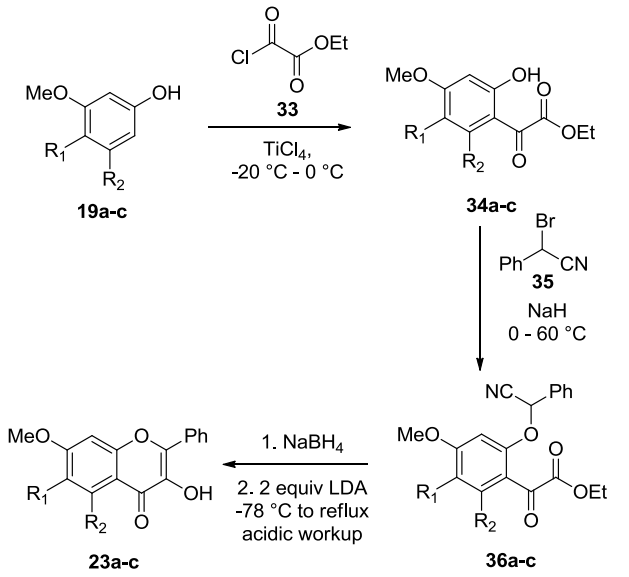
Scheme 10. Proposed mechanism of compound **38** to flavones **23**.

In order to test the scope and limitations of this reaction we decided to vary the substituents on the A ring of the flavonol. We started with 4-chloropehenol (**43**) and reacted it with ethyl chlorooxoacetate (**33**) under Friedel-Crafts conditions, but unfortunately the *O*-acylated product **44** resulted (Scheme 11). A Fries rearrangement was attempted to generate the *C*-acylated product, however this reaction was unsuccessful.



Scheme 11. O-Acylation of 4-chlorophenol (**43**) with **33**.

Alternatively, 3,5-dimethoxyphenol (**19b**) and 3-methoxyphenol (**19c**) were subjected to the Friedel-Crafts conditions and gave the desired *C*-acylated products **34b-c** (Scheme 12). These products were taken forward to the *O*-alklyation step with **35** to give benzyl ethers **36a-c**. The yield of **36b** is significantly lower than the previous reaction due to an unidentified side reaction, with this side-product being more pronounced at higher temperatures. Reduction of the ketone with $NaBH_4$ in ethanol yielded diastereomers that were taken to the cyclization step without purification. The base-mediated cyclization step was successful in generating the corresponding flavonols **23a-c**.



#	R_1	R_2	Yield (%) 34	Yield (%) 36	Yield (%) 23
a	OMe	OMe	80	70	51
b	H	OMe	89	25*	63
c	H	H	85	67*	60

Scheme 12. Synthesis of flavonols **23a-c**. *brsm

Our synthetic pathway provides an efficient new way to synthesize flavonols. Further optimization of these reaction conditions could provide a valuable route towards these biologically active molecules.

Experimental:

Friedel-Crafts Acylation:

To a solution of phenol **19a-c** (1.0 equiv) in CH_2Cl_2, was added titanium tetrachloride (1.1 equiv) at -20 °C under argon. To this dark brown solution, ethyl chlorooxoacetate (**33**) (1.1 equiv) was added dropwise while maintaining temperature at or below -15 °C. The resulting reaction mixture was stirred for 4 h with a steady increase in temperature to 0 °C. After the completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 and poured over cold HCl (1.0 M) solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with HCl (1.0 M) solution and brine followed by drying over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to obtain the crude compound **34a-c**. The crude compounds were then purified by silica gel column chromatography.

***O*-alkylation:**

To a slurry of NaH (1.1 equiv) in dry DMF under argon, phenols **34a-c** (1.0 equiv) was added at 0 °C. The resulting reaction mixture was stirred at 0 °C for 15 minutes followed by the addition of phenylacetonitrile **35** (1.1-1.5 equiv) at the same temperature. The reaction mixture was then stirred at 60 °C for 2-10 h. After the completion of the reaction, the reaction mixture was quenched by adding saturated NH_4Cl solution. The reaction mixture was then extracted with EtOAc (3 x 100 ml). The combined organic extracts were then washed with water and brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*.

The crude compound was purified by column chromatography to give pure **36a-c** respectively.

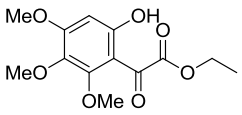
Reduction and Base-Mediated Cyclization:

In a round bottom flask, ketone **36a-c** (1.0 equiv) was suspended in anhydrous ethanol under inert conditions in an ice-acetone bath. To this, $NaBH_4$ (1.1 equiv) was added and the reaction mixture was warmed to room temperature over 1-3 h. After the completion of reaction, the reaction mixture was quenched with HCl (2.0 M) solution until the gas evolution stopped. The mixture was then diluted with water and extracted with EtOAc (2 x 100 ml). The combined organic extracts were then washed with water and brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to obtain crude as a mixture of diastereomers. The crude compounds were purified by column chromatography and were taken to next step as diastereomeric mixtures.

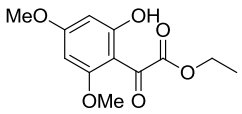
To a solution of diisopropylamine (2.3 equiv) in dry THF under argon, was added *n*-BuLi (2.5 M in hexanes) (2.2 equiv) at -78 °C. The mixture was warmed to -40 °C and stirred at this temperature for 45 minutes. The solution was returned to -78 °C and a solution of α-hydroxy-ester in dry THF was added to it. The resulting reaction mixture was warmed to rt and then refluxed for 8 h. After the completion of the reaction, the reaction mixture was quenched with HCl (1.0 M) solution until acidic and then returned to neutral pH with saturated $NaHCO_3$ solution. Most of the THF was evaporated *in vacuo*. The residue was then diluted with water and extracted with EtOAc (3 x 50 ml). The combined organic extracts were then washed with water and brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude compound was then purified by column chromatography.

Preparation of 2:

Flavonol **15** (0.04 g, 0.12 mmol) was taken in dry acetone and anhydrous K_2CO_3 was added to it under argon. To this, methyl iodide (0.03 g, 0.18 mmol) was added and resulting reaction mixture was refluxed for 6 h. After the completion of reaction, the reaction mixture was filtered through celite and evaporated to dryness. The residue was then diluted with water and extracted with EtOAc (3 x 20 ml). The combined organic extracts were then washed with water and brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to obtain crude 2. The crude compound was then purified by column chromatography using 50% EtOAc/hexanes as eluent to get pure flavonol **2** (0.03 g, 0.10 mmol) in 80 % yield.

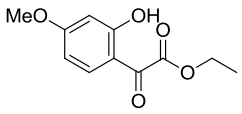


Ethyl 2-(6-hydroxy-2,3,4-trimethoxyphenyl)-2-oxoacetate (19a). (15% EtOAc/hexanes, 80% yield). yellow solid, recrystalized EtOAc/hexanes, mp 50-51 °C; ^{1}H-NMR (400MHz, $CDCl_3$) δ 11.95 (s, 1H), 6.25 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.91 (s, 3H), 3.77 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 189.3, 164.2, 162.9, 154.2, 134.1, 104.7, 96.0, 62.0, 61.6, 61.1, 56.5, 14.1; MS (*m/z*): 307 ($M+Na^+$), 239, 211; HRMS calcd for $C_{13}H_{16}O_7$: 284.0900, found: 284.0896.

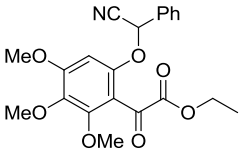


Ethyl 2-(2-hydroxy-4,6-dimethoxyphenyl)-2-oxoacetate (19b). (25% EtOAc/hexanes, 89% yield). orange solid, recrystalized EtOAc/hexanes, mp 52-53 °C; ^{1}H-NMR (400MHz, $CDCl_3$)

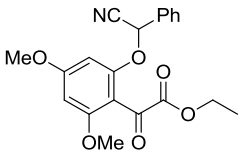
δ 12.35 (s, 1H), 6.09 (s, 1H), 5.92 (s, 1H), 4.38 (q, J = 8 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 1.40 (t, J = 8 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 188.5, 168.9, 168.2, 164.5, 162.5, 102.3, 94.0, 91.4, 61.9, 56.3, 56.0. 14.3; MS (*m/z*): 277 ($M+Na^+$), 209, 181; HRMS calcd for $C_{12}H_{15}O_6$: 255.0863, found: 255.0863.



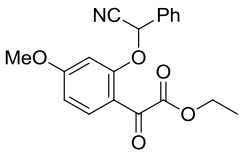
Ethyl 2-(2-hydroxy-4-methoxyphenyl)-2-oxoacetate (19c). (20% EtOAc/hexanes, 85% yield). yellow oil; ^{1}H-NMR (300MHz, $CDCl_3$) δ 11.76 (s, 1H), 7.66 (d, J = 9 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 6 Hz, J = 2.4 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 188.4, 167.8, 167.1, 162.8, 133.9, 110.4, 109.0, 101.0, 62.6, 55.9, 14.2; MS (*m/z*): 247 ($M+Na^+$), 191, 170, 151; HRMS calcd for $C_{11}H_{13}O_5$: 225.0757, found: 225.0754.



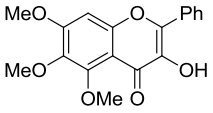
Ethyl 2-(6-(cyano(phenyl)methoxy)-2,3,4-trimethoxyphenyl)-2-oxoacetate (34a). (20% EtOAc/ hexanes, 70% yield). yellow oil; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.63 – 7.69 (m, 2H), 7.35 – 7.50 (m, 3H), 6.62 (s, 1H), 5.96 (s, 1H), 4.21 (m, 2H), 3.91 (s, 6H), 3.83 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 184.7, 163.6, 158.5, 155.0, 152.9, 138.5, 132.5, 130.4, 129.3, 127.9, 116.9, 114.3, 100.0, 72.4, 62.4, 62.3, 61.2, 56.6, 14.2; MS (*m/z*): 399 (M^+), 327, 325, 283, 282, 254, 211, 210, 209; HRMS calcd for $C_{21}H_{21}NO_7$: 399.1318, found: 399.1326



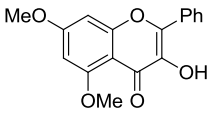
Ethyl 2-(2-(cyano(phenyl)methoxy)-4,6-dimethoxyphenyl)-2-oxoacetate (34b). (50% EtOAc/hexanes, 17% yield, 25% based on SM recovered). yellow solid, recrystalized EtOAc/hexanes, mp 146 °C; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.49-7.46 (m, 3H), 6.41 (s, 1H), 6.28 (s, 1H), 5.95 (s, 1H), 4.18-4.13 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 1.28 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 184.2, 164.5, 163.9, 162.6, 158.4, 132.1, 130.4, 129.3, 127.7, 117.5, 109.1, 95.8, 93.9, 70.4, 62.0, 56.4, 55.9, 14.2; MS (*m/z*): 392 ($M+Na^+$), 370, 276, 256, 203, 144; HRMS calcd for $C_{20}H_{20}NO_6$: 370.1285, found: 370.1279.



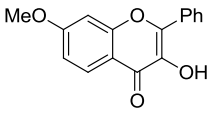
Ethyl 2-(2-(cyano(phenyl)methoxy)-4-methoxyphenyl)-2-oxoacetate (34c). (33% EtOAc/hexanes, 48% yield, 76% based on SM recovered). yellow oil; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.97 (d, J = 8.7 Hz, 1H), 7.62-7.60 (m, 2H), 7.53-7.51 (m, 3H), 6.74 (dd, J = 9 Hz, J = 2.1 Hz 1H), 6.64 (d, J = 2.1 Hz 1H), 5.91 (s, 1H), 3.90 (s, 3 H), 3.81 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 6.6 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 184.7, 166.4, 165.2, 158.2, 133.8, 131.5, 130.8, 129.5, 128.1, 116.7, 115.9, 108.7, 100.5, 69.0, 61.8, 56.1, 14.0; MS (*m/z*): 362 ($M+Na^+$), 340, 266, 246; HRMS calcd for $C_{19}H_{17}NNaO_5$: 362.0999, found: 362.1004.



3-Hydroxy-5,6,7-trimethoxy-2-phenyl-4H-chromen-4-one (23a). (40% EtOAc/hexanes, 51% yield). brown solid, recrystalized EtOAc/hexanes, mp 150-152 °C; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.21 (d, J = 8.6 Hz, 2H), 7.51 (t, J = 6.8 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 6.79 (s, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 172.0, 158.6, 154.0, 151.9, 142.7, 140.1, 138.3, 131.3, 130.0, 128.7, 127.5, 110.0, 96.3, 62.5, 61.8, 56.6; MS (*m/z*): 329 ($M+H^+$), 328, 326, 314, 313, 267, 167, 105, 77, 69; HRMS calcd for $C_{18}H_{17}O_6$: 329.1011, found 329.1020.

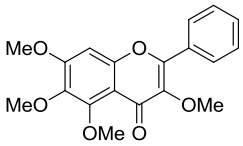


3-Hydroxy-5,7-dimethoxy-2-phenyl-4H-chromen-4-one (23b). (5% CH_3OH/CH_2Cl_2, 63% yield). brown solid, recrystalized EtOAc/hexanes, mp 169-170 °C; ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.23 (d, J = 9 Hz, 2H), 7.55-7.45 (m, 3H), 6.59 (d, J = 3 Hz, 1H), 6.38 (d, J = 3 Hz, 1H), 4.00 (s, 3H), 3.93 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 172.1, 164.6, 160.6, 159.0, 141.9, 138.4, 131.1, 129.7, 128.6, 127.3, 106.2, 95.9, 92.5, 56.5, 56.0; MS (*m/z*): 299 ($M+H^+$), 237, 144; HRMS calcd for $C_{17}H_{15}O_5$: 299.0914, found: 299.0919.



3-**hydroxy-7-methoxy-2-phenyl-4H-chromen-4-one (23c)**. (2% CH_3OH/CH_2Cl_2, 60% yield). brown solid, recrystalized EtOAc/hexanes, mp 167-169 °C; ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.25 (d, J = 9 Hz, 2H), 8.16 (d, J =9 Hz, 1H), 7.57-7.47 (m, 3H), 7.03-6.98 (m, 2H), 3.95 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 173.0, 164.5, 157.6, 144.4, 138.3, 131.4, 130.1, 128.8,

127.7, 127.0, 115.1, 114.8, 100.1, 56.1; MS (*m/z*): 269 ($M+H^+$), 239, 189, 150; HRMS calcd for $C_{16}H_{13}O_4$: 269.0808, found: 269.0808.



3,5,6,7-tetramethoxyflavone (2) yellow oil; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.06 (dd, J = 8.0 Hz, J = 2.0 Hz, 2H), 7.45 – 7.53 (m, 3H), 6.75 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$): δ 174.0, 157.9, 153.9, 153.5, 152.6, 141.6, 140.4, 131.0, 130.6, 128.7, 128.6, 128.4, 113.4, 96.3, 62.4, 61.8, 60.3, 56.5; MS (*m/z*): 342, 327, 323, 297, 284, 283, 241, 195, 167, 129, 105, 88, 76, 68; HRMS calcd for $C_{19}H_{18}O_6$: 342.1103, found: 342.1108.

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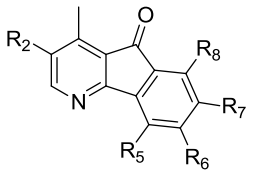
CHAPTER 4. Synthesis of azafluorenones

Introduction:

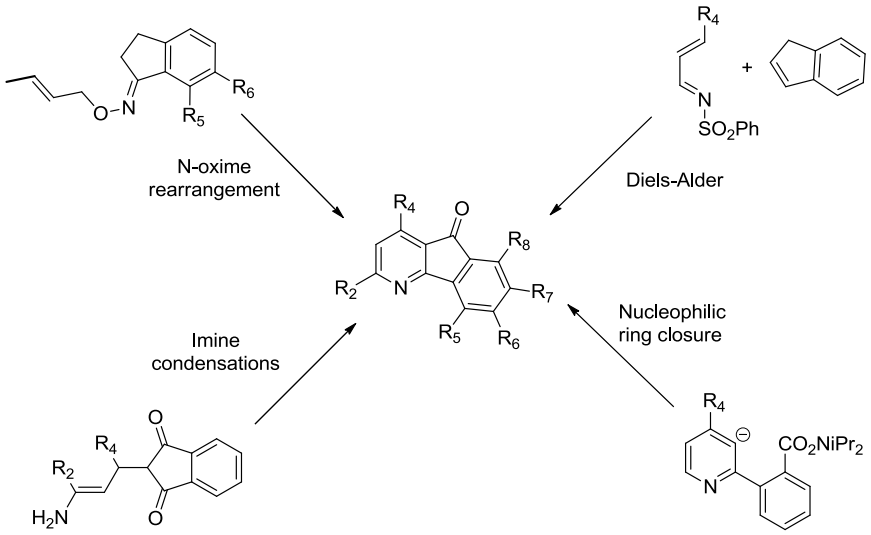
Azaflouorenones are fused tricyclic compounds that are pyridine analogs to fluorenones. In 1976, researchers discovered the first azafluorenone natural product, onychine (**1**, Table 1, entry 1).[1] Since then, 24 different azafluorenone natural products have been reported (Table 1, entry 2-25). These azafluorenones have been isolated from a variety of plants and are believed to derive from aporphine during their biosynthesis.[2] They have shown a wide range of antimicrobial activity against several microorganisms including *C. albicans*, *Escherichia coli* and *Saccharomyces cerevisiae*.[3,4,5] The isolated azafluorenones contain a methyl group at C-1, and different substituents at the R_2, R_5, R_6, R_7 and R_8 positions thus far.



Compound	R_2	R_5	R_6	R_7	R_8	Compound	R_2	R_5	R_6	R_7	R_8
1[6]	H	H	H	H	H	**14**[7]	H	OAc	OMe	OAc	H
2[8]	H	H	OMe	H	H	**15**[9]	H	OH	OMe	H	OH
3[10]	H	H	OH	H	H	**16**[11]	H	OMe	OMe	OH	H
4[12]	H	OH	OMe	H	H	**17**[11]	H	OMe	OMe	OAc	H
5[10]	OMe	H	OMe	OH	H	**18**[11]	H	OMe	OMe	OMe	H
6[10]	H	OMe	OMe	H	H	**19**[11]	H	H	H	OH	OMe
7[10]	H	H	H	H	OH	**20**[11]	H	H	H	OAc	OMe
8[10]	H	OMe	H	H	OMe	**21**[11]	H	H	H	OMe	OMe
9[10]	H	OAc	OMe	H	H	**22**[13]	H	OMe	H	H	H
10[14]	H	H	OH	OMe	H	**23**[13]	H	H	H	OMe	H
11[14,15]	H	H	OMe	OH	H	**24**[13]	H	H	H	H	OMe
12[14,15]	H	H	OMe	OMe	H	**25**[11,16]	H	OMe	OH	H	H
13[7]	H	OH	OMe	OH	H						

Table 1. The azafluorenone natural products.

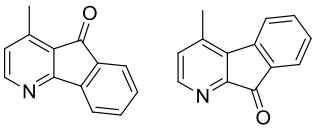
Currently, there are four different methods to synthesize azafluorenones: N-oxime rearrangements, imine condensations, Diels-Alder reactions and nucleophilic ring closures (Scheme 1). Of these four methods, only N-oxime rearrangements have been widely used for the synthesis of a variety of the natural azafluorenones.



Scheme 1. Four pathways to the construction of azafluorenones.

N-oxime rearrangements:

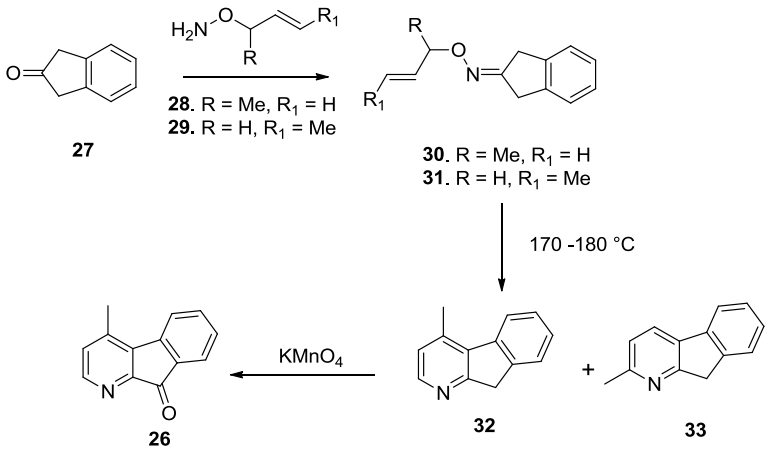
When researchers isolated onychine they had difficulty in unambiguously assigning the structure between compound **26** and **1** (Figure 1).[1] In order to assign the structure they reduced the ketone to the corresponding alcohol which resulted in only a slight high-field shift in the methyl protons in the ^{1}H NMR compared to the parent compound. This small shift insinuated that compound **26** was the correct structure, due to the methyl being further removed from the carbonyl moiety and thus having only a very slight effect on the shift of the methyl peak.[1] However, without more advanced characterization techniques or a synthesis of the molecule to confirm the structure, no definitive assignment could be made.



1 26

Figure 1. Proposed structures of onychine.

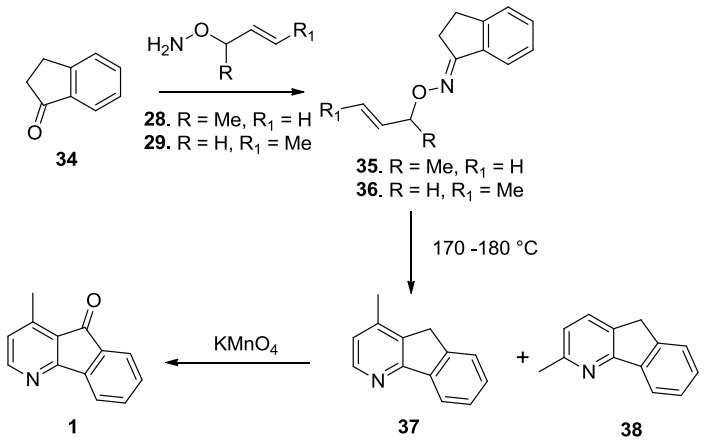
Irie and co-workers were interested in using their newly developed methodology towards the construction of pyridine rings using oxidative thermal rearrangement of N-oxides to confirm the structural assignment of onychine. Their synthesis began with reacting 2-indanone (**27**) with hydroxylamines **28** and **29** to furnish the corresponding N-oximes **30** and **31** (Scheme 2).[17] Each N-oxime was independently heated in a sealed tube at 170-180 °C for 2 days to give the same mixture of azafluorenes **32** and **33**. The two compounds were then separated by preparative TLC chromatography. Compound **32** was oxidized with potassium permanganate ($KMnO_4$) to give azafluorenone **26**.



Scheme 2. The total synthesis of compound **26**.

Unfortunately, the newly synthesized product did not match the spectral data of the isolated compound. Believing the initial characterization assignment was incorrect, Irie and

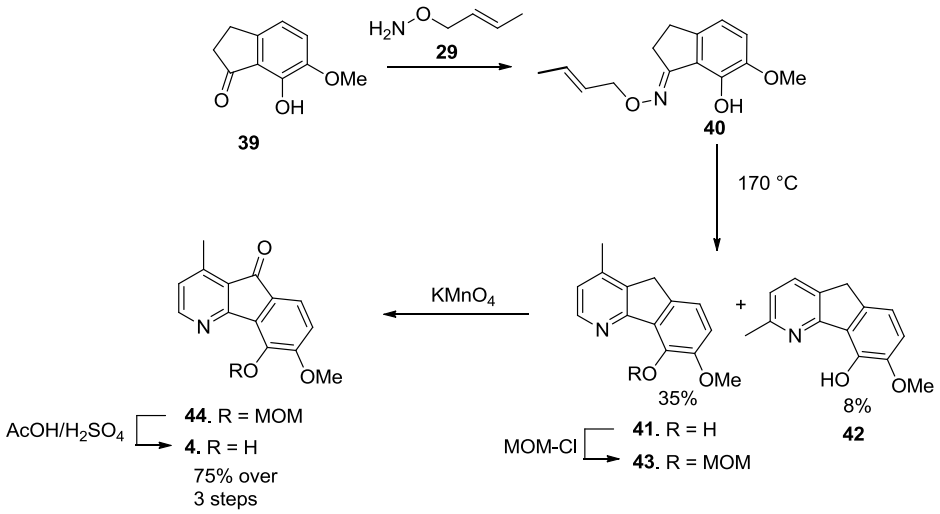
co-workers decided to synthesize **1**. Starting with 1-indanone (**34**), they formed N-oximes **35** and **36**, which were thermally heated to construct the requisite azafluorene mixtures of **37** and **38** (Scheme 3). Compound **13** was oxidized with $KMnO_4$ to give azafluorenone **1**. This compound compared favorably with the spectral data for the isolated onychine and the structure was reassigned. Arango and co-workers later confirmed this reassignment by NOE experiments.[11]



Scheme 3. The total synthesis of azafluorenone **1**.

This method has also proven versatile to substitutions at R_5, R_6 and R_7, including the synthesis of isoursuline (**4**, Scheme 4). The N-oxime **40** was made by reacting 7-hydroxy-6-methoxyindanone (**39**) with crotylhydroxylamine (**5**).[18] This oxime was heated at 170 °C for 20 h to make compounds **41** and **42**. Compound **41** was then protected as the methoxymethyl (MOM) ether **43**. The benzyl position was oxidized with $KMnO_4$ and deprotected under acidic conditions to furnish **17** in 75% yield over 3 steps. Similar routes were used to complete the synthesis of ursuline (**25**),[18] **10**,[14] **11**[14] and **12**.[14,19] The use of N-oximes have proven versatile towards the synthesis of azafluorenone natural products.

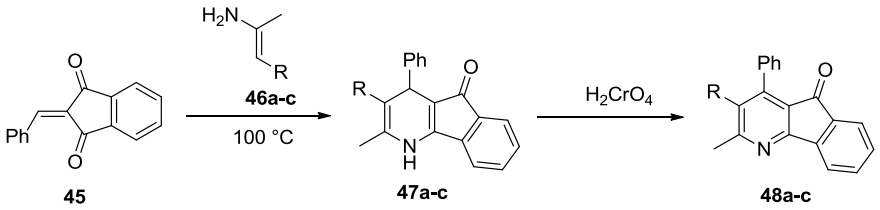
However, their modest yields, harsh conditions and poor regioselectivity suggest better alternatives may be possible.



Scheme 4. The synthesis of isoursuline (**4**).

Imine condensations:

In 1949, Petrow and co-workers reported the first synthesis of an azafluorenone.[20]

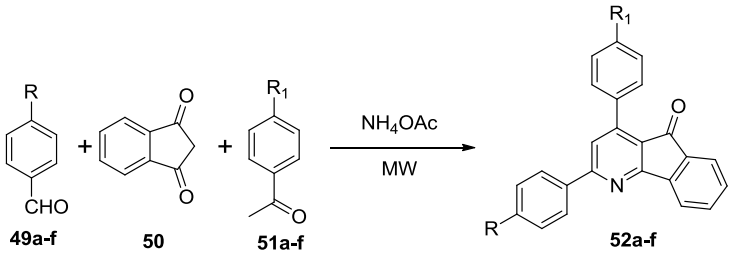


#	R	Yield (%) 47	Yield (%) 48
a	CO_2Et	100	90
b	COMe	100	100
c	COPh	20	100

Scheme 5. The synthesis of azafluoreones **48a-c**.

Their synthesis began with 2-benzylidene-1,3-indandione (**45**) reacting with different enamines (**46a-c**) at 100 °C to give the tricyclic structures **47a-c** (Scheme 5). These compounds were successfully oxidized with chromic acid to give azafluorenones **48a-c**.

In 2007, this method was modified by Tu and co-workers in a one-step three component reaction to make azafluorenones under microwave irradiation.[21] They reacted benzaldehydes (**49a-f**), 1,3-indandione (**50**) and acetophenones (**51a-f**) in the presence of ammonium acetate under microwave conditions to afford azafluorenones **52a-f** (Scheme 6). This reaction was effective with a variety of different functional groups including electron-rich, electron-poor and halogen substituents.



49a-f **50** **51a-f** **52a-f**

#	R	R_1	Yield (%) 52
a	NO_2	OMe	89
b	F	OMe	80
c	OMe	OMe	78
d	Cl	Cl	88
e	Cl	F	84
f	OMe	F	83

Scheme 6. The synthesis of **52a-f** in a one pot three component synthesis.

This methodology was further elaborated to include heteroatom substitution at C-3 and cyano substitution at the C-2 position (Scheme 7). Starting with arylidenemalononitriles

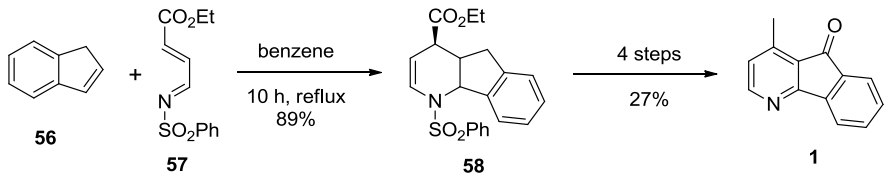
53a-g, **50** and sulfur (**54a-d**) or nitrogen (**54e-g**), they generated azafluorenones **55a-g**.[22] This synthesis allowed easy access to a variety of different derivatives; however, there was no direct route based on these reactions to the azafluorenone natural products with regiocontrol.

#	R	X	R_1	Yield (%) 55
a	4-ClC_6H_4	SH	CH_2CO_2H	87
b	4-$MeOC_6H_4$	SH	CH_2CO_2H	80
c	4-ClC_6H_4	SH	4-MeC_6H_4	85
d	3-$NO_2C_6H_4$	SH	4-MeC_6H_4	88
e	4-ClC_6H_4	NH_2	4-MeC_6H_4	91
f	4-ClC_6H_4	NH_2	C_6H_5	84
g	4-$NO_2C_6H_4$	NH_2	4-OHC_6H_4	84

Scheme 7. Synthesis of **55a-g** under microwave irradiation.

Diels-Alder:

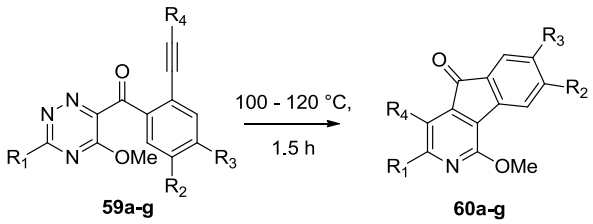
The Diels-Alder reaction has also been utilized to construct azafluorenones. In a synthesis of onychine (**1**), researchers made tricyclic **58** from the cycloaddition of indene (**56**)



Scheme 8. The synthesis of onychine (**1**) using a key Diels-Alder reaction.

with unsaturated imine **57** (Scheme 8). After 4 steps they transformed intermediate **58** into onychine (**1**).[23]

An alternative Diels-Alder strategy resulted in the isomeric 2-azafluorenones. In three steps inverse-electron-demand Diels-Alder reaction precursors **59a-g** were made (Scheme 9). The intramolecular Diels-Alder reaction was heated to 100-120 °C for 1.5 h to generate azafluorenones **60a-g** in good yields.[24] This method is also amenable to the synthesis of 1-azafluorenones.[25] While these syntheses provide an elegant use of the Diels-Alder reaction, their lengthy synthetic precursors make the synthesis inefficient.



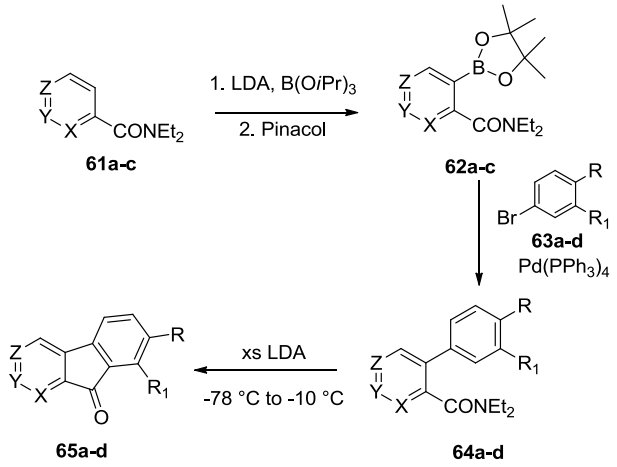
59a-g **60a-g**

#	R_1	R_2	R_3	R_4	Yield (%) 60
a	Ph	H	H	$SiMe_3$	88
b	Ph	H	H	CH_2OH	84
c	Ph	H	H	CH_2NMe_2	76
d	Ph	H	H	$(CH_2)_3Me$	79
e	Ph	OMe	OMe	$(CH_2)_3Me$	78
f	Ph	OCH_2O		CH_2NMe_2	57
g	4-$MeOC_6H_4$	OMe	OMe	CH_2NMe_2	68

Scheme 9. Synthesis of azafluorenones **60a-g** *via* an intramolecular Diels Alder reaction.

Nucleophilic ring closure:

The last conceptually different strategy to synthesize azafluorenones involves nucleophilic attack of carbonyls to close the cyclopentanone ring. Snieckus' groupsynthesized biaryl compounds **64a-d** *via* a Suzuki coupling (Scheme 10). These intermediates were exposed to excess lithium diisopropylamide (LDA) to facilitate ring closure to make azafluorenones **65a-d**. The amides not only served as ortho-directing groups, but also as the carbonyl source of the azafluorenone.[26] Snieckus' group also reported a similar cross-coupling procedure toward the synthesis of onychine (**1**).[27]

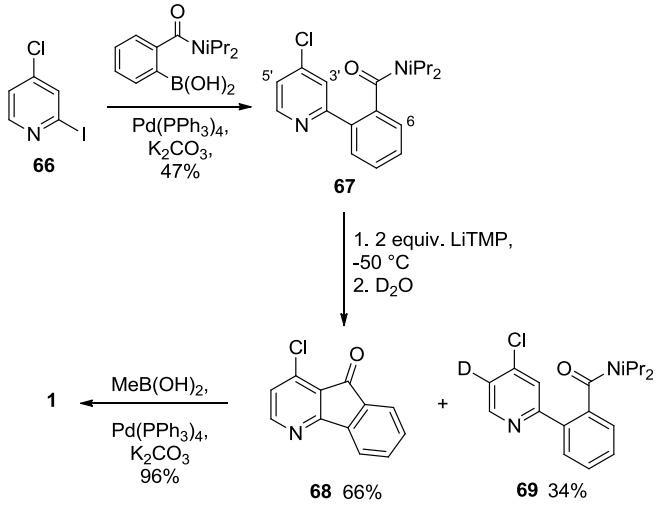


#	X	Y	Z	R	R_1	Yield (%) 64	Yield (%) 65
a	N	C	C	CN	H	71	55
b	C	N	C	OMe	H	71	56
c	C	N	C	H	OMe	57	63
d	C	C	N	H	Cl	61	81

Scheme 10. The synthesis of azafluorenone compounds **65a-d**.

Mongin's group had a similar approach; however, they had difficulty in selectivity generating the anion to cyclize the cyclopentanone ring. Initial attempts of metallation at -

78 °C of compound **67** led to deprotonation of the C-5' position compared to C-3' based on D_2O quenching (Scheme 11). When the temperature was raised to -50 °C, the compound cyclized to product **68** in 68% yield.[28] They completed the synthesis of **1** by using a Suzuki coupling to install the methyl at the C-1 position. Mechanistic studies on these systems have shown that selectivity of the deprotonation is dependent on if the carbonyl is an acid, ester or amide.[29] There are also reports of Friedel-Crafts acylation to close the cyclopentenone.[30,31]



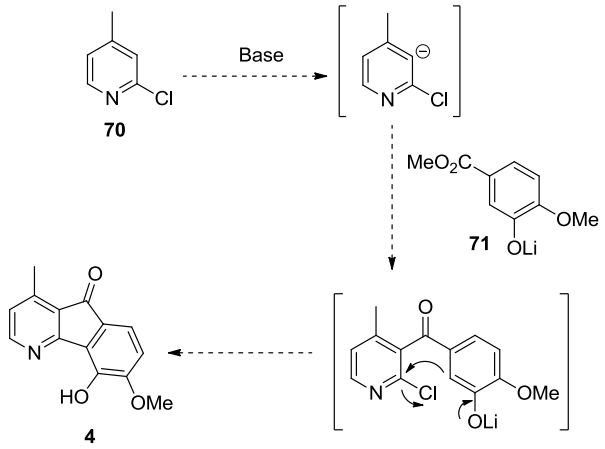
Scheme 11. Nucleophilic ring closure to synthesize **1**.

Results and Discussion:

Our interest in azafluorenones came from a recent report on the encouraging antimalarial activity of isoursuline (**4**). It had IC_{50} values of 9.9 and 11.4 μM against 3D7 and Dd2 strains of the malaria causing parasite *Plasmodium falciparum*, respectively.[9] Current commercially available malaria drugs are rapidly losing their efficacy.[32] Moreover, there is a constant need for the development of new antimalarial drugs to combat the emergence of drug-resistant strains of the disease.[33] There are 600 million new malarial infections each

year with 1 million people dying from the disease.[9] The WHO suggests the majority of new antimalarial drugs will come from current natural products.[34]

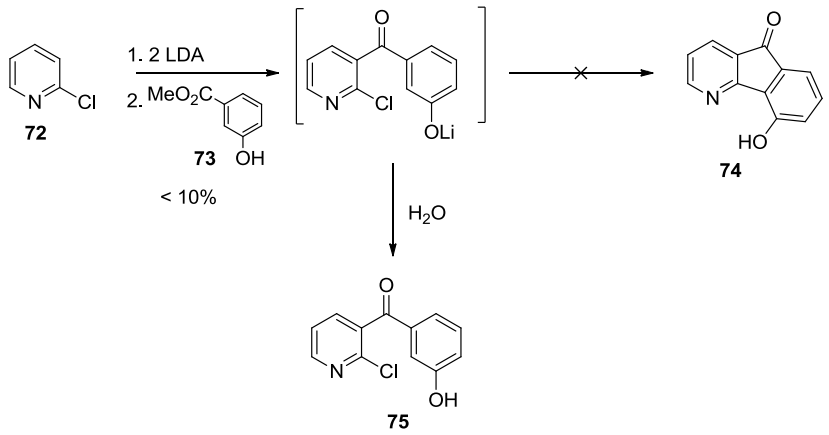
Currently there is one synthesis of **4**;[18] however, this route is plagued with the excessive use of protecting groups, poor yields and regioselectivity issues. We were interested in improving this route and developing a more universal synthesis toward azafluorenone natural products. We envisioned a one-step synthesis of **4**, starting with commercially available 2-chloro-4-methyl pyridine (**70**, Scheme 12). Deprotonation *ortho* to the activating chloride, followed by quenching with methyl benzoate **71** would give the corresponding ketone. We expected this intermediate to undergo nucleophilic aromatic substitution to produce **4**. This method would provide an efficient route to this biologically active compound and access to other azafluorenone natural products.



Scheme 12. Proposed one-step synthesis of isoursuline (**4**).

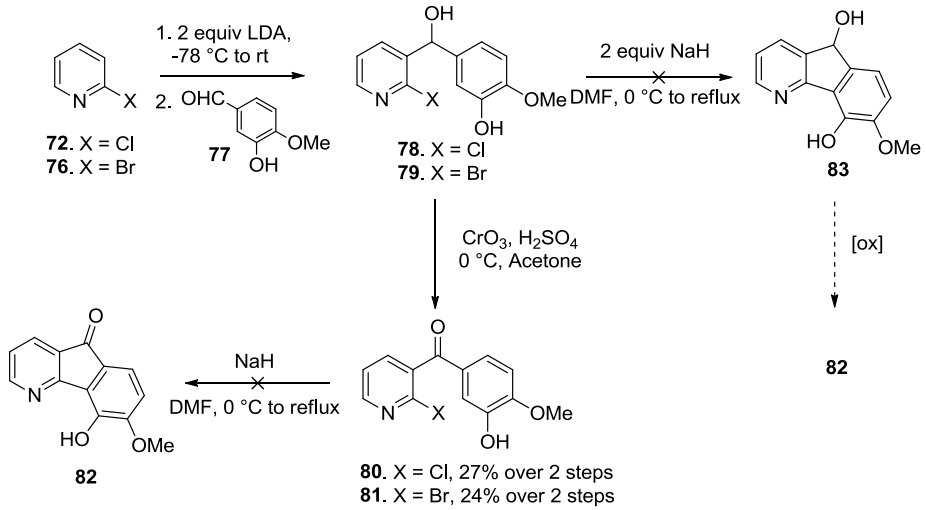
Due to the cost of 2-chloro-4-methylpyridine (**70**), the feasibility of this reaction was first tested with 2-chloropyridine (**72**) in a model system study (Scheme 13). LDA successfully deprotonated the 3-position of the pyridine, which reacted with methyl benzoate

73 to generate the ketone intermediate. However, the reaction did not continue through the intramolecular nucleophilic aromatic substitution reaction envisioned.[35]



Scheme 13. Model system study of the synthesis of **74**.

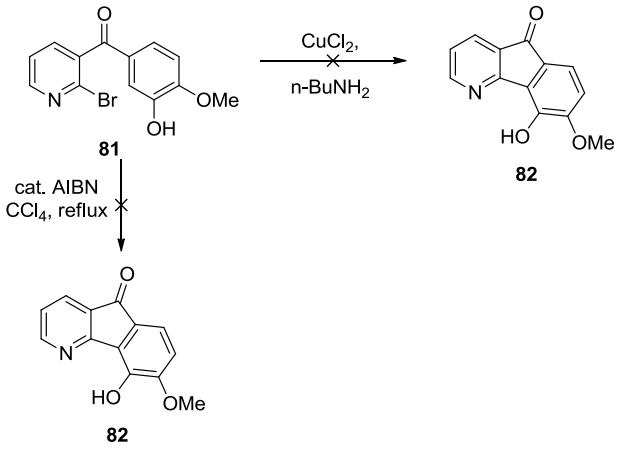
We decided to push the intramolecular cyclization under different reaction conditions. Due to the poor yield of the ketone, methyl benzoate **73** was switched to the more electrophilic isovanillin (**77**) to improve reactivity and better replicate the real system. Compound **72** was subjected to our previous deprotonation conditions and quenched with **77** to yield alcohol **78** (Scheme 14). Initial attempts to oxidize benzyl alcohol to the ketone with a variety of different oxidizing agents, including; pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), Swern oxidation and manganese dioxide (MnO_2), were all unsuccessful. However, the oxidation proceeded smoothly under Jones oxidation conditions to furnish compound **80**. The phenol was deprotonated with sodium hydride to induce nucleophilic aromatic substitution but instead only starting material was returned up until 100 °C. At higher temperatures the starting material decomposed. We thought it was possible the sp^2 hybridized carbonyl was restricting the ability of the molecule to orient itself properly to perform this substitution reaction. The cyclization reaction was attempted on



Scheme 14. Attempts at nucleophilic aromatic substitution to make model system **82**.

compound **78**, which allowed free rotation at this C-9 position. However, this reaction returned starting material under 60 °C and decomposition above that temperature. Both of these cyclizations were also attempted with 2-bromopyridine (**76**) but there was no product formation.

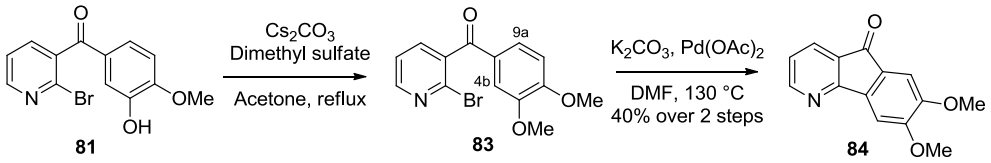
After several unsuccessful attempts on utilizing anion ring closures, our focus shifted toward radical cyclization. Using our previously described reaction conditions for oxidative



Scheme 15. Attempts at radical cyclization of compound **81** to **82**.

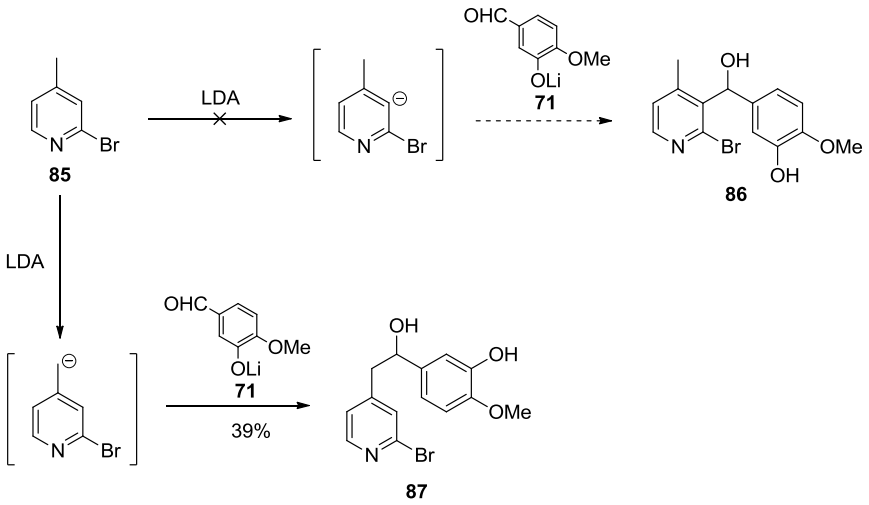
ring closure of ellagitannins (Chapter 2) we found no conversion of **81** to **82** (Scheme 15). Cyclization with catalytic azobisisobutyronitrile (AIBN) as a radicial initiatior was also attempted; however, this reaction only returned the starting material.

Undeterred, our focus turned toward a Heck reaction to form this crucial aryl-aryl bond. Initial efforts with the unprotected phenol led to a complex mixture of products. The phenol was protected as methyl ether **83** using cesium carbonate and dimethyl sulfate (Scheme 16). This precursor was subjected to standard Heck reaction conditions and cleanly afforded azafluorenone **84**.[36] The selectivity of this reaction can be explained by C-9a being less sterically congested than C-4b.



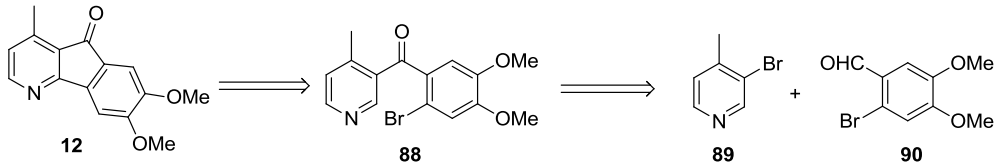
Scheme 16. Synthesis of azafluorenone **84** *via* a Heck coupling.

The Heck reaction provided access to the azafluorenone scaffold, however this route led our efforts away from the synthesis of **4**. Instead of focusing on this natural product, we decided to develop a general synthesis of azafluorenone natural products. Our approach was strategically different than any other azafluorenone synthesis and would provide an efficient route towards these compounds. Due to the similarity of **82** to polyfothine (**25**), **25** became our initial target. The synthesis started with deprotonation of 4-methyl-3-bromopyridine (**83**) with LDA, which was reacted with isovanillin (**77**, Scheme 17). However, instead of deprotonation at the 3-position, lateral deprotonation occurred and afforded compound **86**.



Scheme 17. Unexpected reaction of **85** to form **87.**

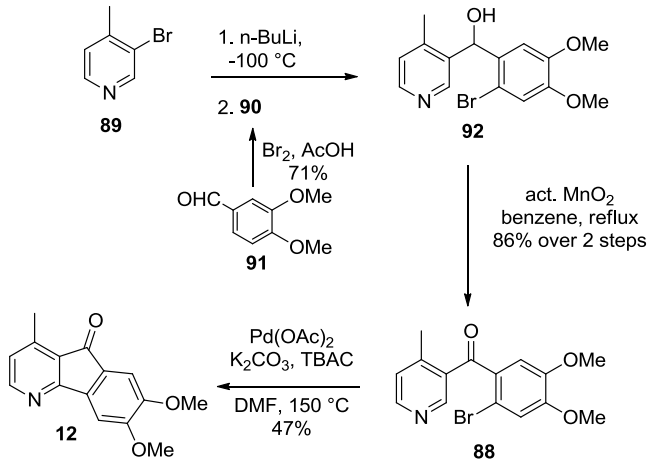
This unexpected result made us re-examine our previous retrosynthesis. We envisioned a similar reaction pathway as our previous method; utilizing the Heck reaction to close the ring and coupling between the pyridine anion and a benzaldehyde to tether the two components (Scheme 18). We would selectively generate the anion on the 3-position of the pyridine with metal halogen-exchange.



Scheme 18. The retrosynthesis of compound **25**.

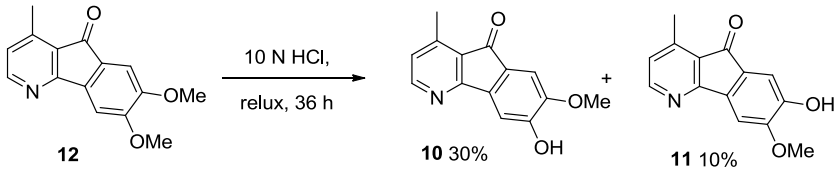
3-Bromo-4-methylpyridine (**89**) underwent metal-halogen exchange with *n*-BuLi which was then quenched with bromobenzaldehyde **90**[37] to give product **92** (Scheme 19). The benzyl alcohol was oxidized with MnO_2 in 86% yield to give ketone **88**. The key Heck reaction proceeded smoothly to give us polyfothine (**12**) in moderate yield.[38] The use of The

use of tetra-butylammonium chloride (TBAC) was instrumental in lowering the temperature and shortening the length of the Heck reaction.



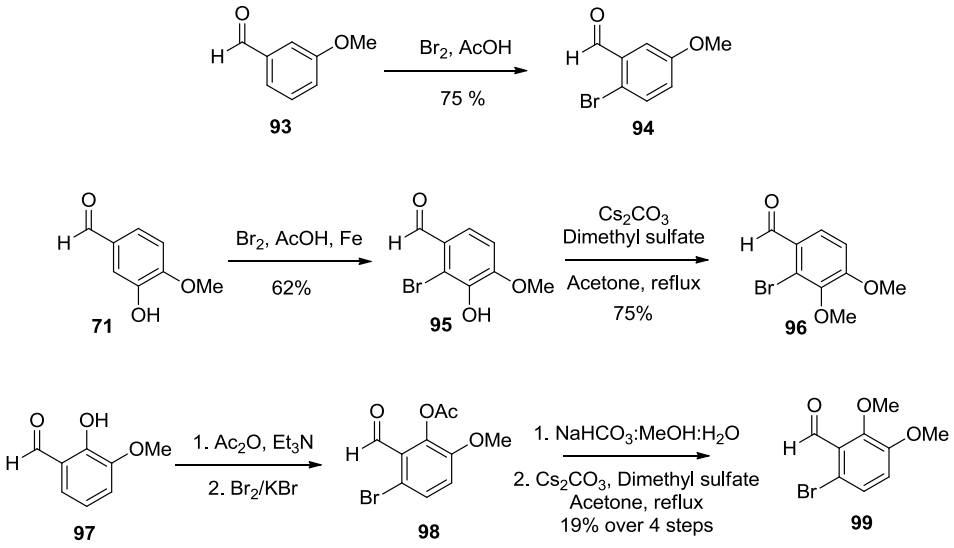
Scheme 19. The synthesis of polyfothine (**12**).

The synthesis of polyfothine (**12**) also constituted a formal synthesis of azafluorenones **10** and **11**. When compound **12** was heated in 10 N HCl, demethylated products **10** and **11** were generated in 30% and 10% yield, respectfully (Scheme 20).[14]



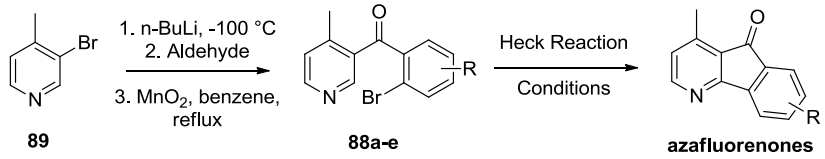
Scheme 20. The synthesis of **10** and **11** from azafluorenone **12**.

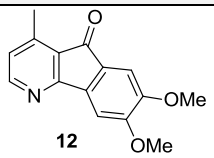
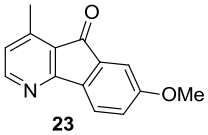
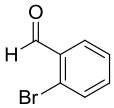
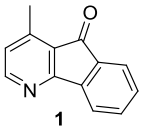
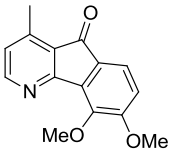
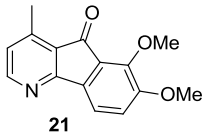
In order to test the scope and limitations of the newly designed methodology required the synthesis of a variety of different bromobenzaldehydes **94**, **96** and **99**.[39,40,41] These compounds could adequately examine the substitution patterns at the R_5, R_6, R_7 and R_8 positions (Scheme 21).



Scheme 21. Synthesis of bromobenzaldehydes **94**, **96** and **99**.

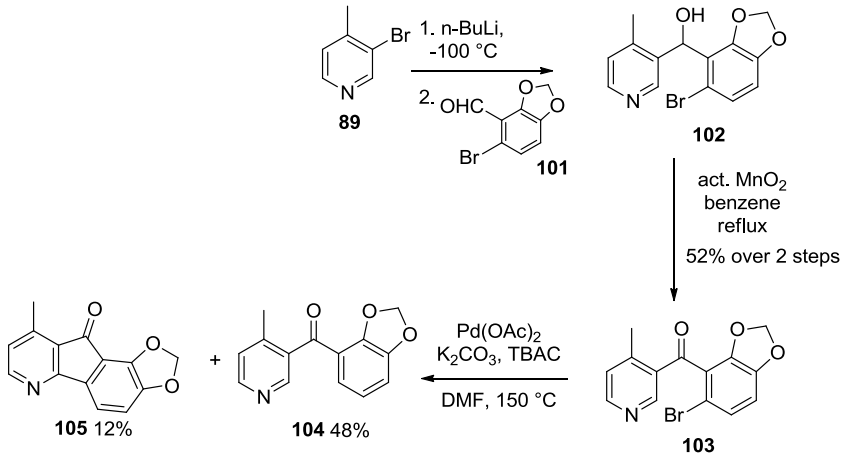
Following the previously described reaction conditions, ketones **88b-e** were made without precedent (Scheme 22). Unfortunately, cyclization with the Heck reaction was not general and slight alterations to the base, the temperature and the length of the reaction were necessary. Ketones **88a-c** afforded the desired azafluoreones. However, when the R_5 or R_8 position was substituted the Heck reaction failed. Under our previous Heck reaction conditions the starting material was recovered, while using a stronger base or higher temperatures led to the dehalogenated starting material. Due to the proximity of the R_5 substituent to the bromide it is believed that sterics were interfering with the palladium insertion. One possible theory for the failure of the reaction with the R_8 substituent has to do with the methoxy interfering with the transition state.



Aldehyde	Yield (%) 88	Heck Reaction Conditions	Azafluorenone	Yield (%) pdt
90	86 %	Na_2CO_3, TBAC, $Pd(OAc)_2$, DMF, 150 °C, 6 h	 **12**	47 %
94	80 %	K_2CO_3, TBAC, $Pd(OAc)_2$, DMF, 150 °C, 6 h	 **23**	50 %
 **100**	68 %	Na_2CO_3, TBAC, $Pd(OAc)_2$, DMF, 130 °C, 2 h	 **1**	53 %
96	42 %	Na_2CO_3, TBAC, $Pd(OAc)_2$, DMF, 150 °C, 6 h	 **6**	-
99	58 %	Na_2CO_3, TBAC, $Pd(OAc)_2$, DMF, 150 °C, 6 h	 **21**	-

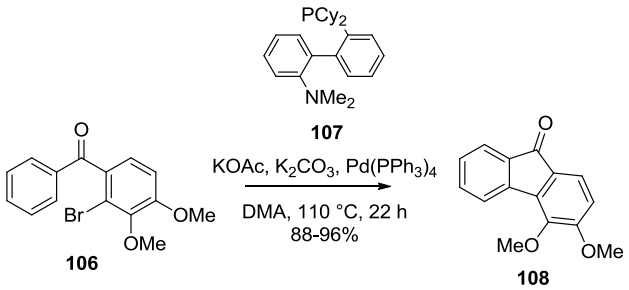
Scheme 22. Synthesis of azafluorenones **12**, **23** and **1**.

In order to validate this hypothesis, the isoelectronic methylenedioxy derivative was synthesized. Bromo-pyridine **89** underwent metal-halogen exchange and was quenched with the commercially available bromobenzaldehyde **101** (Scheme 23). Oxidation with MnO_2 gave ketone **103**. This compound was subjected to standard Heck reaction conditions and afforded a mixture of the azafluorenone product **104** and dehalogenated product **105**. From this information we could infer that the methoxy wasinterfering slightly with the reaction; however, there are other factors that were limiting the cyclization.



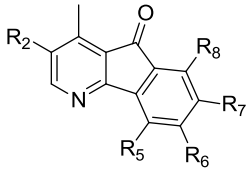
Scheme 23. Synthesis of methylenedioxy azafluorenone **104**.

In the future we would like to find general reaction conditions to facilitate ring closure with substitutions at the R_5 and R_8 positions. One promising lead is the development of designer ligands for problematic palladium couplings. One specific example is the use of DavePhos (**107**) to affect the transformation of **106** to fluorenone **108** (Scheme 24).[42] This reaction did not work with standard Heck reaction conditions and required ligand optimization to receive acceptable yields. DavePhos (**107**) was necessary because the bulky electron rich ligand facilitates both the oxidative addition step and the dissociation of the halide giving a more reactive palladium species.



Scheme 24. Use of DavePhos (**107**) to improve yields of fluorenone **108**

Our method for the synthesis of azafluorenones is strategically different than any known route to these molecules. We provide an efficient and regioselective route towards the azafluorenone natural products. Looking back on the 25 isolated azafluorenones, all of the examples except for one are within reach from this synthesis through optimization (Table 2).



Compound	R_2	R_5	R_6	R_7	R_8	Compound	R_2	R_5	R_6	R_7	R_8
1[6]	H	H	H	H	H	**14**[7]	H	OAc	OMe	OAc	H
2[8]	H	H	OMe	H	H	**15**[9]	H	OH	OMe	H	OH
3[10]	H	H	OH	H	H	**16**[11]	H	OMe	OMe	OH	H
4[12]	H	OH	OMe	H	H	**17**[11]	H	OMe	OMe	OAc	H
5[10]	OMe	H	OMe	OH	H	**18**[11]	H	OMe	OMe	OMe	H
6[10]	H	OMe	OMe	H	H	**19**[11]	H	H	H	OH	OMe
7[10]	H	H	H	H	OH	**20**[11]	H	H	H	OAc	OMe
8[10]	H	OMe	H	H	OMe	**21**[11]	H	H	H	OMe	OMe
9[10]	H	OAc	OMe	H	H	**22**[13]	H	OMe	H	H	H
10[14]	H	H	OH	OMe	H	**23**[13]	H	H	H	OMe	H
11[14,15]	H	H	OMe	OH	H	**24**[13]	H	H	H	H	OMe
12[14,15]	H	H	OMe	OMe	H	**25**[11,16]	H	OMe	OH	H	H
13[7]	H	OH	OMe	OH	H						

Table 2. The azafluorenone natural products. The compounds highlighted in yellow are synthesized by our method, compounds in white could be synthesized by our method with optimization and compounds in red could not be synthesized directly by our method.

Experimental:

Deprotonation of 2-bromopyridine substrates:

To a solution of DIPA (2.1 equiv) in THF (0.05 M), was added *n*-BuLi (2 equiv) at -78 °C. The mixture was warmed to -40 °C and stirred at this temperature for 45 min. The solution was returned to -78 °C then the bromopyridine (1 equiv) was added dropwise and allowed to

stir at -78 °C for 30 min. Next, a solution of 3-hydroxy-4-methoxybenzaldehyde (1 equiv) in THF was added dropwise. The reaction was allowed to warm up to rt over 10 h. After completion of the reaction, it was quenched with water and extracted with EtOAc, washed with brine (10 mL) and dried over $MgSO_4$, followed by filtration and concentrated *in vacuo*. The crude material was taken to the next step without further purification.

Oxidation with Jones reagent:

The alcoholic product (1 equiv) was dissolved in acetone (0.10 M) and Jones reagent (2 equiv) was slowly added to the stirred solution at 0 °C. The reaction was stirred for 1 hour at this temperature until completion, after which it was quenched with excess sodium bisulfite. The solution was washed with water and extracted with diethyl ether. It was washed with brine and dried over $MgSO_4$, followed by filtration and concentrated *in vacuo*. The residue was purified with flash chromatography (2:1-1:2 hexanes:EtOAc).

Methylation of phenol:

To phenol (1 equiv) dissolved in DMF (0.10 M) was added Cs_2CO_3 (1.5 equiv) and the reaction was stirred for 10 minutes followed by the addition of dimethyl sulfate (1.2 equiv). The reaction mixture was heated to 60 °C for 18 h. Upon completion the reaction was quenched with water followed by extraction with diethyl ether, washed with brine and dried over $MgSO_4$, followed by filtration and concentrated *in vacuo*. The residue was purified with flash chromatography (1:1 hexanes:EtOAc).

Metal-halogen exchange:

To a solution of 3-bromo-4-methylpyridine (**89**, 1 equiv) in THF (0.05 M) was added *n*-BuLi (1 equiv) at -100 °C. The mixture was stirred at this temperature for 10 min followed by the addition of corresponding bromobenzaldehyde (1 equiv) as a solution in THF. The reaction

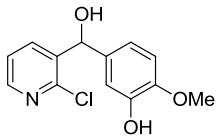
was warmed up to -78 °C for 2 h and then stirred at rt for 8 h. The reaction was quenched with water and extracted with EtOAc. The organic phase was then washed with brine, dried over $MgSO_4$, followed by filtration and concentration *in vacuo*.

Manganese dioxide oxidation:

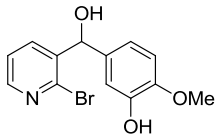
To the crude alcoholic solution was added act. MnO_2 (5 equiv) in benzene. The solution was refluxed with a Dean Stark trap for 18 h. The MnO_2 was filtered off and the solution was concentrated *in vacuo*. The residue was purified with flash chromatography (3:1-1:2 hexanes:EtOAc).

Heck reaction:

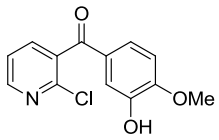
A solution of bromobenzoylpyridines, TBAC (1.5 equiv), $Pd(OAc)_2$, (0.1 equiv) and base (1.5 equiv) in DMF (0.05 M) was heated and stirred until completion. After the reaction was completed, the solutions were extracted with diethyl ether and washed with water, followed by brine and dried over $MgSO_4$. The organic phase was then filtered and concentrated *in vacuo*. The residue was purified with flash chromatography (1:1-1:3 hexanes:EtOAc).



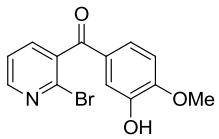
5-((2-chloropyridin-3-yl)(hydroxy)methyl)-2-methoxyphenol (78): ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 5.63 (br, 1 H), 6.06 (s, 1 H), 6.81-6.92 (m, 3 H), 7.31 (dd, J = 4.8 Hz, J = 7.8 Hz, 1 H), 8.05 (dd, J = 2.4 Hz, 7.2 Hz, J = 1 H), 8.32 (dd, J = 1.8 Hz, 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.18, 72.17, 110.8, 113.5, 119.2, 123.0, 134.9, 136.9, 138.0, 146.0, 146.7, 148.5, 149.7.



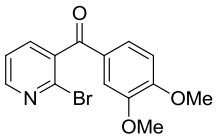
5-((2-bromopyridin-3-yl)(hydroxy)methyl)-2-methoxyphenol (79): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 5.63 (br, 1 H), 6.03 (s, 1 H), 6.82-6.94 (m, 3 H), 7.36 (dd, J = 4.8 Hz, J = 7.5 Hz, 1 H), 7.99 (dd, J = 2.1 Hz, J = 7.8 Hz, 1 H), 8.30 (dd, J = 2.1 Hz, J = 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, d-acetone) δ 56.76, 74.21, 112.6, 115.4, 118.8, 119.8, 124.8, 137.1, 138.3, 143.0, 143.1, 147.8, 150.0.



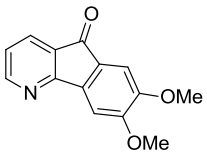
(2-chloropyridin-3-yl)(3-hydroxy-4-methoxyphenyl)methanone (80): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3 H), 6.89 (d, J = 8.4 Hz, 1 H), 7.28-7.38 (m, 2 H), 7.40 (d, 2.1 Hz, 1 H), 7.69 (dd, J = 1.8 Hz, J = 7.5 Hz, 1 H), 8.51 (dd, J = 2.1 Hz, 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.44, 110.3, 115.8, 122.4, 124.5, 129.7, 135.5, 137.9, 146.0, 147.9, 150.7, 151.9, 192.1.



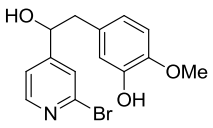
(2-bromopyridin-3-yl)(3-hydroxy-4-methoxyphenyl)methanone (81): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.31-7.40 (m, 2 H), 7.41 (d, 2.1 Hz, 1 H), 7.63 (dd, J = 1.8 Hz, J = 7.5 Hz, 1 H), 8.49 (dd, J = 1.8 Hz, 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.45, 110.3, 115.9, 122.7, 124.7, 129.5, 137.2, 138.2, 138.7, 146.0, 151.0, 152.0, 192.7.



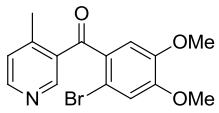
(2-bromopyridin-3-yl)(3,4-dimethoxyphenyl)methanone (83): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3 H), 3.97 (s, 3 H), 6.87 (d, J = 9.0 Hz, 1 H), 7.18 (d, J = 9.0 Hz, 1 H), 7.39 (m, 1H), 7.59 (b, 1H), 7.66 (d, J = 3.0 Hz, 1 H), 8.51 (d, J = 3.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.29, 56.41, 110.2, 110.9, 122.6, 126.7, 128.8, 137.2, 138.2, 138.7, 149.7, 151.0, 154.6, 192.6. m.p: 212-214 °C



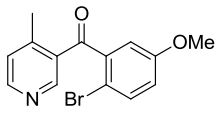
7,8-dimethoxy-5H-indeno[1,2-b]pyridin-5-one (84): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 4.05 (s, 3 H), 7.13 (t, J = 6.3 Hz, 1 H), 7.24 (s, 1 H), 7.41 (b, 1 H), 7.79 (d, J = 7.2 Hz, 1 H), 8.48 (d, J = 5.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.59, 56.89, 104.1, 106.9, 122.7, 128.1, 129.4, 131.0, 138.5, 151.6, 152.8, 155.4, 164.9, 190.9; m/z: 242 $[M+H]^+$, 121; HRMS: calcd. for $C_{14}H_{11}NO_3$: 242.0812 $[M+H]^+$; found 242.0815. m.p: 219-221 °C



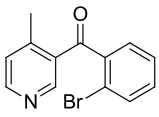
5-(2-(2-bromopyridin-4-yl)-2-hydroxyethyl)-2-methoxyphenol (87): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88-3.03 (s, 2 H), 3.90 (s, 3 H), 4.83 (t, J = 6.3 Hz, 1 H), 5.75 (br, 1 H), 6.74-6.83 (m, 2 H), 6.93 (s, 1 H), 7.06 (d, J = 5.1 Hz, 1 H), 7.34 (s, 1 H), 8.21 (dd, J = 1.2 Hz, J = 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.57, 56.22, 74.09, 110.7, 112.2, 117.7, 124.3, 129.2, 136.6, 142.3, 146.0, 146.6, 149.8, 150.9.



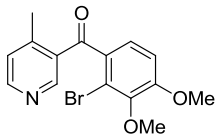
(2-bromo-4,5-dimethoxyphenyl)(4-methylpyridin-3-yl)methanone (88a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3 H), 3.87 (s, 3 H), 3.93 (s, 3 H), 7.04 (d, J = 2.7 Hz, 1 H), 7.23 (d, J = 5.1 Hz, 1 H), 8.48 (s, 1 H), 8.56 (d, J = 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.30, 56.15, 56.34, 112.6, 113.0, 116.0, 126.4, 132.0, 133.7, 148.0, 148.3, 150.9, 151.6, 151.8, 195.7; m/z: 336 $[M+H]^+$; HRMS: calcd. for $C_{15}H_{14}BrNO_3$: 336.023 $[M+H]^+$; found 336.0239



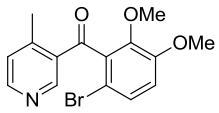
(2-bromo-5-methoxyphenyl)(4-methylpyridin-3-yl)methanone (88b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3 H), 3.79 (s, 3 H), 6.89 (m, 2 H), 7.23 (d, J = 5.1 Hz, 1 H), 7.47 (d, J = 8.7 Hz, 1 H), 8.48 (s, 1 H), 8.55 (d, J = 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.46, 55.36, 109.8, 114.8, 117.8, 126.4, 132.1, 134.0, 141.0, 148.5, 151.7, 151.9, 158.6, 195.8; m/z: 306 $[M+H]^+$, 276, 228, 121; HRMS: calcd. for $C_{14}H_{12}BrNO_2$: 306.0124 $[M+H]^+$; found 306.013. m.p: 58-60 °C



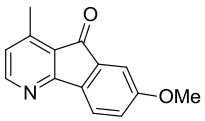
(2-bromophenyl)(4-methylpyridin-3-yl)methanone (88c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3 H), 3.79 (s, 3 H), 7.25 (d, J=5.1 Hz 1 H), 7.43 (m, 3 H), 7.63 (d, J=7.5 Hz 1 H), 8.47 (s, 1 H), 8.56 (d, J = 5.1 Hz 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.40, 119.6, 126.3, 127.2, 129.5, 131.8, 132.2, 133.1, 140.2, 148.4, 151.5, 151.8, 195.9; m/z: 276 $[M+H]^+$, 198, 121; HRMS: calcd. for $C_{13}H_{10}BrNO$: 276.0019 $[M+H]^+$; found 276.0018



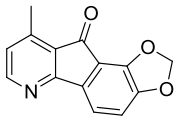
(2-bromo-3,4-dimethoxyphenyl)(4-methylpyridin-3-yl)methanone (88d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3 H), 3.87 (s, 3 H), 3.95 (s, 3 H), 6.94 (d, J = 8.4 Hz, 1 H), 7.21-7.24 (m, 2 H), 8.48 (s, 1 H), 8.56 (d, J = 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.57, 56.35, 60.75, 110.9, 117.1, 126.6, 126.9, 133.5, 133.9, 147.0, 148.4, 151.3, 151.8, 156.2, 195.6.



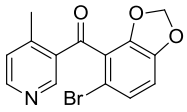
(6-bromo-2,3-dimethoxyphenyl)(4-methylpyridin-3-yl)methanone (88e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 3 H), 3.71 (s, 3 H), 3.90 (s, 3 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.24 (d, J = 5.1 Hz, 1 H), 7.29 (d, J = 8.7 Hz, 1 H), 8.55 (d, J = 5.4 Hz, 1 H), 8.57 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.06, 56.03, 61.49, 108.5, 114.6, 126.8, 128.1, 131.8, 135.9, 146.8, 149.2, 152.2, 152.3, 152.6, 194.6.



7-methoxy-4-methyl-5H-indeno[1,2-b]pyridin-5-one (12): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 3.85 (s, 3 H), 6.83 (d, J = 5.4 Hz, 1 H), 7.02 (dd, J = 8.1 Hz, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 56.0, 109.1, 120.7, 122.3, 125.1, 126.2, 135.8, 137.1, 147.5, 153.0, 162.5, 165.9, 193.3; m/z: 226 $[M+H]^+$; HRMS calcd. for $C_{14}H_{11}NO_2$: 226.0863 $[M+H]^+$; found 226.0866. m.p: 137-138 °C;



9-methyl-10H-[1,3]dioxolo[4',5':4,5]indeno[1,2-b]pyridin-10-one (105): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3 H), 6.17 (s, 2 H), 6.90-6.94 (m, 2 H), 7.35 (d, J = 7.5 Hz, 1 H), 8.39 (d, J = 5.1 Hz, 1 H).



(5-bromobenzo[d][1,3]dioxol-4-yl)(4-methylpyridin-3-yl)methanone (103): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (s, 3 H), 6.00 (s, 2 H), 6.81 (d, J = 8.4 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 1 H), 7.26 (d, J = 5.1 Hz, 1 H), 8.59 (d, J = 5.1 Hz, 1 H), 8.64 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.02, 102.6, 110.4, 111.0, 122.7, 126.1, 126.9, 132.0, 146.7, 147.6, 149.4, 152.5, 152.6, 192.3.

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GENERAL CONCLUSION

This dissertation has examined the synthesis and methodology development on the synthesis of tannins, flavonols and azafluorenones.

The first chapter discusses a direct route to the total synthesis of (±)-1,3,4,5-tetragalloylapiitol. The synthesis was completed in 7 steps and allowed flexibility to allow for future derivatives to be made.

Chapter two focused on the synthesis of natural and unnatural ellagitannins. Our studies show the necessity of protection of the *para*-phenol of gallic acids to form the HHDP moiety *via* oxidative coupling. Preliminary biological testing of the compounds shows good activity against HIV.

The third chapter describes a base-mediated cyclization step towards the synthesis of flavonols. This method constructs flavonols in the proper oxidation state without the necessity of harsh oxidizing agents.

The fourth chapter examines a new synthetic route towards the synthesis of azafluorenones. The synthesis utilizes a key intramolecular Heck coupling to form the 6-5-6 scaffold. Through optimization this synthesis could allow for the construction of almost all known azafluorenone natural products.

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