HETEROCYCLES, Vol. 84, No. 2, 2012, pp. 983 - 1012. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 1st July, 2011, Accepted, 26th September, 2011, Published online, 7th October, 2011
DOI: 10.3987/COM-11-S(P)73

SYNTHESIS OF 8-HYDROXYISOCHROMENES AND 8-HYDROXYISOCOUMARINS FROM 3-ETHOXYCYCLOHEX-2-EN-1-ONE[§]

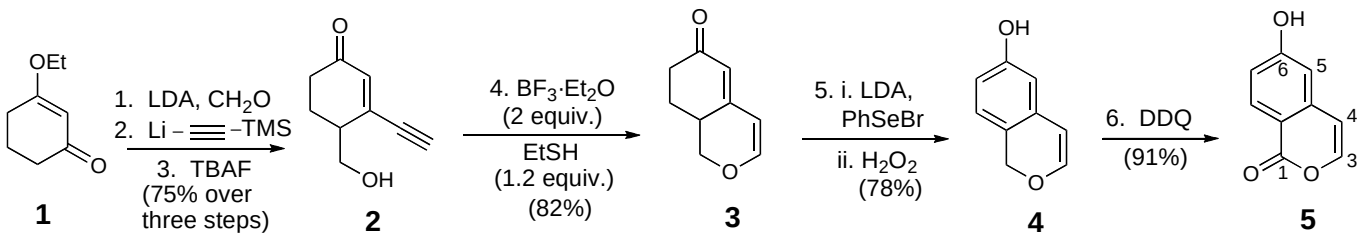
George Majetich* and Jeremy L. Grove[†]

Department of Chemistry, The University of Georgia, Athens, Georgia 30602, U.S.A. majetich@chem.uga.edu

Abstract – Two strategies were developed to prepare 8-hydroxyisocoumarins from substituted 3-ethoxycyclohex-2-en-1-ones. The key reactions in the first strategy were the cyclization of a 2-hydroxymethyl-3-ethynyl-cyclohex-2-en-1-one, followed by the aromatization of the resulting cyclohexenone-pyran intermediate. The second approach featured the reaction of 2-hydroxymethyl-3-vinyl-cyclohex-2-en-1-ones with DDQ to directly produce isocoumarins. This new two-step sequence was used to prepare oospolactone in 57% overall yield.

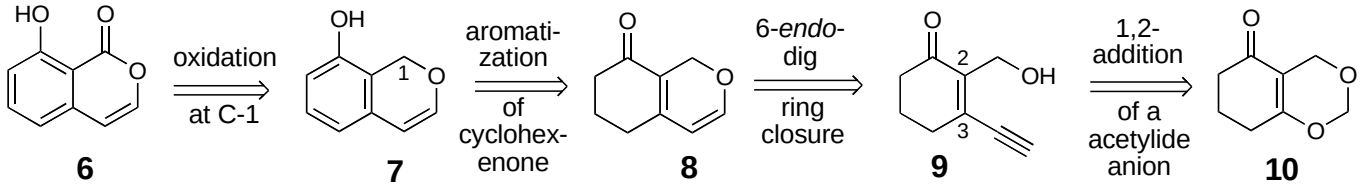
INTRODUCTION

In the preceding manuscript we reported that enynone **2**, prepared in straightforward manner from 3-ethoxy-cyclohex-2-en-1-one (**1**), cyclized to produce dihydropyran **3** in 82% yield. Subsequent aromatization of the cyclohexenone ring of **3**, followed by the oxidation of the methylene group of **4**, produced 6-hydroxyisocoumarin **5** in 71% overall yield (Scheme 1).[1]



Scheme 1

We recognized that an enynone with a hydroxymethyl substituent at the C-2 position (i.e., **9**) would produce pyran **8** (Scheme 2). Aromatization of the cyclohexenone ring of **8** would provide phenol **7** and oxidation of C-1 of **7** would furnish isocoumarin **6**, (also known as a benzopyran-1-one). Enynone **9** would be produced by adding an acetylide anion in 1,2-fashion to known 1,3-dioxin **10**.



Scheme 2

The 8-hydroxyisochromene and 8-hydroxyisocoumarin scaffolds are present in a large number and wide variety of naturally-occuring compounds with antifungal, phytotoxic, and antimicrobial activity;[2] ten representative examples are shown in Figure 1. Not surprisingly, general methods for the synthesis of these two classes have been widely studied and several excellent reviews focused on the isolation and synthetic approaches related to isocoumarins can be found in the literature.[3] A comprehensive review on the isolation, activity, or synthesis of the isochromenes (also known as a 2-benzopyran) has not been published despite the extensive work from the laboratories of Larock,[4] Yamamoto,[5] and others.[6] Our concise synthesis of multiply alkylated 8-hydroxyisochromenes and 8-hydroxyisocoumarins from 1,3-dioxin **10** is the focus of this article.

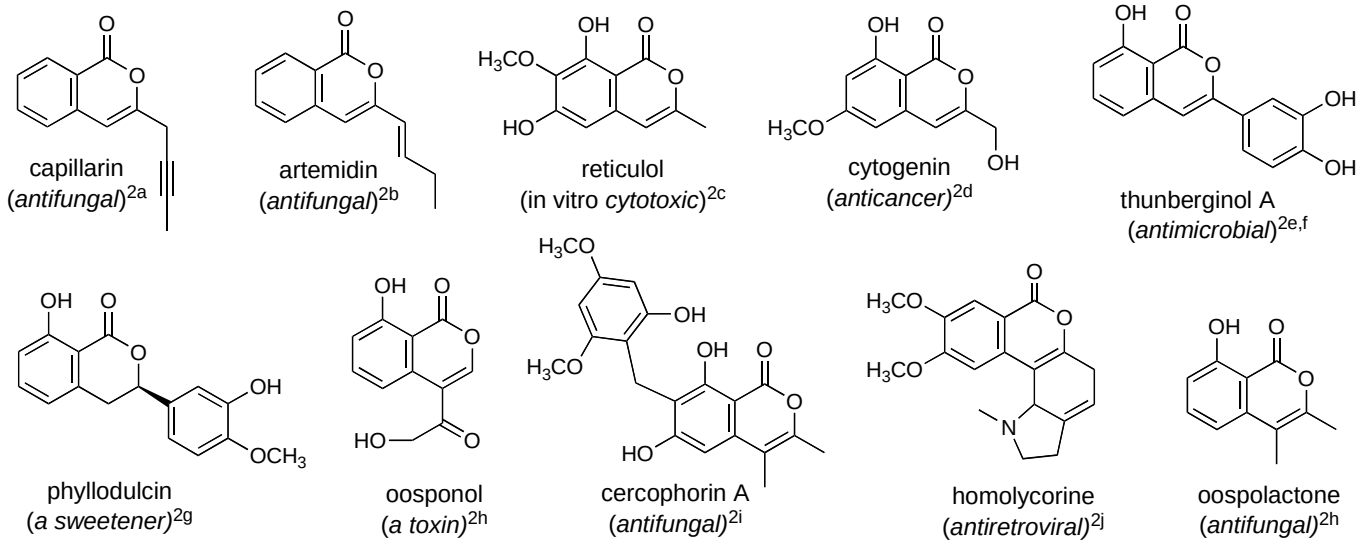
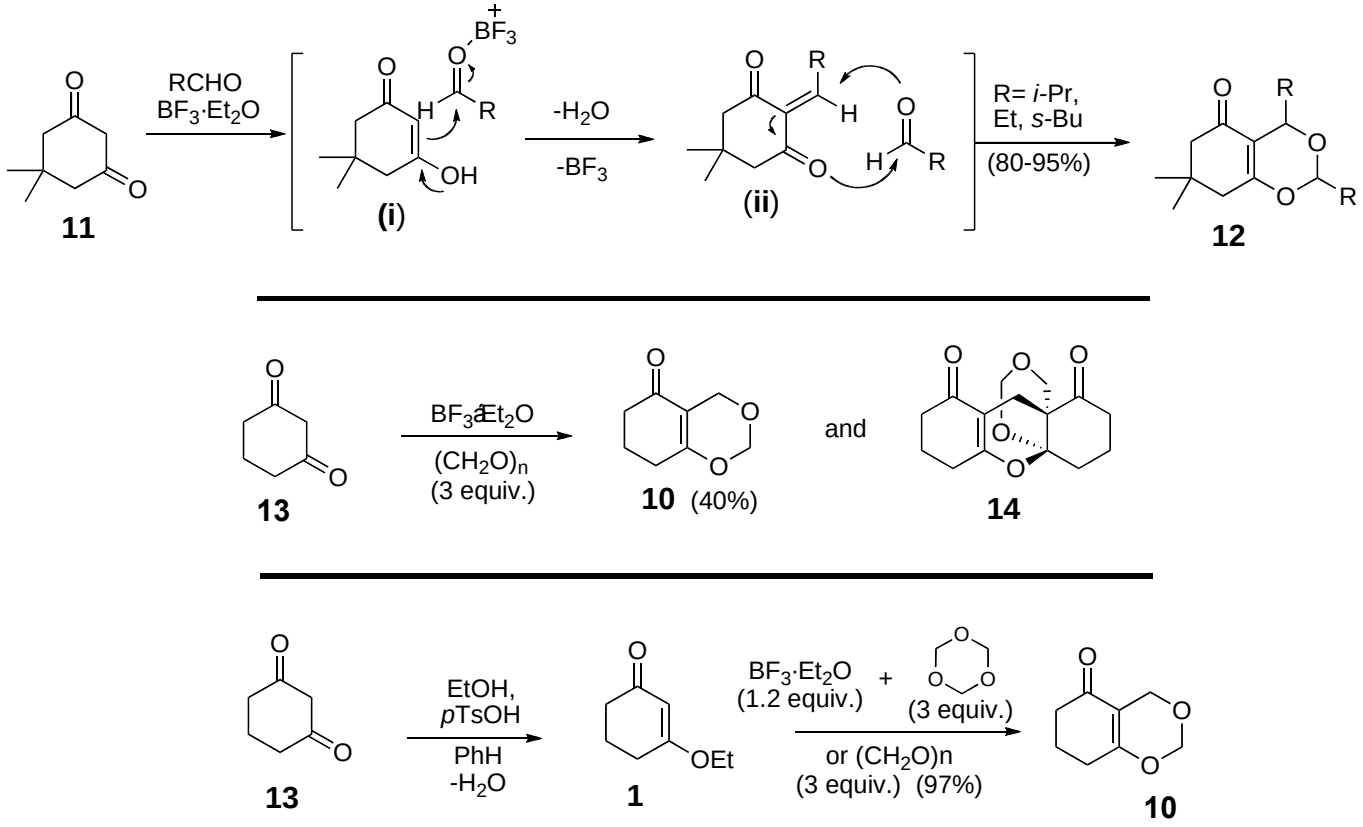


Figure 1

RESULTS AND DISCUSSION

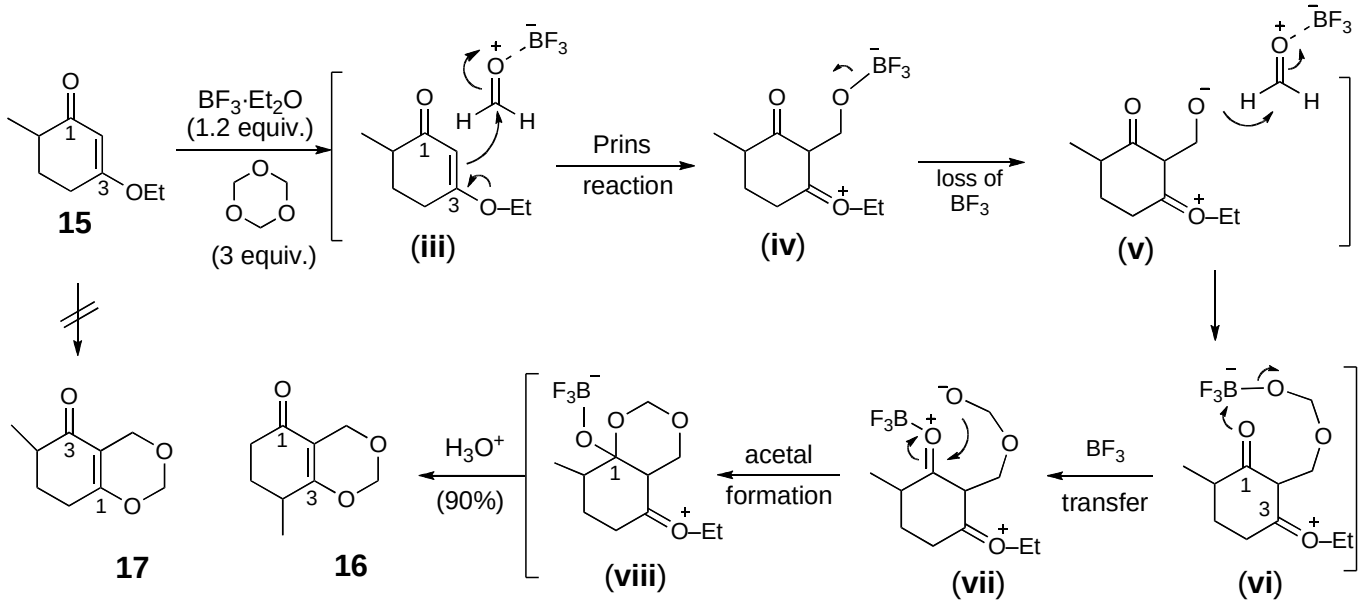
In 1982 Crow and co-workers[7] reported that dimedone (**11**) undergoes a Prins reaction with aliphatic aldehydes in the presence of $BF_3 \cdot Et_2O$ to produce 1,3-dioxin **12** in 80-95% yield (Scheme 3). They proposed a mechanism wherein the Lewis acid-activation of an aldehyde equivalent catalyzes the initial Prins reaction with enol **i**, followed by dehydration to give intermediate enedione **ii**. 1,3-Dioxin **12** is formed when a second aldehyde molecule undergoes a [4+2]-cycloaddition with **ii**.



Scheme 3

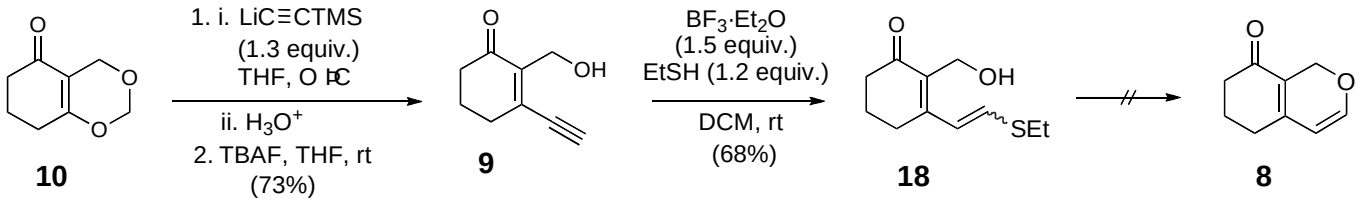
Smith *et al.* prepared 1,3-dioxin **10** from cyclohexane-1,3-dione (**13**) in 40% yield using 3 equivalents of $BF_3 \cdot Et_2O$ with a slight excess of paraformaldehyde or in 84% yield when 1,3,5-trioxane was used.[8] High dilution of the reagents and slow addition of diketone **13** minimized the formation of dimer **14**. In our hands, using Smith's conditions to prepare **10** from **13** instead favored the formation of **14**. However, using 3-ethoxycyclohex-2-en-1-one (**1**) and Smith's conditions produced dioxin **10** in 97% yield independent of the source of the formaldehyde. Furthermore, it did not require special methods of addition or high dilution; nor was dimer **14** detected. The mechanism for this modifcation to make 1,3-dioxin **10** was revealed due to a single alkylation (Scheme 4). When 3-ethoxy-6-methylcyclohex-2-en-1-one (**15**)[9] was subjected to dioxin formation only dioxin **16** was

produced (cf. isomeric dioxin **17**). As independently proposed by Crow and Smith, the first step of this mechanism is an intermolecular Prins reaction between **15** and the Lewis-activated aldehyde (**iii** → **iv**). However, instead of eliminating to form enedione **ii**, the Lewis acid is transferred to a second molecule of aldehyde that reacts with alkoxide **v** to form acetal **vi**. The intramolecular transfer of the Lewis acid to the C-1 carbonyl group activates it for 1,2-addition by the resulting alkoxide **vii**. Although 1,2-addition to the alkylated, and thus activated, C-3 carbonyl is possible, steric effects between the C-3 alkylated carbonyl group and the C-2-sidechain preclude 1,2-addition at this site. The hydrolysis of acetal **viii** produces 1,3-dioxin **16** in 90% yield.



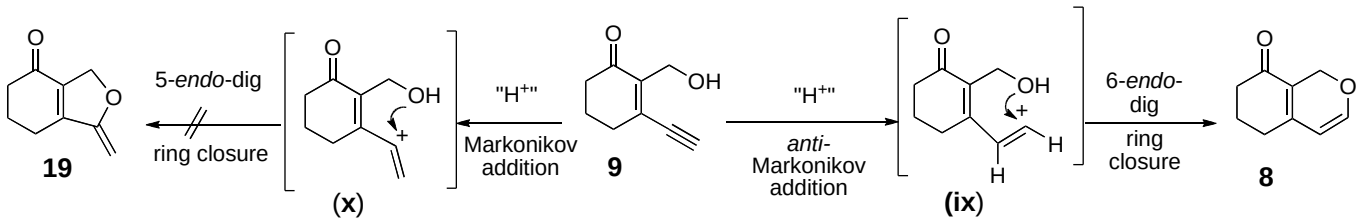
Scheme 4

With an efficient route to 1,3-dioxin **10** in hand, we next sought to introduce the pyran motif (i.e., **9** → **8**, Scheme 2). In their preparation of **10**, Smith *et al.* also reported that 1,3-dioxin **10** underwent 1,2-addition with hydrides, Grignard reagents or organolithium reagents to give β-substituted α-hydroxymethylcyclohex-2-en-1-ones in high yield.[8] 1,2-Addition of lithium (trimethylsilyl)acetylide to **10**, followed by acid hydrolysis and desilylation, produced enynone **9** in 73% yield (Scheme 5).



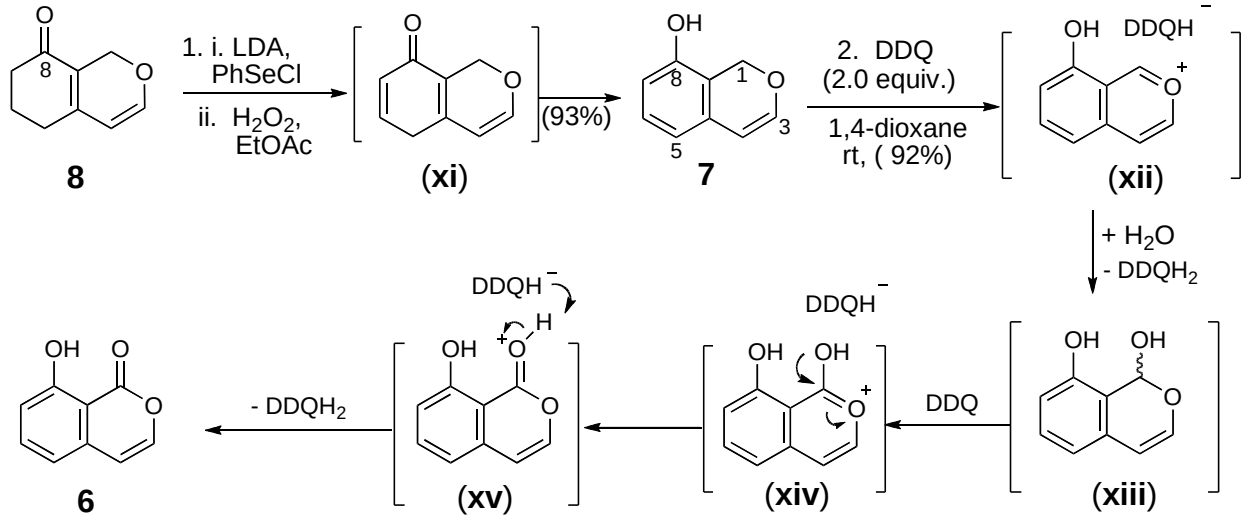
Scheme 5

While enynone **9** underwent the expected 1,6-addition of EtSH in the presence of $BF_3 \cdot Et_2O$ (cf. **18**), longer reaction times, higher reaction temperatures, or larger amounts of $BF_3 \cdot Et_2O$, did not promote pyran formation and led to decomposition. Treatment of enynone **9** with H_2SO_4 also caused decomposition, whereas HCl added to the triple bond instead of promoting cyclization. Pryan formation was achieved by using organic Brönsted acids such as *p*-TsOH or triflic acid (TfOH). We observed, however, that TfOH is not very soluble in DCM and that the addition of co-solvents to increase its solubility decreased its reactivity. Optimal results for pyran formation were obtained using methanesulfonic acid (MsOH) (Scheme 6). While catalytic quantitities of MsOH produced pyran **8**, the conversion was low. Treatment of enynone **9** with 1 equivalent of MsOH in dilute DCM gave pyran **8** in 61% yield *via* a 6-*endo*-dig cyclization (cf. **ix**).[10] Enol ether **19**, a 5-*endo* dig cyclization product produced by the addition of the alcohol to carbocation **x**, was not observed. When 2 equivalents of MsOH were used in refluxing DCM, pyran **8** was produced in 79% yield. Pyran **8** was unstable when isolated neat but could be stored for up to two weeks when left in solution and stored at -20 °C.



Scheme 6

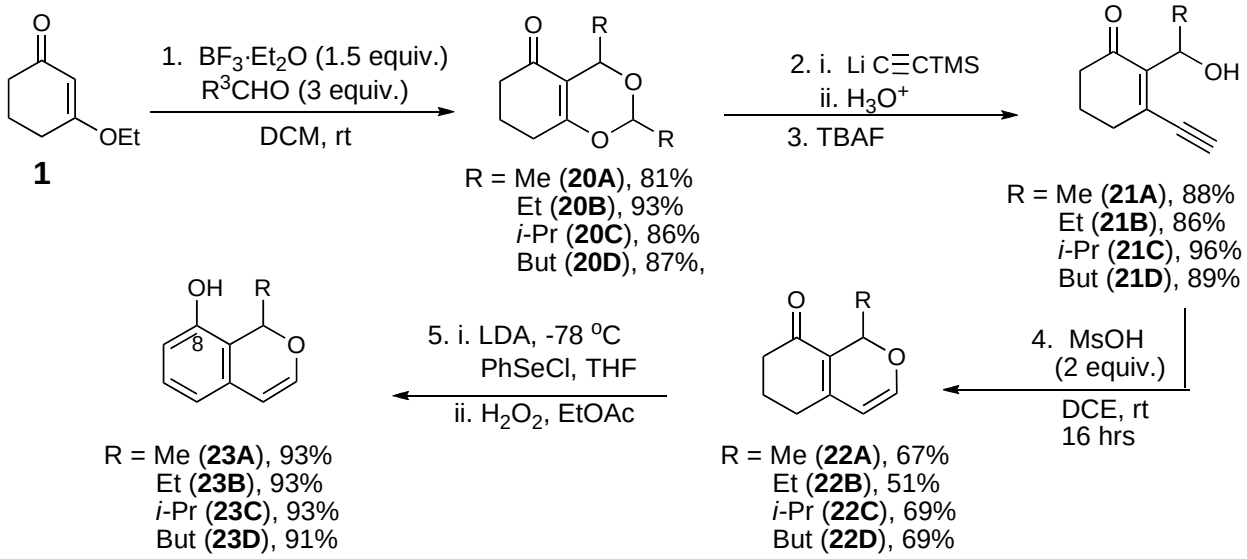
α-Selenylation of **8**, followed by oxidative elimination,[11] would produce dienone **xi** which would tautomerize (cf. **xi**) to produce 8-hydroxyisochromene **7** (Scheme 7). Simply stirring **8** in an appropriate



Scheme 7

solvent in the presence of PhSeCl or PhSeBr did not generate the desired α-phenylselenide and instead caused decomposition.[1] Fortunately, treatment of **8** with LDA at -78 °C, followed by the addition of freshly prepared PhSeCl, introduced a phenylselenyl group adjacent to the C-8 carbonyl. Oxidation of the selenylated material with H_2O_2 in EtOAc produced 8-hydroxyisochromene **7** in 93% yield. All attempts to oxidize isochromene **7** to isocoumarin **6** using selenium dioxide, Jones reagent, PCC, or manganese(II) oxide failed. Benzylic, allylic, and heteroatom-stabilized methylene and methine carbons can be oxidized using DDQ.[12] To our satisfaction, treatment of isochromene **7** with 2.0 equivalents of DDQ in dioxane at room temperature and exposure to the air produced isocoumarin **6** in 92% yield. Isocoumarin **6** was also produced when **7** was oxidized with DDQ in degassed, or wet *p*-dioxane confirming that water is the oxygen source. Based on the work of Xu[13] and others,[14] the the DDQ first oxidizes **7** to isochromenylium intermediate **xii**. The trace water present in the *p*-dioxane adds to **xii** to generate hemiacetal **xiii** which is further oxidized to intermediate **xiv** by the excess DDQ. Intermediate **xv** forms isocoumarin **6** after tautomerization and deprotonation.

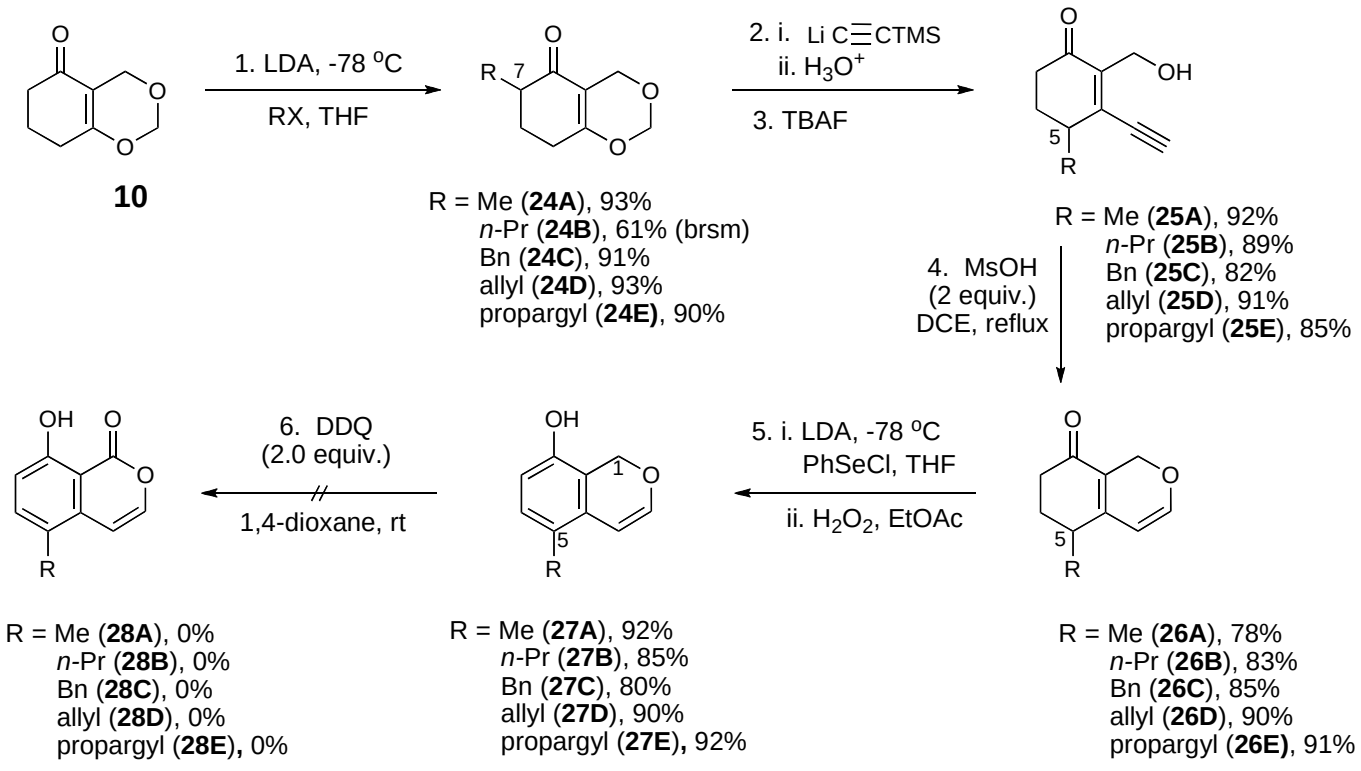
Subtle changes in our synthetic strategy would facilitate the preparation of more functionalized analogues of **6** and **7** (Scheme 8). For example, the reaction of **13** with acetaldehyde, propionaldehyde, isobutyraldehyde, or pentanal produced 1,3-dioxins **20A-D**, respectively, as a mixture of diastereomers. All attempts to prepare aryl-substituted dioxins ($R_2 = C_6H_5$) using either cyclohexane-1,3-dione (**13**) or **1** failed. Establishing the enynone motif was straightforward. Treating 1,3-dioxins **20A-D** with 1.5 equivalents of lithium (trimethylsilyl)acetylide at 0 °C, followed by hydrolysis and TBAF deprotection, gave enynones **21A-D** in excellent overall yield. When 1 equivalent of enynone **21A-D** and an equal amount of MsOH were heated at reflux in DCM, pyran formation occurred albeit in only good yield. The



Scheme 8

yield for these cyclizations improved when 2 equivalents of MsOH were added to the enynones dissolved in dichloroethane and stirred overnight at room temperature. The aromatization of the cyclohexenone-fused pyrans **22A-D** gave C-1 substituted isochromenes **23A-D** in very high yield.

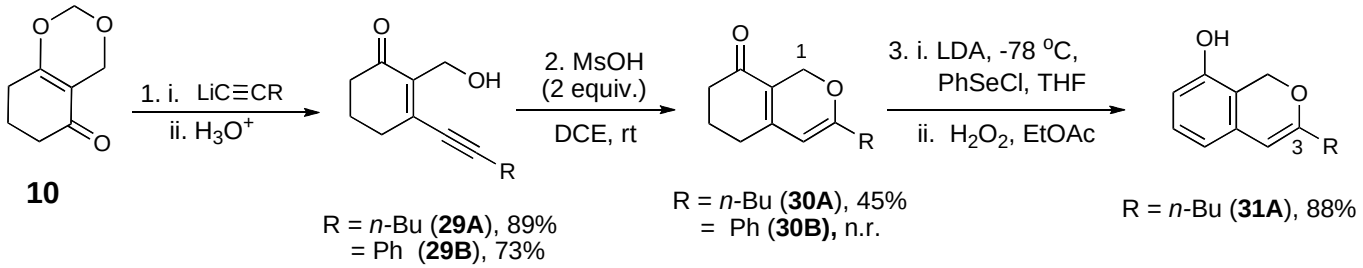
The introduction of an alkyl substituent α to the C-8 carbonyl of **10** enables the formation of C-7 alkylated isochromenes and isocoumarins (Scheme 9). Thus, treatment of the kinetic enolate derived from 1,3-dioxin **10** at -78 °C with either methyl iodide, *i*-iodopropane, benzyl bromide, allyl chloride, or propargyl bromide produced alkylation products (2**4A-E**) in excellent yield. In the case of preparation of **24B** this alkylation failed -78 °C and generated propene at higher reaction temperatures; hence, the modest yield of 61%. Acetylide addition to 1,3-dioxins **24-E**, followed by removal of the trimethylsilyl moiety, gave enynones **25A-E** in excellent yield. The best conditions for pyran formation required that enynones **25A-E** were dissolved in DCE, heated to reflux, followed by the addition of 2 equivalents of MsOH, for a total reaction time of only 15 minutes. Pyrans **26A-E** were not stable on concentration; thus, they were purified and stored as a dilute solution at -20 °C. The aromatization of the cyclohexenone ring was achieved *via* a phenylselenylation/oxidation sequence to give C-5 substituted isochromenes **27A-E** in good overall yield. In stark contrast to the oxidation of isochromene **7** to the oxidation of isochromene **7** to isocoumarin **6** (Scheme 7), the oxidation of the C-5 isocohromenes **27A-E**



Scheme 9

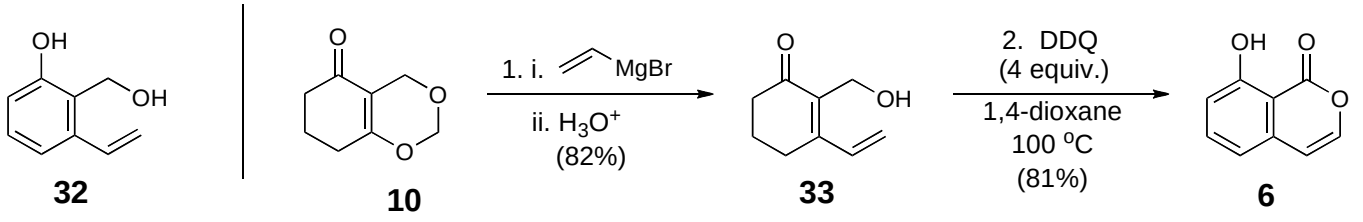
with excess DDQ failed to produce isocoumarins **28A-E** mostly likely because of abstraction of a hydrogen atom by the DDQ from the C-5 benzylic position to generate a quinone-methide intermediate that decomposes despite the mild conditions used.

The preparation of C-3 substituted 8-hydroxyisochromenes required that different acetylide anions add to 1,3-dioxin **10** (Scheme 10). For example, 1-hexyne and phenylacetylene were each treated with *n*-BuLi at -78 °C, and then added to **10**; acid hydrolysis of the 1,2-adduct afforded substituted enynones **29A** and **29B** in good yield. Butyl-substituted enynone **29A** gave a 45% yield of pyran **30A** whereas aryl-enynone **29B** did not react with either TfOH or MsOH under a variety of reaction conditions. Pyran **30A** was converted to C-3 alkylated isochromene **31A** using the aforementioned aromatization conditions. Disappointingly, isochromene **31A** could not be oxidized to its corresponding isocoumarin with DDQ, presumably because of the competing reactivity of the C-3 allylic position.



Scheme 10

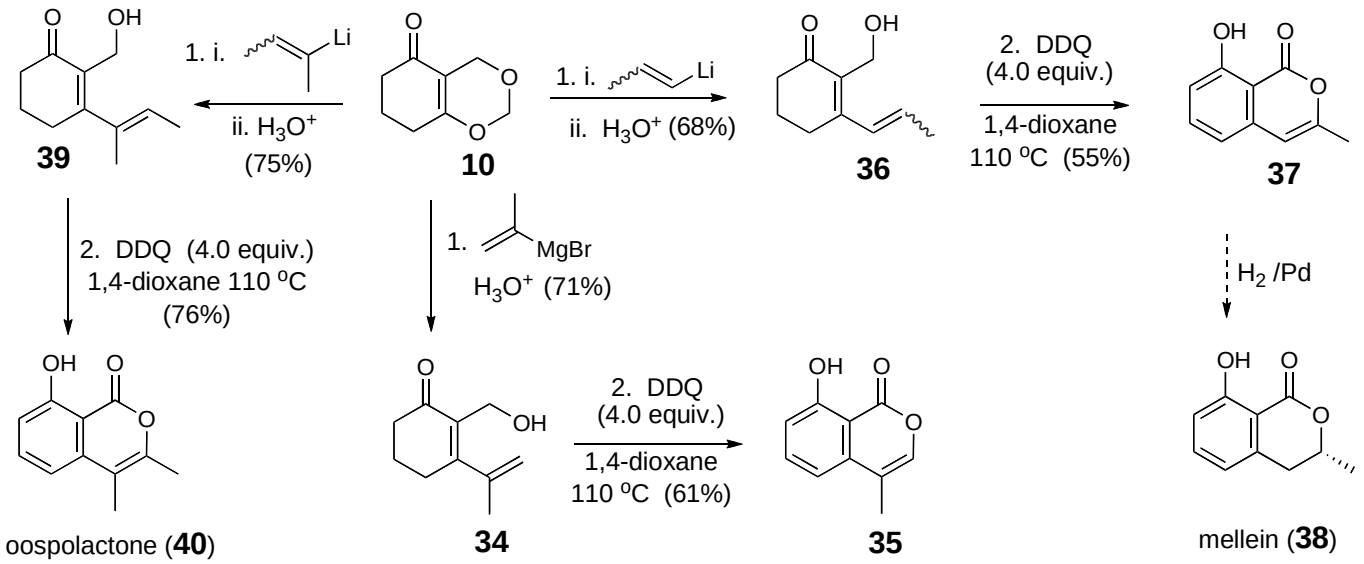
Concurrent with our study of alkylated enynones **25** and **29**, dienone **33** was prepared from 1,3-dioxin **10** (Scheme 11). Many reagents are useful for the aromatization of cyclohexenones.[15-17] DDQ has been used in the synthesis of chromenes from chromans, quinolines from saturated precursors, aromatic compounds from substituted cyclohexa-1,4-dienes, as well as in the oxidation of benzylic positions to carbonyl groups.[18] We hoped that DDQ would first aromatize the cyclohexenone ring to form phenol **32**, followed by the oxidation of the benzylic alcohol to a carboxylic acid, a known isocoumarin precursor.[4] Our initial attempt to oxidize dienone **33** with excess DDQ in hot 1,4-dioxane directly gave isocoumarin **6** in good yield. Decreasing the quantity of oxidant used gave mostly recovered starting material, but the



Scheme 11

formation of some 8-hydroxyisocoumarin **6** demonstrates that once formed the reaction intermediates are rapidly converted to **6**. No reaction was observed when the reaction was carried out at room temperature. These results prompted us to extend its application to more substituted systems.

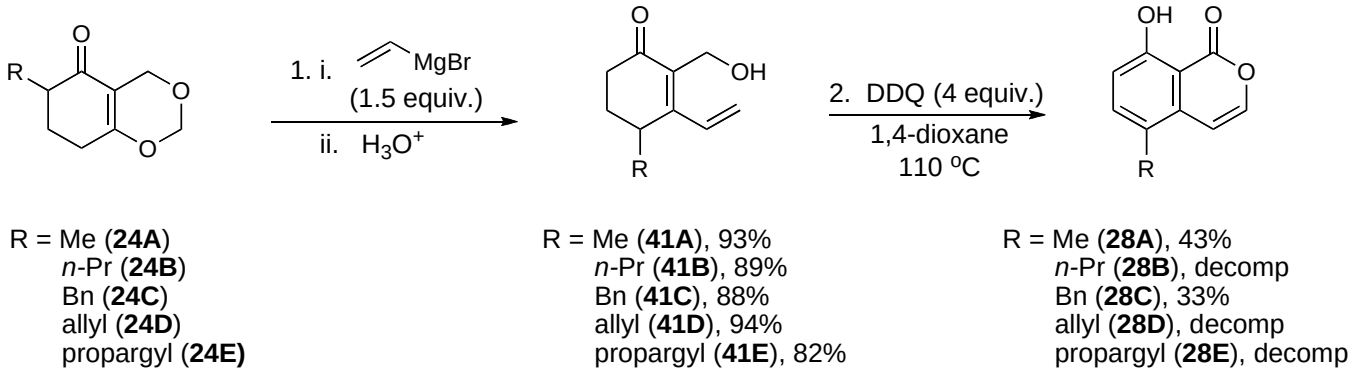
Scheme 12 shows the two steps needed to prepare three isocoumarins in good yield. For example, treatment of **10** with 2-propenyllithium gave dienone **34** which was cyclized with excess DDQ to isocoumarin **35** in 61% yield. Similarly, a C-3 methyl group was introduced by treating **10** with 1-propenyllithium and the resulting dienone product (**36**) was oxidized with DDQ to produce isocoumarin **37** in 55% yield. The hydrogenation of the C-3, C-4 double bond of **37** would produce mellein, a secondary fungal metabolite.[2h,19] It is important to note that 1-propenyllithium was prepared from a 1:1 mixture of *E:Z* 1-bromopropene, giving **36** as a 1:1 mixture of *E:Z* dienones. Both geometric isomers cyclized to give **37**. Oospolactone (**40**), a prominent toxin with antibiotic activity against plants and Gram-positive bacteria,[2h] was prepared when **10** was treated with 2-buten-2-yllithium, obtained from a 3:1 mixture of *E:Z* 2-bromo-2-butene, and the product (**39**) was oxidized with DDQ.[19] Changing the vinyl equivalent and further functionalization of the products represents an attractive method for the preparation of C-3 substituted and C-4 substituted 8-hydroxyisocoumarins.



Scheme 12

The preparation of 1,3-dioxins **24A-E** that have an alkyl substituent at C-5 was discussed earlier (Scheme 9). 1,2-Addition of a vinylmagnesium bromide to enones **24A-E** generated dienones **41A-E** in high yield (Scheme 13). Treating these dienones with 4.0 equivalents of DDQ in 1,4-dioxane at 100 °C gave mixed results. For example, when an *n*-propyl, allyl, or propargyl group was present at the C-4 position, reaction with DDQ resulted in decomposition. Dienones **41A** and **41C**, on the other hand, yielded

isocoumarins **28A** and **28C** in 43% and 33% yield, respectively. Clearly, additional studies are needed to fully understand the mechanism and the scope and limitations of this one-pot transformation.



R = Me (**24A**)
n-Pr (**24B**)
Bn (**24C**)
allyl (**24D**)
propargyl (**24E**)

R = Me (**41A**), 93%
n-Pr (**41B**), 89%
Bn (**41C**), 88%
allyl (**41D**), 94%
propargyl (**41E**), 82%

R = Me (**28A**), 43%
n-Pr (**28B**), decomp
Bn (**28C**), 33%
allyl (**28D**), decomp
propargyl (**28E**), decomp

Scheme 13

Two new strategies were developed for the synthesis of 8-hydroxyisocoumarins. Both strategies form the pyran first, followed by the aromatization of the cyclohexenone ring. Presently, the preparation of multiply alkylated isocoumarins using this strategy is limited. A simple two-step synthesis of 8-hydroxyisocoumarins using DDQ was developed, albeit not fully investigated. This strategy introduced alkyl substituents at C-3 and C-4 and permitted a two-step synthesis of oopsolactone (**40**) from 1,3-dioxin **10** in good overall yield. Additional studies are planned to expand the generality of this isocoumarin synthesis and to understand the mechanism of the one-pot DDQ oxidation.

EXPERIMENTAL SECTION

General Procedures: All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all extractive workups consisted of the following procedure: The reaction was slowly quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with two portions of Et_2O. The combined ether extracts were washed with water, brine, and dried over anhydrous sodium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 100 torr to a constant weight, afforded a crude residue which was purified using silica gel 60 (230-400 mesh ASTM) and reagent grade petroleum ether (pet ether), Et_2O, and EtOAc. ^1H and ^{13}C NMR spectra were recorded on Bruker AVB-400 and DRX-500 MHz spectrometers with ^{13}C operating frequencies of 100 MHz and 125 MHz, respectively. ^1H NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. ^{13}C NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 77.23) as an internal reference.

Preparation of 7,8-dihydro-4*H*-benzo[d][1,3]dioxin-5(6*H*)-one (10): To a solution of **1** (30.8 g, 0.22

mol) and 1,3,5-trioxane (42.0 g, 0.47 mol) in DCM (300 mL) at 0 °C was added dropwise BF_3-Et_2O (53 mL, 0.42 mmol) over 5-min. The resulting solution was stirred at rt for 16 h, at which time it was filtered through a short pad of Celite, which was rinsed with two 50 mL portions of DCM. The resulting solution was cooled to 0 °C and slowly quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL). Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 33.7 g (97%) of **10** as a yellow oil which was homogeneous by TLC analysis [R_f (**10**) = 0.37, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.10 (s, 2H), 4.39 (s, 2H), 2.33-2.40 (m, 2H), 2.27-2.35 (m, 2H), 1.90-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.5, 170.5, 112.0, 91.6, 63.0, 36.7, 27.8, 20.8.

Preparation of 8-methyl-7,8-dihydro-4*H*-benzo[d][1,3]dioxin-5(6*H*)-one (16): To a solution of **15**[9] (1.20 g, 8 mol) and 1,3,5-trioxane (1.35 g, 16 mmol) in DCM (15 mL) at 0 °C was added dropwise BF_3-Et_2O (2.1 mL, 16 mmol) over 5-min. The resulting solution was stirred at rt for 16 h, at which time it was filtered through a short pad of Celite, which was rinsed with two 10 mL portions of DCM. The resulting solution was cooled to 0 °C and slowly quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 1.15 g (88%) of **16** as a yellow oil which was homogeneous by TLC analysis [R_f (**16**) = 0.46, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.10-5.16 (m, 1H), 5.03-5.12 (m, 1H), 4.43 (s, 2H), 2.55-2.62 (m, 1H), 2.40-2.49 (m, 1H), 2.27-2.36 (m, 1H), 2.03-2.10 (m, 1H), 1.66-1.73 (m, 1H), 1.18-1.25 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.4, 173.4, 111.0, 91.6, 63.0, 34.6, 32.4, 28.8, 16.5.

General Procedure A (1,2-Addition of an Acetylide Anion to a 1,3-Dioxin 10): To a solution of TMS-acetylene (1.4 equiv., ~21 mmol) in 50 mL of THF at -78 °C was added *n*-butyllithium (1.2 equiv., 2.5 *M*, ~18 mmol) over a 2-min period. The resulting mixture was stirred at -78 °C for 30-min, and then warmed to 0 °C over a 30-min period. A solution of **10** (1.0 equiv., ~15 mmol) dissolved in 15 mL of THF was then added *via* cannulation over a 5-min period. The resulting reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of water (10 mL), followed by the portion-wise addition of aqueous 6*M* HCl (40 mL). The resulting solution was subjected to standard extractive workup to yield the crude TMS-enynone, which was used in the next step without further purification or characterization. To a solution of crude TMS-enynone dissolved in 100 mL of THF at rt was added TBAF-trihydrate (1.5 equiv., ~23 mmol) in a single portion. The resulting solution was stirred at rt for a 5-min period. Standard extractive workup yielded the crude enynone.

Preparation of 3-ethynyl-2-(hydroxymethyl)cyclohex-2-en-1-one (9): 1,3-Dioxin **10** (4.20 g, 27 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2.1) gave 2.92 g (73%) of **9** as a yellow oil which was homogeneous by TLC analysis [R_f (**9**) = 0.35, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.53 (d, *J* = 5.5 Hz, 2H), 3.81 (s, 1H), 2.87 (bt, *J* = 6.2 Hz, 1H), 2.54 (t, *J* = 5.8 Hz, 2H), 2.54 (t, *J* = 6.2 Hz, 2H), 2.49 (t, *J* = 5.8 Hz, 2H), 2.04 (pentet, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 142.1, 139.1, 92.3, 80.9, 59.9, 38.0, 31.2, 23.3.

General Procedure B (Acid-catalyzed Pyran Formation): To a solution of enynone (~7 mmol) in either DCM or DCE (40 mL) heated to a vigorous reflux was added MsOH (2 equiv., ~14 mmol) in one portion. The resulting solution was stirred at reflux for 15-min. The reaction mixture was cooled to rt and diluted with Et_2O (60 mL) and filtered through a short pad of silica. The silica is flushed with three 15 mL portions of EtOAc. The organic portions were combined and concentration under reduced pressure gave pyran, which was immediately purified by silica gel chromatography, concentrated almost completely, and stored in the remaining column eluent for further use.

Preparation of 6,7-dihydro-1*H*-isochromen-8(5*H*)-one (8): Enynone **9** (1.00 g, 6.7 mmol) was reacted according to general procedure B using DCM. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 785 mg (79%) of **8** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**8**) = 0.52, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.74 (d, *J* = 5.1 Hz, 1H), 5.29 (d, *J* = 5.1 Hz, 1H), 4.83 (s, 2H), 2.29-2.42 (m, 4H), 1.93-2.01 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.0, 153.1, 150.5, 117.5, 105.3, 63.3, 37.5, 28.1, 22.4.

General Procedure C (Aromatization of the Cyclohexenone Ring): To a solution of pyran (~3 mmol) in THF (8 mL) at -78 °C was added dropwise a solution of LDA (1.8*M*, 3.6 mmol). The resulting solution was stirred at -78 °C for 1 h, at which time PhSeCl (4.2 mmol) in THF (1 mL) was added rapidly in one portion and the reaction mixture was stirred at -78 °C for a 30-min period. Standard ethereal workup gave the crude α-phenylselenide, which was used directly in the next step without purification or characterization. To a solution of phenylselenide in EtOAc (20 mL) at rt was added a solution of hydrogen peroxide (30% in water, 9 mmol). The resulting solution was stirred at rt for 30-min, at which time Et_2O (20 mL) was added to the reaction mixture. The organic layer was washed with water (5 mL), 10% aqueous $NaHCO_3$ (5 mL), four portions of water (5 mL), and brine (5 mL). The crude isochromene was obtained by drying over anhydrous sodium sulfate and concentration under reduced pressure.

Preparation of 1*H*-isochromen-8-ol (7): Pyran **8** (650 mg, 4 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 595 mg (93%) of **7** as a red oil which was homogeneous by TLC analysis [R_f (**7**) = 0.37, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.03 (t, *J* = 7.8 Hz, 1H), 6.56 (m, 3H), 5.73 (d, *J* = 5.6 Hz, 1H), 5.17 (s, 2H), 4.80 (s, 1H); ^{13}C NMR (100 MHz, acetone) δ 152.1, 146.2, 131.9, 128.6, 114.9, 114.3, 114.2, 105.1, 62.7.

Preparation of 8-hydroxy-1*H*-isochromen-1-one (6): To a solution of isochromene **7** (145 mg, 10 mmol) in 1,4-dioxane (~6-15 mL) at rt was added DDQ (2.0 equiv.) in one portion. The resulting suspension was stirred at rt until TLC analysis indicated the consumption of the starting isochromene. To the reaction mixture was added Et_2O (20 mL). The reaction mixture was washed with H_2O (4x4 mL) and brine (5 mL). The crude isocoumarin was obtained by drying over anhydrous sodium sulfate and concentration under reduced pressure. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 146 mg (92%) of isocoumarin **6** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**6**) = 0.43, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, acetone) δ 11.0 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 5.6 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.4, 161.9, 144.1, 137.6, 136.9, 110.1, 110.0, 108.6, 107.5.

General Procedure D (1,3-Dioxin Formation using Cyclohexane-1,3-dione): To a solution of cyclohexane-1,3-dione (**13**) (~45 mmol) and an aldehyde (3 equiv., ~135 mmol) in DCM (125 mL) at 0 ^{o}C was added dropwise BF_3-Et_2O (2 equiv., ~90 mmol) over a 5-min period. The resulting solution was stirred at rt for 5-7h, at which time it was cooled to 0 °C and quenched by the addition of saturated $NaHCO_3$ (20 mL). Standard extractive workup gave the corresponding substituted 1,3-dioxin.

Preparation of 2,4-dimethyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (20A): Diketone **13** (5.00 g, 45 mmol) was reacted with acetaldehyde according to general procedure D. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 6.5 g (81%) of **20A** as a clear colorless oil which was homogeneous by TLC analysis but consisted of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**20A**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.26 (q, *J* = 5.1 Hz) and 5.03 (q, *J* = 5.1 Hz) (1H), 4.66-4.79 (m, 1H), 2.41 (t, *J* = 6.0 Hz, 2H), 2.36 (t, *J* = 6.7 Hz, 2H), 1.99 (pentet, *J* = 6.3 Hz, 2H), 1.38-1.53 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.1, 170.9 + 169.9, 116.7 + 115.5, 97.1 + 91.9, 70.5 + 67.6, 37.2 + 37.1, 28.1 + 28.0, 20.8, 20.3 + 20.1, 19.9 + 19.8.

Preparation of 2,4-diethyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (20B): Diketone **13** (5.00 g, 45 mmol) was reacted with propionaldehyde according to general procedure D and silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 8.7 g (93%) of **20B** as a clear colorless oil which was homogeneous by TLC analysis analysis but consisted of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**20B**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.00 (t, *J* = 5.1 Hz) and 4.81 (t, *J* = 4.9 Hz) (1H), 4.60 (d, *J* = 6.2 Hz) and 4.45 (d, *J* = 10.7 Hz) (1H), 2.25-2.56 (m, 6H), 1.90-2.01 (m, 2H), 1.73-1.84 (m, 2H), 0.97-1.10 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.6 + 196.5, 172.3 + 170.4, 117.6 + 115.1, 100.7, 95.6, 74.6, 73.0, 37.3 + 37.1, 28.4 + 28.1, 27.3 + 27.1, 26.0 + 25.8, 20.9, 20.2 + 20.1.

Preparation of 2,4-diisopropyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (20C): Diketone **13** (5.00 g, 45 mmol) was reacted with isobutyraldehyde according to general procedure D. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 9.2 g (86%) of **20C** as a clear colorless oil which was homogeneous by TLC analysis analysis but consisted of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**20C**) = 0.55, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.92 (d, *J* = 5.0 Hz) and 4.59 (d, *J* = 4.2 Hz) (1H), 4.53 (s) and 4.36 (d, *J* = 7.0 Hz) (1H), 2.21-2.50 (m, 4H), 1.89-1.99 (m, 4H) 0.64-1.09 (m, 12H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.2 + 196.0, 172.5 + 170.3, 114.9 + 113.7, 102.6 + 99.3, 77.3 + 74.9, 37.4 + 37.2, 32.2 + 32.1, 29.2, 28.5, 20.6 + 20.2, 19.5, 19.1 + 19.0, 16.9 + 16.5, 16.4 + 16.3, 14.6.

Preparation of 2,4-dibutyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (20D): Diketone **13** (5.00 g, 45 mmol) was reacted with pentanal according to general procedure D. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 10.3 g (87%) of **20D** as a clear colorless oil which was homogeneous by TLC analysis but consisted of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**20D**) = 0.58, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.07 (t, *J* = 5.1 Hz) and 4.84 (t, *J* = 5.1 Hz)(1H), 4.61 (d, *J* = 7.2 Hz) and 4.54 (d, *J* = 10.2 Hz)(1H), 2.28-2.47 (m, 4H), 1.68-2.07 (m, 4H), 1.24-1.54 (m, 8H), 0.82-0.99 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.4, 171.7 + 170.1, 115.7 + 115.2, 100.1 + 94.8, 74.1 + 71.7, 37.4 + 37.2, 33.8 + 33.6, 32.8 + 32.7, 28.4 + 28.2, 27.7 + 27.0, 25.8 + 25.7, 22.8 + 22.5, 22.6 + 22.5, 20.9 + 20.2, 14.2 +14.2, 14.0 + 14.0.

Preparation of 3-ethynyl-2-(1-hydroxyethyl)cyclohex-2-en-1-one (21A): 1,3-Dioxin **20A** (4.40 g, 24 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 3.49 (88%) of **21A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**21A**) = 0.38, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.87-4.99 (m, 1H), 3.94 (d, *J* = 11.4 Hz, 1H), 3.83 (s, 1H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.47 (t, *J* = 6.2 Hz,

2H), 1.95-2.06 (m, 3H), 1.42 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.4, 144.7, 137.1, 93.2, 80.8, 68.8, 38.7, 31.1, 23.2, 22.2.

Preparation of 3-ethynyl-2-(1-hydroxypropyl)cyclohex-2-en-1-one (21B): 1,3-Dioxin **20B** (4.90 g, 23 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 3.69 g (86%) of **21B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**21B**) = 0.47, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.55-4.69 (m, 2H), 3.80 (s, 1H), 3.74 (d, *J* = 11.4 Hz, 1H), 2.54 (t, *J* = 6.0 Hz, 2H), 2.47 (t, *J* = 6.2 Hz, 2H), 1.93-2.04 (m, 2H), 1.73-1.85 (m, 1H), 1.63-1.72 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.7, 143.8, 138.0, 92.8, 81.1, 74.4, 38.8, 31.3, 30.3, 22.3, 10.8.

Preparation of 3-ethynyl-2-(1-hydroxy-2-methylpropyl)cyclohex-2-en-1-one (21C): 1,3-Dioxin **20C** (4.10 g, 20 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 3.57 g (96%) of **21C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**21C**) = 0.50, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.35 (t, *J* = 9.5 Hz, 1H), 3.79 (s, 1H), 3.64 (d, *J* = 11.4 Hz, 1H), 2.55 (t, *J* = 5.8 Hz, 2H), 2.47 (t, *J* = 6.7 Hz, 2H), 1.85-2.07 (m, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.9, 143.3, 138.9, 92.7, 81.5, 78.7, 38.9, 34.4, 31.5, 22.3, 16.6, 16.5.

Preparation of 3-ethynyl-2-(1-hydroxypentyl)cyclohex-2-en-1-one (21D): 1,3-Dioxin **20D** (4.30 g, 16 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 2.95 g (89%) of **21D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**21D**) = 0.53, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.65-4.76 (m, 1H), 3.81 (s, 1H), 3.73 (d, *J* = 11.4 Hz, 1H), 2.53 (t, *J* = 5.9 Hz, 2H), 2.46 (t, *J* = 6.2 Hz, 2H), 1.97-2.05 (m, 2H), 1.75-1.82 (m, 1H), 1.55-1.64 (m, 1H), 1.40-1.50 (m, 1H), 1.25-1.33 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.7, 144.2, 137.7, 92.8, 81.1, 72.9, 38.9, 37.0, 31.3, 28.3, 22.6, 22.3, 14.2.

Preparation of 1-methyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (22A): Enynone **21A** (1.60 g, 9.8 mmol) was reacted according to general procedure G in DCE, except that the cyclization was performed at rt for 24 h. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.07 g (67%) of **22A** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**22A**) = 0.38, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.63 (d, *J* = 5.4 Hz, 1H), 5.43 (q, *J* = 6.4 Hz, 1H), 5.21 (d, *J* = 5.4 Hz, 1H), 2.29-2.47 (m, 5H), 1.95-2.06 (m, 2H), 1.28 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.0, 150.7, 148.4, 122.5, 103.6, 69.9, 37.8, 28.3, 22.4, 18.8.

Preparation of 1-ethyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (22B): Enynone **21B** (1.30 g, 7.3 mmol) was reacted according to general procedure B in DCE, except that the cyclization was performed at rt for 24 h. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.0 g (51%) of **22B** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**22B**) = 0.38, 4:1 pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.65 (d, *J* = 5.4 Hz, 1H), 5.18-5.25 (m, 2H), 2.29-2.48 (m, 4H), 1.98-2.05 (m, 2H), 1.79-1.91 (m, 1H), 1.39-1.47 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.1, 150.9, 148.9, 121.6, 104.0, 74.8, 37.8, 28.4, 25.9, 22.4, 9.84.

Preparation of 1-isopropyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (22C): Enynone **21C** (1.10 g, 5.7 mmol) was reacted according to general procedure B in DCE, except that the cyclization was performed at rt for 24 h. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 760 mg (69%) of **22C** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**22C**) = 0.41, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.70 (d, *J* = 5.4 Hz, 1H), 5.19 (d, *J* = 5.4 Hz, 1H), 5.09 (d, *J* = 7.3 Hz, 1H), 2.26-2.57 (m, 4H), 1.91-2.17 (m, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.5, 151.8, 149.4, 120.3, 104.1, 78.1, 37.9, 31.5, 28.7, 22.2, 18.4, 18.1.

Preparation of 1-butyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (22D): Enynone **21D** (1.30 g, 6.3 mmol) was reacted according to general procedure B in DCE, except that the cyclization was performed at rt for 24 h. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 900 mg (69%) of **22D** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**22D**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.64 (d, *J* = 5.4 Hz, 1H), 5.21-5.33 (m, 1H), 5.21 (d, *J* = 5.4 Hz, 1H), 2.28-2.49 (m, 5H), 1.77-2.08 (m, 4H), 1.21-1.50 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.1, 150.8, 148.7, 121.8, 104.0, 73.6, 37.8, 32.4, 28.4, 27.5, 22.7, 22.4, 14.2.

Preparation of 1-methyl-1*H*-isochromen-8-ol (23A): Pyran **22A** (523 mg, 3 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 479 mg (93%) of **23A** as a red oil which was homogeneous by TLC analysis [R_f (**23A**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.04 (t, *J* = 7.8 Hz, 1H), 6.57 (t, *J* = 6.9 Hz, 2H), 6.45 (d, *J* = 5.7 Hz, 1H) 5.60-5.72 (m, 3H), 1.48 (d, *J* = 4.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 150.5, 143.7, 130.4, 128.5, 119.3, 116.3, 114.1, 103.8, 69.2, 19.7.

Preparation of 1-ethyl-1*H*-isochromen-8-ol (23B): Pyran **22B** (379 mg, 2 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 350 mg (93%) of **23B** as a red oil which was homogeneous by TLC analysis [R_f (**23B**) = 0.42, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.05 (t, *J* = 7.7 Hz, 1H), 6.57 (m,

2H), 6.4 (d, *J* = 5.7 Hz, 1H), 5.71 (d, *J* = 5.7 Hz), 5.45 (dd, *J* = 9.2, 4.0 Hz, 1H), 5.07 (s, 1H), 1.99-2.07 (m, 1H), 1.55-1.66 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 150.6, 143.9, 130.9, 128.5, 118.4, 116.5, 114.1, 104.3, 74.3, 26.8, 10.4.

Preparation of 1-isopropyl-1*H*-isochromen-8-ol (23C): Pyran **22C** (451 mg, 2 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 415 mg (93%) of **23C** as a red oil which was homogeneous by TLC analysis [R_f (**23C**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.06 (t, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 6.1 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.24 (d, *J* = 7.2 Hz, 1H), 5.19 (bs, 1H), 2.31 (sextet, *J* = 6.9 Hz, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CHCl_3$) δ 151.3, 144.7, 131.4, 128.6, 117.0, 116.4, 114.2, 104.7, 77.8, 32.3, 18.8, 18.7.

Preparation of 1-butyl-1*H*-isochromen-8-ol (23D): Pyran **22D** (610 mg, 3 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 550 mg (91%) of **23D** as a red oil which was homogeneous by TLC analysis [R_f (**23D**) = 0.50, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.05 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 6.7 Hz, 1H), 6.49 (d, *J* = 5.7 Hz, 1H), 5.74 (d, *J* = 5.78 Hz, 1H), 5.70 (bs, 1H), 5.57 (dd, *J* = 9.7, 2.6 Hz, 1H), 2.08-2.17 (m, 2H), 1.29-1.64 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 150.7, 143.6, 130.8, 128.5, 118.8, 116.4, 114.2, 104.6, 73.1, 32.2, 28.0, 22.7, 14.3.

General Procedure E (Alkylation at C–7): To a solution of 1,3-dioxin **10** (~25 mmol) in THF (50 mL) at -78 °C was added dropwise a solution of LDA (1.8M, 1.2 equiv., 30 mmol) over a 5-min period. The resulting solution was stirred at -78 °C for 30-min, at which time a corresponding alkylating agent (1.4, equiv., ~35 mmol) in THF (10 mL) was added dropwise over a 1-min period. The resulting solution was allowed to stir at -78 °C for 1 h, warmed to -30 °C over 30-min, then stirred at -30 °C for 1 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (10 mL). Standard extractive workup, followed by silica gel chromatography, gave the crude alkylation product.

Preparation of 6-methyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (24A): Ketone **10** (4.10 g, 27 mmol) was reacted with iodomethane according to general procedure E. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 4.16 g (93%) of **24A** as a yellow oil which was homogeneous by TLC analysis [R_f (**24A**) = 0.32, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.18 (d, *J* = 5.4 Hz, 1H), 5.07 (d, *J* = 5.4 Hz, 1H), 4.43 (dq, *J* = 14.8, 9.7 Hz, 2H), 2.27-2.55 (m, 3H), 1.98-2.09 (m, 1H), 1.66-1.79 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.7, 169.5, 111.1, 91.5, 63.1, 40.0, 28.8, 27.1, 15.3.

Preparation of 6-propyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (24B): Ketone **10** (4.20 g, 27 mmol) was reacted with *n*-propyl iodide according to general procedure E, but the temperature was increased from -30 °C to rt until no further reaction was observed by TLC analysis. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.4 g (61% brsm, 73% conversion,) of **24B** as a yellow oil which was homogeneous by TLC analysis [R_f (**24B**) = 0.47, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.16 (d, *J* = 5.4 Hz, 1H), 5.09 (d, *J* = 5.4 Hz, 1H), 4.43 (s, 2H), 2.33-2.48 (m, 2H), 2.16-2.27 (m, 1H), 2.04-2.13 (m, 1H), 1.71-1.82 (m, 2H), 1.30-1.39 (m, 3H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.4, 169.2, 111.2, 91.4, 63.0, 44.7, 31.6, 26.6, 25.7, 20.3, 14.2.

Preparation of 6-benzyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (24C): Ketone **10** (4.10 g, 27 mmol) was reacted with benzylbromide according to general procedure E. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 5.93 g (91%) of **24C** as a yellow oil which was homogeneous by TLC analysis [R_f (**24C**) = 0.38, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.23-7.33 (m, 2H), 7.10-7.20 (m, 3H), 5.18 (d, *J* = 5.4 Hz, 1H), 5.08 (d, *J* = 5.4 Hz, 1H), 4.46 (dq, *J* = 14.6, 6.1 Hz, 2H), 3.37 (dq, *J* =9.6, 8.4 Hz, 1H), 2.40-2.52 (m, 2H), 2.34-2.43 (m, 2H), 1.87-1.99 (m, 1H), 1.59-1.70 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 197.0, 169.7, 140.1, 129.6, 128.6, 126.3, 111.3, 91.6, 63.1, 46.9, 35.7, 27.0, 25.2.

Preparation of 6-allyl-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (24D): Ketone **10** (4.20 g, 27 mmol) was reacted with allyl bromide according to general procedure E. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 4.91 g (93%) of **24D** as a yellow oil which was homogeneous by TLC analysis [R_f (**24D**) = 0.44, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.76 (septet, *J* = 7.4, 1H), 5.18 (d, *J* = 5.4 Hz, 1H), 5.02-5.12 (m, 3H), 4.44 (dd, *J* = 15.0, 3.8 Hz, 2H), 2.60-2.71 (m, 1H), 2.41-2.49 (m, 2H), 2.22-2.35 (m, 1H), 2.05-2.16 (m, 2H), 1.68-1.81 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 197.2, 169.6, 136.3, 116.9. 111.3, 91.5, 63.0, 44.5, 34.0, 26.9, 25.4.

Preparation of 6-(prop-2-yn-1-yl)-7,8-dihydro-4*H*-benzo[*d*][1,3]dioxin-5(6*H*)-one (24E): Ketone **10** (4.10 g, 27 mmol) was reacted with propargyl bromide according to general procedure E. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 4.68 g (90%) of **24E** as a yellow oil which was homogeneous by TLC analysis [R_f (**24E**) = 0.32, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.21 (d, *J* = 5.4, 1H), 5.07 (d, *J* = 5.4, 1H), 4.43 (q, *J* = 17.4 Hz, 2H), 2.71-2.83 (m, 1H), 2.36-2.60 (m, 2H), 2.25-2.36 (m, 2H), 1.80-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.5, 170.1, 111.2, 91.6, 82.3, 70.2, 62.9, 43.9, 27.3, 25.7, 19.1.

Preparation of 3-ethynyl-2-(hydroxymethyl)-4-methylcyclohex-2-en-1-one (25A): 1,3-Dioxin **24A** (3.7 mg, 22 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 3.34 g (92%) of **25A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**25A**) = 0.35, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.49 (d, *J* = 5.4, Hz, 2H), 3.83 (s, 1H), 2.90-3.02 (m, 1H), 2.50-2.65 (m, 2H) 2.37-2.48 (m, 1H), 2.10-2.21 (m, 1H), 1.69-1.79 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.8, 144.1, 141.4, 93.4, 80.1, 59.9, 35.8, 34.4, 29.8, 19.1.

Preparation of 3-ethynyl-2-(hydroxymethyl)-4-propylcyclohex-2-en-1-one (25B): 1,3-Dioxin **24B** (2.80 g, 14 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.45 g (89%) of **25B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**25B**) = 0.45, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.50 (s, 2H), 3.84 (s, 1H), 2.95 (bs, 1H), 2.44-2.53 (m, 2H), 2.34-2.41 (m, 1H), 2.06-2.15 (m, 1H), 1.79-1.88 (m, 2H), 1.43-1.50 (m, 2H), 1.30-1.39 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 143.7, 141.7, 93.2, 80.4, 60.3, 39.2, 35.3, 34.6, 26.1, 20.6, 14.2.

Preparation of 4-benzyl-3-ethynyl-2-(hydroxymethyl)cyclohex-2-en-1-one (25C): 1,3-Dioxin **24C** (4.15 g, 17 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 3.36 g (82%) of **25C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**25C**) = 0.48, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.29-7.39 (m, 2H), 7.16-7.23 (m, 3H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.93 (s, 1H), 3.39 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.95 (bs, 1H), 2.69-2.81 (m, 1H), 2.49-2.70 (m, 2H), 2.30-2.39 (m, 1H), 1.92-2.02 (m, 1H), 1.69-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.7, 142.4, 142.4, 139.3, 129.2, 128.8, 126.8, 93.8, 80.3, 60.2, 41.4, 38.7, 35.1, 25.5.

Preparation of 4-allyl-3-ethynyl-2-(hydroxymethyl)cyclohex-2-en-1-one (25D): 1,3-Dioxin **24D** (3.30 g, 17 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.93 g (91%) of **25D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**25D**) = 0.48, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.77 (sextet, *J* = 9.3 Hz, 1H), 5.09-5.16 (m, 2H), 4.50 (d, *J* = 14.6, 2H), 2.95 (t, *J* = 6.5 Hz, 1H), 2.57-2.64 (m, 1H), 2.50-2.61 (m, 2H), 2.33-2.41 (m, 1H), 2.22-2.31 (m, 1H), 2.06-2.13 (m, 1H), 1.80-1.89 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.7, 142.5, 142.2, 135.5, 117.9, 93.7, 80.1, 59.9, 39.0, 37.0, 35.4, 25.9.

Preparation of 3-ethynyl-2-(hydroxymethyl)-4-(prop-2-yn-1-yl)cyclohex-2-en-1-one (25E): 1,3-Dioxin **24E** (3.10 g, 16 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.6 g (85%) of **25E** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**25E**) = 0.35, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.52 (d, *J* = 5.8 Hz, 2H), 3.87 (s, 1H), 2.90 (bs, 1H), 2.73-2.81 (m, 1H), 2.58-2.73 (m, 2H), 2.39-2.56 (m, 2H), 2.23-2.32 (m, 1H), 2.02-2.10 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.5, 142.9, 140.3, 93.9, 81.3, 79.4, 71.2, 60.3, 38.4, 35.9, 26.5, 22.9.

Preparation of 5-methyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (26A): Enynone **25A** (1.50 g, 9 mmol) was reacted according to general procedure B in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.16 g (78%) of **26A** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**26A**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.80 (d, *J* = 5.5 Hz, 1H), 5.40 (d, *J* = 5.5 Hz, 1H), 4.84 (dd, *J* = 3.2, 16.3, Hz, 2H), 2.41-2.56 (m, 2H), 2.28-2.36 (m, 1H), 2.09-2.18 (m, 1H), 1.70-1.78 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.8, 153.3, 153.6, 116.7, 104.0, 63.3, 34.9, 31.7, 29.8, 18.3.

Preparation of 5-propyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (26B): Enynone **25B** (1.10 g, 6 mmol) was reacted according to general procedure B in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 910 mg (83%) of **26B** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**26B**) = 0.11, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.77 (d, *J* = 5.5 Hz, 1H), 5.37 (d, *J* = 5.5 Hz, 1H), 4.83 (s, 2H), 2.42-2.53 (m, 1H), 2.23-2.31 (m, 2H), 2.01-2.11 (m, 1H), 1.83-1.92 (m, 1H), 1.29-1.61 (m, 4H), 0.94 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.8, 154.1, 153.3, 116.9, 104.6, 63.3, 36.6, 34.1, 34.0, 26.0, 20.9, 14.3.

Preparation of 5-benzyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (26C): Enynone **25C** (1.20 g, 5 mmol) was reacted according to general procedure B in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.01mg (85%) of **26C** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**26C**) = 0.42, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.29 (t, *J* = 7.3 Hz, 2H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 6.76 (d, *J* = 5.4 Hz, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 4.84 (q, *J* = 10.8 Hz, 2H), 2.97 (dd, *J* = 4.1, 13.1 Hz, 1H), 2.39-2.69 (m, 3H), 2.27 (dt, *J* = 4.8, 17.4 Hz, 1H), 1.88-1.96 (m, 1H), 1.70-1.81 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.5, 153.5, 153.0, 139.5, 129.2, 128.8, 126.8, 117.3, 104.6, 63.4, 38.7, 38.3, 33.8, 25.6.

Preparation of 5-allyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (26D): Enynone **25D** (1.6 mg, 7 mmol) was reacted according to general procedure B in DCE. Purification using silica gel

chromatography (elution with pet ether/EtOAc = 4:1) gave 1.42 g (90%) of **26D** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**26D**) = 0.12, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.80 (d, *J* = 6.8 Hz, 1H), 5.71-5.82 (m, 1H), 5.42 (d, *J* = 5.5 Hz, 1H), 5.13 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 1H), 4.86 (s, 2H), 2.20-2.55 (m, 5H), 2.01-2.09 (m, 1H), 1.88-1.95 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 192.7, 153.5, 152.9, 135.9, 117.7, 117.4, 104.3, 63.3, 36.5, 36.4, 34.2, 26.0.

Preparation of 5-(prop-2-yn-1-yl)-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (26E): Enynone **25E** (1.70 g, 7 mmol) was reacted according to general procedure B in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.54 g (91%) of **26E** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**26E**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.82 (d, *J* = 5.2 Hz, 1H), 5.44 (d, *J* = 5.2 Hz, 1H), 4.84 (s, 2H), 2.20-2.64 (m, 4H), 1.93-2.24 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.2, 153.8, 151.1, 117.7, 103.7, 81.7, 70.9, 63.3, 36.0, 34.4, 26.7, 22.0.

Preparation of 5-methyl-1*H*-isochromen-8-ol (27A): Pyran **26A** (740 mg, 5 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 670 mg (92%) of **27A** as a red oil which was homogeneous by TLC analysis [R_f (**27A**) = 0.30, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.89 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 5.8 Hz, 1H), 6.50 (d, *J* = 8.2 Hz, 1H), 5.89 (d, *J* = 5.9 Hz, 1H), 5.24 (bs, 1H), 5.18 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 148.7, 146.3, 129.9, 129.9, 123.4, 114.6, 113.9, 102.9, 63.2, 17.9.

Preparation of 5-propyl-1*H*-isochromen-8-ol (27B): Pyran **26B** (440 mg, 2 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 370 mg (85%) of **27B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**27B**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.88 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 5.9 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.89 (d, *J* = 5.9 Hz, 1H), 5.16 (s, 2H), 4.74 (bs, 1H), 2.50 (t, *J* = 7.9 Hz, 2H), 1.50-1.63 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 148.6, 146.4, 129.5, 129.3, 128.3, 114.8, 113.8, 102.6, 63.2, 34.0, 24.4, 14.2.

Preparation of 5-benzyl-1*H*-isochromen-8-ol (27C): Pyran **26C** (490 mg, 2 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 390 mg (80%) of **27C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**27C**) = 0.42, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.90-7.15 (m, 5H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 6.0 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 5.65 (d, *J* = 6.0 Hz, 1H), 4.98 (s, 2H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 149.3, 146.8, 141.2, 131.1, 130.3, 128.8, 128.7, 128.6,

128.3, 126.2, 114.1, 102.7, 63.3, 37.7.

Preparation of 5-allyl-1*H*-isochromen-8-ol (27D): Pyran **26D** (517 mg, 3 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 510 mg (90%) of **27D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**27D**) = 0.35, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.89 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 5.9 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 5.86-5.94 (m, 1H), 5.87 (d, *J* = 5.9 Hz, 1H), 5.16 (s, 2H), 5.05 (d, *J* = 10 Hz, 1H), 4.99 (d, *J* = 16.9 Hz, 1H), 4.89 (bs, 1H), 3.30 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 149.1, 146.7, 137.3, 130.0, 129.5, 125.3, 115.8, 114.8, 114.0, 102.5, 63.2, 36.2.

Preparation of 5-(prop-2-yn-1-yl)-1*H*-isochromen-8-ol (27E): Pyran **26E** (600 mg, 3 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 535 mg (92%) of **27E** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**27E**) = 0.25, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.13 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 5.8 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.88 (d, *J* = 5.8 Hz, 1H), 5.16 (s, 2H), 5.09 (bs, 1H), 3.46 (s, 2H), 2.18 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 149.6, 147.1, 129.6, 128.7, 121.3, 114.8, 114.0, 101.8, 82.2, 70.8, 63.1, 21.5.

Preparation of 3-(hex-1-yn-1-yl)-2-(hydroxymethyl)cyclohex-2-en-1-one (29A): To a solution of 1-hexyne (4.4 mL, 38 mmol) in 75 mL of THF at -78 °C was added *n*-butyllithium (13.1 mL, 2.5*M*, ~33 mmol) over a 2-min period. The resulting mixture was stirred at -78 °C for 30-min, and then warmed to 0 °C over a 30-min period. To the resulting solution was added a solution of **10** (4.20 g, 27 mmol) dissolved in 20 mL of THF *via* cannulation over a 5-min period. The resulting reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of water (20 mL), followed by the portion-wise addition of aqueous 6*M* HCl (50 mL). After warming the resulting solution to rt, and stirring for 30-min, the resulting solution was subjected to standard extractive workup. Silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 5.02 g (89%) of **29A** as a yellow oil which was homogeneous by TLC analysis [R_f (**29A**) = 0.55, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.42 (s, 2H), 3.13 (bs, 1H), 2.35-2.43 (m, 6H), 1.90-1.99 (m, 2H), 1.43-1.52 (m, 2H), 1.32-1.40 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 141.5, 139.8, 107.6, 78.9, 59.9, 38.0, 31.8, 30.5, 22.4, 21.1, 19.8, 13.7.

Preparation of 2-(hydroxymethyl)-3-(phenylethynyl)cyclohex-2-en-1-one (29B): To a solution of phenylacetylene (2.2 mL, 20 mmol) in 50 mL of THF at -78 °C was added *n*-butyllithium (6.9 mL, 2.5*M*, 17 mmol) over a 2-min period. The resulting mixture was stirred at -78 °C for 30-min, and then warmed

to 0 °C over a 30-min period. To the resulting solution was added a solution of **10** (2.20 g, 14 mmol) dissolved in 10 mL of THF *via* cannulation over a 5-min period. The resulting reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of water (20 mL), followed by the portion-wise addition of aqueous 6*M* HCl (30 mL). After warming the resulting solution to rt, and stirring for 30-min, the resulting solution was subjected to standard extractive workup. Silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 2.37 g (73%) of **29B** as a yellow oil which was homogeneous by TLC analysis [R_f (**29B**) = 0.57, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.43-7.52 (m, 2H), 7.30-7.41 (m, 3H), 4.62 (s, 2H), 3.03 (bs, 1H), 2.64 (t, *J* = 5.7 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.07 (pentet, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.2, 140.3, 140.2, 132.1, 129.9, 128.8, 122.1, 104.9, 86.9, 60.5, 38.1, 31.5, 22.5.

Preparation of 3-butyl-6,7-dihydro-1*H*-isochromen-8(5*H*)-one (30A): Enynone **29A** (1.40 g, 7 mmol) was reacted according to general procedure B in DCE, except that the cyclization was performed at rt for 24 h. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 284 mg (45% brsm, 55% conversion) of **30A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**30A**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.14 (s, 1H), 4.84 (s, 2H), 2.35 (t, *J* = 6.4 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.15 (t, *J* = 6.2 Hz, 2H), 1.95 (pentet, *J* = 7.6 Hz, 2H), 1.49 (pentet, *J* = 7.5 Hz, 2H), 1.32 (sextet, *J* = 7.5 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.5, 167.6, 152.5, 115.6, 101.6, 64.2, 37.6, 33.9, 29.2, 28.3, 22.5, 22.4, 14.0.

Preparation of 3-butyl-1*H*-isochromen-8-ol (31A): Pyran **30A** (540 mg, 3 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 470 mg (88%) of **31A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**31A**) = 0.43, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.03 (t, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 2H), 5.60 (s, 1H), 5.17 (s, 2H), 4.78 (bs, 1H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.49-1.58 (m, 2H), 1.31-1.40 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 159.3, 150.4, 133.9, 128.6, 115.6, 113.6, 113.2, 100.6, 63.5, 33.6, 29.3, 22.5, 14.0.

General Procedure F (Dienone Formation from a Dioxin): To a solution of 1,3-dioxin (~13 mmol) in THF (50 mL) at 0 °C is added a solution of vinylmagnesium bromide (1.0*M,* 1.5 equiv., 20 mmol). The resulting reaction mixture is warmed to rt and stirred at rt for an additional 1 h. After cooling to 0 °C, H_2O (20 mL) is added, followed by portionwise addition of 6*M* HCl (30 mL). The resulting solution is allowed to rise to rt and stirred for an additional 1 h. Standard extractive workup gave the crude enone.

Preparation of 2-(hydroxymethyl)-3-vinylcyclohex-2-en-1-one (33): 1,3-Dioxin **10** (2.50 g, 16 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 2.05 g (82%) of **33** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**33**) = 0.30, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.00 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.76 (d, *J* = 17.4 Hz, 1H), 5.56 (d, *J* = 11.0 Hz, 1H), 4.49 (s, 2H), 2.73 (bs, 1H), 2.57 (t, *J* = 6.0 Hz, 2H), 2.48 (t, *J* = 6.0 Hz, 2H), 2.04 m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.3, 153.4, 134.7, 133.9, 122.5, 55.6, 33.8, 25.8, 21.7.

General Procedure G (One-pot Isocoumarin Synthesis): To a solution of dienone (~5 mmol) in 1,4-dioxane (~10 mL) at rt was added DDQ (4 equiv., ~20 mmol) in one-portion. The resulting solution was stirred at 110 °C until the reaction was complete. The reaction mixture was then diluted with Et_2O (50 mL) and the supernatant was decanted. The remaining solid was rinsed with Et_2O (3 x 10 mL). The combined organic extractions were washed with H_2O (5 x 5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave the crude isocoumarin.

Preparation of 8-hydroxy-1*H*-isochromen-1-one (6): Dienone **33** (560 mg, 4 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 486 mg (81%) of **6** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**6**) = 0.43, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, acetone) δ 11.0 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 5.6 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.4, 161.9, 144.1, 137.6, 136.9, 110.1, 110.0, 108.6, 107.5.

Preparation of 2-(hydroxymethyl)-4-methyl-3-vinylcyclohex-2-en-1-one (41A): 1,3-Dioxin **24A** (1.70 g, 10 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.57 g (93%) of **41A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**41A**) = 0.36, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.84 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.74(d, *J* = 17.4 Hz, 1H), 5.62 (d, *J* = 11.0 Hz, 1H), 4.44 (s, 2H), 2.95 (bs, 1H), 2.76 (bs, 1H), 2.56-2.65 (m, 1H), 2.39-2.48 (m, 1H), 2.09-2.19 (m, 1H), 1.82-1.90 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.6, 158.7, 133.7, 133.0, 126.7, 55.5, 32.7, 28.8, 28.5, 18.4.

Preparation of 2-(hydroxymethyl)-4-propyl-3-vinylcyclohex-2-en-1-one (41B): 1,3-Dioxin **24B** (1.20 g, 6mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.1 g (89%) of **41B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**41B**) = 0.42, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz,

$CHCl_3$) δ 6.84 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.72(d, *J* = 17.4 Hz, 1H), 5.57 (d, *J* = 11.0 Hz, 1H), 4.42 (s, 2H), 2.68-2.95 (m, 2H), 2.48-2.57 (m, 1H), 2.31-2.39 (m, 1H), 1.97-2.06 (m, 2H), 1.28-1.60 (m, 3H), 0.90-0.99 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 157.2, 132.7, 132.0, 121.3, 55.1, 32.7, 32.5, 31.7, 23.1, 20.5, 13.0.

Preparation of 2-(hydroxymethyl)-4-benzyl-3-vinylcyclohex-2-en-1-one (41C): 1,3-Dioxin **24C** (1.50 g, 6 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.29 g (88%) of **41C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**41C**) = 0.39, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.30-7.38 (m, 2H), 7.20-7.27 (m, 3H), 6.93 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.91 (d, *J* = 17.4 Hz, 1H), 5.69 (d, *J* = 11.0 Hz, 1H), 4.42-4.52 (s, 2H), 2.97-3.08 (m, 2H), 2.66-2.73 (m, 3H), 2.39-2.48 (m, 1H), 1.57-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.9, 156.9, 140.0, 134.6, 133.1, 128.9, 128.9, 126.8, 122.8, 37.7, 36.2, 32.8, 23.7, 21.2.

Preparation of 2-(hydroxymethyl)-4-allyl-3-vinylcyclohex-2-en-1-one (41D): 1,3-Dioxin **24D** (1.60 g, 8 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.49 g (94%) of **41D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**41D**) = 0.39, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.82 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.70-5.78 (m, 1H), 5.69 (d, *J* = 17.4 Hz, 1H), 5.54 (d, *J* = 11.0 Hz, 1H), 5.05 (d, *J* = 8.0 Hz, 1H), 5.01 (s, 1H), 4.35 (s, 2H), 3.05 (bs, 1H), 2.72-2.80 (m, 1H), 2.43-2.52 (m, 1H), 2.28-2.35 (m, 2H), 2.15-2.23 (m, 1H), 1.94-2.02 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.8, 157.2, 136.5, 134.4, 133.0, 122.7, 117.2, 55.9, 36.0, 33.9, 32.7, 24.2.

Preparation of 2-(hydroxymethyl)-4-(prop-2-yn-1-yl)-3-vinylcyclohex-2-en-1-one (41E): 1,3-Dioxin **24E** (1.80 g, 9 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.46 g (82%) of **41E** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**41E**) = 0.36, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.84 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.76 (d, *J* = 17.4 Hz, 1H), 5.62 (d, *J* = 11.0 Hz, 1H), 4.41 (s, 2H), 2.94-3.02 (m, 1H), 1.94-2.77 (m, 8H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.3, 155.1, 134.9, 132.6, 122.9, 82.1, 70.9, 55.8, 33.6, 32.8, 24.9, 21.7.

Preparation of 2-(hydroxymethyl)-3-(prop-1-en-2-yl)cyclohex-2-en-1-one (34): To a suspension of magnesium metal (1.00 g, 40 mmol), 2-bromopropene (360 μL, 4 mmol) and an I_2 crystal in THF (30 mL) was dropwise added a solution of 2-bromopropene (3.3 mL, 36 mmol) in THF (10 mL) at such a rate as to maintain a gentle reflux. Once the magnesium metal is consumed, the solution of

propenylmagnesium bromide was cannulated to a solution of **10** (3.00 g, 19 mmol) in THF (10 mL) at 0 °C. The resulting reaction mixture is allowed to rise to rt and stirred at rt for an additional 1 h. After cooling to 0 °C, H_2O is added, followed by 6*M* HCl (15 mL). The resulting solution is allowed to rise to rt and stirred for an additional 1 h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 1:1), gave 2.3 g (71%) of **34** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**34**) = 0.38, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.08 (s, 1H), 4.84 (s, 1H), 4.32 (s, 2H), 2.45 (t, *J* = 6.3 Hz, 4H), 1.97-2.06 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.9, 162.4, 143.4, 132.9, 114.6, 57.8, 37.8, 29.9, 22.3, 21.7.

Preparation of 2-(hydroxymethyl)-3-(prop-1-en-1-yl)cyclohex-2-en-1-one (36): To a suspension of lithium metal (222 mg, 37 mmol), 1-bromopropene (310 μL, 4 mmol, ~1:1 *E:Z* mixture) and an I_2 crystal in THF (30 mL) was dropwise added a solution of 1-bromopropene (2.8 mL, 33 mol) in THF (10 mL) at such a rate as to maintain a gentle reflux. Once the lithium metal is consumed, the solution of 1-propenyllithium was cannulated to a solution of **10** (2.70 g, 18 mmol) in THF (10 mL) at 0 °C. The resulting reaction mixture is allowed to rise to rt and stirred at rt for an additional 1 h. After cooling to 0 °C, H_2O is added, followed by 6*M* HCl (15 mL). The resulting solution is allowed to rise to rt and stirred for an additional 1 h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 1:1), gave 2.0 g (68%) of **36** as a clear colorless oil of two components (**36-NP**: nonpolar component; **36-P**: polar component) by TLC analysis [R_f (**36-NP**) = 0.29, 1:1, pet ether/EtOAc, R_f (**36-P**) = 0.38, 1:1, pet ether/EtOAc]. **36-NP:** ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.02 (d, *J* = 11.7 Hz, 1H), 5.71-5.80 (m, 1H), 4.24 (s, 2H), 3.01-3.09 (m, 1H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 6.4 Hz, 2H), 1.93-2.00 (m, 2H), 1.59 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.6, 156.0, 134.0, 130.1, 128.2, 59.1, 38.2, 31.1, 22.5, 15.4. **36-P:** ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.68 (d, *J* = 15.5Hz, 1H), 6.28 (m, 1H), 4.41 (s, 2H), 2.92-3.01 (m, 1H), 2.44-2.52 (m, 2H), 2.35-2.42 (m, 2H), 1.89-1.95 (m, 2H), 1.88 (d, *J* = 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.4, 153.8, 135.9, 132.9, 128.8, 56.0, 37.9, 26.5, 21.9, 19.6.

Preparation of 3-(but-2-en-2-yl)-2-(hydroxymethyl)cyclohex-2-en-1-one (39): To a suspension of lithium metal (205 mg, 34 mmol), 2-bromo-2-butene (350 μL, 3 mmol, ~3:1 *E:Z* mixture) and an I_2 crystal in THF (30 mL) was dropwise added a solution of 2-bromo-2-butene (3.1 mL, 30 mmol) in THF (10 mL) at such a rate as to maintain a gentle reflux. Once the lithium metal is consumed, the solution of 2-butenyllithium was cannulated to a solution of dioxin **10** (2.50 g, 16 mol) in THF (10 mL) at 0 °C. The resulting reaction mixture is allowed to rise to rt and stirred at rt for an additional 1 h. After cooling to 0 °C, H_2O is added, followed by 6*M* HCl (15 mL). The resulting solution is allowed to rise to rt and stirred for an additional 1 h. Standard extractive workup, followed by silica gel chromatography

(elution with pet ether/EtOAc = 1:1), gave 2.2 g (75%) of **39** as a clear colorless oil which was homogeneous by TLC analysis but consisted of two components by ^{1}H and ^{13}C NMR analysis [R_f (**39**) = 0.44, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.23-5.31 (m, 1H), 4.17 + 4.06 (s, 2H), 3.06 (bs, 1H), 2.28-2.42 (m, 4H), 1.87-1.99 (m, 2H), 1.73 + 1.68 (s, 2H), 1.59 (d, *J* = 6.7 Hz) + 1.36 (d, *J* = 6.6 Hz)(3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.4, 161.2, 135.2, 133.4, 121.5, 58.8, 38.1, 38.0, 29.7, 22.6, 22.4.

Preparation of 8-hydroxy-5-methyl-1*H*-isochromen-1-one (28A): Dienone **41A** (606 mg, 4 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 277 mg (43%) of **28A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**28A**) = 0.49, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 10.98 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 6.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.7, 160.1, 143.7, 138.9, 134.7, 123.3, 115.6, 107.4, 105.6, 17.9.

Preparation of 8-hydroxy-5-benzyl-1*H*-isochromen-1-one (28C): Dienone **41C** (710 mg, 3 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 248 mg (33%) of **29C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**29C**) = 0.53, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.63 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 6.8 Hz, 1H), 7.42 (t, *J* = 6.8 Hz, 2H), 7.21 (d, *J* = 5.6 Hz, 1H), 7.10 (d, *J* = 6.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.63 (s, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.4, 164.6, 145.6, 140.2, 138.1, 137.7, 133.5, 130.3, 128.9, 124.8, 114.9, 108.1, 106.2, 67.3.

Preparation of 8-hydroxy-4-methyl-1*H*-isochromen-1-one (35): Dienone **34** (508 mg, 3 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 329 mg (61%) of **35** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**35**) = 0.46, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.3 (s, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.8, 162.2, 140.5, 138.2, 137.5, 116.0, 114.6, 113.6, 106.8, 13.4.

Preparation of 8-hydroxy-3-methyl-1*H*-isochromen-1-one (37): Dienone **36** (690 mg, 4 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 402 mg (55%) of **37** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**37**) = 0.49, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.0 (s, 1H), 7.56 (t, *J* =

8.0 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.27 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.4, 161.2, 153.5, 137.6, 136.9, 114.8, 114.2, 105.3, 104.3, 19.0.

Preparation of 8-hydroxy-3,4-dimethyl-1*H*-isochromen-1-one [oospolactone] (40): Dienone **39** (510 mg, 3 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 411 mg (76%) of **40** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**40**) = 0.49, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.30 (s, 1H), 7.61 (t, J = 8.1 Hz, 1H), 6.92 (t, J = 7.6 Hz, 2H), 2.31 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.8, 162.1, 149.8, 139.3, 137.4, 114.6, 113.1, 109.4, 106.1, 17.3, 12.7.

ACKNOWLEDGEMENTS

We thank the National Science Foundation (CHE-0506486) for support of this research.

REFERENCES AND NOTES

§ This article is part of a special issue honoring the many scientific contributions of Professor Al Padwa and in celebration of his 75th birthday.

† Taken in part from the Ph.D. dissertation of Jeremy Grove, *University of Georgia* (2010).

1. The preceding paper in this journal authored by G. Majetich and J. L. Grove and is entitled: *"Synthesis of 6-Hydroxyisochromenes and 6-Hydroxycoumarins from 3-Ethoxycyclohex-2-en-1-one."*

2. (a) A. Ulubelen, Y. Aynehchi, M. Somogyi, A. Souri, and T. Mabry, *J. Nat. Prod.*, 1984, **47**, 170; (b) A. Whyte, J. Gloer, J. Scott, and D. Malloch, *J. Nat. Prod.*, 1996, **59**, 765; (c) D. S. Lim, Y. S. Kwak, J. H. Kim, S. H. Ko, W. H. Yoon, and C. H. Kim *Chemotherapy,* 2003, **49**, 146; (d) A. Saeed, *J. Heterocycl. Chem.*, 2004, **41**, 975; (e) M. Yoshikawa, E. Uchida, N. Chatani, H. Kobayashi, Y. Naitoh, Y. Okuno, H. Matsuda, J. Yamahara, and N. Murakami, *Chem. Pharm. Bull.,* 1992, **40**, 3352; (f) G. Qadeera, N. Ramaa, and S. Shahb, *ARKIVOC,* 2007, **14**, 12; (g) G. Crosby and L. Beidler, *Crit. Rev. Food Sci. Nutr.,* 1976, **7**, 297; (h) J. Sonnenbichler, I. Sonnenbichler, and D. Schwarz, *Phytochemistry,* 1997, **44**, 267; (i) S. Nakajima, K. Kawai, S. Yamada, and Y. Sawai, *Agr. Biol. Chem.*, 1976, **40**, 811; (j) L. Szlavik, A. Gyuris, J. Minarovits, P. Forgo, J. Molnar, and J. Hohmann, *Planta Med.*, 2004, **70**, 871.

3. (a) R. Barry, *Chem. Rev.*, 1964, **64**, 229; (b) N. Narasimhan and R. Mali, *Synthesis,* 1983, 957; (c) R. Hill, *Prog. Chem. Org. Nat. Prod.,* 1986, **49**, 1; (d) E. Napolitano, *Org. Prep. Proc. Int.*, 1997, **29**, 631.

4. (a) R. Larock, S. Varaprath, H. Lau, and C. Fellows, *J. Am. Chem. Soc.*, 1984, **106**, 5274; (b) R. Larock and T. Hightower, *J. Org. Chem.*, 1993, **58**, 5298; (c) R. Larock, M. Doty, and X. Han, *J.*

Org. Chem., 1999, **64**, 8770; (d) S. Mehta, J. Waldo, and R. Larock, *J. Org. Chem.*, 2009, **74**, 1141; (e) T. Yao and R. Larock, *Tetrahedron Lett.*, 2002, **43**, 7401; (f) T. Yao and R. Larock, *J. Org. Chem.*, 2003, **68**, 5936; (g) S. Roy, B. Neuenswander, D. Hill, and R. Larock, *J. Comb. Chem.*, 2009, **11**, 1128; (h) D. Yue, N. Della Cà, and R. Larock, *Org. Lett.*, 2004, **6**, 1581; (i) D. Yue, N. Della Cà, and R. Larock, *J. Org. Chem.*, 2006, **71**, 3381.

5. (a) N. Asao, T. Nogami, K. Takahashi, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **124**, 764; (b) N. Asao, C. Chan, K. Takahashi, and Y. Yamamoto, *Tetrahedron*, 2005, **61**, 11322; (c) S. Mondal, T. Nogami, N. Asao, and Y. Yamamoto, *J. Org. Chem.*, 2003, **68**, 9496; (d) N. Patil and Y. Yamamoto, *J. Org. Chem.*, 2004, **69**, 5139.

6. *For the preparation of isochromenes from O-alkynyl benzoic acids, see:* (a) R. G. F. Giles, I. R. Green, and C. P. Taylor, *ARKIVOC,* 2001, **7**, 166; (b) R. Larock, S. Varaprath, H. Lau, and C. Fellows, *J. Am. Chem. Soc.*, 1984, **106**, 5274; (c) R. Larock and T. Hightower, *J. Org. Chem.*, 1993, **58**, 5298. *For the preparation of isochromenes from aryl alkynes:* (d) B. Gabriele, G. Salerno, A. Fazio, and R. Pittelli, *Tetrahedron*, 2003, **59**, 6251; (e) X. Li, A. Chianese, T. Vogel, and R. Crabtree, *Org. Lett.*, 2005, **7**, 5437; (f) A. Varela-Fernandez, C. Gonzalez-Rodriguez, J. Varela, L. Castedo, and C. Saa, *Org. Lett.*, 2009, **11**, 5350; (g) R. Mancuso, S. Mehta, B. Gabriele, G. Salerno, W. S. Jenks, and R. C. Larock, *J. Org. Chem.*, 2009, **75**, 897; (h) D. Korte, L. Hegedus, and R. Wirth, *J. Org. Chem.*, 1977, **42**, 1329; (i) G. Batu and R. Stevenson, *J. Org. Chem.*, 1980, **45**, 1532; (j) H. Liao and C. Cheng, *J. Org. Chem.*, 1995, **60**, 3711.

7. M. Bolte, W. Crow, and S. Yoshida, *Aust. J. Chem.*, 1982, 1411.

8. A. B. Smith, III, A. B. Dorsey, M. Ohba, A. Lupo, Jr., and M. Malamas, *J. Org. Chem.*, 1988, **53**, 4314.

9. G. Stork and R. L. Danheiser, *J. Org. Chem.*, 1973, **38**, 1775.

10. J. E. Baldwin, *J. Chem. Soc., Chem. Commum.*, 1976, 734.

11. H. Reich, J. Renga, and I. Reich, *J. Am. Chem. Soc.*, 1975, **97**, 5434.

12. (a) L. Liu and P. Floreancig, *Org. Lett.*, 2009, **11**, 3152; (b) W. Tu, L. Liu, and P. E. Floreancig, *Angew. Chem. Int. Ed.*, 2008, **47**, 4184; (c) W. Tu and P. E. Floreancig, *Angew. Chem. Int. Ed.*, 2009, **48**, 4567.

13. (a) Y.-C. Xu, E. Lebeau, J. W. Gillard, and G. Attardo, *Tetrahedron Lett.*, 1993, **34**, 3841; (b) Y.-C. Xu, C. Roy, and E. Lebeau, *Tetrahedron Lett.*, 1993, **34**, 8189; (c) Y.-C. Xu, E. Lebeau, P. L. Myers, and J. W. Gillard, *J. Org. Chem.*, 1994, **59**, 4868; (d) W. Wang, T. Li, and G. Attardo, *J. Org. Chem.*, 1997, **62**, 6598.

14. (a) D. Walker and J. D. Hiebert, *Chem. Rev.*, 1963, **67**, 153; (b) J. N. Marx and Y.-S. P. Hahn, *J. Org. Chem.*, 1988, **53**, 2868; (c) A. Begouin, S. Hesse, and G. Kirsch, *ARKIVOC,* 2008, **7**, 84; (d)

M. S. Islam, K. Ishigami, and H. Watanabe, *Tetrahedron,* 2007, **63**, 1074; (e) E.-C. Wang, Y.-S. Wein, and Y.-H. Kuo, *Tetrahedron Lett.,* 2006, 47, 9195; (f) V. K. Ahluwaliar, S. Jolly, and A. K. Tehim, *Tetrahedron,* 1982, 38, 3673; (g) L. Y. Chen, S. R. Li, P. Y. Chen, H. C. Chang, T. P. Wang, I. L. Tsai, and E. C. Wanga, *ARKIVOC,* 2010, **11**, 64.

15. *Aromatizations of methylenecyclohexadienes, see*: G. Majetich and S. Allen, *ARKOVIC,* 2010, **11**, 104.

16. *Aromatization of cyclohexenones using Pd/C, see:* (a) E. Mosettig and H. M. Duvall, *J. Am. Chem. Soc.*, 1937, **59**, 367; (b) E. C. Horning and M. G. Horning, *J. Am. Chem. Soc.*, 1947, **69**, 1359; (c) E. C. Horning, M. G. Horning, and G. N. Walker, *J. Am. Chem. Soc.*, 1949, **71**, 169; *Aromatization of cyclohexenones using iodine, see:* (d) A. S. Kotnis, *Tetrahedron Lett.*, 1990, **31**, 481.

17. R. P. Thummel, W. E. Cravey, and D. B. Cantu, *J. Org. Chem.,* 1980, **45**, 1633.

18. For related syntheses, see: (a) V. K. Ahluwalia, R. S. Jolly, and A. K. Tehim, *Tetrahedron,* 1982, **38**, 3673; (b) S. K. Ghosh, G. S. Buchanan, Q. A. Long, Y. Wei, Z. F. Al-Rashid, H. M. Sklenicka, and R. P. Hsung, *Tetrahedron,* 2007, **64**, 883.

19. For a recent synthesis, see: M. Islam, K. Ishigami, and H. Watanabe, *Tetrahedron,* 2007, **63**, 1074.