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UMI
IDENTIFICATION OF SYNTHETIC BENZOPYRANONES AS SELECTIVE AGENTS FOR MOLECULAR TARGETS IN BREAST CANCER

DISSEPTION

Presented in Partial Fulfillment of the Requirements for

The Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

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Currently, one out of eight American women will develop breast cancer in her lifetime, making breast cancer the second highest cause of mortality of all female cancers. The majority of breast cancer cases (60-70%) are hormone-dependent, meaning that estrogens are needed for the growth of the tumor. Various antiestrogens, including tamoxifen, are widely used for the treatment of hormone-dependent breast cancer. However, the need for newer antiestrogens with greater specificity and reduced side effects exists. The hypothesis of this research is that the design, synthesis, and screening of substituted benzopyranone libraries would allow us to utilize the biological potential of these molecules and develop more selective therapeutic agents for molecular targets in breast cancer.

The benzopyranone ring system is the core structure found in a number of natural products such as the flavonoids and isoflavonoids. Substituted 4H-1-benzopyran-4-ones have shown activity as protein tyrosine kinase inhibitors, estrogen receptor agonists or antagonists, or inhibitors of steroidogenic enzymes. The prevalent literature methods for constructing benzopyranones were not ideally suited for making libraries as these methods suffer from harsh reaction conditions, poor substituent tolerance, and low yields. Initial synthetic chemistry produced a novel synthetic route utilizing readily
available salicylic acids and terminal alkynes as starting materials to construct the benzopyranone nucleus. This approach is characterized by mild and high yielding reactions with good functional group tolerance, and it is ideal for developing combinatorial libraries centered around the benzopyranone ring system.

The novel solution-phase chemistry developed to synthesize the benzopyranones can be accomplished in several steps. Retrosynthetically, it was envisioned to make the benzopyranones by the cyclization of alkynones. Substituted bis-TBDMS-salicylic acids underwent a one-pot acid chlorination-Sonogashira coupling resulting in the synthesis of the critical intermediate, alkynone, in excellent yields. To date, electronic and steric requirements for these coupling reactions have been determined. Substitutions at the 3-, 4-, and 5-position of salicylic acid, including halogens, aromatic, and methoxy functionalities, have been used in coupling and result in yields ranging from 40-96%. For the Sonogashira coupling, various terminal alkynes were used (aromatic, alkyl, acetal). The one-pot acid chlorination-Sonogashira coupling, key for introducing diversity, displays a wide substituent tolerance in both of the coupling partners.

Michael addition of the secondary amine to the alkynone, followed by a 6-endo-trig cyclization results in the formation of the six-membered benzopyranone with yields from 70-96%. By using a secondary amine addition to the alkynone, the synthetic strategy prevents the cyclization of the competing five-membered benzofuranone and thus resolves the regioselectivity problem encountered by previous efforts.
approaches for diversifying the benzopyranone skeleton have also been pursued; substituents at the 3-position on the ring system would dramatically increase the diversity of our library. Evaluation of a library with more than forty synthetic benzopyranones in initial bioassays (cell proliferation, estrogen receptor binding, and aromatase) using human breast cancer cell lines has resulted in agents exhibiting enhanced and differential activities on breast cancer cell growth and on aromatase inhibition. Continued synthetic efforts will concentrate on development of more selective agents for molecular targets in breast cancer based upon the benzopyranone nucleus.
Dedicated to

Shawn

Mom, Dad, Beth, & Matt
ACKNOWLEDGMENTS

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CHAPTER 1

TARGETING BREAST CANCER WITH FLAVONOIDS

1.1 Breast Cancer Statistics

Cancer is the leading cause of death among women between the ages of 30 and 54. A woman living in the United States has a one in eight lifetime risk of developing breast cancer [1]. In 2001, the American Cancer Society estimates that 192,200 new invasive cases of breast cancer will be diagnosed among women in the United States, as well as nearly 47,100 additional cases of in situ breast cancer [1]. A total of 40,200 women are expected to die from this disease in 2001, making breast cancer the second highest cause of mortality of all female cancers. The reality is that many women, and their families, are affected by breast cancer.

With treatment options that exist today, the 5-year survival rate for localized breast cancer is 97%. If the breast cancer has spread regionally or with distant metastases, 5-year survival rates decrease dramatically to 77% and 21%, respectively [2]. Survival rates also continue to decline beyond five years and the need for newer therapies with greater specificity and reduced side effects still exists.
1.1.1 Risk Factors for Breast Cancer

Various factors that increase the relative risk for breast cancer in women are presented in Table 1.1. Risk factors for breast cancer can be grouped into several categories: hormonal, genetic, geographical, and environmental factors. The primary risk factors for developing breast cancer are gender and age. Women with a family history of breast cancer (first-degree relative like mother, sister, or daughter) are at higher risk due to genetic predisposition. Approximately 5% to 10% of breast cancer cases are a result of inherited mutations in breast cancer susceptibility genes (BRCA1 and BRCA2) [1]. Although the majority of risk factors are not modifiable (age, family history, age at first birth, early menarche, late menopause), other factors such as alcohol consumption, use of postmenopausal hormones, and obesity after menopause are modifiable. Because the exact cause of breast cancer is unknown and it is impossible to eliminate all risks of breast cancer, prevention and early detection through mammography and breast self-examinations are the best strategy for women to fight this disease.

1.2 Estrogens and Breast Cancer

The regulation of normal breast development, initiation of breast carcinogenesis, and growth and progression of breast cancer are dependent on hormonal factors. The majority of breast cancer cases (60-70%) are hormone-dependent, meaning that estrogen receptors are present and estrogens are needed for the growth of the tumor. 17β-Estradiol is the most potent endogenous estrogen (Figure 1.1). At the molecular level, estrogens bind to the estrogen receptor (ER) and cause the expression of various
<table>
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| > 4.0         | Certain inherited genetic mutations for breast cancer  
                Two or more first-degree relatives with breast cancer diagnosed at an early age  
                Personal history of breast cancer  
                Age (65+ vs. < 65 years, although risk increases across all ages until age 80) |
| 2.1 – 4.0     | One first-degree relative with breast cancer  
                Nodular densities on mammogram (> 75% of breast volume)  
                Atypical hyperplasia  
                High-dose ionizing radiation to the chest  
                Ovaries not surgically removed < age 40 |
| 1.1 – 2.0     | High socioeconomic status  
                Urban residence  
                Northern US residence |
| Reproductive Factors | Early menarche (< 12 years)  
                        Late menopause (≥ 55 years)  
                        No full-term pregnancies (for breast cancer diagnosed at age 40+ years)  
                        Late age at first full-term pregnancy (≥ 30 years) |
| Other factors that affect circulating hormones or genetic susceptibility | Postmenopausal obesity  
                                                                          Alcohol consumption  
                                                                          Recent hormone replacement therapy  
                                                                          Recent oral contraceptive use  
                                                                          Tall  
                                                                          Personal history of cancer of endometrium, ovary, or colon  
                                                                          Jewish heritage |

Table 1.1: Factors that increase the relative risk for breast cancer in women [1].
genes important for growth, i.e. growth factors, protein tyrosine kinases, and cyclin dependent kinases. These proteins act by endocrine, paracrine, autocrine, and intracrine interactions to promote the growth of breast cancer cells.

![Chemical structures of 17β-estradiol, estrone, and estriol](image)

**Figure 1.1:** 17β-Estradiol, estrone, and estriol.

1.2.1 *Estrogen Receptor α and Estrogen Receptor β*

Estrogens not only exert their effects on the growth, differentiation, and functioning of reproductive tissues, but also have important actions on other tissues including bone, liver, cardiovascular system, and central nervous system. The majority of actions influenced by estrogen are through two estrogen receptor (ER) subtypes, estrogen receptor α (ERα) and the more recently discovered estrogen receptor β (ERβ) [3,4]. The tissue distribution and relative ligand binding affinity for ERα and ERβ are different and could contribute to the selective action of ER agonists and antagonists in different tissues [5].
ER is a member of the steroid hormone receptor superfamily which includes receptors for steroids (progesterone, cortisol, aldosterone, and testosterone), thyroid hormone, vitamin D, and retinoic acids. In humans, a single gene encodes for ERα (595 amino acids) and ERβ (530 amino acids) protein and is found on chromosomes 6 and 14, respectively [6]. ERα and ERβ proteins are similar in architecture to other steroid receptors; each is composed of five independent but interacting functional domains: A/B, C, D, E, and F domains (Figure 1.2). The N-terminal A/B domain encodes the ligand-independent activation function (AF-1) and is involved in protein:protein interactions and the transcriptional activation of gene expression. ERα and ERβ differ the most in the A/B domain, having only 18% amino acid homology [7]. The most conserved domain among nuclear hormone receptors is the C domain. It is the DNA binding domain and contains two zinc finger structures, which allow for DNA sequence-specific receptor binding and dimerization. Domain D is known as the hinge region and allows for ligand mediated conformational changes. The ligand-binding domain (LBD), domain E, of ERα and ERβ shows 56% amino acid homology. It is responsible for ligand binding, receptor dimerization, nuclear translocation, and ligand-dependent transaction (AF-2) of target genes. When a ligand is not present, a heat-shock protein Hsp90 binds and stabilizes the ER, and prevents dimerization and/or recognition of the estrogen responsive elements (ERE).
1.2.2 MECHANISM OF ESTROGEN RECEPTOR ACTIVATION

Steroids, like estrogens, are lipophilic molecules that are bound to steroid binding proteins in the bloodstream to aid in transport as well as protection from metabolism. Upon arrival at a target tissue, an equilibrium exists between bound and unbound estrogen. Due to its lipophilic nature, estrogens can diffuse into the plasma membrane of the target tissue and translocate across the nuclear membrane to the nucleus. In the nucleus, estrogens will bind to an ER, displace the stabilizing heat-shock protein, and induce a conformational change (Figure 1.3). The conformational change of the estrogen-ER complex allows for homodimerization with another estrogen-ER complex via a zinc finger in the LBD. The homodimerized estrogen-ER complex recognizes specific sequences in the promoter regions of DNA called estrogen responsive elements (ERE). The DNA ERE is a palindromic consensus sequence of 12 base pairs separated by three-nucleotides (AGGTCAnnnTGACCT) [8]. Upon binding to the ERE, transcriptional machinery is recruited and results in the transcription of the gene. The
mRNA formed undergoes processing and translocation to the cytoplasm, followed by translation to form a protein which can alter cellular function by endocrine, paracrine, or autocrine interactions.

Figure 1.3: Mechanism of steroid hormone action.

The action of estrogen receptors is tripartite, involving the receptor (ERα or ERβ), its ligands, and the coregulatory proteins needed for transcription [7]. If the structural requirements of ligands needed to bind specifically to ERα and ERβ can be determined, the cell-specific and promoter-specific activities of estrogens in target cells could enable researchers to have an understanding of the exact role of estrogens in breast cancer cells and provide new insight into treatment. The role of ERβ in the breast remains to be fully defined; however, it may have a protective role in breast tissue [9]. Structural
information from x-ray crystallography is currently available for the ERα-LBD bound to 17β-estradiol [10,11], raloxifene [10], diethylstilbestrol [12], and 4-hydroxy-tamoxifen [12] and ERβ-LBD bound to raloxifene and genistein [13].

![Diagram](attachment:image.png)

Figure 1.4: Tripartite nature of nuclear hormone receptors involving the interactions between ligands, receptor, and effectors [7].

1.3 Current Chemotherapy of Breast Cancer

The optimal treatment of breast cancer primarily depends on the stage of the breast cancer, the patient’s age and preferences, and the risks and benefits ascribed to each treatment. Surgery to remove the tumor is often combined with other treatments such as radiation therapy, chemotherapy, hormone therapy, and/or monoclonal antibody therapy [1]. The majority of human breast cancers are initially hormone-dependent and regress upon deprivation of the supporting hormone. The status of hormone dependence is usually determined by testing positive for the presence of estrogen or progesterone receptors. Because of the role of endogenous estrogens in the
development and maintenance of breast cancer, two main approaches have been
developed to block or antagonize the action of these hormones. The first-line therapy
for metastatic breast cancer is treatment that blocks the action of 17β-estradiol at the ER
by means of antagonists, of which various antiestrogens including tamoxifen
(Novaldex®) are used (Figure 1.5). About two-thirds of patients with ERα-positive
breast tumors will respond favorably to tamoxifen treatment or other endocrine
manipulations. Unfortunately, patients on tamoxifen therapy can relapse or acquire
tamoxifen-resistant tumors as well as suffer from side effects such as increased
incidence of uterine cancer, deep vein thrombosis and hot flushes [14]. The second
approach is to inhibit the biosynthesis of 17β-estradiol locally within breast tissue by
inhibiting aromatase, the cytochrome P450 enzyme that catalyzes the conversion of
androgens into estrogens [15]. Aromatase inhibitors are the second-line defense for
patients with ERα-positive breast tumors who fail tamoxifen treatment.

Various combinations of chemotherapy drugs are used in breast cancer, including
cyclophosphamide, methotrexate, fluorouracil, doxorubicin (adriamycin), epirubicin,
and paclitaxel (taxol). A recent clinical trial has demonstrated that tamoxifen can be
used to reduce the risk of breast cancer in women at increased risk for developing the
disease. A 47% reduction in the risk of invasive breast cancer and a 50% reduction in
the risk of noninvasive breast cancer were observed in women taking tamoxifen as a
preventative agent [14]. Table 1.2 provides a list of new anticancer treatments under
development in breast cancer [16].
## New Anticancer Treatments under Development

- **Cytotoxic drugs**
  - New analogs
  - New molecular/mechanistic classes
- **Modulators of drug resistance**
- **Immunologic approaches**
  - Antibodies: monoclonal or polyclonal
  - Immunonoconjugates:
    - With cytotoxic drugs
    - With radioactive substances
    - With toxins
  - ADEPT systems
  - Fusion proteins
  - Vaccines
- **Growth factor or growth factor receptor directed**
  - HER-2/neu
  - EGFR
  - IGF-I
  - Steroid hormones and their receptors
  - Osteoclast activating factors
  - Mammmastatin
- **Signal transduction inhibitors**
  - Tyrosine kinase inhibitors
  - Farnesyl protein transferase inhibitors
  - Grb2 inhibitors
- **Angiogenesis inhibitors**
  - Anti-VEGF agents
  - Inhibitors of endothelial proliferation
- **Inhibitors of tissue invasion and metastasis**
  - Inhibitors of adhesion molecules, integrins
  - Matrix metalloprotease inhibitors
- **Modulators of apoptosis**
  - Telomerase inhibitors

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Table 1.2: New anticancer treatments under development in breast cancer [16].
1.3.1 Targeting the ER with SERMs and Other ER Antagonists

The structure activity requirements (SAR) of 17β-estradiol binding to ERα has been extensively researched [17]. The SAR of 17β-estradiol has been described as a planar hydrophobic structure which contains a phenol that acts as a H-bond donor (A-ring) separated from a second hydroxyl group that acts as a H-bond acceptor (D-ring) (Figure 1.5). Larger hydrophobic substituents are tolerated at positions 7α, 11β, and 17α. Nonsteroidal estrogens that possess this pharmacophore and bind to the ER exist and include synthetic potent estrogens (diethylstilbestrol, DES) and phytoestrogens (Figure 1.5). Phytoestrogens are weakly estrogenic compounds that have been isolated from plants. A few examples include the isoflavonoid genistein, coumestrol (found in clover), equol (plant metabolite), and the fungal metabolite zearalenone (Figure 1.5). These hormonal mimics, or agonists, bind to the ER and elicit a hormonal response.

Antiestrogens bind to the ER but due to structural differences prevent the expression of the genes that lead to cancerous growths. Antiestrogens are antagonists of the ER and includes derivatives of various backbones such as triphenylethylene, benzothiophene, steroidal, indole [18,19], napthalene [20,21], benzopyran [22], arylcoumarin [23], constrained tetracyclic cores [24], and other heterocyclic compounds (Figure 1.5-1.6) [25-27]. Although estrogens have a deleterious effect in breast tumors, they have protective effects in other tissues. Selective estrogen receptor modulators (SERMs) are a relatively diverse set of compounds that demonstrate both ER agonist and antagonist activity dependent upon the cell type and gene promoter targeted.
Tamoxifen, a triphenylethylene derivative, was among the first reported classes of SERMs and has been widely used for decades as treatment for breast cancer and more recently as a preventative agent for breast cancer. Tamoxifen functions as an antiestrogen in breast tissue, but has estrogenic activity in the uterus, liver, and bone. Tamoxifen has a triphenylethylene ring system with a basic amine side chain projecting off an aromatic ring and is hydroxylated \textit{in vivo} to produce the active metabolite, 4-hydroxytamoxifen. Because tamoxifen produces an increased incidence of uterine cancer, efforts to modify this structure and reduce the effects in the uterus have been performed without much improvement (Figure 1.5). Toremifene is marketed for treatment of breast cancer with the same side effects in the uterus. Droloxifene and idoxifene were recently terminated from late stage clinical trials [28,29].

The majority of non-steroidal antiestrogens contain a common pharmacophore that includes two aryl groups separated by two atoms, often in a stilbene type arrangement. Typically one of these aryl groups contains a hydroxyl group and mimics the A-ring of 17β-estradiol. A third aryl group bearing a basic amine side chain is present and corresponds to the 11β-position of 17β-estradiol. This bulky basic amine side chain confers antiestrogenic activity by projecting into the estrogen receptor and displacing helix 12, which prevents interaction of the receptor with certain nuclear coactivator proteins and thus interferes with cellular transcription [10].
Raloxifene (Evista®) is a benzothiophene derivative that was approved in December 1997 for the treatment and prevention of osteoporosis in postmenopausal women. Raloxifene, like tamoxifen, antagonizes the effects of estrogen on breast tissue and mimics estrogens actions on bone; however, raloxifene does not induce significant uterine stimulation [30]. The orientation of the basic amine side chain has been determined to be critical in the selectivity of antiestrogens. The carbonyl hinge connecting the basic amine side chain to the benzothiophene ring system of raloxifene induces an orthogonal orientation [30]. The basic amine side chain is coplanar to the stilbene ring system of tamoxifen. Basic amine side chains have been appended to a variety of phytoestrogens and heterocyclic ring systems in appropriate positions in attempts to develop additional SERM-like molecules (Figure 1.5-1.6).
Figure 1.5: SAR of 17β-estradiol. Nonsteroidal, phytoestrogen, triphenylethylene, and benzothiophene derivatives of estrogen antagonists.
Figure 1.6: Steroid, indole, naphthalene, benzopyran, and arylcoumarin derivatives of estrogen antagonists.
1.4 Estrogen Biosynthesis

The biosynthesis of estrogens, including 17β-estradiol, estrone, and estriol, occurs primarily in the ovaries in mature premenopausal women and is under the hormonal regulation of the hypothalamus-pituitary axis. The hypothalamus releases gonadotropin releasing hormone (GnRH) which acts on the pituitary to release follicle stimulating hormone (FSH) and leutinizing hormone (LH). FSH and LH bind to cell membrane receptors on granulosa and theca cells of the ovary, and through cAMP dependent cascade of events increases the amount of cholesterol and cytochrome P450 aromatase. In the theca cells of the ovary, cholesterol, a C27 precursor to the steroid hormones, is converted to pregnenolone (C21) in the rate determining step in steroid biosynthesis by the cytochrome P450 cholesterol side chain cleavage enzyme. Through a series of enzymatic steps, pregnenolone is converted to the androgen androstenedione (C19), which is transferred to the granulosa cells. In the granulosa cells of the ovary, androgens are converted to estrogens (C18) by the cytochrome P450 enzyme aromatase (estrogen synthase) (Figure 1.7).

Aromatase is encoded by the CYP19 located on chromosome 15q21.1 as a single gene. There are nine exons that encode to make aromatase, a 503 amino acid, 55 kDa NADPH-dependent cytochrome P450 reductase, which contains an iron-porphyrin prosthetic group. The regulation and expression of aromatase in different tissues is due to promoter switching of the CYP19 gene [31,32].
Estrogen biosynthesis does not exclusively occur in the ovaries. Other tissues that produce estrogens are the placenta, muscle, adipose tissue, brain, skin, and normal breast stromal cells. In addition, the biosynthesis of 17β-estradiol at low levels occurs locally with breast tumor tissue and is an important source of estrogen in postmenopausal women [33-39]. Because aromatase catalyzes the rate-limiting step in estrogen biosynthesis and is present locally within breast tumors, it is a potential treatment strategy in hormone dependent breast cancer.

Figure 1.7: Biosynthesis of estrogens from androgens via aromatase.

1.4.1 AROMATASE INHIBITORS

Aromatase inhibitors are primarily used as a second-line treatment for ER-positive breast cancer patients who fail tamoxifen treatment. Two classes of aromatase inhibitors, steroidal and nonsteroidal, are currently in use (Figure 1.8).
4-Hydroxyandrostenedione (Lentaron®) is a steroidal competitive inhibitor of aromatase resulting in either covalent or very tight binding of the inhibitor to the enzyme causing the inactivation of aromatase [40]. 7α-Thiosubstituted androstenedione inhibitors were synthesized by this laboratory as potent competitive (7α-APTA) or enzyme-activated irreversible inhibitors (7α-APTADD) [41-45]. The nonsteroidal aromatase inhibitors possess a heteroatom, usually a nitrogen-containing heterocycle that interferes with steroidal hydroxylation by coordinating with the iron of the heme group at the active site of aromatase and thus competing with androstenedione for the
steroid binding site. Arimidex® and Femara® are highly potent, competitive, reversible aromatase inhibitors and are approved for the treatment of postmenopausal breast cancer [40].

1.5 Flavonoids as Targets in Breast Cancer

Found predominantly in higher plants, flavonoids are a class of natural products that encompasses the flavones, isoflavones, flavanones, and flavonols, each possessing the 4H-1-benzopyran-4-one ring system as the common chemical scaffold (Figure 1.9). Present in many food sources including fruits, vegetables, legumes, and whole grains, flavonoids have attracted considerable interest as dietary factors. Flavonoids may be responsible for the lower incidence of breast cancer in women from certain regions of the world, e.g., Japan and Finland [46,47]. A four to six-fold lower risk of breast cancer development exists in Asian women and has been linked to a traditional low-fat high-soy diet; flavonoids being present in soy [48,49]. The chemopreventive effects of vegetable- and fruit-rich diets may also be attributable to flavonoids.

![Flavonoids: a class of natural products.](image)

Figure 1.9: Flavonoids: a class of natural products.
1.5.1 Biological Activities of Flavonoids

Over 4000 chemically unique flavones have been isolated from plants and exhibit a wide range of biological activities because of their ability to interact with various enzymes and receptor systems of pharmacological significance (Figure 1.10). Flavonoids demonstrate antiviral, anti-inflammatory, anti-allergic, antimutagenic, antioxidant, and anticarcinogenic activities [50-56]. Sharing structural similarities to the endogenous hormone 17β-estradiol, flavones and isoflavones possess many of the features (two phenols separated by approximately 11-12Å with a planar conformation) needed to satisfy the estrogen pharmacophore. It is not surprising that they possess estrogenic or antiestrogenic activities [48,51,53,57,58,58-60], bind to both ERα and ERβ [5,61], inhibit aromatase [62-64], and inhibit 17β-hydroxysteroid oxidoreductases type 1 [65,66]. Flavonoids have also shown activity as protein tyrosine kinase inhibitors [67-69], topoisomerase inhibitors [70], osteoclast inhibitors [71,72], angiogenesis inhibitors [73,74], and inhibit tubulin polymerization [75]. Because the 4H-1-benzopyran-4-one ring system is found in many different compounds that possess biological activity, we believe that modifications to this core skeleton can result in more selective therapeutic agents for molecular targets in breast cancer.
1.5.2 Phytoestrogens

A phytoestrogen has been loosely defined as any plant-derived compound that can regulate gene expression mediated by an ERE, in a manner either comparable or apparently antagonistic to 17β-estradiol, as a result of direct binding to ER [76]. There are several groups of phytoestrogenic compounds which includes the lignans, isoflavones (genistein), flavones (apigenin), chalcones (phloretin), flavanones (naringenin) and mycotoxins (zearalenone) (Figure 1.5, 1.11). Isoflavonoids may reduce the risk in developing breast cancer [77] and have been shown to inhibit the in vitro growth of MCF-7, T47D, MD-MBA-231, SKBR3, and ZR-75-1 human breast cancer cells [78-81]. Genistein, a principle isoflavone present in soy, has weak estrogenic activity [48], exhibits differential affinities for ERα and ERβ [5], inhibits protein tyrosine kinases (PTK) [67,68], regulates specific phases of the cell cycle,
inhibits DNA topoisomerase II activity, induces cellular differentiation, inhibits production of reactive oxygen species, and may have dietary chemopreventive benefits [46,47,82]. The SAR for genistein, as well as other flavonoids, have been determined with respect to genistein’s estrogenic and PTK inhibitory activity [58,68]. For maximal estrogenic activity, the diaryl ring structure and hydroxyl substituents at the 4’- and 7-positions are necessary, and a hydroxyl group at the 5-position increases the estrogenicity of genistein [58]. The hydroxy group at the 5-position is essential for PTK activity and the hydroxyl groups at the 4’- and 7-position are necessary for full expression of PTK activity [68]. The dietary exposure of phytoestrogenic compounds and their risk/benefit to various cancers, including breast cancer, remains to be fully elucidated.

Figure 1.11: Phytoestrogenic compounds.

1.5.3 Flavonoids That Inhibit Aromatase

Various flavonoids have shown activity as aromatase inhibitors in vitro (Figure 1.12) [62,63,83-85]. It has also been shown that apigenin, naringenin, and chrysin did not significantly reduce androstenedione-induced uterine growth, indicating a lack of aromatase-inhibiting effect in vivo [64]. The SAR for various flavonoids has been
determined with respect to aromatase inhibition. Kao et al. suggested from site-directed mutagenesis studies that flavonoids bind to the active site in an orientation such that their A and C rings mimic rings D and C of the steroid, respectively [86]. As seen in the SAR of genistein for ER binding and PTK activity, the number and placement of hydroxyl groups are also important for aromatase inhibition [63,64,86]. For maximal aromatase inhibition, a 7-hydroxyl on a flavone skeleton is necessary. It was shown that reduction of the C-2, C-3 double bond or methylation of the 7-hydroxyl reduces the inhibitory effect. The farther the hydroxyl group was from the C-4 carbonyl, the higher the inhibition. Dihydroxyl groups at the 3'- and 4'-position or hydroxyl groups at the 4'- or 3-positions decrease the inhibitory capacity of the flavones.

Recanatini et al. recently designed a new class of nonsteroidal aromatase inhibitors based upon the chromone and xanthone skeletons with either an imidazole or 1,3,4-triazole linked to the aromatic moiety (Figure 1.13) [87]. The xanthone derivatives were able to potently and selectively inhibit cytochrome P450 aromatase (IC50 = 43 and 40 nM) while showing minimal inhibition of 17α-hydroxylase/C17,20-lyase (P45017).
**Figure 1.12:** Flavonoids as inhibitors of aromatase. For reference, the $K_m$ for the substrate androstenedione is approximately 20 nM. The current clinical drugs of anastrozole and letrozole have IC$_{50}$ values of 15 nM and 11.5 nM, respectively.

**Figure 1.13:** Xanthone and chromone nucleus as aromatase and 17α-hydroxylase inhibitors [87].
1.6 Targeting Breast Cancer with Flavonoids

The 4H-1-benzopyran-4-one skeleton is present in the class of natural products known as the flavonoids. It has been shown that minor changes in flavonoid structure have resulted in major changes of biological activity. Structure activity requirements of flavonoids for ER binding, PTK, aromatase, and 17β-hydroxysteroid oxidoreductase, type 1 have been described [64]. The design, synthesis, and screening of a novel substituted 4H-1-benzopyran-4-ones solution phase library will allow us to harvest the biological potential of these molecules and develop selective agents for molecular targets in breast cancer.
CHAPTER 2

HYPOTHESIS

2.1 THE 4H-1-BENZOPYRAN-4-ONE RING SYSTEM AS A POTENTIAL TARGET

The 4H-1-benzopyran-4-one ring system is the core structure found in a number of natural products termed flavonoids which includes such classes as the flavones and isoflavones. Flavonoids exhibit numerous biological properties and interact with various enzymes and receptor systems of pharmacological significance. These natural products have shown antiviral, anti-inflammatory, anti-allergic, antifungal, and anticarcinogenic activities [50-53,55,88]. In fact, flavones and isoflavones share structural similarities to the endogenous 17β-estradiol, and substituted 4H-1-benzopyran-4-ones have shown activity as protein tyrosine kinase inhibitors, estrogen receptor agonists/antagonists, or inhibitors of steroidogenic enzymes including P450 aromatase [5,57-59,62,63,67,68]. Because the benzopyranone ring system is found in many different compounds that possess biological activity, we believe that modifications to this core skeleton can result in more selective therapeutic agents for molecular targets in breast cancer (Figure 2.1). Modifications to this skeleton could include alkyl, hydroxyl, ether, ester, amine, halogen, aromatic, heteroaromatic, or cycloalkyl substitutents.
2.1.1 **Inhibitor Design**

Although nature has provided many examples of natural products containing the benzopyranone skeleton, we believe that the opportunity still exists to make novel compounds targeted to breast cancer. With the advent of combinatorial chemistry, chemists are employing solid-phase techniques to quickly make libraries of compounds. The first example of 2,3-disubstituted benzopyran-4-ones has just recently been synthesized using a solid-phase diisopropylsilyloxy traceless linker yielding only a nine-membered library with limited side chain diversity [89] (Figure 2.2). Thus, our objective was to develop a novel solution-phase methodology that would not only be amenable to solid-phase but also have the potential to introduce multiple sites of chemical diversity with diverse side chains not found readily in nature (Figure 2.1). Existing synthetic methods for constructing benzopyranones are not ideally suited for making solid phase combinatorial chemistry libraries; they suffer from harsh reaction conditions, low yields, and poor substituent tolerance. Thus, we envisioned making benzopyranones retrosynthetically by cyclization of alkynones; which can in turn be made from salicylic acids and terminal alkynes (Figure 2.3). A synthetic chemistry
approach has been accomplished using these starting materials and is characterized by mild, high yielding reactions with good functional group tolerance; ideal for developing combinatorial libraries centered around the benzopyranone ring system.

Figure 2.2: Retrosynthetically, 2,3-disubstituted-benzopyran-4-ones were derived from salicyl aldehydes, amide acetals, and organometallic reagents [89].

Figure 2.3: Retrosynthetic approach of substituted-4H-1-benzopyran-4-ones.
2.2 Classical Methods for Flavone Synthesis

The synthetic methods in the literature that have been used to synthesize flavones can be grouped into 3 categories: (I) the heterocyclic ring is formed during the synthesis; (II) the heterocyclic ring is found in the starting material but in a different oxidation state or different ring size; and (III) alteration of another flavone. By far, the majority of the synthetic methodologies rely on the synthesis of the 4H-1-benzopyran-4-one ring system. Because of our interest in the synthesis of a diverse library of benzopyranones, alteration of another flavone is not applicable and therefore will not be discussed.

2.2.1 Forming the 2-Phenyl-4H-1-Benzopyran-4-one Ring System

The majority of synthetic methodologies for synthesis of the 4H-1-benzopyran-4-one involve the synthesis of the heterocyclic ring system. Four possible disconnection approaches (A-D) that are predominantly found in the literature for the synthesis of the benzopyranone skeleton can be seen in Figure 2.4 [90]. The carbon skeleton is usually formed by the reaction of two aromatic compounds. The primary approaches that have gained importance for the laboratory synthesis of flavones are approaches A and B: (A) acylation of phenols with a cinnamic acid derivative which corresponds to the biosynthetic pathway; and (B) condensation of a 2-hydroxyacetophenone with either an aromatic aldehyde or an aromatic carboxylic ester [91]. Approach C is the condensation of an o-alkoxycarboxylic ester with an acetophenone. No method based
upon approach D is known. Approach B is the most widely used method for the synthesis of flavonoids with the majority using an o-hydroxyaryl alkyl ketone as the starting material.

![Diagram](image)

Figure 2.4: Four possible disconnection approaches (A-D) that are predominantly found in the literature for the synthesis of the benzopyranone skeleton.

### 2.3 Synthesis of Flavonoids from an o-Hydroxyaryl Alkyl Ketone

#### 2.3.1 Claisen Condensation

The Claisen condensation of o-hydroxyaryl alkyl ketones with a carboxylic ester is one of the most frequently used preparative methods of the 4H-1-benzopyran-4-one skeleton (Figure 2.5) [91]. It involves the condensation of 2-hydroxyacetophenone in the presence of a strong base to form a 1,3-diketone intermediate, which is cyclized upon heating in acidic medium to give the benzopyranone. Substituents on the aromatic ring
of the acetophenone have minimal effects on the condensation and both electron-donating and electron-withdrawing groups are compatible. The variation of the $R_2$ acetyl group is less because of the reactivity of some substituents towards nucleophiles. Because substituents on the acetyl group have a direct effect on the condensation, an alternative method for 3-substituted benzopyranones involves alkylation of the intermediate 1,3-diketone. The C-2 substituent arises from the ester component, which is commonly an alkyl or ethoxycarbonyl. This is a major limitation in forming flavones which have an aromatic group at $R_3$. The Claisen condensation requires a strong base for the condensation and acidic conditions for the cyclization, and therefore is not ideal for our synthetic pursuits.

![Figure 2.5: Claisen condensation](image)

2.3.2 **Baker-Venkataraman Rearrangement** [92]

Another source of the 1,3-diketone intermediate involves the $O$-acylation of 2-hydroxyacetophenone to form an acyloxyacylbenzene intermediate followed by a Baker-Venkataraman rearrangement. Treatment of the acyloxyacylbenzene intermediate with base in pyridine initiates an intramolecular rearrangement in which the acyl moiety migrates from the oxygen to the carbon atom $\alpha$ to the carbonyl of the other acyl group.
This intramolecular rearrangement is known as the Baker-Venkataraman rearrangement. An advantage to this method is that the migrating acyl group may be aliphatic or aryl in nature and thus lead to the synthesis of flavones. The rearrangement occurs under a variety of basic catalysts including potassium carbonate, potassium hydroxide, sodium hydroxide, sodium metal, and sodium hydride. It has been suggested that the stronger basic species are more effective than potassium carbonate.

The proposed mechanism (Figure 2.6) is probably a base-catalyzed intramolecular Claisen condensation followed by ring opening to the diketone. The subsequent cyclization can be effected not only in sulfuric acid in ethanol, but also with glacial acetic acid and sodium acetate, or by heating the diketone in a vacuum.

Mechanism:

![Mechanism Diagram](image)

Figure 2.6: Baker-Venkataraman Rearrangement
Figure 2.7: Synthesis of flavonols from acetophenones and aroyl chlorides using a Baker-Venkataraman rearrangement [93].

1,3-Diketone is a common intermediate for the synthesis of flavones and construction of the 4H-1-benzopyran-4-one skeleton. Fougerousse et al. have recently reported a new approach to synthesize flavonols using a Baker-Venkataraman rearrangement to form a 1,3-diketone intermediate (Figure 2.7) [93]. Other methodologies exist for the synthesis of the 1,3-diketone: (1) the Claisen reaction between salicylic acid derivatives like methyl 2-methoxybenzoate and acetone; (2) the direct acylation of lithium enolates of acyl phenols; and (3) the DBU catalyzed reaction of acetophenones with aryl or alkanoyl chlorides (Figure 2.8) [69,92,94]. Methyl salicylates have also been condensed with dilithiated β-diketones for the preparation of 2-phenacyl-4H-1-benzopyran-4-ones via a triketone intermediate) [95] or bromocrotononitrile for the preparation of 2-cyano-methylthiomethyl-4H-1-benzopyran-4-ones (Figure 2.9) [96]. These routes provide new classes of 2-substituted benzopyranones that were not easily obtainable by previous synthetic efforts.
Figure 2.8: Other sources of 1,3-diketones

Figure 2.9: Condensation and cyclization of methyl salicylates with dilithiated β-diketones [95] or bromocrotononitrile [96].
2.3.3 **ALLAN-ROBINSON CONDENSATION**

The Allan-Robinson condensation is a one step condensation of an o-hydroxy-acetophenone with the anhydride of an aromatic acid in the presence of the salt of the same acid, followed by alkaline hydrolysis (Figure 2.10). This reaction is performed at an oil bath temperature with either trimethylamine or pyridine as catalyst. The best results of this method occur when the ketone has oxygen in the o-position (either as an alkoxy or aroyloxy group) and thus is suitable for the synthesis of 3-hydroxy- and 3-alkoxyflavones [90]. This method has been primarily used for the synthesis of 3-methoxyflavones. The first step of the Allan-Robinson reaction is evidently the formation of an o-aryloxyacetophenone, which undergoes a Baker-Venkatakrishnan rearrangement. Upon loss of water, the cyclized flavone is formed.

![Figure 2.10: Allan-Robinson Condensation.](image)

2.4 **SYNTHESIS OF THE 4H-1-BENZOPYRAN-4-ONE RING FROM CHALCONES**

The second method for synthesis of the 4H-1-benzopyran-4-one ring system is one in which the heterocyclic ring is found in the starting material but in a different oxidation state or different ring size. Reactions belonging to this class include the conversion of other flavonoids, such as flavanones or the chalcones, into the corresponding flavones.
2.4.1 Algar, Flynn, and Oyamada (AFO) Reaction

The Algar, Flynn, and Oyamada (AFO) reaction of 1934 is one of the most frequently used synthetic methods for the oxidative conversion of 2'-hydroxychalcones into flavonols. This reaction involves the one step oxidation of 2'-hydroxychalcone to the flavonol (20-40% yield) with hydrogen peroxide in alkaline medium (Figure 2.11).

Limitations for the AFO method exist. If the chalcone has a substituent in the 6'-position, the resulting yield of the flavonol is low due to the opening of the intermediate epoxide and results in the formation of aurones [93].

![Figure 2.11: Algar, Flynn, and Oyamada (AFO) Reaction](image)

Other methodologies exist for the cyclization of 2'-hydroxychalcones into flavones including the addition of bromine, refluxing with selenium dioxide, heating with DMF or disulfides, or stirring with palladium. Many of these methods are not successful for the general synthesis of flavones due to low yields and the formation of different products (flavone, aurones, flavanols, and flavanones) depending on the reaction conditions.
2.5 Heteroannulation Reactions

Substituted 4H-1-benzopyran-4-ones have classically been synthesized via a Claisen ester condensation followed by oxidative cyclization or a Baker-Venkataraman rearrangement. Besides requiring harsh acidic conditions for the final condensation step, these approaches also suffer from poor substituent tolerance and low yields. An alternative approach for the synthesis of benzopyranones involves heteroannulation reactions in which o-iodophenols react with terminal acetylenes in the presence of a base and palladium catalyst to undergo a carbonylative cyclization (Figure 2.12). A drawback to this chemistry in the past has been the requirement of high CO pressures and the formation of a mixture of benzopyranones and benzofuranones [97-99]. Recently, by using a new palladium complex as a catalyst (PdCl$_2$(Ph$_3$P)$_2$-thiourea-dppp), a highly efficient carbonylative cyclization of o-acetoxyiodobenzenes with aryl acetylenes to construct the corresponding flavones under mild conditions has been developed [100]. In developing our synthetic strategy, we wanted mild, high yielding reactions that would tolerate various functional groups to give exclusively the benzopyranone ring system, and still be amenable to solid-phase chemistry.
Figure 2.12: Prevalent literature methods for the synthesis of benzopyranones include heteroannulation reactions.

2.6 SYNTHETIC RATIONALE

Many investigators have researched the palladium-catalyzed carbonylative coupling of o-iodophenols with terminal alkynes and subsequent cyclization to form a mixture of 4H-1-benzopyran-4-ones and 3-(2H)-benzofuranones. A major drawback of this chemistry is the requirement for high carbon monoxide (CO) pressures and elevated temperatures to afford the alkynone intermediate, which upon cyclization produces a mixture of products. Because of our exclusive interests in the synthesis of benzopyranones and using chemistry applicable to solid phase, this chemistry at first glance was not ideally suited to our synthetic needs. However, upon closer inspection, this chemistry was more tolerant of various functional groups and provided higher yields than other existing protocols. If these problems could be resolved (i.e.; high CO pressure, high temperature, and non-regiospecific cyclization), a novel route for the regioselective formation of 4H-1-benzopyran-4-ones could possibly be developed.
Our solution phase chemistry studies started with the approach to synthesize 2-substituted-4'H-1-benzopyran-4-ones from the palladium-catalyzed oxidative coupling of salicylic acids with terminal alkynes. By beginning with salicylic acids, instead of O-iodophenols, we could alleviate the high CO pressures and high temperatures need for the CO insertion to make the alkynone intermediate. Not to mention, the use of inexpensive, commercially available starting materials like salicylic acids and terminal alkynes would be ideal. The carboxylic acid of salicylic acids is not able to directly couple with a terminal alkyne. However, the conversion of the carboxylic acid on the salicylic acid to an acid chloride would enable the palladium-catalyzed Sonogashira coupling. The scope of this one-step Sonogashira coupling for the preparation of 1-alkynyl-ketones (alkynones) by coupling acyl chlorides with terminal alkynes can be accomplished in good yields [101]. Thus, by making an acyl-chloride from salicylic acids, and coupling it with terminal alkynes under Sonogashira conditions, we could make our key carbon-carbon bond.

The second major problem to resolve was the non-regiospecific cyclization of the alkynone intermediate. As seen in the literature, a free phenolic hydroxyl can effect either a 6-endo-dig or 5-exo-dig cyclization resulting in the nonselective formation of benzopyranones and benzofuranones. We rationalized that if the phenol was protected via protecting group like tert-butyldimethylsilyl (TBS); cyclization would be prevented until its removal. Michael addition of a secondary amine to the alkynone would result in the formation of enaminoketones (β-aminovinyl ketones) [102]. We reasoned that if
the alkynones were first converted to enaminoketones and then subjected to TBS
deprotection, the system would be prone to undergo a 6-endo-trig cyclization resulting
in the regioselective formation of the 4\(H\)-1-benzopyran-4-ones. By using a secondary
amine addition to the alkynone, the synthetic strategy prevents the cyclization of the
competing five-membered benzofuranone and thus resolves the regioselectivity problem
encountered by previous efforts.

![Chemical structure](image)

**Figure 2.13:** Synthetic methodology for synthesis of substituted-4\(H\)-1-benzopyran-4-
one.

Depending upon the variety of salicylic acids and terminal alkynes chosen, a diverse
library of 2-substituted-4\(H\)-1-benzopyran-4-ones can be synthesized. Synthetic
approaches for diversifying the benzopyranone skeleton have also been pursued;
substituents at the 3-position on the ring system would dramatically increase the
diversity of our library. Evaluation of the synthetic benzopyranone library in initial
bioassays (cell proliferation, aromatase inhibition, and estrogen receptor binding) using
human breast cancer cell lines has resulted in agents exhibiting enhanced and differential activities on breast cancer cell growth and aromatase inhibition. Continued synthetic efforts will concentrate on development of more selective agents for molecular targets in breast cancer based upon the benzopyranone nucleus.
CHAPTER 3

FORMATION OF ALKYNONE INTERMEDIATES VIA ACID CHLORINATION AND SONOGASHIRA COUPLINGS

3.1 ACID CHLORINATION

Various methods of acid chloride formation from carboxylic acids are reported in the literature. Table 3.1 compares the features of various reagents including thionyl chloride, oxalyl chloride, phosphorus compounds, and benzoyl chlorides for the formation of acid chlorides from carboxylic acids. The volatile reagents thionyl chloride and oxalyl chloride are often used for the formation of acid chlorides from carboxylic acids not only because they may be used in excess but evaporation of excess reagent affords the acid chloride product with good levels of purity [103]. An additional advantage for these reactions is the formation of gaseous by-products, both sulfur dioxide and HCl gas with thionyl chloride and carbon monoxide, carbon dioxide, and HCl gas with oxalyl chloride. Because this conversion involves acidic conditions, its application is limited to starting materials that lack acid-sensitive functionalities. The end point of this reaction is often judged once the evolution of gas has stopped. DMF (dimethylformamide) is often added as a catalyst to accelerate the reaction;
allowing the reaction to be conducted at room temperature or for shorter reaction times [103]. The amount of DMF added is typically catalytic, such as one or two drops of DMF are added.

<table>
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<th>(COCl)₂</th>
<th>PPh₃CCl₂</th>
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<td>63-64</td>
<td>198-199</td>
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<tr>
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<td>126.93</td>
<td>140.57</td>
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<td>Relative cost</td>
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<td>15</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>By-products</td>
<td>SO₂, HCl</td>
<td>CO₂, HCl, HCl</td>
<td>Ph₂CO, HCl₃</td>
<td>PhCO₂H</td>
</tr>
<tr>
<td>Advantages</td>
<td>Simple workup</td>
<td>DMF catalyzed</td>
<td>Neutral conditions</td>
<td>Good for low b.p. products</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Harsh conditions</td>
<td>Pyridine to remove</td>
<td>Removal of Ph₃PO</td>
<td>Need excess reagent</td>
</tr>
<tr>
<td></td>
<td>Not compatible with alkynes or acid-sensitive compounds</td>
<td>HCl if necessary</td>
<td>Expensive</td>
<td>Not well documented</td>
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<tr>
<td></td>
<td>Storage problems</td>
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<td>Not good for high b.p. products</td>
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<td>Expensive</td>
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</tr>
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</table>

Table 3.1: Comparison of reagents for the formation of acid chlorides [103].

3.2 USING OXALYL CHLORIDE

Adams and Ulich first introduced oxalyl chloride as a reagent for the conversion of carboxylic acids to the corresponding acid chlorides in 1920 [103]. The general reaction scheme is shown in Figure 3.1. Oxalyl chloride reacts with a carboxylic acid forming the desired acid chloride as well as carbon monoxide, carbon dioxide, and hydrogen chloride gas. In most cases, this reaction is performed at room temperature in an inert solvent such as benzene or dichloromethane in the presence of catalytic

43
amounts of DMF. Typically, the reaction is complete after 12h; however, the reaction is often substrate dependent. This reaction can often be judged complete when gas evolution ceases.

\[
\text{Cl}_2\text{CCl}_2 + \text{R} \cdot \text{OH} \rightarrow \text{R} \cdot \text{Cl} + \text{HCl} + \text{CO} + \text{CO}_2
\]

Figure 3.1: General reaction scheme for acid chlorination of carboxylic acids using oxalyl chloride to produce acid chloride with carbon monoxide, carbon dioxide, and hydrogen chloride.

Until 1978, most methods accomplished the conversion of carboxylic acids into acid chlorides under acidic conditions. At that time, Wissner and Grudzinskas reported a methodology for forming carboxylic acid chlorides under neutral conditions [104]. In this communication, it was demonstrated that the reaction of tert-butyldimethylsilyl (TBS) esters with oxalyl chloride in the presence of catalytic amounts of DMF was an effective way to generate acid chlorides under neutral conditions [104]. In this reaction, TBS esters react with oxalyl chloride with catalytic amounts of DMF to generate the acid chloride, carbon dioxide, carbon monoxide, and TBS chloride in excellent yields (87-92%) (Figure 3.2). The proposed mechanism for the acid chlorination is shown in Figure 3.3 and involves the formation of dimethylformiminium chloride as the reactive intermediate. From the mechanism, it can be seen that tert-butyldimethylchlorosilane is generated instead of HCl, thus occurring under neutral conditions. Wissner et al. also reported that TBS ethers are stable to oxalyl chloride-DMF in the presence of TBS.
Figure 3.2: Preparation of acid chlorides under neutral conditions using tert-butyldimethylsilyl esters with oxalyl chloride and DMF [104].

Figure 3.3: Proposed mechanism of the acid chlorination of tert-butyldimethylsilyl esters with oxalyl chloride in the presence of DMF implicating dimethylformiminium chloride as the reactive intermediate.

esters under these reaction conditions [104]. In fact, this method was shown to be particularly useful for the preparation of acid chlorides derived from hydroxy-benzoic acids. The hydroxy-benzoic acid can be bis-silylated in a single step, converted to the corresponding acid chloride and then to the ethyl ester in yields of 98% [104] (Figure 3.4).
The key alkynone intermediate is synthesized by coupling acyl chlorides with terminal alkynes via a Sonogashira coupling. Acid chloride generation using oxalyl chloride produces volatile by-products that simply can be removed in vacuo. Therefore, we believed that the acid chloride generation could be followed directly by the Sonogashira coupling without intermediate purification resulting in a one-pot acid chlorination/Sonogashira coupling. To demonstrate the feasibility of a one-pot acid chlorination/Sonogashira coupling, 4-methoxy-bis-TBS-salicylic acid was used to determine if the acid chloride was generated cleanly and in high yield. To synthesize the acid chloride, oxalyl chloride (1.2 mmol) was added to a cold solution (0°C) of bis-TBS-salicylic acid in dichloromethane with 3 drops of DMF [104]. The resulting solution was stirred at 0°C for two hours. The reaction was then warmed to room temperature and stirred overnight. When the reaction was quenched with an ethanol in pyridine/ether (1:1:1) mixture, the ethyl ester was isolated in 77-91%, indicative of the clean formation of the acid chloride. Figure 3.5 illustrates the yields of the conversion of the TBS esters to the ethyl ester with various methoxy substituents.
3.3 PROTECTIONS OF SALICYLIC ACIDS

Our synthetic rationale of using substituted salicylic acids as starting materials to synthesize the benzopyranone ring system is a direct application of Wissner and Grudzinskas communication. Thus, commercially available salicylic acid was used to optimize tert-butyldimethylsilyl (TBS) protection procedures. Both the carboxylic acid and phenolic hydroxyl of salicylic acid can be silylated in a single step. Initial protection procedures using tert-butyl(dimethyl)silane, imidazole, and DMAP in DMF were not always successful. Protection of 2,4-dihydroxybenzoic acid or 5-bromo-salicylic acid with tert-butyldimethylchlorosilane, imidazole, 4-dimethylaminopyridine (DMAP) in DMF provided the tri-silated derivative in 66% yield and the bis-silated in 43-75% yield [105]. Although these conditions provided the silylated salicylic acids in good yields, these conditions did not always work in all cases at all times. Often, the steric bulk of the tert-butyl group significantly diminishes the rate of silylation. Even when using the
basic activators, imidazole and DMAP, and performing the reaction in the dipolar aprotic solvent DMF, silylation was slow and inconsistent [106]. Salicylic acid was treated with 2.2 equiv of t-BuMe₂SiCl and triethylamine in CH₂Cl₂ to generate the bis-TBS protected salicylic acid in quantitative yield [107]. Salicylic acid could be protected in most cases in quantitative yields using tert-butyldimethylchlorosilane with Et₃N in dichloromethane regardless of the substitution pattern as illustrated in Figure 3.6.

![Figure 3.6: Protection of salicylic acid using tert-butyldimethylsilyl chloride and triethylamine in dichloromethane occurs in quantitative yield [107].](image)

3.4 SUBSTITUTED SALICYLIC ACIDS USED

This methodology was used to protect a variety of substituted salicylic acids including halogen, aromatic, methoxy, amine, and alkyl functionalities at the three, four, five, and six positions. The salicylic acids that were formed following the TBS protection in yields ranging from 88-100% can be seen in Figure 3.7.

Many salicylic acids are commercially available or can be readily synthesized. 4-Methoxysalicylic acid can also be prepared in 50% yield by selective methylation of the 4-hydroxyl group of 2,4-dihydroxybenzoic acid using dimethylsulfate in a 20%
solution of sodium hydroxide (Figure 3.8) [108]. 5-Phenylsalicylic acid was prepared in 91% yield by an aqueous Suzuki coupling of 5-bromosalicylic acid and phenylboronic acid in the presence of Pd(OAc)$_2$ as the base [109]. 5-(tert-Butoxycarbonyl)-aminosalicylic acid was synthesized via the Boc protection of 5-aminosalicylic acid with di-tert-butyloxycarbonate in dioxane-H$_2$O and Et$_3$N [110].

![Figure 3.7: Substituted salicylic acids and the yields resulting from the protection with TBS-Cl.](image)

![Figure 3.8: Preparation of 4-methoxysalicylic acid by selective methylation of 2,4-dihydroxybenzoic acid using dimethylsulfate $((CH_3O)_2SO_2$) in a 20% solution of sodium hydroxide [108].](image)
Figure 3.9: Preparation of 5-phenylsalicylic acid and NHBoc-salicylic acid. 5-Phenylsalicylic acid was prepared by an aqueous Suzuki coupling of 5-bromosalicylic acid and phenylboronic acid in the presence of Pd(OAc)$_2$ with Na$_2$CO$_3$ as the base [109]. 5-((tert-Butoxycarbonyl)aminosalicylic acid was synthesized via the Boc protection of 5-aminoosalicylic acid with di-tert-butylcarbonate in dioxane-H$_2$O and Et$_3$N [110].

3.5 THE SONOGASHIRA COUPLING

Carbon-carbon bond forming reactions, especially those that are simple, efficient, high yielding, and tolerant of a wide range of functional groups, are important in organic synthesis. One such reaction, developed in 1975 by Sonogashira, typically involves the coupling of terminal alkynes with aryl or alkenyl halides in the presence of catalytic amounts of palladium (II) and copper (I) iodide in an amine solvent [111]. The general forms of this reaction are shown in Figure 3.10.
Kenkichi Sonogashira developed this reaction at the same time as both Heck and Cassar reported a similar process. However, their methods for making a carbon-carbon bond lacked the involvement of copper as a catalyst and required more forcing conditions. The most common derivation of the Sonogashira coupling is the coupling of an aromatic iodide with a terminal alkyne at room temperature. Typically, this reaction is complete in a few hours, although often left overnight. It has been noted that dramatic color changes occur during the time course of the reaction but not in a predictive manner.
Sonogashira originally used palladium (II) (i.e., \( \text{PdCl}_2(\text{PPh}_3)_2 \)) and copper (I) iodide as co-catalysts in this reaction. However, other palladium (I) and (II) catalysts can be found in the literature to catalyze the reaction (i.e. \( \text{Pd(PPh}_3)_4 \), \( \text{Pd(0Ac)}_2\text{PPh}_3 \), and polymer-bound palladium-phoshine) \[113\]. Copper (I) iodide has been found to be essential for the Sonogashira reaction to proceed at room temperature, which agrees with synthetic efforts in this laboratory. In our laboratory, Sonogashira couplings in the presence of \( \text{PdCl}_2(\text{PPh}_3)_2 \) without copper iodide were not successful.

More recent reports challenge the use of palladium as a co-catalyst. Chowdhury et al. report that acylation of terminal alkynes can be effected in the presence of 5 mol% copper (I) iodide without the need for a palladium catalyst to synthesize \( \alpha,\beta \)-acetylenic ketones with yields ranging from 48-83% (Figure 3.11) \[114,115\]. This reaction has been shown to be applicable to aryl, heteroaryl, or alkyl terminal alkynes and aryl or branched acid chlorides \[114\]. Under these conditions, the acid chloride had to be aromatic; straight chain aliphatic acid chlorides did not work. Mechanistically, it is proposed that the acid chloride reacts with a copper acetylide reactive intermediate leading to the formation of the acetylenic ketone. This process eliminates the possibility of the competing oxidative homocoupling of alkynes, known as the Glaser coupling which are usually formed in the presence of palladium \[115\]. This methodology was used to prepare a uracil derivative with an acetylenic ketone functionality substituted at the C-5 position from the corresponding 5-ethynyl-2,4-dimethoxy pyrimidine and \( p \)-toluoyl chloride \[115\].
The scope of this one-step Sonogashira coupling was extended to include the preparation of 1-alkynyl ketones (Figure 3.10). Aliphatic and acyl chlorides can be coupled with terminal alkynes in triethylamine with \( \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \) and \( \text{CuI} \) as seen in Figure 3.10 to afford the desired ketones in good yields [112]. Under these conditions, the highest yield was observed for coupling an acyl chloride with phenylacetylene. Yields decreased when either coupling partner is aliphatic.

Thorand et al. have shown that by coupling \( p \)-substituted-aryl bromides with terminal alkynes with catalytic amounts of \( \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \) and \( \text{CuI} \) in triethylamine and THF as solvent at room temperature produce arylalkynes in excellent yields (>82%) [116]. Their results suggest an increase of reactivity when the coupling is performed in THF instead of an amine as solvent. This is a marked improvement to literature methods for aryl bromide couplings, which due to their rather low reactivity require harsh conditions.
(i.e., high temperatures). The Glaser coupling was seen only in trace amounts (<5%). This side reaction is believed to be minimized due to the slow addition of the alkyne which keeps its concentration in the reaction mixture low [116].

Fu et al. reports the use of Pd(PhCN)2Cl2/P(r-Bu)3 as an efficient catalyst for room-temperature Sonogashira reactions of aryl bromides, which are the least reactive of the commonly employed organic halides (vinyl iodide, vinyl bromide > aryl iodide > vinyl chloride >> aryl bromide) [117].

The exact mechanism of the Sonogashira coupling is not known; however, the proposed mechanism is shown in Figure 3.12 [118]. It follows the normal oxidative addition-reductive elimination process common to palladium-catalyzed carbon-carbon bond forming reactions. The process involves generating the active palladium (0) species 1 which inserts via oxidative addition into the acyl chloride bond to give the acylpalladium (II) intermediate 2. Subsequent transmetallation of the acylpalladium intermediate 2 with the terminal alkyne, possibly via a transient copper acetylide species, leads to the alkynylpalladium (II) derivative 3. Derivative 3 can collapse via a reductive elimination to form the product and regeneration of the Pd(PPh3)2Cl2 catalyst. The rate determining step of the reaction is the oxidative addition (step i) of the aryl/acyl halide to the palladium (0) species. The reaction can be carried out without the presence of the copper (I) iodide with more stringent forcing conditions and more active substrates [118].
Figure 3.12: Proposed mechanism of the Sonogashira coupling which involves (i) oxidative addition, (ii) transmetallation, and (iii) reductive elimination steps [118,119].

The proposed mechanism, as shown in Figure 3.12 in one catalytic cycle, is more accurately believed to be a combination of two catalytic cycles [119]. Figure 3.13 shows the second catalytic cycle, which involves the formation of the unsaturated 14-electron complex Pd(0)(PPh₃)₂. The complex Pd(0)(PPh₃)₂ is produced by the reductive elimination of a Pd-acetylide complex generated by the transmetallation of the palladium (II) catalyst, PdCl₄(PPh₃)₂ with a terminal acetylene.
Various reaction conditions have been used for the Sonogashira coupling depending upon the reactivity profile of the starting materials. The reactivity of the organic halides for coupling decreases in the order vinyl iodide \( \approx \) vinyl bromide > aryl iodide > vinyl chloride >> aryl bromide [119]. Aryl halides that have electron-withdrawing groups ortho or para to the halide react more readily [118]. This can be correlated to the mechanism in that the more electron-deficient the aryl halide, the more rapidly the Pd(0) species can insert, or rather undergo oxidative addition to the aryl-halide [118]. Various amines have been used as solvent and play a critical role in the coupling. The rate of the reaction depends upon the type of amine used and decreases in the order \( n{-}BuNH_2 > Et_3N > i{-}Pr_2NH > Et_2NH > K_2CO_3 \) [119].
3.6 SYNTHESIS OF THE PALLADIUM CATALYST

The palladium (II) catalyst dichlorobis(triphenylphosphine)palladium (Pd(PPh3)2Cl2) is commercially available. It also can be readily synthesized following the literature procedure of Herrman & Salzer in which sodium tetrachloropalladate (II) (0.5 g, 1.7 mmol) and triphenylphosphine (0.95 g, 3.6 mmol) are suspended in EtOH (50 mL) under argon and stirred at room temperature for 24 h [120]. Upon addition of triphenylphosphine to sodium tetrachloropalladate solution, color change from brownish red to yellow. The resulting reaction mixture was filtered by gravity to give a yellow precipitate, which was further washed with H2O, EtOH, and Et2O. Solid was recrystallized from CHCl3/petroleum ether to yield 1.1 g (90%) of the title compound as a yellow powder. The Pd catalyst is stable for long term storage.

3.7 GLASER COUPLING

In 1869, the synthesis of the symmetrical diphenylbutadiyne from phenylacetylene and air was performed by Glaser [121]. Glaser's procedure involved using preformed copper acetylides that undergo an oxidative homocoupling according to the equation in Figure 3.14. Variations of this chemistry have since been used to produce a large variety of acetylenic compounds that have been in essence dimerized to form diynes. The amount of copper needed is usually stoichiometric. The Glaser coupling of terminal alkynes is an important side reaction that sometimes occurs during the Sonogashira coupling. Hence, reaction conditions need to minimize the Glaser homocoupling in the presence of the Sonogashira coupling.
The overall equation of the Glaser homocoupling of terminal alkynes in the presence of copper [121].

**3.8 Functional Group Compatibility Of The Sonogashira Coupling**

**3.8.1 Initial Couplings With Phenylacetylene**

Efforts to synthesize the alkynyl ketones via the Sonogashira coupling were initially investigated using salicylic acid and phenylacetylene. The scope of the Sonogashira coupling includes the condensation of copper(I) salts of alkynes with acylhalides to provide a useful synthesis of 1-alkynyl ketones. As seen in Figure 3.15, acyl chloride can be coupled with phenylacetylene in Et₃N in presence of CuI and Pd(PPh₃)₂Cl₂ as catalysts to provide the alkynyl ketone in a yield of 96% [112]. This method seemed advantageous to synthesize the alkynyl ketones that we were interested in because it is a one step condensation reaction, employs mild reaction conditions, and is amenable to combinatorial applications.

![Diagram of chemical reaction](image-url)

Figure 3.15: An acyl chloride can be coupled with phenylacetylene under Sonogashira conditions (Et₃N in the presence of CuI and Pd(PPh₃)₂Cl₂ as co-catalysts) to provide the alkynyl ketone in a yield of 96% [112].
Figure 3.16 shows one example from the literature where a salicyloyl chloride was coupled with phenylacetylene. In this example, salicyloyl chloride was coupled with phenylacetylene in trioctylamine at 50°C for six hours with Pd₂(dba₃) catalyst resulting in the formation of the alkynyl ketone in 56% yield, the benzopyranone in 14% yield, and the benzofuranone in 19% yield [122]. The outcome and product distribution of this reaction suggests that the free phenol in the ortho position influences the reaction.

Previous efforts in our laboratory attempting to synthesize the alkynone from the salicyloyl chloride and phenylacetylene failed using various conditions (Figure 3.17). A Stille reaction with allyltributyltin also failed to give any coupled product (Figure 3.17) [105]. These coupling experiments emphasized the need for protecting the phenol during the coupling reaction. It was our hypothesis that, as a result of protecting the latent hydroxy group as a TBS ether, the cyclization forming both the benzopyranone and benzofuranone would be prevented and the alkynone could be isolated in high yield. Initial attempts of a Stille coupling of TBS-salicyloyl chloride with allyltributyltin also failed (Figure 3.18).
Figure 3.17: Previous attempts in this laboratory to synthesize alkynyl ketones from salicyloyl chloride via Sonogashira or Stille reaction conditions failed [105].

Figure 3.18: Stille coupling of TBS-salicyloyl chloride with allyltributyltin using either Pd(PPh₃)₂Cl₂ in refluxing toluene or Pd(PPh₃)₄ in refluxing THF failed to provide a coupled product.

Our laboratory initially examined the coupling reactions between phenylacetylene and the acid chlorides generated from bis-TBS-salicylic acid under Sonogashira coupling conditions. The acid chloride (1 mmol) in 4 mL of Et₃N was treated with phenylacetylene (1 equiv), 1 mg of Cul, and 1 mg of Pd(PPh₃)₂Cl₂. The reaction was stirred for 15 hours under argon and after workup and flash chromatography provided the alkynyl ketone in >80% yield. This reaction was unsuccessful when attempted with only the copper salts (Cul or CuCl) in absence of the Pd catalyst. In addition, other
palladium catalysts were evaluated including Pd(PPh₃)₄ and PhCH₂Pd(PPh₃)Cl₂, however, complex mixtures of unidentifiable products were obtained.

The usefulness of the Sonogashira coupling as it relates to electronic and steric requirements of the terminal alkyne was determined. When using aliphatic and aromatic alkynes in conjunction with the Pd(PPh₃)₂Cl₂ and CuI catalysts in Et₃N, it was determined that using an excess of alkyne was optimal. Previous experimentation in our laboratory established that using 7 equivalents of aliphatic or 4 equivalents of aromatic alkynes was often necessary [105,123]. Because the homocoupling of alkynes is catalyzed in the presence of molecular oxygen, the reaction mixtures were deoxygenated by bubbling argon directly into the reaction mixture thereby reducing the formation of dieynes [116]. In order to determine the generality of the one-pot acid chlorination/Sonogashira coupling, various terminal alkynes including 4-ethynyl-toluene, 5-chloro-1-pentyne, methyl propargyl ether, propiolaldehyde diethyl acetal, 2-methyl-3-butyn-2-ol, and 1-ethynyl-1-cyclohexene were coupled to salicylic acid under these procedures resulting in alkynone formation in moderate to excellent yields (74-96%) (Figure 3.19) [105,123]. Initial investigations of Sonogashira coupling illustrated the usefulness for the formation of alkynones from silylated salicylic acids.
Figure 3.19: Various terminal alkynes including 4-ethynyltoluene, 5-chloro-1-pentyne, methyl propargyl ether, propiolaldehyde diethyl acetal, 2-methyl-3-butyn-2-ol, and 1-ethynyl-1-cyclohexene were coupled to bis-TBS-salicylic acid via a one-pot acid chlorination/Sonogashira coupling resulting in alkynone formation in moderate to excellent yields (74-96%) [105,123].

3.8.2 Sonogashira Coupling of Phenylacetylene with Substituted Salicylic Acids

Substituted bis-TBS-salicylic acids were coupled with phenylacetylene to evaluate the effect of substitutions of the salicylic acid component on the coupling reaction. The bis-TBS-salicylic acids used were 4-methoxy-bis-TBS-salicylic acid, 4-chloro-bis-TBS-salicylic acid, 5-phenyl-bis-TBS-salicylic acid, and 5-NHBoc-bis-TBS-salicylic acid. All of the coupling reactions gave the desired alkynones in excellent yields (78-92%).
The acid sensitive NH-Boc functionality is successfully carried through the acid chlorination step, emphasizing the mild nature of the reaction conditions. The synthesis of 5-phenylsalicylic acid and 5-NHBoc-salicylic acid is depicted in Figure 3.9.

The acid sensitive NH-Boc functionality is successfully carried through the acid chlorination step, emphasizing the mild nature of the reaction conditions. The synthesis of 5-phenylsalicylic acid and 5-NHBoc-salicylic acid is depicted in Figure 3.9.

\[ \begin{align*}
\text{Salicylic Acid} & \xrightarrow{\text{(COCl)}_2, \text{cat. DMF}} \text{Cl-Salicylic Acid} \\
\text{Cl-Salicylic Acid} & \xrightarrow{\text{Ph$_2$P(Ph)$_3$, CuI, Et$_2$N}} \text{Alkynone}
\end{align*} \]

<table>
<thead>
<tr>
<th>R</th>
<th>% Yield of Alkynone</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Ph</td>
<td>99%</td>
</tr>
<tr>
<td>4-OCH$_3$</td>
<td>92%</td>
</tr>
<tr>
<td>4-Cl</td>
<td>83%</td>
</tr>
<tr>
<td>5-NHBoc</td>
<td>78%</td>
</tr>
</tbody>
</table>

Figure 3.20: Substituted bis-TBS-salicylic acids (i.e.; 4-methoxy-bis-TBS-salicylic acid, 4-chloro-bis-TBS-salicylic acid, 5-phenyl-bis-TBS-salicylic acid, and 5-NHBoc-bis-TBS-salicylic acid) undergo a one-pot acid chlorination/Sonogashira coupling with phenylacetylene to provide the corresponding alkynones [105,123].

3.9 EXAMINING THE SCOPE OF THE SONOGASHIRA COUPLING

3.9.1 SONOGASHIRA COUPLING VARIATIONS USED

Various conditions (scale of reaction, equivalents of alkyne, time, and coupling procedure) used for the Sonogashira coupling of bis-TBS-salicylic acid, 3-methyl-bis-TBS-salicylic acid, 3-methoxy-bis-TBS-salicylic acid, 4-methoxy-bis-TBS-salicylic acid, 4-methyl-bis-TBS-salicylic acid, 4-chloro-bis-TBS-salicylic acid, 5-chloro-bis-TBS-salicylic acid, and 5-phenyl-bis-TBS-salicylic acid are illustrated in Table 3.2 and Table 3.3. There were four different procedures used for the couplings and include:
**Coupling A:** Et$_3$N added to acid chloride followed by deoxygenation. Alkyne, Pd(PPh$_3$)$_2$Cl$_2$, and Cul added followed by deoxygenation. **Coupling A**: This is the same procedure as A but without deoxygenation. **Coupling B:** Et$_3$N added to acid chloride and deoxygenated. Alkyne and Cul added and deoxygenated. Pd(PPh$_3$)$_2$Cl$_2$ added and deoxygenated. **Coupling C:** Et$_3$N, alkyne, and Cul are stirred under argon for 15 min, followed by cannulation into acid chloride and finally addition of Pd(PPh$_3$)$_2$Cl$_2$. Deoxygenation is defined as bubbling argon directly into the reaction to remove any trace amounts of oxygen. **Coupling D:** Et$_3$N added to acid chloride followed by deoxygenation. Pd(PPh$_3$)$_2$Cl$_2$ and Cul added and deoxygenated. Alkyne (1.2 equiv) is added followed by an additional 1.2 equiv of alkyne added 4 h later. It is believed that the slow addition of alkyne keeps its concentration low in the reaction, thus reducing the Glaser coupling [116].

### 3.9.2 Sonogashira Couplings with 4-Methoxysalicylic Acid

Because the one-pot acid chlorination/Sonogashira coupling reaction is key for introducing diversity to our solution phase library of benzopyranones, the scope of this reaction was examined in closer detail. 4-Methoxysalicylic acid was initially chosen to examine more closely because of the placement of the methoxy group. Many active flavonoids have hydroxyl groups at this position; therefore it would be advantageous to make 7-hydroxy or 7-methoxybenzopyranones for further biological evaluation.
4-Methoxy-"bis"-TBS-salicylic acid coupled with phenylacetylene in high yield (92%) and the effect of an electron-donating group para to the acid chloride could also be determined.

![Chemical structure of 4-Methoxy-6-TBS-salicylic acid coupled with phenylacetylene.]

**Figure 3.21:** % Yields of one-pot acid chlorination and Sonogashira coupling of various terminal alkynes with 4-methoxysalicylic acid. The alkynes used were phenylacetylene, 4-ethynyltoluene, 1-ethynyl-1-cyclohexene, propiolaldehyde diethyl acetal, 5-chloro-1-pentyne, and 1-pentyne.

4-Methoxysalicylic acid was treated with TBS-Cl (2.2 equiv) and Et₃N in CH₂Cl₂ to generate 4-methoxy-"bis"-TBS-salicylic acid in quantitative yield (Figure 3.7) [107]. The protected salicylic acid was reacted with 1.2 equivalents of oxalyl chloride in the presence of catalytic amounts of DMF in CH₂Cl₂ to provide the acid chloride under neutral conditions [104]. Previous experiments demonstrated the clean formation of the acid chloride in high yields (Figure 3.5). The acid chloride was concentrated *in vacuo* and followed directly by the Sonogashira coupling. Following *Coupling A* for the
Sonogashira coupling, the acid chloride in triethylamine was reacted with phenylacetylene, in the presence of catalytic amounts of Pd(PPh3)2Cl2 and CuI to give the desired alkynone in 92% yield (Figure 3.21, Table 3.2) [112]. As seen in Table 3.2, the effect of varying the equivalents of phenylacetylene and reaction time were examined for this coupling. Shorter reaction times (3-5 h) gave higher yields (92-96%), in both small scale (0.7 mmol) and large scale (5.1 mmol) reactions. In the majority of experiments, an excess (4-5 mol excess) of phenylacetylene was used. The % yield of alkynone decreased to 54% when DMF was not used in the acid chlorination reaction.

To determine the generality of the one-pot acid chlorination/Sonogashira coupling, various terminal alkynes (aromatic, alkyl, acetal) were coupled to 4-methoxysalicylic acid under the same procedures (Figure 3.21) resulting in alkynone formation in moderate to excellent yields (42-90%). Based on further experimentation (Table 3.2), optimal yields of alkynone can be achieved on a case by case basis. For example, a yield of 96% resulted when phenylacetylene (4 equiv) was coupled for 4 hours with Coupling C; a yield of 57% resulted with 5-chloro-1-pentyne (10 equiv) was coupled for 5 hours with Coupling B; and finally a yield of 84% resulted when propiolaldehyde diethyl acetal (5 equiv) was coupled for 19.5 hours with Coupling A.
<table>
<thead>
<tr>
<th>Notebook #</th>
<th>Salicylic acid</th>
<th>Alkyne</th>
<th>Scale (mmol)</th>
<th>Alkyne (equival)</th>
<th>Time (h)</th>
<th>Procedure</th>
<th>% Yield</th>
</tr>
</thead>
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<td>I-108</td>
<td>4-OCH₃</td>
<td>phenylacetylene</td>
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<td>3</td>
<td>22</td>
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<td>91%</td>
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<td>5</td>
<td>3.5</td>
<td>A</td>
<td>92-95%</td>
</tr>
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<td>phenylacetylene</td>
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<td>5</td>
<td>24</td>
<td>A</td>
<td>64%</td>
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<td>1.2</td>
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<td>A&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>phenylacetylene</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>C</td>
<td>81%</td>
</tr>
<tr>
<td>I-212</td>
<td>4-OCH₃</td>
<td>phenylacetylene</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>C</td>
<td>96%</td>
</tr>
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<td>4-OCH₃</td>
<td>phenylacetylene</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>C</td>
<td>76%</td>
</tr>
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<td>I-114</td>
<td>4-OCH₃</td>
<td>4-ethyltoluene</td>
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<td>4-OCH₃</td>
<td>4-ethyltoluene</td>
<td>2.7</td>
<td>3</td>
<td>4</td>
<td>A</td>
<td>no reaction; H&lt;sup&gt;N&lt;/sup&gt;M indicates MNA ester</td>
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<td>1-ethyl-1-cyclohexene</td>
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<td>1-ethyl-1-cyclohexene</td>
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<td>50%</td>
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<td>1-ethyl-1-cyclohexene</td>
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<td>89%</td>
</tr>
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<td>5-chloro-1-pentyl</td>
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<td>21</td>
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<td>10</td>
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<td>A</td>
<td>42%</td>
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<td>I-201</td>
<td>4-OCH₃</td>
<td>5-chloro-1-pentyl</td>
<td>1.1</td>
<td>10</td>
<td>5</td>
<td>B</td>
<td>57%</td>
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<tr>
<td>II-024</td>
<td>4-OCH₃</td>
<td>1-pentyl</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>A</td>
<td>99%</td>
</tr>
<tr>
<td>II-032</td>
<td>4-OCH₃</td>
<td>1-pentyl</td>
<td>2.5</td>
<td>3</td>
<td>4.5</td>
<td>A</td>
<td>89%</td>
</tr>
<tr>
<td>I-115</td>
<td>4-OCH₃</td>
<td>propiolaldehyde diethyl acetal</td>
<td>1</td>
<td>5</td>
<td>19.5</td>
<td>A</td>
<td>84%</td>
</tr>
<tr>
<td>I-135</td>
<td>4-OCH₃</td>
<td>propiolaldehyde diethyl acetal</td>
<td>0.53</td>
<td>5</td>
<td>20.5</td>
<td>A</td>
<td>66%</td>
</tr>
<tr>
<td>I-195</td>
<td>4-OCH₃</td>
<td>propiolaldehyde diethyl acetal</td>
<td>1</td>
<td>2.4</td>
<td>25</td>
<td>D</td>
<td>29% benzofuranone</td>
</tr>
<tr>
<td>I-219</td>
<td>4-OCH₃</td>
<td>propiolaldehyde diethyl acetal</td>
<td>1</td>
<td>5</td>
<td>19</td>
<td>C</td>
<td>24%</td>
</tr>
</tbody>
</table>

A: Et₃N added to acid chloride followed by decarboxylation. Alkyne, Pd(PPh₃)₂Cl₂, and CuI added followed by decarboxylation.
B: Et₃N added to acid chloride followed by decarboxylation. Alkyne and CuI added followed by decarboxylation. Pd(PPh₃)₂Cl₂ added followed by decarboxylation.
C: Et₃N, alkene, and CuI are cannulated into acid chloride after being stirred under argon for 15 min, followed by cannulation into acid chloride and addition of Pd(PPh₃)₂Cl₂.
D: Et₃N added to acid chloride followed by decarboxylation. Pd(PPh₃)₂Cl₂ and CuI added and decarboxylated. Alkyne (1.2 eq) is added, another 1.2 eq added 4 h later.

Table 3.2: Effects of various procedures on the % yield of alkenyne formation for the Sonogashira coupling of 2-[[((1,1-dimethylethyl)dimethylsilyl]oxy]-4-methoxy-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester with terminal alkenes (phenylacetylene, 4-ethynyltoluene, 1-ethyl-1-cyclohexene, 5-chloro-1-pentyl, 1-pentene, propiolaldehyde diethyl acetal). The effects due to changing the scale of the reaction (mmol), the reaction time (h), and amount of alkyne (equivalents) can be evaluated (Notebook # refers to either JLW-I-xxx or JLW-II-xxx).
The electronics and steric s of the alkyne as well as the salicylic acid need to be considered when determining the optimal coupling conditions. The lowest yields (23-57%) were found when coupling 5-chloro-1-pentyne to 4-methoxy-bis-TBS-salicylic acid. To determine if this effect was due to an alkyl alkyne, 1-pentyne was coupled with 4-methoxy-bis-TBS-salicylic acid and resulted in yields of 89-99%. A dramatic difference in yield exists when comparing 5-chloro-1-pentyne and 1-pentyne. One suggestion is that the base Et$_3$N could be displacing the chloro group; however, no evidence of this has been found. Another possibility is that the Pd catalyst could be complexing with the chloro group on the alkyne forming an alternative palladium intermediate and thus not available for the coupling reaction. Yields are improved when a large excess (10 equiv) of 5-chloro-1-pentyne is used, suggesting another possibility that a higher amount of alkyne homocoupling exists which may explain thin-layer chromatography results.

3.9.3 SONOGASHIRA COUPLINGS WITH 3-METHOXY, 5-METHOXY, AND 6-METHOXY-SALICYLIC ACID

The effect of a methoxy substituent at the 3-, 4-, 5-, and 6-position of bis-silylated salicylic acid on the Sonogashira coupling was determined. A comparison of the yields of the one-pot acid chlorination and Sonogashira coupling for the various methoxy substitutions is illustrated in Figure 3.22. Details of the conditions of the reactions can be found in Table 3.3. Coupling 3-methoxy- and 5-methoxy-bis-TBS-salicylic acid with phenylacetylene resulted in similar coupling yields, i.e. 70% and 75% respectively. In both these cases, the methoxy was meta to the acid chloride. When the methoxy was
para to the acid chloride, as with 4-methoxy-*bis*-TBS-salicylic acid, a higher coupling yield was found only when coupling phenylacetylene. 6-Methoxy-*bis*-TBS-salicylic acid did not couple with phenylacetylene under the conditions used. As seen in Figure 3.5, the acid chloride was generated with 6-methoxy-*bis*-TBS-salicylic acid in good yield. Further studies investigating the effects of substituents at the 6-position (ortho) would be useful to determine if this is a general limitation of the Sonogashira coupling of acyl chlorides with terminal alkynes.

![Table showing coupling yields](image)

Figure 3.22: Comparison of % yields of one-pot acid chlorination and Sonogashira coupling of various terminal alkynes with 4-methoxy, 3-methoxy, 5-methoxy, and 6-methoxy-*bis*-TBS-salicylic acid. The alkynes used were phenylacetylene, 4-ethynyl-toluene, 1-ethynyl-1-cyclohexene, and 5-chloro-1-pentyne. ** The overall yield for coupling and cyclization is 22%. 

69
<table>
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<th>Alkyne</th>
<th>Scale (mmol)</th>
<th>Alkyne (µl)</th>
<th>Time (h)</th>
<th>Coupling Procedure</th>
<th>Alkyne</th>
<th>% Yield</th>
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<td>overnight</td>
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<td>no reaction</td>
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<td>4</td>
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<td></td>
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<td>23%</td>
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<td>ASB</td>
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<td>5-Ph</td>
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<td></td>
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<td></td>
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<td>3</td>
<td>overnight</td>
<td>B</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>ASB</td>
<td>5-Ph</td>
<td>propionaldehyde diethyl acetal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>81%</td>
</tr>
</tbody>
</table>

A Ei,N added to acid chloride followed by deoxygenation. Alkyne, Pd(PPh₃)₃Cl₂, and Cul added followed by deoxygenation.

A* Ei,N, alkyne, Pd(PPh₃)₃Cl₂, and Cul added to acid chloride sequentially without deoxygenation.

B Ei,N added to acid chloride followed by deoxygenation. Alkyne and Cul added followed by deoxygenation. Pd(PPh₃)₃Cl₂, added followed by deoxygenation.

C Ei,N, alkyne, and Cul are stirred under argon for 15 min, followed by cannulation.

Table 3.3: Effects of various procedures on the % yield of alkynone formation for the Sonogashira coupling (Notebook # refers to either JLW-I-xxx, JLW-II-xxx, or ASB [105]).
3.9.4 **SONOGASHIRA COUplings WITH 3-METHYLSALICYLYC ACID**

3-Methyl-bis-TBS-salicylic acid was coupled with phenylacetylene resulting in the formation of the alkynone in 88-92% yield following Coupling A (Table 3.3). Because the yield of this reaction was excellent, further examples of coupling 3-methyl-bis-TBS-salicylic acid with alkynes followed Coupling C and were immediately cyclized without isolation of the alkynone.

3.9.5 **SONOGASHIRA COUplings WITH 4-CHLOROSALICYLC ACID**

4-Chloro-bis-TBS-salicylic acid was coupled with of 4-ethynyltoluene (3 equiv) following Coupling B (allowing preformation of the copper acetylide species). The major product synthesized was the corresponding alkynone, isolated in 62% yield (Table 3.3). After flash chromatography, a minor amount of the cyclized benzopyranone (15 mg, 5% yield) and benzofuranone (57 mg, 21% yield) was evident by $^1$H NMR. Previous coupling attempts with 4-ethynyltoluene and 4-chloro-bis-TBS-salicylic acid resulted in the formation of a 40% mixture of two alkynones: one in which the alkyne not only coupled with the acid chloride, but also the aryl chloride at the 4-position (Figure 3.23).

![Figure 3.23: Sonogashira coupling of 4-chloro-bis-TBS-salicylic acid with 4-ethynyltoluene produces a mixture of products in 40% yield.](image-url)
Other couplings were examined with 4-chloro-\textit{bis}-TBS-salicylic acid, in each case following Coupling B. When coupling 4-chloro-\textit{bis}-TBS-salicylic acid with phenylacetylene (3 equiv), the alkynone was isolated in 84% yield, while a small amount of the corresponding benzopyranone was also isolated (~3% yield). When coupling with 1-ethynyl-1-cyclohexene (3 equiv), the coupling worked very well (~96%), however, cyclization resulted in an overall yield from the protected salicylic acid of 47% (previous efforts 70%). 4-Ethynyltoluene (3 equiv) was coupled with 4-chloro-\textit{bis}-TBS-salicylic acid at room temperature overnight under these conditions to yield 62% of the alkynone, 21% benzofuranone, and 5% benzopyranone. In each of these experiments, the coupling yields were moderate to high (62-96%) and yielded a small amount of either benzopyranone and/or benzofuranone. Coupling efforts with 5-chloro-1-pentyne (5 equiv) for 30 hours resulted in direct formation of the benzopyranone in 42% yield and no isolation of alkynone.

From experimental data collected, one can compare the effect of a methoxy and chloro substituent at the 4-position of silylated salicylic acids. In general, Sonogashira coupling yields are slightly lower with the 4-chloro-\textit{bis}-TBS-salicylic acid. However, it can also be said that lower yields are seen when the 4-chloro is coupled with aromatic alkynes. This is exemplified by the example shown in Figure 3.23 where 4-ethynyltoluene in fact coupled with the aryl chloride. Possibly, the chloro group when \textit{para} to the acid chloride can become activated for coupling with a fairly electron rich
alkyne like 4-ethynyltoluene. This is noteworthy because in most cases the reaction of aryl chlorides under Sonogashira conditions only occurs when electron-withdrawing groups, particularly nitro, are located at the ortho or para position [118].

3.9.6 Sonogashira Couplings with 5-Chlorosalicylic Acid

5-Chloro-bis-TBS-salicylic acid was reacted with phenylacetylene, 4-ethynyltoluene, 1-ethynyl-1-cyclohexene, or propiolaldehyde diethyl acetal following Coupling A resulting in the corresponding alkynes being isolated in yields ranging from 62-84% (Table 3.3). When 5-chloro-1-pentyne was coupled overnight with 5-chloro-bis-TBS-salicylic acid, 6-chloro-2-(3-chloropropyl)-4H-1-benzopyran-4-one was isolated in 14-29% instead of the alkynone.

3.9.7 Sonogashira Coupling Variations with 5-Phenylsalicylic Acid

To determine how to increase yields, variations of the standard Sonogashira coupling procedure were examined with 5-phenyl-bis-TBS-salicylic acid. As discussed earlier, the exact mechanism of the Sonogashira coupling and the role of the copper catalyst are not known. One possible mechanism involves a transient copper acetylide species reacting with an arylpalladium (II). If a copper acetylide species is allowed to form first without interference from other reactants, yields may be increased. In order to test this hypothesis, Coupling C was followed in which copper iodide and 3 equiv of phenylacetylene were preincubated in triethylamine for 10 min. This was then
cannulated into the acid chloride followed by the addition of Pd(Ph3)2Cl2 catalyst. The result of this coupling was isolation of the alkynone in 76% yield, lower than previous coupling results of 90%.

In attempting Coupling B, triethylamine was added to the acid chloride, followed by addition of copper iodide and alkyne. This was allowed to stir at room temperature while bubbling argon directly into the reaction for 5 min before the addition of the palladium catalyst. This method was used to couple 4-ethynyl-toluene, 1-ethynyl-1-cyclohexene, and 5-chloropentyne and resulted in formation of alkynones. The alkynones were then cyclized resulting in overall yields over the 3 steps of 77%, 68% and 39% of the corresponding benzopyranones, respectively. The overall yields when a phenyl substituent is located at the five position were excellent. There was no evidence of a marked improvement in coupling yields when the copper iodide was preincubated with the alkyne for 5-phenylsalicylic acids.

3.10 CONCLUSIONS ABOUT ONE-POT ACID CHLORINATION-SONOGASHIRA COUPLING REACTION

The highest yield for the alkynone formation from the one-pot acid chlorination/Sonogashira coupling for the nine substituted bis-silylated-salicylic acids and the six terminal alkynes used is presented in Figure 3.24.
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<th>% Yield of Alkynone</th>
<th>Terminal Alkynes</th>
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<td>R</td>
</tr>
<tr>
<td>OTBS</td>
<td>OTBS</td>
</tr>
<tr>
<td>92%</td>
<td>95%</td>
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<td>70%</td>
<td>72%</td>
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<td>92%</td>
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<td>70%</td>
</tr>
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<td>84%</td>
</tr>
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<td>75%</td>
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</tr>
<tr>
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<td>OTBS</td>
</tr>
<tr>
<td>CH₃OTBS</td>
<td>CH₃OTBS</td>
</tr>
<tr>
<td>No rxn</td>
<td></td>
</tr>
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</table>

Figure 3.24: Highest % yield of alkynone formation.
CHAPTER 4

CYCLIZATIONS OF ALKYNONES TO FORM 4H-1-BENZOPYRAN-4-ONES

4.1 COMPETING CYCLIZATION OF BENZOPYRANONES VERSUS BENZOFURANONES, MECHANISM OF CYCLIZATION

The palladium catalyzed carbonylative cyclization of o-iodophenols and terminal acetylenes in the presence of base (usually Et₂NH or Et₃N) is known to produce a mixture of six-membered benzopyranones and five-membered benzofuranones (Figure 4.1) [97-99]. The mechanistic rationale for the formation of benzopyranones versus benzofuranones is shown in Figure 4.2 [100]. In this catalytic cycle, the o-iodophenol undergoes oxidative addition by the Pd[0], CO insertion, and complexation with the alkyne to form intermediate D, an alkynone. It is hypothesized that intermediate D can then undergo three different routes to form either the benzopyranones or the benzofuranones. The alkynone can form benzopyranones by two possible routes: (1) a 6-endo-dig cyclization of the alkynone or (2) a 6-endo-trig cyclization of the enaminoketone E formed by the Michael addition of a secondary amine to the alkynone D. Benzofuranone formation could arise by the complexation of alkynone D with palladium (0) to form complex G. Intermediate G following a rearrangement and reductive elimination could give rise to the benzofuranones.
Figure 4.1: Palladium catalyzed carbonylative cyclization of o-iodophenols and acetylenes produces a mixture of benzopyranones and benzofuranones.

Figure 4.2: The mechanistic rationale for the formation of benzopyranones versus benzofuranones [100].
Evidence by Korshunov et al. supports the idea of the alkynone being a critical intermediate for benzopyranone and benzofuranone formation. Korshunov et al. examined the role of the hydroxyl group in the intramolecular cyclization of 3-aryl-1-(4-hydroxyaryl)-2-propyn-1-ones (an alkynone) with various primary, secondary, and tertiary amines (Figure 4.3) [102]. They found that the product formed from the reaction of the alkynone with an amine was controlled by the nature of the amine. The reaction of the alkynone with a primary, secondary, or tertiary amine resulted in the formation of a β-aminovinyl ketone (enaminoketone). Depending on the amine used, the enaminoketone could further undergo an intramolecular cyclization with the participation of the ortho hydroxyl group. The end result was that a primary amine led only to enaminoketone formation, a secondary amine led to benzopyranone formation, and a tertiary amine led to benzofuranone formation [102]. Their results suggest that product formed by the intramolecular cyclization of an alkynone can be controlled by the nature of the amine. Depending on reaction conditions, 3-aryl-1-(4-hydroxyaryl)-2-propyn-1-ones can also be cyclized in basic media (potassium carbonate in acetone or sodium ethoxide in EtOH) to afford a mixture of benzopyranones or benzofuranones [124].
Figure 4.3: The reaction of 3-aryl-1-(2-hydroxyaryl)-2-propyn-1-ones with a primary, secondary, or tertiary amine resulting in the formation of β-aminovinylketone (enaminoketone), benzopyranone, or benzofuranone, respectively [102].

The factors controlling the regioselectivity for benzopyranone and benzofuranone formation have been examined in the reaction of substituted o-iodophenols with substituted phenylacetylene [98,99]. Ciattini et al. carried out this reaction in DMF at 60°C under 1 atm CO pressure using DBU as the base and Pd(OAc)$_2$(DPPF)$_2$ as the catalyst to afford a mixture of benzopyranones and benzofuranones (Figure 4.4). In this experiment, the carbonylative coupling was accomplished using milder conditions and ambient CO pressure than previous experimental attempts. The regioselectivity of the palladium-catalyzed cyclization could be controlled depending on the base used. It should be noted that only the more stable Z-isomer of the benzofuranone was isolated.
The synthesis of benzopyranones and quinolones via the palladium-catalyzed carbonylation of o-iodophenols and o-iodoanilines in the presence of acetylenes via a one-pot reaction has been performed (Figure 4.5) [97,99]. Torii et al. accomplished a one-pot coupling and cyclization of alkynones using an autoclave and an excess of diethylamine for use as base and solvent, 5 mol% Pd(PPh₃)₂Cl₂, high CO pressures (20 kg/cm²) at 120°C for 6 h to give exclusively the 6-membered benzopyranones or quinolones. By using an excess of diethylamine as base and solvent, the enaminoketone intermediate was generated thus resolving regioselectivity problems encountered by previous efforts. Benzofuranones or the indoxyl derivatives were not detected when secondary amines were used. This reaction is general for secondary amines; diethylamine, morpholine and piperidine worked; however, the basicity and steric of the amine were found to influence the reaction. Because of the high temperatures and pressures used, this reaction is not ideally suited for combinatorial synthesis of flavonoid libraries.
Figure 4.5: Regioselective synthesis of benzopyranones and quinolones via a one-pot palladium catalyzed carbonylation of o-iodophenols and o-iodoanilines in the presence of acetylenes [97,99].

4.2 Cyclization of Alkynones Using Diethylamine and EtOH

As seen in the literature, a free phenolic hydroxyl can effect either a 6-endo-dig or 5-exo-dig cyclization resulting in the nonselective formation of benzopyranones and benzofuranones, respectively. Because of our exclusive interest in the benzopyranone ring system, we were interested in synthetic methodology that would allow us to regioselectively synthesize the benzopyranones. We reasoned that if the latent ortho hydroxyl group is protected as a TBS ether, the cyclization of the alkynones could not occur until the protecting group was removed. If the alkynones were first converted to enaminoketones and then subjected to TBS deprotection, the system would be prone to undergo Michael addition followed by elimination of secondary amine to yield the desired benzopyranones as a 6-endo-trig cyclization (Figure 4.6). The potential for benzofuranone formation by the 5-exo-dig cyclization option would thus be eliminated. The enaminoketone intermediate could also be used to introduce various electrophiles at the three-position [125].
Figure 4.6: Alkynone is reacted with diethylamine to form the enaminoketone intermediate. The enaminoketone undergoes TBS deprotection, allowing the hydroxy group to attack the sp\(^2\) carbon resulting in a 6-endo-trig cyclization to form exclusively the benzopyranones [123].

4.2.1 Initial Studies of Cyclizations

In order to determine if this synthetic rationale would work, *bis*-TBS-salicylic acid was first coupled with phenylacetylene to form the alkynone by methodology previously discussed. To an ethanolic solution of alkynone, diethylamine (1.2 equiv) was added and stirred at room temperature under argon for 4 hours to afford the protected enaminoketone intermediate in 72% yield (Table 4.1, entry I-102). When an excess of diethylamine (10 equiv) was added to the alkynone in EtOH, the reaction yielded 51% of the protected enaminoketone, 16% of the deprotected enaminoketone, and 6% of the benzopyranone (Table 4.1, entry I-156). This led us to investigate the direct conversion of the alkynones to the benzopyranones in a single step.

To our surprise, it was discovered that the conversion of the alkynones to enaminoketones and subsequent cyclization could be effected in a single step. Thus, an ethanolic solution of an alkynone and 10 equiv of diethylamine could afford the TBS-protected-enaminoketone in less than 2 hours. Upon rotary evaporation of diethylamine and ethanol, the TBS-protected-enaminoketone was resuspended in ethanol and
refluexed for 18 hours to provide the benzopyranone in yields of 96% (Figure 4.7). After conditions for the cyclization were worked out, the protocol was applied to a diverse set of alkynones as seen in Figure 4.7 to provide 2-substituted-benzopyranones in yields ranging from 54-96% [105,123]. Similar cyclization results were obtained by using other secondary amines such as dimethylamine (2M solution in THF), pyrrolidine, and N-benzyl-ethylamine. Diisopropylamine reacted sluggishly with an ethanolic solution of 1-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-3-phenyl-2-propyn-1-one, so the reaction mixture was refluxed for 24 hours and after workup, the enaminoketone was isolated in quantitative yield [105].
Figure 4.7: Cyclization of alkynone with excess of diethylamine in EtOH to provide the enaminoketone intermediate, which can undergo 6-endo-trig cyclization when refluxed in EtOH [105,123].
<table>
<thead>
<tr>
<th>Notebook</th>
<th>Salicylic acid</th>
<th>Alkene</th>
<th>Cyclization Procedure</th>
<th>% Yield</th>
<th>Product</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-98</td>
<td>H phenylacetylene</td>
<td>H</td>
<td>&gt;95%</td>
<td>10</td>
<td>2-Phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-101</td>
<td>H phenylacetylene</td>
<td>I</td>
<td>45%</td>
<td>10</td>
<td>2-Phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-102</td>
<td>H phenylacetylene</td>
<td>B</td>
<td>72%</td>
<td>10</td>
<td>Protected enaminoketone</td>
<td></td>
</tr>
<tr>
<td>I-150</td>
<td>H phenylacetylene</td>
<td>B</td>
<td>6%</td>
<td>10</td>
<td>2-Phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-157</td>
<td>H phenylacetylene</td>
<td>C</td>
<td>65%</td>
<td>10</td>
<td>2-Phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>ASB</td>
<td>H phenylacetylene</td>
<td>C</td>
<td>96%</td>
<td>10</td>
<td>2-Phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-246</td>
<td>H phenylacetylene</td>
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<td>73%</td>
<td>10</td>
<td>2-Phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-240</td>
<td>H phenylacetylene</td>
<td>F</td>
<td>50%</td>
<td>10</td>
<td>2-Phenyl-4H-1-benzopyran-4-one</td>
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<tr>
<td>ASB</td>
<td>H 4-ethylthiophene</td>
<td>C</td>
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<td>11</td>
<td>2-(4'-Methyl-phenyl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-247</td>
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<td>F</td>
<td>48%</td>
<td>11</td>
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<td></td>
</tr>
<tr>
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<td>H 1-ethylthi-1-cyclohexene</td>
<td>C</td>
<td>82%</td>
<td>12</td>
<td>2-(1-Cyclohexen-1-yl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-248</td>
<td>H 1-ethylthi-1-cyclohexene</td>
<td>F</td>
<td>71%</td>
<td>12</td>
<td>2-(1-Cyclohexen-1-yl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>ASB</td>
<td>H 5-chloro-1-pentene</td>
<td>C</td>
<td>73%</td>
<td>13</td>
<td>2-(3-Chloropropyl)-4H-1-benzopyran-4-one</td>
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<td>F</td>
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<td>13</td>
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<td>14</td>
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</tr>
<tr>
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<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; phenylacetylene</td>
<td>C</td>
<td>88%</td>
<td>20</td>
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</tr>
<tr>
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<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; phenylacetylene</td>
<td>C</td>
<td>95%</td>
<td>41%</td>
<td>20</td>
<td>8-Methoxy-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
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<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; phenylacetylene</td>
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<td>89%</td>
<td>20</td>
<td>8-Methoxy-2-phenyl-4H-1-benzopyran-4-one</td>
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</tr>
<tr>
<td>I-42</td>
<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; 4-ethylthiophene</td>
<td>C</td>
<td>82%</td>
<td>21</td>
<td>8-Methoxy-2-(4'-methyl-phenyl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-229</td>
<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; 4-ethylthiophene</td>
<td>C</td>
<td>80%</td>
<td>21</td>
<td>8-Methoxy-2-(4'-methyl-phenyl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-230</td>
<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; 1-ethylthi-1-cyclohexene</td>
<td>C</td>
<td>72%</td>
<td>22</td>
<td>2-(1-Cyclohexen-1-yl)-8-methoxy-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-235</td>
<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; 1-ethylthi-1-cyclohexene</td>
<td>F</td>
<td>65%</td>
<td>22</td>
<td>2-(1-Cyclohexen-1-yl)-8-methoxy-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-233</td>
<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; 5-chloro-1-pentene</td>
<td>F</td>
<td>22%</td>
<td>23</td>
<td>2-(3-Chloropropyl)-8-methoxy-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-230</td>
<td>3-OCH&lt;sub&gt;3&lt;/sub&gt; propiolaldehyde diethyl acetal</td>
<td>C</td>
<td>53%</td>
<td>24</td>
<td>2-(Diethoxymethyl)-8-methoxy-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-172</td>
<td>3-CH&lt;sub&gt;3&lt;/sub&gt; phenylacetylene</td>
<td>C</td>
<td>87%</td>
<td>40</td>
<td>8-Methyl-2-phenyl-4H-1-benzopyran-4-one</td>
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</tr>
<tr>
<td>I-177</td>
<td>3-CH&lt;sub&gt;3&lt;/sub&gt; phenylacetylene</td>
<td>C</td>
<td>82%</td>
<td>40</td>
<td>8-Methyl-2-phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-252</td>
<td>3-CH&lt;sub&gt;3&lt;/sub&gt; phenylacetylene</td>
<td>C</td>
<td>64%</td>
<td>40</td>
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<td>I-232</td>
<td>3-CH&lt;sub&gt;3&lt;/sub&gt; 4-ethylthiophene</td>
<td>C</td>
<td>81%</td>
<td>41</td>
<td>8-Methyl-2-(4'-methyl-phenyl)-4H-1-benzopyran-4-one</td>
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</tr>
<tr>
<td>I-233</td>
<td>3-CH&lt;sub&gt;3&lt;/sub&gt; 1-ethylthi-1-cyclohexene</td>
<td>F</td>
<td>83%</td>
<td>42</td>
<td>2-(1-Cyclohexen-1-yl)-8-methyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-251</td>
<td>3-CH&lt;sub&gt;3&lt;/sub&gt; 5-chloro-1-pentene</td>
<td>F</td>
<td>40%</td>
<td>43</td>
<td>2-(3-Chloropropyl)-8-methyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>II-36</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt; phenylacetylene</td>
<td>C</td>
<td>80%</td>
<td>45</td>
<td>7-Methyl-2-phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1: % Yield of substituted-4H-1-benzopyran-4-one resulting from the appropriate cyclization procedure (Notebook # refers to either JLW-I-xxx, JLW-II-xxx, or ASB [105]).

continued
<table>
<thead>
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<th>Product</th>
<th>Cycles to failure</th>
<th>Product</th>
<th>Cycles to failure</th>
<th>Product</th>
<th>Cycles to failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product 1</td>
<td>1000</td>
<td>Product 2</td>
<td>1500</td>
<td>Product 3</td>
<td>2000</td>
</tr>
<tr>
<td>Product 4</td>
<td>2500</td>
<td>Product 5</td>
<td>3000</td>
<td>Product 6</td>
<td>3500</td>
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</table>

Table 4.1 continued
Table 4.1, continued

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<tr>
<th>Notebook</th>
<th>Salicylic acid</th>
<th>Alkynl</th>
<th>Cyclization Procedure</th>
<th>% Yield</th>
<th>Product</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASB 8-CI</td>
<td>phenacyclylene</td>
<td>C</td>
<td>83%</td>
<td>90</td>
<td>6-Chloro-2-phenyl-4H-1-benzopyran-4-one</td>
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</tr>
<tr>
<td>I-290</td>
<td>phenacyclylene</td>
<td>D</td>
<td>60%</td>
<td>39%</td>
<td>90</td>
<td>6-Chloro-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>I-235</td>
<td>phenacyclylene</td>
<td>F</td>
<td>60%</td>
<td>90</td>
<td>6-Chloro-2-phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-238</td>
<td>4-ethyltoltipene</td>
<td>F</td>
<td>85%</td>
<td>91</td>
<td>6-Chloro-2-(4&quot;-methylphenyl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>II-6</td>
<td>4-ethyltoltipene</td>
<td>D</td>
<td>65%</td>
<td>39%</td>
<td>91</td>
<td>6-Chloro-2-(4&quot;-methylphenyl)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>I-296</td>
<td>4-ethyltoltipene</td>
<td>E</td>
<td>7%</td>
<td>91</td>
<td>6-Chloro-2-(4&quot;-methylphenyl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-289</td>
<td>1-ethyl-1-cylohexane</td>
<td>G</td>
<td>23%</td>
<td>92</td>
<td>6-Chloro-2-(1-cylohexen-1-yl)-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>ASB 5-Ph</td>
<td>phenacyclylene</td>
<td>C</td>
<td>94%</td>
<td>110</td>
<td>2,6-Diphenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-284</td>
<td>5-Ph phenacyclylene</td>
<td>C</td>
<td>61%</td>
<td>46%</td>
<td>110</td>
<td>2,6-Diphenyl-4H-1-benzopyran-4-one</td>
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<td>I-287</td>
<td>5-Ph 4-ethyltoltipene</td>
<td>C</td>
<td>77%</td>
<td>111</td>
<td>2-(4'-(Methylphenyl))-8-phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>ASB 5-Ph</td>
<td>1-ethyl-1-cylohexane</td>
<td>C</td>
<td>92%</td>
<td>112</td>
<td>2-(1-Cylohexen-1-yl)-8-phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
<tr>
<td>I-288</td>
<td>5-Ph 1-ethyl-1-cylohexane</td>
<td>C</td>
<td>68%</td>
<td>112</td>
<td>2-(1-Cylohexen-1-yl)-8-phenyl-4H-1-benzopyran-4-one</td>
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</tr>
<tr>
<td>I-277</td>
<td>5-Ph 5-chloro-1-phenyl</td>
<td>C</td>
<td>53%</td>
<td>113</td>
<td>2-(3-Chloropropyl)-8-phenyl-4H-1-benzopyran-4-one</td>
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</tr>
<tr>
<td>I-285</td>
<td>5-OCH3 phenacyclylene</td>
<td>C</td>
<td>71%</td>
<td>120</td>
<td>6-Methoxy-2-phenyl-4H-1-benzopyran-4-one</td>
<td></td>
</tr>
</tbody>
</table>

(A) Et3NH, mmol; (B) Et3NH, EtOH; (C) 1. Et3NH, EtOH, 2. EtOH, reflux; (D) 1. Pyridilidine, 2. EtOH, reflux; (E) Pyridilidine; (F) Et3N, alkynl and CuI are carboxylated into solid chloride after being stirred under argon for 15 min, followed by carboxylation into solid chloride and addition of Pd(PPh3)2Cl2.

Intermediate alkyne is filtered through celite and concentrated. 1. Et3NH & EtOH; 2. EtOH, reflux; (G) 1. Pyridilidine, EtOH, 2. EtOH, reflux; (H) KF, 18-crown-6, DMF; (I) pyridilidine p-toluene sulfonate, MeOH.

181% enaminoalatone and 16% of deprotonated enaminoalatone formed in reaction. 12% benzofuranone formed in coupling step. Methyl ester formed in coupling step. Majority of product is deprotected alkyne.
4.2.2 Cyclizations with the Alkynone 1-{2-[1,1-Dimethylethyl]-dimethylsilyl[oxyl]-4-methoxyphenyl]-3-phenyl-2-propyn-1-one

The next step was to examine the effect that a 4-methoxy substituent on the alkynone has on the cyclization yield. Diethylamine (10 equiv) and EtOH were added to the alkynone isolated from the coupling of 4-methoxysalicylic acid and phenylacetylene (Figure 4.8). After stirring under argon for 45 minutes, the protected enaminoketone was isolated in 78% yield. When the secondary amine pyrrolidine was added to an ethanolic solution of the alkynone, the alkynone disappeared by TLC in less than 5 minutes and led to isolation of the protected enaminoketone in 69% yield (Figure 4.8, Table 4.1). Although the pyrrolidine underwent a faster 1,4 addition, the Et₂NH provided the enaminoketone in higher yield. The 4-methoxy did not seem to affect the formation of the enaminoketone.

![Figure 4.8: Enaminoketone generation using different secondary amines (i.e. diethylamine and pyrrolidine).](image)

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The one-pot acid chlorination/Sonogashira coupling of 4-methoxysalicylic acid with various terminal alkynes generated various methoxyalkynones (Table 3.2). The alkynones were reacted with diethylamine in EtOH to first generate the enaminoketone intermediates. The enaminoketones were resuspended in EtOH and refluxed to provide the 2-substituted-7-methoxy-4H-1-benzopyran-4-ones in yields ranging from 73-92% as seen in Figure 4.9. The cyclization to provide 2-(1-cyclohexen-1-yl)-7-methoxy-4H-1-benzopyran-4-one resulted in the lowest yield (73%). The lower yield may be due to the ability of the nitrogen nucleophile of the amine to do a 1,6-Michael addition to the double bond of the cyclohexene. However, the product from the 1,6 addition has not been detected.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>4-Methoxy salicylic acid</th>
<th>Terminal Alkynes</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure" /></td>
<td><img src="image" alt="Chemical structures" /></td>
</tr>
<tr>
<td><strong>Coupling Yields</strong></td>
<td><strong>Cyclization Yields</strong></td>
</tr>
<tr>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>70%</td>
<td>88%</td>
</tr>
<tr>
<td>65%</td>
<td>73%</td>
</tr>
<tr>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>42%</td>
<td>80%</td>
</tr>
<tr>
<td>90%</td>
<td>85%</td>
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Figure 4.9: Coupling yields of 4-methoxysalicylic acids with various alkynes followed by their cyclization with diethylamine and EtOH to produce 2-substituted-7-methoxy-4H-1-benzopyran-4-ones.
4.2.3 Cyclization Yields of the Alkynones

All of the alkynones made from the Sonogashira couplings were cyclized to the benzopyranone. The highest yields of these cyclizations can be seen in Figure 4.10 and Table 4.1.

% Yield of Benzopyranone | Terminal Alkynes
--- | ---
96% | 87% | 82% | 73% | 75%
95% | 82% | 72%
87%
92% | 88% | 73% | 80% | 89% | 85%
80%
85% | 68%
83% | 63%
94% | 92% | 53%
71%

Figure 4.10: Cyclization yields of the alkynones derived from the coupling of the salicylic acids and terminal alkynes via methodology in Table 4.1.
4.2.4 Protecting the Hydroxyl Group to Prevent Cyclization

Since our initial publication of this chemistry, Miao and Yang have developed a highly efficient synthetic technology for carbonylative cyclization of o-acetoxyiodobenzenes with arylacetylenes to construct the corresponding benzopyranones under mild conditions (40°C under a balloon pressure of CO) using PdCl₂(Ph₃P)₂-thiourea-dppp (1:1:1) complex as the catalyst (Figure 4.11) [100]. They also reasoned that if the latent ortho-hydroxy group was protected, in this case as an acetoxy, they could prevent the formation of aurones. By protecting the hydroxyl, they determined that the reaction rate of the Pd-catalyzed coupling was also increased. This possibly could be due to the electron-withdrawing effect of the acetoxy, since it reduces the electron density of the aromatic ring, thus increasing the oxidative addition of Pd. Using these conditions, the benzopyranones were formed in a one-pot reaction with overall yields ranging from 68-92% and the five-membered benzofuranone formation was prevented.

![Figure 4.11](image)

Figure 4.11: Regiospecific carbonylative annulation of iodophenol acetates and arylacetylenes to construct benzopyranones by a new catalyst of palladium-thiourea-1,3-bis(diphenylphosphino)propane (dppp) complex [100].
4.3 Other Cyclization Protocols Attempted

Various cyclization protocols of alkynones have been attempted in the literature. It has been shown that the reaction of various secondary amines with alkynones results in the formation of the enaminoketone intermediate, which can then undergo cyclization to the benzopyranone.

Theoretical calculations on the cyclization of o-hydroxyphenyl ethynyl ketones (alkynones) have shown that both the 6-endo-dig and 5-endo-dig cyclizations are endothermic and reversible in aprotic media, and the irreversible protonation of the resulting anions is critical for the distribution of products [126]. To determine the distribution of products in aprotic media, Nakatani et al. desilyated o-silyloxyphenyl ethynyl ketones using sources of fluoride ion to generate a phenoxide ion which cyclized to give either benzopyranones or benzofuranones. They showed that KF in aprotic media allows the irreversible protonation of the resulting vinyl anion from a 6-endo-dig cyclization to give rise to the benzopyranone with high selectivity. The basis for this selectivity is unknown. The theoretical potential energy diagram is Figure 4.12 suggests that the transition states are very close to each other; however, the benzopyranone vinyl anion is more stable than the benzofuranone vinyl anion. The irreversible protonation of the benzopyranone vinyl anion results in the formation of the benzopyranone over the benzofuranone. Application of this methodology (i.e., KF,
18-crown-6, DMF) to our alkynones resulted in the formation of the benzopyranones in less than 4 hours in excellent yields (>95%) (Figure 4.13). This methodology did not work as well when the substitution of the alkynone was changed.

Figure 4.12: A. Alkynones can be cyclized under basic conditions using potassium fluoride, 18-crown-6, and DMF via a 6-endo or 5-exo-digonal cyclization resulting in the selective formation of benzopyranones. The reaction of an alkynone with a solution of TBAF in THF produced a mixture of benzopyranone and benzofuranone in 90% yield with low selectivity (47:53) [126]. B. The theoretical potential energy diagram for this selectivity.
Figure 4.13: Alkynones can be cyclized using potassium fluoride, 18-crown-6, and DMF or pyridinium p-toluenesulfonate (PPTS) in MeOH via a 6-endo-\textit{dig} cyclization resulting in the selective formation of benzopyranones.

4.4 Benzofuranone Formation during Sonogashira Couplings

The chemistry that we have developed has allowed us to regioselectively synthesize the benzopyranones. The competing 5-exo-\textit{dig} cyclization yielding benzofuranones has not been observed following our cyclization protocols. As seen in Figures 4.2 and 4.14, there are 3 possible mechanisms of cyclization of alkynones. Alkynones could undergo a 5-exo-\textit{dig} cyclization to form either the Z or E isomer of a benzofuranone. Both a 6-endo-\textit{dig} cyclization of the alkynone or a 6-endo-\textit{trig} cyclization of the enaminketone would result in the formation of benzopyranones. An ethanolic solution of a secondary amine, predominantly diethylamine, has been used to cyclize the alkynone intermediate, without any evidence of benzofuranone formation. However, in six cases, the Z-benzofuranone has been isolated in low yields during the Sonogashira coupling of acid chlorides and terminal alkynes which uses triethylamine as solvent and
base (Figure 4.15). Korshunov et al. demonstrated that diarylpropynones containing a hydroxyl group ortho to the alkyne in triethylamine led to the formation of only benzofuranones [102].

If the TBS protecting group was removed during the reaction, the nucleophilic attack of the unmasked phenolic hydroxyl on the alkyne could proceed via two routes: a 5-exo-dig pathway to provide the benzofuranone or the 6-endo-dig pathway to provide the benzopyranones. According to Baldwin's cyclization rules, both of these modes are favored [127].

![Figure 4.14: Mechanism of cyclization of the alkynone to the benzopyranone and benzofuranone.](image-url)
The Z-benzofuranone and benzopyranone have been isolated in yields of 3-29% and 3-42%, respectively, during the Sonogashira coupling of various salicylic acids and terminal alkynes (Figure 4.15, Table 3.3). During the course of our experimentation, the coupling of salicylic acid and phenylacetylene has been performed numerous times and under a variety of conditions. Only in one case has the benzofuranone been detected in 12% yield (Table 3.3). The largest yield (29%) of benzofuranone isolated was formed in the coupling of 4-methoxysalicylic acid and propiolaldehyde diethyl acetal. In this case, the Et$_3$N used in the Sonogashira coupling was distilled from KOH instead of the usual distillation procedure from phthalic anhydride and calcium hydride. In this instance, no alkynone was even detected. When this coupling was repeated with Et$_3$N distilled from CaH$_2$, the alkynone coupling yield ranged from 24-84%, without detection of the benzofuranone. Each time 5-chloro-bis-TBS-salicylic acid was coupled to 5-chloro-1-pentyne, only the benzopyranone was isolated (14-29%); the alkynone was not detected each time. This is the only example when a specific alkynone could not be isolated after a Sonogashira coupling.
Figure 4.15: Formation of Z-benzofuranones during the Sonogashira coupling of salicylic acids and terminal alkynes.

4.5 NAMING OF THE FLAVONOIDs

All flavonoids contain fifteen carbon atoms in the parent skeleton and feature two phenyl rings linked by a three-carbon chain. There are countless examples of flavonoids in the literature since they represent one of the most diverse and widespread groups of natural products. Many flavonoids bear numerous hydroxy or methoxy groups and often exist as O-glycosides or as dimers. The class of flavonoids includes the flavones, flavonols, isoflavones, flavanones, dihydroflavonols, aurones, and finally chalcones. The skeletons and numbering schemes commonly found in the literature for the flavonoids can be seen in Figure 4.16 [128,129].
Many of the flavonoids have a fused benzene and pyran ring and are thus called benzopyrans. There are two classes of benzopyrans which depend on the placement of the oxygen, 1-benzopyran and 2-benzopyran (Figure 4.17). Note that the placement of the double bond in the 1-benzopyrans can be in the 2,3 or the 3,4 position. When trying to search for the flavonoids in the literature, one also has to be aware of the nomenclature of the 1-benzopyran classes, which includes the chroman, 2H-chromene, 4H-chromene, 3-chromanone, 4-chromanone, 2,4-chromandione, and chromone (Figure 4.18).

Figure 4.16: Skeletons and numbering schemes commonly employed in the literature for the class of flavonoids.

Figure 4.17: Types of benzopyrans.
A variety of names have been used for the chromone ring system including benzo-γ-pyrone, γ-benzopyrone, pheno-γ-pyrone, 2,3-benzopyrone-(4), 4-oxo[1,4-chromen], 4-oxochromen, and 4H-1-benzopyran-4-one. In 1972, *Chemical Abstracts* replaced the trivial name of chromone with the systematic name of 4H-1-benzopyran-4-one [130]. Thus, the benzopyranones and the benzofuranones shown in Figure 4.19 have the systematic names of 2-phenyl-4H-1-benzopyran-4-one and 2-phenyl-(2Z)-3(2H)-benzofuranone, respectively, and belong to the larger class of flavonoids. Other names for the benzofuranone ring system include β-coumaranone, 2,3-dihydro-1-benzofuran-3-one, 2,3-dihydro-3-oxobenzofuran, benzo[b]furan-3(2H)-one, coumaran-3-one, and coumaranone.
4.6 Structure Elucidation

Although often taken for granted, structure elucidation of the benzopyranones and the benzofuranones should not be overlooked and is not a trivial task. All products synthesized in our laboratory have been fully characterized by $^1$H and $^{13}$C Nuclear Magnetic Resonance Spectroscopy (NMR), Infrared Spectroscopy (IR), Ultraviolet-visible Spectroscopy (UV-Vis) and High Resolution Mass Spectrometry (HRMS). Figure 4.19 reveals the general structures of unsubstituted benzopyranones and benzofuranones. The olefin bond of the benzofuranones introduces two possible geometric isomers, most of the naturally occurring aurones possess Z-olefinic configuration and are named Z-aurones or Z-benzofuranones [129].

There are numerous sources of information for isolation, purification, and identification of the flavonoids. In particular, much work has been accumulated on the physical properties and spectra (including UV, $^1$H, and $^{13}$C NMR) of various flavonoids [128-132].

Figure 4.19: Systematic naming of the benzopyranones and benzofuranones.
4.6.1 **$^1$H NMR Spectroscopy**

The distinguishing characteristic between these two classes of compounds begins with the distinction of the H-3 of benzopyranones and the benzylic methine of benzofuranones [129]. The chemical shifts of these protons both would appear as singlets in the $^1$H NMR spectra, each having a chemical shift from 6.0-8.0 ppm. Figure 4.20 shows that the $^1$H NMR chemical shifts for the H-3 of 6-methoxy-2-phenyl-4$H$-1-benzopyran-4-one and the benzylic proton of 6-methoxy-2-phenyl-3(2$H$)-benzofuranone both appear as singlets at 6.80 and 6.85 ppm, respectively. $^1$H NMR data by itself is not adequate to differentiate the structures from each other and other experimental proof like $^{13}$C NMR and UV are needed to confirm these structures.

![Figure 4.20: $^1$H NMR chemical shifts for the H-3 of 6-methoxy-2-phenyl-4$H$-1-benzopyran-4-one and the benzylic H of 6-methoxy-2-phenyl-3(2$H$)-benzofuranone from data collected in CDCl₃.](image)

For benzopyranones with non-aromatic substituents at the C-2 position, like 2-(diethoxymethyl)-7-methoxy-4$H$-1-benzopyran-4-one in Figure 4.21, chemical shift and coupling constants from $^1$H NMR data is adequate to determine the structure. For
the benzopyranone, H-3 appears as a singlet at 6.49 ppm and the allylic proton appears as a singlet at 5.26 ppm. These two protons are not coupled to each other because they are four bonds away. However, the benzofuranone H-2 and the allylic proton are three bonds apart and are coupled. They both appear as doublets with $^3J = 7.5$ Hz.

![Figure 4.21: $^1$H NMR chemical shifts for the H-3 of 2-(diethoxymethyl)-7-methoxy-4H-1-benzopyran-4-one and the H-2 of 7-methoxy-2-(diethoxymethyl)-3(2H)-benzofuranone from data collected in CDCl$_3$.](image)

4.6.2 $^{13}$C NMR Spectroscopy

$^{13}$C NMR spectroscopy has been widely used for the characterization of various categories of flavonoids. From $^{13}$C NMR data, one can not only determine if the compound is a benzopyranone or benzofuranone, but also determine the geometry of the olefin bond of the benzofuranones.

Figure 4.22 presents the $^{13}$C NMR chemical shifts of 2-phenyl-4H-1-benzopyran-4-one and 2-phenyl-3(2H)-benzofuranone in CDCl$_3$ [129]. As seen in Figure 4.22, the carbon resonances from the aromatic A and B rings for the benzopyranone and benzofuranone
overlap and cannot be readily distinguished from each other. $^{13}$C NMR can be used to
differentiate the sp$^2$ hybridized olefin bond (C-2 and C-3) of benzopyranones and
benzofuranones. The C-3 resonance of flavonoids typically appears from 102.3-113.7,
depending on substitution patterns found on the ring system; however, for the majority
of flavonoids, the C-2 appears at ~107 ppm [129]. The resonance at ~107 ppm is
unique and distinct from resonances from aurones. The exocyclic olefin methine (C-2)
of unsubstituted Z-aurones typically absorbs at 108.1-112.8 ppm, while the methine C-2
of E-aurones is deshielded and appears at 119.9-122.2 ppm. If the Z-aurone has a
2′-oxy substituent, the C-2 is shifted upfield to 104.0-105.9 ppm. As can be seen in
Figure 4.22, the C-3 resonance of the flavonoids appears at 107.6 ppm and the closest
resonance to this in aurones appears at 112.8 ppm (C-2 and C-8 of Z-aurone) or 112.1
ppm (C-8 of E-aurone).
### Figure 4.22: \(^{13}\text{C}\) NMR chemical shifts of 2-phenyl-4H-1-benzopyran-4-one and 2-phenyl-3(2H)-benzofuranone in CDCl\(_3\) [129,133].

#### 4.6.3 Two-Dimensional \(^{13}\text{C}\) NMR Spectroscopy

2D NMR experiments have been used to fully assign the proton and carbon skeleton of a few model systems. Heteronuclear shift correlation (XHCORR) spectroscopy is a very useful 2D technique used to determine which protons are directly bonded to which \(^{13}\text{C}\) nuclei. In this technique, only \(^{13}\text{C}\)'s directly attached to \(^{1}\text{H}\)'s are detected, all quaternary carbons are missing. A COLOC (Correlation Spectroscopy via Long Range Coupling) experiment is a 2D heteronuclear correlation technique that can be used to
determine which $^1$H's are bonded to which $^{13}$C nuclei via small long-range couplings ($^3J_{CH}$, $n>1$). Thus, in this experiment, all $^{13}$C resonances are detected, not just those bonded directly to protons. Figures 4.23 to 4.26 present various 2D experiments used to establish either the benzopyranone or benzofuranone skeleton. In Figure 4.23, a cross peak exists for the H-3 and the carbon at 106.7 ppm, thus indicating that the compound is a benzopyranone.

Benzofuranones can be readily distinguished by the chemical shift of the exocyclic olefinic methine (C-2). The exocyclic olefinic methine carbon appears at 104.0-112.8 ppm in most Z-benzofuranones. However, the methine C-2 is deshielded by 10 ppm in E-isomers and absorbs at 119.9-122.2 ppm [129,133,134]. It should be noted that according to past $^{13}$C NMR experiments in the literature, the E and Z-isomers cannot be distinguished on basis of the chemical shifts of the C-3 olefinic quaternary carbon or the C-4 carbonyl carbon because they absorb almost at the same position (Figure 4.27) [134]. The olefinic quaternary carbon C-3 absorbs in the range of 147.0-148.5 ppm while the C-4 carbonyl carbon absorbs in the range of 178.9-185.8 ppm for both isomers.
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<tbody>
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</tr>
<tr>
<td>C-3</td>
<td>106.7</td>
</tr>
<tr>
<td>C-4</td>
<td>176.3</td>
</tr>
<tr>
<td>C-5</td>
<td>125.6</td>
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<tr>
<td>C-6</td>
<td>115.1</td>
</tr>
<tr>
<td>C-7</td>
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<td>157.5</td>
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<td>116.2</td>
</tr>
<tr>
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<td>131.3</td>
</tr>
<tr>
<td>C-2'</td>
<td>126.2</td>
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<td>129.1</td>
</tr>
<tr>
<td>C-6'</td>
<td>128.2</td>
</tr>
</tbody>
</table>

Figure 4.23: Heteronuclear shift correlation experiment of 7-hydroxy-2-phenyl-4H-1-benzopyran-4-one (60).
Figure 4.24: Heteronuclear shift correlation experiment (upper) and COLOC (Correlation Spectroscopy via Long Range Coupling) (lower) of 7-hydroxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (61).
Figure 4.25: Heteronuclear shift correlation experiment of 7-chloro-2-phenyl-3(2H)-benzofuranone. A cross peak exists for the H-2 and the carbon at 114.1 ppm, thus indicating that the compound is a benzofuranone.
Figure 4.26: Heteronuclear shift correlation experiment of 6-methoxy-2-phenyl-3(2H)-benzofuranone. A cross peak exists for the H-2 and the carbon at 113.1 ppm, thus indicating that the compound is a benzofuranone.
4.6.4 **Ultraviolet–Visible Absorption Spectroscopy**

Ultraviolet-visible (UV-Vis) absorption spectroscopy has been extensively used for flavonoid structure analysis. This technique can be used to aid in the identification of the flavonoid type and is often used to determine the oxygenation pattern. UV-Vis analysis has been performed on all flavonoids synthesized. This method offers a quick, yet accurate determination of the ring structure due to the differences in absorption profiles of different flavonoids. The UV-Vis absorption spectra of different flavonoid types can be seen in Figure 4.28 [132]. The UV-Vis spectrum of flavonoids is typically determined for a methanol or ethanol solution of the flavonoid. The spectrum typically consists of two absorption maxima in the ranges of 240-285 nm (band II) and 300-550 (band I). Table 4.2 displays the absorption ranges for band II and band I for the classes of flavonoids. Band I is considered to be associated with absorption due to the B-ring while band II with absorption due to the A-ring [128].
Figure 4.28: Ultraviolet-visible spectra of different flavonoid types with equivalent hydroxylation patterns [132].
One can easily differentiate a flavonoid from an aurone based upon the band I absorption from the UV spectra. Aurones characteristically have a band I absorption at a longer wavelength position (380-430 nm) as compared to flavones (330-360 nm). The UV-Vis absorption spectrum for 7-methyl-2-phenyl-4\(H\)-1-benzopyran-4-one and 7-methyl-2-phenyl-(2\(Z\))-3-(2\(H\))-benzofuranone can be seen in Figure 4.29. The band I absorption is shifted in the benzofuranone (371 nm) relative to the benzopyranone (298 nm) which is consistent with the literature. Figure 4.30 presents the UV-Vis absorption spectrum for 6-methoxy-2-phenyl-4\(H\)-1-benzopyran-4-one and 6-methoxy-2-phenyl-(2\(Z\))-3-(2\(H\))-benzofuranone. Reference spectra for many flavonoids can be found in the literature and are an invaluable tool for the interpretation of UV spectrum [128,132]. Table 4.3 presents the Band I and II absorptions for all synthetic benzopyranones.
Figure 4.29: UV-Vis absorption spectrum for 7-methyl-2-phenyl-4H-1-benzopyran-4-one and 7-methyl-2-phenyl-(2Z)-3-(2H)-benzofuranone.

Figure 4.30: UV-Vis absorption spectrum for 6-methoxy-2-phenyl-4H-1-benzopyran-4-one and 6-methoxy-2-phenyl-(2Z)-3-(2H)-benzofuranone.
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<tr>
<td>55</td>
<td>I-191</td>
<td>250</td>
<td>305</td>
<td>3-Bromo-7-methoxy-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>56</td>
<td>II-033</td>
<td>248</td>
<td>292</td>
<td>7-Methoxy-2-propyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>57</td>
<td>II-037</td>
<td>252</td>
<td>295</td>
<td>3-Bromo-7-methoxy-2-propyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>60</td>
<td>II-017</td>
<td>251</td>
<td>308</td>
<td>7-Hydrazine-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>61</td>
<td>II-019</td>
<td>253</td>
<td>311</td>
<td>7-Hydrazine-2-(4'-methylphenyl)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>70</td>
<td>II-036</td>
<td>255</td>
<td>296</td>
<td>7-Methyl-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>80</td>
<td>I-273</td>
<td>249</td>
<td>296</td>
<td>7-Chloro-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>81</td>
<td>I-274</td>
<td>250</td>
<td>307</td>
<td>7-Chloro-2-(4'-methylphenyl)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>82</td>
<td>I-278</td>
<td>246</td>
<td>301</td>
<td>7-Chloro-2-(1-cyclohexene-1-yl)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>83</td>
<td>I-280</td>
<td>248</td>
<td>303</td>
<td>7-Chloro-2-(3-chloropyrrol)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>90</td>
<td>I-235 (II-290)</td>
<td>254</td>
<td>298</td>
<td>6-Chloro-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>91</td>
<td>I-236 (II-007)</td>
<td>256</td>
<td>307</td>
<td>6-Chloro-2-(4'-methylphenyl)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>92</td>
<td>I-289</td>
<td>252</td>
<td>298</td>
<td>6-Chloro-2-(1-cyclohexene-1-yl)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>93</td>
<td>I-284</td>
<td>267</td>
<td>305</td>
<td>6-Chloro-2-(3-chloropyrrol)-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>110</td>
<td>I-264</td>
<td>271</td>
<td>303</td>
<td>2,6-Diphenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>111</td>
<td>I-267</td>
<td>273</td>
<td>309</td>
<td>2-(4'-Methylphenyl)-2,6-diphenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>112</td>
<td>I-266</td>
<td>270</td>
<td>301</td>
<td>2-(1-Cyclohexene-1-yl)-6-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>113</td>
<td>I-277</td>
<td>250</td>
<td>314</td>
<td>2-(3-Chloropyrrol)-6-phenyl-4H-1-benzopyran-4-one</td>
</tr>
<tr>
<td>120</td>
<td>II-065</td>
<td>270</td>
<td>304</td>
<td>6-Methoxy-2-phenyl-4H-1-benzopyran-4-one</td>
</tr>
</tbody>
</table>

Table 4.3: UV absorptions for synthetic benzopyranones.
4.7 HIGH-THROUGHPUT SYNTHESIS OF BENZOPYRANONES

4.7.1 RESIN CAPTURE

Our laboratory is interested in the high-throughput solid phase synthesis of a benzopyranone library of compounds. The synthetic methods developed thus far involve the solution phase synthesis of a benzopyranone library and should facilitate the transfer of this chemistry to solid phase. A resin capture strategy has been applied to this chemistry. Resin capture involves the solution phase reaction between an intermediate and a solid support resulting in the product being bound to the resin. In essence, resin capture is often viewed as a purification strategy wherein the desired product from the reaction mixture is trapped onto the solid support, leaving the by-products in solution which can simply be filtered away.

This resin capture strategy was successfully applied to our synthetic methodology resulting in the rapid and high yielding synthesis of substituted benzopyranones. The use of secondary amines for the cyclization step provided an opportunity to use a secondary amine bound to a resin. The resin capture of alkynones with a piperazinyl Merrifield resin in a solution of THF and MeOH resulted in the formation of support bound enaminoketones. Enaminoketones can undergo an on-resin cyclization to release the substituted benzopyranone and regeneration of the resin in yields of 70-82% (Figure 4.31) [105,135].
Figure 4.31: Resin capture of alkynones using a piperazinyl Merrifield resin resulting in the synthesis of 2-substituted-4H-1-benzopyran-4-ones [105,135].

4.7.2 HIGH-THROUGHPUT SYNTHESIS

In an attempt to increase efficiency and determine the feasibility of a high-throughput synthesis, intermediate purification of the alkynones from the Sonogashira couplings was terminated. In lieu of flash chromatography purification of the alkynones, the reaction mixture was filtered through a pad of celite with EtOAc to remove any solids such as the triethylamine salt and palladium catalyst. The reaction mixture was concentrated in vacuo followed by the cyclization protocol resulting in the formation of benzopyranones. This protocol was first applied to the synthesis of 8-methoxy-2-phenyl-4H-1-benzopyran-4-one resulting in the yield of the benzopyranone in 89% from the silated salicylic acid. This yield was dramatically higher as compared to the same reaction conditions except purifying the intermediate alkynone (62%). These results suggest that impurities do not interfere with the cyclization step. Although the stability of the alkynone has been questionable, it has been found to be relatively stable
stored in the freezer overnight. Direct use of the alkynone could eliminate possible degradation. Because of the slightly acidic nature of silica gel, it has been postulated that the TBS-protecting group could be removed during purification; no experimental proof for this exists. This methodology was then applied to various starting materials resulting in the synthesis of twelve benzopyranones in overall yields ranging from 22-91% (Figure 4.32).

<table>
<thead>
<tr>
<th>Benzopyranone</th>
<th>% Yield of Benzopyranone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R₂ Terminal alkyn</td>
</tr>
<tr>
<td>TBS</td>
<td>73% 48% 71% 51%</td>
</tr>
<tr>
<td>OTBS</td>
<td>89% 88% 44% 22%</td>
</tr>
<tr>
<td>OTBS</td>
<td>64% 91% 83% 40%</td>
</tr>
</tbody>
</table>

Figure 4.32: High-throughput synthesis of substituted-4H-1-benzopyran-4-ones.
4.8 Overall Yields of Coupling and Cyclization

The highest overall yields of the synthesis of substituted-4H-1-benzopyran-4-ones from the protected salicylic acids can be found in Figure 4.33.

![Chemical Structures]

<table>
<thead>
<tr>
<th>alkyne</th>
<th>OCH₃</th>
<th>CH₃</th>
<th>OCH₃</th>
<th>CH₃</th>
<th>OCH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>88%</td>
<td>83%</td>
<td>67%</td>
<td>62%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>83%</td>
<td>62%</td>
<td>47%</td>
<td>34%</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>77%</td>
<td>68%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>74%</td>
<td>42%</td>
<td>70%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>39%</td>
<td>23%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>91%</td>
<td>83%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>89%</td>
<td>88%</td>
<td>49%</td>
<td>22%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Figure 4.33: Overall cyclization yields of substituted-4H-1-benzopyran-4-ones from the coupling and cyclization of bis-silylated-salicylic acids and terminal alkynes.
4.9 **Numbering System of Benzopyranones**

The numbering scheme used for the library of benzopyranones is based upon the combination of the numbering of the individual starting materials (i.e.; salicylic acids and terminal alkynes). The first number (Ix) of the benzopyranone is derived from the salicylic acid component while the second number from the alkyne used (x0) (Figure 4.34). For example, if salicylic acid (Ix) were combined with phenylacetylene (x0), the product 2-phenyl-4H-1-benzopyran-4-one would be number 10. Figure 4.25 shows the numbering scheme for the benzopyranones synthesized.

![Diagram of numbering scheme for benzopyranones](image)

Figure 4.34: Numbering scheme of salicylic acids and terminal alkyne series.
Figure 4.35: Numbering system for the benzopyranone library.
CHAPTER 5

ADDING DIVERSITY TO THE 4H-1-BENZOPYRAN-4-ONE SKELETON

5.1 FUNCTIONALIZING THE 4H-1-BENZOPYRAN-4-ONE SKELETON

In order to understand what functional groups are present on benzopyranones isolated from natural products, one has to look at the biosynthetic pathway of flavonoids (Figure 5.1). The basic skeleton of flavonoids is derived from 4-coumaroyl-CoA and malonyl-CoA and consists of two aromatic rings connected by a three carbon spacer. The hydroxylation patterns of the three rings systems (A, B, and C) is derived from the biosynthetic pathway. The most common hydroxylation pattern of the A-ring is 5,7-hydroxylation; however, occasionally, a 5,7,8- or 5,6,7-hydroxylation pattern is found. The B-ring typically has either a 4'-, a 3',4'-, or a 3',4',5'-hydroxylation pattern. The C-ring is normally a six-membered ring system that contains a carbonyl, hydroxyl, a double bond between carbons 2 and 3, or it can be completely unsubstituted.

Two types of hydroxylases that add hydroxyl groups to the B- and C-rings have been identified: microsomal monooxygenases that are NADPH-dependent cytochrome P-450 enzymes and soluble dioxygenases [136]. Flavonoids can be methylated by O-methyltransferases using S-adenosyl-L-methionine (SAM) as the cofactor. Acylation
Figure 5.1: Overall pathway to the major flavonoids groups [136].
and prenylation of the flavonoids can also occur, however, prenylation is more common in isoflavonoids. Sulfated flavonoids have been isolated and are mainly based on the apigenin or luteolin derivatives. Glycoslation, forming O- and C-glycosides, is an important step that occurs in a late or terminal step of flavonoid biosynthesis resulting in a more water-soluble flavonoid. This is believed to be important for retaining the flavonoids in the vacuole. O-Glycosyltransferases catalyze the reaction using UDP-sugars. Flavones and flavonols, either as aglycones or as the glycosides, are the most variable and abundant of all the flavonoids classes [136]. Although a wide variety of flavonoids with different hydroxylation, methylation, and glycosylation patterns exist, there is also the need to add elements of diversity to the benzopyranone skeleton that are not readily found in nature.

5.2 Reactions to the 4H-1-Benzopyran-4-one Skeleton

Our laboratory has developed a novel solution phase method for constructing 2-substituted-4H-1-benzopyran-4-ones from functionalized salicylic acids and terminal alkynes. The application of this chemistry to solid phase to produce a library of compounds would result in the synthesis of even more compounds that could be screened. Because there are only two sets of building blocks, the salicylic acids and terminal alkynes, the possible combinations of these two building blocks is limited. If the benzopyranones could then be reacted with a third set of building blocks, the number of molecules that could be synthesized could be greatly increased (Figure 5.2).
Figure 5.2: To fully functionalize the 4H-1-benzopyran-4-one ring system, substituents are needed at the 3-position.

Direct hydroxylation of 2-phenyl-4H-1-benzopyran-4-one at the 3-position to form the corresponding flavonols has been described by using hypervalent iodine oxidation (Figure 5.3) [137]. This procedure also has been successful for the oxidation of chromones and α-naphthoflavone. Alternative methods for the formation of 3-hydroxyflavones include phenyl iodosyl diacetate and Phl(OAc)₂; presumably by rearrangement of the intermediary epoxides. Epoxidation of the double bond of the benzopyranone ring system could result in useful intermediates in flavone chemistry. Classical oxidants like alkaline H₂O₂ and m-CPBA fail to epoxidize flavonoids; while other oxidants like KMnO₄, NiO₂, SeO₂, and Tl(OAc)₃ are inert to the flavone moiety [138]. Dimethyldioxirane in acetone, however, has proved to be a mild and selective oxidant of flavonoids (Figure 5.4) [138,139], isoflavones [140-142], aurones [143], and chalcones [144-146]. Labile flavone epoxides have been isolated (>95%) and upon warming to room temperature afford the 3-hydroxy-flavone or upon treatment with MeOH led to the formation of 3-hydroxy-2-methoxyflavanones [138].
Figure 5.3: C-3 hydroxylation of flavone, α-naphthoflavone, and chromone via iodobenzene diacetate-potassium hydroxide methanol oxidation [137].

Flavonoids halogenated α to the carbonyl (C-3) could be useful intermediates in the synthesis of 3-alkyl, alkenyl, and aryl flavonoids. 3-Iodo derivatives of flavones and thioflavones, and thiochromones can be synthesized by iodine-cerium(IV) ammonium nitrate system under mild conditions (Figure 5.5) [147] or by iodination of
3-lithioflavone [148]. Protocols for the palladium-catalyzed cross coupling of α-haloenones with organometals containing Zn, Sn, B, and Cu to give α-organylenones in high yields have been developed [149].

![Figure 5.5: Iodination of flavones, thioflavones, and thiochromones at the 3-position using iodine-cerium (IV) ammonium nitrate system [147].](image)

Flavones are readily attacked by lithium diisopropylamide in tetrahydrofuran at -78°C to form 3-lithioflavone, which can react with various electrophiles to form previously unavailable products (Figure 5.6) [148]. In this way, various groups (i.e., CO₂H, CO₂Et, SiCH₃, I, SH, SCh₃, and OH) can be introduced at the 3-position with relative ease and in excellent yields. Many of these groups can be further derivatized.
5.3 Bromination of the Benzopyranone Skeleton

The structural basis for SERM selectivity is believed to stem from the third aryl group that bears a 4-aminoethoxy substitution. This basic amine side chain of tamoxifen and raloxifene has been shown by x-ray co-crystallographic studies to project into the estrogen receptor (ER) displacing helix 12, blocking the interaction between ER and its cellular transcription machinery, giving rise to the antagonistic effects on target genes. The isoflavonoid genistein has been shown to bind to the ER in the orientation shown in Figure 5.7. It has been proposed in our laboratory that adding a basic amine side chain to the 4\(\beta\)-1-benzopyran-4-one skeleton of genistein could give rise to a new class of ER antagonists.

**Figure 5.6:** Lithiation of flavones with lithium diisopropylamide in tetrahydrofuran [148].
Figure 5.7: Adding a basic amine side onto the 4H-1-benzopyran-4-one skeleton of genistein.

To synthesize genistein analogs bearing a third aryl group containing a 4-aminoethoxy side chain, introduction of aromatic substituents at the 3-position of the benzopyranone nucleus is necessary. Figure 5.8 shows the proposed addition of an aromatic group at the C-3 position by bromination of the benzopyranone followed by a Suzuki coupling.

![Figure 5.8: Proposed synthesis of 3-aryl-4H-1-benzopyran-4-ones via a Suzuki coupling of the 3-bromo derivative.](image)

The initial approach to make 3-bromobenzopyranones was to treat the enaminoketone intermediate with a chloroform solution of bromine, and in one step perform the cyclization and bromination (Figure 5.9) [125,150]. Initial attempts of this reaction...
failed. Thus, an alternative direct synthesis of 3-bromobenzopyranones from the corresponding benzopyranones by pyridinium tribromide/pyridine system was examined [151]. This reaction has worked in all cases with yields ranging from 75-89%. Pyridinium tribromide is an easy to handle stable solid compared to molecular bromine.

![Reaction Scheme]

**Figure 5.9:** Bromination of benzopyranones.

Current efforts in this synthetic strategy involve the Suzuki palladium-catalyzed cross-coupling reaction of 3-bromo-2-substituted-benzopyranones with arylboronic acids (Figure 5.10) [152]. Suzuki et al. reported the novel synthesis of isoflavones by the coupling of 3-bromochromone and phenylboronic acid in the presence of 3 mol% of Pd(PPh3)4 and Na2CO3 (2M) under refluxing benzene in yields ranging from 71-94% [152]. This methodology was applied to 3-bromo-2-phenyl-4H-1-benzopyran-4-one.
using phenylboronic acid and $p$-methoxyphenylboronic acid resulting in isolation of starting material. To minimize steric interactions between substituents at the C-2 and C-3, 3-bromo-7-methoxy-2-propyl-4H-1-benzopyran-4-one was used in the Suzuki coupling again resulting in no reaction. The palladium-catalyzed cross-coupling reactions of organoboron compounds has been extensively studied [153,154]. Optimization of the Suzuki coupling needs to be performed pertaining to the base, catalyst, and solvent used (cite). The completion of the Suzuki coupling will result in formation of 2,3-disubstituted-benzopyranones.

![Suzuki cross-couplings of arylboronic acids with benzopyranones](image)

**Figure 5.10:** Suzuki cross-couplings of arylboronic acids with benzopyranones [152].

### 5.4 DEMETHYLATIONS OF 4H-1-BENZOPYRAN-4-ONES

The pharmacophore for 17β-estradiol binding to the estrogen receptor involves an A-ring phenol separated by a hydrophobic spacer of a specified distance to a second
hydroxyl group on the D-ring. Because hydrophobic pockets exist in the α face of the B-ring and β face of the C-ring, larger groups on estradiol can be accommodated at these positions. This information can be applied to functional groups on the benzopyranone ring system. In order to evaluate the synthetic benzopyranones, methoxy groups need to be demethylated to fully determine the structure activity requirements needed to bind to the estrogen receptor. To date, two series of benzopyranones with methoxy substitutions at the 7- and 8-position have been synthesized (Figure 5.11). Using a solution of boron tribromide in dichloromethane, 8-methoxy-2-phenyl-benzopyranone was successfully demethylated in 60% yield as shown in Figure 14 [155]. Because these conditions failed to demethylate 7-methoxy-2-phenyl-benzopyranone, other conditions were examined. Ethanethiol in combination with either the Lewis acid AlCl₃ in CH₂Cl₂ or sodium hydride in DMF have been employed to demethylate both the series of benzopyranones in yields ranging from 2-98%.
Figure 5.11: Demethylations of benzopyranones.

| $R_1$ | $R_1$ product | $R_2$ | Conditions          | % Yield 
|-------|---------------|-------|---------------------|--------
| 7-OCH$_3$ | 7-OCH$_3$ | phenyl | BBr$_3$, CH$_2$Cl$_2$ | No reaction |
| 8-OCH$_3$ | 8-OH | phenyl | BBr$_3$, CH$_2$Cl$_2$ | 60% |
| 7-OCH$_3$ | 7-OH | phenyl | Et$_3$SiH, AlCl$_3$, CH$_2$Cl$_2$ | 79% |
| 7-OCH$_3$ | 7-OH | phenyl | Et$_3$SiH, NaH, DMF | >95% |
| 7-OCH$_3$ | 7-OH | 4'-methylphenyl | Et$_3$SiH, NaH, DMF | 92-98% |
| 8-OCH$_3$ | 8-OH | 4'-methylphenyl | Et$_3$SiH, NaH, DMF | 62% |
| 7-OCH$_3$ | 3'-chloropropyl | Et$_3$SiH, NaH, DMF | unidentified product |
| 7-OCH$_3$ | 1-Cyclohexenyl | Et$_3$SiH, NaH, DMF | unidentified product |
| 8-OCH$_3$ | 1-Cyclohexenyl | Et$_3$SiH, NaH, DMF | unidentified product |
6.1 Molar Targets of Benzopyranones

Using solution phase chemistry, a library of synthetic 4H-1-benzopyranones has been synthesized in an effort to develop novel agents to treat breast cancer. These compounds have the potential to affect multiple molecular targets in breast cancer including estrogen receptor signaling, estrogen biosynthesis and metabolism, and growth factor signaling cascades (Figure 6.1). Therefore, the screening of benzopyranones against multiple targets needs to be performed. The ability of a benzopyranone to disrupt one or more of these molecular targets could result in potent new therapies for the treatment of hormone dependent breast cancer.

6.2 Initial Screening of Benzopyranone Library

The synthesized benzopyranone analogs were initially evaluated in an cellular proliferation assay in collaboration with S. Joomprabutra to determine the biological effects on human breast cancer cell lines [156]. Cellular proliferation assays are used to assess the cytotoxicity of chemical substances in a simple and rapid fashion. The conditions used in this in vitro assay can be controlled with respect to cell type and
exposure to hormones and/or growth factors. Two different human breast cancer cell lines, estrogen dependent MCF-7 and estrogen independent MDA-MB-231, were used in a primary screening.

Figure 6.1: Molecular targets in breast cancer include inhibition of binding of 17β-estradiol to the estrogen receptor, inhibition of protein tyrosine kinases, inhibition of cyclooxygenases, inhibition of estrogen biosynthesis via aromatase, and metabolism of estradiol to estrogendically weaker or inactive metabolites.
6.2.1 MTS Breast Cancer Cell Cytotoxicity Assay

Various methods for determining cell viability are used including the MTS, BrdU, and
\(^{3}\text{H}\)-thymidine assay. The MTS assay correlates cellular metabolism of tetrazolium salts
into colored, water-soluble formazan products to determine cell viability. The amount
of formazan produced by dehydrogenase enzymes in the cells is directly proportional to
the number of viable cells in culture. The conversion of MTS (3-(4,5-dimethylthiazol-
2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) into the water-
soluble formazan product is accompanied by a color change from yellow to purple
which can be measured at 490 nm (Figure 6.2). This assay has been adapted to 24-well
plates and allows for the rapid screening of compounds.

![Conversion of MTS into its formazan product](image)

Figure 6.2: Conversion of MTS into its formazan product is presumed to be
accomplished by succinate dehydrogenase enzymes in metabolically active cells.

Various controls were used including 17\(\beta\)-estradiol (E2, 10 nM), 4-hydroxymoxifen
(4-OHT, 1\(\mu\)M), ICI 182,780 (ICI, 1 \(\mu\)M), and genistein (Gen, 1 and 10 \(\mu\)M) (Figure
6.3). By incorporating the biological and molecular modeling data, a pharmacophore
model of the benzopyranone analogs targeting growth inhibition of breast cancer cells can be determined and used for directing future synthetic endeavors.

![Chemical Structures]

Figure 6.3: Controls used in the MTS Breast Cancer Cell Proliferation Assay.

6.2.2 Results of Breast Cancer Cell Cytotoxicity Assay

The initial breast cancer cell cytotoxicity assay was used to evaluate the effects of the agents on the growth and cytotoxicity of MCF-7 cells and MDA-MB-231 cells according to the procedure by Joomprabutra [156]. Differential activities were observed with clusters of structurally similar compounds at concentrations of 1.0 μM. The effect of benzopyranones on MCF-7 and MDA-MD-231 breast cancer cell growth can be seen in Figures 6.4 and 6.5. The synthetic 4H-1-benzopyran-4-ones tested had substituents at the 6-, 7-, and 8-positions (H, OCH3, OH, Cl, Ph) and 2-position (phenyl, 4'-methylphenyl, 3-chloropropyl, cyclohexen-1-yl) and can be seen in Figure 4.35. The effect of benzopyranones on the proliferation of MCF-7 cells varies, with the majority of the compounds showing no effect or a stimulatory effect. In general, the strongest stimulatory effects for each class of compounds was with a 2-phenyl substituent. Only three compounds, 83, 93, and 112, show a decrease in proliferation of MCF-7 cells.
Compound 93 and 112 also show this effect in MDA-MB-231 cells. The benzopyranones demonstrate either no effect or an inhibitory effect on MDA-MB-231 cells. Two compounds, 60 and 80, each possessing a 2-phenyl and 7-substituent (OH and Cl, respectively), show proliferative effects on MDA-MB-231 cells. Inhibitory effects on MDA-MB-231 cells were seen with the following compounds: 15, 22, 23, 41, 43, 55, 82, 83, 90, 91, 93, 110, and 112. Compounds with a 2-(3-chloropropyl) side chain or 3-bromo substituent are inhibitory. In general, a 7-chloro, 6-chloro, or 6-phenyl substituent has greater inhibitory effect than a 7-methoxy, 7-hydroxyl, or 8-hydroxy group. Preliminary screening in the proliferation assay demonstrates that the compounds do stimulate and inhibitory effects on human breast cancer cells. Further testing is needed to determine the molecular target of the benzopyranones.
Figure 6.4: Summary of cell proliferation studies on MCF-7 and MDA-MB-231 breast cancer cells using a library of benzopyranones [156].
Figure 6.5: Effects of benzopyranones on A. MCF-7 and B. MDA-MB-231 breast cancer cell proliferation [156].
6.3 Radioligand Estrogen Receptor Displacement Assay

Results from the breast cancer cell cytotoxicity assay suggest that the biological activities of the benzopyranones may be mediated through various biological targets. A decrease or increase only in MCF-7 cell proliferation (no effect on MDA-MB-231 proliferation) could indicate a dependence on estrogen receptor signaling pathways. In order to determine if the agents bind to the estrogen receptor, a radioligand estrogen receptor displacement assay was performed by S. Joomprabutra [156]. This competitive radioligand-binding assay measures the ability of compounds to bind and compete with $^3$H-17β-estradiol for the estrogen receptor. The controls used for this assay were 17β-estradiol (E2, 5 nM), 4-hydroxytamoxifen (4-OHT, 1 μM), ICI 182,780 (ICI, 1 μM), and genistein (Gen, 1 μM). The benzopyranones were tested at 1 μM. The relative binding affinity of benzopyranones for ERα can be seen in Figure 6.6.

6.3.2 Results of $^3$H-E$_2$ Displacement Assay

The method of the cytosolic $^3$H-E$_2$ displacement assay used is that according to Joomprabutra [156] using rat uteri from 3 week old ovariectomized Sprague Dawley. The results from the cytosolic estrogen receptor displacement assay and the molecular docking studies performed by Joomprabutra [156] show that the compounds in native form have relatively low estrogen receptor binding activity (Figure 6.6). Benzopyranones at 1 μM have the ability to bind to ERα in the range of 2% to 20% relative to controls. Genistein displaced 33.5% of $^3$H-17β-estradiol. Compounds 30 and 51 show the highest binding abilities of all the compounds tested. The results from
the proliferation and displacement assays for compounds 30 and 51 (growth stimulation in MCF-7 cells, no activity in MDA-MB-231 cells) suggest that they may be weak partial agonists for the estrogen receptor.

Figure 6.6: Relative binding affinity to ERα by synthetic benzopyranones [156].
6.4 AROMATASE AS A POTENTIAL MOLECULAR TARGET

Because the biosynthesis of 17β-estradiol by the enzyme aromatase occurs locally within breast tissue, inhibition of aromatase is an alternative target for treating estrogen-dependent breast cancer (Figure 6.7). Screening of the benzopyranone library (1 μM) in a human placental microsome aromatase assay was performed by J. Baker, Jr. to determine if the synthetic benzopyranones could inhibit aromatase [157].

Figure 6.7: Endocrine control of breast cancer.
6.4.1 Human Placental Microsome Aromatase Assay

The aromatase assay according to the procedure used by Baker [157] uses cytosolic aromatase enzyme from human placental tissues to catalyze the conversion of \([1\beta-^3H]\)-androst-4-ene-3,17-dione to estrone and \(^3H_2O\) in the presence of NADPH and \(O_2\) (Figure 6.8). The tritiated \(H_2O\) released is counted via liquid scintillation and is an index of estrogen formation. A NADPH regeneration system is needed to reduce NADP\(^+\) to NADPH because aromatase is an NADPH dependent enzyme. 7α-Aminophenylthio-androsta-1,4-diene,3,17-dione (7α-APTADD) is an enzyme-activated irreversible inhibitor of aromatase and was used as a positive control (Figure 6.9). 7α-APTADD was designed and initially synthesized in our laboratory [158]. It has an apparent \(K_i\) of 10 nM. Chrysin (5,7-dihydroxyflavone) is marketed in supplement stores as an aromatase inhibitor to increase or maintain higher levels of androgens [83] and was used as a positive control.
Figure 6.8: Aromatase assay.

Figure 6.9: 7α-(Aminophenylthio)-androsta-1,4-diene,3,17-dione is an enzyme-activated irreversible inhibitor of aromatase used as a positive control. Chrysin and apigenin were also used as positive controls in the aromatase assay.
6.4.2 Results of Human Placental Microsome Aromatase Assay

The results from the human placental microsome aromatase assay for the 4H-1-benzopyran-4-one library (1μM) are found in Figure 6.10. IC₅₀ values were determined for fifteen of the benzopyranones (Table 6.1) [157]. The best aromatase inhibitor of the synthetic benzopyranones was 113, 2-(3-chloropropyl)-6-phenyl-4H-1-benzopyran-4-one (IC₅₀ = 1.34 μM) followed closely by 52 2-(1-cyclohexen-1-yl)-7-methoxy-4H-1-benzopyran-4-one (IC₅₀ = 1.72 μM). Changing the 6-phenyl substituent of 113 to a 6-chloro 93 increases the IC₅₀ to 25.58 μM. Substituents at the 7-position have lower IC₅₀ values than substituents at the 8-position, which correlates to known SAR of flavonoids for aromatase [64].
Figure 6.10: Effects of benzopyranones on % aromatase activity in a cytosolic aromatase assay. P < 0.05 shown with *.

The concentration of 7α-APTADD was 50 nM. Benzopyranones were tested at 1 μM, n = 3 or 4 [157].
Table 6.1: IC\textsubscript{50} values for Aromatase Assay [157].
CHAPTER 7

CONCLUSIONS

2,3-Substituted-4H-1-benzopyran-4-ones have been synthesized in moderate to excellent yields from readily available starting materials (salicylic acids and terminal alkynes) via a one-pot acid chlorination, Sonogashira coupling followed by a 6-endo-trig cyclization. In developing this synthetic strategy, we have accomplished mild, high yielding reactions that are tolerant of various functional groups to give exclusive formation of the 4H-1-benzopyran-4-one ring system while remaining amenable to solid phase.

Silylated salicylic acids are converted to the corresponding acid chlorides under neutral conditions using oxalyl chloride. Quenching of the acid chloride with an ethanol in pyridine/ether mixture resulted in the isolation of the ethyl ester in 77-91%, indicative of the clean formation of the acid chloride. The acid chlorination can be directly followed by the Sonogashira coupling resulting in the one-pot synthesis of alkynone intermediates. The electronic and steric requirements of the alkyne and salicylic acid and their usefulness in the Sonogashira coupling have been determined. Aryl and alkyl alkynes couple in yields ranging from 40-90%. Reaction conditions were optimized
based on both of the reactants while minimizing the competing Glaser homocoupling of alkynes. Four variations for the Sonogashira coupling were employed.

As seen in the literature, a free phenolic hydroxyl can effect either a 6-endo-*trig* or 5-exo-*dig* cyclization resulting in the nonselective formation of benzopyranones and benzofuranones, respectively. The benzopyranones have been regioselectively synthesized by converting the alkynones into enaminoketone intermediates and protection of the ortho phenol. Upon removal of the protecting group, the system is prone to Michael addition followed by elimination of the secondary amine to yield the desired benzopyranone as a 6-endo-*trig* cyclization in yields ranging from 53-96%. A high-throughput synthesis of benzopyranones has also been developed, eliminating the need for intermediate purification of alkynones by flash chromatography. Structure elucidation via heteronuclear shift correlation experiments and UV absorption have confirmed the presence of the benzopyranone ring system. Bromination of the benzopyranone ring system at the three-position via pyridinium tribromide/pyridine system allows for the potential to add aryl groups via a Suzuki coupling in order to make isoflavonoid analogs. Conditions for demethylation of the aryl methylethers have been accomplished via BBr₃ or ethanethiol. Future synthetic efforts need to examine the utilization of other protecting groups for hydroxyl groups at R₁ because of difficulty removing aryl methylethers in the presence of 2-(3-chloropropyl) and 2-(1-cyclohexen-1-yl) substituents.
This chemistry has potential application to solid-phase to make a larger library of novel synthetic benzopyranones. This ring system can also undergo diversification to make a large array of compounds. In the future, the completion of the Suzuki coupling will allow the generation of the isoflavonoid ring system. Although outside the scope of this dissertation, I have proposed to exploit the isoflavonoid template of genistein to develop a series of novel antiestrogenic isoflavonoid analogs as possible therapeutic agents to treat human breast cancer. Pharmacophores present in nonsteroidal or steroidal antiestrogens are basic amine and long unsubstituted aliphatic chains. It is my hypothesis that substitutions at the 2-position of the 4H-1-benzopyran-4-one ring system could mimic the long aliphatic 7α-side chain of the ICI compounds or the basic amine of tamoxifen and raloxifene to produce novel modulators of ERα and ERβ (Figure 7.1, 7.2). The proposed isoflavonoids could enable binding to ER in two distinct orientations, thus, substituents at the 2-position could occupy either of the two large hydrophobic cavities that exist in ER (α face of B-ring or β-face of C-ring). Modifications of 4H-1-benzopyran-4-one ring system at the 2-position, mimicking the side chains of known antiestrogens, should yield novel antiestrogens that could aid in fully understanding the tissue selectivity differences of ERα and ERβ.
1. Basic amine side chains (raloxifene mimics)

\[ R = (\text{CH}_2)_n \text{-OH} \]

where \( n = 0, 1 \)

where \( Y = \text{H, } \text{CH}_3, \text{CH}_2\text{N(CH}_3)_2, \text{N(Et)}_2\text{N} \)

2. Alkyl amine, sulfide, and carboxylic acid side chains

\[ R_1 = \text{CH}_2\text{SCH}_3, \text{CH}_2\text{SCH}_2\text{CH}_3, \text{CH}_2\text{N(CH}_3)_2, \text{CH}_2\text{N(Et)}_2\text{N}, \text{CH}_2\text{N-C-H}_2\text{N-C} \]

3. Long unsubstituted aliphatic side chains (ICI mimics)

\[ R_1 = \text{CH}_2\text{SCH}_3, \text{CH}_2\text{SCH}_2\text{CH}_3, \text{CH}_2\text{N(CH}_3)_2, \text{CH}_2\text{N(Et)}_2\text{N}, \text{CH}_2\text{N-C-H}_2\text{N-C} \]

Figure 7.1: Potential isoflavonoid analogs that could be synthesized based upon the 4/7-1-benzopyran-4-one ring system.
Figure 7.2: Synthetic strategy of isoflavonoid analogs as ICI mimics, raloxifene/tamoxifen mimics, and alkyl amine and sulfide derivatives.
CHAPTER 8

EXPERIMENTAL METHODS

8.1 General Methods

Chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) or Lancaster Chemical Inc. (Windham, NH) and were used as received unless otherwise indicated. Anhydrous solvents were dried by standard procedures. To remove traces of primary and secondary amines, triethylamine was refluxed with phthalic anhydride, then distilled, refluxed with CaH₂, distilled again, and stored over sieves. All reactions were carried out under an inert atmosphere of argon unless otherwise specified. Glassware was flame dried under a flow of argon. Thin layer chromatography was performed on Whatman precoated silica gel F₂₅₄ aluminum foils and were purchased from Fisher Scientific (Fair Lawn, NJ). Visualization was accomplished with a UV lamp and/or staining with 5% ethanolic phosphomolybdic acid or KMNO₄. Intermediates were purified by flash column chromatography using a glass column wet packed with silica gel (32-63 μm particle size, 230-400 mesh) using the indicated solvent systems. ¹H NMR and ¹³C NMR (proton decoupled) spectra were recorded using a Bruker AF 250, Bruker DPX 250, or Bruker DRX 400 model spectrometer in CDCl₃ solutions unless otherwise indicated using the residual protiosolvent signal as internal reference. Two-
dimensional experiments were carried out using a Bruker DRX 400. IR spectra were recorded on a Nicolet Protégé 460 model spectrometer in the phase indicated. UV spectra were recorded on a Perkin Elmer Lambda 10. All melting points were determined in open glass capillaries using a Thomas Hoover apparatus and are uncorrected. Formula conformations (HR) and molecular weight measurements (LR) were obtained at The Ohio State Chemical Instrumentation Center using a Micromass OTOF II ESI, a Bruker Esquire ESI, or a Finnigan MAT900 EI. HPLC-grade MeOH and acetonitrile were obtained from Fisher Scientific. HPLC mobile phase was filtered through a 0.45 μm Nylon-66 membrane filter before use. HPLC was conducted on a Beckman system using a Spectroflow 757 UV detector (254 nm) and a reverse-phase column. Two HPLC solvent systems were used to determine purity: System #1- 70/30 MeOH/H₂O using a Beckman Ultrasphere ODS column (5 micron, 4.5 μm ID x 15 cm) and System #2- 65/35 acetonitrile/H₂O using a Phenomenex Luna phenyl-hexyl column (5 micron, 4.6 μm ID x 25 cm) with a flow rate of 1 mL/min.
8.2 SYNTHETIC METHODS

8.2.1 SYNTHESIS OF PALLADIUM CATALYST

Dichlorobis(triphenylphosphine)palladium (JLW-I-200): Following literature procedure of Herrman & Salzer, sodium tetrachloropalladate (II) (0.5 g, 1.7 mmol) and triphenylphosphine (0.95 g, 3.6 mmol) are suspended in EtOH (50 mL) under argon and stirred at room temperature for 24 h [120]. Upon addition of triphenylphosphine to sodium tetrachloropalladate solution, color change from brownish red to yellow. The resulting reaction mixture was filtered by gravity to give a yellow precipitate, which was further washed with H₂O, EtOH, and Et₂O. Solid was recrystallized from CHCl₃/petroleum ether to yield 1.1 g (90%) of the title compound as a yellow powder.

8.2.2 GENERAL METHOD FOR PREPARATION OF 2-[[1,1-DIMETHYLETHYL]DIMETHYSILYL]OXY]-BENZOIC ACID, ETHYL ESTER DERIVATIVES.

Under argon atmosphere, oxalyl chloride (0.10 mL, 1.2 mmol) was added dropwise to a cold (0°C) solution of 2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester derivative (0.38 g, 1.0 mmol) in CH₂Cl₂ (4 mL) containing 3 drops of DMF. The resulting solution was stirred at 0°C for 2 h. The reaction was warmed to room temperature and stirred for 17 h followed by concentration in vacuo. A 1:1:1 ratio of EtOH:ether:pyridine (3 mL) was added dropwise to the residue and stirred at room temperature under argon for 2 hours. The reaction mixture was concentrated in vacuo. Ether was added to the residue and the
precipitate was filtered through a glass sintered filter. The filtrate was concentrated in vacuo and purified via flash chromatography (silica gel, 4.5:1 hexanes:EtOAc) to yield desired product.

2-[[1,1-Dimethylsilyl]oxy]-3-methoxybenzoic acid, ethyl ester (JLW-II-080):

Using the previous procedure and starting from 0.40 g (1.0 mmol) of 2-[[1,1-dimethylsilyl]oxy]-3-methoxybenzoic acid, (1,1-dimethylsilyl)dimethylsilyl ester, 0.27 g (86%) of the title compound was obtained as a colorless oil: IR (neat, cm⁻¹) 2953, 2857, 1731, 1288, 1062; ¹H NMR (CDCl₃) δ 7.19 (dd, J = 7.1, 2.3 Hz, 1H), 6.89-6.86 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 0.96 (s, 9H), 0.13 (s, 6H); ¹³C NMR (CDCl₃) δ 166.9, 151.0, 144.4, 124.5, 121.9, 120.6, 114.3, 60.7, 55.1, 25.6, 18.7, 14.2, -4.3; HRMS m/z (M + Na⁺) calculated for C₁₆H₂₆O₄Si was 333.1493, found 333.1489.
2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-4-methoxybenzoic acid, ethyl ester (JLW-II-084):

Using the previous procedure and starting from 0.41 g (1.0 mmol) of 2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-4-methoxybenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester, 0.29 g (90%) of the title compound was obtained as a colorless oil: IR (neat, cm⁻¹) 2956, 2858, 1725, 838; ¹H NMR (CDCl₃) δ 7.75 (d, J = 8.8 Hz, 1H), 6.49 (dd, J = 8.8, 2.3 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H), 0.20 (s, 6H); ¹³C NMR (CDCl₃) δ 165.9, 163.3, 157.1, 133.2, 115.5, 106.7, 106.6, 60.2, 55.2, 25.7, 18.3, 14.4, -4.4; HRMS m/z (M + Na⁺) calculated for C₁₆H₂₆O₄Si was 333.1493, found 333.1474.

2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-5-methoxybenzoic acid, ethyl ester (JLW-II-081):

Using the previous procedure and starting from 0.42 g (1.1 mmol) of 2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-5-methoxybenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester, 0.30 g (91%) of the title compound was obtained as a colorless oil: IR (neat, cm⁻¹) 2956, 2858, 1731, 1284, 1073; ¹H NMR (CDCl₃) δ 7.19 (d, J = 3.2 Hz, 1H), 6.87 (dd, J = 8.9, 3.2 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.71 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H), 0.20 (s, 6H); ¹³C NMR (CDCl₃) δ 165.9, 163.3, 157.1, 133.2, 115.5, 106.7, 106.6, 60.2, 55.2, 25.7, 18.3, 14.4, -4.4; HRMS m/z (M + Na⁺) calculated for C₁₆H₂₆O₄Si was 333.1493, found 333.1474.
1.31 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.13 (s, 6H); $^1$H NMR (CDCl$_3$) δ 166.6, 157.5, 153.2, 130.3, 116.5, 111.8, 103.9, 61.1, 55.9, 25.5, 18.0, 14.1, -4.4; HRMS m/z (M + Na$^+$) calculated for C$_{16}$H$_{26}$O$_4$Si was 333.1493, found 333.1475.

2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-6-methoxybenzoic acid, ethyl ester (JLW-II-068):

Using the previous procedure and starting from 0.26 g (0.6 mmol) of 2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-6-methoxybenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester, 0.16 g (77%) of the title compound was obtained as a colorless oil: IR (neat, cm$^{-1}$) 2957, 2858, 1736, 1311, 1291, 1258, 1069, 839; $^1$H NMR (CDCl$_3$) δ 7.14 (t, J = 8.3 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.19 (s, 6H); $^{13}$C NMR (CDCl$_3$) δ 166.6, 157.5, 153.2, 130.3, 116.5, 111.8, 103.9, 61.1, 55.9, 25.5, 18.0, 14.1, -4.4; LRMS m/z (M + Na$^+$) calculated for C$_{16}$H$_{26}$O$_4$Si was 333.1493, found 333.15.
2-Hydroxy-4-methoxybenzoic acid (JLW-I-104): Dihydroxybenzoic acid (15.4 g, 0.1 mol) was added to a 20% NaOH solution (50 mL) under argon. The resulting orange-yellow solution was stirred for 30 min until almost all solid was dissolved. Dimethyl sulfate (10.41 mL, 0.11 mol) was added and stirred for 2 h. The reaction was neutralized to pH = 7 with conc. HCl and extracted with Et₂O (3 x 100 mL). The aqueous layer was acidified to pH 1 and the resulting white precipitate was collected by vacuum filtration, washed with H₂O, and dried. Recrystallization from EtOH/H₂O to yield 8.3 g (50%) of the title compound as a white solid; mp 156-158°C; IR (KBr, cm⁻¹) 3441, 1648; ¹H NMR (DMSO-d₅) δ 7.69 (d, J = 9.6 Hz, 1H), 6.50-6.45 (m, 2H), 3.78 (s, 3H); ¹³C NMR (DMSO-d₅) δ 171.7, 165.0, 163.3, 131.5, 106.9, 105.5, 100.6, 55.5; HRMS m/z (M⁺) calculated for C₈H₆O₄ was 168.0420, found 168.0430.
5-(tert-Butoxycarbonyl)-amino-2-hydroxy-benzoic acid (JLW-I-255):

According to procedure by Chen et al.[110], triethylamine (5.8 mL, 40 mmol) and di-
tert-butylcarbonate (8.73 g, 40 mmol) were added to a mixture of 5-aminosalicylic acid
(3.06 g, 20 mmol) in undistilled dioxane (53 mL) and water (27 mL). The reaction was
stirred at room temperature under argon for 3 hours. The reaction mixture was
concentrated in vacuo to reduce the volume by half. The reaction mixture was
acidified with 3 M HCl, a precipitate was collected by filtration, washed with water, and dried to
afford 4.9 g (96%) of the title compound as a pale brown solid: mp 274-276°C
(decomposition); IR (KBr, cm⁻¹) 1670.5, 1689.4, 3004.1, 3273.1, 3344.4; ¹H NMR
(DMSO-d₆) δ 9.25 (s, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.9, 2.7 Hz, 1H), 6.86
(d, J = 8.9 Hz, 1H), 1.45 (s, 9H); ¹³C NMR (DMSO-d₆) δ 171.8, 156.4, 152.9, 131.2,
126.6, 119.2, 117.1, 112.3, 78.9, 28.1; HRMS m/z (M + Na⁺) calculated for C₁₂H₁₃NO₅
was 276.0848, found 276.0868.
2-Hydroxy-5-phenyl-benzoic acid (JLW-I-254):

5-Bromosalicylic acid (1.08 g, 5 mmol), sodium carbonate (1.59 g, 15 mmol), and phenylboronic acid (0.67 g, 5.5 mmol) were dissolved in water (25 mL) under argon[109]. Palladium (II) acetate (11.2 mg, 0.05 mmol, 1 mol%) was added and reaction mixture was stirred at room temperature for 1 h to give a gray color with a precipitate present. The slurry was then dissolved in water (300 mL) and treated with HCl until it was acidic to litmus. The precipitate was filtered off and dissolved in ether (20 mL). The ether solution was filtered through a sintered glass funnel to remove Pd-black. The filtrate was concentrated in vacuo and the resulting residue was dissolved in water and treated with dilute NaOH until it was basic to litmus and filtered. The filtrate was treated with HCl, precipitate was filtered off, washed with water, and dried to afford 1.07 g (91%) of the title compound as a white solid: mp 211-212°C; IR (KBr, cm\(^{-1}\)) 1666.9, 3037.1, 3250.6, 3500; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 8.02 (d, \(J = 2.4\) Hz, 1H), 7.82 (dd, \(J = 8.6, 2.4\) Hz, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 7.44 (t, \(J = 7.8, 7.2\) Hz, 2H), 7.32 (t, \(J = 7.2\) Hz, 1H), 7.05 (d, \(J = 8.6\) Hz, 1H); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 171.6, 160.5, 139.0, 133.8, 131.2, 128.9, 127.9, 127.0, 126.1, 117.8, 113.4; HRMS \(m/z\) (M + Na\(^+\)) calculated for C\(_{13}\)H\(_{10}\)O\(_3\) was 237.0528, found 237.0549.
8.2.4 General Method for Preparation of 2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, ethyl ester, (1,1-dimethylethyl)dimethylsilyl ester derivatives.

Et$_3$N (2.8 mL, 20 mmol) was added to a solution of 2-hydroxybenzoic acid derivative (0.84 g, 5 mmol) in freshly distilled CH$_2$Cl$_2$ (13 mL). A solution of tert-butyldimethylchlorosilane (1.7 g, 11 mmol) in CH$_2$Cl$_2$ (3.5 mL) was cannulated dropwise into the reaction mixture resulting in a cloudy solution. After the reaction was stirred at room temperature for 27 h, toluene (50 mL) was added and the suspension was concentrated to approximately 20 mL in vacuo followed by vacuum filtration to remove the precipitated Et$_3$N-HCl salt. The precipitate was thoroughly washed with hexanes and toluene and the combined organics were concentrated. The residue was purified on a short column (silica gel, 4.5:1 hexane:EtOAc) to yield desired product.
2-[[((1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxybenzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (JLW-I-166):

Using the previous procedure and starting from 2-hydroxy-3-methoxybenzoic acid (0.84 g, 5 mmol), 1.88 g (95%) of the title compound as a pale peach oil: IR (neat, cm\(^{-1}\)) 2954, 2932, 2888, 2859, 1711, 1325, 1291, 1255, 1060; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.27 (dd, \(J = 2.1, 2.0\) Hz, 1H), 6.93 (dd, \(J = 2.1, 2.0\) Hz, 1H), 6.86 (t, \(J = 7.6, 8.1\) Hz, 1H), 3.77 (s, 3H), 0.98 (s, 9H), 0.98 (s, 9H), 0.34 (s, 6H), 0.15 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\)) 165.9, 151.8, 146.0, 125.4, 123.0, 120.7, 115.1, 55.7, 26.2, 26.1, 19.2, 18.2, -3.8, -4.3; HRMS \(m/z\) (M\(^+\)) calculated for C\(_{20}\)H\(_{36}\)O\(_4\)Si\(_2\) was 396.2142, found 396.2199.

2-[[((1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methylbenzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (JLW-I-167):

Using the previous procedure and starting 2-hydroxy-3-methylbenzoic acid (1.53 g, 10 mmol, 3.64 g (95%) of the title compound was obtained as a colorless oil: IR (neat, cm\(^{-1}\)) 2955, 2932, 2888, 2859, 1711, 1279, 840, 806; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.92 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.61 (dd, \(J = 7.5, 1.1\) Hz, 1H), 7.22 (t, \(J = 7.8, 1\) Hz, 1H), 2.59 (s, 3H), 1.38 (s,
9H), 1.35 (s, 9H), 0.71 (s, 6H), 0.47 (s, 6H); $^{13}$C NMR (CDCl$_3$) 165.9, 153.9, 134.8, 131.0, 129.0, 124.5, 120.7, 26.0, 25.7, 18.5, 17.8, 17.4, -3.6, -4.7; HRMS m/z (M$^+$) calculated for C$_{20}$H$_{36}$O$_3$Si$_2$ was 380.2193, found 380.2245.

![](image)

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxybenzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (JLW-I-118):

Using the previous procedure and starting from 2-hydroxy-4-methoxybenzoic acid (1.7 g, 10 mmol), 3.8 g (95%) of the title compound was obtained as a colorless oil: IR (CCl$_4$, cm$^{-1}$) 2859, 1700, 1607, 1259, 843, 761; $^1$H NMR (CDCl$_3$) $\delta$ 7.75 (d, $J = 8.8$ Hz, 1H), 6.49 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.38 (d, $J = 2.7$ Hz, 1H), 3.78 (s, 3.2H), 1.00 (s, 9.7H), 0.98 (s, 8.7H), 0.32 (s, 6.6H), 0.20 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 164.5, 163.5, 158.2, 133.4, 116.5, 107.2, 106.7, 55.3, 25.9, 25.8, 18.5, 17.8, -4.4, -4.6; HRMS m/z (M$^+$) calculated for C$_{20}$H$_{36}$O$_3$Si was 396.2142, found 396.2139.
2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxybenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (JLW-II-034):

Using the previous procedure and starting from 4-methylsalicylic acid (5.0 g, 33 mmol), 12.4 g (99%) of the title compound was obtained as a pale yellow oil: IR (neat, cm⁻¹) 2956, 2930, 2868, 2859, 1712, 1611, 1250, 1081, 840; ¹H NMR (CDCl₃) δ 7.65 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.67 (s, 1H), 2.30 (s, 3H), 1.00 (s, 9H), 0.98 (s, 9H), 0.33 (s, 6H), 0.19 (s, 6H); ¹³C NMR (CDCl₃) δ 165.5, 156.5, 144.2, 132.1, 122.8, 122.1, 121.5, 26.3, 26.2, 21.9, 18.9, 18.2, -3.9, -4.3; LRMS m/z (M + H⁺) calculated for C₂₀H₃₆O₃Si₂ was 381.2271, found 381.1.

4-Chloro-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (JLW-I-258):

Using the previous procedure and starting from 4-chlorosalicylic acid (1.7 g, 10 mmol), 3.6 g (91%) of the title compound was obtained as a pale yellow-brown oil: IR (neat, cm⁻¹) 841.3, 955.5, 1094.3, 1141.8, 1254.3, 1363.2, 1403.2, 1591.2, 1715.4, 2859.5-2955.4; ¹H NMR (CDCl₃) δ 7.67 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.4, 2.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.34 (s, 6H), 0.21 (s, 6H); ¹³C NMR
(CDCl₃) δ 164.3, 156.8, 138.3, 132.5, 122.6, 121.8, 121.1, 25.7, 25.7, 18.4, 17.8, -4.4, -4.7; HRMS m/z (M + H⁺) calculated for C₁₉H₃₃ClO₃Si₂ was 401.1735, found 401.1718.

5-Chloro-2-[(1,2-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (JLW-I-222):

Using the previous procedure and starting from 5-chlorosalicylic acid (0.86 g, 5 mmol), 1.79 g (99%) of the title compound was obtained as a colorless oil: IR (neat, cm⁻¹) 2955, 2931, 2886, 2859, 1716: ¹H NMR (CDCl₃) δ 7.65 (d, J = 2.8 Hz, 1H), 7.28 (dd, J = 8.8, 2.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 0.98 (s, 9H), 0.98 (s, 9H), 0.33 (s, 6H), 0.18 (s, 6H); ¹³C NMR (CDCl₃) δ 164.0, 154.5, 132.6, 131.1, 125.5, 125.3, 122.9, 25.7, 18.4, 17.8, -4.4, -4.7; HRMS m/z (M + Na⁺) calculated for C₁₉H₃₃ClO₃ was 423.1554, found 423.1528.

5-(tert-Butoxycarbonyl)-amino-2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (JLW-I-257):

Using the previous procedure and starting from 5-(tert-butoxycarbonyl)amino-2-hydroxy benzoic acid (2.5 g, 10 mmol), 4.5 g (94%) of the title compound was obtained as a pale brown solid: mp 111-113°C; IR (KBr, cm⁻¹) 842.6, 1252.8, 1503.3, 1529.2,
1697.9, 1713.2, 2860.0, 2933.8, 2957.5, 3354.9; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.51 (d, \(J = 2.5\) Hz, 2H), 6.79 (d, \(J = 9.4\) Hz, 1H), 6.40 (s, 1H), 1.48 (s, 9H), 0.97 (s, 9H), 0.97 (s, 9H), 0.32 (s, 6H), 0.15 (s, 6H); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 164.4, 152.5, 151.2, 130.9, 123.7, 123.5, 121.7, 121.5, 80.0, 27.9, 25.4, 25.3, 17.9, 17.4, -4.9, -5.1; HRMS \(m/z\) (M + Na\(^+\)) calculated for C\(_{24}\)H\(_{43}\)NO\(_5\)Si\(_2\) was 504.2578, found 504.2589.

![Chemical Structure](image)

**2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-phenylbenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (JLW-I-256):**

Using the previous procedure and starting from 2-hydroxy-5-phenylbenzoic acid (0.96 g, 4.5 mmol), 1.7 g (88%) of the title compound was obtained as a white solid: mp 88-90°C; IR (KBr, cm\(^{-1}\)) 845.6, 928.1, 1085.3, 1231.3, 1272.5, 1482.0, 1709.0, 2856.8, 2928.6, 2953.8; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.01 (d, \(J = 2.5\) Hz, 1H), 7.60 (dd, \(J = 8.6, 2.5\) Hz, 2H), 7.56 (s, 1H), 7.46 (t, \(J = 7.7\) Hz, 2H), 7.37-7.35 (m, 1H), 6.98 (d, \(J = 8.5\) Hz, 1H), 1.05 (s, 9H), 1.04 (s, 9H), 0.40 (s, 6H), 0.27 (s, 6H); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 165.3, 155.3, 140.1, 133.7, 131.3, 130.0, 128.8, 127.0, 126.6, 124.4, 121.9, 25.8, 25.8, 18.4, 17.8, -4.3, -4.6; HRMS \(m/z\) (M + Na\(^+\)) calculated for C\(_{25}\)H\(_{38}\)O\(_3\)Si\(_2\) was 465.2257, found 465.2266.
2-[(1,1-Dimethylethyl)dimethysilyloxy]-5-methoxybenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (JLW-II-061):

Using the previous procedure and starting from 5-methoxysalicylic acid (3.4 g, 20 mmol), 7.7 g (97%) of the title compound was obtained as a yellow oil: IR (neat, cm⁻¹) 2931, 2897, 2859, 1713, 1574, 12779, 1072, 841; ¹H NMR (CDCl₃) δ 7.25 (s, 1H), 6.91 (dd, J = 8.9, 3.2 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 3.76 (s, 3H), 0.98 (s, 18H), 0.33 (s, 6H), 0.15 (s, 6H); ¹³C NMR (CDCl₃) δ 165.0, 153.1, 149.8, 124.2, 122.6, 119.1, 115.6, 55.6, 25.9, 25.8, 18.4, 17.8, -4.4, -4.7; LRMS m/z (M + H⁺) calculated for C₂₀H₃₆O₄Si₂ was 397.2220, found 297.17.

2-[(1,1-Dimethylethyl)dimethysilyloxy]-6-methoxybenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (JLW-II-062):

Using the previous procedure and starting from 6-methoxysalicylic acid, 8.0 g (100%) of the title compound was obtained as a colorless oil: IR (neat, cm⁻¹) 2931, 2887, 2859, 1716, 1595, 840; ¹H NMR (CDCl₃) δ 7.11 (t, J = 8.3 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 3.76 (s, 3H), 0.95 (s, 9H), 0.94 (s, 9H), 0.33 (s, 6H), 0.20 (s,
$^1$H; $^{13}$C NMR (CDCl$_3$) δ 166.3, 157.3, 152.8, 129.6, 118.5, 112.0, 103.8, 55.7, 25.7, 25.5, 18.2, 17.8, -4.3, -4.6; LRMS m/z (M + H$^+$) calculated for C$_{25}$H$_{36}$O$_4$Si$_2$ was 396.2142, found 397.20.

8.2.5 General Method for Preparation of Acid Chlorides of 2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-benzoic acid, ethyl ester, (1,1-dimethylethyl)dimethylsilyl ester derivatives.

Under an argon atmosphere, oxalyl chloride (0.1 mL, 1.2 mmol) was added dropwise to a cold (0°C) solution of 2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-4-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester derivative (0.40 g, 1.0 mmol) in CH$_2$Cl$_2$ (4 mL) containing 3 drops of DMF. The resulting solution was stirred at 0°C for 2 h. The reaction was warmed to room temperature and stirred for 17 h to afford a pale yellow solution, followed by concentration *in vacuo*. The residue from the acid chlorination immediately underwent a Sonogashira coupling according to procedures described.

8.2.6 General Method for Preparation of Alkynone 1-[2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-phenyl]-2-propyn-1-one derivatives via Sonogashira Coupling.

There were four different procedures used for the one-pot acid chlorination Sonogashira couplings used. Detailed experimental conditions including effects of the scale of the reaction (mmol), the reaction time (h), and the amount of alkyne (equiv) can be seen in Tables 3.2 and 3.3.
**Coupling A:** Et₃N (4 mL) was slowly added to the residue from the acid chlorination and argon was bubbled into solution for 5 min. The alkyne, Pd(P₃Ph)₂Cl₂ (1 mg/mmol alkyne), and CuI (1 mg/mmol alkyne) were added and argon gas was again bubbled through solution for 5 min. The reaction was stirred at room temperature for specified amount of time. The reaction mixture was concentrated *in vacuo* after adding MeOH (5 mL). The residue was taken up into Et₂O, washed with H₂O, 10% NH₄OH, brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified via flash chromatography (silica gel, 4.5:1 hexanes:EtOAc) to yield the desired product.

**Coupling A**: The same as Procedure A, except deoxygenation was not performed.

**Coupling B:** Et₃N (4 mL) was slowly added to the residue from the acid chlorination and argon was bubbled into solution for 5 min. The alkyne and CuI (1 mg/mmol alkyne) were added and argon gas was again bubbled through solution for 5 min, followed by the addition of Pd(P₃Ph)₂Cl₂ (1 mg/mmol alkyne) and deoxygenation. The reaction was stirred at room temperature for specified amount of time. The reaction mixture was concentrated *in vacuo* after adding MeOH (5 mL). The residue was taken up into Et₂O, washed with H₂O, 10% NH₄OH, brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified via flash chromatography (silica gel, 4.5:1 hexanes:EtOAc) to yield the desired product.
**Coupling C:** A solution of alkyne and Cul (1 mg/mmol alkyne) in Et₃N (4 mL) under argon was stirred at room temperature for 15 min. This solution was cannulated into the concentrated residue from the acid chlorination, treated with Pd(PPh₃)₂Cl₂ (1 mg/mmol alkyne) and any residual Cul, and argon was bubbled through the solution for 15 min. Reaction progress was followed closely by TLC (4.5:1 hexanes:EtOAc). The reaction was stirred at room temperature for a specified amount of time and concentrated in vacuo after addition of MeOH (5 mL). The residue was either adhered to silica gel and purified via flash chromatography (silica gel, 4.5:1 hexanes:EtOAc) to yield the desired product or dissolved in EtOAc, filtered through a pad of celite, concentrated, and used in the subsequent cyclization step without further purification.

**Coupling D:** Et₃N (4 mL) was slowly added to the residue from the acid chlorination and argon was bubbled into solution for 5 min. Cul (1 mg/mmol alkyne) Pd(PPh₃)₂Cl₂ (1 mg/mmol alkyne) were added and argon gas was again bubbled through solution for 5 min. Alkyne (1.2 equiv) was added to reaction mixture followed by another 1.2 equiv of alkyne 4 h later. The reaction was stirred at room temperature for a specified time. The reaction mixture was concentrated in vacuo after adding MeOH (5 mL). The residue was taken up into Et₂O, washed with H₂O, 10% NH₄OH, brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified via flash chromatography (silica gel, 4.5:1 hexanes:EtOAc) to yield the desired product.
1-[[2-[[1,1-Dimethylethyl]dimethylsilyloxy]-3-methoxyphenyl]-3-phenyl-2-propyn-1-one (JLW-I-169):

2-[[1,1-Dimethylethyl]-dimethylsilyloxy]-4-methoxy-benzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (0.40 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.49 mL, 4 mmol) according to Coupling A to yield 0.26 g (70%) of the title compound as a yellow-orange oil: IR (CCl₄, cm⁻¹) 3065, 2931, 2895, 2857, 2203, 1647, 1297, 1259, 1021; ¹H NMR (CDCl₃) δ 7.60-7.56 (m, 2H), 7.51 (dd, J = 7.0, 2.6 Hz, 1H), 7.40-7.33 (m, 3H), 7.10-6.96 (m, 2H), 3.78 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); ¹³C NMR (CDCl₃) δ 176.9, 151.4, 133.1, 133.0, 130.4, 128.8, 128.5, 123.3, 120.7, 120.7, 115.8, 98.8, 55.3, 25.8, 18.9, -4.0.

1-[[2-[[1,1-Dimethylethyl]dimethylsilyloxy]-3-methylphenyl]-3-phenyl-2-propyn-1-one (JLW-I-170):

2-[[1,1-Dimethylethyl]-dimethylsilyloxy]-4-methyl-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (0.38 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.49 mL, 4 mmol) according to Procedure A to yield 0.30 g (88%) of the title compound as a yellow-
orange oil: IR (CCl₄, cm⁻¹) 2954, 2930, 2858, 2204, 1645, 1586, 1261; ¹H NMR (CDCl₃) δ 7.64 (dd, J = 7.8, 1.8 Hz, 1H), 7.45-7.41 (m, 2H), 7.40-7.14 (m, 4H), 6.81 (t, J = 7.8 Hz, 1H), 2.09 (s, 3H), 0.86 (s, 9H), -0.03 (s, 6H); ¹³C NMR (CDCl₃) 177.5, 152.2, 135.0, 132.0, 131.4, 130.2, 129.5, 129.5, 128.8, 127.5, 127.4, 120.1, 119.4, 90.4, 87.9, 24.9, 17.5, 16.2, -4.6; HRMS m/z (M⁺) calculated for C₂₂H₂₆O₂Si was 350.1695, found 350.1672.

1-[2-[[[(1,1-Dimethylethyl)dimethylsilyloxy]-4-methoxyphenyl]-3-phenyl-2-propyn-1-one (JLW-I-111):

2-[[[(1,1-Dimethylethyl)dimethylsilyloxy]-4-methoxy-benzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (0.41 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.64 mL, 5 mmol) according to Coupling A to yield 0.35 g (92%) of the title compound as a brown oil: IR (CCl₄, cm⁻¹) 3063, 2853, 2197, 1638, 1603, 1272, 841; ¹H NMR (CDCl₃) δ 8.05 (d, J = 8.8 Hz, 1H), 7.56-7.53 (m, 2H), 7.32-7.29 (m, 3H), 6.57 (dd, J = 8.8, 2.3 Hz, 1H), 1.27 (d, J = 2.4 Hz, 1H), 3.75 (s, 3H), 1.00 (s, 9H), 0.23 (s, 6H); ¹³C NMR (CDCl₃) δ 175.7, 164.7, 158.2, 135.2, 132.8, 130.1, 128.5, 122.9, 120.9, 107.0, 107.0, 90.5, 88.7, 55.5, 25.9, 18.5, -4.2; HRMS m/z (M⁺) calculated for C₂₂H₂₆O₂Si was 366.1644, found 366.1674.
1-[2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-4-methoxyphenyl]-3-(4-methylphenyl)-2-propyn-1-one (JLW-I-114):

2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]4-methoxybenzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (0.60 g, 1.5 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 4-ethynyltoluene (0.95 mL, 7.5 mmol) according to Coupling A to yield 0.40 g (70%) of the title compound as a orange-brown oil: IR (CCl₄, cm⁻¹) 3014, 2859, 2195, 1631, 1604; °H NMR (CDCl₃) δ 7.92 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.44 (dd, J = 8.8, 2.2 Hz, 1H), 6.24 (d, J = 2.2 Hz, 1H), 3.64 (s, 3H), 2.17 (s, 3H), 0.89 (s, 9H), 0.10 (s, 6H); °C NMR (CDCl₃) δ 175.4, 164.4, 157.8, 140.5, 134.9, 132.7, 132.5, 129.3, 129.1, 122.6, 117.4, 106.8, 106.7, 90.8, 88.2, 55.1, 25.6, 21.3, 18.2, -4.5; HRMS m/z (M⁺) calculated for C₂₃H₂₈O₃Si was 380.1828, found 380.1806.

3-(1-Cyclohexen-1-yl)-1-[2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-4-methoxyphenyl]-2-propyn-1-one (JLW-I-116):

2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-4-methoxy-benzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (0.42 g, 1.0 mmol) was used for the previously described one-
pot acid chlorination Sonogashira coupling with 1-ethynyl-1-cyclohexene (0.76 mL, 6.5 mmol) according to Coupling A to yield 0.39 g (65%) of the title compound as a yellow-orange oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.90 (d, $J$ = 8.8 Hz, 1H), 6.48 (dd, $J$ = 8.8, 2.2 Hz, 1H), 6.35 (m, 1H), 6.29 (d, $J$ = 2.3 Hz, 1H), 3.72 (s, 3H), 2.12-2.05 (m, 4H), 1.55-1.51 (m, 4H), 0.94 (s, 9H), 0.15 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 175.6, 164.2, 157.6, 140.6, 135.0, 122.6, 119.2, 106.8, 106.6, 92.6, 86.6, 55.1, 28.2, 25.8, 25.6, 21.8, 21.0, 18.2, -4.5; HRMS $m/z$ (M$^+$) calculated for C$_{22}$H$_{30}$O$_3$Si was 370.1956, found 370.1965.

6-Chloro-1-[2-[(1,1-dimethylethyl)dimethylsilyloxy]-4-methoxyphenyl]-2-hexyn-1-one (JLW-HIO):

2-[(1,1-Dimethylethyl)dimethylsilyloxy]-4-methoxy-benzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (0.42g, 1.1 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 5-chloro-1-pentyne (1.1 mL, 10 mmol) according to Coupling A to yield 0.15 g (42%) of the title compound as a yellow-orange oil: IR (CCl$_4$, cm$^{-1}$) 3012, 2960, 2932, 2859, 2220, 1638, 1601, 1258, 840; $^1$H NMR (CDCl$_3$) $\delta$ 7.93 (d, $J$ = 8.8 Hz, 1H), 6.53 (dd, $J$ = 8.8, 2.4 Hz, 1H), 6.33 (d, $J$ = 2.2 Hz, 1H), 3.78 (s, 3H), 3.64 (t, $J$ = 6.4, 6.1 Hz, 2H), 2.60 (t, $J$ = 6.8 Hz, 2H), 2.07-2.00 (m, 2H), 0.98 (s, 9H), 0.20 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 175.5, 164.5, 158.0, 135.2, 122.5, 106.9, 106.9, 91.2, 81.9, 55.4, 43.4, 30.6, 25.8, 18.5, 16.6, -4.3; HRMS $m/z$ (M$^+$) calculated for C$_{19}$H$_{27}$ClO$_3$Si was 366.1411, found 366.1418.
4,4-Bisethoxy-1-[2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-4-methoxyphenyl]-2-butyn-1-one (JLW-I-115):

2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-4-methoxy-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (0.40 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with propiolaldehyde diethyl acetal (0.72 mL, 5 mmol) according to Coupling A to yield 0.33 g (70%) of the title compound as a orange-yellow oil: IR (CCl₄, cm⁻¹) 3019, 2400, 1700, 1604, 1216; ¹H NMR (CDCl₃) δ 7.86 (d, J = 8.9 Hz, 1H), 6.45 (dd, J = 8.8, 2.4 Hz, 1H), 6.24 (d, J = 2.2 Hz, 1H), 5.32 (s, 1H), 3.68 (s, 1H), 3.66-3.49 (m, 4H), 1.12 (t, J = 7.2, 7.0 Hz, 6H), 0.90 (s, 9H), 0.12 (s, 6H); ¹³C NMR (CDCl₃) δ 174.1, 164.7, 158.0, 135.2, 121.8, 106.7, 106.6, 91.1, 84.9, 82.9, 61.1, 55.1, 25.6, 18.2, 14.7, -4.5; HRMS m/z (M⁺) calculated for C₂₁H₃₂O₅Si was 392.2042, found 392.2028.
1-[[{(1,1-Dimethylethyl)dimethylsilyl}oxy]-4-methoxyphenyl]-2-hexyn-1-one (JLW-II-032):

2-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-4-methoxy-benzoic acid, (1,1-dimethyl-ethyl)dimethylsilyl ester (0.99 g, 2.5 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-pentyne (0.75 mL, 7.6 mmol) according to Coupling A to yield 0.71 g (89%) of the title compound as an orange-brown oil: IR (neat, cm⁻¹) 2962, 2858, 2216, 1644, 1603, 1559, 841; ¹H NMR (CDCl₃) δ 7.93 (d, J = 8.8 Hz, 1H), 6.50 (dd, J = 8.8, 2.1 Hz, 1H), 6.30 (d, J = 2 J Hz, 1H), 3.75 (s, 3H), 2.33 (t, J = 7.0 Hz, 2H), 1.59 (m, 2H), 0.97 (m, 3H), 0.96 (s, 9H), 0.18 (s, 6H); ¹³C NMR (CDCl₃) δ 176.3, 164.8, 158.3, 135.7, 123.1, 107.4, 107.2, 94.1, 81.8, 55.8, 26.2, 21.8, 21.5, 18.9, 14.0, -3.9; LRMS m/z (M + H⁺) calculated for C₁₉H₂₈O₃Si was 332.1800, found 333.2.

1-[[{(1,1-Dimethylethyl)dimethylsilyl}oxy]-4-methylphenyl]-3-phenyl-2-propyn-1-one (JLW-II-035):

2-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-4-methylbenzoic acid, (1,1-dimethyl-ethyl)-dimethylsilyl ester (1.14 g, 3.0 mmol) was used for the previously described one-pot
acid chlorination Sonogashira coupling with phenylacetylene (1.10 mL, 9.0 mmol) according to **Coupling A** to yield 0.85 g (81%) of the title compound as a orange-brown oil and 44 mg (6%) of 7-methyl-2-phenyl-3(2H)-benzofuranone: IR (neat, cm⁻¹) 2954, 2929, 2858, 2196, 1644, 1608, 841; ¹H NMR (CDCl₃) δ 7.94 (d, J = 8.0 Hz, 1H), 7.60 (m, 2H), 7.37 (m, 3H), 6.86 (d, J = 6.6 Hz, 1H), 6.70 (broad s, 1H), 2.34 (s, 3H), 1.00 (s, 9H), 0.27 (s, 6H); ¹³C NMR (CDCl₃) δ 177.4, 156.4, 146.1, 133.4, 133.3, 130.7, 128.9, 127.3, 122.6, 122.5, 121.1, 91.4, 89.2, 26.3, 22.2, 18.9, -3.7; LRMS m/z (M + H⁺) calculated for C₂₂H₂₆O₂Si was 351.1773, found 351.2.

![Image](image_url)

3-(1-Cyclohexen-1-yl)-1-[4-chloro-2-[[[1,1-dimethylethyl]dimethylsilyl]oxy]phenyl]-2-propyn-1-one (JLW-I-275):

4-Chloro-2-[[[1,1-dimethylethyl]dimethylsilyl]oxy]benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.40 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-ethynyl-1-cyclohexene (0.35 mL, 3.0 mmol) according to **Coupling B** to yield 0.36 g (96%) of the title compound as a brown oil: ¹H (CDCl₃) δ 7.82 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.5, 1.8 Hz, 1H), 6.83 (d, J = 1.7 Hz, 1H), 6.44 (m, 1H), 2.19-2.05 (m, 4H), 1.60-1.56 (m, 4H), 0.97 (s, 9H), 0.20 (s, 6H).
1-2-[[1,1-Dimethylpropyl]dimethylsilox]-5-phenyl-2-propyn-1-one (JLW-I-261):

2-[[1,1-Dimethylpropyl]dimethylsilox]-5-phenylbenzoic acid, (1,1-dimethylpropyl)-dimethylsiloxyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.37 mL, 3.0 mmol) according to Coupling A to yield 0.36 g (96%) of the title compound as an oil: $^1$H NMR (CDCl$_3$) δ 8.25 (d, $J$ = 2.5 Hz, 1H), 7.68 (dd, $J$ = 8.5, 2.5, 1H), 7.64-7.32 (m, 10H), 7.01 (d, $J$ = 8.5 Hz, 1H), 1.05 (s, 9H), 0.30 (s, 6H).

1-2-[[1,1-Dimethylpropyl]dimethylsilox]-5-phenyl-3-(4-methylphenyl)-2-propyn-1-one (JLW-I-263):

2-[[1,1-Dimethylpropyl]dimethylsilox]-5-phenylbenzoic acid, (1,1-dimethylpropyl)-dimethylsiloxyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 4-ethynyltoluene (0.38 mL, 3.0 mmol)
according to Coupling A to yield the title compound as an oil: $^1$H NMR (CDCl$_3$) δ 8.25 (d, $J = 2.4$ Hz, 1H), 7.69-7.18 (m, 10H), 7.01 (d, $J = 8.5$ Hz, 1H), 2.38 (s, 3H), 1.06 (s, 9H), 0.30 (s, 6H).

3-(1-Cyclohexen-1-yl)-1-[(14-

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-phenylphenyl]-2-propyn-1-one (JLW-I-262):

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-phenylbenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-ethynyl-1-cyclohexene (0.38 mL, 3.2 mmol) according to Coupling A to yield the title compound as an oil: $^1$H NMR (CDCl$_3$) δ 8.15 (d, $J = 2.5$ Hz, 1H), 7.61 (dd, $J = 8.5$, 2.5 Hz, 1H), 7.58-7.29 (m, 5H), 6.95 (d, $J = 8.5$ Hz, 1H), 6.47 (m, 1H), 2.21-2.15 (m, 4H), 1.64-1.62 (m, 4H), 1.03 (s, 9H), 0.26 (s, 6H).
6-Chloro-1-[2-][(1,1-dimethylethyl)dimethylsilyl]oxy]-5-phenyl-phenyl-2-hexyn-1-one (JLW-1-270):

2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-phenylbenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 5-chloro-1-pentyne (0.31 mL, 3.0 mmol) according to Coupling A to yield 0.30 g (74%) of the title compound as an orange-brown oil: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.14 (d, \(J = 2.5\) Hz, 1H), 7.63 (dd, \(J = 8.5, 2.5\) Hz, 1H), 7.58-7.32 (m, 5H), 6.95 (d, \(J = 8.5\) Hz, 1H), 3.68 (t, \(J = 6.2\) Hz, 2H), 2.64 (t, \(J = 6.9\) Hz, 2H), 2.07 (m, 3H), 1.04 (s, 9H), 0.27 (s, 6H).

1-[2-][(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-methoxyphenyl-3-phenyl-2-propyn-1-one (JLW-2-064):

2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-methoxybenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (1.01 g, 2.6 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.95 mL, 7.8 mmol) according to Coupling A to yield 0.70 g (75%) of the title compound as an orange-brown oil: IR (neat, cm\(^{-1}\)) 2930, 2857, 2199, 1650; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.61 (s, 1H), 7.58 (d, \(J = 1.6\) Hz, 1H), 7.46 (d, \(J = 3.2\) Hz, 1H), 7.43-7.33 (m, 3H), 6.99 (dd, \(J = 8.9, 181\) Hz, 1H).
3.2 Hz, 1H), 6.83 (d, J = 8.9 Hz, 1H), 3.81 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H);\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 177.4, 153.5, 149.7, 133.0, 130.4, 129.6, 128.6, 122.6, 121.0, 120.6, 115.5, 91.8, 89.0, 55.8, 25.9, 18.4, -4.2; LRMS \(m/z\) (M + Na\(^+\)) calculated for C\(_{22}\)H\(_{26}\)O\(_3\)Si was 389.1644, found 389.16.
8.2.7 General Method for Preparation of 4H-1-Benzopyran-4-one Derivatives via Cyclization of Alkynone 1-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-phenyl]-2-propyn-1-one Derivatives.

Cyclization A: Neat anhydrous diethylamine (10 equiv) was added to an alkynone 1-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-2-propyn-1-one derivatives under argon and stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to remove excess diethylamine. The residue was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) to yield the desired product.

Cyclization B: Anhydrous diethylamine (10 equiv) was added to an alkynone 1-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-2-propyn-1-one derivatives in EtOH (1 mL) under argon and stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to remove excess diethylamine. The residue was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) to yield the desired product.

Cyclization C: Anhydrous diethylamine (10 equiv) was added to an alkynone 1-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-2-propyn-1-one derivatives in EtOH (1 mL) under argon and stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to remove excess diethylamine. EtOH (1 mL) was added to the residue and heated to reflux overnight, followed by concentration in vacuo. The residue was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) to yield the desired product.
Cyclization D: Neat anhydrous pyrrolidine (10 equiv) was added to an alkynone 1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-2-propyn-1-one derivatives under argon and stirred at room temperature for 2 h. The reaction mixture was concentrated \textit{in vacuo} to remove excess pyrrolidine. EtOH (1 mL) was added to the residue and heated to reflux overnight, followed by concentration \textit{in vacuo}. The residue was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) to yield the desired product.

Cyclization E: Neat anhydrous pyrrolidine (10 equiv) was added to an alkynone 1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-2-propyn-1-one derivatives under argon and stirred at room temperature for 2 h. The reaction mixture was concentrated \textit{in vacuo} to remove excess pyrrolidine. The residue was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) to yield the desired product.

Cyclization G: Anhydrous pyrrolidine (10 equiv) was added to an alkynone 1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-2-propyn-1-one derivatives in EtOH (1 mL) under argon and stirred at room temperature for 2 h. The reaction mixture was concentrated \textit{in vacuo} to remove excess pyrrolidine. EtOH (1 mL) was added to the residue and heated to reflux overnight, followed by concentration \textit{in vacuo}. The residue was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) to yield the desired product.
10: 2-Phenyl-4H-1-benzopyran-4-one (JLW-I-246):

2-[[1,1-Dimethyl]ethyl(dimethylsilyl)oxy]-benzoic acid, (1,1-dimethyl)dimethylsilyl ester (0.39 g, 1.1 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.37 mL, 2.2 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.18 g (73%) of the title compound as a off-white solid: mp 93-94°C; IR (KBr, cm⁻¹) 3072, 1654, 1606, 1376; 'H NMR (CDCl₃) δ 8.21 (dd, J = 7.9, 0.7 Hz, 1H), 7.92-7.88 (m, 2H), 7.68 (t, J = 7.0 Hz, 1H), 7.56-7.49 (m, 4H), 7.39 (t, J = 7.9, 7.1 Hz, 1H), 6.80 (s, 1H); '³C NMR (CDCl₃) δ 178.2, 163.2, 156.1, 133.6, 131.7, 131.5, 128.9, 126.2, 125.6, 125.1, 124.0, 118.0, 107.5; UV (EtOH) λmax 251, 294; HRMS m/z (M⁺) calculated for C₁₅H₁₀O₂ was 245.0578, found 245.0589.

11: 2-([4’-Methylphenyl]-4H-1-benzopyran-4-one (JLW-I-247):

2-[[1,1-Dimethyl]ethyl(dimethylsilyl)oxy]-benzoic acid, (1,1-dimethyl)dimethylsilyl ester (0.42 g, 1.1 mmol) was used for the previously described one-pot acid
chlorination Sonogashira coupling with 1-ethylnyl-toluene (0.28 mL, 2.2 mmol) according to Coupling C. The alkyne from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.13 g (48%) of the title compound as a off white solid: mp 106-107.5°C; IR (KBr, cm⁻¹) 3059, 2919, 1638, 1228, 1043; ¹H NMR (CDCl₃) δ 8.20 (dd, J = 7.9, 1.6 Hz, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.66 (t, J = 8.5, 7.0 Hz, 1H), 7.52 (dd, J = 8.4, 0.5 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 6.76 (s, 1H), 2.40 (s, 3H); ¹³C NMR (CDCl₃) δ 178.3, 163.6, 156.2, 142.2, 133.6, 129.7, 128.9, 126.2, 125.6, 125.1, 123.9, 112.0, 106.9, 21.4; UV (MeOH) λmax 253, 302; HRMS m/z (M⁺) calculated for C₁₈H₁₂O₂ was 236.0834, found 236.0831.

12: 2-(1-Cyclohexen-1-yl)-4H-1-benzopyran-4-one (JLW-I-248):

2-[[1-(1-Dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (0.35 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-ethynyl-cyclohexene (0.23 mL, 1.9 mmol) according to Coupling C. The alkyne obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.15 g (71%) of the title compound as an orange oil: IR (KBr, cm⁻¹) 2932, 1645, 1633; ¹H NMR (CDCl₃) δ 8.12 (dd, J = 7.9, 1.7 Hz, 1H), 7.63-7.56 (m, 1H), 7.40 (d, J = 7.8 Hz, 1H),
7.31 (t, J = 8.0 Hz, 1H), 6.96-6.95 (m, 1H), 6.26 (s, 1H), 2.27-2.25 (m, 4H), 1.80-1.62 (m, 4H); $^{13}$C NMR (CDCl$_3$) δ 179.4, 164.1, 156.4, 134.4, 133.9, 130.0, 125.9, 125.1, 124.2, 118.2, 106.5, 26.4, 24.6, 22.6, 21.9; UV (EtOH) λmax 253, 257, 295; HRMS m/z (M + H$^+$) calculated for C$_{15}$H$_{14}$O$_2$ was 227.1072, found 227.1076.

13: 2-(3-Chloropropyl)-4H-1-benzopyran-4-one (JLW-I-249):

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (0.38 g, 1.3 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 5-chloro-1-pentyne (0.22 mL, 2 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.12 g (51%) of the title compound as a orange/brown oil: IR (neat, cm$^{-1}$) 3056, 2924, 1644, 1606; $^1$H NMR (CDCl$_3$) δ 8.12 (dd, J = 7.9, 1.7 Hz, 1H), 7.63-7.56 (m, 1H), 7.39-7.30 (m, 2H), 6.15 (s, 1H), 3.58 (t, J = 6.3 Hz, 2H), 2.78 (t, J = 7.8 Hz, 2H), 2.18 (q, J = 7.8, 6.2 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 178.0, 167.6, 156.4, 133.5, 125.6, 125.0, 123.6, 117.7, 110.3, 43.5, 31.4, 29.4; UV (EtOH) λmax 224, 295; HRMS m/z (M$^+$) calculated for C$_{12}$H$_{11}$ClO$_2$ was 222.0445, found 222.0442 (M$^+$, 100%), 224.0417 (M$^{+2}$, 34%).
14: 2-(Diethoxymethyl)-4H-1-benzopyran-4-one (JLW-I-250):

2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethyl-
silyl ester (0.39 g, 1.1 mmol) was used for the previously described one-pot acid
chlorination Sonogashira coupling with propiolaldehyde diethyl acetal (0.47 mL, 3
mmol) according to Coupling C. The alkynone obtained from the Sonogashira
coupling was used in the subsequent cyclization step according to Cyclization C to yield
54 mg (21%) of the title compound as a dark orange oil: IR (KBr, cm⁻¹) 3083, 2983,
2946, 2878, 1738, 1664, 1614, 1471, 1323, 1118, 1069, 790, 759 [105]; ¹H NMR
(CDCl₃) δ 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.66 (t of d, J = 7.8, 1.7 Hz, 1H), 7.49 (d, J =
8.4 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 6.59 (s, 1H), 5.31 (s, 1H), 3.74-3.61 (m, 4H), 1.26
(t, J = 7.0 Hz, 6H); ¹³C NMR (CDCl₃) δ 178.7, 163.7, 156.7, 134.2, 126.1, 125.6, 124.5,
118.7, 110.4, 98.1, 62.6, 15.5; UV (EtOH) λ max 298; HRMS m/z (M + Na⁺) calculated
for C₁₄H₁₆O₄ was 271.0946, found 271.0943.
15: 3-Bromo-2-phenyl-4H-1-benzopyran-4-one (JLW-I-189):

Anhydrous pyridine (1 mL, 12.5 mmol) was added dropwise to a solution of 2-phenyl-4H-1-benzopyran-4-one (0.11 g, 0.5 mmol) in CH₂Cl₂ (5 mL). Upon addition of pyridinium tribromide (0.81 g, 2.5 mmol), the reaction mixture turned a dark brown color. The reaction mixture was stirred at room temperature for 22 h at which time saw little starting material by TLC (2:1 hexanes:EtOAc). Reaction diluted with CH₂Cl₂ and washed with several portions of 10% Na₂S₂O₃. The organic layer was dried (MgSO₄) and concentrated in vacuo. Because there was not good separation of the aqueous and organic layers, the aqueous layer was extracted with EtOAc. The organic layer was then washed with CuSO₄, brine, dried (MgSO₄), and concentrated in vacuo to afford an orange solid. The solid was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) to yield 0.11 g (75%) of the title compound as a white solid: mp 122-123°C; IR (KBr, cm⁻¹) 3104, 3064, 1656, 1615, 1067; ¹H NMR (CDCl₃) δ 8.29 (dd, J = 8.0, 1.3 Hz, 1H), 7.85-7.83 (m, 2H), 7.74-7.67 (m, 1H), 7.56-7.42 (m, 5H); ¹³C NMR (CDCl₃) 173.1, 162.0, 155.7, 134.2, 132.9, 131.1, 129.3, 128.3, 126.6, 125.7, 121.8, 117.9, 109.3; UV (EtOH) λmax 248, 309; HRMS m/z (M⁺) calculated for C₁₅H₉BrO₂ was 299.9783, found 299.9784 (M⁺, 100%), 301.9793 (M⁺², 93%).
20: 8-Methoxy-2-phenyl-4H-1-benzopyran-4-one (JLW-I-171):

Using the previously described Cyclization C procedure and starting from 0.14 g (0.4 mmol) of 1-[2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-3-methoxyphenyl]-3-phenyl-2-propyn-1-one, 86 mg (88%) of the title compound was obtained as a white solid: mp 198-198.5°C; IR (KBr, cm⁻¹) 3066, 3009, 2975, 2848, 1641, 1603, 1281, 1061; ^1H NMR (CDCl₃) δ 7.87-7.85 (m, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.42-7.40 (m, 3H), 7.21 (t, J = 7.9, 7.3 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.73 (s, 1H), 3.91 (s, 3H); ^13C NMR (CDCl₃) 177.4, 161.9, 148.0, 145.5, 130.7, 130.5, 128.0, 125.3, 123.9, 123.8, 115.3, 113.3, 106.2, 55.3; UV (EtOH) λmax 265; HRMS m/z (M⁺) calculated for C₁₆H₁₂O₃ was 252.0783, found 252.0791.

2-[[1,1-Dimethylethyl]dimethylsilyl]oxy]-3-methoxybenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.41 g, 1 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.49 mL, 4 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.23 g (89%) of the title compound as a solid, which was further recrystallized in EtOH to afford pale yellow crystals: mp 198-198.5°C.
21: 8-Methoxy-2-(4’-methylphenyl)-4H-1-benzopyran-4-one (JLW-I-229):

2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxybenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.41 g, 1 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 4-ethynyltoluene (0.66 mL, 5.2 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.24 g (88%) of the title compound as a solid which was further recrystallized (1:1 hexanes:EtOAc) to afford pale yellow crystals: mp 229.5-230°C; IR (KBr, cm⁻¹) 3053, 2698, 2844, 1637, 1377, 1282, 1062; ¹H NMR (CDCl₃) δ 7.85 (dd, J = 6.8, 1.8 Hz, 2H), 7.76 (dd, J = 8.0, 1.8 Hz, 1H), 7.33-7.27 (m, 3H), 7.17 (dd, J = 8.0, 1.4 Hz, 1H), 6.79 (s, 1H), 4.00 (s, 3H), 2.42 (s, 3H); ¹³C NMR (CDCl₃) δ 178.4, 163.2, 149.1, 146.7, 142.1, 129.7, 129.1, 126.3, 125.1, 124.7, 116.5, 114.4, 106.8, 56.4, 21.5; UV (EtOH) λ_max 266, 304; HRMS m/z (M + H⁺) calculated for C₁₇H₁₄O₃ was 267.1021, found 267.1026.
22: 2-(1-Cyclohexen-1-yl)-8-methoxy-4H-1-benzopyran-4-one (JLW-I-225):

2-[[[1,1-Dimethylethyl]dimethylsilyloxy]-3-methoxybenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.42 g, 1.1 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-ethynyl-cyclohexene (0.50 mL, 4.2 mmol) according to Coupling C to yield 0.26 g (68%) of 3-(1-cyclohexen-1-yl)-1-[[[1,1-dimethylethyl]dimethylsilyloxy]-3-methoxy-phenyl]-2-propyn-1-one. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.12 g (44% overall yield, 65% yield for cyclization) of the title compound as off-white rod-like crystals: mp 137.5-139°C; IR (KBr, cm⁻¹) 3052, 2940, 2874, 1643, 1594, 1222, 1059; ¹H NMR (CDCl₃) δ 7.70 (dd, J = 8.0, 1.5 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.12 (dd, J = 8.0, 1.4 Hz, 1H), 7.04 (m, 1H), 6.28 (s, 1H), 3.96 (s, 3H), 2.31-2.27 (m, 4H), 1.78-1.66 (m, 4H); ¹³C NMR (CDCl₃) δ 179.4, 163.8, 149.3, 146.8, 134.6, 130.1, 125.2, 124.7, 116.8, 114.7, 106.5, 56.8, 26.4, 24.5, 22.6, 22.0; UV (EtOH) λmax 265; HRMS m/z (M⁺ + H) calculated for C₁₅H₁₆O₃ was 257.1177, found 257.1171.
23: 2-(3-Chloropropyl)-8-methoxy-4H-1-benzopyran-4-one (JLW-I-253):

2-[[[1,1-Dimethylethyl]dimethylsilyloxy]-3-methoxybenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.31 g, 0.8 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 5-chloro-1-pentyne (0.24 mL, 2.3 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 43 mg (22%) of the title compound as a off-white solid: mp 82°C; IR (KBr, cm⁻¹) 2970, 2928, 2846, 1664, 1583, 1273, 1057; ¹H NMR (CDCl₃) δ 7.74 (dd, J = 8.0, 1.4 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.16 (dd, J = 8.0, 1.3 Hz, 1H), 6.27 (s, 1H), 3.97 (s, 3H), 3.65 (t, J = 6.3 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.24 (q, J = 7.7, 6.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 178.1, 167.5, 148.6, 146.8, 124.7, 116.5, 114.2, 110.3, 56.2, 43.6, 31.4, 29.5; UV EtOH λmax 230, 308; HRMS m/z (M + H⁺) calculated for C₁₃H₁₃ClO₃ was 253.0631, found 253.0634 (M + H⁺, 100%), 255.0650 (M⁺² + H⁺, 29.2%).
24: 2-(Diethoxymethyl)-8-methoxy-4H-1-benzopyran-4-one (JLW-I-230):

2-[[1,1-Dimethylethyl]dimethylsilyloxy]-3-bietioxybenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.41 g, 1.2 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with propiolaldehyde diethylacetal (0.73 mL, 5.1 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.15 g (53%) of the title compound as a solid which was further recrystallized (1:1 hexanes:EtOAc): mp 64.5-65.5°C; IR (KBr, cm⁻¹) 2977, 2935, 2899, 1650, 1489, 1330, 1275, 1123, 1106, 1059; ¹H NMR (CDCl₃) δ 7.65 (dd, J = 8.0, 1.5 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.08 (dd, J = 8.0 Hz, 1H), 6.54 (s, 1H), 5.30 (s, 1H), 3.89 (s, 3H), 3.65 (m, 4.5H), 1.19 (t, J = 7.0 Hz, 6.7 H); ¹³C NMR (CDCl₃) δ 178.3, 163.4, 149.0, 146.7, 125.2, 124.8, 116.5, 114.4, 109.8, 97.7, 62.4, 56.3, 25.7, 15.0; UV (MeOH) λmax 229, 252, 311; HRMS m/z (M + Na⁺) calculated for C₁₅H₁₈O₅ was 301.1052, found 301.1050.
25: 3-Bromo-8-methoxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (JLW-II-047):

Using the same procedure described for 3-bromo-2-phenyl-4H-1-benzopyran-4-one 15, the title compound was obtained from 80 mg (0.3 mmol) of 8-methoxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one to yield 92 mg (89%) as a white solid: mp 170.5-171.5°C; IR (KBr, cm⁻¹) 1656, 1643, 1275, 1075, 754; ¹H NMR (CDCl₃) δ 7.81 (dd, J = 8.0, 1.4 Hz, 1H), 7.82 (s, 1H), 7.79 (s, 1H), 7.38-7.31 (m, 3H), 7.18 (dd, J = 8.0, 1.2 Hz, 1H), 3.95 (s, 3H), 2.44 (s, 3H); ¹³C NMR (CDCl₃) δ 173.2, 161.8, 148.7, 146.1, 141.7, 130.0, 129.5, 125.4, 122.8, 117.1, 114.5, 109.0, 56.3, 21.6; UV (EtOH) λmax 262, 307; HRMS m/z (M + Na⁺) calculated for C₁₇H₁₃BrO₃ was 366.9946, found 366.9950 (M + Na⁺, 100%), 368.9943 (M⁺² + Na⁺, 95%).
30: 8-Hydroxy-2-phenyl-4H-1-benzopyran-4-one (JLW-I-176):

To a solution of 8-methoxy-2-phenyl-4H-1-benzopyran-4-one (0.12 mmol) in CH$_2$Cl$_2$ (1.5 mL) at $-78^\circ$C under argon was added 1.0 M BBr$_3$ solution in CH$_2$Cl$_2$ (0.29 mL, 2.5 equiv) dropwise. The reaction was allowed to stir at $-78^\circ$C for 2 h, then allowed to warm to room temperature and stirred overnight. The mixture was cooled to 0°C and small amount of MeOH was added and concentrated in vacuo. The residue was taken up into EtOAc, washed with H$_2$O, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified via flash chromatography (silica gel, 1:1 hexanes:EtOAc) followed by recrystallization in EtOH to yield 17 mg (60%) of the title compound as white crystals: mp 243-244°C; IR (KBr, cm$^{-1}$) 2962, 2637, 1631, 1297, 1048; $^1$H NMR (CDCl$_3$) $\delta$ 10.49 (s, 1H), 8.11-8.07 (m, 2H), 7.59-7.57 (m, 3H), 7.45 (m, 1H), 7.29-7.27 (m, 2H), 6.98 (s, 1H); $^{13}$C NMR (DMSO-$_d_6$) $\delta$ 177.3, 162.1, 147.0, 145.4, 131.7, 131.3, 129.1, 126.4, 125.3, 124.7, 119.4, 114.2, 106.6; UV (MeOH) $\lambda_{max}$ 266; HRMS $m/z$ (M$^+$ + Na$^+$) calculated for C$_{13}$H$_{10}$O$_3$ was 261.0522, found 261.0501.
31: 8-Hydroxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (JLW-II-050):

To a solution of NaH (3.1 equiv of a 60% w/w dispersion) in 2.3 mL DMF at 0°C was added dropwise ethanethiol (3.0 equiv) to generate a 0.5 M NaSEt solution in DMF. After 30 min, the mixture was warmed to rt cannulated dropwise into a solution of 8-methoxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (0.10 g, 0.4 mmol) in DMF (2 mL). The reaction mixture was heated to reflux for 4 h; then cooled in a ice-bath and acidified with dilute (< 1M)HCl to pH 3. The reaction mixture was extracted with EtOAc, washed with H2O, brine, and dried (Na2SO4), and concentrated in vacuo. The aqueous layer was reextracted with CHCl3 and monitored by TLC. The residue was purified via flash chromatography (silica gel, CHCl3/5% MeOH) followed by recrystallization in MeOH to yield 60 mg (62%) of the title compound as a white solid: mp 263-264°C; IR (KBr, cm⁻¹) 3047, 1626, 1249, 1044, 805; ¹H NMR (CDCl3) δ 10.66-10.16 (broad s, 1H), 8.00 (s, 1H), 7.98 (s, 1H), 7.42 (dd, J = 5.8, 3.5 Hz, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 7.24-7.23 (m, 2H), 6.93 (s, 1H), 2.36 (s, 3H); ¹³C NMR (CDCl3) δ 177.2, 162.2, 146.8, 145.3, 141.9, 129.7, 128.5, 127.0, 126.3, 125.2, 124.7, 119.3, 114.2, 106.0, 21.1; UV (EtOH) λmax 268, 306; HRMS m/z (M + Na⁺) calculated for C₁₆H₁₂O₃ was 275.0679, found 275.0670.
40: 8-Methyl-2-phenyl-4'H-1-benzopyran-4-one (JLW-I-172):

Using the previously described Cyclization C procedure and starting from 0.21 g (0.61 mmol) of 1-[2-[[1(1-dimethylethyl)dimethylsilyloxy]-3-methylphenyl]-3-phenyl-2-propyn-1-one, 125.7 mg (87%) of the title compound as a white solid: mp 157-159°C; IR (KBr, cm⁻¹) 3069, 1638, 1600, 1375; ¹H NMR (CDCl₃) δ 7.87 (d, J = 7.8 Hz, 1H), 7.73-7.69 (m, 2H), 7.35-7.30 (m, 4H), 7.09 (t, J = 7.6 Hz, 1H), 6.61 (s, 1H), 2.39 (s, 3H); ¹³C NMR (CDCl₃) 178.3, 162.4, 154.3, 134.4, 131.3, 131.6, 129.8, 127.2, 125.8, 124.4, 123.6, 123.0, 106.9, 15.5; UV (EtOH) λmax 258, 295; HRMS m/z (M⁺) calculated for C₁₆H₁₂O₂ was 236.0834, found 236.0833.

41: 8-Methyl-2-(4'-methylphenyl)-4'H-1-benzopyran-4-one (JLW-I-232):

2-[[1(1-Dimethylethyl)dimethylsilyloxy]-3-methylbenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (0.39 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 4-ethynyltoluene (0.66 mL, 5.2 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used without purification in the subsequent cyclization step according to Cyclization C to yield 0.23 g (91%) of the title compound as a solid which was further recrystallized.
(1:1 hexanes:EtOAc) to afford very pale orange plate-like crystals: mp 147.5-148.5°C; IR (KBr, cm⁻¹) 3071, 2975, 2925, 1636, 1481, 1371, 1219, 1073; ¹H NMR (CDCl₃) δ 8.06 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 7.3 Hz, 1H), 7.30-7.27 (m, 3H), 6.75 (s, 1H), 2.57 (s, 3H), 2.41 (s, 3H); ¹³C NMR (CDCl₃) δ 178.3, 162.6, 154.2, 141.9, 134.2, 129.5, 128.8, 127.2, 125.7, 124.3, 123.5, 122.9, 106.2, 21.2, 15.5; UV (EtOH) 258, 302; HRMS m/z (M⁺) calculated for C₁₁H₁₄O₂ was 250.0990, found 250.0995.

42: 2-(1-Cyclohexen-1-yl)-8-methyl-4H-1-benzopyran-4-one (JLW-I-233):
2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methylbenzoic acid, (1,1-dimethyl ethyl)-dimethylsilyl ester (0.39 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-ethynylcyclohexene (0.48 mL, 4.1 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used without purification in the subsequent cyclization step according to Cyclization C to yield 0.20 g (83%) of the title compound as a yellow solid which was further recrystallized in EtOH: mp 82-84°C; IR (KBr, cm⁻¹) 2931, 2868, 1652, 1595, 1585, 1218, 1021; ¹H NMR (CDCl₃) δ 7.98 (dd, J = 7.4, 0.4 Hz, 1H), 7.44 (dd, J = 6.4, 0.8 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.27 (s, 1H), 2.48 (s, 3H), 2.30 (s, 4H), 1.78-1.65 (m, 4H); ¹³C NMR (CDCl₃) δ 179.2, 163.3, 154.4, 134.4, 133.5, 130.0,
UV (MeOH) λmax 258, 295; HRMS m/z (M⁺) calculated for C₁₆H₁₆O₂ was 240.1146, found 240.1149.

43: 2-(3-Chloropropyl)-8-methyl-4H-1-benzopyran-4-one (JLW-I-251):

2-[[1,1-Dimethylethyl]dimethylsilyloxy]-3-methylbenzoic acid, (1,1-dimethylethyl)- dimethylsilyl ester (0.37 g, 0.9 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 5-chloro-1-pentyne (0.29 mL, 3 mmol) according to Coupling C. The alkyne obtained from the Sonogashira coupling was used without purification in the subsequent cyclization step according to Cyclization C to yield 0.09 g (40%) of the title compound as a tan solid: mp 53-54°C; IR (KBr, cm⁻¹) 2941, 2928, 1651, 1213, 1070; ¹H NMR (CDCl₃) δ 7.97 (d, J = 7.9, 1.1 Hz, 1H), 7.44 (dd, J = 7.3, 0.8 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 6.16 (s, 1H), 3.61 (t, J = 6.3 Hz, 2H), 2.81 (t, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.20 (q, 2H); ¹³C NMR (CDCl₃) δ 178.4, 167.2, 154.8, 134.4, 127.1, 124.5, 123.5, 123.2, 110.1, 43.5, 31.4, 29.6, 15.5; UV (EtOH) λmax 225, 300; HRMS m/z (M⁺ + H) calculated for C₁₃H₁₅ClO₂ was 237.0682, found 237.0677 (M⁺ + H⁺, 100%), 239.0667 (M⁺² + H⁺, 33%).
44: 2-(Diethoxymethyl)-8-methyl-4H-1-benzopyran-4-one (JLW-I-234):

2-[[1,1-Dimethylethyl]dimethylsilyloxy]-3-methylbenzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.23 g, 0.8 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with propiolaldehyde diethyl acetal (0.57 mL, 4 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used without purification in the subsequent cyclization step according to Cyclization C to yield the title compound as a dark orange solid: IR (KBr, cm\(^{-1}\)) 2977, 2932, 2898, 1659, 1210, 1111, 1065; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.01 (dd, \(J = 7.9, 1.0\) Hz, 1H), 7.49 (dd, \(J = 7.3, 0.8\) Hz, 1H), 7.26 (t, \(J = 7.8\) Hz, 1H), 6.59 (s, 1H), 5.35 (s, 1H), 3.75-3.62 (m, 4H), 2.47 (s, 3H), 1.26 (t, \(J = 7.1\) Hz, 6H); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 178.6, 163.2, 154.7, 134.6, 127.6, 124.7, 124.0, 123.3, 109.7, 97.7, 62.2, 15.5, 15.1; UV (EtOH) \(\lambda_{\text{max}}\) 225, 245, 303; HRMS \(m/z\) (M\(^+\)) calculated for C\(_{15}\)H\(_{18}\)O\(_4\) was 262.1200, found 262.1204.
50: 7-Methoxy-2-phenyl-4H-1-benzopyran-4-one (JLW-I-128):

Using the previously described Cyclization C procedure and starting from 77 mg (0.21 mmol) of 1-[2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-4-methoxyphenyl]-3-phenyl-2-propyn-1-one, 47 mg (90%) of the title compound was obtained as a tan solid, recrystallization in EtOH afforded a white solid: mp 102-104°C; IR (CCl4, cm⁻¹) 3058, 2959, 2866, 1652, 1602, 1273; ^1H NMR (CDCl3) δ 8.05 (d, J = 9 Hz, 1H), 7.84-7.80 (m, 2H), 7.46-7.43 (m, 3H), 6.92-6.88 (m, 2H), 6.68 (s, 1H), 3.86 (s, 3H); ^13C NMR (CDCl3) δ 177.7, 164.1, 162.9, 157.9, 131.8, 131.3, 128.9, 127.0, 126.1, 117.8, 114.3, 107.5, 100.4, 55.8; UV (MeOH) λmax 251, 307; HRMS m/z (M⁺) calculated for C₁₆H₁₂O₃ was 252.0783, found 252.0782.

51: 7-Methoxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (JLW-I-120):

18-Crown-6 (0.41 g, 1.6 mmol) was added to a solution of 1-[2-[[1,1-dimethyl-ethyl]dimethylsilyl]oxy]-4-methoxyphenyl]-3-(4-methylphenyl)-2-propyn-1-one (0.23 g, 0.62 mmol) in anhydrous DMF (8 mL) under argon and stirred for 5 min. The resulting solution was then cooled to 0°C, potassium fluoride (72 mg, 1.2 mmol) added,
and stirred in ice bath for 5 min. The reaction mixture, monitored by TLC (3:1 hexanes:EtOAc), was stirred at room temperature for 3.5 h to give a dark brown color. Saturated NH₄Cl (5 mL) was added to quench reaction and product extracted into EtOAc. Organics were washed with H₂O, brine, dried (Na₂SO₄), and concentrated in vacuo to afford a yellow-orange oil. The residue was purified via flash chromatography (silica gel, 2:1.5 hexanes:EtOAc) to yield 0.10 g (64%) of the title compound as a pale yellow solid: mp 130-131°C; IR (CCl₄, cm⁻¹) 2957, 2923, 2854, 1621, 1600, 1262, 1087; ¹H NMR (CDCl₃) δ 8.01 (d, J = 8.9 Hz, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 6.82 (m, 2H), 6.60 (s, 1H), 3.82 (s, 3H), 2.32 (s, 3H); ¹³C NMR (CDCl₃) δ 177.5, 163.9, 162.9, 157.7, 141.8, 129.5, 128.7, 126.7, 125.8, 117.6, 114.1, 106.6, 100.2, 55.6, 21.3; UV (MeOH) λmax 309; HRMS m/z (M⁺) calculated for C₁₇H₁₄O₃ was 266.0939, found 266.0949.

Using the previously described Cyclization C procedure and starting from 48 mg (0.13 mmol) of 1-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]-3-(4-methyl-phenyl)-2-propyn-1-one, 30 mg (88%) of the title compound was obtained as a white solid: mp 130-131°C; IR (CCl₄, cm⁻¹) 2957, 2923, 2854, 1621, 1600, 1262, 1087; ¹H NMR (CDCl₃) δ 8.09 (d, J = 9 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.29-7.26 (m, 2H), 6.96-6.92 (m, 2H), 6.69 (s, 1H), 3.89 (s, 3H), 2.40 (s, 3H); ¹³C NMR (CDCl₃) δ 177.8, 164.1, 163.1, 157.9, 141.9, 129.7, 129.0, 127.0, 126.0, 114.2, 106.9, 100.4, 55.8, 21.4; HRMS m/z (M⁺) calculated for C₁₇H₁₄O₃ was 266.0939, found 266.0949.
52: 2-(1-Cyclohexen-1-yl)-7-methoxy-4H-1-benzopyran-4-one (JLW-I-133):

Using the previously described Cyclization C procedure and starting from 45 mg (0.12 mmol) of 3-(1-cyclohexen-1-yl)-1-[2-[[1,1-dimethylethyl]dimethylsilyl]oxy]phenyl]-2-propyn-1-one, 23 mg (73%) of the title compound was obtained as a yellow-orange solid: mp 101-102°C; IR (KBr, cm⁻¹) 3051, 2941, 2861, 1622, 1594, 1238, 1213, 1028, 1019; ¹H NMR (CDCl₃) δ 8.04 (d, J = 9 Hz, 1H), 6.90 (dd, J = 8.7, 2.3 Hz, 2H), 6.82 (d, J = 2.3 Hz, 1H), 6.21 (s, 1H), 3.87 (s, 3H), 2.29-2.27 (m, 4H), 2.27-2.25 (m, 4H);¹³C NMR (CDCl₃) δ 178.3, 164.0, 163.3, 157.7, 133.3, 129.7, 126.9, 117.7, 113.8, 106.1, 100.2, 55.7, 26.0, 24.2, 22.2, 21.6; UV (MeOH) λmax 234; 303; HRMS m/z (M⁺) calculated for C₁₆H₁₆O₃ was 256.1095, found 256.1098.

53: 2-(3-Chloropropyl)-7-methoxy-4H-1-benzopyran-4-one (JLW-I-132):

Using the previously described Cyclization C procedure and starting from 46 mg (0.13 mmol) of 6-chloro-1-[2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-4-methoxyphenyl]-2-hexyn-1-one, 25 mg (80%) of the title compound was obtained as a tan solid: mp 104-104.5°C; IR (KBr, cm⁻¹) 3075, 3018, 2965, 2931, 1651, 1604, 1237, 1089; ¹H NMR (CDCl₃) δ 8.05 (d, J = 8.8 Hz, 1H), 6.92 (dd, J = 8.8, 2.3 Hz, 1H), 6.80 (d, J = 2.3 Hz, 204
1H), 6.11 (s, 1H), 3.87 (s, 3H), 3.61 (t, J = 6.5, 6.1 Hz, 2H), 2.76 (t, J = 7.6, 7.3 Hz, 2H), 2.21-2.15 (m, 1H); $^{13}$C NMR (CDCl₃) δ 177.5, 167.1, 164.0, 158.2, 127.1, 117.6, 114.2, 110.2, 100.2, 55.8, 43.6, 31.4, 29.5; UV (MeOH) λmax 216, 241, 248, 293;
HRMS m/z (M⁺) calculated for C₁₃H₁₃ClO₃ was 252.0550, found 252.0568 (M⁺, 100%), 254.0543 (M⁺², 32%).

54: 2-(Diethoxymethyl)-7-methoxy-4H-1-benzopyran-4-one (JLW-I-136):
Using the previously described Cyclization C procedure and starting from 45 mg (0.12 mmol) of 4,4-bisethoxy-1-[2-[[1,1-dimethylethyl]dimethylsilyloxy]-4-methoxyphenyl]-2-butyn-1-one, 32 mg (89%) of the title compound was obtained as a yellow/orange oil: IR (CCl₄, cm⁻¹) 3076, 2975, 2932, 2897, 1651, 1612, 1279, 1062; $^1$H NMR (CDCl₃) δ 8.05 (d, J = 8.8 Hz, 1H) 6.87-6.86 (m, 2H), 6.49 (s, 1H), 5.26 (s, 1H), 3.85 (s, 3H), 3.67-3.61 (m, 4H), 1.23 (t, J = 7.0, 6.9 Hz, 6H); $^{13}$C NMR (CDCl₃) 177.6, 164.2, 162.7, 158.0, 127.0, 118.0, 114.5, 110.0, 100.5, 97.8, 62.1, 55.8, 25.6, 15.0, 0.9; UV (EtOH) λmax 241, 248, 294; HRMS m/z (M⁺) calculated for C₁₃H₁₈O₅ was 278.1149, found 278.1130.
55: 3-Bromo-7-methoxy-2-phenyl-4H-1-benzopyran-4-one (JLW-I-191):

Using the same procedure described for 3-bromo-2-phenyl-4H-1-benzopyran-4-one 15, the title compound was obtained from 0.25 g (1.0 mmol) of 8-methoxy-2-phenyl-4H-1-benzopyran-4-one to yield 0.28 g (85%) as white plates: mp 152-154°C; IR (KBr, cm\(^{-1}\)) 3060, 2924, 2854, 1639, 1247, 1068; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.17 (d, \(J = 8.9\) Hz, 1H), 7.84-7.80 (m, 2H), 7.53-7.50 (m, 3H), 7.00 (dd, \(J = 8.9, 2.3\) Hz, 1H), 6.86 (d, \(J = 2.3\) Hz, 1H), 3.89 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 172.4, 164.4, 161.5, 157.4, 133.0, 131.0, 129.3, 128.3, 127.9, 115.7, 115.2, 109.3, 99.9, 55.9; UV (MeOH) 250, 305; HRMS \(m/z\) (M\(^+\)) calculated for C\(_{16}\)H\(_{11}\)BrO\(_3\) was 329.9888, found 329.9898 (M\(^+\), 100%), 331.9863 (M\(^+\)\(^2\), 87%).

56: 7-Methoxy-2-propyl-4H-1-benzopyran-4-one (JLW-II-033):

Using the previously described Cyclization C procedure and starting from 0.71 g (2.2 mmol) of 1-[2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-4-methoxyphenyl]-2-hexyn-1-one, 0.42 g (76%) of the title compound was obtained as a yellow solid: mp 70-71°C; IR (KBr, cm\(^{-1}\)) 2967, 2932, 2875, 1645, 1602, 1437, 1390, 1266, 1202, 1020, 992; \(^1\)H NMR(CDCl\(_3\)) \(\delta\) 8.07 (d, \(J = 8.9\) Hz, 1H), 6.93 (d, \(J = 8.9, 2.4\) Hz, 1H), 6.81 (d, \(J = 2.4\) Hz, 1H), 4.60 (s, 2H), 3.89 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 172.3, 164.4, 161.5, 157.4, 133.0, 131.0, 129.3, 128.3, 127.9, 115.7, 115.2, 109.3, 99.9, 55.9, 15.7; UV (MeOH) 250, 305; HRMS \(m/z\) (M\(^+\)) calculated for C\(_{18}\)H\(_{17}\)BrO\(_3\) was 331.9863, found 331.9863 (M\(^+\), 100%), 333.9898 (M\(^+\)\(^2\), 87%).
Hz, 1H), 6.11 (s, 1H), 3.88 (s, 3H), 2.55 (t, \( J = 7.5 \) Hz, 2H), 1.75 (m, 2H), 1.00 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 178.3, 169.5, 164.4, 158.7, 127.4, 117.9, 114.5, 110.1, 100.6, 56.2, 36.5, 20.6, 13.9, UV (EtOH) \( \lambda_{max} \) 217, 241, 248, 285; HRMS \( m/z \) (M + H\(^+\)) calculated for C\(_{13}\)H\(_{14}\)O\(_3\) was 219.1021, found 219.1024.

CH\(_3\)O

57: 3-Bromo-7-methoxy-2-propyl-4H-1-benzopyran-4-one (JLW-II-037):
Using the same procedure described for 3-bromo-2-phenyl-4H-1-benzopyran-4-one 15, the title compound was obtained from 92 mg (0.4 mmol) of 8-methoxy-2-propyl-4H-1-benzopyran-4-one to yield 0.11 g (88%) as a white solid: mp 95-95.5°C; IR (KBr, cm\(^{-1}\)) 2968, 2870, 1638, 1433, 1337, 1240, 1191, 1020; \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 8.11 (d, \( J = 8.9 \) Hz, 1H), 6.96 (dd, \( J = 8.9 \), 2.4 Hz, 1H), 6.81 (d, \( J = 2.4 \) Hz, 1H), 3.89 (s, 3H), 2.90 (t, \( J = 7.4 \) Hz, 2H), 1.82 (sishet, \( J = 7.5 \) Hz, 2H), 1.04 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 172.1, 166.6, 164.4, 157.4, 128.0, 116.0, 115.0, 109.8, 100.0, 56.1, 36.8, 20.4, 13.9; UV (EtOH) \( \lambda_{max} \) 225, 252, 295; HRMS \( m/z \) (M + Na\(^+\)) calculated for C\(_{13}\)H\(_{13}\)BrO\(_3\) was 318.9946, found 318.9952 (M + Na\(^+\), 100%), 320.9935 (M\(^2+\) + Na\(^+\), 93.8%).
60: 7-Hydroxy-2-phenyl-4H-1-benzopyran-4-one (JLW-II-017):

To a solution of NaH (3.1 equiv of a 60% w/w dispersion) in 0.7 mL DMF at 0°C was added ethanethiol (3.0 equiv) dropwise to generate a 0.5 M NaSEt solution in DMF. After 30 min, the mixture was warmed to rt and a solution of 7-methoxy-2-phenyl-4H-1-benzopyran-4-one (29 mg, 0.11 mmol) in DMF (0.5 mL) was added dropwise. The reaction mixture was heated to reflux for 3.5 h; then cooled in a ice-bath and acidified with dilute (< 1M)HCl to pH 3. The reaction mixture was extracted with EtOAc, washed with H2O, brine, and dried (Na2SO4), and concentrated in vacuo. The aqueous layer was reextracted with CHCl3 and monitored by TLC. The residue was purified via flash chromatography (silica gel, 2:1 hexanes:EtOAc) followed by recrystallization in MeOH to yield 62 mg (62%) of the title compound as a off-white solid: mp 237-238°C; IR (KBr, cm⁻¹) 3055, 2924, 2594, 1626, 1612, 1261; ¹H NMR (DMSO-δ6) δ 10.80 (s, 1H), 8.03 (dd, 2H), 7.86 (d, J = 8.7 Hz, 1H), 7.56-7.49 (m, 3H), 6.98 (d, J = 2.1 Hz, 1H), 6.90 (dd, J = 8.7, 2.2 Hz, 1H), 6.87 (s, 1H); ¹³C NMR (DMSO-δ6) δ 176.4, 162.7, 161.9, 157.5, 131.5, 131.3, 129.0, 126.5, 126.1, 116.1, 115.1, 106.6, 102.5; UV (EtOH) λmax 251, 308; HRMS m/z (M + Na⁺) calculated for C₁₅H₁₀O₃ was 261.0528, found 261.0527.
61: 7-Hydroxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (JLW-II-019):

To a solution of NaH (3.1 equiv of a 60% w/w dispersion) in 0.6 mL DMF at 0°C was added ethanethiol (3.0 equiv) dropwise to generate a 0.5 M NaSEt solution in DMF. After 30 min, the mixture was warmed to rt and added dropwise to a solution of 7-methoxy-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (24 mg, 0.10 mmol) in DMF (0.5 mL). The reaction mixture was heated to reflux for 3.5 h; then cooled in an ice-bath and acidified with dilute (< 1M)HCl to pH 3. The reaction mixture was extracted with EtOAc, washed with H2O, brine, and dried (Na2SO4), and concentrated in vacuo. The aqueous layer was reextracted with CHCl3 and monitored by TLC. The residue was purified via flash chromatography (silica gel, CHCl3/5% MeOH) followed by recrystallization in MeOH to yield 21 mg (92%) of the title compound as yellow solid:

mp 276-280°C; IR (KBr, cm⁻¹) 3032, 2962, 1625, 1248, 1090; ¹H NMR (DMSO-d₆) δ 10.77 (s, 1H), 7.91 (s, 1H), 7.88 (s, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.90 (dd, J = 8.7, 2.1 Hz, 1H), 6.80 (s, 1H), 2.33 (s, 3H); ¹³C NMR (DMSO-d₆) δ 176.3, 162.5, 162.0, 157.4, 141.6, 129.6, 128.4, 126.4, 126.0, 116.1, 114.8, 105.9, 102.4, 20.9; UV (EtOH) λmax 311; HRMS m/z (M+ + H) calculated for C₁₆H₁₂O₃ was 253.0864, found 253.0863.
70: 7-Methyl-2-phenyl-4H-1-benzopyran-4-one (JLW-II-036):

Using the previously described Cyclization C procedure and starting from 0.85 g (2.4 mmol) of 1-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-methylphenyl]-3-phenyl-2-propyn-1-one, 0.46 g (80%) of the title compound was obtained as orange crystals which was further recrystallized with MeOH: mp 118-119°C; IR (KBr, cm⁻¹) 3031, 2919, 1646, 1627; ¹H NMR (CDCl₃) δ 8.09 (d, J = 8.1 Hz, 1H), 7.90 (m, 2H), 7.50 (m, 3H), 7.35 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.78 (s, 1H), 2.49 (s, 3H); ¹³C NMR (CDCl₃) δ 178.8, 163.5, 156.8, 145.5, 132.3, 131.9, 129.4, 127.1, 126.7, 125.9, 122.1, 118.3, 108.0, 22.3; UV (EtOH) λmax 255, 298; HRMS m/z (M + Na⁺) calculated for C₁₆H₁₂O₂ was 259.0735, found 259.0735.

80: 7-Chloro-2-phenyl-4H-1-benzopyran-4-one (JLW-II-273):

4-Chloro-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.39 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.37 mL, 3.0 mmol) according to Coupling B to yield 0.31 g (84%) of an impure sample of 1-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-chloro-phenyl]-3-phenyl-2-propyn-1-one as a
brown oil, which was used without further purification. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.12 g (49%) of the title compound as a yellow/brown solid: mp 154°C; IR (KBr, cm⁻¹) 3061, 1638, 1369, 1251, 1070, 813, 768; ¹H NMR (CDCl₃) δ 8.16 (d, J = 8.6 Hz, 1H), 7.91-7.87 (m, 2H), 7.60 (d, J = 1.8 Hz, 1H), 7.54-7.51 (m, 3H), 7.38 (dd, J = 8.3, 1.4 Hz, 1H), 6.80 (s, 1H); ¹³C NMR (CDCl₃) δ 177.5, 163.6, 156.4, 139.8, 131.8, 131.5, 129.1, 127.2, 126.3, 126.1, 122.6, 118.2, 107.9; UV (MeOH) λmax 249, 298; HRMS m/z (M + Na⁺) calculated for C₁₅H₉ClO₂ was 279.0189, found 279.0184 (M⁺Na⁺; 100%), 281.0177 (M⁺² + Na⁺; 34.6%).

81: 7-Chloro-2-(4'-methylphenyl)-4H-1-benzopyran-4-one (JLW-I-274):

4-Chloro-2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.40 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 4-ethynyltoluene (0.47 mL, 3.8 mmol) according to Coupling B to yield 0.29 g (77%) of an impure sample of 1-[[1,1-dimethylethyl]dimethylsilyl]oxy]-4-chloro-phenyl]-3-(4-methylphenyl)-2-propyn-1-one as a yellow solid, which was used without further purification. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.11 g (42%) of the title compound as a pale yellow solid: mp 211
191-192.5°C; IR (KBr, cm⁻¹) 3064, 1639, 1434, 1367, 1260, 1039, 818; ¹H NMR (CDCl₃) δ 8.15 (d, J = 8.5 Hz, 1H), 7.80 (s, 1H), 7.77 (s, 1H), 7.59 (d, J = 1.8 Hz, 1H), 7.37 (dd, J = 8.5, 1.9 Hz, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 6.77 (s, 1H), 2.43 (s, 3H); ¹³C NMR (CDCl₃) δ 177.5, 163.8, 156.4, 142.5, 139.6, 129.8, 128.6, 127.1, 126.2, 126.0, 122.6, 118.1, 107.2, 21.5; UV (EtOH) λmax 250, 307; HRMS m/z (M + H⁺) calculated for C₁₈H₁₁ClO₂ was 271.0526, found 271.0510 (M + H⁺, 100%), 273.0501 (M⁺² + H⁺, 35%).

82: 7-Chloro-2-(1-cyclohexen-1-yl)-4H-1-benzopyran-4-one (JLW-I-278):

Using the previously described Cyclization C procedure and starting from 0.36 g (1.0 mmol) of 1-[4-chloro-2-[[[1,1-dimethylethyl]dimethylsilyl]oxy]-phenyl]-3-phenyl-2-propyn-1-one, 0.12 g (47%) of the title compound was obtained as an orange solid: mp 118-119°C; IR (KBr, cm⁻¹) 2934, 1646, 1605, 1209, 1068, 1017; ¹H (CDCl₃) δ 8.08 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 1.9 Hz, 1H), 7.31 (dd, J = 8.5, 1.9 Hz, 1H), 6.97 (m, 1H), 6.26 (s, 1H), 2.33-2.25 (m, 4H), 1.79-1.64 (m, 4H); ¹³C NMR (CDCl₃) δ 178.0, 163.9, 156.1, 139.5, 134.4, 129.4, 127.0, 125.5, 122.4, 117.9, 106.3, 26.0, 24.2, 22.1, 21.5; UV (EtOH) λmax 246, 301; HRMS m/z (M + H⁺) calculated for C₁₅H₁₃ClO₂ was 261.0681, found 216.0676 (M + H⁺, 100%), 263.0681 (M⁺² + H⁺, 35%).
83: 7-Chloro-2-(3-chloropropyl)-4H-1-benzopyan-4-one (JLW-I-280):

4-Chloro-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.41 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.47 mL, 3.8 mmol) according to Coupling B. Crude $^1$H NMR before workup reveals absence of TBS peaks and singlet at 5.8 ppm. The residue was dissolved in EtOAc, washed with H$_2$O, 10% NH$_4$OH, brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified via flash chromatography (silica gel, 4:1 hexanes:EtOAc) to yield 0.11 g (42%) of the title compound as a orange/brown oil. This oil solidified over time and was crystallized from EtOH/H$_2$O to give an off-white solid: mp 66-67°C; IR (KBr, cm$^{-1}$) 3061, 1642, 1604, 1431, 1164; $^1$H NMR (CDCl$_3$) $\delta$ 7.96 (d, $J = 8.6$ Hz, 1H), 7.32 (d, $J = 1.5$ Hz, 1H), 7.22 (dd, $J = 8.7, 1.4$ Hz, 1H), 6.08 (s, 1H), 3.54 (t, $J = 6.2$ Hz, 2H), 2.71 (t, $J = 7.7$ Hz, 2H), 2.16-2.05 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 176.8, 167.7, 156.2, 139.3, 126.8, 125.6, 117.8, 110.3, 43.3, 31.2, 29.1; UV (EtOH) $\lambda_{max}$ 303; HRMS m/z (M + Na$^+$) calculated for C$_{12}$H$_{10}$Cl$_2$O$_2$ was 278.9956, found 278.9960 (M + Na$^+$, 100%), 281.0034 (M$^{+2}$ + Na$^+$, 65.2%), 283.0220 (M$^{+4}$ + Na$^+$, 10.6%).
90: 6-Chloro-2-phenyl-4H-1-benzopyran-4-one (JLW-I-235):

5-Chloro-2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.33 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.47 mL, 3.8 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used without further purification in the subsequent cyclization step according to Cyclization C to yield 59 mg (23%) of the title compound which was further washed with petroleum ether to yield 0.15 g (60%) of the title compound which was further recrystallized from EtOH/hexanes to give brown solid: mp 178-179°C; IR (KBr, cm⁻¹) 3086, 1656, 1253, 1022, 772; ¹H NMR (CDCl₃) δ 8.19 (d, J = 2.5 Hz, 1H), 7.92 (d, J = 1.9 Hz, 1H), 7.90-7.88 (m, 1H), 7.64 (dd, J = 8.9, 2.6 Hz, 1H), 7.54-7.50 (m, 4H), 6.82 (s, 1H); ¹³C NMR (CDCl₃) δ 177.3, 163.8, 154.8, 134.1, 132.0, 131.6, 131.4, 129.3, 126.5, 125.4, 125.1, 119.9, 107.7; UV (MeOH) λmax 254, 298; HRMS m/z (M⁺) calculated for C₁₅H₁₃ClO₂ was 256.0289, found 256.0298 (M⁺, 100%), 258.0273 (M⁺², 35%).
91: 6-Chloro-2-(4'-methylphenyl)-4H-1-benzopyranon-4-one (JLW-II-007):

Using the previously described Cyclization D procedure and starting from 0.24 g (0.6 mmol) of 1-[2-[[1,1-dimethylethyl]dimethylsilyloxy]-5-chlorophenyl]-3-phenyl-2-propyn-1-one, 0.11 g (63%) of the title compound was obtained as a white solid: mp 185-185.5°C; IR (KBr, cm⁻¹) 3068, 2913, 1641, 1614, 816; ¹H NMR (CDCl₃) δ 8.17 (d, J = 2.5 Hz, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.62 (dd, J = 8.9, 2.5 Hz, 1H), 7.51 (d, J = 8.9 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 6.78 (s, 1H), 2.43 (s, 3H); ¹³C NMR (CDCl₃) δ 177.2, 163.9, 154.6, 142.6, 133.8, 131.1, 129.8, 128.6, 126.3, 125.2, 125.0, 119.8, 106.9, 21.5; UV (EtOH) λmax 256, 307; HRMS m/z (M + H⁺) calculated for C₁₆H₁₁O₂Cl was 271.0523, found 271.0524 (M + H⁺, 100%), 273.0485 (M⁺² + H⁺, 23%).
92: 6-Chloro-2-(1-cyclohexen-1-yl)-4H-1-benzopyran-4-one (JLW-I-289):

5-Chloro-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-benzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (0.40 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-ethynyl-1-cyclohexene (0.47 mL, 4.0 mmol) according to Coupling C. The alkynone obtained from the Sonogashira coupling was used without further purification in the subsequent cyclization step according to Cyclization G to yield 59 mg (23%) of the title compound which was further washed with petroleum ether to yield a orange-brown solid: mp 94.5-97°C; IR (KBr, cm⁻¹) 2927, 1644, 1632, 1606, 1110; ¹H NMR (acetone-d₆) δ 7.95 (d, J = 2.6 Hz, 1H), 7.74 (dd, J = 8.9, 2.6 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.04-7.01 (m, 1H), 6.22 (s, 1H), 2.35-2.27 (m, 4H), 1.82-1.63 (m, 4H); ¹³C NMR (acetone-d₆) δ 176.5, 164.0, 154.9, 134.6, 134.1, 130.4, 129.8, 125.2, 124.5, 120.8, 105.9, 26.1, 24.2, 22.4, 21.7; UV (EtOH) λmax 222, 252, 298; HRMS m/z (M + Na⁺) calculated for C₁₅H₁₃ClO₂ was 283.0502, found 283.0502 (M + Na⁺, 100%), 285.0489 (M⁺² + Na⁺, 33%).
93: 6-Chloro-2-(3-chloropropy1)-4H-1-benzopyran-4-one (JLW-I-284):

5-Chloro-2-[(1,1-dimethylethyl)dimethylsilyloxy]-benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.43 g, 1.1 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 5-chloro-1-pentyne (0.69 mL, 6.5 mmol) according to Coupling C to yield 80 mg (29%) of the title compound which was further washed with petroleum ether to yield off-white solid: mp 66-67°C; IR (KBr, cm⁻¹) 3061, 1642, 1604, 1431, 1164; ¹H NMR (CDCl₃) δ 8.12 (d, J = 2.6 Hz, 1H), 7.58 (dd, J = 8.9, 2.6 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 6.21 (s, 1H), 3.61 (t, J = 6.2 Hz, 2H), 2.81 (t, J = 7.8 Hz, 2H), 2.20 (m, 2H); ¹³C NMR (CDCl₃) δ 177.1, 168.3, 154.9, 134.0, 131.2, 1253, 124.8, 119.7, 110.5, 43.7, 31.7, 29.6; UV (EtOH) λmax 227, 305; HRMS m/z (M + H⁺) calculated for C₁₂H₁₀Cl₂O₂ was 257.0136, found 257.0133 (M + H⁺, 100%), 259.0125 (M⁺² + H⁺, 54%), 261.0164 (M⁺³ + H⁺, 5%).
110: 2,6-Diphenyl-4H-1-benzopyran-4-one (JLW-I-264):

2-[[1,1-Dimethylethyl]dimethylsilyloxy]-5-phenylbenzoic acid, (1,1-dimethylethyl)dimethylsilyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with phenylacetylene (0.37 mL, 3.0 mmol) according to Coupling C to yield 0.31 g (76%) of an impure sample of 1-[2-[[1,1-dimethylethyl]dimethylsilyloxy]-5-phenyl-phenyl]-3-phenyl-2-propyn-1-one. The alkynone obtained from the Sonogashira coupling was used without further purification in the subsequent cyclization step according to Cyclization C to yield 0.17 g (57%) of the title compound which was further washed with petroleum ether to yield 0.14 g (46%) as a pale pink solid; mp 152-153°C; IR (KBr, cm⁻¹) 3061, 1642, 1358, 1249, 769; 

\[
\begin{align*}
\text{H} \text{NMR (CDCl}_3\text{)} & \delta 8.44 (d, J = 2.3 \text{ Hz}, 1\text{H}), 7.95-7.92 (m, 3\text{H}), 7.69 (d, J = 1.3 \text{ Hz}, 1\text{H}), 7.65-7.62 (m, 2\text{H}), 7.54-7.37 (m, 6\text{H}), 6.85 (s, 1\text{H}); \\
\text{C} \text{ NMR (CDCl}_3\text{)} & \delta 178.9, 163.8, 156.1, 139.7, 138.8, 133.0, 132.2, 132.0, 129.5, 129.4, 128.3, 127.6, 126.7, 124.5, 124.0, 119.0, 108.0; \\
\end{align*}
\]

UV (EtOH) \( \lambda_{\text{max}} \) 271; HRMS m/z (M + H⁺) calculated for C₂₁H₁₄O₂ was 299.1072, found 299.1068.
111: 2-(4′-Methylphenyl)-6-phenyl-4H-1-benzopyran-4-one (JLW-1-267):

2-[[[(1,1-Dimethylethyl)dimethylsilyloxy]-5-phenyl-benzoic acid, (1,1-dimethylethyl)-
dimethylsilyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot
acid chlorination Sonogashira coupling with 1-ethynyl-toluene (0.38 mL, 3.0 mmol)
according to Coupling B. The alkynone obtained from the Sonogashira coupling was
used in the subsequent cyclization step according to Cyclization C to yield 0.24 g (77%)
of the title compound as a pale yellow solid: mp 202-202.5°C; IR (KBr, cm⁻¹) 3056,
1636, 1616, 1455, 1355, 1253, 1045, 823, 763; \(^1\)H NMR (CDCl₃) \(\delta\) 8.41 (d, \(J =\)
2.3 Hz, 1H); 7.90 (dd, \(J = 8.7, 2.4\) Hz, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.66 (m, 1H),
7.63-7.57 (m, 2H), 7.47-7.35 (m, 3H), 7.31 (s, 1H); 7.27 (s, 1H), 6.79 (s, 1H), 2.41 (s,
3H); \(^1^\)C NMR (CDCl₃) \(\delta\) 178.4, 163.5, 155.6, 142.2, 139.3, 138.2, 132.4, 129.7, 128.9,
127.8, 127.1, 126.6, 126.2, 124.1, 123.5, 118.5, 106.9, 21.5; UV (EtOH) 273, 309;
HRMS m/z (M + H⁺) calculated for C₂₂H₁₆O₂ was 313.1228, found 313.1219.

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112: 2-(1-Cyclohexen-1-yl)-6-phenyl-4H-1-benzopyran-4-one (JLW-1-266):

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-phenyl-benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 1-ethynyl-cyclohexene (0.38 mL, 3.2 mmol) according to Coupling B. The alkynone obtained from the Sonogashira coupling was used in the subsequent cyclization step according to Cyclization C to yield 0.21 g (68%) of the title compound as a orange solid: mp 128-129°C; IR (KBr, cm⁻¹) 2919, 1648, 1615, 1427, 833, 767; H NMR (CDCl₃) δ 8.34 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.62-7.59 (m, 2H), 7.44-7.31 (m, 4H), 6.93 (m, 1H), 6.26 (s, 1H), 2.26-2.22 (m, 4H), 1.75-1.60 (m, 4H); C NMR (CDCl₃) δ 179.3, 164.6, 155.9, 139.7, 138.4, 135.2, 133.1, 130.1, 129.4, 128.2, 127.6, 124.0, 123.8, 118.8, 106.3, 26.5, 24.6, 22.6, 21.9; UV (EtOH) 270; HRMS m/z (M + Na⁺) calculated for C₂₁H₁₆O₂ was 325.1204, found 325.1200.
113: 2-(3-Chloropropyl)-6-phenyl-4H-1-benzopyran-4-one (JLW-I-277):

2-[[((1,1-Dimethylethyl)dimethylsilyloxy]-5-phenyl-benzoic acid, (1,1-dimethylethyl)-dimethylsilyl ester (0.44 g, 1.0 mmol) was used for the previously described one-pot acid chlorination Sonogashira coupling with 5-chloro-1-pentyne (0.31 mL, 3 mmol) according to Coupling B to yield 0.30 g (74%) of an impure sample of 6-chloro-1-[2-[[((1,1-dimethylethyl)dimethylsilyloxy]-5-phenyl-phenyl]-2-hexenyn-1-one (JLW-I-270) as a orange-brown oil. The alkynone obtained from the Sonogashira coupling was used without further purification in the subsequent cyclization step according to Cyclization C to yield 0.12 g (39%) of the title compound as a tan solid: mp 109-111°C; IR (KBr, cm⁻¹) 2920, 1641, 1473, 1456, 1351, 767; ¹H (CDCl₃) δ 8.39 (d, J = 2.3 Hz, 1H), 7.89 (dd, J = 8.7, 2.3 Hz, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 7.55-7.33 (m, 4H), 6.23 (s, 1H), 3.63 (t, J = 6.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.23 (q, 2H); ¹³C NMR (CDCl₃) δ 178.6, 168.2, 156.3, 139.7, 138.7, 132.9, 129.4, 128.3, 127.6, 124.2, 124.0, 118.8, 110.8, 44.0, 32.0, 29.9; UV (MeOH) λmax 250, 314; HRMS m/z (M + H⁺) calculated for C₁₈H₁₄ClO₂ was 299.0839, found 299.0850 (M + H⁺, 100%), 301.0862 (M⁺² + H⁺, 34.8%).
120: 6-Methoxy-2-phenyl-4H-1-benzopyran-4-one (JLW-II-065):

Using the previously described *Cyclization C* procedure and starting from 0.69 g (1.9 mmol) of 1-[2-[(1,1-dimethylethyl)dimethylsilyloxy]-5-methoxyphenyl]-3-phenyl-2-propyn-1-one, 0.34 g (71%) of the title compound was obtained as an off-white solid: mp 158.5-159°C; IR (KBr, cm⁻¹) 1640, 1360, 1254, 1076; ¹H NMR (CDCl₃) δ 7.91 (d, J = 2.3 Hz, 1H), 7.89-7.88 (m, 1H), 7.59 (d, J = 3.1 Hz, 1H), 7.54-7.47 (m, 4H), 7.28 (dd, J = 9.1, 3.1 Hz, 1H), 6.80 (s, 1H), 3.90 (s, 3H); ¹³C NMR (CDCl₃) δ 178.3, 163.2, 157.0, 151.1, 131.9, 131.5, 129.0, 126.3, 124.6, 123.8, 119.5, 106.9, 104.9, 56.0; UV (EtOH) 270, 304; HRMS m/z (M + Na⁺) calculated for C₁₆H₁₂O₃ was 275.0684, found 275.0671.

7-Methyl-2-phenyl-3(2H)-benzofuranone (JLW-II-035):

¹H NMR (CDCl₃) δ 7.90-7.87 (m, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.46-7.33 (m, 3H), 7.10 (s, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.83 (s, 1H), 2.46 (s, 3H); ¹³C NMR (CDCl₃) δ 184.8, 167.1, 149.5, 147.8, 132.9, 132.9, 131.8, 130.1, 129.3, 128.9, 125.3, 124.7, 119.7, 113.5, 112.9, 23.1; UV (MeOH) λmax 325, 371.
7-Chloro-2-(4-methylphenyl)-3(2H)-benzofuranone (JLW-I-272):

IR (KBr, cm⁻¹) 3065, 1707, 1650, 1606, 125, 1058; ¹H NMR (acetone-d₆) δ 7.74 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.15 (dd, J = 8.2, 1.6 Hz, 1H), 6.85 (s, 1H), 2.37 (s, 3H); ¹³C NMR (CDCl₃) δ 183.1, 166.0, 146.5, 142.6, 140.8, 131.6, 129.7, 129.2, 125.3, 124.2, 120.4, 114.1, 113.5, 21.6; UV (EtOH) λ max 264, 328, 379.

2-Diethoxymethyl-7-methoxy-3(2H)-benzofuranone (JLW-I-195):

IR (KBr, cm⁻¹) 2979, 2898, 1723, 1614, 1286, 1158, 1053; ¹H NMR (CDCl₃) δ 7.62 (d, J = 8.7 Hz, 1H), 6.67 (dd, J = 8.7, 2.0 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.02 (d, J = 7.5 Hz, 1H), 5.54 (d, J = 7.6 Hz, 1H), 3.87 (s, 3H), 3.74-3.56 (m, 4H), 1.22 (t, J = 7.3 Hz, 6H); ¹³C NMR (CDCl₃) δ 182.4, 169.0, 167.9, 149.4, 126.0, 114.7, 112.1, 109.5, 96.6, 96.1, 61.4, 56.0, 15.2; UV(EtOH) λ max 274, 318.
JLW-II-064 #11-12: 6-Methoxy-2-phenyl-3(2H)-benzofuranone:

$^1$H NMR (CDCl$_3$) $\delta$ 7.90 (s, 1H), 7.87 (s, 1H), 7.46-7.37 (m, 3H), 7.22 (m, 2H), 7.20 (s, 1H), 6.85 (s, 1H), 3.81 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 185.0, 161.3, 156.0, 147.7, 132.3, 131.5, 129.8, 128.9, 126.2, 121.7, 113.8, 113.1, 105.2, 55.8; UV (EtOH) $\lambda_{max}$ 259, 336, 381.
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#1 = 70/30 MeOH/H2O, C18 column
#2 = 65/35 Acetonitrile/H2O, Phenyl-hexyl column

Table 8.1: Numbering system of notebooks (JLW-I-xxx, JLW-II-xxx) and HPLC % purity data for solvent System #1 (70/30 MeOH/H2O) and System #2 (65/35 CH3CN/H2O).


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120. Herrmann, W. A. *Synthetic Methods of Organometallic and Inorganic Chemistry*; 1996.


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149. Negishi, E. Novel and selective \( \alpha \)-substitution of ketones and other carbonyl compounds based on Pd-catalyzed cross coupling of \( \alpha,\beta \)-unsaturated carbonyl derivatives containing \( \alpha \)-halogen or \( \alpha \)-metal groups. *J. Organomet. Chem.* 1999, 576, 179-194.


