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Direct approaches toward natural product synthesis

Aniket Mohan Thite
Iowa State University

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by

Aniket Mohan Thite

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Program of Study Committee:
George A. Kraus, Major Professor
Richard C. Larock
Patricia A. Murphy

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GENERAL INTRODUCTION

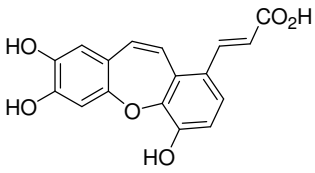
Organic chemistry has always rewarded creativity and innovation whether it is in developing new synthetic strategies or novel laboratory techniques. Over the past several decades, organic synthesis has flourished with the accrual of useful synthetic methodologies and total syntheses of complex organic molecules. Interdisciplinary research has been a forte of organic chemistry. In collaboration with biology and medicinal chemistry, it has led to discovery and the ensuing syntheses of biologically potent natural products, which have been translated into drug applications. For pharmaceutical applications, readily makeable biologically active molecules are best suited. To meet that end, concise syntheses have been highly desirable and sought after.

In this context, we explored direct routes to several biologically significant natural products. In course of the syntheses, novel synthetic methodologies were developed. These studies will be helpful to design approaches to other structurally related natural products.

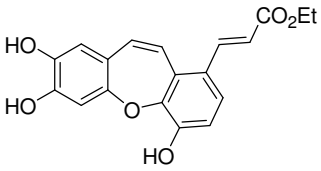
CHAPTER 1: SYNTHESIS OF BENZOXEPIN SKELETON VIA A RING-CLOSING METATHESIS REACTION

Introduction

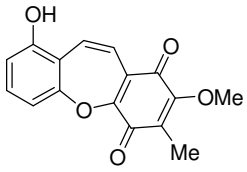
Among the recently isolated natural products, which possess a benzoxepin skeleton, are tournefolic acid B, its ethyl ester and bauhiniastatins (1-4) (Figure 1). Tournefolic acid B and its ethyl ester have been obtained from *Tournefortia* sarmentosa, which is used in Taiwan as a detoxicant, an anti-inflammatory agent and for promoting blood circulation for removal of blood stasis.[1]



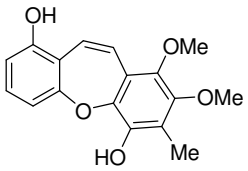
tournefolic acid B



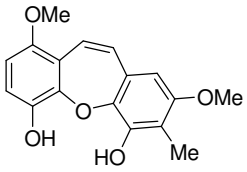
tournefolic acid B ethyl ester



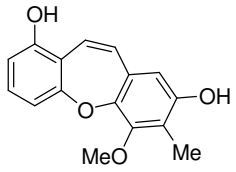
bauhiniastatin 1



bauhiniastatin 2



bauhiniastatin 3



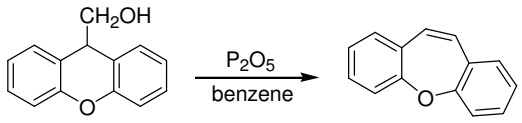
bauhiniastatin 4

Figure 1

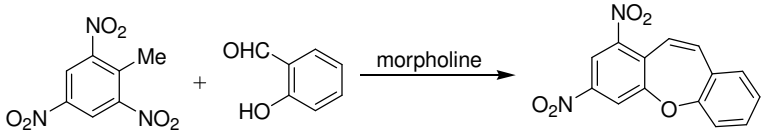
Bauhiniastatins 1-4 have been obtained from *Bauhinia purpurea*, a well known ornamental tree in Taiwan. Careful chemical studies of the heartwood[2] and bark[3] led to isolation of 27 components, which included a chromone, carbohydrates, flavonoids, lipids, phenols, steroids, and triterpenes.[4] Traditional use of *B. purpurea* in sub-Himalayan regions of India point to gastrointestinal activities with applications as a laxative (flowers),[5] a

carminative drug (roots) and for diarrhea (bark).[6] A novel flavone rhamnopyranoside has been isolated from this source[6] and there is an earlier evidence for a chalcone glycoside component.[7] Other chemical investigations of *B. purpurea* components have been related to flavonoids[8] such as the hypoglycemic and antioxidant kaempferol dirhamnoside from *B. forficata*, a conventional antidiabetic treatment in Brazil,[9] and earlier with hypoglycemic flavonoid-containing fractions from leaves of *B. purpurea* grown in Egypt.[10] Currently, *B. purpurea* seems best known for a lectin agglutinin that binds to dense cell surface glycoconjugates and could be of use in medical applications.[11] Bauhiniastatins 1-4 are reported to exhibit significant growth inhibition against a minipanel of human cancer cell lines and bauhiniastatin 1 was also found to inhibit the P388 cancer cell line.[4]

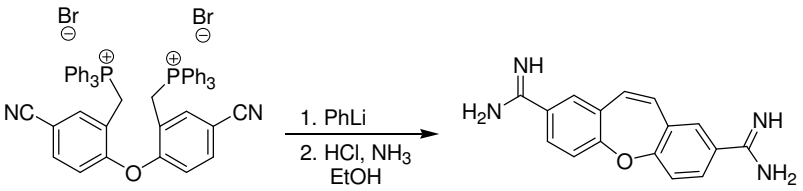
Searching through the literature provided three examples to make the benzoxepin skeleton. The first one involved acid-catalyzed rearrangement of xanthene-9-carbinol to yield the product (Scheme 1).[12] The second one entailed displacement of one nitro group followed by cyclization and dehydration (Scheme 2).[13] The third one used a diphosphorane to make the benzoxepin core structure (Scheme 3).[14]



Scheme 1



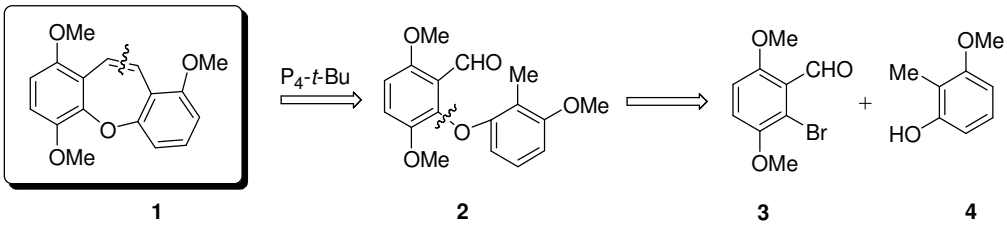
Scheme 2



Scheme 3

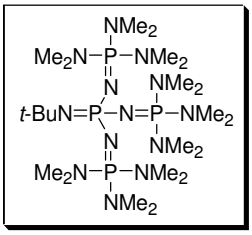
Results and Discussion

As shown in the retrosynthetic analysis, we envisioned that the benzoxepin core unit **1** could be assembled via cyclization of compound **2** using the phosphazine base P_4-*t*-Bu (**5**). Compound **2** could be prepared by the S_NAr reaction of **3** and **4** (Scheme 4).



1 **2** **3** **4**

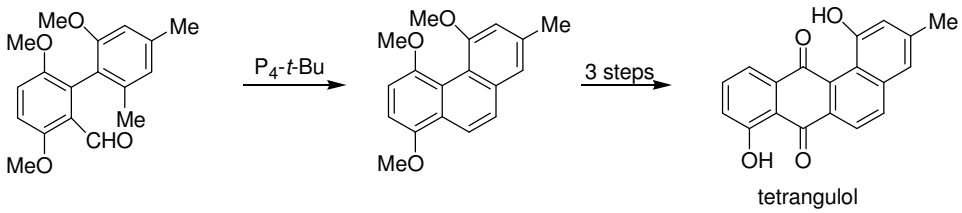
Scheme 4



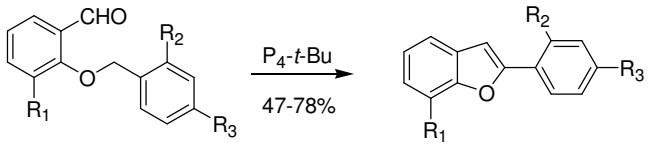
Phosphazene base P_4-*t*-Bu

5

Kraus and co-workers have employed P_4-*t*-Bu (**5**) to synthesize phenanthrenes.[15] In the synthesis of tetrangulol, P_4-*t*-Bu cyclization was used to obtain a key phenanthrene intermediate (Scheme 5).[16] In another application, Kraus and co-workers used P_4-*t*-Bu to prepare benzofurans from *ortho*-substituted benzaldehydes (Scheme 6).[17]

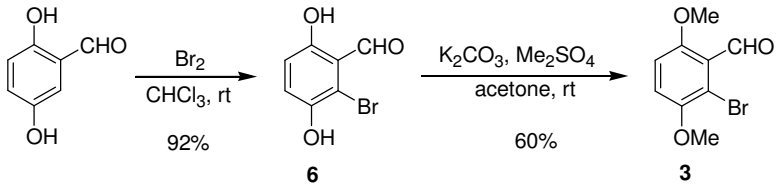


Scheme 5

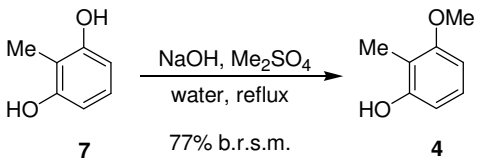


Scheme 6

Towards the synthesis of **1**, 2,5-dihydroxy benzaldehyde was brominated using bromine in chloroform to afford compound **6** in 92% yield.[18] Diol **6** was methylated using dimethyl sulfate and potassium carbonate in acetone to furnish the dimethoxy compound **3** in 60% yield (Scheme 7). The other coupling partner **4** was synthesized from 2-methyl resorcinol (**7**) using sodium hydroxide and dimethyl sulfate in water in 77 % yield based on recovered starting material (Scheme 8).[19]

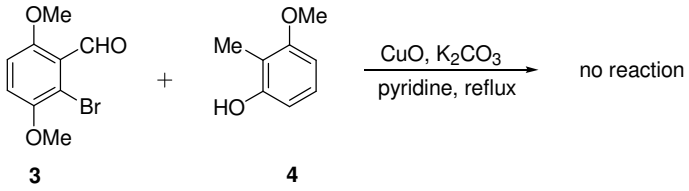


Scheme 7



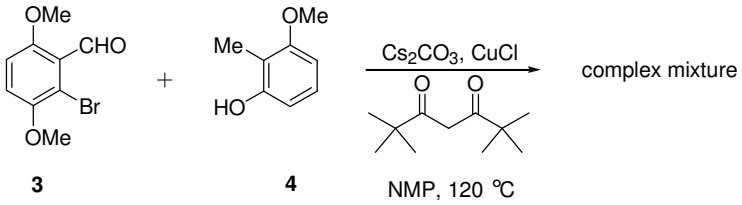
Scheme 8

First, we attempted to couple compounds **3** and **4** under standard Ulmann conditions using potassium carbonate and copper(II) oxide in pyridine (Scheme 9).[20] This just returned the starting materials.



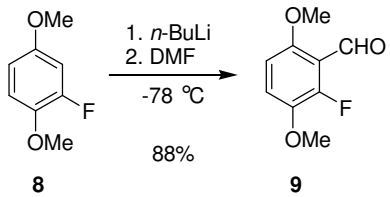
Scheme 9

We then employed a modified procedure for Ulmann coupling using cesium carbonate, copper(I) chloride and 2,2,6,6-tetramethyl-3,5-heptanedione as the ligand in *N*-methylpyrrolidone (Scheme 10).[21] Unfortunately, it gave a complex mixture.



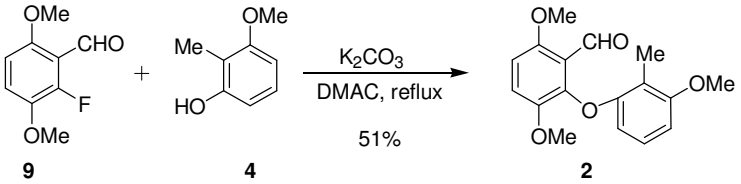
Scheme 10

At this stage, we decided to change the halogen atom in **3** from bromine to fluorine. The underlying rationale was to enhance the S_NAr reaction by reducing the size of the halogen atom. To that end, 2,5-dimethoxy-6-fluorobenzaldehyde (**9**) was prepared from 2,5-dimethoxybenzaldehyde (**8**) using *n*-BuLi and *N,N*-dimethylformamide (Scheme 11).[22]



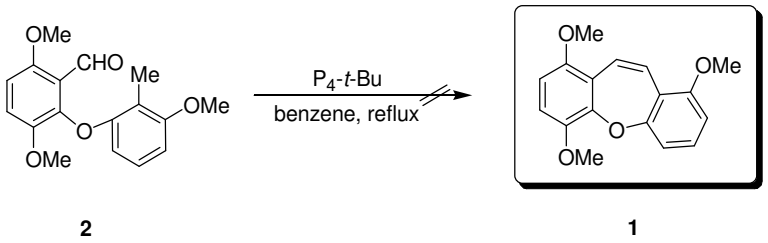
Scheme 11

Pleasingly, the S_NAr reaction of phenol **4** with aldehyde **9** using potassium carbonate in *N,N*-dimethylacetamide provided diphenylether **2** in 51% isolated yield (Scheme 12).[23]

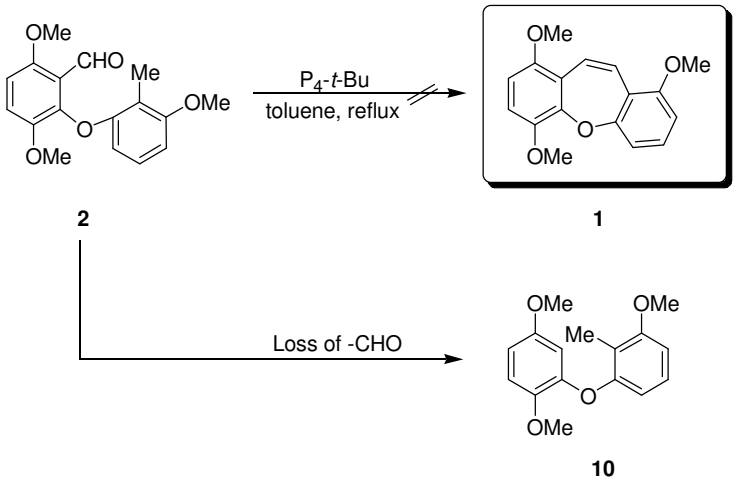


Scheme 12

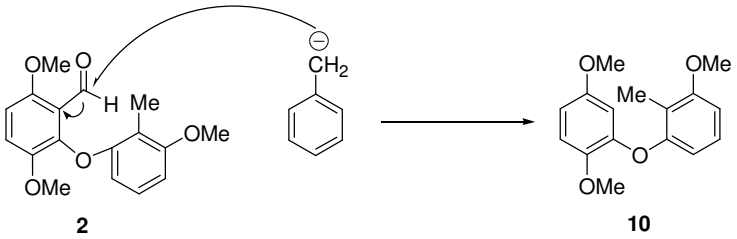
However, to our dismay, the crucial P_4-*t*-Bu cyclization reaction returned the starting materials when boiled in benzene (Scheme 13).[17] When toluene was used as the solvent, instead of getting the product, we observed loss of aldehyde functionality (Scheme 14). Perhaps, P_4-*t*-Bu deprotonated the more acidic methyl group on toluene, which attacked the aldehyde group intermolecularly to cleave the carbon-carbon bond (Scheme 15).



Scheme 13



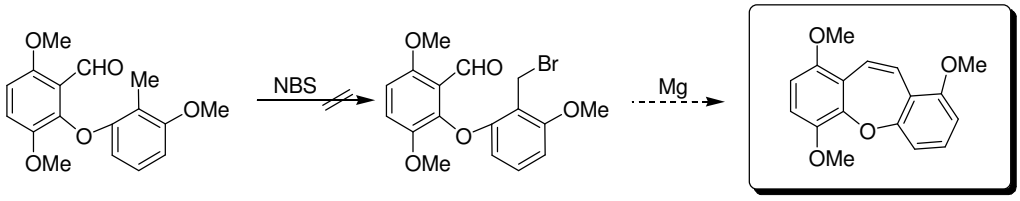
Scheme 14



2 **10**

Scheme 15

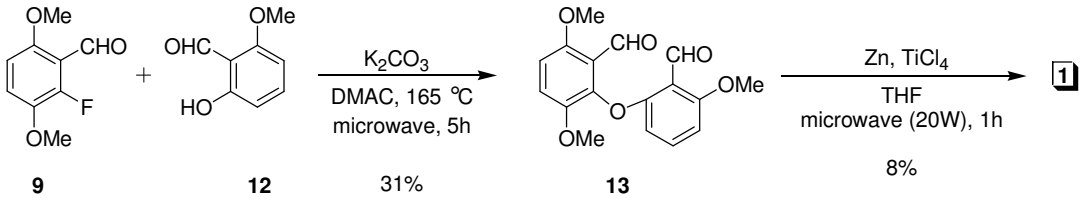
At this juncture, we attempted brominating the aromatic methyl group in **2** to try the intramolecular Grignard reaction. Unfortunately, the bromination gave multiple products, which were hard to separate from each other using column chromatography (Scheme 16). Presumably, ring bromination might have competed with desired bromination of the aromatic methyl group.



2 **11** **1**

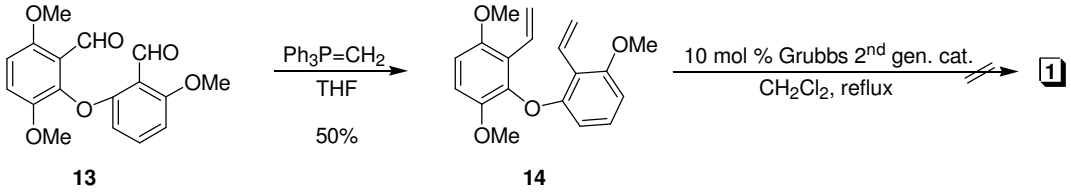
Scheme 16

We redesigned our strategy and tried to apply the McMurry coupling to get the benzoxepin skeleton. To obtain the requisite precursor **13**, we coupled the dimethoxy compound **9** with phenol **12** to get the dialdehyde **13** in 31% yield. The stage was now set for us to try the key McMurry coupling. Upon treatment of dialdehyde **13** with zinc and titanium tetrachloride in tetrahydrofuran under microwave conditions, benzoxepin **1** was obtained, although in an unsatisfactory 8% yield (Scheme 17).[24]



Scheme 17

In pursuit of developing an improved method, we planned to use ring closing metathesis (RCM) to attain the bauhinoxepin skeleton. To that end, we converted the dialdehyde **13** into the divinyl compound **14** using Wittig olefination.[25] The ring-closing metathesis reaction, however, returned the starting material (Scheme 18).



Scheme 18

We speculated that non-bonded interactions might have played a significant part in failure of the RCM. Upon extensively searching the literature, we found that there were no examples of RCM where all positions ortho to the vinyl groups were substituted.[26,27] To test our hypothesis, we decided to synthesize **15** (Figure 2).

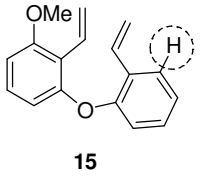
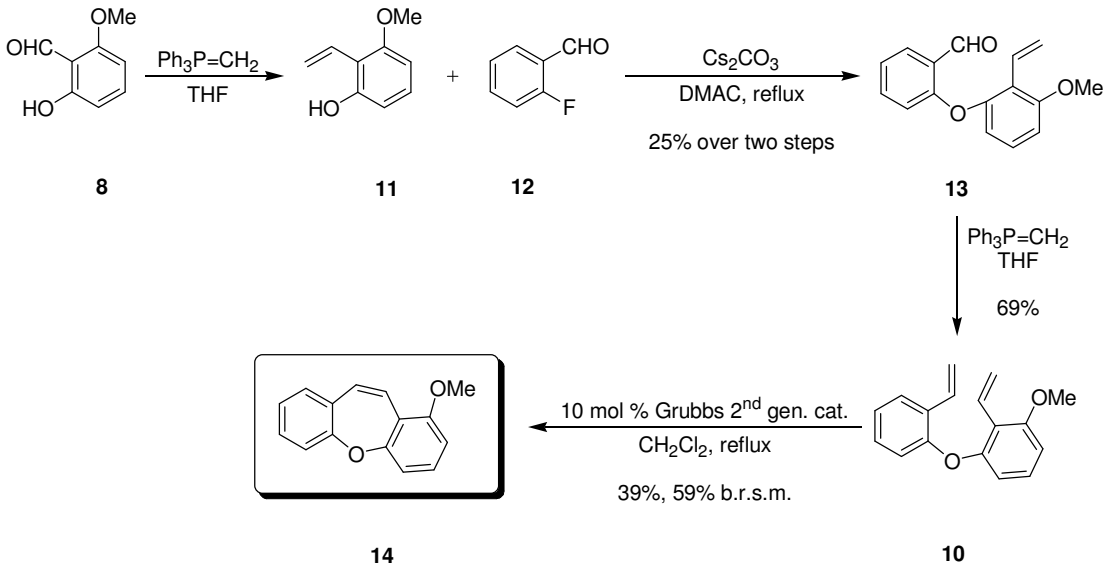


Figure 2

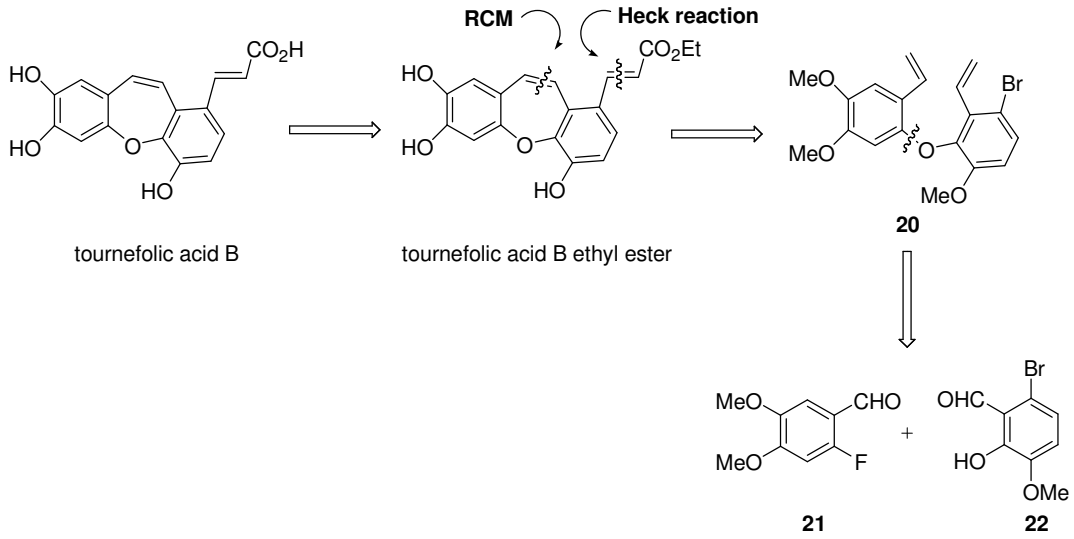
To prepare the desired precursor **15**, we coupled 3-methoxy-2-vinylphenol (**16**) with 2-fluorobenzaldehyde (**17**) using cesium carbonate in boiling *N,N*-dimethylacetamide to

provide diphenylether **18**. Wittig olefination of aldehyde **18** furnished the divinyl compound **15**.[25] To our delight, the ring-closing metathesis reaction of **15** using 10 mole percent of Grubbs 2nd generation catalyst in boiling dichloromethane gave the desired benzoxepin **19** in 39% yield (59% based on recovered starting material) (Scheme 19).[26,27]



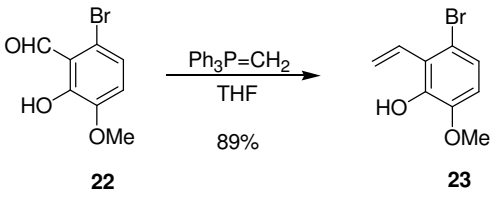
Scheme 19

Encouraged by the success of RCM, we focused on making tournefolic acid B and its ethyl ester. As shown in the retrosynthetic analysis, we visualized making tournefolic acid B from its ethyl ester, which in turn could be assembled via a ring-closing metathesis (RCM) and a Heck reaction. Divinyl compound **20** could be made from 6-fluoroveratraldehyde (**21**) and 6-bromo-2-hydroxy-3-methoxybenzaldehyde (**22**) (Scheme 20).



Scheme 20

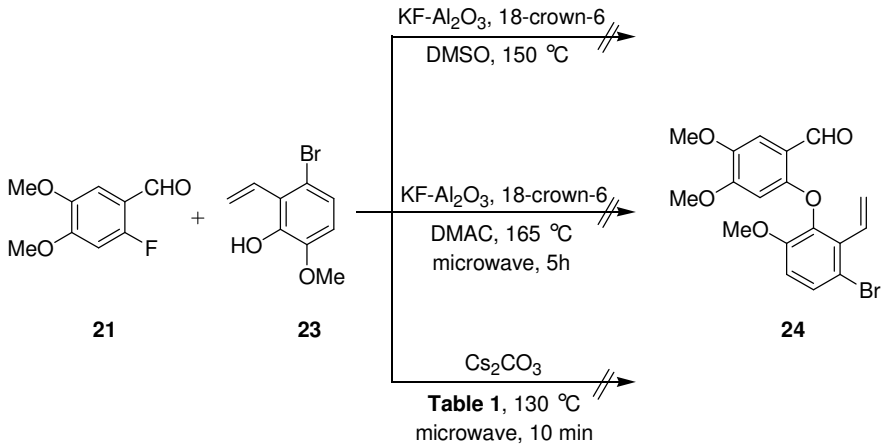
Wittig olefination of aldehyde **22** provided the vinyl compound **23** in 89% yield (Scheme 21). At this point, we were faced with the challenge of forming the C-O bond. Even extensive searching through the literature did not provide us with relevant examples in which both the electronic and the steric factors were unfavorable for the S_NAr reaction. The phenol **23** is quite hindered whereas 6-fluoroveratraldehyde (**21**) has two strong electron donating groups on the phenyl ring.



Scheme 21

To proceed with our plan, we attempted to form the C-O bond using a variety of different conditions. We used potassium fluoride-alumina or cesium carbonate as the base. We changed the solvents and tried dimethyl sulfoxide, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, acetonitrile and 1,4-dioxane. We also subjected the reaction to different

heating conditions, like heating in an oil bath, as well as in a microwave (Scheme 22, Table 1). To our dismay, none of the above combinations gave us the desired adduct **24** (Table 1).

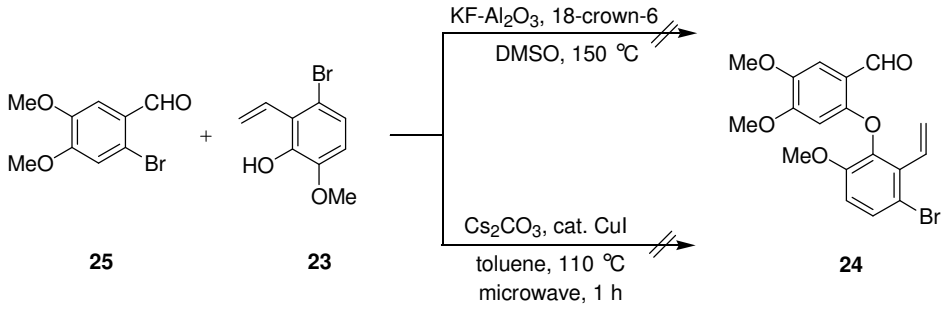


Scheme 22

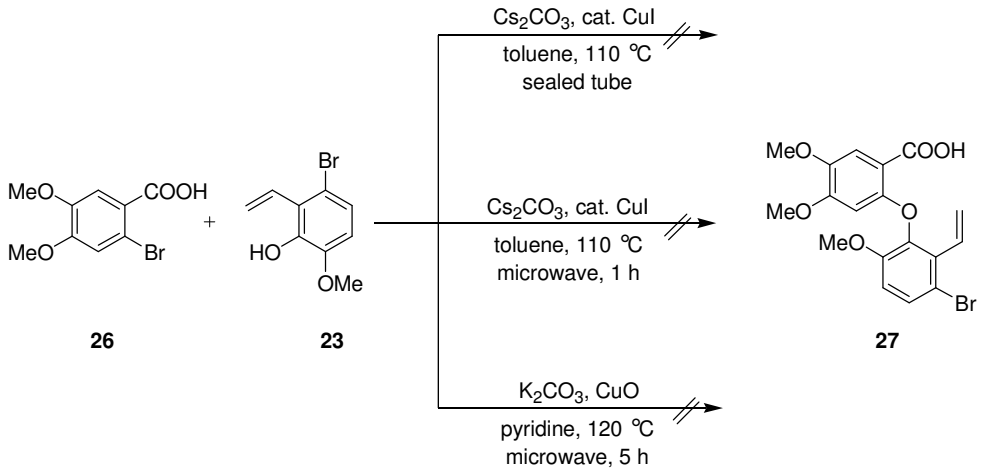
Solvent	Outcome
N,N-dimethylacetamide	decomposition
N,N-dimethylformamide	decomposition
acetonitrile	no reaction
1,4-dioxane	no reaction

Table 1

Changing the coupling partner to 6-bromoveratraldehyde (**25**) did not help either (Scheme 23). Using 2-bromo-4,5-dimethoxybenzoic acid (**26**) as the coupling partner with compound **23** was equally ineffective (Scheme 24).

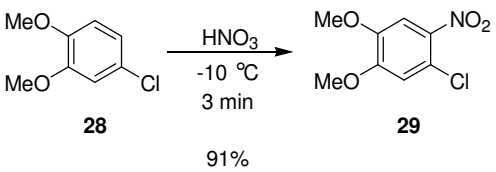


Scheme 23

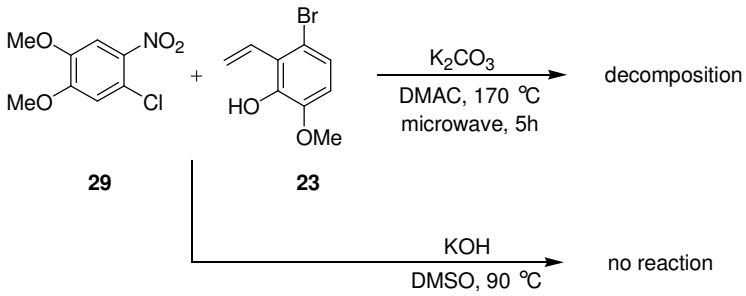


Scheme 24

To form the elusive C-O bond, we introduced a nitro group at the position ortho to the halogen atom. Nitration of dimethoxy compound **28** afforded the nitro compound **29** in 91% yield (Scheme 25).[28] Subjecting the coupling reaction of **23** with **29** to comparatively mild conditions gave back the starting materials. Exposing the reaction to harsh microwave conditions led to decomposition (Scheme 26).

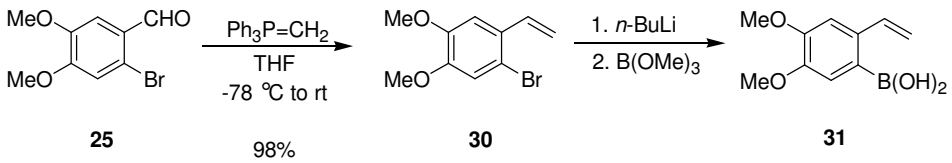


Scheme 25

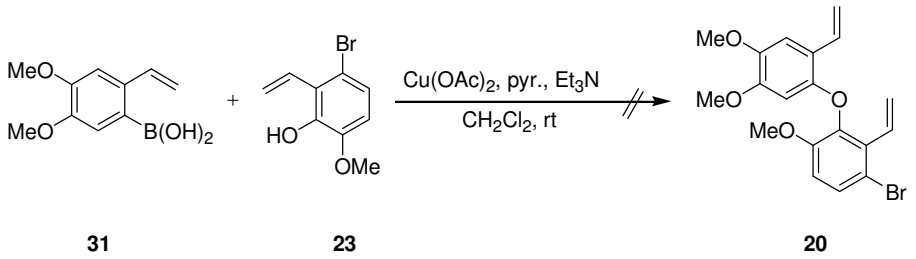


Scheme 26

In a different route to form the C-O bond, we also tried coupling the substituted phenol **23** with boronic acid **31**, prepared from 6-bromoveratraldehyde (**25**) in two steps (Scheme 27).[29] The modified Ulmann conditions, however, gave a complex mixture of products (Scheme 28).[30,31]



Scheme 27



Scheme 28

Conclusion

In summary, we have developed a novel method for building the benzoxepin skeleton, which entailed use of ring-closing metathesis reaction as the key step. Although, our efforts were impeded by not being able to form the C-O bond, we are currently targeting other

natural products with the same core structure wherein the C-O bond would be easily makeable.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or a Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR) unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan TSQ700 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for flash column chromatography.

Compound 1

To zinc dust (20 mg, 0.31 mmol) in tetrahydrofuran (1 mL) were added titanium tetrachloride (0.02 ml, 0.16 mmol) and dialdehyde **13** (41 mg, 0.13 mmol) in tetrahydrofuran (0.5 mL) in a microwave vial. After heating in the microwave for 1 h at 20 W power, the reaction mixture was poured into water and extracted with diethyl ether. The organic layer was dried over magnesium sulfate, passed through a pad of basic alumina and then evaporated *in vacuo*. The residue was purified using preparative TLC (hexanes : ethyl acetate

= 3:1) to afford the cyclized compound **1** (3 mg, 8%).[1]H NMR (400 MHz, $CDCl_3$) δ7.22-7.26 (m, 1H), 7.03-7.12 (m, 2H), 6.97 (d, 1H, *J* = 8.4 Hz), 6.86 (d, 1H, *J* = 8.8 Hz), 6.67 (d, 1H, *J* = 8.4 Hz), 6.57 (d, 1H, *J* = 8.8 Hz), 3.89 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H); LRMS (EI): *m/z* 284 (M^+, 100%), 269, 254, 241.

Compound 2

To a stirred solution of **4** (190 mg, 1.36 mmol) in *N,N*-dimethylacetamide (7 mL) were added potassium carbonate (190 mg, 1.36 mmol) and **9** (250 mg, 1.36 mmol) in *N,N*-dimethylacetamide (6 mL) at rt. After heating to reflux for 16 h, the reaction mixture was cooled to rt, diluted with ethyl acetate and washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford the diphenylether **2** (210 mg, 51%).[1]H NMR (300 MHz, $CDCl_3$) δ10.31 (s, 1H), 7.19 (d, 1H, *J* = 9.3 Hz), 6.91-6.98 (m, 1H), 6.81 (d, 1H, *J* = 9.3 Hz), 6.56 (d, 1H, *J* = 8.1 Hz), 6.06 (d, 1H, *J* = 8.4 Hz), 3.91 (s, 3H), 3.86 (s, 3H), 3.72 (s, 3H), 2.31 (s, 3H).

Compound 3

To a stirred solution of 6-bromo-2,5-dihydroxybenzaldehyde (**6**) (0.5 g, 2.3 mmol) in acetone (6 mL) was added potassium carbonate (0.95 g, 6.9 mmol) at rt. After stirring for 30 min at rt, was added dimethyl sulfate (0.55 mL, 5.75 mmol) and the stirring continued for 20 h upon which the reaction mixture was passed through a pad of Celite and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes :

ethyl acetate = 9:1 to 7:3) to afford the dimethoxy compound **3**[29] (0.3 g, 54%) as a white solid: mp 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.08 (d, 1H, J = 8.8 Hz), 6.94 (d, 1H, J = 9.2 Hz), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 155.6, 150.6, 124.9, 117.3, 115.0, 111.6, 57.4, 56.8.

Compound 4

To a stirred solution of 2-methylresorcinol **7** (1 g, 8.1 mmol) in water (5 mL) were added sodium hydroxide (0.32 g, 8.1 mmol) and dimethyl sulfate (0.77 mL, 8.1 mmol) at rt. After refluxing for 8.5 h, the reaction mixture was cooled to rt and additional sodium hydroxide (0.32 g, 8.1 mmol) was added to it. The resulting solution was diluted with diethyl ether and the aqueous layer developed was acidified with aqueous 4 N hydrochloric acid. This acidified aqueous layer was then extracted with diethyl ether and washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford **4**[17] (0.43 g, 40%, 77% based on recovered starting material). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, 1H, J = 8.1 Hz), 6.48 (t, 2H, J = 7.5 Hz), 4.67 (s, 1H), 3.83 (s, 3H), 2.13 (s, 3H).

Compound 6

To a solution of 2,5-dihydroxybenzaldehyde (0.69 g, 5 mmol) in chloroform (20 mL) stirred for 2 h, was added bromine (0.28 mL, 5.5 mmol) in chloroform (10 mL) at rt. After stirring the reaction mixture for 5 h at rt, saturated aqueous sodium thiosulfate solution was

added to consume the excess bromine. The resulting solution was diluted with dichloromethane, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford **6** (1 g, 92%).^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 10.27 (s, 1H), 7.24 (d, 1H, J = 9.2 Hz), 6.8 (d, 1H, J = 9.2 Hz), 5.36 (s, 1H).

Compound 9

To a stirred solution of 2-fluoro-1,4-dimethoxybenzene (**8**) (1 g, 6.41 mmol) in tetrahydrofuran (40 mL) was added *n*-BuLi (2.5 M solution in hexanes, 2.6 mL, 6.41 mmol) at -78 $^\circ$C. After 1 h at the same temperature, *N,N*-dimethylformamide (1 mL, 12.82 mmol) was added to it and the reaction was continued to stir for 35 min at the same temperature upon which it was quenched with glacial acetic acid in tetrahydrofuran at -78 $^\circ$C. After warming to room temperature, the resulting solution was diluted with diethyl ether and washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 2:1) to afford aldehyde **9** (1 g, 88%).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (d, 1H, J = 1.2 Hz), 7.16 (t, 1H, J = 9.2 Hz), 6.69 (dd, 1H, J = 9.2 Hz, 2.0 Hz), 3.90 (s, 3H), 3.88 (s, 3H).

Compound 13

To a stirred solution of **12** (87 mg, 0.57 mmol) in *N,N*-dimethylacetamide (5 mL) were added potassium carbonate (79 mg, 0.57 mmol) and **9** (100 mg, 0.54 mmol) in a microwave vial. After subjecting the reaction mixture to microwave heating for 5 h at 165 °C, it was cooled to rt, diluted with ethyl acetate and washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 1:1) to afford the dialdehyde **13** (53 mg, 31%).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 10.36 (s, 1H), 7.25-7.31 (m, 2H), 7.20 (d, 1H, J = 9.2 Hz), 6.85 (d, 1H, J = 9.2 Hz), 6.63 (d, 1H, J = 8.4 Hz), 6.13 (d, 1H, J = 8.4 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.73 (s, 3H).

Compound 14

To a stirred solution of the methyltriphenylphosphonium iodide (193 mg, 0.48 mmol) in tetrahydrofuran (3 mL) was added sodium bis(trimethylsilyl)amide (97 mg, 0.53 mmol) in tetrahydrofuran (3 mL). After 3 h at rt, the solution was cooled to – 78 °C, **13** (54 mg, 0.17 mmol) in tetrahydrofuran (4 mL) was added to it and the reaction mixture was allowed to warm gradually to rt and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride solution and the resulting solution was diluted with diethyl ether, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 6:1) to afford the divinyl compound **14** (26 mg, 50%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.20 (m, 1H), 6.97 (t, 1H, J = 8.4 Hz), 6.86 (d, 1H, J = 8.8 Hz), 6.71-6.80 (m, 2H), 6.56 (d, 1H, J = 8.4 Hz), 6.22 (dd, 1H, J = 18

Hz, 2.8 Hz), 6.02-6.10 (m, 2H), 5.54 (dd, 1H, *J* = 12.4 Hz, 2.8 Hz), 5.38 (dd, 1H, *J* = 12.0 Hz, 2.4 Hz), 3.89 (s, 3H), 3.86 (s, 3H), 3.68 (s, 3H).

Compound 15

To a stirred solution of the methyltriphenylphosphonium iodide (130 mg, 0.33 mmol) in tetrahydrofuran (10 mL) was added sodium bis(trimethylsilyl)amide (55 mg, 0.3 mmol) in tetrahydrofuran (5 mL). After 3 h at rt, the solution was cooled to – 78 °C, **18** (55 mg, 0.22 mmol) in tetrahydrofuran (5 mL) was added to it and the reaction mixture was warmed to rt over 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution and the resulting solution was diluted with diethyl ether, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 19:1) to afford the divinyl compound **15** (38 mg, 69%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, 1H, *J* = 7.5 Hz, 1.8 Hz), 7.17-7.25 (m, 1H), 6.94-7.15 (m, 4H), 6.81 (dd, 1H, *J* = 8.1 Hz, 1.2 Hz), 6.69 (d, 1H, *J* = 8.1 Hz), 6.40 (d, 1H, *J* = 8.4 Hz), 6.15 (dd, 1H, *J* = 18.0 Hz, 2.4 Hz), 5.83 (dd, 1H, *J* = 17.7 Hz, 1.2 Hz), 5.48 (dd, 1H, *J* = 12.0 Hz, 2.4 Hz), 5.30 (dd, 1H, *J* = 11.4 Hz, 1.5 Hz), 3.91 (s, 3H).

Compound 16

To a stirred solution of the methyltriphenylphosphonium iodide (1.17 g, 2.9 mmol) in tetrahydrofuran (7 mL) was added sodium bis(trimethylsilyl)amide (0.53 g, 2.9 mmol) in tetrahydrofuran (3 mL). After 3 h at rt, the solution was cooled to – 78 °C, **12** (0.2 g, 1.3

mmol) in tetrahydrofuran (7 mL) was added to it and the reaction mixture was warmed to rt over 2 h. The reaction was quenched with saturated aqueous ammonium chloride solution and the resulting solution was diluted with diethyl ether, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 9:1) to afford the vinyl compound **16** (0.16 g, 83%, 98% yield based on recovered starting material). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, 1H, J = 8.4 Hz), 6.79-6.88 (m, 1H), 6.57 (d, 1H, J = 8.4 Hz), 6.47 (d, 1H, J = 8.4 Hz), 5.72 (dd, 1H, J = 18.4 Hz, 2.0 Hz), 5.62 (dd, 1H, J = 12.0 Hz, 2.0 Hz), 5.61 (s, 1H), 3.84 (s, 3H).

Compound 18

To a solution of **16** (150 mg, 1 mmol) in *N,N*-dimethylacetamide (10 mL) were added cesium carbonate (360 mg, 1.1 mmol), **17** (0.10 mL, 1 mmol) in *N,N*-dimethylacetamide (5 mL) and the reaction mixture was heated to reflux overnight. The reaction solution was then diluted with diethyl ether, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford diphenylether **18** (63 mg, 25% unoptimized yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.93 (dd, 1H, J = 7.6 Hz, 1.6 Hz), 7.44-7.50 (m, 1H), 7.21 (t, 1H, J = 8.4 Hz), 7.15 (t, 1H, J = 8.4 Hz), 6.81-6.90 (m, 1H), 6.79 (d, 1H, J = 8.4 Hz), 6.76 (d, 1H, J = 8.4 Hz), 6.59 (d, 1H, J = 8.0 Hz), 6.05 (dd, 1H, J = 17.6 Hz, 2.0 Hz), 5.45 (dd, 1H, J = 12.0 Hz, 2.4 Hz), 3.92 (s, 3H).

Compound 19

To a solution of **15** (35 mg, 0.14 mmol) in dichloromethane (10 mL) was added Grubbs' 2nd generation catalyst (12 mg, 0.014 mmol). The reaction mixture was stirred for 10 h at rt and then heated to reflux for 20 h. After cooling to rt, the reaction solution was passed through a pad of Celite and evaporated *in vacuo*. The residue was purified by preparative TLC (hexanes : ethyl acetate = 49:1, eluted three times) to afford the cyclized compound **19** (12 mg, 39%, 59% based on recovered starting material). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.31 (m, 2H), 7.15-7.20 (m, 2H), 7.09-7.15 (m, 1H), 7.06 (d, 1H, J = 11.6 Hz), 6.85 (d, 1H, J = 8.4 Hz), 6.78 (d, 1H, J = 11.6 Hz), 6.68 (d, 1H, J = 8.4 Hz), 3.85 (s, 3H); LRMS (EI): *m/z* 224 (M^+), 181 (100%), 152.

Compound 23

To a stirred solution of the methyltriphenylphosphonium iodide (2.71 g, 6.71 mmol) in tetrahydrofuran (15 mL) was added sodium bis(trimethylsilyl)amide (1.19 g, 6.5 mmol) in tetrahydrofuran (10 mL). After 3 h at rt, the reaction solution was cooled to – 78 $^{\circ}$C, **22** (0.5 g, 2.16 mmol) in tetrahydrofuran (10 mL) was added to it and the reaction mixture was gradually warmed to rt overnight. The reaction was quenched with saturated aqueous ammonium chloride solution and the resulting solution was diluted with diethyl ether, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford the vinyl compound **23** (0.44 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1 (d, 1H, J = 9.0 Hz), 6.78-6.89 (m, 1H),

6.65 (d, 1H, *J* = 8.7 Hz), 6.15 (s, 1H), 6.1 (dd, 1H, *J* = 17.7 Hz, 1.8 Hz), 5.63 (dd, 1H, *J* = 11.7 Hz, 2.1 Hz), 3.91 (s, 3H).

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CHAPTER 2: CONCISE SYNTHESIS OF BAUHINOXEPIN J USING INTRAMOLECULAR RADICAL CYCLIZATION

Introduction

Bauhinoxepin J (**3**),[1] a dihydrodibenzoxepin, belongs to a family of secondary metabolites (Figure 1) isolated from a shrubby tree, *Bauhinia purpurea* L. (family Leguminosae), commonly known as "Chong Kho" or "Siao Dok Daeng" (in Thai). This plant is reported to contain cytotoxic oxepins,[2] flavone glycosides,[3] flavanones[4] and lectins.[5] *B. purpurea* lectins are of significant interest and have been utilized as potential biological tools to bind with cellular proteins and carbohydrates.[6-8] The genus *Bauhinia* has been found to be a rich source of bioactive metabolites,[9] bibenzyls[9a,c] and dibenzo[b,f]oxepins.[9b]

Bauhinoxepin J has been reported to exhibit potent antimycobacterial activity (MIC 24.4 μM), excellent antimalarial activity (IC_{50} 5.8 μM) and also cytoxicity toward KB and BC cell lines with IC_{50} values of 10.5 and 12.1 μM, respectively.[1]

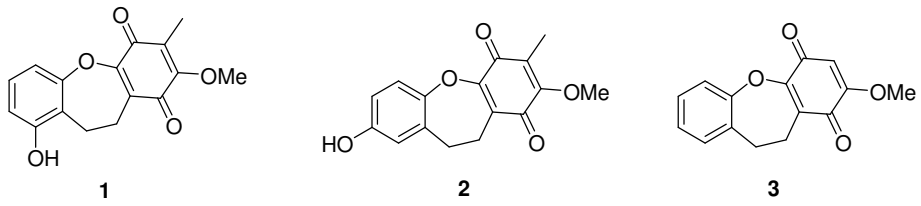
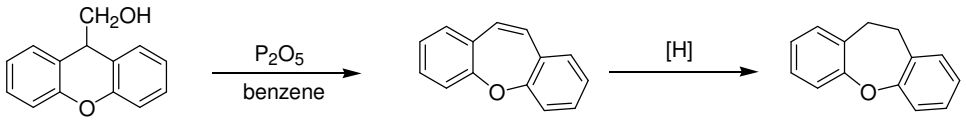


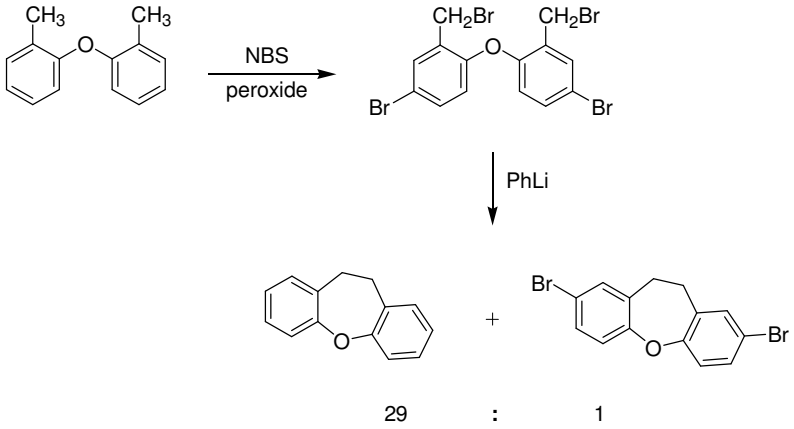
Figure 1

Bauhinoxepin J has a dihydrodibenzoxepin skeleton with a seven membered central ring flanked by a benzene ring on one side and a benzoquinone on the other. There have been two syntheses reported to make the dihydrodibenzoxepin skeleton. The first one involved acid-catalyzed rearrangement of xanthene-9-carbinol followed by reduction[10] (Scheme 1).

The second method entailed tetrabromination of 2,2´-dimethyldiphenyl ether with *N*-bromosuccinimide followed by cyclization[11] (Scheme 2).



Scheme 1

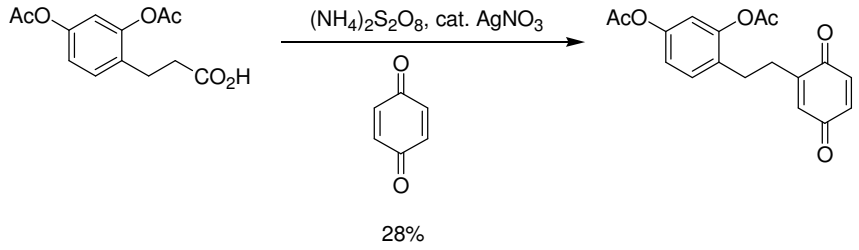


Scheme 2

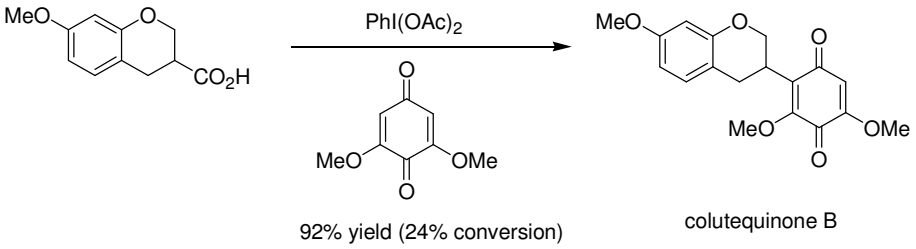
Herein, we report an effective way to make the natural product, bauhinoxepin J **3**, in 13% overall yield starting from readily available **9** and **11** in just three steps. (Schemes 11 and 12) The key step in the synthesis is an intramolecular decarboxylative radical addition to a quinone. To the best of our knowledge, there is no precedent for the intramolecular radical addition to a quinone to make a seven membered ring, although the intermolecular version has been reported.

Kraus and coworkers have reported addition of radicals, generated by decarboxylation, to substituted and unsubstituted quinones[12,13] (Schemes 3-5). Phenyliodoso

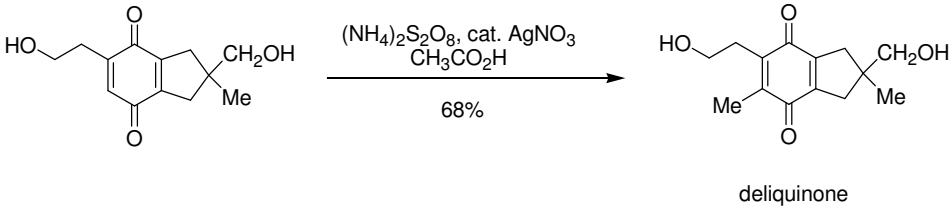
diacetate and the combination of ammonium persulfate in presence of catalytic silver nitrate have both been effectively employed to generate a radical from the carboxylic acid functionality.



Scheme 3



Scheme 4

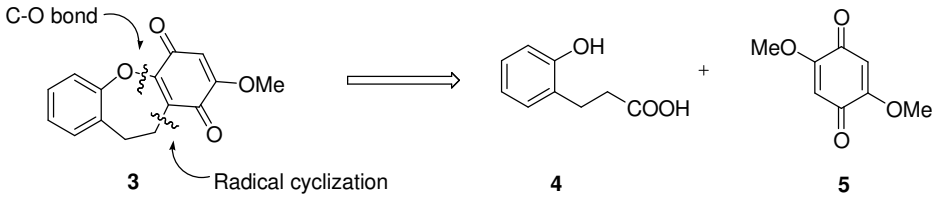


Scheme 5

Results and Discussion

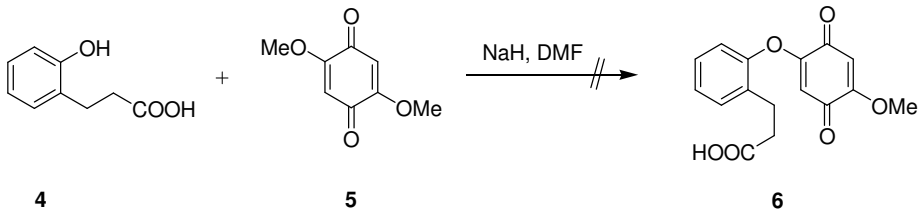
As shown in the retrosynthetic analysis, we envisioned that **3** could be assembled via the C-O bond formation followed by decarboxylative radical cyclization. This pathway

directed us to our starting materials: 3-(2-hydroxyphenyl)-propionic acid **4** and 2,5-dimethoxy-1,4-benzoquinone **5** (Scheme 6).



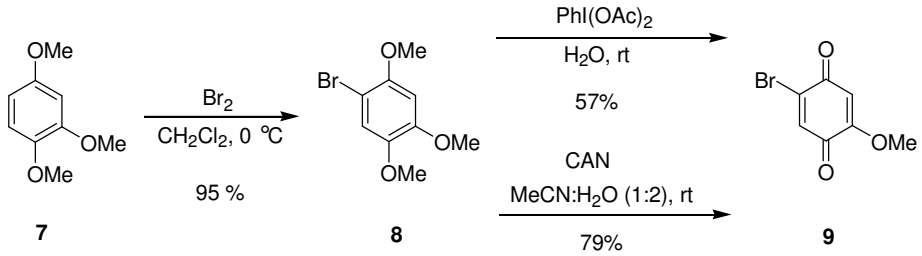
Scheme 6

Due to the extremely poor solubility of 2,5-dimethoxy-1,4-benzoquinone **5** in *N*,*N*-dimethylformamide, the C-O bond forming reaction did not work. **5** was practically insoluble even in other polar solvents like dimethyl sulfoxide, acetone and *N*,*N*-dimethylacetamide. (Scheme 7).



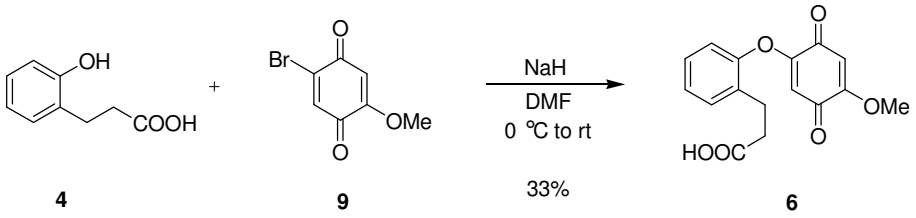
Scheme 7

Therefore, we decided to use 2-bromo-5-methoxy-1,4-benzoquinone **9**, which was made in two steps from 1,2,4-trimethoxybenzene **7** (Scheme 8), as the coupling partner.[14,15]



Scheme 8

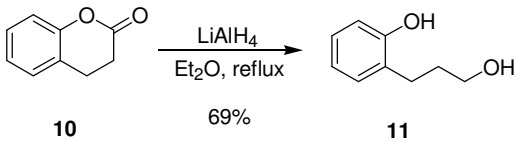
We screened an array of different bases to find the best conditions. Unfortunately, the best yield obtained (using sodium hydride as the base in *N*,*N*-dimethylformamide) was 33% and the reaction was not reproducible (Scheme 9). Presumably, this could be attributed to the poor solubility of the formed dianion.



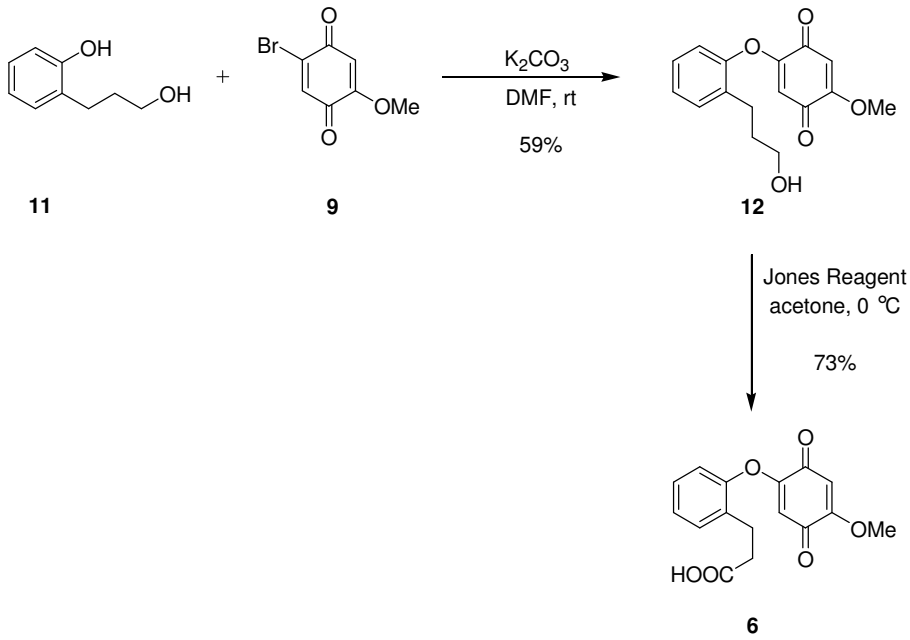
Other bases screened: K_2CO_3, pyridine, triton B, Cs_2CO_3
very low to no yield!

Scheme 9

To circumvent this difficulty, we decided to begin with diol **11**, which was prepared by treating dihydrocoumarin **10** with lithium aluminum hydride[16] (Scheme 10). We generated the monoanion from the diol **11** using potassium carbonate and reacted it with **9** to give the adduct **12** in 59% yield. The primary alcohol **12** was then oxidized to the carboxylic acid **6** using Jones reagent in 73% yield (Scheme 11).

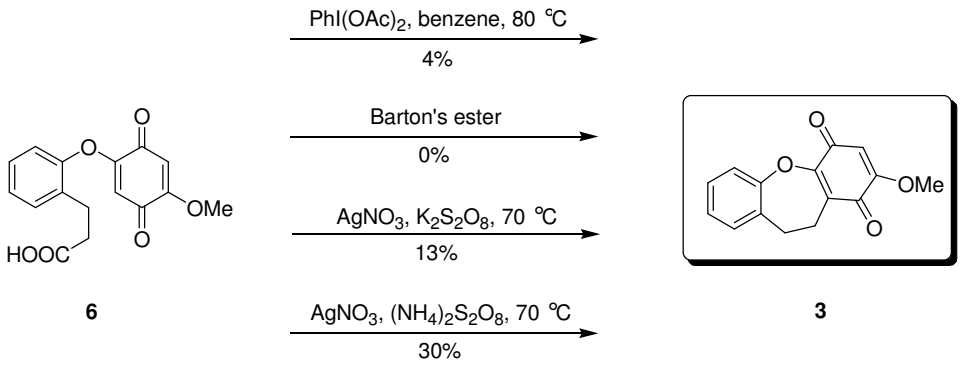


Scheme 10



Scheme 11

The stage was set for us to try the pivotal decarboxylative radical cyclization. First, we attempted to use phenyliodoso diacetate[17,18] to generate the radical from **6**. To our disappointment, it provided a meager 4% yield of the target compound. We employed Barton's ester,[19,20] made from the carboxylic acid, in order to get the seven membered ring. Unfortunately, this method did not provide any desired product. We then decided to use the silver (I)-catalyzed persulfate reaction.[21,22] To our delight, ammonium persulfate with equivalent proportions of the silver salt afforded **3** in 30% yield for that step, which constitutes a 13% overall yield of bauhinoxepin J from **11** and **9**. The identity of synthesized bauhinoxepin J (**4**) was confirmed by comparison of the obtained ^{1}H NMR, ^{13}C NMR, LRMS and HRMS data with the published ones. We also tried using a different counter ion, potassium persulfate, instead of ammonium persulfate. However, it provided only 13% yield of the product (Scheme 12).



Scheme 12

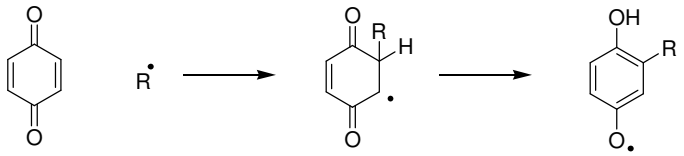
The mechanism of silver (I)-catalyzed persulfate reaction is shown below as proposed by Minisci.[22a]

(i) Generation of carbon centered radical

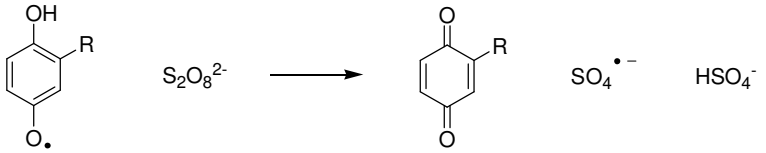
$$S_2O_8^{2-} + 2\ Ag^{+} \longrightarrow 2\ SO_4^{2-} + 2\ Ag^{2+}$$

$$RCO_2H + Ag^{2+} \longrightarrow CO_2 + H^{+} + Ag^{+} + R^{\cdot}$$

(ii) Addition to quinone



(iii) Oxidation of the radical adduct in a redox chain



Conclusion

In summary, we have succesfully synthesized bauhinoxepin J using a novel persulfate-mediated intramolecular decarboxylative radical addition to a quinone. In our

effort to expand this strategy, we are currently working on making xanthones and other biologically important natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or a Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR) unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan TSQ700 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for flash column chromatography.

Compound 3

To a solution of the acid **6** (16 mg, 0.05 mmol) in acetonitrile : water (1:1, 3 mL) were added silver nitrate (9 mg, 0.05 mmol) and ammonium persulfate at rt. After being heated at 70 °C for 5 h, the mixture was cooled to rt. The solvent was evaporated *in vacuo*. The residue was diluted with ethyl acetate and washed with water and saturated aqueous sodium carbonate solution, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash

column chromatography on silica gel (ethyl acetate) to afford **3** (4 mg, 30% yield). IR (thin film): 2915, 2849, 1661, 1607, 1582, 1488, 1463, 1380, 1228, 1193 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.25-7.22 (m, 2H), 7.18 (d, 1H, J = 6.8 Hz), 7.15-7.11 (m, 1H); ^{13}C NMR (100 MHz , $CDCl_3$) δ182.8, 181.9, 158.9, 155.7, 152.9, 133.2, 129.6, 128.0, 126.0, 123.7, 121.2, 105.4, 56.7, 29.9, 26.5; LRMS (EI): *m/z* 256 (M^+, 100%), 241, 115, 69; HRMS (EI) calcd for $C_{15}H_{12}O_4$: 256.0736, found: 256.0740.

Compound 6

To a solution of the alcohol **12** (125 mg, 0.43 mmol) in acetone (10 mL) at 0 $^{\circ}$C was added 8N Jones reagent (1.5 mL). The mixture was stirred at the same temperature for additional 3.5 h upon which 2-propanol was added to consume the excess Jones reagent. The solution was then evaporated *in vacuo*. The resulting residue was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford **6** (96 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.31 (dd, 1H, J = 7.2 Hz, 1.6 Hz), 7.31-7.23 (m, 2H), 7.02 (dd, 1H, J = 8.0 Hz, 1.6 Hz), 5.97 (s, 1H), 5.58 (s, 1H), 3.88 (s, 3H), 2.85 (t, 2H, J = 7.6 Hz), 2.67 (t, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz , $CDCl_3$) δ182.0, 181.4, 177.7, 159.6, 159.1, 150.8, 132.2, 131.2, 128.8, 127.3, 121.5, 108.8, 105.9, 56.9, 34.0, 25.0.

Compound 8

To a solution of 1,2,4-trimethoxybenzene **7** (1g, 5.95 mmol) in dichloromethane (20 mL) at 0 $^{\circ}$C was added bromine (0.34 mL, 6.54 mmol) in dichloromethane (5 mL). After stirring for 2.5 h at the same temperature, saturated aqueous sodium thiosulfate solution was added to quench the reaction. The resulting solution was diluted with dichloromethane, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 3:1) to afford **8**[14] (1.39 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.04 (s, 1H), 6.57 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H).

Compound 9

To a solution of **8** (1g, 4.05 mmol) in acetonitrile : water (1:2, 45 mL) was added ceric ammonium nitrate (6 g, 10.93 mmol). After 3 h at rt, the reaction mixture was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford **9**[15] (0.69 g, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.25 (s, 1H), 6.14 (s, 1H), 3.87 (s, 3H).

Compound 11

To a suspension of lithium aluminum hydride (0.62 g, 16.20 mmol) in diethyl ether (15 mL) at 0 ^{O}C, was added 3,4-dihydrocoumarin **10** (1.71 mL, 13.50 mmol) in diethyl ether (15 mL). The reaction mixture was gently warmed to rt and then heated to reflux for 4 h, after

which, it was cooled to rt and stirred for 7.5 h at rt. 0.6 mL water, 0.6 mL of 15% aqueous sodium hydroxide solution and 1.8 mL water were then added, successively, to quench the reaction. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (dichloromethane : ethyl acetate = 4:1) to afford **11**[16] (1.42 g, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.14-7.10 (m, 2H), 7.05 (s, 1H), 6.90-6.84 (m, 2H), 3.66 (t, 2H, J = 6.0 Hz), 2.79 (t, 2H, J = 6.8 Hz), 2.46 (s, 1H), 1.93-1.86 (m, 2H).

Compound 12

To a solution of 2-(3-hydroxypropyl)-phenol **11** (220 mg, 1.44 mmol) in *N*,*N*-dimethylformamide (5 mL) was added potassium carbonate (200 mg, 1.44 mmol). After 30 min at rt, **9** (300 mg, 1.38 mmol) in *N*,*N* -dimethylformamide (10 mL) was added to the reaction mixture. The mixture was stirred at rt for additional 3.5 h upon which it was quenched with 1N hydrochloric acid. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 1:1) to afford **12** (234 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.31 (dd, 1H, J = 6.8 Hz, 2.4 Hz), 7.28-7.21 (m, 2H), 7.00 (dd, 1H, J = 7.2 Hz, 2.0 Hz), 5.95 (s, 1H), 5.58 (s, 1H), 3.85 (s, 3H), 3.58 (s, 2H), 2.58 (t, 2H, J = 7.2 Hz) 2.23 (s, 1H), 1.83-1.77 (m, 2H); ^{13}C NMR (100 MHz , $CDCl_3$) δ181.9, 181.7, 159.7, 158.9, 150.7, 133.8, 131.6, 128.1, 127.3, 121.1, 108.5, 105.7, 61.2, 56.9, 33.5, 25.8.

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CHAPTER 3: DIRECT SYNTHESIS OF NATURAL PRODUCTS FROM *HYPERICUM* AND *GARCINIA*

Introduction

Natural products derived from plants are increasingly being investigated as leads for pharmaceutical development. Using bio-activity directed fractionation of plants reported to be useful as folk medicines, valuable bioactive compounds have been discovered. The recently found new plant derived pharmaceuticals include Taxotere, Camptosar and teniposide.[1] As part of a multidisciplinary endeavor to identify new antiviral agents from *Echinacea* and *Hypericum*,[2] we required a flexible synthetic route to aurones and benzophenones.

Aurones are less common than flavones and have been reported to arise from chalcones by a biosynthetic pathway catalyzed by aureusidin synthase, a polyphenol oxidase homolog responsible for flower coloration.[3,4] Certain aurones show in vitro activity against *Cryptosporidium parvum* and *Plasmodium falciparum*.[5] Some naturally occurring 4,6-dioxygenated aurones show high-affinity binding to the cytosolic domain of P-glycoprotein and inhibit respiratory functions of mitochondria of *Leishmania* parasites (Figure 1).[6]

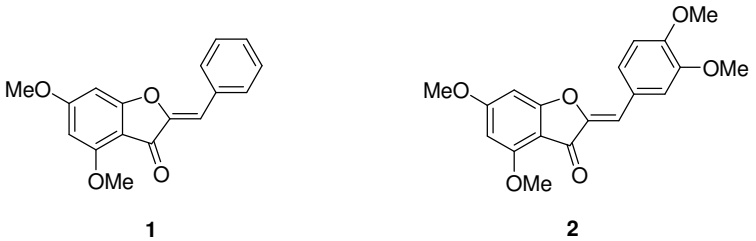
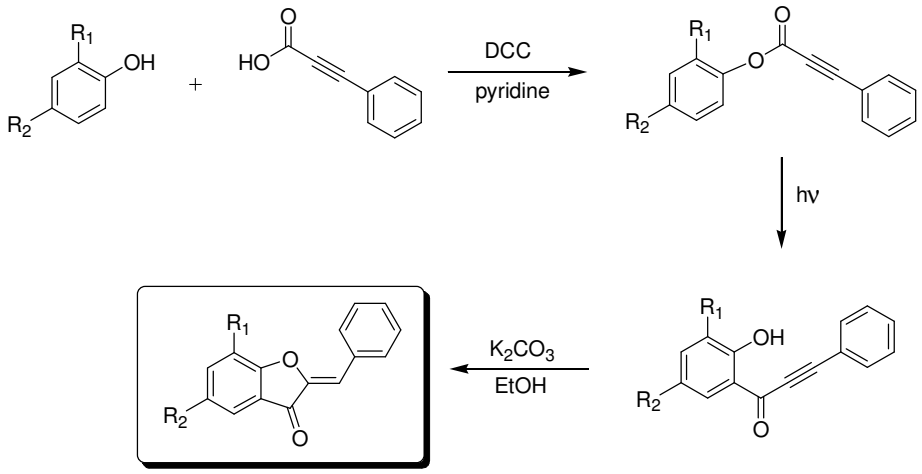
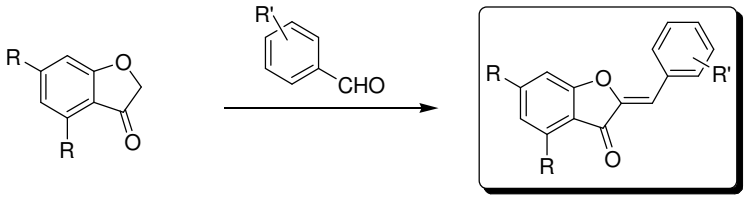


Figure 1

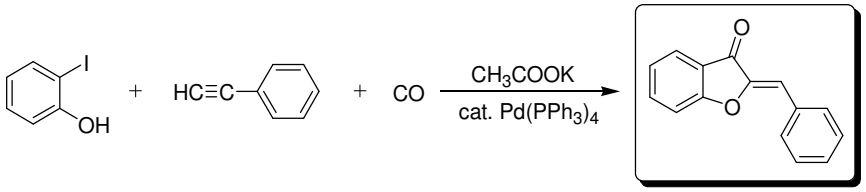
Aurones have been synthesized, chiefly, by three methods. The first one involves cyclization of alkynyl ketones (Scheme 1).[7] The second route to aurones entails condensation of aromatic aldehydes with substituted benzofuran-3-ones, which are used as the key building blocks (Scheme 2).[8] The third method prepares an aurone by reaction of *o*-iodophenol with phenylacetylene in presence of potassium acetate and catalytic $Pd(PPh_3)_4$ under carbon monoxide atmosphere (Scheme 3).[9]



Scheme 1

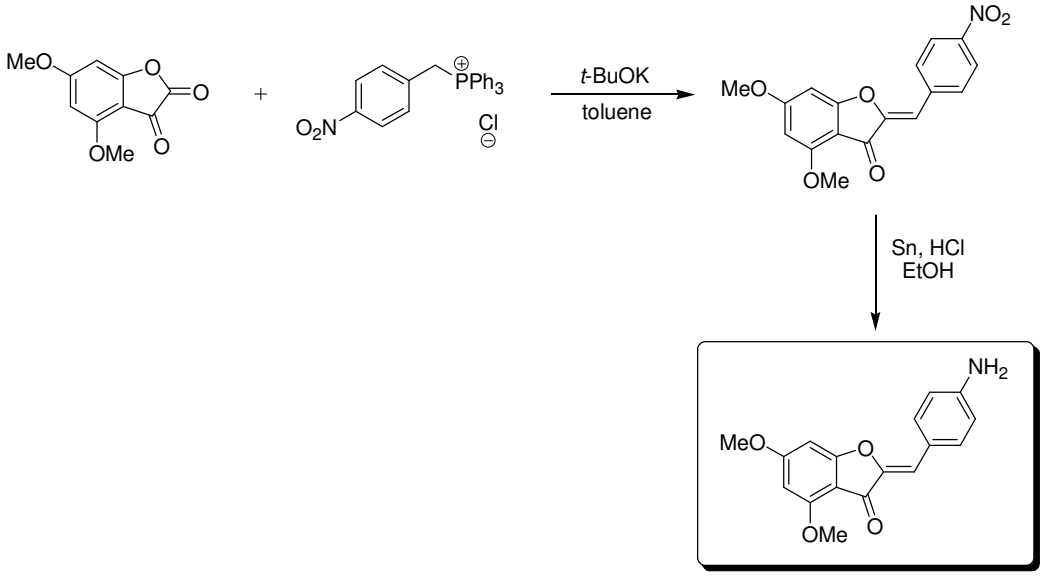


Scheme 2



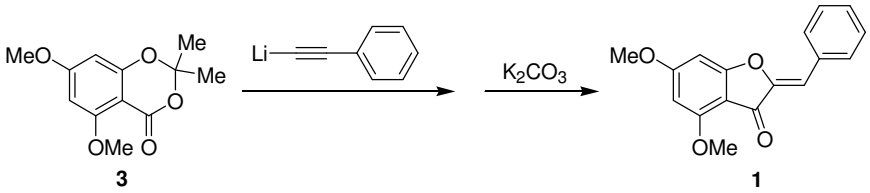
Scheme 3

Our group has successfully developed a novel one-step approach to aurones. A Wittig reaction of 4-nitrobenzyltriphenylphosphorane with 4,6-dimethoxybenzofuran-2,3-dione affords an aurone in a single step. The nitro group is reduced by tin and hydrochloric acid to provide an amino aurone (Scheme 4).



Scheme 4

Recently, our group has also developed a novel way to make aurones using 1,3-benzodioxin-4-one **3** as the key starting unit. Reaction of acetonide **3** with phenylacetylide followed by cyclization of the intermediate using potassium carbonate furnished aurone **1** (Scheme 5).[10]



Scheme 5

Benzophenones, especially the prenylated ones, derived from *Garcinia* species (Figure 2) often show a broad range of pharmacological and biological activities like antioxidant, anti-inflammatory, antimicrobial, cytotoxic and inhibitory effects on monoamine oxidase and xanthine oxidase.[11]

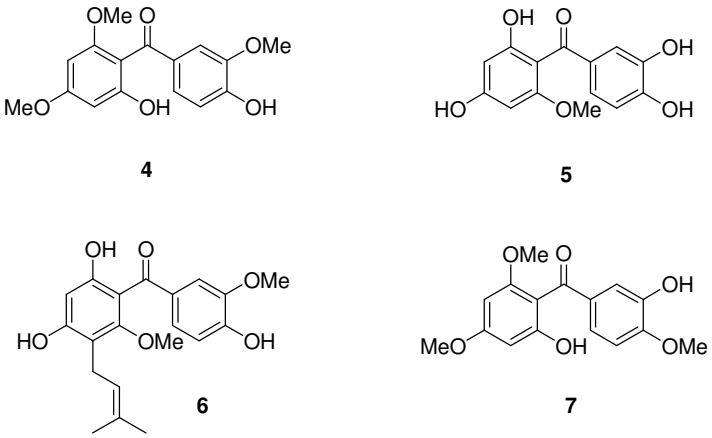
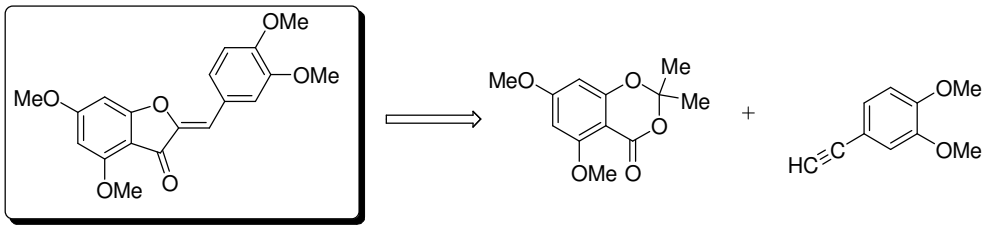


Figure 2

The key structural feature of these benzophenones is the multiple oxygen atoms attached to the phenyl rings, of which a few functional groups are methylated. The disposition of these groups on both aromatic rings makes them interesting molecules to synthesize using a common methodology. Herein, we describe syntheses of a naturally occurring aurone **2** (Scheme 9) along with two other plant derived benzophenones **4** and **5** (Schemes 11 and 14) using 1,3-benzodioxin-4-ones and substituted phenyl acetylene or aryl bromide species.

Results and Discussion

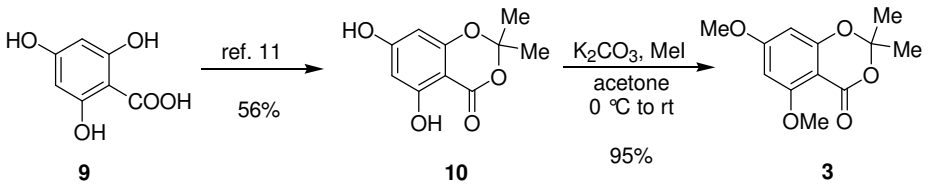
As shown in the retrosynthetic analysis, we envisioned that aurone **2** could be assembled via a reaction of 1,3-benzodioxin-4-one **3** with 3,4-dimethoxyphenyl acetylene (**8**) (Scheme 6).



2 **3** **8**

Scheme 6

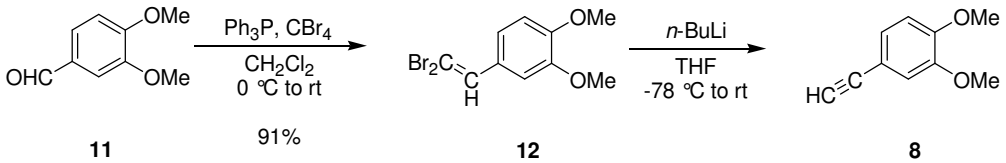
The 1,3-benzodioxin-4-one **3** could in turn be synthesized from the commercially available 2,4,6-trihydroxybenzoic acid (**9**) (Scheme 7). The acetonide **10** was synthesized from **9** using thionyl chloride, acetone and catalytic *N*,*N*-dimethylaminopyridine in 1,2-dimethoxyethane according to the procedure reported by Kamisuki and coworkers.[12] Diol **10** was methylated using methyl iodide and potassium carbonate in acetone to furnish 1,3-benzodioxin-4-one **3** in 95% isolated yield (Scheme 7).[10]



9 **10** **3**

Scheme 7

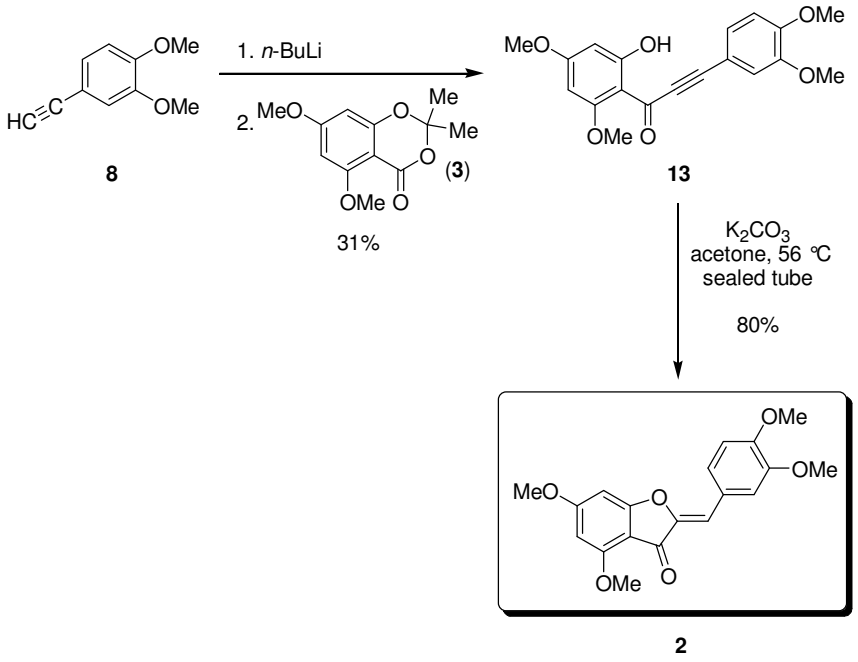
The 3,4-dimethoxyphenylacetylene (**8**) was made from commercially available 3,4-dimethoxybenzaldehyde (**11**) using the Corey-Fuchs sequence in two steps (Scheme 8).[13]



11 **12** **8**

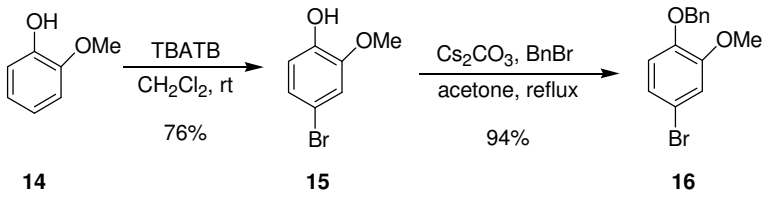
Scheme 8

Treatment of acetonide **3** with the lithium anion of **8** generated the acetylenic ketone **13**, which readily cyclized to aurone **2** upon reaction with potassium carbonate in acetone at 56 °C under sealed tube conditions (Scheme 9). The exclusive 5-exo reaction pathway has precedent in the work of Garcia.[7] The identity of synthesized aurone **2** was confirmed by comparison of the obtained ^{1}H NMR, LRMS and HRMS data with the published ones.[14]



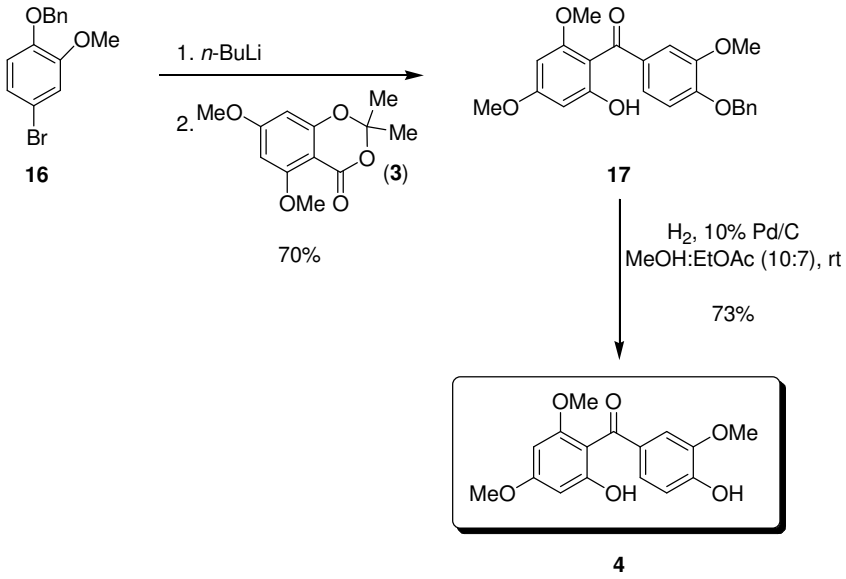
Scheme 9

In the second part of the project, we employed the above methodology to synthesize natural products **4** and **5** with benzophenone skeleton and thus demonstrated versatility of the strategy. Guaiacol (**14**) was selectively brominated at the position para to the hydroxyl group using tetrabutylammoniumtribromide (TBATB) in dichloromethane to give **15** in 76% yield.[15] Benzyl protection of the hydroxyl group in **15** afforded **16** in 94% isolated yield (Scheme 10).[16]



Scheme 10

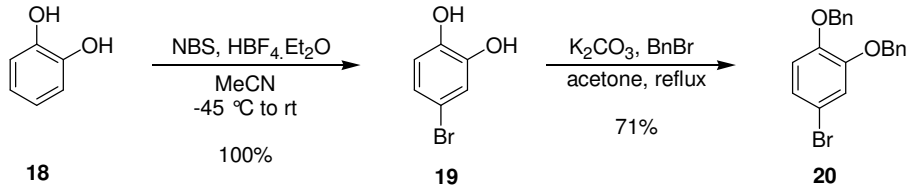
The bromo compound **16** was lithiated and allowed to react with **3** to give benzophenone **17** in 70% yield. Removal of the benzyl protecting group in **17** using H_2 and 10% palladium on carbon afforded the natural product **4** in 73% yield (Scheme 11). The identity of synthesized benzophenone **4** was confirmed by comparison of the obtained ^{1}H NMR, ^{13}C NMR, LRMS and HRMS data with the published ones.[17]



Scheme 11

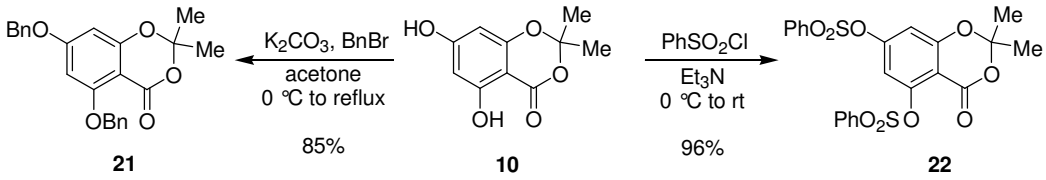
After successfully employing the methodology to synthesize **4**, we directed our attention to the natural product **5**. The first component, **20**, was prepared in two steps starting from catechol (**18**). Catechol was mono-brominated in quantitative yield using *N*-bromosuccinimide and tetrafluoroboric acid (54 weight percent solution in diethyl ether) in

acetonitrile.[18,19] Benzyl protection of diol **19** using benzyl bromide and potassium carbonate provided **20** in 71% yield (Scheme 12).[19]



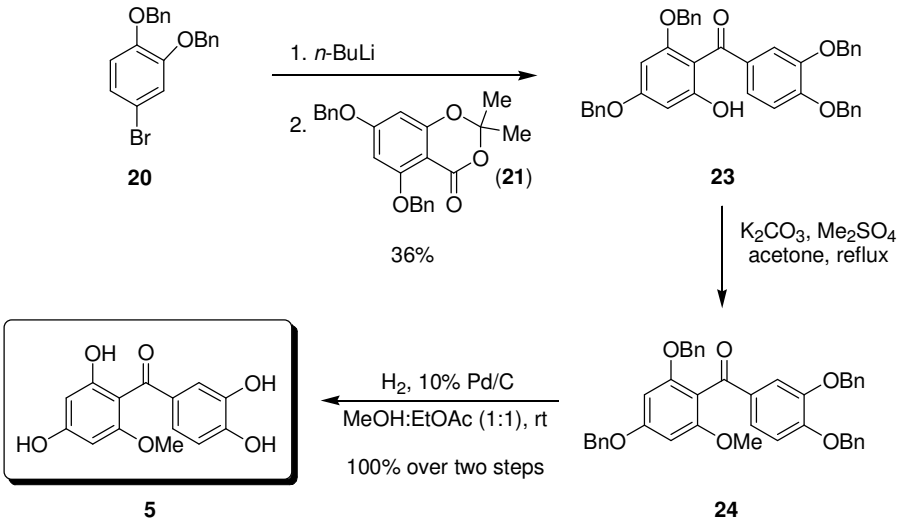
Scheme 12

Benzylation of diol **10** using benzyl bromide and potassium carbonate afforded 1,3-benzodioxin-4-one **21**[20] in 85% yield. Benzenesulfonylation of **10** using benzenesulfonyl chloride and triethylamine provided **22** in 96% yield (Scheme 13).



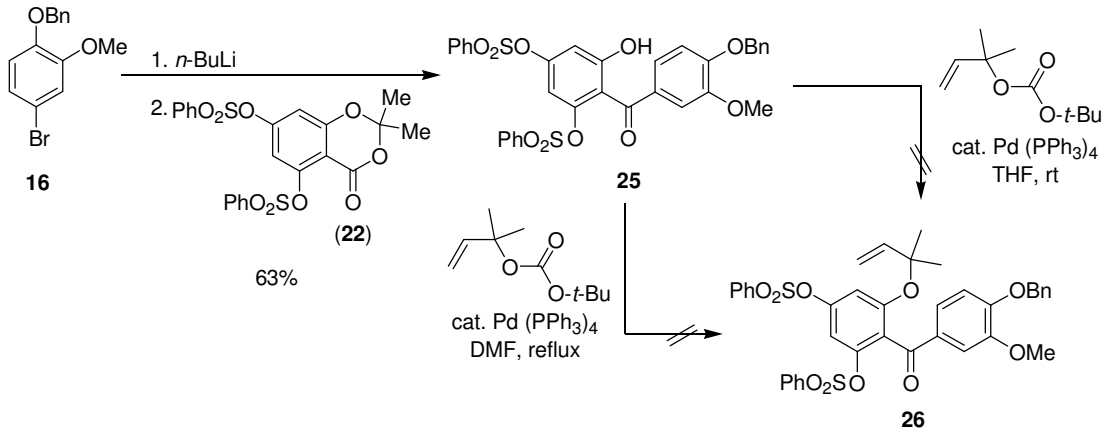
Scheme 13

Having the two components for the reaction ready, **20** was lithiated and allowed to react with acetonide **21** to provide benzophenone **23** in 36% yield. Methylation of **23** using dimethyl sulfate and potassium carbonate in acetone followed by removal of the benzyl protecting groups in **24** afforded the target molecule **5** in quantitative yield over two steps (Scheme 14). The identity of synthesized benzophenone **5** was confirmed by comparison of the obtained ^{1}H NMR, ^{13}C NMR, LRMS and HRMS data with the published ones.[21]



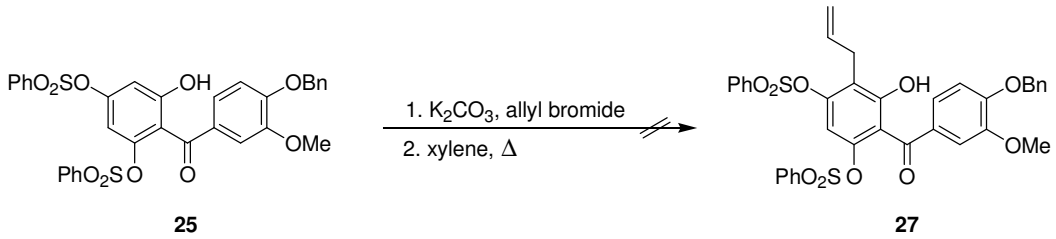
Scheme 14

In a parallel effort, we tried to apply the above developed strategy to synthesize the natural product **6**. With that in mind, the lithium anion of **16** was made to react with 1,3-benzodioxin-4-one **22** to furnish benzophenone **25** in 63% isolated yield. Unfortunately, our attempts to make the precursor **26** for the Claisen rearrangement were not fruitful (Scheme 15).



Scheme 15

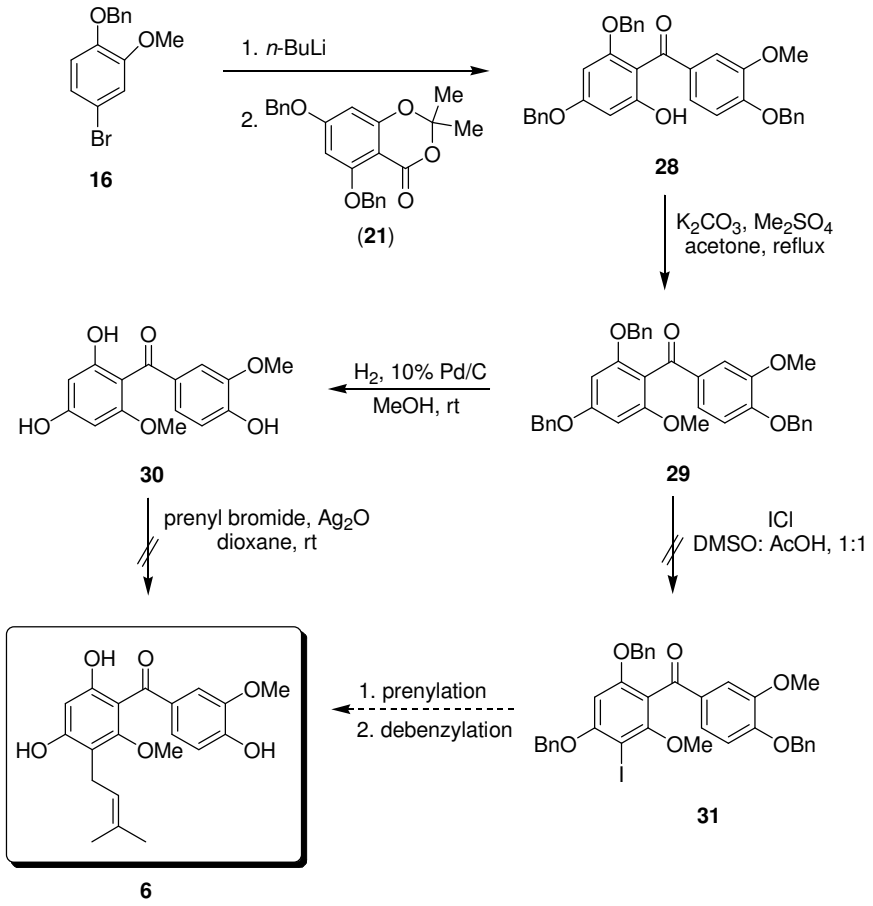
Adduct **25** was O-allylated using allyl bromide and potassium carbonate. However, the attempted Claisen rearrangement failed, presumably due to decomposition of the synthesized intermediate at 185 °C under sealed tube conditions (Scheme 16). To avoid subjecting the compounds to the harsh thermal conditions involved in Claisen rearrangement, we planned to introduce the prenyl group by a different approach.



25 **27**

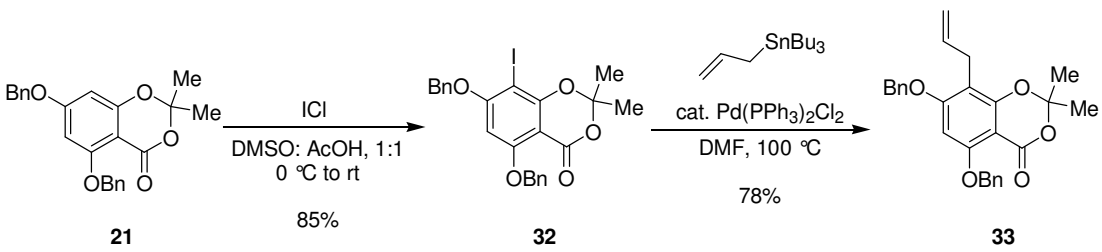
Scheme 16

Compound **16** was lithiated and allowed to react with acetonide **21** to afford benzophenone **28**, which was methylated using dimethyl sulfate and potassium carbonate to provide the intermediate **29**. Iodination of **29** was not regioselective and led to multiple iodinated products. Removal of the benzyl protecting groups in **29** using H_2 and 10% palladium on carbon provided **30**. Unfortunately, the attempted regioselective prenylation led to decomposition of the starting material **30** (Scheme 17).



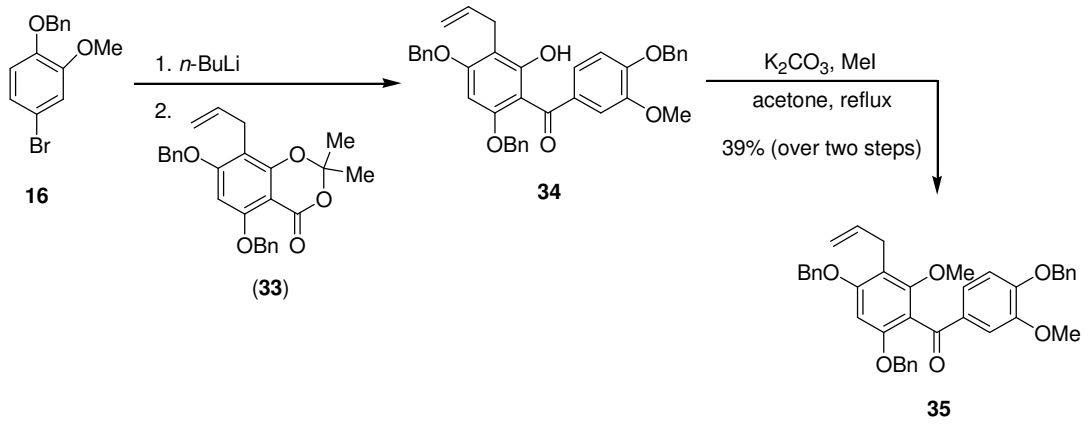
Scheme 17

In an altered approach to get the target compound **6**, acetonide **21** was regioselectively iodinated using iodine monochloride to provide the iodo compound **32** in 85 % isolated yield.[22] Stille coupling of **32** with allyltributylstannane afforded the allylated product **33** in 78% yield (Scheme 18).[23]



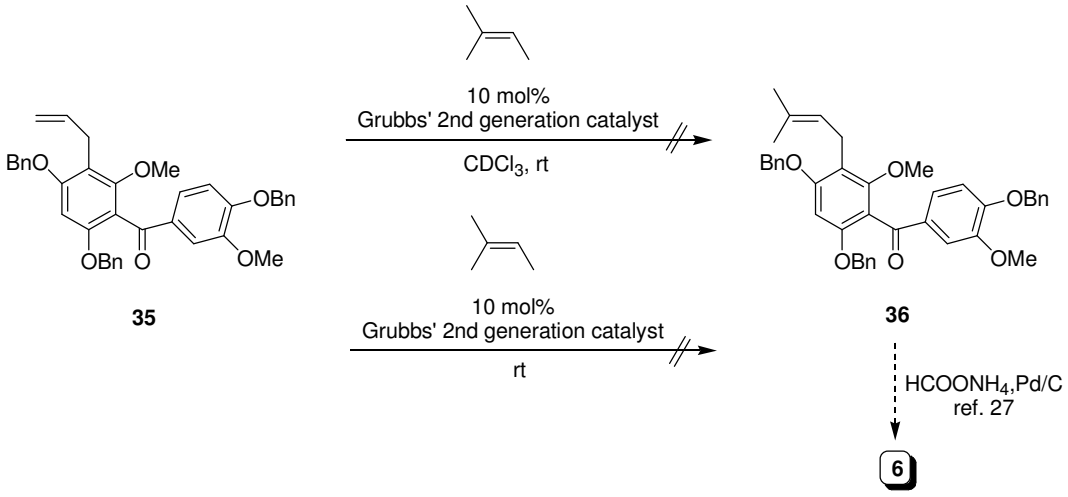
Scheme 18

Compound **16** was made to react with the allylated compound **33** to provide benzophenone **34**, which was methylated using methyl iodide and potassium carbonate in acetone to afford **35** in 39% yield over two steps (Scheme 19).



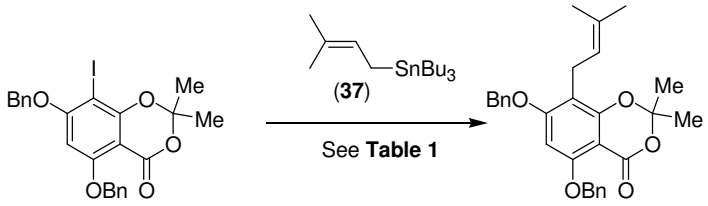
Scheme 19

At this stage, we were only two steps away from the target molecule **6**. We tried converting the allyl group of **35** into a prenyl group using cross metathesis.[24] To our dismay, both attempts to react **35** with 2-methyl-2-butene, under solvent as well as solvent-free (neat) conditions, returned the starting material (Scheme 20).



Scheme 20

In a different route to target molecule **6**, we planned to make the prenyl compound **38** first. Prenylation of the iodo compound **32**, however, was not straight forward. Although the allylation of **32** under the Stille coupling conditions went smoothly (Scheme 18), the coupling with prenyltributylstannane[25,26] (**37**) was far more challenging (Table 1).



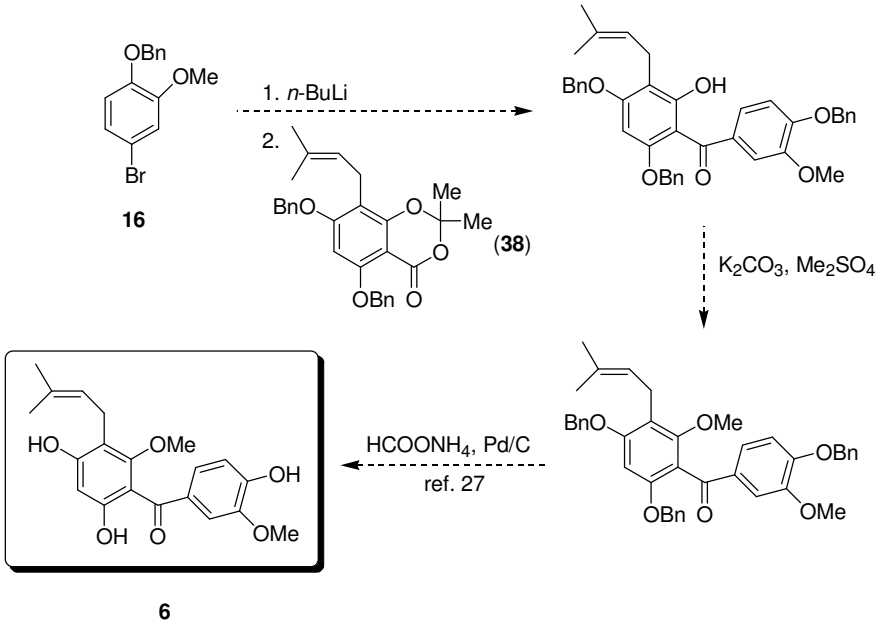
32 **38**

Prenylation condition	Outcome
1. cat. Pd_2dba_3, cat. P(2-furyl)$_3$, CsF, NMP, reflux	deiodinated compd + SM recovered
2. cat. Pd_2dba_3, cat. P(2-furyl)$_3$, CsF, NMP, 100 °C, sealed tube	SM recovered
3. cat. Pd_2dba_3, cat. $Pd(PPh_3)_2Cl_2$, cat. P(2-furyl)$_3$, CsF, DMF, 100 °C	Trace amount of pdt
4. cat. $Pd(PPh_3)_2Cl_2$, cat. P(2-furyl)$_3$, CsF, DMF,100 °C	37% yield + SM recovered
5. cat. $Pd(PPh_3)_2Cl_2$, cat. P(2-furyl)$_3$, CsF, DMF, microwave, 150 °C	compound decomposed

Table 1

We tried a variety of different conditions by modifying the catalyst from palladium (0) to palladium (II), changing the solvent from *N*-Methylpyrrolidone to *N,N*-dimethylformamide and also varying the mode of heating from reflux conditions to heating in a sealed tube to making use of the microwave. Either starting material was recovered (entries

1 and 2, Table 1) or the harsh thermal conditions led to decomposition (entry 5). The entry 4 was the sole acceptable one, which gave the desired product **38** in 37% yield. The pathway we intend to follow from **38** to the target compound **6** has been outlined in Scheme 21.



Scheme 21

Conclusion

In summary, we have successfully developed a methodology to synthesize aurones and benzophenones, both of which have been reported to exhibit potent biological activity. Using 1,3-benzodioxin-4-ones as our key unit gives us a useful intermediate for the synthesis of other structurally related natural products in a direct approach.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. All experiments were performed under argon atmosphere unless

otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or a Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR) unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan TSQ700 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for flash column chromatography.

Compound 2

To a solution of **13** (25 mg, 0.073 mmol) in acetone (5 mL), taken in a sealable tube, was added potassium carbonate (31 mg, 0.22 mmol) at rt. The reaction mixture was heated in the sealed tube for 6 h at 56 °C after which it was cooled to rt, passed through a pad of Celite and then evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 1:4) to afford aurone **2**[13] (20 mg, 80% yield). ^1H NMR (400 MHz, $CDCl_3$) δ7.46-7.44 (m, 2H), 6.93 (d, 1H, J = 8.4 Hz), 6.75 (s, 1H), 6.36 (d, 1H, J = 1.6 Hz), 6.14 (d, 1H, J = 1.6 Hz), 3.97 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H); LRMS (EI): *m/z* 342 (M^+, 100%), 311, 180; HRMS (EI) calcd for $C_{19}H_{18}O_6$: 342.1103, found: 342.1108.

Compound 3

To a solution of **10** (0.36 g, 1.7 mmol) in acetone (20 mL) was added potassium carbonate at rt. After cooling to 0 °C, methyl iodide (1.1 mL, 17 mmol) was added and the reaction mixture was gradually warmed to rt and stirred overnight. The reaction was quenched with 0.5 M acetic acid. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford the dimethoxy compound **3**[9] (0.38 g, 95% yield) as a white solid: mp 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ6.15 (d, 1H, J = 2.0 Hz), 6.08 (d, 1H, J = 2.0 Hz), 3.93 (s 3H), 3.85 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.6, 163.0, 160.0, 158.5, 105.2, 96.8, 94.0, 93.6, 56.5, 55.9, 25.8; LRMS (EI): *m/z* 238 (M^+), 180 (100%), 152, 137; HRMS (EI) calcd for $C_{12}H_{14}O_5$: 238.0841, found: 238.0845.

Compound 4

To a solution of **17** (50 mg, 0.13 mmol) in methanol : ethyl acetate (10:7, 17 mL) was added 10 % palladium on carbon (30 mg). After 18 h at rt under H_2 atmosphere (H_2 balloon), the reaction mixture was passed through a pad of Celite and then evaporated *in vacuo*. The residue was purified by preparative TLC on silica gel (hexanes : ethyl acetate = 2:1) to afford the natural product **4**[16] (28 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ11.64 (s, 1H), 7.25 (d, 1H, J = 2.0 Hz), 7.16 (dd, 1H, J = 8.4 Hz, 2.0 Hz), 6.89 (d, 1H, J = 8.4 Hz), 6.18 (d, 1H, J = 2.4 Hz), 6.04 (s, 1H), 5.97 (d, 1H, J = 2.0 Hz), 3.93 (s, 3H), 3.86 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ197.4, 166.0, 165.1, 161.6, 149.2, 146.1, 133.5, 124.3, 113.4,

111.0, 106.0, 93.9, 91.6, 56.3, 55.8, 55.4; LRMS (EI): *m/z* 304 (M^+), 303 (100%), 287, 181; HRMS (EI) calcd for $C_{16}H_{16}O_6$: 304.0947, found: 304.0952.

Compound 5

To a solution of **24** (153 mg, 0.24 mmol) in methanol : ethyl acetate (1:1, 30 mL) was added 10 % palladium on carbon (100 mg). After 6 h at rt under H_2 atmosphere (H_2 balloon), the reaction mixture was passed through a pad of Celite and then evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford the natural product **5**[20] (66 mg, 100% yield over two steps). ^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (d, 1H, J = 2.0 Hz), 7.09 (dd, 1H, J = 8.4 Hz, 2.0 Hz), 6.73 (d, 1H, J = 8.4 Hz), 5.96 (d, 1H, J = 5.6 Hz), 3.55 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 198.3, 163.2, 161.7, 160.8, 151.7, 146.0, 133.2, 124.3, 117.4, 115.6, 108.7, 96.7, 92.2, 56.0; LRMS (EI): *m/z* 276 (M^+, 100%), 260, 167; HRMS (EI) calcd for $C_{14}H_{12}O_6$: 276.0634, found: 276.0638.

Compound 8

To a solution of **12** (1.75 g, 5.43 mmol) in tetrahydrofuran (50 mL) at -78 $^\circ$C was added *n*-BuLi (2.5 M solution in hexanes, 5.44 mL, 13.59 mmol). The reaction mixture was gradually warmed to rt and stirred overnight upon which it was quenched with saturated aqueous ammonium chloride solution. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 6:1) to afford **8**[12] as a pale yellow

solid: mp 66-68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.12 (dd, 1H, J = 8.1 Hz, 1.8 Hz), 7.0 (d, 1H, J = 1.8 Hz), 6.81 (d, 1H, J = 8.1 Hz), 3.90 (s, 3H), 3.89 (s, 3H), 3.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ149.9, 148.7, 125.6, 114.8, 114.3, 111.0, 83.9, 75.9, 56.0.

Compound 10[11]**:** ^{1}H NMR (300 MHz, acetone-d_6) δ10.45 (s, 1H), 9.74 (br s, 1H), 6.07 (d, 1H, J = 2.4 Hz), 6.00 (d, 1H, J = 2.4 Hz), 1.71 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.2, 165.8, 164.1, 158.2, 107.7, 98.0, 96.3, 93.1, 25.7.

Compound 12

To a solution of 3,4-dimethoxybenzaldehyde **11** (1 g, 6.02 mmol) in dichloromethane (50 mL) was added triphenylphosphine (3.16 g, 12.05 mmol) at rt. After cooling to 0 °C, carbon tetrabromide (2.2 g, 6.63 mmol) in dichloromethane (10 mL) was added dropwise. The reaction mixture was stirred for 2 h at 0 °C and then 2 h at rt before being quenched by adding water. The resulting solution was diluted with dichloromethane, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 9:1) to afford the dibromo compound **12**[12] (1.77 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.42 (s, 1H), 7.2 (d, 1H, J = 1.6 Hz), 7.11 (dd, 1H, J = 8.4 Hz, 2.0 Hz), 6.87 (d, 1H, J = 8.4 Hz), 3.91 (s, 3H), 3.90 (s, 3H).

Compound 13

To a solution of 3,4-dimethoxyphenylacetylene (**8**) (200 mg, 1.24 mmol) in tetrahydrofuran (10 mL) at 0 °C was added *n*-BuLi (2.5 M solution in hexanes, 0.5 mL, 1.24 mmol). After 1 h at 0 °C, the solution was cooled further to – 78 °C and **3** (150 mg, 0.62 mmol) in tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was gradually warmed to rt and stirred overnight upon which it was quenched with 4.3 N acetic acid. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified twice by flash column chromatography on silica gel (hexanes : ethyl acetate = 6:1 and dichloromethane : ethyl acetate, 19:1) to afford the acetylenic ketone **13** (66 mg, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.28-7.27 (m, 1H), 7.14 (s, 1H), 6.89 (d, 1H, J = 8.4 Hz), 6.09 (d, 1H, J = 2.4 Hz), 5.96 (d, 1H, J = 2.0 Hz), 3.95 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H).

Compound 15

To a solution of guaiacol (**14**) (0.65 mL, 8.06 mmol) in CH_2Cl_2 (80 mL) was added tetrabutylammonium tribromide (3.88 g, 8.06 mmol) at rt. After stirring for 16 h at rt, the reaction mixture was quenched with saturated aqueous sodium thiosulfate solution. The resulting solution was diluted with dichloromethane, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 6:1) to afford the bromo compound **15**[14] (1.23 g, 76% yield). ^{1}H NMR (300

MHz, $CDCl_3$) δ7.01 (d, 1H, J = 2.4 Hz), 6.98 (t, 1H, J = 2.4 Hz), 6.81 (d, 1H, J = 8.1 Hz), 5.54 (s, 1H), 3.90 (s, 3H).

Compound 16

To a solution of **15** (5.5 g, 27.0 mmol) in acetone (150 mL) were added cesium carbonate (9.24 g, 28.4 mmol) and benzylbromide (3.06 mL, 25.7 mmol) at rt. After boiling for 4.5 h, the reaction mixture was cooled to rt, passed through a pad of Celite and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 19:1) to afford the benzyloxy compound **16**[15] (7.05 g, 94% yield) as a white solid: mp 59-61 °C (lit[15] 61-61.2 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ7.44-7.32 (m, 5H), 7.01 (d, 1H, J = 2.0 Hz), 6.97 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 6.75 (d, 1H, J = 8.4 Hz), 5.14 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ150.6, 147.5, 136.8, 128.8, 128.1, 127.4, 123.5, 115.4, 115.3, 113.5, 71.3, 56.3.

Compound 17

To a solution of **16** (295 mg, 1.01 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *n*-BuLi (2.5 M solution in hexanes, 0.38 mL, 0.94 mmol). After stirring for 1.5 h at -78 °C was added **3** (80 mg, 0.34 mmol) in tetrahydrofuran (5 mL). The reaction mixture was warmed to -50 °C over 45 min and then quenched with glacial acetic acid in tetrahydrofuran. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes :

ethyl acetate = 9:1 to 4:1) to afford benzophenone **17** (93 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ11.75 (s, 1H), 7.46-7.30 (m, 5H), 7.23 (d, 1H, J = 1.6 Hz), 7.15 (dd, 1H, J = 8.4 Hz, 1.6 Hz), 6.87 (d, 1H, J = 8.4 Hz), 6. 18 (d, 1H, J = 2.4 Hz), 5.96 (d, 1H, J = 2.4 Hz), 5.23 (s, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 3.50 (s, 3H).

Compound 19

To a solution of catechol (**18**) (1g, 9.08 mmol) in acetonitrile (10 mL) at -45 $^\circ$C, were added tetrafluoroboric acid in diethyl ether (54 wt% solution in diethyl ether, 2.25 mL, 16.35 mmol) and *N*-bromosuccinimide (1.70 g, 9.54 mmol) successively. The reaction mixture was allowed to gradually warm to rt and stirred for 12 h, after which it was poured into water and extracted with diethyl ether. The ether layer was washed with 4% aqueous sodium bisulfite solution and brine, successively. The organic layer was then dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 3:2) to afford the bromo compound **19**[18] (1.72 g, 100% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.03 (d, 1H, J = 2.4 Hz), 6.93 (dd, 1H, J = 8.4 Hz, 2.0 Hz), 6.76 (d, 1H, J = 8.4 Hz), 5.79 (br s, 1H), 5.62 (br s, 1H).

Compound 20

To a solution of **19** (1.70 g, 8.99 mmol) in acetone (70 mL) were added potassium carbonate (4.96 g, 35.96 mmol) and benzyl bromide (4.06 mL, 34.16 mmol). After boiling for 7 h, the reaction mixture was cooled to rt, passed through a pad of Celite and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes :

ethyl acetate = 19:1) to afford compound **20**[18] (2.34 g, 71% yield) as a white solid: mp 65-67 °C (lit[18] 64-66 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.47-7.33 (m, 10H), 7.09 (d, 1H, J = 2.4 Hz), 7.01 (dd, 1H, J = 8.4 Hz, 2.4 Hz), 6.81 (d, 1H, J = 8.8 Hz), 5.14 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ150.0, 148.3, 137.0, 136.7, 128.8, 128.7, 128.2, 128.1, 127.5, 127.4, 124.3, 118.2, 116.6, 113.6, 71.6, 71.5.

Compound 21

To a solution of diol **10** (300 mg, 1.43 mmol) in acetone (20 mL) at 0 °C, were added potassium carbonate (986 mg, 7.14 mmol) and benzyl bromide (0.68 mL, 5.71 mmol). The reaction mixture was gradually warmed to rt and then heated to reflux for 18 h after which the reaction mixture was cooled to rt, passed through a pad of Celite and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 3:1) to afford acetonide **21**[19] (476 mg, 85% yield) as a pale yellow solid: mp 117-119 °C (lit[19] 119-120 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.55-7.53 (m, 2H), 7.42-7.29 (m, 8H), 6.27 (d, 1H, J = 2.4 Hz), 6.16 (d, 1H, J = 2.4 Hz), 5.20 (s, 2H), 5.04 (s, 2H), 1.72 (s, 6H); ^{13}C NMR (100 MHz , $CDCl_3$) δ165.4, 161.8, 159.5, 158.1, 136.3, 135.7, 128.9, 128.8, 128.6, 128.0, 127.8, 126.8, 105.2, 97.5, 96.1, 94.8, 70.7, 70.6, 25.8.

Compound 22

To a solution of **10** (0.52 g, 2.48 mmol) in tetrahydrofuran (20 mL) was added triethylamine (1.73 mL, 12.4 mmol). The reaction solution was cooled to 0 °C, benzenesulfonyl chloride (1.43 mL, 11.2 mmol) was added and the reaction mixture was

gradually warmed to rt overnight. The reaction was quenched with 0.5 M acetic acid and the resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford compound **22** (1.16 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87-8.00 (m, 4H), 7.54-7.78 (m, 6H), 6.77 (s, 1H), 6.89 (s, 1H), 1.62 (s, 6H).

Compound 23

To a solution of **20** (850 mg, 2.31 mmol) in tetrahydrofuran (20 mL) at -78 $^\circ$C was added *n*-BuLi (2.5 M solution in hexanes, 0.86 mL, 2.15 mmol). After stirring for 1.5 h at –78 $^\circ$C, **21** (300 mg, 0.77 mmol) in tetrahydrofuran (10 mL) was added and the reaction mixture was warmed to rt over 4 h. After stirring for a further 2.5 h at rt, the reaction was quenched with saturated aqueous ammonium chloride solution. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 9:1) to afford benzophenone **23** (170 mg, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.47-7.12 (m, 20H), 6.81 (d, 1H, J = 8.4 Hz), 6.71 (d, 2H, J = 6.3 Hz), 6.28 (d, 1H, J = 2.1 Hz), 6.08 (d, 1H, J = 2.1 Hz), 5.13 (s, 2H), 5.11 (s, 2H), 5.08 (s, 2H), 4.68 (s, 2H).

Compound 24

To a solution of **23** (150 mg, 0.24 mmol) in acetone (10 mL) were added potassium carbonate (133 mg, 0.96 mmol) and dimethyl sulfate (0.08 mL, 0.84 mmol). After heating to reflux for 9 h, the reaction mixture was cooled to rt, passed through a pad of Celite and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 3:1) to afford compound **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.62-7.16 (m, 20H), 7.08-7.02 (m, 2H), 6.88 (d, 1H, J = 8.4 Hz), 6.24 (s, 2H), 5.23 (s, 2H), 5.16 (s, 2H), 5.07 (s, 2H), 4.92 (s, 2H), 3.66 (s, 3H); LRMS (EI): *m/z* 636 (M^+), 545, 372, 347, 181 (100%); HRMS (EI) calcd for $C_{42}H_{36}O_6$: 636.2512, found: 636.2522.

Compound 25

To a solution of **16** (610 mg, 2.08 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *n*-BuLi (2.5 M solution in hexanes, 0.79 mL, 1.98 mmol). After stirring for 2 h at – 78 °C, **22** (255 mg, 0.52 mmol) in tetrahydrofuran (10 mL) was added and the reaction mixture was warmed to 5 °C over 3 h. The reaction was quenched with saturated aqueous ammonium chloride solution. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 2:1) to afford benzophenone **25** (213 mg, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ9.97 (s, 1H), 7.34-7.95 (m, 15H), 7.20 (d, 1H, J = 1.8 Hz), 7.08 (dd, 1H, J = 8.4 Hz, 2.1 Hz), 6.80 (d, 1H, J = 8.4 Hz), 6.68 (d, 1H, J = 2.4 Hz), 6.52 (d, 1H, J = 2.1 Hz), 5.21 (s, 2H), 3.91 (s, 3H).

Compound 30

To a solution of **16** (450 mg, 1.54 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *n*-BuLi (2.5 M solution in hexanes, 0.58 mL, 1.46 mmol). After 1.5 h at -78 °C, **21** (150 mg, 0.39 mmol) in tetrahydrofuran (10 mL) was added and the reaction mixture was warmed to -45 °C over 45 min. The reaction was quenched with glacial acetic acid in tetrahydrofuran and the resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo* to give crude benzophenone **28**. 1H NMR (400 MHz, $CDCl_3$) δ 7.13-7.48 (m, 15H), 6.72-6.79 (m, 3H), 6.29 (d, 1H, J = 2.0 Hz), 6.14 (d, 1H, J = 2.0 Hz), 5.12 (s, 2H), 5.11 (s, 2H), 4.81 (s, 2H), 3.87 (s, 3H). The crude compound **28** was used directly for the next step without further purification.

To the above crude compound **28** taken up in acetone (10 mL) were added potassium carbonate (100 mg) and dimethyl sulfate (0.05 mL) and the reaction mixture was heated to reflux for 3 h. The reaction solution was cooled to rt, passed through a pad of Celite and evaporated *in vacuo* to give the crude compound **29**. 1H NMR (400 MHz, $CDCl_3$) δ7.17-7.64 (m, 15H), 7.03-7.08 (m, 2H), 6.81 (d, 1H, J = 8.4 Hz), 6.25 (s, 2H), 5.22 (s, 2H), 5.05 (s, 2H), 4.96 (s, 2H), 3.94 (s, 3H), 3.69 (s, 3H). The crude compound **29** was used directly for the next step without further purification.

To a solution of the above crude compound **29** in methanol (10 mL) was added 10 % palladium on carbon (50 mg). After stirring for 16 h at rt under H_2 atmosphere (H_2 balloon), the reaction mixture was passed through a pad of Celite and then evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford

30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 1H, J = 2.0 Hz), 7.14 (dd, 1H, J = 8.4 Hz, 2.0 Hz), 6.87 (d, 1H, J = 8.0 Hz), 6.09 (d, 1H, J = 2.0 Hz), 5.95 (d, 1H, J = 2.0 Hz), 3.92 (s, 3H), 3.52 (s, 3H).

Compound 32

To a solution of **21** (100 mg, 0.26 mmol) in dimethyl sulfoxide : glacial acetic acid (1:1, 10 mL) at 0 $^{\circ}$C was added iodine monochloride (1 M solution in dichloromethane, 0.46 mL, 0.46 mmol) under dark (flask covered with aluminum foil). The reaction mixture was gradually warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous sodium thiosulfate solution. The resulting solution was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 4:1) to afford the iodo compound **32** (123 mg, 85% yield) as a white solid: mp 157-159 $^{\circ}$C; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.46-7.51 (m, 2H), 7.28-7.46 (m, 8H), 6.25 (s, 1H), 5.21 (s, 2H), 5.13 (s, 2H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ163.6, 162.5, 158.2, 157.6, 136.0, 135.5, 129.0, 128.9, 128.5, 128.2, 127.1, 126.9, 105.9, 98.5, 93.9, 71.3, 71.2, 66.4, 26.0; LRMS (EI): *m/z* 516 (M^+), 458 (100%), 390, 366, 332; HRMS (EI) calcd for $C_{24}H_{21}IO_5$: 516.0434, found: 516.0445.

Compound 33

To a solution of the iodo compound **32** (360 mg, 0.64 mmol) in *N,N*-dimethyformamide (10 mL) were added allyltributylstannane (0.40 mL, 1.29 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (45 mg, 0.064 mmol) and the reaction mixture was heated to 100 °C for 5 h. The reaction solution was cooled to rt, diluted with ethyl acetate, washed with aqueous ammonium hydroxide solution (29% solution in water) and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 9:1) to afford the allyl compound **33** (238 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.54 (m, 2H), 7.26-7.44 (m, 8H), 6.25 (s, 1H), 5.81-5.93 (m, 1H), 5.20 (s, 2H), 5.06 (s, 2H), 4.98 (s, 1H), 4.94 (s, 1H), 3.32 (d, 2H, J = 6.0 Hz), 1.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ162.7, 160.5, 158.7, 156.2, 136.6, 136.2, 136.1, 128.9, 128.8, 128.5, 128.1, 127.3, 126.9, 114.9, 109.3, 105.1, 97.8, 93.4, 71.1, 70.5, 26.9, 26.0.

Compound 35

To a solution of **16** (161 mg, 0.55 mmol) in diethyl ether : tetrahydrofuran (1:1, 10 mL) at -78 °C was added *n*-BuLi (2.5 M solution in hexanes, 0.22 mL, 0.55 mmol). After 2 h at -78 °C, **33** (65 mg, 0.14 mmol) in tetrahydrofuran (5 mL) was added and the reaction mixture was warmed to 5 °C over 4 h. The reaction was quenched with aqueous saturated ammonium chloride solution and the resulting solution was diluted with diethyl ether, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude compound **34** was used directly for the next step without further purification.

To the above crude residue (**34**) taken up in acetone (10 mL) were added potassium carbonate (50 mg) and methyl iodide (0.01 mL) and the reaction mixture was heated to reflux for 3 h. The reaction solution was cooled to rt, passed through a pad of Celite and evaporated *in vacuo*. . The residue was purified by preparative TLC on silica gel (hexanes : ethyl acetate = 4:1) to afford **35** (34 mg, 39% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.64 (m, 15H), 7.03-7.09 (m, 2H), 6.82 (d, 1H, J = 8.4 Hz), 6.37 (s, 1H), 5.95-6.07 (m, 1H), 5.23 (s, 2H), 5.04 (s, 2H), 4.96-5.03 (m, 2H), 4.94 (s, 2H), 3.94 (s, 3H), 3.68 (s, 3H), 3.41 (d, 2H, J = 5.6 Hz).

Compound 38

To a solution of **32** (100 mg, 0.18 mmol) in *N,N*-dimethylformamide (10 mL) were added **37** (0.12 mL, 0.36 mmol), dichlorobis(triphenylphosphine)-palladium(II) (26 mg, 0.036 mmol), cesium fluoride (81 mg, 0.54 mmol) and tri(2-furyl)phosphine (13 mg, 0.054 mmol). The reaction mixture was heated for 60 h at 100 $^{\circ}$C after which it was cooled to rt, quenched with saturated aqueous potassium fluoride solution. The resulting solution was diluted with ethyl acetate, washed with water and brine, successively. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes : ethyl acetate = 2:1) to afford the prenylated compound **38** (33 mg, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.49-7.53 (m, 2H), 7.30-7.41 (m, 8H), 6.23 (s, 1H), 5.19 (s, 2H), 5.11 (m, 1H), 5.04 (s, 2H), 3.25 (d, 2H, J = 7.2 Hz), 1.70 (s, 6H), 1.66 (s, 6H).

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GENERAL CONCLUSIONS

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

Chapter 1 describes a novel way to prepare benzoxepin core using a ring-closing metathesis reaction. Bauhiniastatins, which are reported to possess anti-cancer activities and contain benzoxepin skeleton, can thus be synthesized using this methodology.

Chapter 2 illustrates a short synthesis of bauhinoxepin J, which entails use of an environmentally benign radical reaction. This innovative intramolecular radical cyclization opens new avenues for constructing natural products with embeded quinone subunit.

Chapter 3 depicts a direct route for the synthesis of aurones and benzophenones, which makes use of 1,3-benzodioxin-4-ones as the key intermediate. This strategy led to successful synthesis of three natural products in a straightforward fashion.

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