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Synthetic studies of diphenyl ether and anthraquinone natural products

Ganeshkumar Lakshminarayan
Iowa State University

Synthetic studies of diphenyl ether and anthraquinone natural products

by

Ganeshkumar Lakshminarayan

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Program of Study Committee:

George A. Kraus, Major Professor

Richard C. Larock

John G. Verkade

Klaus Schmidt-Rohr

Suzanne Hendrich

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GENERAL INTRODUCTION

Organic chemistry is the most important branch of chemistry as it serves many aspects of human life. Organic chemistry is all around us, involved in our day-to-day life, like the drugs we take, the clothes we wear, the fuel that propels our car, the food we eat, the digestive process, wood, paper, plastics and paints. As the involvement of organic chemistry in our life increases, the need for the development of new synthetic methods for biologically active molecules also increases. In the age of green chemistry, with the increased concern about our fragile environment, the development of more efficient and environmentally friendly procedures for valuable synthetic targets is needed the most. This has become the main purpose of organic chemistry. The development of synthetic pathways for some biologically active compounds is explored in this thesis.

Chapter one describes the total synthesis of littorachalcone. Littorachalcone shows a significant enhancement of nerve growth factor-mediated neurite outgrowth from PC12D cells. Compounds which possess this activity may be useful in the treatment of neurological disorders, such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and human immune deficiency virus associated dementia. This was the first total synthesis of littorachalcone. This method is straightforward and operationally convenient so that it can be easily scaled up and applied for the preparation of littorachalcone and related compounds.

Chapter two outlines a synthetic approach towards topopyrone-D. Topopyrones A, B, C and D show inhibitory action against human topoisomerase. Hence, they could be used as anticancer agents. Topopyrones also showed antibacterial and antiviral properties making them important synthetic targets. Metal-hydrogen exchange and metal-halogen exchange reactions were studied as key steps.

Chapter three describes an approach towards the synthesis of rubianine. It is found in madder, which is one of the most important natural dyes known to man. Rubianine is a C-glycoside which makes it a structurally unique and very important synthetic target and its total synthesis has not been reported in the literature. In this chapter, various reactions were studied to make the C-glycoside bond to the anthraquinone moiety in an efficient manner.

Chapter four describes a flexible synthesis for indoles. Indoles are present in many natural compounds and many of them have interesting biological activity. The effect of different substituents at the *ortho*-position of the starting aniline compound was studied.

In this thesis, all the chapters are treated as separate sections. The numbering of the compounds, schemes and references are therefore listed independently in each section.

CHAPTER 1

Synthesis of littorachalcone and related diphenyl ethers

Introduction

During the course of their investigations of neuritogenically active substances from medicinal plants, Ohizumi and coworkers isolated a new dimeric dihydrochalcone, littorachalcone (**1**) from the aerial parts of *V. littoralis* H. B. K. along with several flavonoids.[1] A related compound, verbenachalcone (**2**), was discovered by Li in 2001.[2] Both of these compounds show significant enhancement of nerve growth factor-mediated neurite outgrowth from PC12D cells. Compounds which possess this activity may be useful in the treatment of neurological disorders, such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and human immune deficiency virus-associated dementia.[1] The activities of littorachalcone and verbenachalcone were comparable.

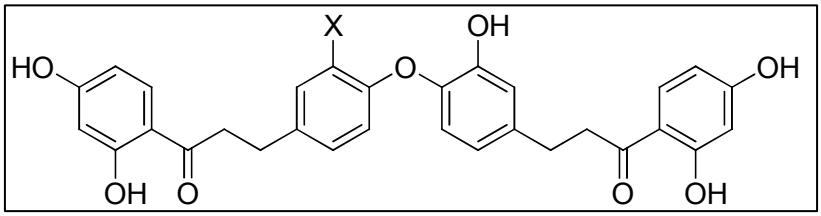


Figure 1

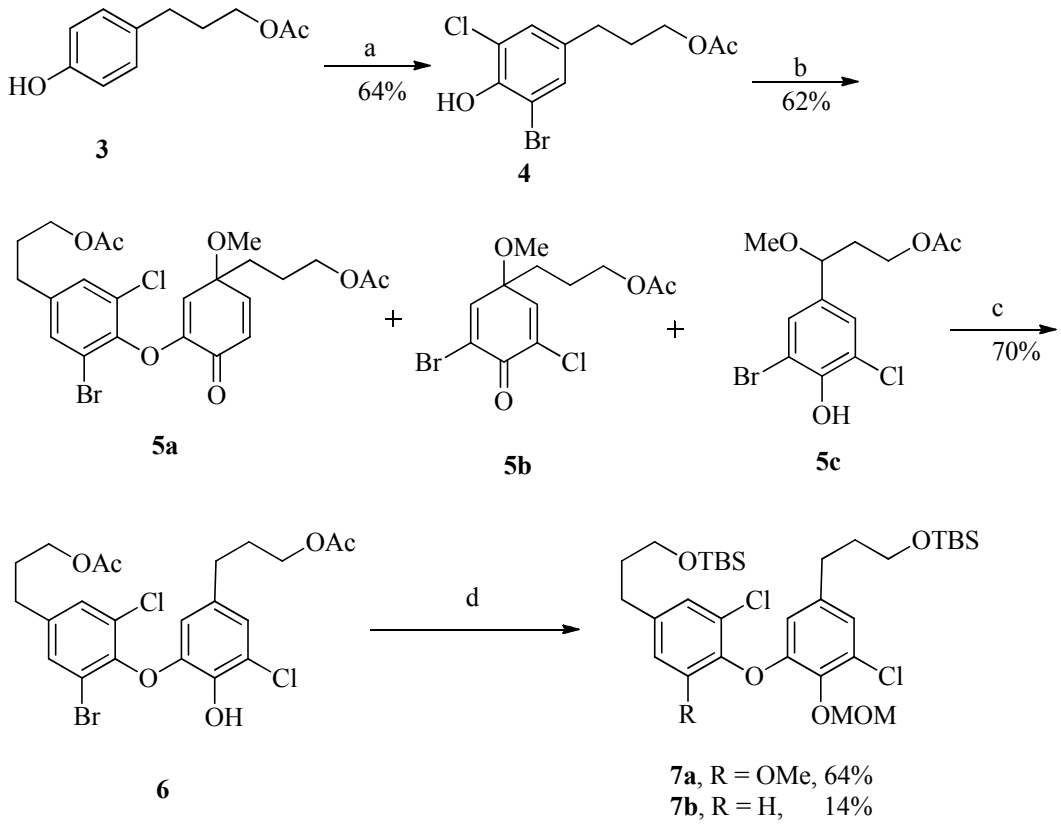
1 Littorachalcone : X = H
2 Verbenachalcone : X = OMe

The first syntheses of littorachalcone and verbenachalcone were described by Nishiyama and coworkers.[3] In their synthesis, as shown in Scheme 1, diaryl ether **4** was an important precursor. It was synthesized through stepwise halogenations of **3** in moderate yields. Diaryl ether **4** was converted to **5a** in a 62% yield by anodic oxidation along with other by-products (**5b** and **5c**). The diaryl compound **5a** was reduced with zinc to give **6**. Then the hydroxyl group of compound **6** was protected with a MOM group and the acetyl

groups were hydrolyzed and protected with TBS groups through a three-step sequence. The bromo substituent of compound **6** was converted to the methoxy group of compound **7a** in a 64% yield and the by-product **7b**.

Compound **7a** was taken further for the synthesis of verbenachalcone. Littorachalcone was synthesized from **7b**. First, **7b** was converted to **11**, which on treatment with lithiated **13** provided the protected form of the title compound, which was then deprotected to give littorachalcone. Thus, the synthesis was achieved in ten steps with very poor yields. Actually this synthesis was intended only for verbenachalcone and littorachalcone was synthesized as a side product.

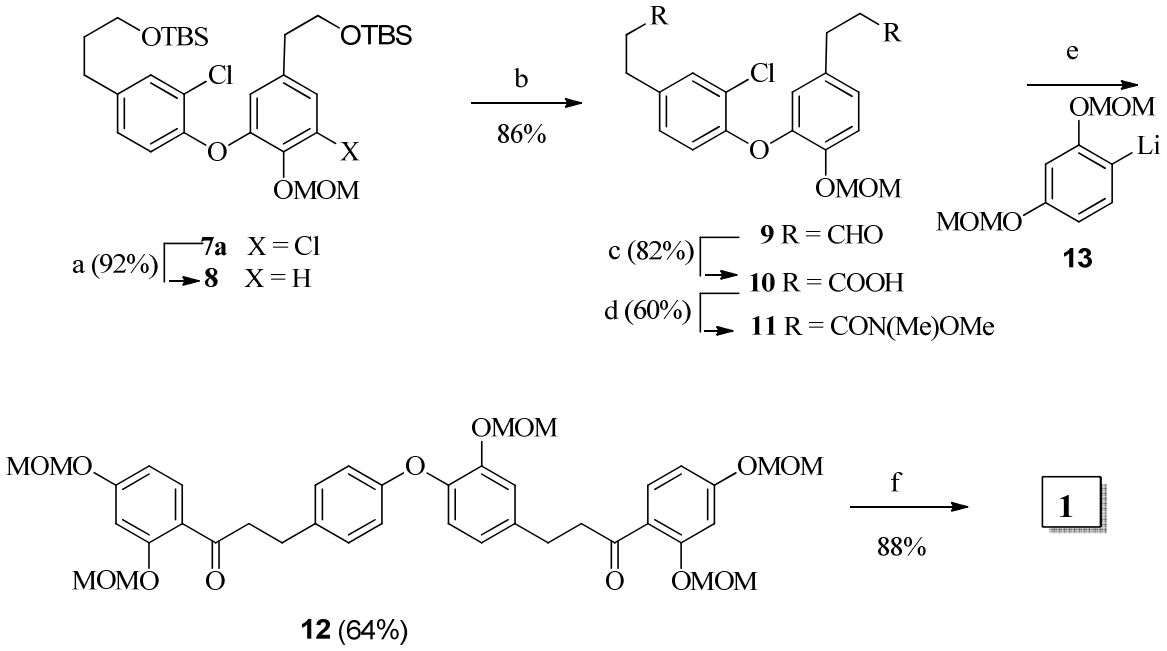
Scheme 1



Reagents and conditions: (a) SO_2Cl_2 then Pyr.HBr_3/$CHCl_3$-Pyr. (b) Constant current electrolysis at 10 mA (**5a** and a mixture of **5b** and **5c**. (c) Zn, AcOH. (d) i- MOMCl,

Diisopropylethylamine; ii- K_2CO_3/MeOH; iii- TBSCl, Imidazole/DMF; iv- *n*-BuLi, $B(OMe)_3$, then NaOH, 30% H_2O_2.

Scheme 2



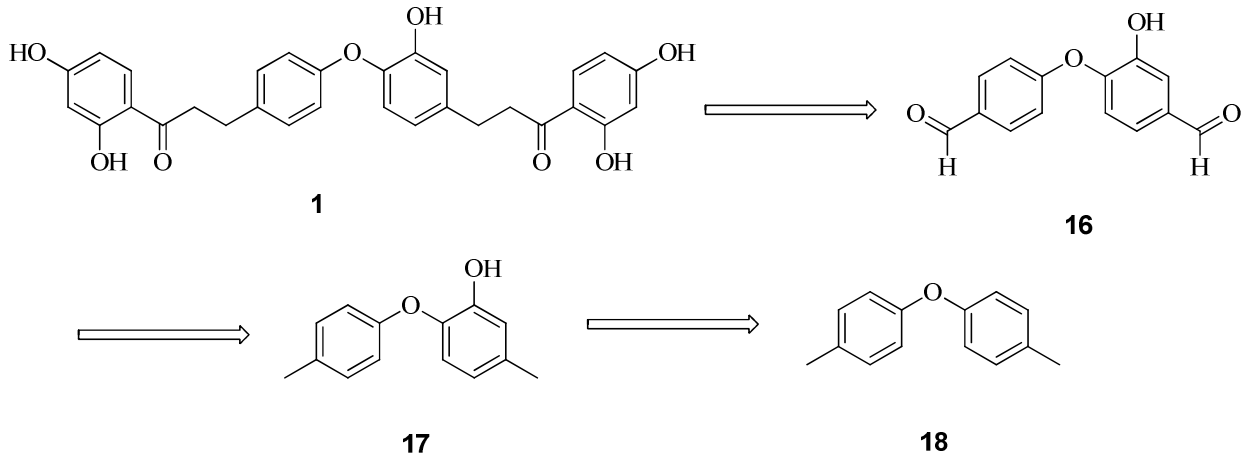
Reagents: (a) Pd-C, HCO_2NH_4/EtOH. (b) i. TBAF; ii. Et_3N, SO_3-Pyr, DMSO. (c) PDC/DMF. (d) Et_3N, 1-hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, (MeO)MeNH.HCl/CH_2Cl_2. (e) *n*-BuLi, **13**/THF. (f) TsOH/MeOH.

Results and Discussion

When the total synthesis of littorachalcone was initiated, there was no direct synthesis reported in the literature, even though it showed similar activity to verbenachacone. Our first plan for the synthesis of littorachalcone is shown in Scheme 3. Dialdehyde **16** was reacted with two equivalents of the protected 2,4-dihydroxyacetophenone **15** to generate the target compound. The dialdehyde **16** could be generated by benzylic oxidation of hydroxytolyl ether **17**, which in turn could be generated from commercially available *para*-tolyl ether **18**

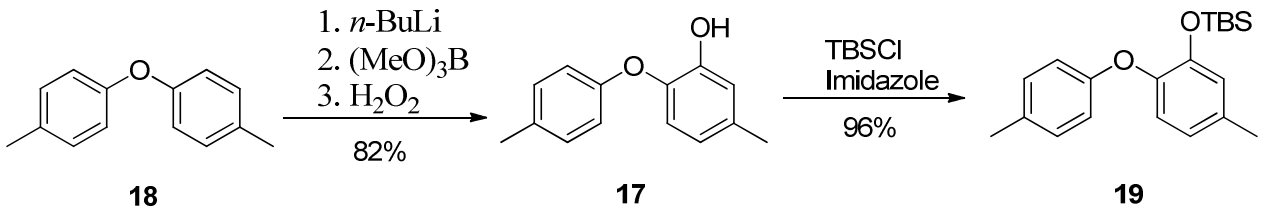
by partial hydroxylation. Our route is significantly more straight forward and operationally convenient than that of Nishiyama, because we started from commercially available *para*-tolyl ether, thus avoiding the protection and deprotection steps necessary in the Nishiyama diaryl ether synthesis.

Scheme 3



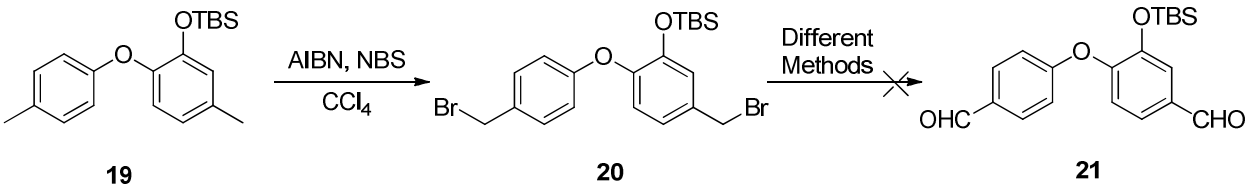
Ether **18** was hydroxylated by taking advantage of the selective metalation of diaryl ethers developed initially by Gilman and coworkers.[4] Treatment of **18** with *n*-butyl lithium at 0 ^{o}C, followed by the addition of trimethyl borate afforded a boronic acid ester. Subsequent hydrogen peroxide-mediated oxidation of the aryl boronic acid ester provided **17** in 82% yield. Protection of the alcohol with TBSCl and imidazole provided **19** in 96% yield.

Scheme 4



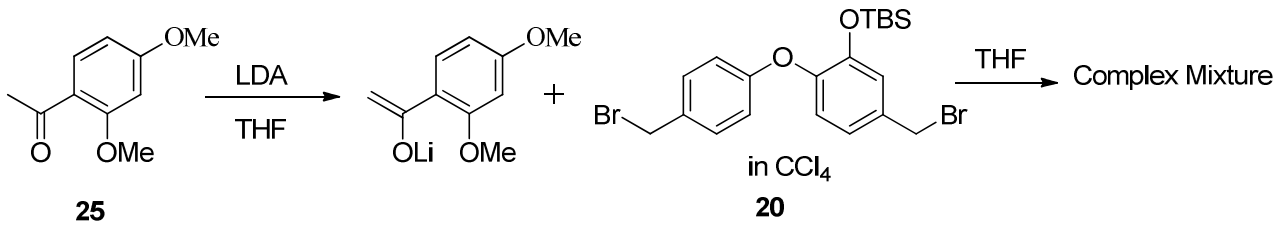
Benzylic oxidation of compound **19** to a dialdehyde **21** was attempted through a two-step reaction sequence as shown in Scheme 5. The conversion of **19** to dibromo ether **20** proceeded smoothly under the standard conditions of free radical bromination.[5] However, this compound was unstable during work-up or on storage. Attempted purification resulted in decomposition. Hence, the conversion of dibromo ether to dialdehyde **21** was tried with the unpurified material. Attempts to convert the unpurified dibromide **20** to dialdehyde **21** using either tetraalkylammonium chromate or N-methylmorpholine oxide afforded a mixture of mono and dialdehydes along with unidentified polar by-products.

Scheme 5



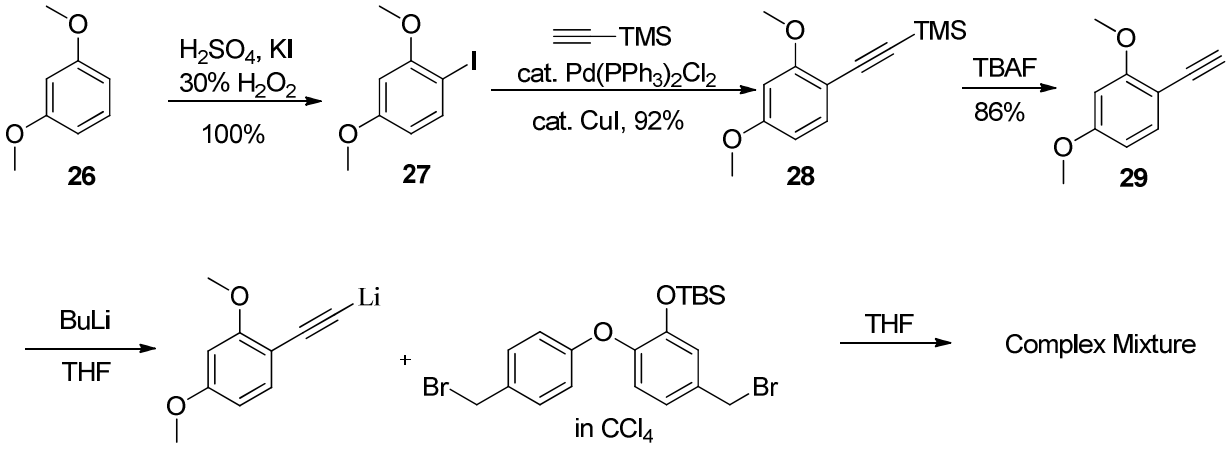
Since the dibromo ether, **20** was obtained with significant purity in solution, attempts to use it in solution were tried. The freshly prepared dibromo ether **20** in carbon tetrachloride was added to two equivalents of the enolate anion of compound **25**, which was prepared separately. This resulted in decomposition of **20.**

Scheme 6



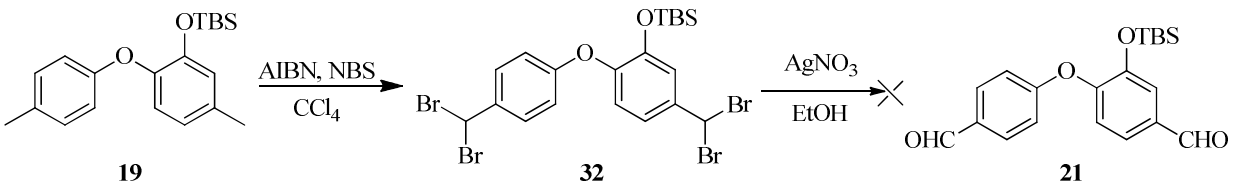
Since the treatment with enolates led to decomposition, the dibromide **20** was then treated with acetylide ion as this would be a softer ion. However, this also led to decomposition. The formation of the alkyne compound is shown in Scheme 7. Dimethoxybenzene **26** was partially iodinated[6] to give compound **27**, which was converted to TMS protected alkyne **28** by a Sonagashira reaction[7] and this was then deprotected[8] to give alkyne **29**.

Scheme 7



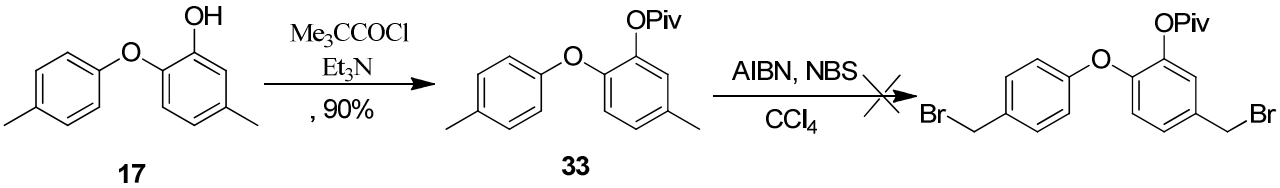
Since the dibromide **20** was unstable, it was thought that the tetrabromo compound **32** could be more stable and could be oxidized to the dialdehyde **21**. The tetrabromide **32** was prepared by the usual free radical bromination reaction by using excess NBS. However, it was found that this also was not stable on concentration or storage. Oxidation of the unpurified tetrabromide **32** was attempted with silver nitrate[9]. However, this resulted in an inseparable mixture.

Scheme 8



Since many attempts to convert compound **19** to dibromo or tetrabromo compounds and then subsequent oxidation to dialdhyde **21** failed, it was thought that the instability of the dibromo compound could be because the aromatic rings have high electron density. The electronic density could be reduced by changing the protecting group from TBS to a pivalate group as shown in Scheme **9**. However, when the pivalate-protected hydroxy *p*-tolyl ether **33** was converted to dibromo compound, it was also unstable on concentration or storage.

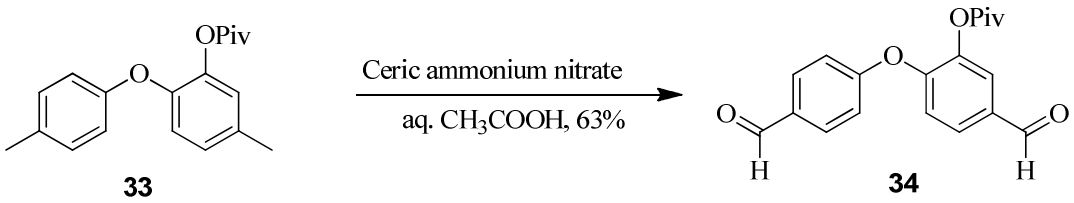
Scheme 9



17 **33**

Instead of going through the bromination and then oxidation, benzylic oxidation was tried to convert diphenyl ether **33** to the dialdehyde **34** with ceric ammonium nitrate.[10] This worked nicely to give **34** in good yields.

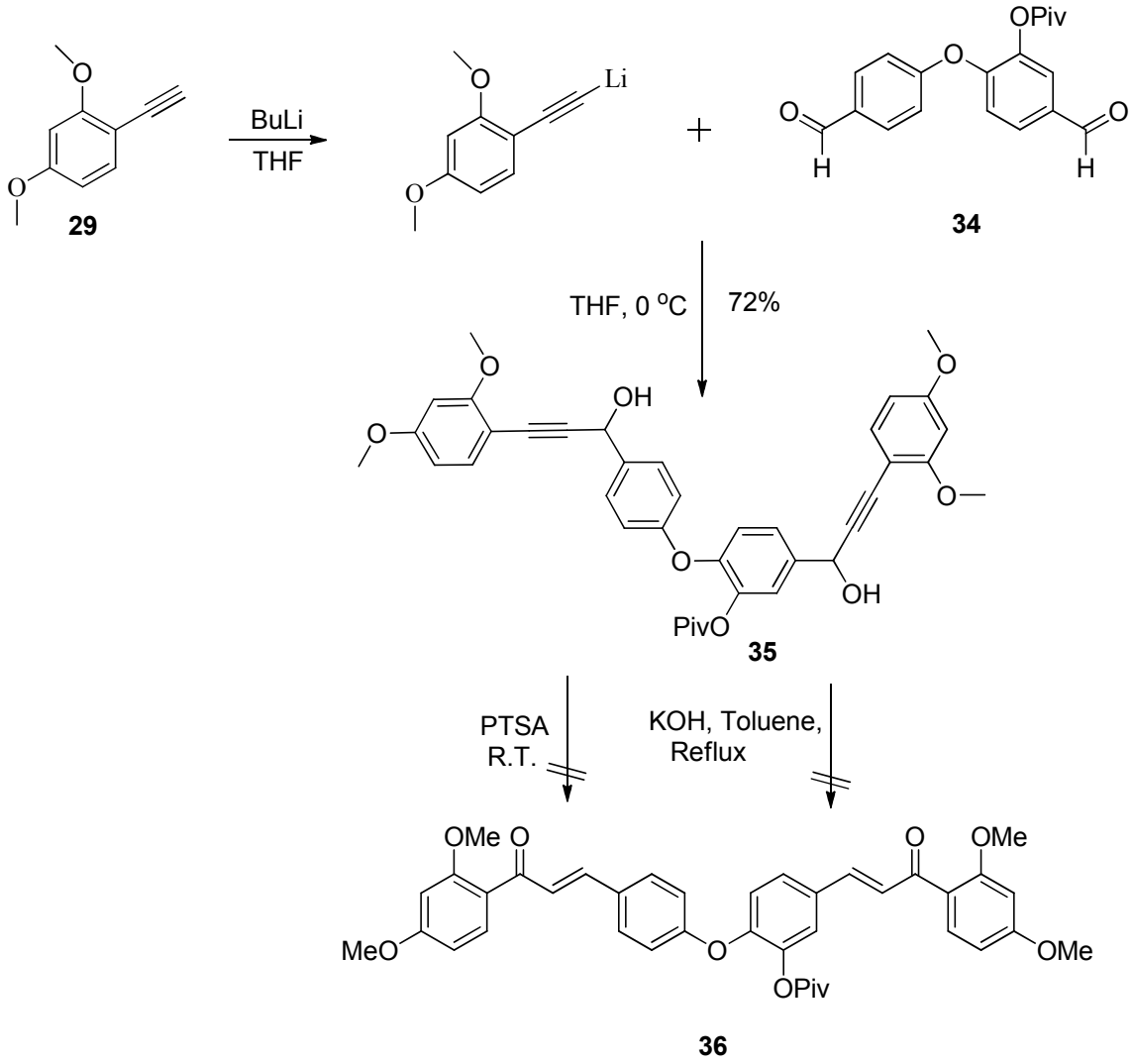
Scheme 10



33 **34**

The Coupling of dialdehyde **34** with two equivalents of alkyne **29** gave the dialkyne **35**. [11] However, the isomerization of compound **35** under acidic or basic conditions did not produce the enone **36**.

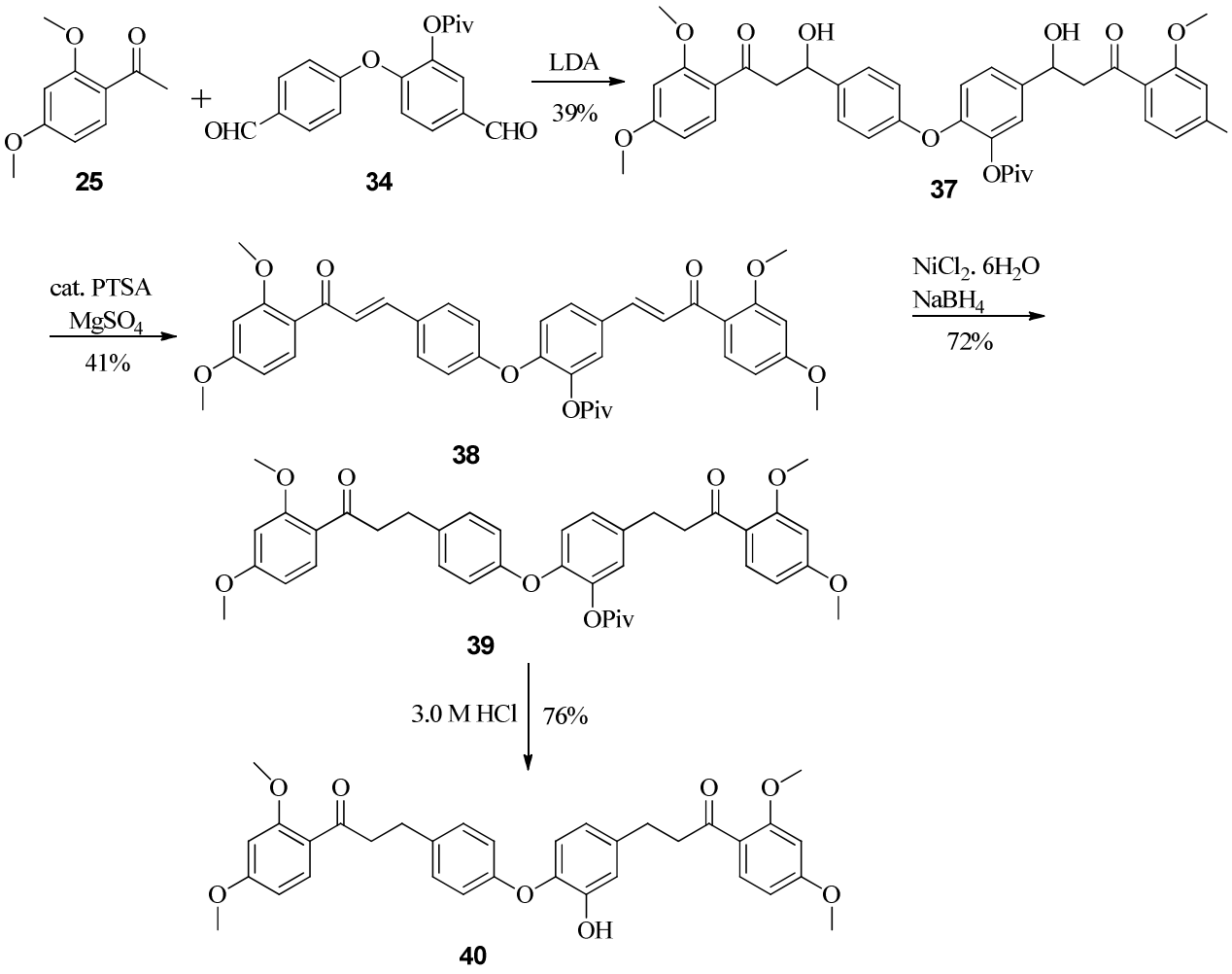
Scheme 11



29 **34** **35** **36**

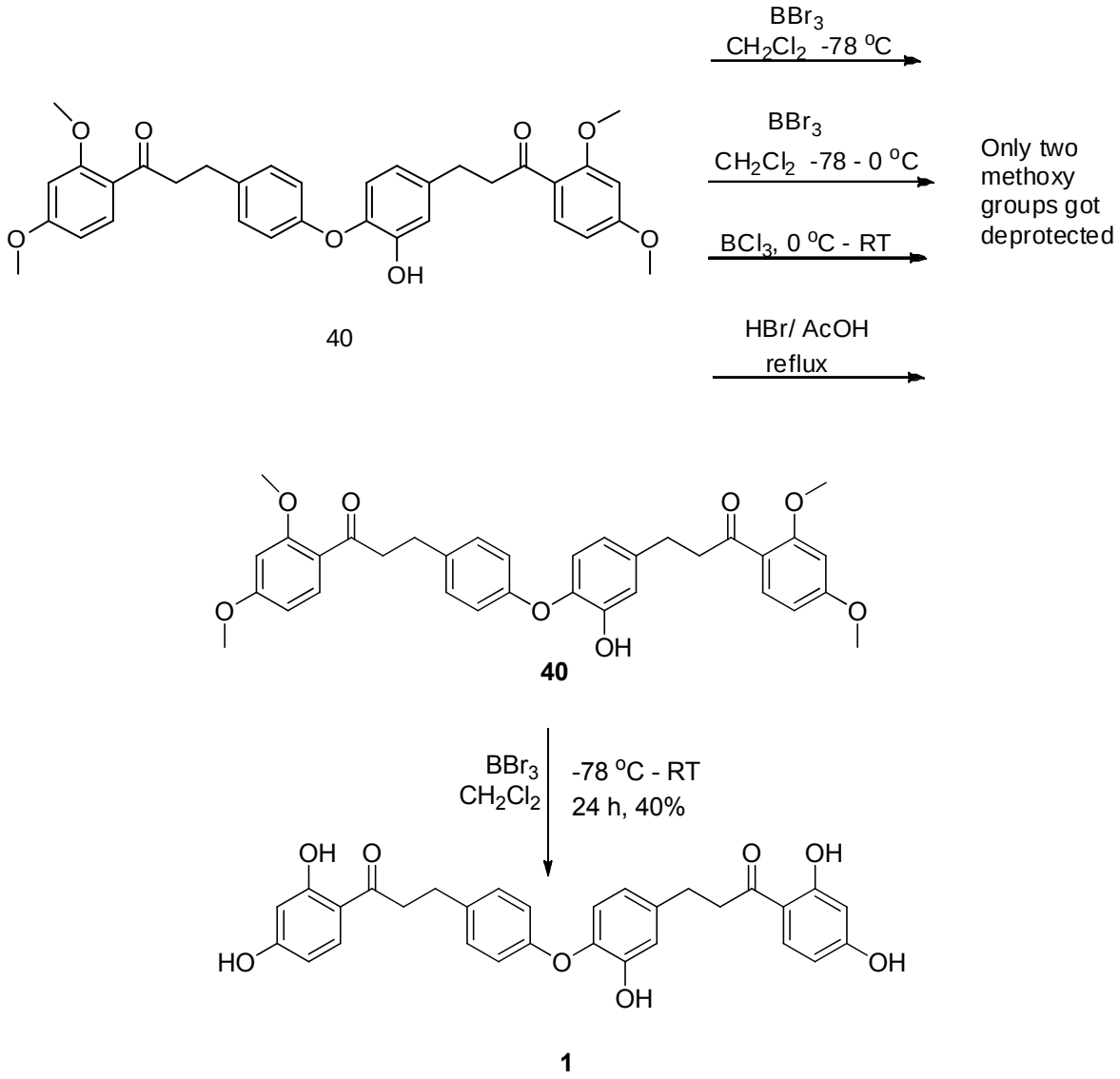
The aldol reaction of dialdehyde **34** with two equivalents of dimethoxyacetophenone **25** was attempted.[12] The bis-aldol adduct **37** was produced in 39% yield, with approximately 30% of the mono-aldol product and about 20% of the dialdehyde **34**. The resulting hydroxy ketone **37** was then dehydrated with PTSA[13] to give the enone **38**. This was then hydrogenated with nickelous chloride and sodium borohydride[14] to give the protected littorachalcone **39**. The pivalate group of this compound was then deprotected with 3M hydrochloric acid in dioxane[15] to give tetramethoxy littorachalcone **40**.

Scheme 12



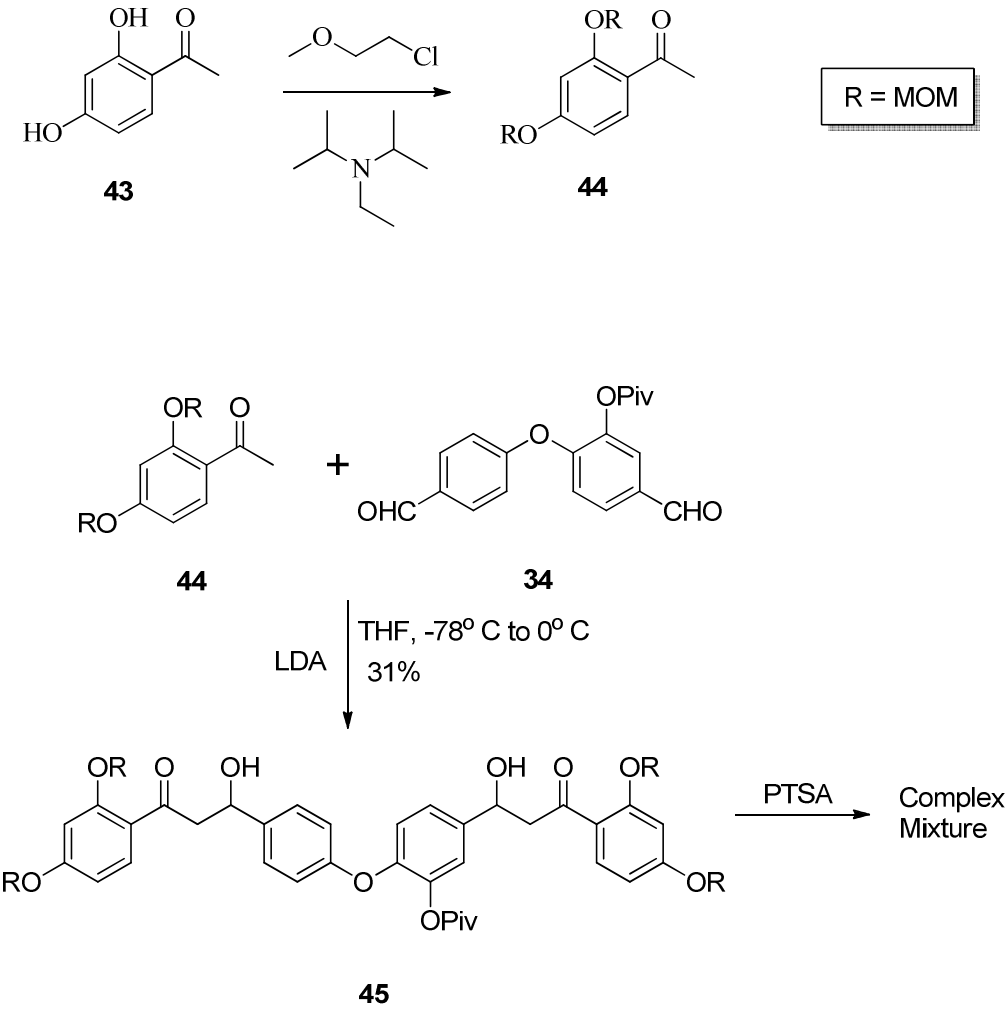
With the tetramethoxy littorachalcone **40** in hand, the deprotection of the methyl groups under different conditions was attempted as shown in Scheme 13. In many cases only the deprotection of methyl groups near the carbonyl groups was observed. This could be because of the coordination of the reagents with the carbonyl groups. Once these methoxy groups were deprotected, the compound became highly polar and crashed out of the solution at low temperatures and hence further reaction was not possible. Finally, the use of an excess of boron tribormide[16] with reaction temperature from 0 ^{o}C to room temperature was successful in giving littorachalcone **1** in moderate yields.

Scheme 13



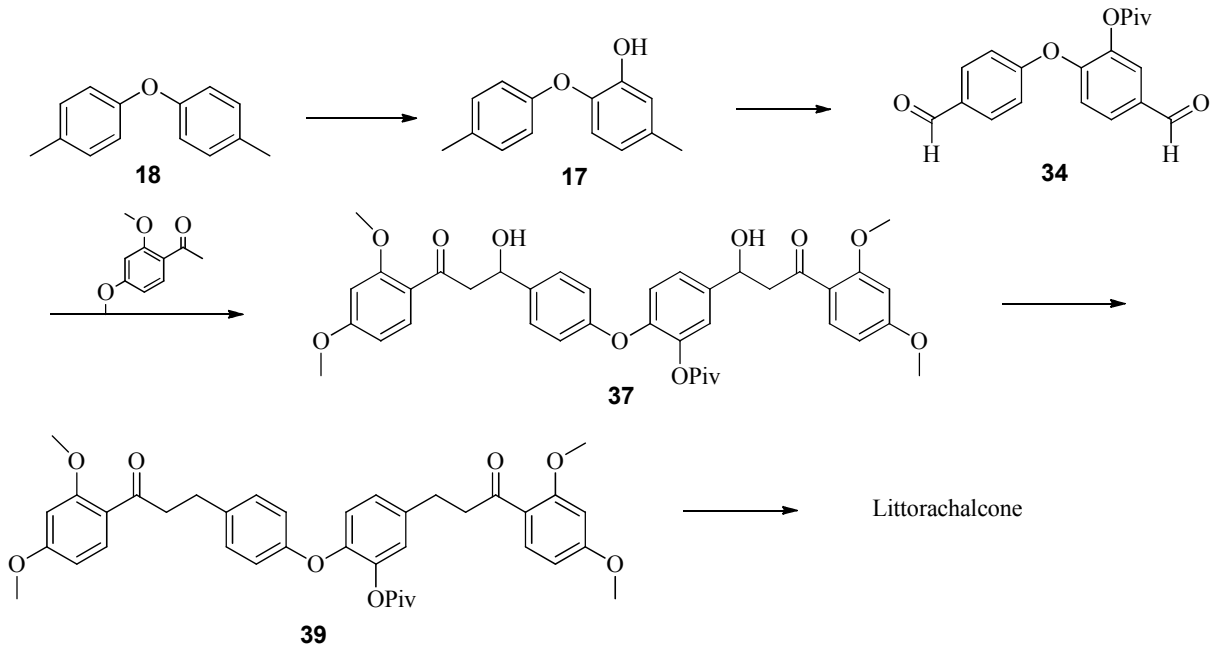
To improve the yield of the final step, it was thought that the deprotection of the MOM groups would be easier than the deprotection of methoxy groups. Hence, first bis-MOM protected acetophenone **44** was prepared.[17] Two equivalents of this enolate anion were treated with dialdehyde **34** to give the tetra-MOM protected hydroxyketone **45**. Dehydration resulted in a mixture of compounds, which could be because, the deprotection of one or more MOM groups occurred under acidic conditions. These reactions are shown in Scheme 14.

Scheme 14



The final synthetic pathway to achieve the target molecule is summarized in Scheme 15.[18] Thus, synthesis of littorachalcone was completed in 7 steps in a 4.6% overall yield.

Scheme 15



In addition to littorachalcone, the hydroxy dicarboxylic acid **46**, shown in Figure 2 was also synthesized. Diacid **47** was isolated from *Curcuma chuanyujin* by Takeda and coworkers as a part of their study to identify new plant antioxidants.[19]

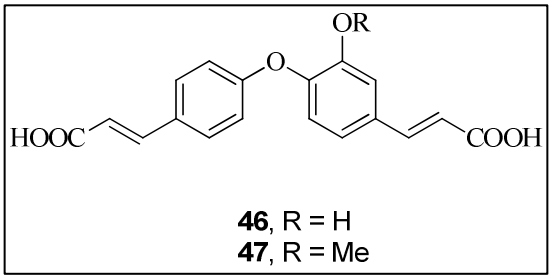
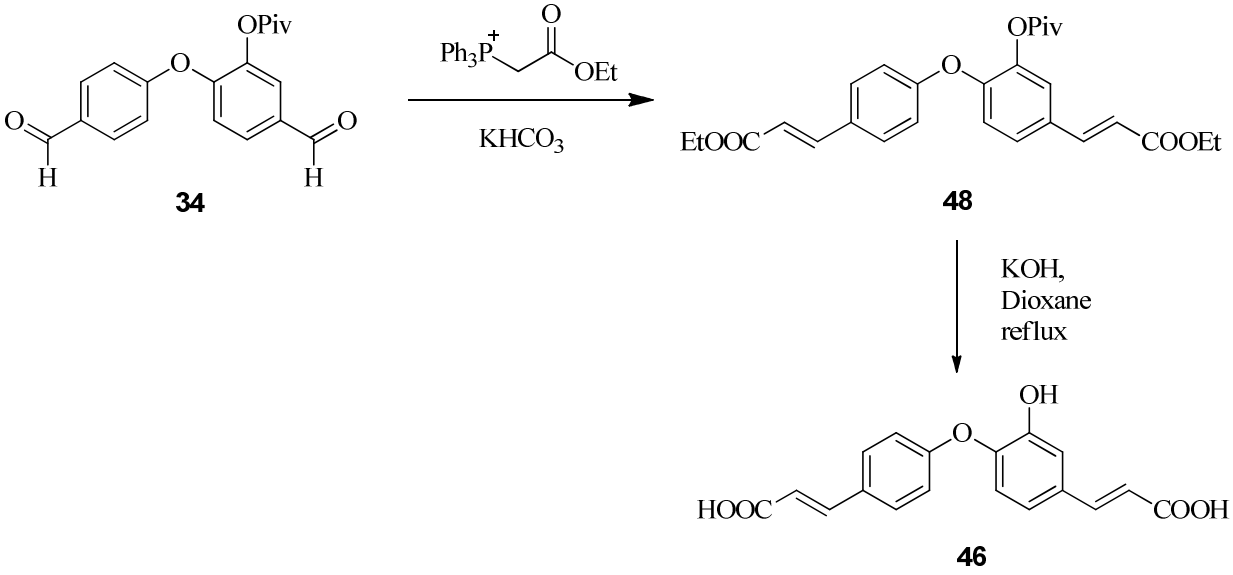


Figure 2

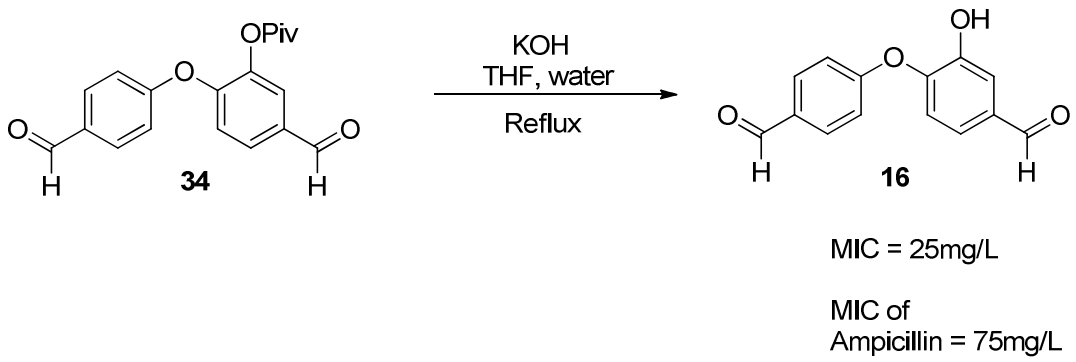
Compound **46** could be readily synthesized from dialdehyde **3** by a Wittig reaction[20] using carboethoxymethylene triphenylphosphorane, followed by hydrolysis of the triester using KOH in methanol.

Scheme 16



Further, the antibacterial activity of littarochalcone **1**, its synthetic precursors **16** and **17**, and the diacid compound **46** were analyzed by measuring the minimum inhibitory concentration (MIC) using the microdilution method described by Andrews.[21] Among these compounds, the dialdehyde **16** showed potent antibacterial activity. The MIC value for compound **16** was approximately 25 mg/L, while the MIC for ampicillin was 75 mg/L. The hydroxy dialdehyde **16** was prepared[22] as shown in Scheme **17**

Scheme 17



In conclusion we have successfully developed a total synthetic pathway for littorachalcone. Hydroxy dicarboxylic acid **46** was also synthesized from a common intermediate. The antibacterial activity of these compounds and the synthetic precursors have been evaluated. Dialdehyde **16** showed potent antibacterial activity.

Experimental Section

5-Methyl-2-(4-methylphenoxy)phenol (17)

To the stirred solution of *p*-tolyl ether (1.98 g, 10 mmol) in 20 mL of THF and 20 mL of ether, *n*-BuLi (2.5 M solution in hexane, 4.4 mL, 11 mmol) was added at room temperature. This solution was refluxed for six hours. Trimethyl borate (1.14 g, 11.0 mmol) was then added dropwise and boiled for six more hours. The reaction mixture was cooled to 0 ^{o}C and hydrogen peroxide solution (30% solution in water, 12 mL), followed by aqueous sodium hydroxide (3 N, 12 mL) solution were added. It was stirred at room temperature for one hour and then at 40 ^{o}C for two hours. The reaction mixture was cooled to room temperature, acidified with 10% HCl solution and then extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:10) to give compound **17** (1.75 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.85 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H).

^{13}CNMR (100 MHz, $CDCl_3$) δ 155.08, 147.35, 141.59, 134.79, 133.08, 130.48, 130.36, 121.27, 118.85, 117.84, 116.86, 115.56, 21.25, 20.90.

2,2-Dimethylpropionic acid 2-(4-methylphenoxy)phenyl ester (33)

To a stirred solution of compound **17** (1.8 g, 8.4 mmol) in THF (20 mL), triethyl-amine (0.976 g 9.66 mmol) was added. The mixture was cooled to 0 ^{o}C and trimethylacetyl chloride (1.08 g, 8.98 mmol) was added. The solution was warmed to room temperature and stirred for two hours. After this, the reaction mixture was filtered through celite, diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous

$MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:10) to furnish compound **33** (2.25 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8 Hz, 2H), 6.98–6.95 (m, 2H), 6.89 (d, *J* = 8 Hz, 1H), 6.83 (d, *J* = 6.8 Hz, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 1.21 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.78, 155.67, 145.91, 142.48, 134.37, 132.28, 130.36, 130.18, 127.43, 124.30, 120.89, 118.81, 117.44, 39.26, 27.29, 21.02, 20.86.

2,2-Dimethylpropionic acid 5-formyl-2-(4-formyl-phenoxy)phenyl ester (34)

Compound **33** (1.10 g, 3.69 mmol) was dissolved in 20 mL of aqueous acetic acid. To this solution was added ceric ammonium nitrate (11 g, 20 mmol) solution in 20 mL of aqueous acetic acid in 10 minutes at room temperature. The reaction was stirred overnight, diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by silica gel chromatography (EtOAc/hexanes, 1:3) to yield compound **34** (0.76 g, 63% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.95 (s, 1H), 7.89 (d, *J* = 9 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 2 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 1.21 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.79, 190.13, 176.25, 161.33, 152.26, 143.39, 133.85, 132.58, 132.30, 132.25, 129.19, 125.21, 121.45, 119.59, 118.26, 39.38, 27.16.

1-(2,4-Dimethoxyphenyl)-3-[4-[4-[3-(2,4-dimethoxyphenyl)-3-oxoprop-2-enyl]-2-pivaloxyphenoxy]phenyl]-2-propene-1-one (38).

To a stirred solution of diisopropyl amine (0.55 g, 5.5 mmol) in THF (10 mL), *n*-BuLi (2.5 M solution in hexane, 2 mL, 5 mmol) at 0 ^{o}C was added and the solution was cooled to -78 ^{o}C. To this, a solution of 2,4-dimethoxyacetophenone (0.86 g, 4.8 mmol) in THF (5 mL) was added at -78 ^{o}C and stirred for 30 minutes. A solution of compound **34** (0.52 g, 1.6 mmol) in THF (5 mL) was added to the reaction at the same temperature. The

resulting mixture was warmed to 0 ^{o}C and the reaction was quenched by adding acetic acid (1 mL in 5 mL of THF). The reaction was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (EtOAc/hexanes, 1:1) to provide the aldol product (0.42 g, 39% yield).

To a stirred solution of the above aldol product (0.10 g, 0.15 mmol) in 1,2-dichloroethane, was added a catalytic amount of *p*-toluenesulfonic acid. The solution was heated to 50 ^{o}C and stirred for six hours. After this, the reaction was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous $MgSO_4$, concentrated and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:1) to provide compound **38** (0.040 g, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.57–7.53 (m, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.37–7.32 (m, 3H), 7.28 (d, *J* = 2 Hz, 1H), 6.96 (d, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.47 (d, *J* = 8 Hz, 2H), 6.40 (s, 2H), 3.81– 3.77 (m, 16H), 1.13 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.55, 190.41, 176.52, 164.47, 164.39, 160.63, 160.59, 158.54, 148.95, 143.02, 141.37, 140.52, 133.13, 132.83, 131.01, 130.20, 128.56, 127.69, 127.24, 126.48, 123.54, 122.44, 122.32, 121.32, 118.15, 105.41, 98.89, 98.87, 56.05, 56.00, 55.81, 39.36, 27.26.

1-(2,4-Dihydroxyphenyl)-3-[4-[4-[3-(2,4-dihydroxyphenyl)-3-oxopropyl]-2-hydroxyphenoxy]phenyl]-1-propanone (1).

Compound **38** (40 mg, 0.06 mmol) was dissolved in 5 mL of methanol and $NiCl_2.6H_2O$ (285 mg, 1.2 mmol) followed by 0.5 mL of water were added to this solution with stirring. After ten minutes, sodium borohydride (18 mg, 0.48 mmol) was added and the reaction was stirred vigorously at room temperature. After six hours the reaction mixture was poured into water and the aqueous layer was extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (EtOAc/hexanes, 1:1) to furnish diketone **39** (0.03 g, 72% yield).

Diketone **39** (0.10 g, 0.15 mmol) was dissolved in 5 mL of ethanol and potassium hydroxide (0.080 g, 1.5 mmol) in 5 mL of water was added with stirring. The resulting mass was boiled for two hours. The reaction mixture was then poured into brine and acidified with 10% HCl solution. The product was extracted with Ethyl acetate, the organic layer was dried over anhydrous $MgSO_4$, concentrated and the crude product was filtered through silica gel column to provide the hydroxyl diketone **40** (0.060 g, 76% yield).

To a stirred solution of the hydroxy diketone **40** (0.040 g, 0.07 mmol) was added boron tribromide (0.17 g, 0.70 mmol) at 0 ^{o}C. The solution was stirred for 24 h at room temperature. The reaction mixture was quenched with water and poured into brine. The mixture was extracted with ethyl acetate. (3x50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed. The crude product was purified by preparative thin layer chromatography (EtOAc/hexanes, 1:1) to yield **1** (0.010 g, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.83 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 2 Hz, 1H), 6.85–6.79 (m, 4H), 6.44–6.41 (m, 2H), 6.33 (t, *J* = 2.4 Hz, 2H), 3.34–3.29 (m, 4H), 3.00–2.96 (m, 4H).

MS: m/e: 514, 363, 352, 313, 286, 264, 185, 163, 149, 108. HRMS: m/e calc 514.1628, m/e found: 514.1635.

2-(4-((E)-2-Carboxyvinyl))phenoxy-5-((E)-2-carboxyvinyl)phenol (46).

To a stirred solution of **34** (0.05 g, 0.15 mmol) in dioxane (5 mL), carboethoxymethylene triphenylphosphorane (0.26 g, 0.6 mmol), potassium bicarbonate (0.12 g, 1.2 mmol) and chloroform (5 ml) were added. The mixture was heated to 110 ^{o}C for 18 hours. It was cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$ and the solvent was removed. The residue was further purified by column chromatography (EtOAc/hexane, 2:3) to give compound **48**.

To the stirred solution of the compound **48** (0.05 g, 0.1 mmol) in 10 mL of 50% aqueous ethanol, potassium hydroxide (0.017 g, 0.3 mmol) was added. The mixture was boiled for three hours. After this the reaction was diluted with ethyl acetate and washed with

10% HCl solution. The organic layer was dried over $MgSO_4$ and concentrated. The residue was further purified by column chromatography (EtOAc/hexane 7:3) to give compound **46** (0.015 g, 92%).

^{1}H NMR (400 MHz, acetone-d6) δ 7.70–7.61 (multiplet, 4H), 7.35 (s, 1H), 7.24 (d, *J* = 8 Hz, 1H) 7.07 (d, *J* = 8 Hz, 1H) 7.69 (d, *J* = 8 Hz, 2H), 6.46 (d, *J* = 4 Hz, 1H), 6.42 (d, *J* = 4 Hz, 1H).

^{13}C NMR (100 MHz, acetone-d6) δ 172.66, 171.5, 158.62, 146.79, 145.33, 140.79, 138.95, 134.92, 131.92, 129.64, 130.21, 119.64, 119.35, 115.48, 115.32, 114.12.

3-(tert-Butyldimethylsiloxy)-4-(4-tolyloxy)toluene (19)

To a stirred solution of compound **17** (1.5 g, 7 mmol) in DMF (70 mL), Imidazole (0.7 g 10 mmol) was added. The mixture cooled to 0 ^{o}C and TBSCl (1.08 g, 8.98 mmol) was added. The reaction was warmed to room temperature and stirred for two hours. At the end of this reaction time, it was diluted with sodium chloride solution, and extracted with 100 mL ether two times. The ether layer was washed with 200 mL of brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:10) to furnish compound **19** (2.25 g, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8 Hz, 2H), 6.88 (d, *J* = 8 Hz, 2H), 6.69 – 6.57 (m, 3H), 2.31 (s, 3H), 2.27 (s, 3H), 0.99 (s, 9H), 0.14 (s, 6H)

4-Iodo-1,3-dimethoxybenzene (27)

Concentrated sulfuric acid (3g, 1.67 mL, 30 mmol) was dissolved in 100 mL methanol and to this solution 1, 3-dimethoxybenzene (2.76 g, 20 mmol) and then potassium iodide (3.32 g, 20 mmol) was added. After stirring for ten minutes hydrogen peroxide solution (15 mL, 40 mmol) was added. This dark brown solution was stirred for three hours and poured into 300 mL dichloromethane. Organic layer was washed with 200 mL of 0.1M sodium bisulfate solution and then with 200 mL of water. Finally organic layer was separated dried over anhydrous $MgSO_4$ and concentrated. The compound was purified by flash

chromatography on silica gel (EtOAc/hexanes, 2:10) to furnish compound **27** (5.3 g, 100% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J*= 8 Hz, 1H), 6.51 (d, *J* = 8 Hz, 1H), 6.48 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H).

((2,4-Dimethoxyphenyl)ethynyl)trimethylsilane (28)

4-iodo-1,3-dimethoxy benzene **27** (1.32 g, 5 mmol) was dissolved in 20 mL of triethylamine and 10 mL of acetonitrile. To this stirred solution Bis(triphenylphosphine)palladium(II) chloride (0.2 g, 0.25 mmol) and copper(I) iodide (0.02 g, 0.1 mmol) were added. This mixture was stirred for 30 minutes. To this, the solution of trimethylsilyl acetylene (0.7 g, 0.96 mL, 7 mmol) in 5 mL of triethylamine was added. This solution was stirred at room temperature for four hours. After this, the reaction was diluted with ethyl acetate (50 mL), filtered through celite and concentrated. Finally the compound was purified by flash chromatography on silica gel (EtOAc/hexanes, 2:10) to furnish compound **28** (1.07 g, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J*= 8, 1H), 7.18 (d, *J* = 12, 1H), 6.56 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 0.27 (s, 9H).

1-Ethynyl-2,4-dimethoxybenzene (29)

Compound **28** (2 g, 8.5 mmol) was dissolved in THF (20 mL). The solution was cooled to 0 ^{o}C and then TBAF solution in THF (1 M, 1.3 mL, 1.3 mmol) was added with stirring. The reaction mixture was warmed to room temperature and stirred for two more hours. After this the reaction mixture was filtered through celite and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 2:10) to furnish compound **29** (1.18g, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*= 8, 1H), 7.14 (d, *J* = 12, 1H), 6.55 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.25 (s, 1H).

Compound 35

1-ethynyl-2,4-dimethoxybenzene **29** (0.78 g, 4.8 mmol) was dissolved in THF (10 mL) and *n*-BuLi (2.5 M solution in hexane, 2 mL, 5 mmol) was added at 0 ^{o}C. This solution was stirred at 0 ^{o}C for 30 minutes and then the solution of compound **34** (0.52 g, 1.6 mmol) in THF (5 mL) was added to the reaction mixture at the same temperature. The reaction was warmed to room temperature and quenched by adding acetic acid (1 mL in 5 mL of THF). The reaction was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (EtOAc/hexanes, 2:5) to provide the product **35** (0.75 g, 72% yield).

1-(2,4-Bis(methoxymethoxy)phenyl)ethanone (44)

First MOMCl was prepared according to the JOC procedure.[17] Dimehoxy methane (1.5 g, 1.76 mL, 20 mmol) and zinc acetate (4 mg, 0.015 mmol) were taken in toluene (20 mL). To this stirred mixture, acetyl chloride (1.57g, 1.42 mL, 20 mmol) was added at room temperature for five minutes under stirring. This reaction was warmed to 45 ^{o}C for four hours. After this, the reaction mixture was cooled to room temperature and checked NMR for reaction completion. This was used as such for the next reaction.

1-(2,4-Dihydroxyphenyl)ethanone (1.14 g, 7.5 mmol) was taken in 20 mL dichloromethane. To this solution diisopropylethylamine (2.1 g, 16.5 mmol) was added with stirring at room temperature. After addition of the amine the reaction mixture became a clear solution. To this solution, the MOMCl (20 mmol) solution prepared as above was added. The reaction was kept under stirring for five hours and then diluted with ethyl acetate (100 mL). The organic layer was first washed with ammonium chloride solution (100 mL) and then with dilute sodium bicarbonate solution (100 mL) and finally with brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (EtOAc/hexanes, 1:5) to provide the product **44** (1.4 g, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J*= 8 Hz, 1H), 6.75 (s, 1H), 6.64 (d, *J* = 8Hz, 1H), 5.26 (s, 2H), 5.22 (s, 2H), 3.48 (s, 3H), 3.42 (s, 3H), 2.56 (s, 3H).

Compound 45

To a stirred solution of diisopropyl amine (0.55 g, 5.5 mmol) in THF (10 mL), *n*-BuLi (2.5 M solution in hexane, 2 mL, 5 mmol) at 0 ^{o}C was added and the solution was cooled to -78 ^{o}C. To this solution was added a solution of 1-(2,4-bis(methoxymethoxy)phenyl)ethanone (**44**) (1.15 g, 4.8 mmol) in THF (5 mL) at -78 ^{o}C and stirred for 30 min. A solution of compound **34** (0.52 g, 1.6 mmol) in THF (5 mL) was added to the reaction at the same temperature. The resulting mixture was warmed to 0 ^{o}C and the reaction was quenched by adding acetic acid (1 mL in 5 mL of THF). The reaction was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (EtOAc/hexanes, 1:1) to provide the aldol product **45** (0.4 g, 31% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.16 – 7.04 (m, 4H), 6.77 – 6.61 (m, 5H), 5.34 – 5.27 (m, 2H), 5.25 (s, 2H), 5.20 (s, 2H), 3.48 (s, 3H), 3.45 (s, 3H), 4.46 – 3.28 (m, 4H), 1.36 (s, 9H).

4-(4-Formylphenoxy)-3-hydroxybenzaldehyde (16)

To a stirred solution of compound **34** (0.5 g, 1.5 mmol) in THF (5 mL), potassium hydroxide (0.17 g, 3 mmol) in water (5 mL) was added at room temperature. The mixture was refluxed for two hours. After this the reaction mixture was cooled to room temperature and diluted with dichloromethane (100 mL). This was washed with dil. HCl solution (1 N, 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (EtOAc/hexanes, 1:1) to provide the hydroxy dialdehyde product **16** (0.28 g, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.96 (s, 1H), 7.88 (d, *J* = 8 Hz, 2H), 7.77 (d, *J* = 8 Hz, 1H), 7.73 (d, J = 2 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 7.10 (d, J = 8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.27, 190.40, 164.52, 151.87, 147.48, 132.21, 131.47, 131.65, 124.57, 118.64, 117.87

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CHAPTER 2

An Approach to the Synthesis of topopyrone D

Introduction

Topoisomerases I and II are nuclear enzymes and their main function is to relax superhelical tension in DNA during replication, transcription and repair events.[1] They do this relaxation by reversibly breaking one (topo-I) or both (topo-II) DNA strands and by unwinding the severed strands, which avoids the buildup of torsional energy in DNA helical structures. Cancerous cells tend to over-express topoisomerases and inhibition of which could be fatal to these cells. Hence, topoisomerase inhibitors could function as important anticancer agents.[2] In chemotherapy of cancer, mainly those agents which inhibit topo-II are used.[3] Selective inhibition of topo-I could also achieve the desired results. The prototype that is widely used as a selective topo-I inhibitor is camptothecin.[4] Other natural products that behave as selective topo-I poisons include the fungal metabolite, hypoxyxylerone and certain marine alkaloids.[5]

During the course of their screening program for specific inhibitors of human topoisomerase using recombinant yeast, Kanazava and coworkers discovered four structurally similar compounds. All these four compounds could be isolated from the culture broth of fungus, *Phomasp. BAUA2861*. They named these compounds as topopyrones A, B, C and D.[6]

All the topopyrones selectively inhibited recombinant yeast growth dependent expression of human topoisomerase I with IC_{50} values of 1.22, 0.15, 4.88 and 19.63 ng/mL, respectively.[7] The activity and selectivity of the topopyrones, especially that of topopyrone B, were comparable with those of camptothecin. The topopyrones did not inhibit human DNA topoisomerase II. However, they inhibited the relaxation of supercoiled pBR322 DNA by human DNA topoisomerase I. Thus, the topopyrones were found to be cytotoxic to all tumor cell lines when they were tested in vitro. All the topopyrones have potent inhibitory activity against herpes virus, especially varicella zoster virus (VZV). Topopyrone B showed

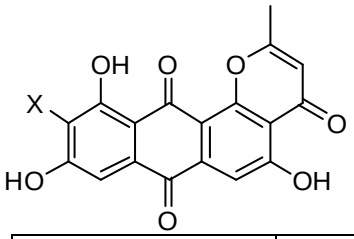
inhibitory action, with EC_{50} value of 0.038 µg/mL, against VZV growth. This is twenty four times stronger than that of acyclovir. The topopyrones showed inhibitory action against gram positive bacteria.[8]

In the antiviral assay, only topopyrone B exhibited potent viral inhibitory activity. However, topopyrone D inhibited viral replication. Hence it also could be used as a mild antiviral agent. Topopyrones A and C did not exhibit any viral inhibitory activity.[6, 8]

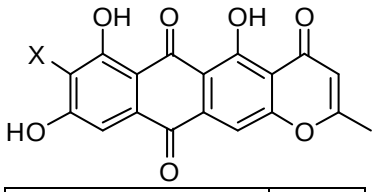
The structural elucidation of topopyrones was also done by Kanazava and coworkers by spectral analysis of the chemical derivatives. These compounds contain an anthraquinone moiety with a fused pyrone moiety. Topopyrones B and D contain a chlorine atom whereas C and D do not have it. They observed that topopyrones B and D could be obtained from topopyrones A and C, respectively, by a Wessely-Moser type rearrangement.[6, 8]

After detailed chemical and spectral studies, the structures of topopyrones were interpreted as given below.

Figure 1 : Topopyrones A, B, C and D.



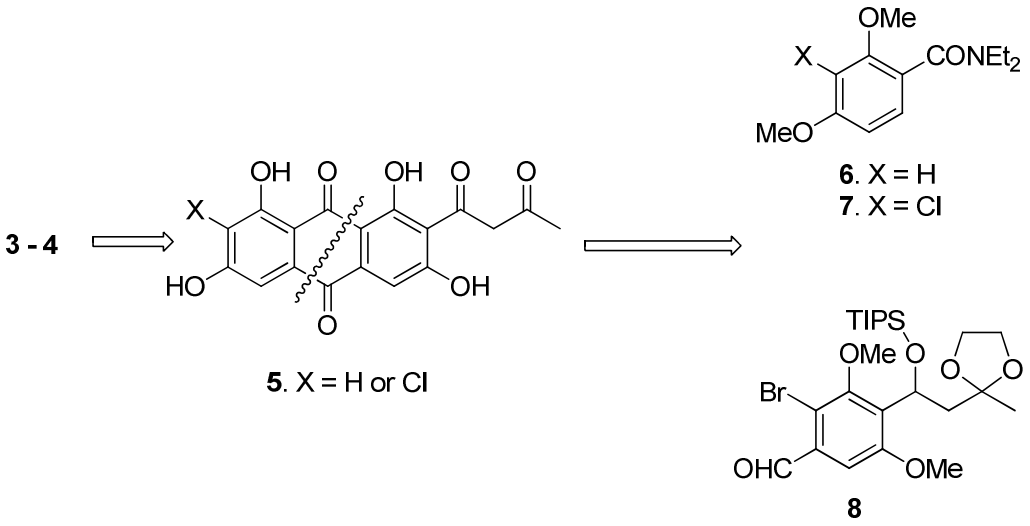
	X
Topopyrone A (**1**)	Cl
Topopyrone C (**2**)	H



	X
Topopyrone B (**3**)	Cl
Topopyrone D (**4**)	H

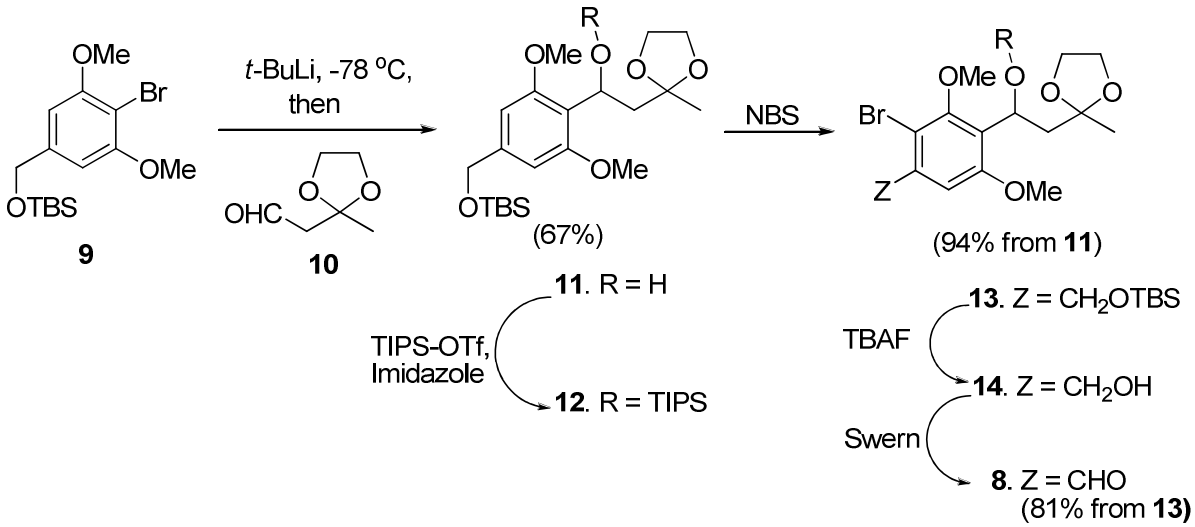
The first synthesis of topopyrones B and D was reported by Ciufolini and coworkers.[9] The authors observed that exposure of **1** and **2** to alkali, led to the rearrangement forming **3** and **4** respectively. This showed that topopyrones B and D are thermodynamically favored. They envisioned that B and D could be formed by cyclization of intermediate **5** under thermodynamically controlled conditions. Their synthetic strategy is shown below.

Figure 2



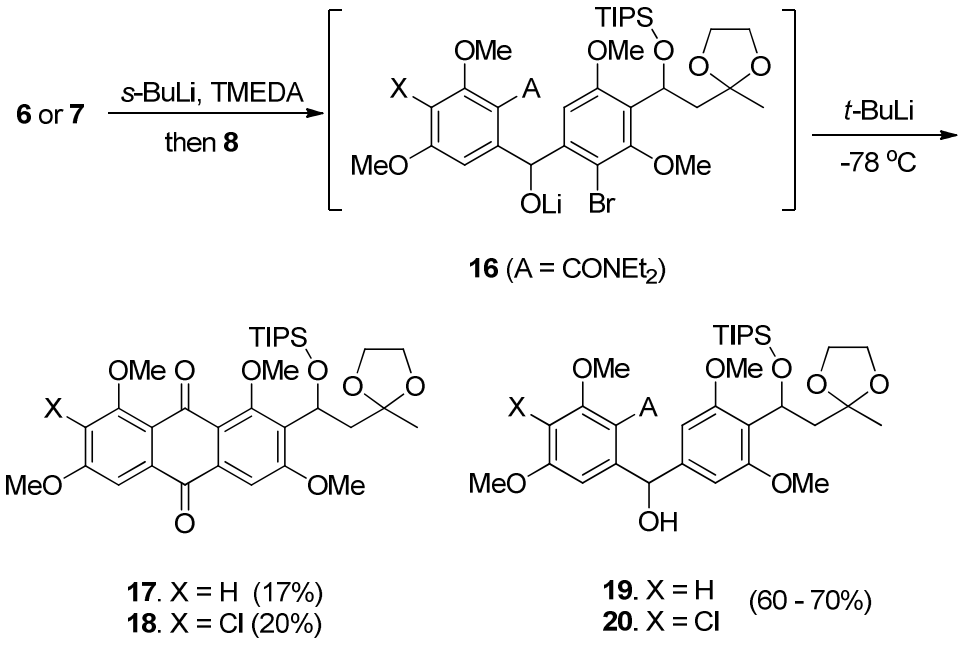
They planned to assemble the anthraquinone core of the target molecule by the condensation of fragments **6** or **7** with **8**. Their synthesis started with the formation of **8**.

Scheme 1: Preparation of Fragment **8**



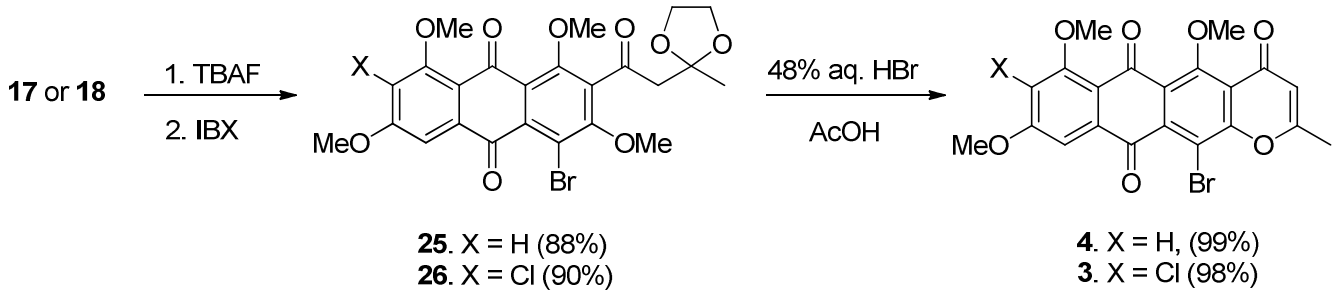
They achieved the condensation of fragments **6** or **7** with **8** by a transformation involving a one-pot, three-step reaction sequence, as shown below.

Scheme 2: Anthraquinone Assembly



From Scheme 2 it can be seen that the desired cyclized products **17** and **18** were obtained in low yields with the debrominated **19** and **20** obtained as the major products. Finally, the synthesis was completed as shown below.

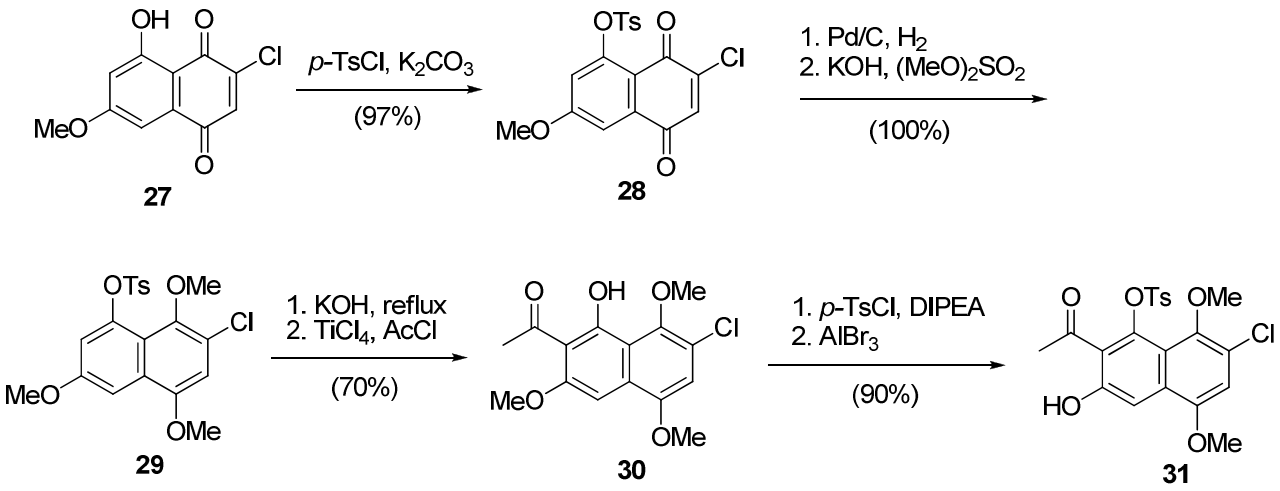
Scheme 3: Synthesis of topopyrones B and D



Thus the syntheses of topopyrones B and D were completed in 11 steps with 8% overall yield. The main disadvantage of this synthesis was the poor yield of the key cyclization step shown in Scheme 2.

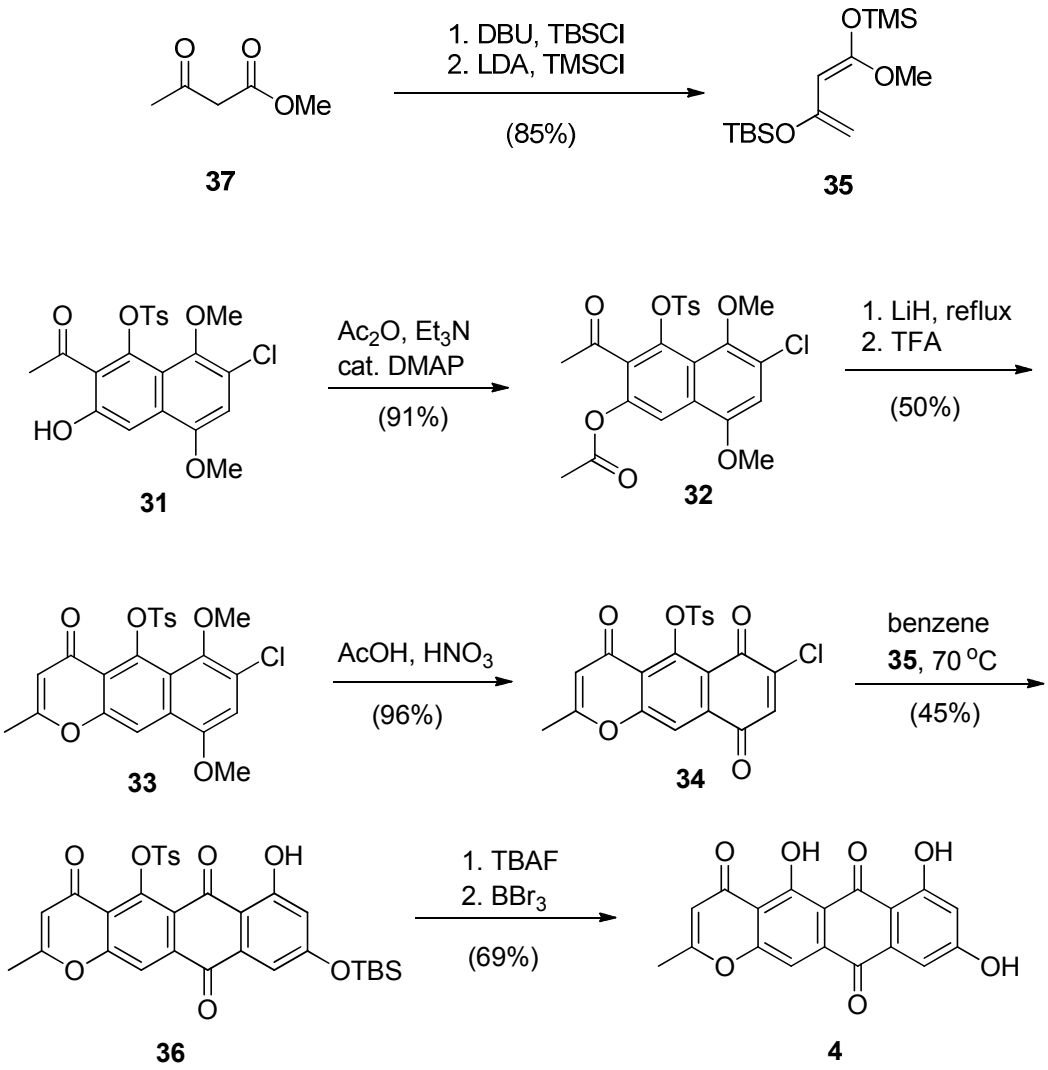
The second synthesis of topopyrones B and D was reported by Hecht and coworkers.[10] They also reported the synthesis of topopyrones A and C. They first assembled the three rings on the right hand side of the topopyrone molecule (as shown in Figure 1) and the final ring on the left hand side was formed by a Diels-Alder reaction. The initial steps are shown in Scheme 4.

Scheme 4: Synthesis of the core structure



After the formation of the core structure, synthesis of topopyrone D was completed as shown in Scheme 5. They used a Diels-Alder reaction of **34** with the butadiene **35** as the key step.

Scheme 5: Completion of the synthesis

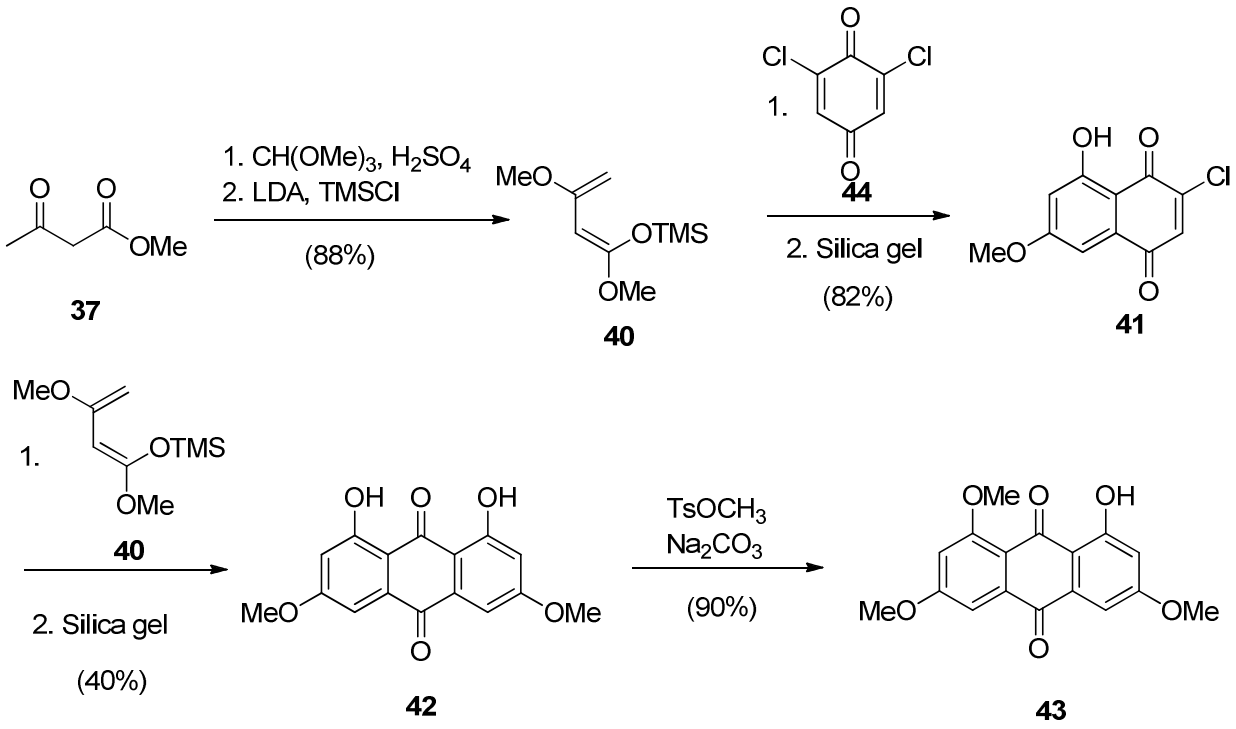


Thus, the synthesis of topopyrone D was completed in 16 steps in 8.7% overall yield. The main drawback of the synthesis was the key Diels-Alder reaction was performed towards the end of the synthesis, decreasing the overall yield of the synthetic sequence.

The first total synthesis of topopyrone C was reported by Dallavalle and coworkers.[11] Their synthetic strategy was similar to our strategy for the synthesis of topopyrone D. Their synthetic approach was based on the Marschalk alkylation reaction of appropriately

substituted anthraquinone, followed by a Baker-Venkataraman chain elongation and an acid-catalyzed cyclization to form the pyrone moiety. The formation of the key intermediate 1-hydroxy-3,6,8-trimethoxyanthraquinone was achieved by two subsequent Diels-Alder reactions with commercially available 2,6-dichloro-1,4-benzoquinone as shown in Scheme 6.

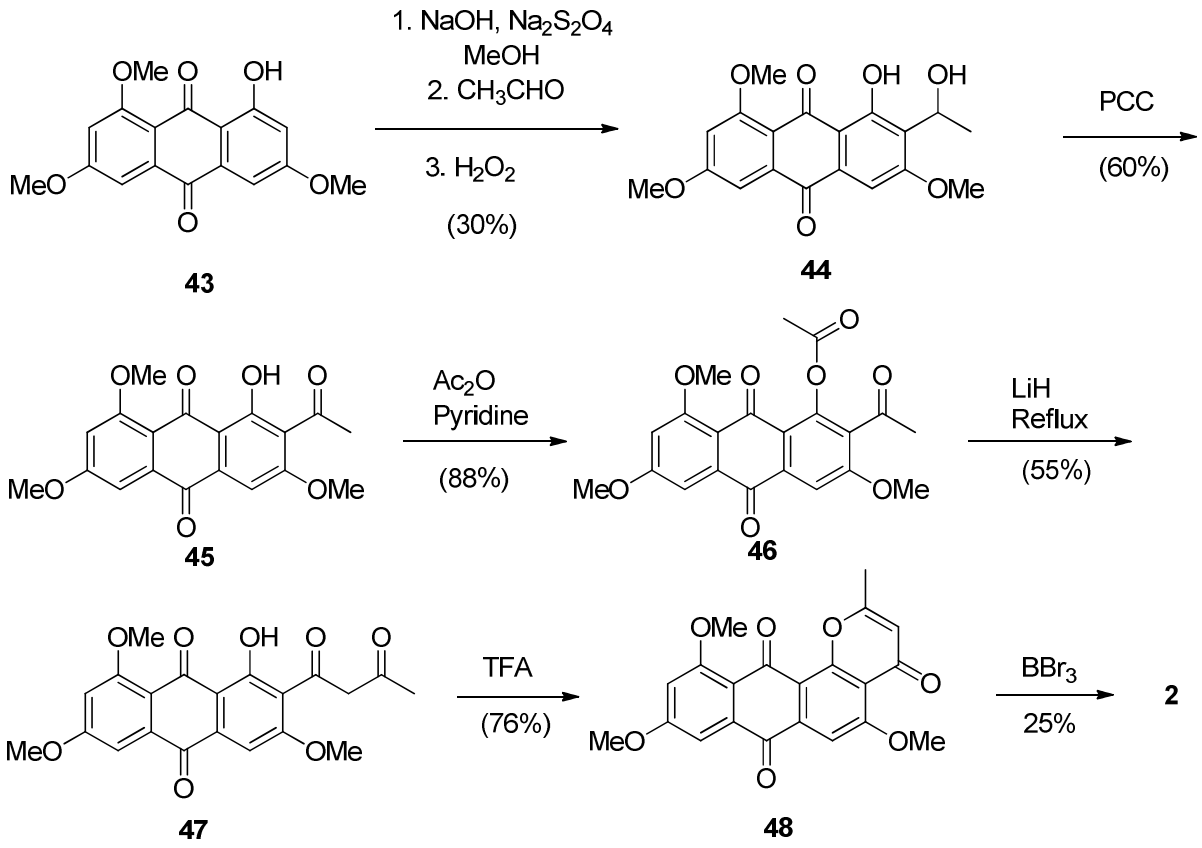
Scheme 6: Formation of anthraquinone core



With the key intermediate **43** in hand, the synthesis of topopyrone C was completed as shown in Scheme 7. First the compound **43** was substituted at the 2 position with acetaldehyde. Then the side chain elongation was done in a two-step reaction sequence. Finally, the cyclization was done by an acid-catalyzed reaction. These steps are summarized below in Scheme 7.

Thus, the synthesis of topopyrone C was completed in 13 steps with an overall yield of 0.43%. The disadvantages of this synthesis were the very poor overall yield and also the side-chain substitution and chain-elongation reactions were performed in multiple steps with poor yields.

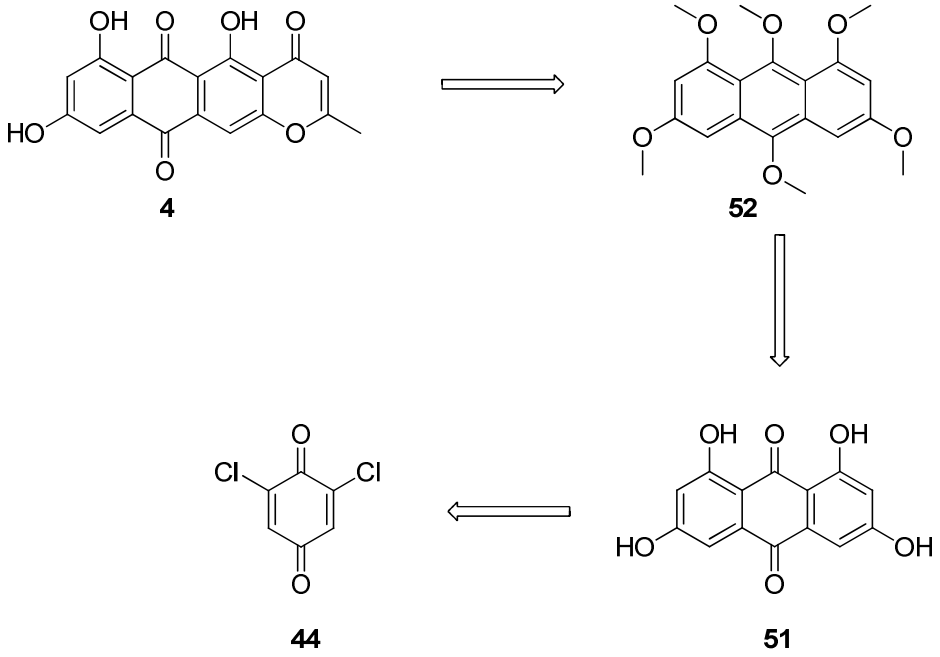
Scheme 7: Completion of synthesis of topopyrone C



Results and Discussion

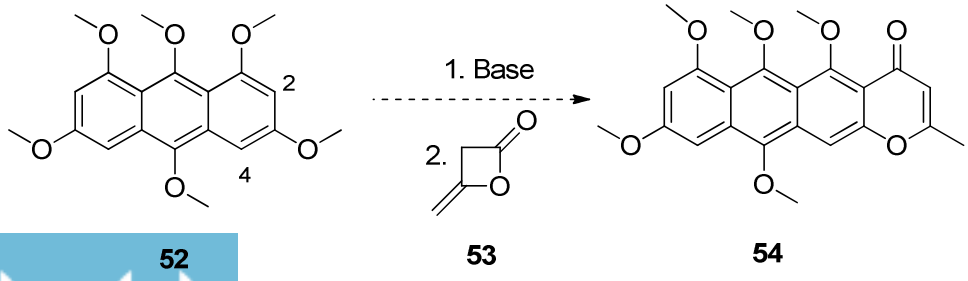
When the synthesis of topopyrone D was started, there was only one direct synthesis reported for this compound with very poor overall yields and a side reaction dominating the key step. Since the title compound could be an important anticancer agent, an effective synthesis was attempted. Our initial synthetic strategy is shown below.

Scheme 8: Retrosynthetic analysis



Thus, our synthesis started from commercially available 2,6-dichlorobenzoquinone **44**. This could be converted to 1,3,6,8-tetrahydroxy-9,10-anthraquinone by two consecutive Diels-Alder reactions with an appropriate diene. This could be converted to hexamethoxy-anthracene by reductive methylation. The final pyrone-ring formation could be achieved in a single step from the commercially available 4-methylene-2-oxetanone **53**. This was the key step in our synthetic strategy.[12]

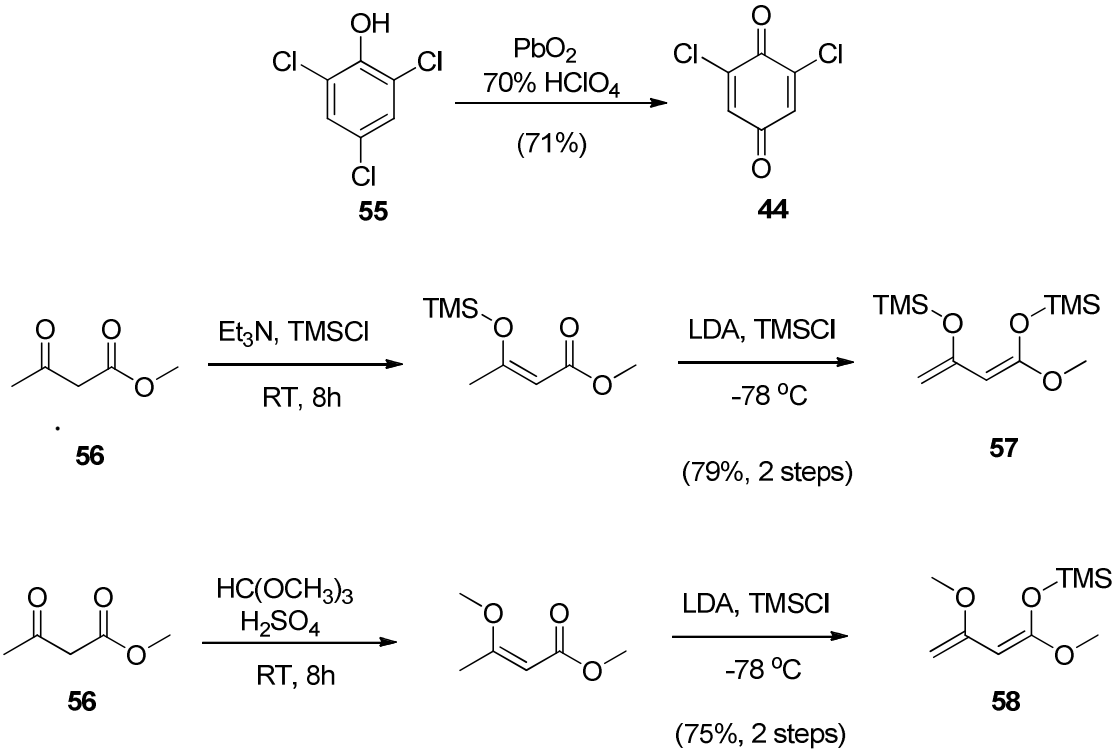
Scheme 9: Key step



The above reaction could occur because the hydrogen at position 2 of compound **52**, is the most acidic, as it is in between the two methoxy groups.[13] This could be abstracted with an appropriate base and the anion so formed could react with compound **53** at the carbonyl carbon as it is electrophilic. This would break open the strained four-membered lactone ring and the alkoxide ion so formed would cyclize on the aromatic ring giving the pyrone moiety. Finally the compound could isomerize to give the more stable enone.

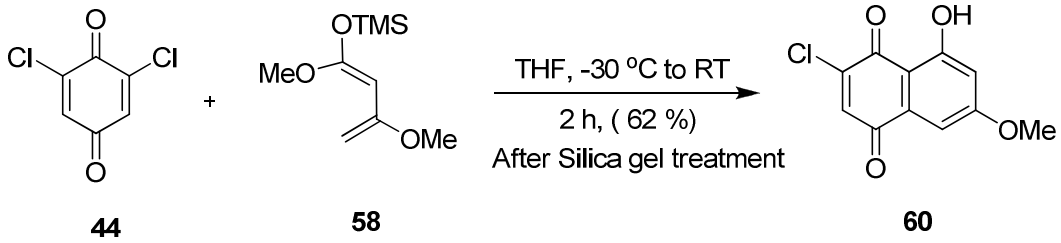
The synthesis started with the formation of 2,6-dichlorobenzoquinone **44** from commercially available 2,4,6-trichlorophenol **55**.[14] The dienes used for the synthesis were prepared as shown in Scheme 10.[15]

Scheme 10



With the diene and dienophile in hand, the Diels-Alder reaction was attempted. First, the quinone **44** and excess of the diene **58** were reacted at room temperature. It was found that even though excess diene was used, only one Diels-Alder reaction occurred to give the adduct, which was then treated with silica gel to give the aromatized product.[16]

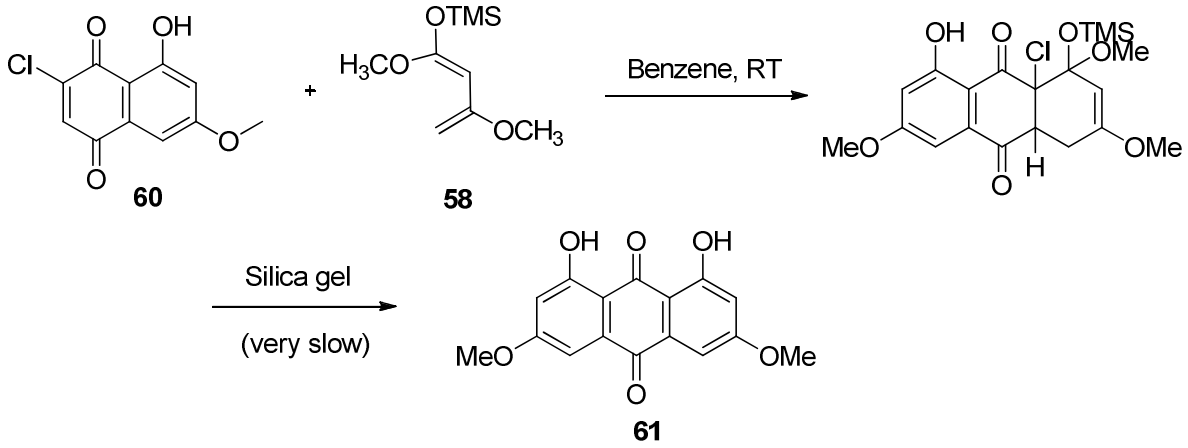
Scheme 11



44 **58** **60**

However, when the second Diels-Alder reaction was attempted, with the same diene, it was found that the adduct could be formed easily. But, when this was treated with silica gel, the aromatization was very sluggish and took days to complete. Also the adduct and the aromatized product had the same $R_{f\ value}$ and could not be purified by column chromatography.[17]

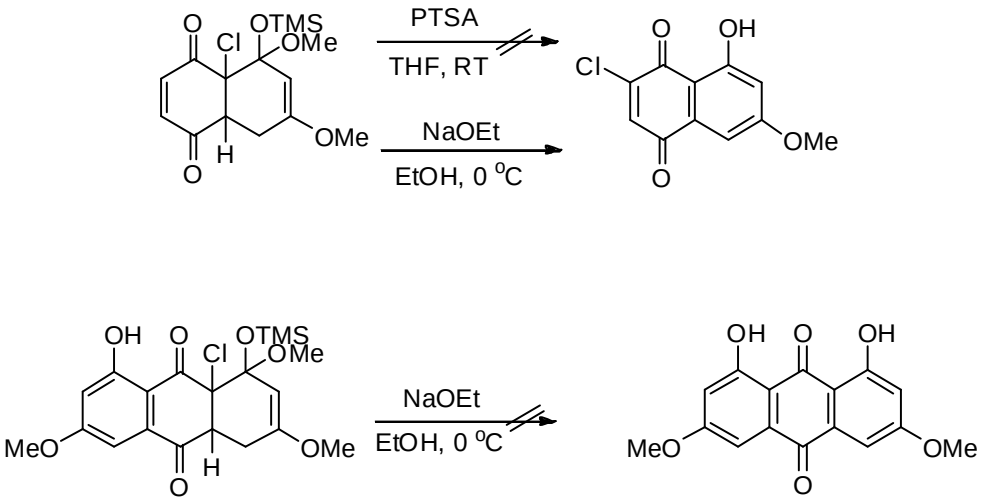
Scheme 12



60 **58** **61**

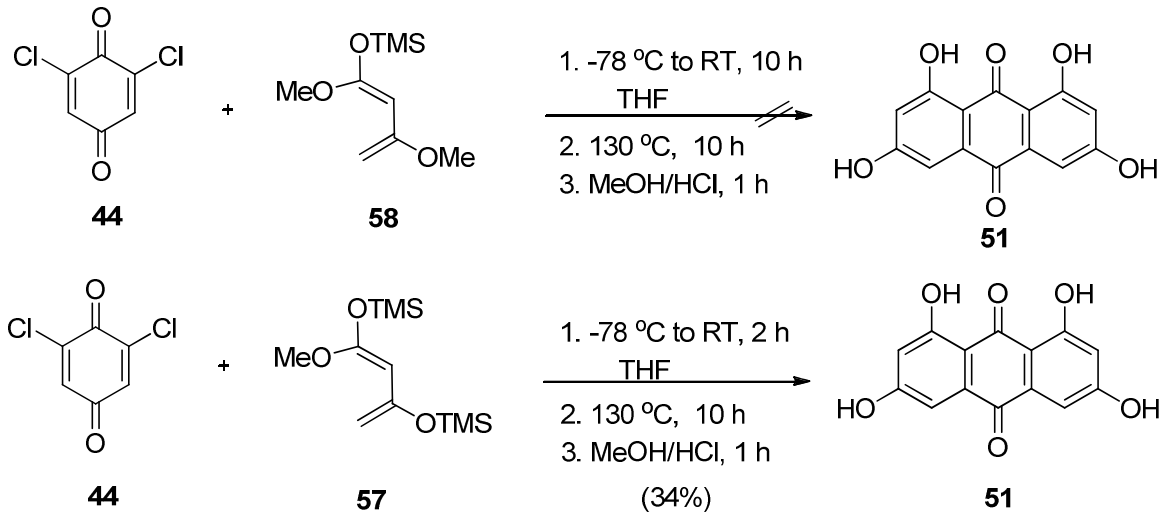
To make the aromatization of the adduct faster and more efficient a stronger acid and base were tried. It was found that the aromatization of the adduct of the first Diels-Alder reaction proceeded smoothly with sodium ethoxide. However, when this was tried on the adduct of the second Diels-Alder reaction was still slow and resulted in decomposition.

Scheme 13



There are methods available in the literature to do both the Diels-Alder reactions in one step. When this reaction was tried with the diene **58**, it gave very poor yields of the anthraquinone. Then, the same reaction was tried with the diene **57** and this gave moderate yields of 1,3,6,8-tetrahydroxy-9,10-anthraquinone.[18]

Scheme 14

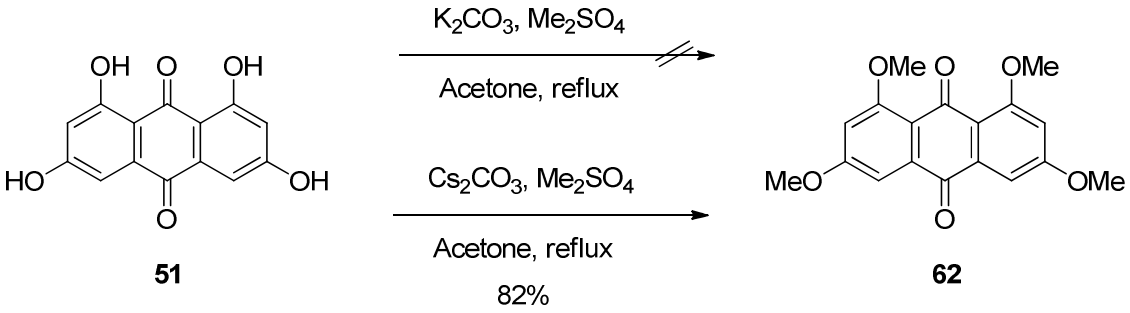


44 **58** **51**

44 **57** **51**

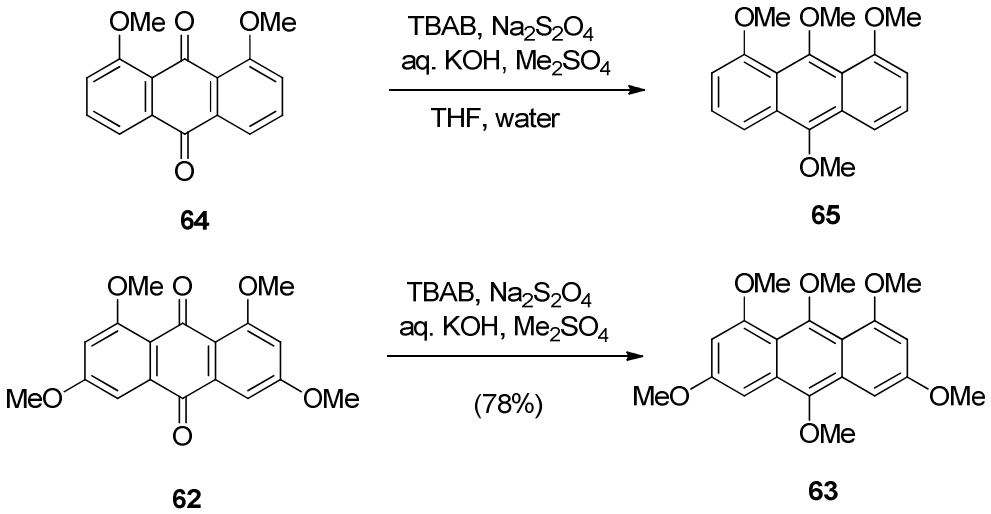
With the anthraquinone **51** in hand, the protection of hydroxyl and carbonyl groups was initiated. The protection of hydroxyl groups as methyl ethers was attempted with dry potassium carbonate as the base. This resulted in a mixture of dimethoxy and trimethoxy compounds. When cesium carbonate was used as a base, the reaction was clean and all the hydroxyl groups were conveniently protected as methoxy groups.[19]

Scheme 15



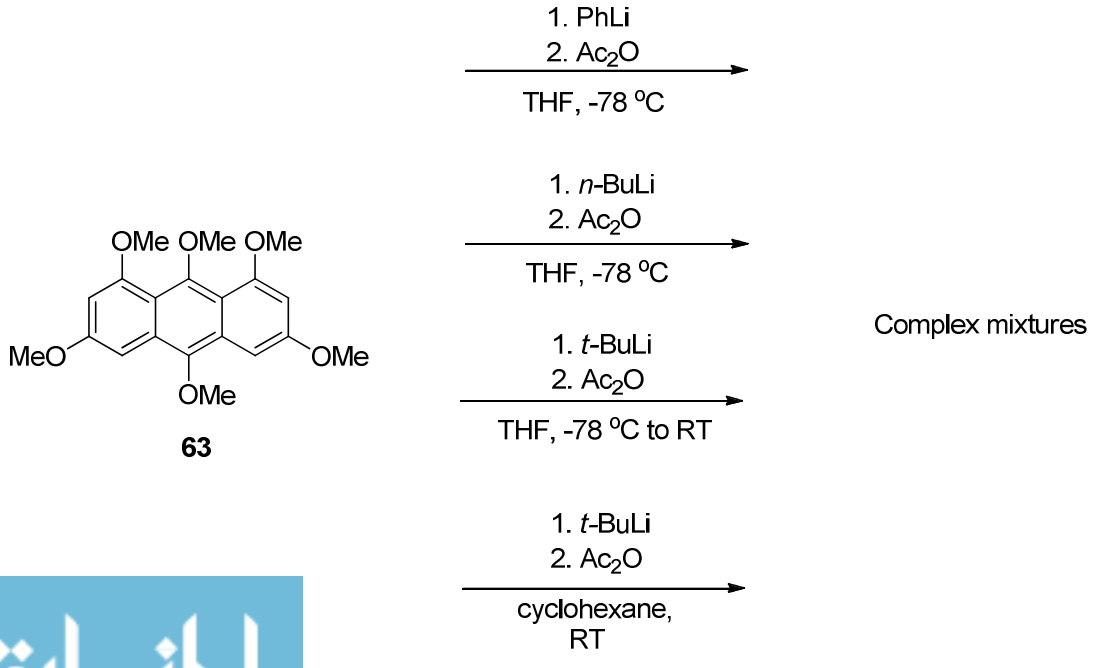
Tetramethoxyanthraquinone **62** was highly polar and not soluble in many organic solvents. Subsequently, the anthraquinone was reduced to an anthracene and the two hydroxyl groups were converted to methoxy groups in one pot. The procedure used for this 'reductive methylation' reaction was developed by Kraus and Man. [20] Before attempting this reaction on compound **62**, it was tried on a model compound and it proceeded smoothly. Then the same reaction was applied on compound **62**, which give the desired hexamethoxy anthracene compound **63** in very good yields.

Scheme 16



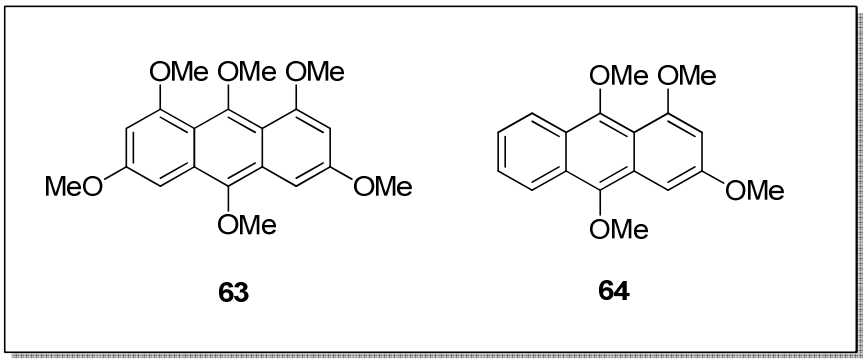
According to our initial hypothesis, the hydrogen at the 2 position of the hexamethoxyanthracene **63** should be the most acidic one. To verify this, compound **63** was treated with different bases under different reaction conditions. These attempts are summarized in Scheme 17. However, all these attempts resulted only in complex mixtures which were very difficult to separate.

Scheme 17



Since the simultaneous Diels-Alder reactions shown in Scheme 14 gave very poor yields of the anthraquinone **51,** the reactions of compound **63** could not be tried on a large scale. Every time compound **63** has to be made in seven steps before trying metal-hydrogen exchange reactions. Hence, it was planned to have a simpler model compound on which these trials could be attempted and if successful they could be reproduced with the original compound **63**. The model compound chosen was 1,3,9,10-tetramethoxyanthracene which could be made in four steps.

Figure 2 : Model compound

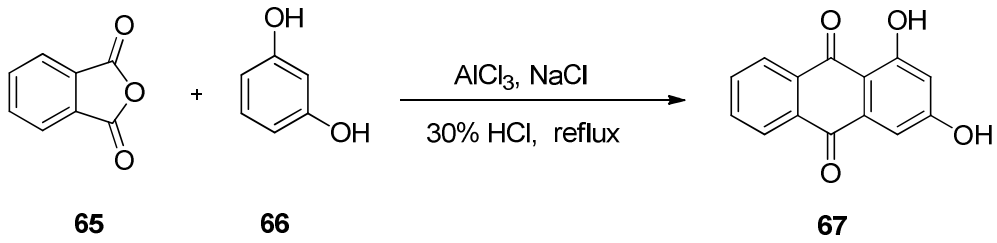


Compound **64** could be made from 1,3-dihydroxy-9,10-anthraquinone which is obtained in a single step by using a literature procedure.[21] According to this procedure, a mixture of aluminum chloride and sodium chloride was heated to 110 ^{o}C to melt and to the molten mass a homogeneous mixture of phthalic anhydride and resorcinol was added and heated to 165 ^{o}C and finally refluxed with 30% hydrochloric acid solution to get the product.

However, in our hands, this reaction gave very poor yields and the aluminum chloride and sodium chloride mixture did not melt at 110 ^{o}C. It was observed, that this mixture actually melted at 130 ^{o}C. Hence, the addition of a mixture of phthalic anhydride and resorcinol was done at 130 ^{o}C. Still, the reaction gave very poor yields. To optimize this

reaction, different initial temperatures and different equivalents of aluminum chloride and sodium chloride were tried to maximize the yield. The results are summarized in Table 1.

Table 1:

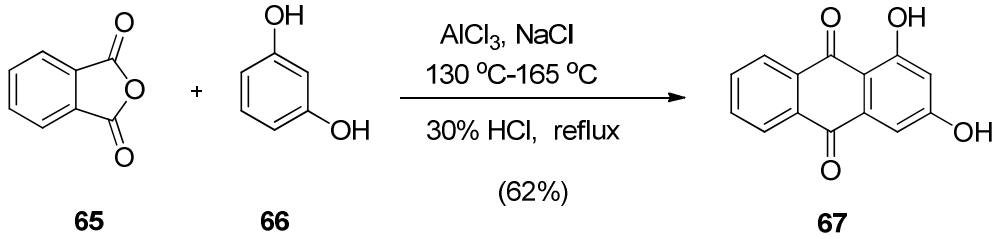


65 **66** **67**

Initial Temp (^{o}C)	Equiv. of $AlCl_3$	Equiv. of NaCl	% Yield
110	5	2.5	0
130	5	2.5	0
160	5	2.5	0
130	5	5	25
130	10	10	40
130	**10**	**5**	**62**

The conditions shown in the final row of the table worked very well giving a 62% yield of dihydroxyanthraquinone. These reaction conditions are depicted in Scheme 18

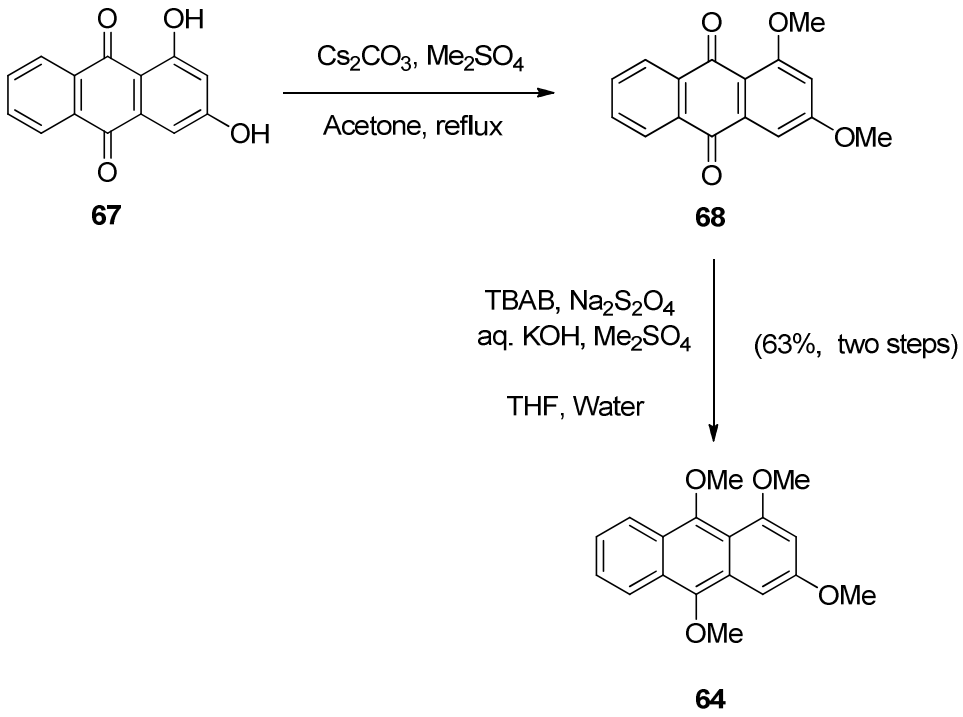
Scheme 18



65 **66** **67**

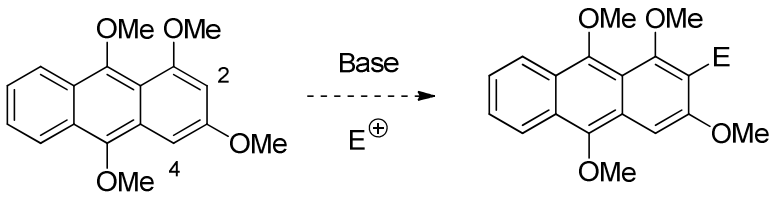
Dihydroxyanthraquinone **67** was converted to dimethoxyanthraquinone **68** by the procedure shown in Scheme 15. This compound was also poorly soluble in organic solvents and was recrystallized from acetone. This resulted in a decrease in the yield of the reaction. However, it was observed that the crude product itself was pure enough to be used for the next reaction. Dimethoxyanthraquinone **68** was converted to tetramethoxyanthracene **64** by the reductive methylation reaction as shown in Scheme 16. These reactions are summarized in Scheme 19.

Scheme 19



With the tetramethoxyanthracene **64** in hand, the anion formation reaction was tried with different bases, different electrophiles and different reaction conditions. The results of these reactions are summarized in Table 2.

Scheme 20



64

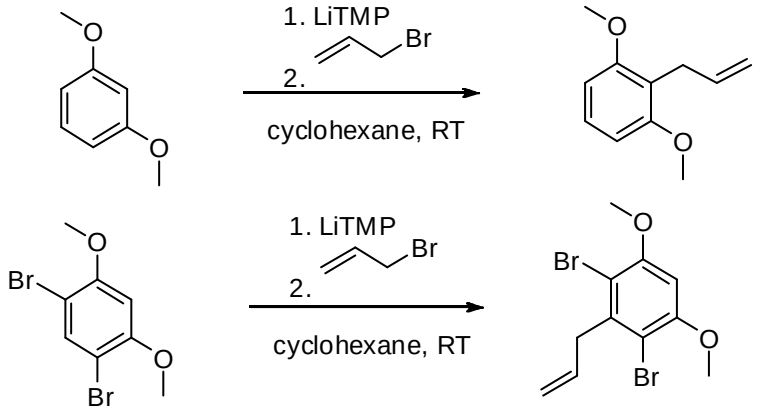
Table 2

Base	Electrophile	Solvent	T (^{o}C)	Results
n-BuLi	Ac_2O	THF	0	No reaction
t-BuLi	Ac_2O	THF	0	Complex mixture
LiTMP	Ac_2O	THF	0	Complex mixture
n-BuLi	MeI	THF	0	No reaction
t-BuLi	MeI	THF	0	Complex mixture
LiTMP	MeI	THF	0	Complex mixture
n-BuLi	MeI	THF	-78	No reaction
t-BuLi	MeI	THF	-78	No reaction
t-BuLi	MeI	Cyclo-hexane	RT	Complex mixture
t-BuLi	Allyl bromide	Cyclo-hexane	RT	Complex mixture

Since so many reactions failed with compound **64**, the same reaction was tried with simpler compounds to confirm that these reactions could occur in our reaction conditions (base, solvent etc). It was observed that both reactions in Scheme 21 proceeded well, giving substitutions at the most acidic positions. This clearly showed that tetramethoxyanthracene

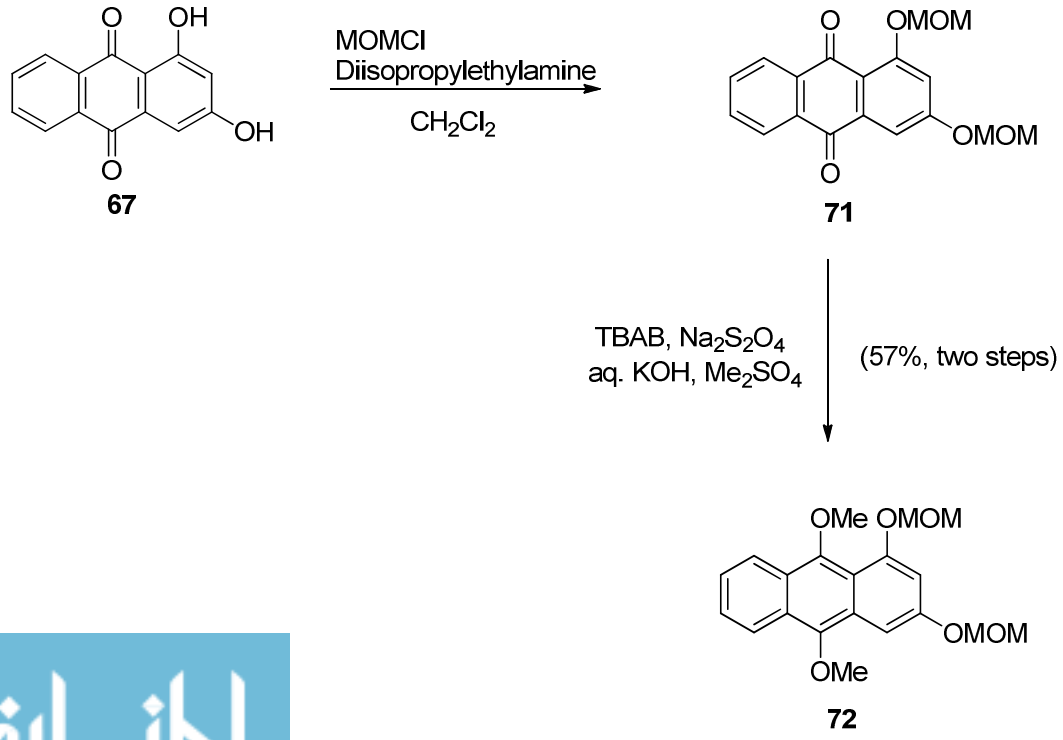
64 was either resistant to metal-hydrogen abstraction or unstable in the presence of the strong bases.

Scheme 21



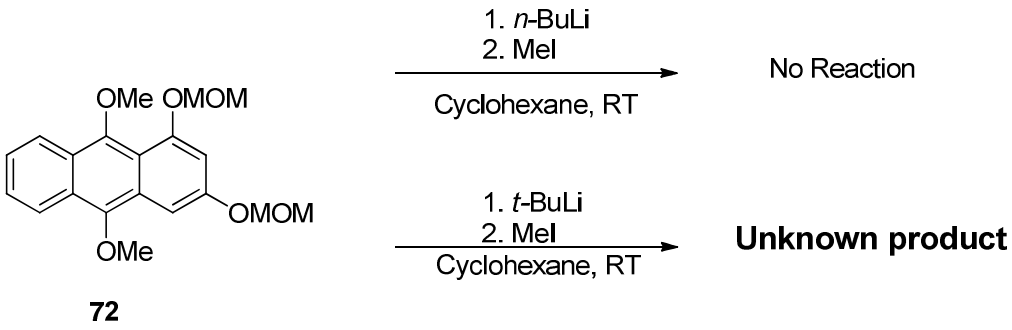
The methoxy groups on tetramethoxyanthracene **64** could not stabilize the anion on position 2 (or 4). For this reason, the hydroxyl groups could be protected with MOM groups which could stabilize the anion at position 2 (or 4), by coordination. The bis-MOM protected anthracene was prepared, as shown in Scheme 22.

Scheme 22



First, the hydroxyl groups were protected with MOM groups to give the bis-MOM anthraquinone **71**. Then this compound was subjected to reductive methylation to furnish the anthracene **72**. Anthracene **72** was then subjected to metal-hydrogen exchange first using *n*-BuLi, which resulted in no reaction, and then with the stronger base *t*-BuLi, which reacted. However, the product formed was not the desired one.

Scheme 23

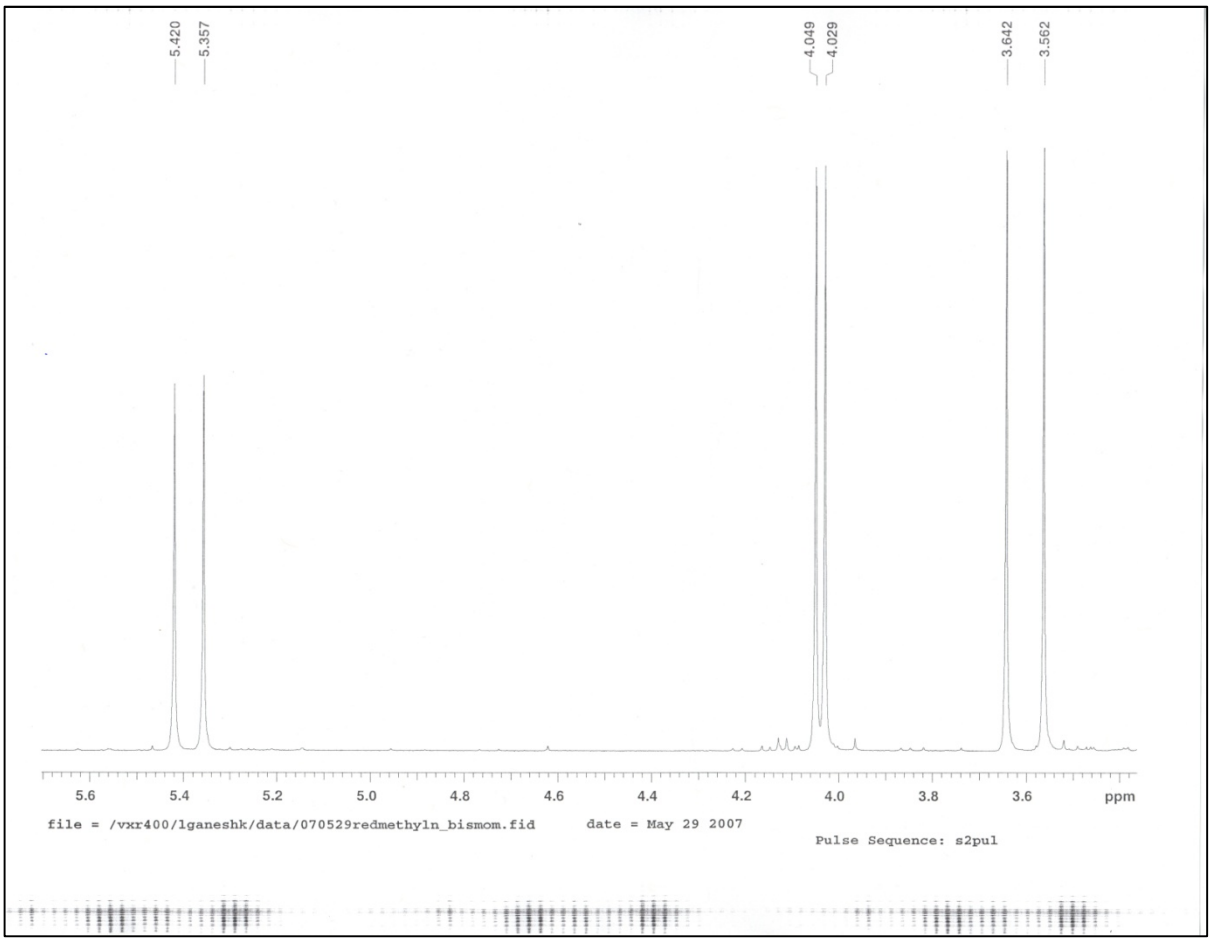


72

The ^{1}H NMR spectrum of the starting compound **72** and the product formed in the above reaction are given in Figures 3 and 4. These NMR spectra clearly showed that one of the methoxy groups at position 9 or 10 of **72** was missing in the final product. Hence, on treatment with the strong base, the methoxy group was substituted by the *tert*-butyl group.

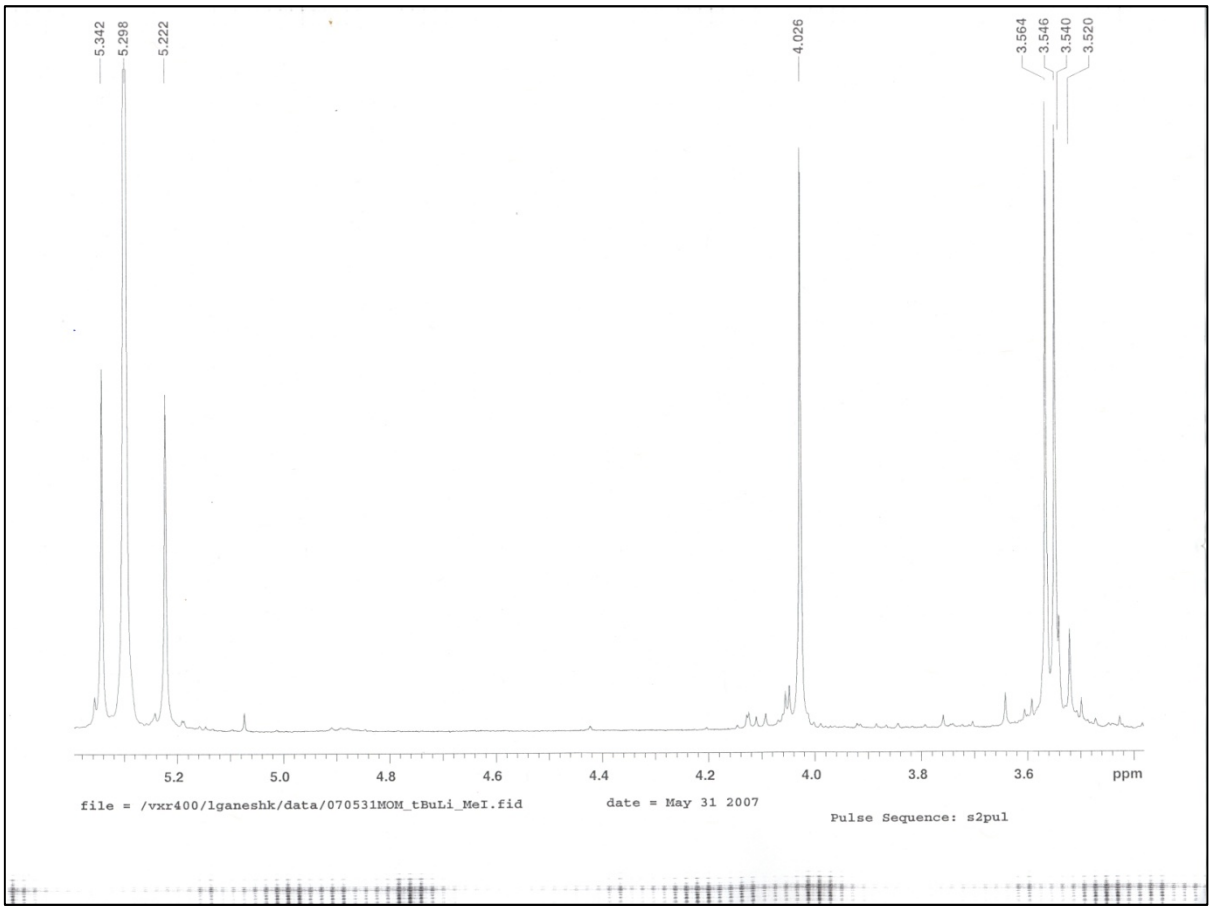
These types of substitutions at the 9 and 10 positions of the anthraquinone moiety were already reported in the literature.[22] It was interesting to observe that these substitutions took place even on an anthracene moiety. Hence, the metal-hydrogen exchange reaction was not a successful strategy for the synthesis of topopyrone D.

Figure 3: Methyl region of ^{1}H NMR spectrum of the starting compound



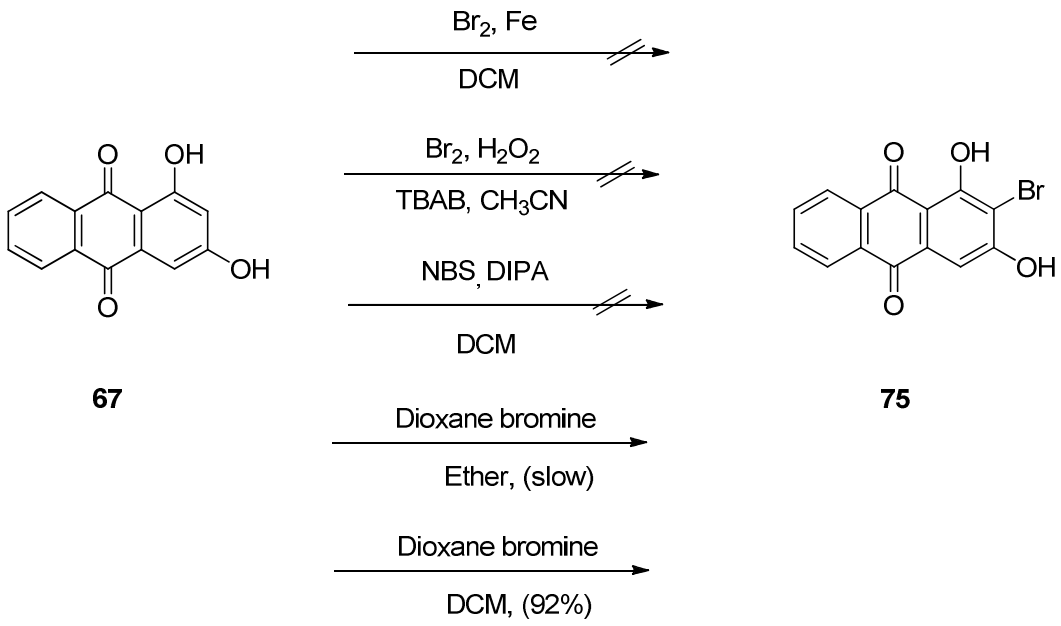
[Figures 3 and 4 show only the region from 3.5 to 5.5 ppm, where the peaks from methoxy and MOM groups could be observed. The peaks around 3.5 ppm were due to the methyl groups from MOM, peaks around 4 were due to the methoxy groups at position 9 and 10 of the anthracene moiety and peaks around 5 were due to the methylene groups from MOM groups. The peak at 5.3 in the spectrum of the product was due to dichloromethane solvent.]

Figure 4: Methyl region of ^{1}H NMR spectrum of the unknown product



Since the metal-hydrogen exchange reactions failed, it was planned to perform a metal-halogen exchange reaction. The advantage of the latter reaction was that the former reaction needed higher temperature, whereas the latter reaction could be performed at lower temperatures. This could avoid the side reactions which were observed with metal-hydrogen exchange reactions. Hence, it was decided to substitute a halogen atom at the 2-position of 1,3 dihydroxy-9,10-anthraquinone **67**. Different conditions of bromination were tried so that the substitution occurred selectively at the 2 position. They are given in Scheme 24.

Scheme 24

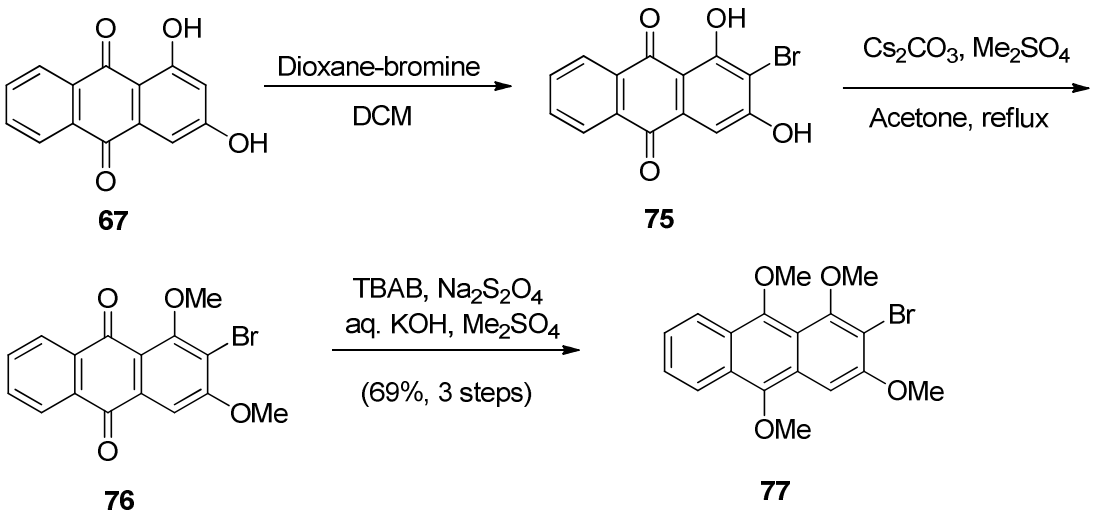


The dioxane-bromine complex was tried according to a literature procedure as it would be a mild brominating agent. The reagent was freshly prepared and used. This reaction was tried in diethyl ether as reported in the literature,[23] which was slow even after using an excess of the dioxane-bromine complex. This could be because the starting compound **67** was only sparingly soluble in ether. Hence, the solvent was changed to dichloromethane in which the reaction proceeded faster and cleaner than before.

Initially the product was recrystallized from ether. Later it was realized that the crude product formed was pure enough to use for the next reaction. So, after the reaction was complete, the solvent was removed and the product was taken for the next step.

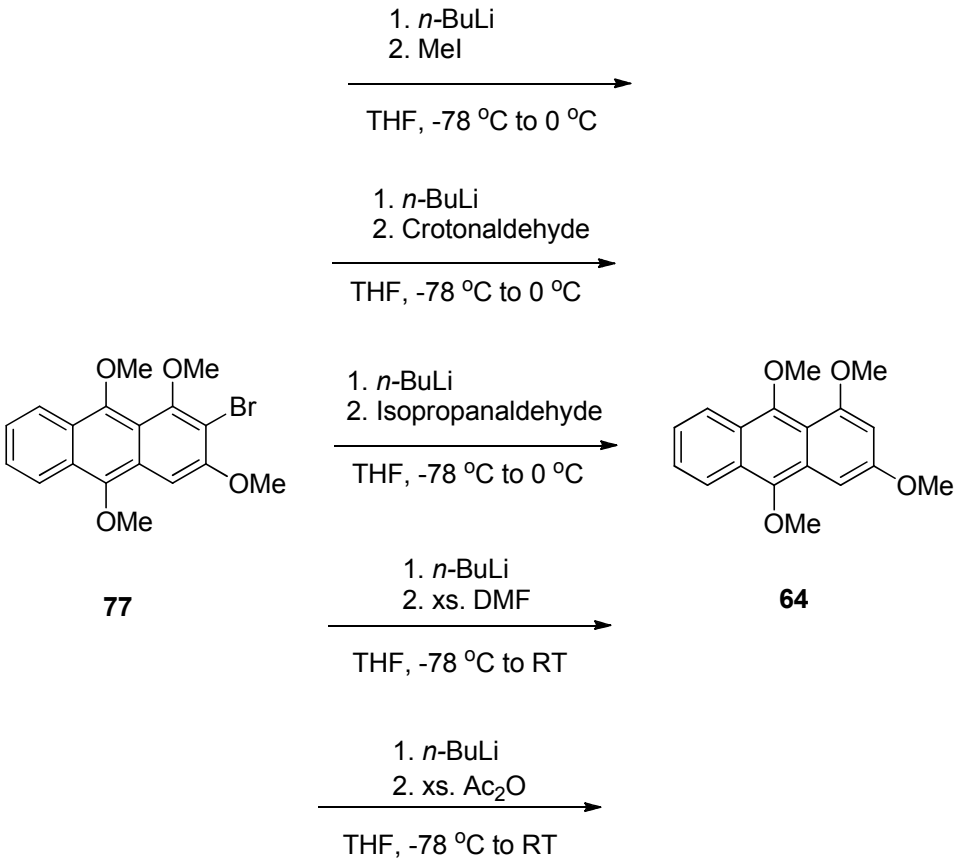
The bromoanthraquinone **75** was then subjected to O-methylation and then to reductive methylation. These two reactions were also performed as one-pot reactions. Hence, the bromination, O-methylation and reductive methylation reactions were completed as a one-pot, three-step reaction sequence as shown in Scheme 25.

Scheme 25



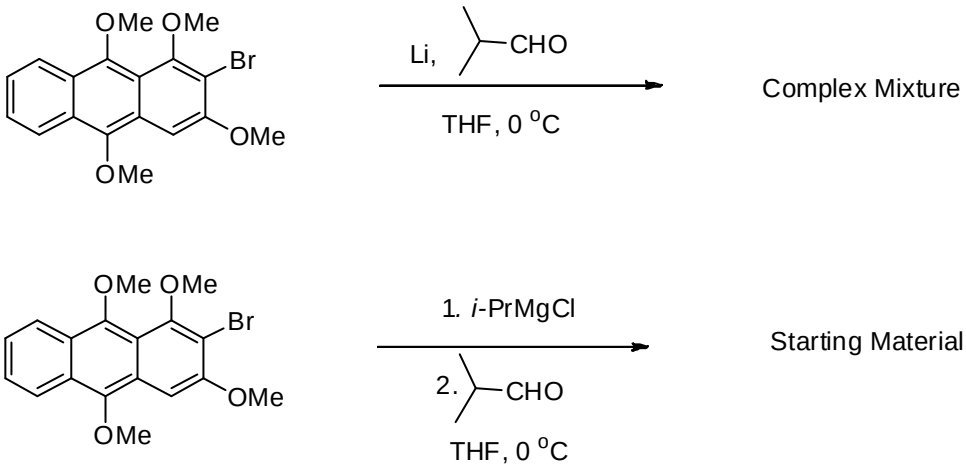
With the bromoanthracene **77** in hand, the metal-halogen exchange reactions were attempted. The anion was generated with *n*-BuLi at -78 ^{o}C and was quenched with the electrophile at the same temperature. This reaction was tried with different electrophiles.[24] In all the cases only the debrominated compound was observed.

Scheme 26



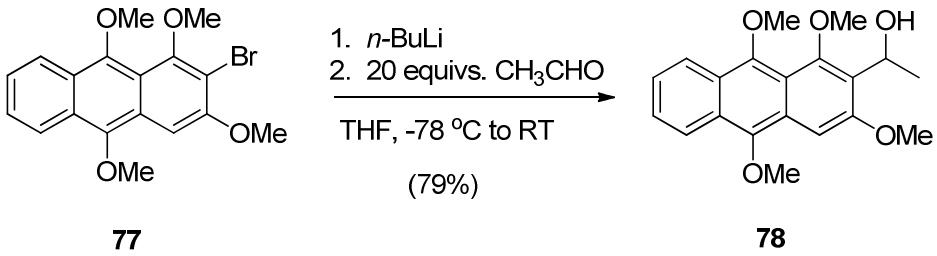
In the first three cases, the reaction temperature was increased only to 0 °C to avoid possible side reactions. In the last two cases, the reaction temperature was warmed to room temperature, after quenching with the electrophile. These conditions did not result in significant side reaction as the debrominated compound **64** was the only major product. Different bases were also tried for the above reaction.

Scheme 27



This clearly showed that the anion was formed when treated with *n*-BuLi, which did not react with the electrophile. However, when an excess of acetaldehyde (20 equivalents) was used as the electrophile, carbon-carbon bond formation occurred with good yields. The debrominated compound was a side product.

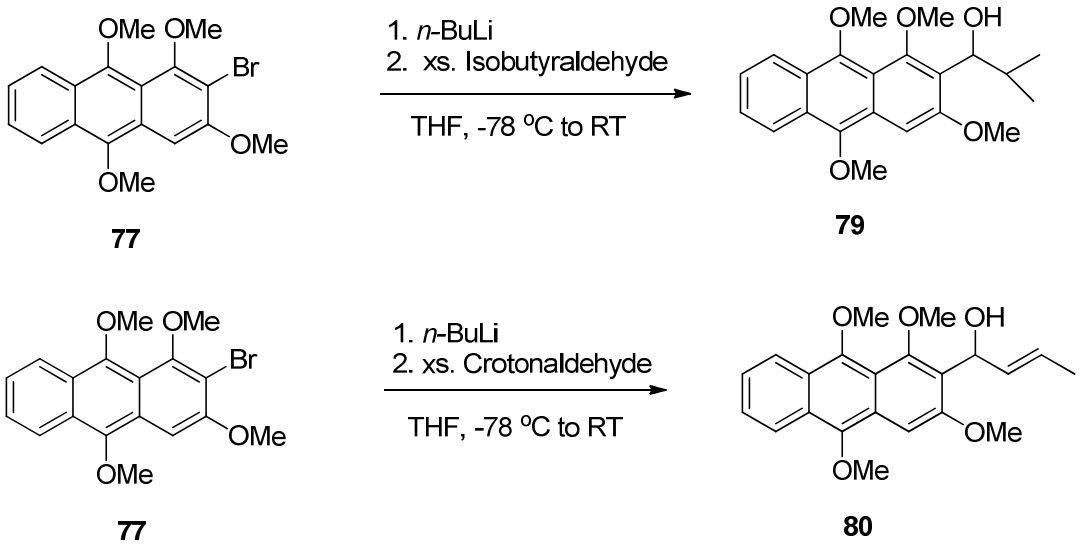
Scheme 28



77 **78**

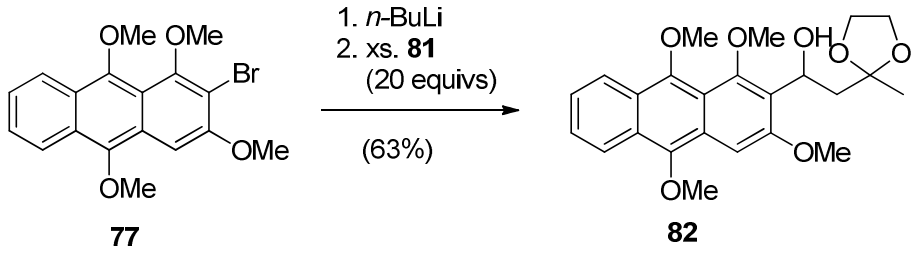
When the same conditions were applied with other aldehydes, the reactions occurred with comparable yields. However, when ketones (acetone) or anhydrides (acetic anhydride) were used, the reaction failed. This showed that only aldehydes could be used. We tried to optimize the above reaction by using ten and then five equivalents of acetaldehyde. The reactions still occurred, but with poorer yields.

Scheme 29



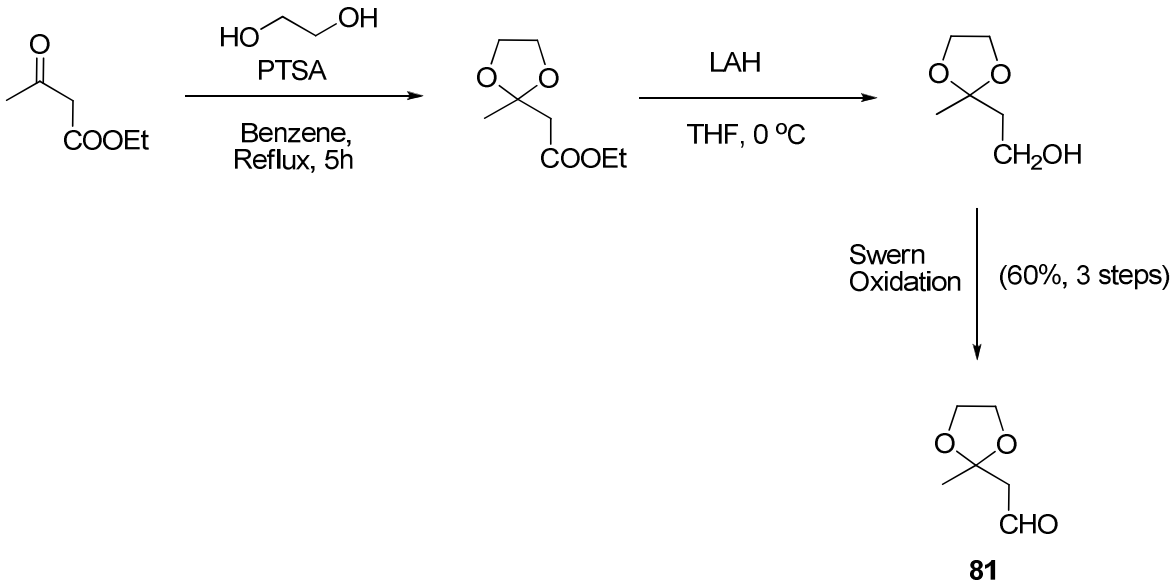
At this point, the synthesis was closer to the previous synthesis of Ciufolini and coworkers if the electrophile used in the above reaction was protected 3-oxobutanal **81** as shown in Scheme 3.[9] This reaction under the same conditions as shown in Scheme 29, gave a 63% yield of the corresponding alcohol.

Scheme 30



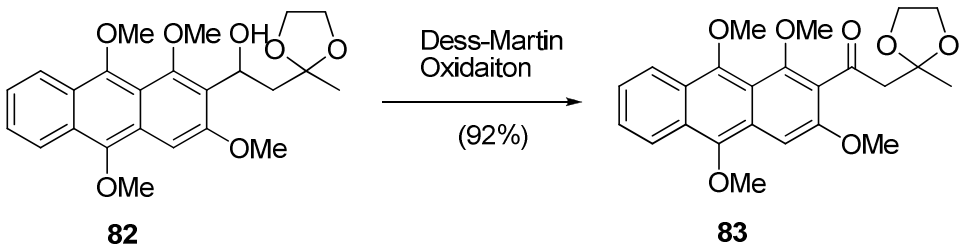
The aldehyde **81** used in Scheme 30 was made from ethyl acetoacetate as shown in Scheme 31.

Scheme 31



The benzylic alcohol **82** was oxidized to the corresponding ketone **83**. Among the few oxidizing agents tried, the Dess-Martin reagent was found to be the most convenient one, producing compound **83** in excellent yields.[25]

Scheme 32



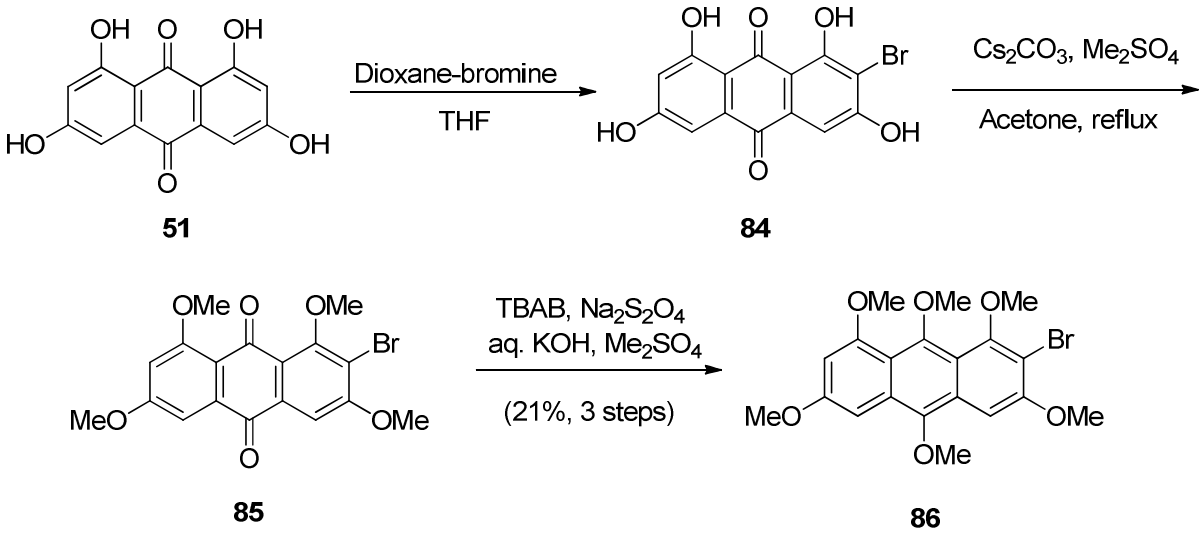
Compound **83** was similar to the intermediate **25** made by Ciufolini and coworkers. This compound could be oxidized to a quinone easily. This on treatment with HBr would form the pyrone ring. Finally, deprotection would give the synthesis of a model compound of

topopyrone-D. The same route has to be applied to 1,3,6,8-tetrahydroxy-9,10-anthraquinone **51**, to complete the formal total synthesis of topopyrone D.

First, the anthraquinone **51** was brominated. The compound **51** was only sparingly soluble in dichloromethane. Hence, THF was used as the solvent. However, this reaction was slower as compared with the model compound, which could be because only one equivalent of dioxane-bromine complex could be used to avoid multiple brominations.

This product was taken for the next reaction, even though this was only 90% pure. The methylation and reductive methylation were completed as one pot reactions. These reactions proceeded with lower yields compared with the model compound.

Scheme 33



Few metal-halogen exchange reactions were tried with compound **86**. It was found, even though the same conditions were applied, only complex mixtures were obtained from this reaction. This step would be optimized to complete the total synthesis of topopyrone D.

Experimental Section

1,3,6,8-Tetrahydroxyanthracene-9,10-dione (51)

To a stirred solution of 2,6-dichloro-1,4-benzoquinone (0.18 g, 1 mmol) in dry THF cooled to -78 ^{o}C, was added 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene (0.78 g, 3 mmol). The solution was warmed to room temperature and stirred for two hours. The solvent was removed and the resulting mass was pyrolyzed at 120 ^{o}C for 12 hours. The mass was cooled to room temperature and 20 mL of 3:1 methanol/10% HCl (aq) was added to the mixture and boiled for one hour. After this the reaction mixture again cooled to room temperature and diluted with 20 mL of brine. The mixture extracted with 3x50 mL of ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated, and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:1) to provide compound **51** (0.09 g, 34% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J*= 3 Hz, 2H), 6.65 (d, *J* = 3 Hz, 2H).

1,3,6,8-Tetramethoxyanthracene-9,10-dione (62)

To a stirred solution of 1,3,6,8-tetrahydroxyanthracene-9,10-dione **51** (0.27 g, 1 mmol) in acetone (20 mL), cesium carbonate (2.6 g, 8 mmol) and dimethyl sulfate (0.76 g, 0.57 mL, 6 mmol) were added. The reaction mixture boiled for six hours and cooled to room temperature. The liquid was decanted and the solid was washed with 2x20 mL of acetone. The acetone washings were combined and the solvent was removed. The crude product was taken as such for the next reaction. The crude product could also be crystalized from ether to give pure 1,3,6,8-tetramethoxyanthracene-9,10-dione **62** (0.27 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*= 4 Hz, 2H), 6.94 (d, *J* = 4 Hz, 2H), 3.98 (s, 3H), 3.94 (s, 3H).

1,3,6,8,9,10-Hexamethoxyanthracene (63)

1,3,6,8-tetramethoxyanthracene-9,10-dione **62** (0.32 g, 1 mmol) and tetrabutylammonium bromide (35 mg, 0.1 mmol) were taken in THF (10 mL) and water (4 mL). To this stirred solution was added aqueous solution of sodium dithionite (1 g, 6 mmol) in 5 mL water. After 30 minutes of stirring at room temperature potassium hydroxide (1.6 g, 28 mmol) in 5 mL water was added. After 15 minutes dimethyl sulfate (2.66 g, 2 mL, 21 mmol) was added. The mixture was stirred for six hours and diluted with 50 mL dichloromethane. This was washed with 50 mL of sodium chloride solution and the organic layer was separated. It was dried over anhydrous $MgSO_4$, concentrated and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:4) to provide compound **63** (0.28 g, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J*= 2.5 Hz, 2H), 6.41 (d, *J* = 2.5 Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H).

1,3-Dihydroxyanthracene-9,10-dione (67)

A mixture of solid aluminum chloride (12 g, 90 mmol) and sodium chloride (3 g, 45 mmol) were taken in a dry argon-flushed 100 mL round bottom flask fitted with a condenser and the mixture heated to 130 ^{o}C to form a molten mass. To this stirred mass, a homogeneous mixture of phthalic anhydride (1.32 g, 9 mmol) and resorcinol (1 g, 9 mmol) were added slowly (white fumes evolved during the addition) and the mixture heated to 165 ^{o}C for five hours. This mixture was cooled to -30 ^{o}C (dry ice + acetonitrile), 90 mL of 10% aqueous HCl was added and then heated to 100 ^{o}C for one hour. Finally the reaction mixture cooled to room temperature and extracted with 3x100 mL of ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$, concentrated and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:2) to provide compound **67** (1.3 g, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J*= 8 Hz, 1H), 8.23 (d, *J* = 8 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.28 (d, *J*= 2.5 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H).

1,3-Dimethoxyanthracene-9,10-dione (68)

To a stirred solution of 1,3-dihydroxyanthracene-9,10-dione **67** (0.24 g, 1 mmol) in acetone (20 mL) were added cesium carbonate (2.6 g, 8 mmol) and dimethyl sulfate (0.76 g, 0.57 mL, 6 mmol). The reaction mixture refluxed for six hours and cooled to room temperature. The liquid was decanted and the solid was washed with 2x20 mL of acetone. The acetone washings were combined and the solvent was removed. The crude product was taken for the next reaction without further purification. The crude product could also be crystalized from acetone to give pure 1,3-dimethoxyanthracene-9,10-dione **68** (0.18 g, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.16 (m, 2H), 7.89 – 7.82 (m, 2H), 7.40 (d, *J* = 3.2 Hz, 1H), 7.02 (d, *J*= 3.2 Hz, 1H), 4.03 (s, 3H), 4.01 (s, 3H).

1,3,9,10-Tetramethoxyanthracene (64)

1,3-dimethoxyanthracene-9,10-dione **68** (0.27 g, 1mmol) and tetrabutylammonium bromide (35 mg, 0.1 mmol) were taken in THF (10 mL) and water (4 mL). To this stirred solution was added aqueous solution of sodium dithionite (1 g, 6 mmol) in 5 mL water. After 30 minutes of stirring at room temperature potassium hydroxide (1.6 g, 28 mmol) in 5 mL water was added. After 15 minutes dimethyl sulfate (2.66 g, 2 mL, 21 mmol) was added. The mixture was stirred for six hours and diluted with 50 mL dichloromethane. This was washed with 50 mL of sodium chloride solution and the organic layer was separated. It was dried over anhydrous $MgSO_4$, the solvent was removed and the crude product was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:4) to provide compound 1,3,9,10-tetramethoxyanthracene **64** (0.28 g, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8 Hz, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.51 – 7.26 (m, 2H), 7.10 (d, *J* = 2 Hz, 1H), 6.49 (d, *J*= 2 Hz, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 4.00 (s, 3H), 3.99 (s, 3H).

1,3-Bis(methoxymethoxy)anthracene-9,10-dione (71)

First, MOMCl was prepared according to the JOC procedure.[26] Dimethoxy methane (1.5 g, 1.76 mL, 20 mmol) and zinc acetate (4 mg, 0.015 mmol) were taken in toluene (20 mL). To this stirred mixture acetyl chloride (1.57 g, 1.42 mL, 20 mmol) was added at room temperature for five minutes under stirring. This reaction mixture was warmed to 45 ^{o}C for four hours. After this, the reaction mixture was cooled to room temperature and checked NMR for reaction completion. This reaction mixture was used as directly for the next reaction.

1,3-Dihydroxyanthracene-9,10-dione **67** (0.18 g, 0.75 mmol) was taken in THF (10 mL) and diisopropylethylamine (0.4 g, 0.52 mL, 3 mmol) was added under stirring at room temperature. After addition of the amine the reaction mixture became a clear solution. To this solution the MOMCl solution (2 mmol from 20 mmol) prepared as above was added. This was kept under stirring for five hours and then reaction mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with ammonium chloride solution (50 mL) and then with brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (EtOAc/hexanes, 1:2) to provide the product 1,3-bis(methoxymethoxy)anthracene-9,10-dione **71** (0.16 g, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8 Hz, 1H), 8.28 (d, *J* = 8 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.46 (d, *J* = 2.5 Hz, 1H), 6.99 (d, *J*= 2.5 Hz, 1H), 5.49 (s, 2H), 5.41 (s, 2H), 3.61 (s, 3H), 3.59 (s, 3H).

9,10-Dimethoxy-1,3-bis(methoxymethoxy)anthracene (72)

1,3-Bis(methoxymethoxy)anthracene-9,10-dione **71** (0.16 g, 0.5 mmol) and tetrabutylammonium bromide (18 mg, 0.05 mmol) were taken in THF (10 mL) and water (4 mL). To this stirred solution was added aqueous solution of sodium dithionite (0.5 g, 3 mmol) in 3 mL water. After 30 minutes of stirring at room temperature potassium hydroxide (0.8 g, 28 mmol) in 3 mL water was added. After 15 minutes dimethyl sulfate (1.33 g, 1 mL, 10 mmol) was added. The mixture was stirred for six hours and diluted with 50 mL

dichloromethane. This was washed with 50 mL of sodium chloride solution and the organic layer was separated. It was dried over anhydrous $MgSO_4$, the solvent was removed and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:4) to provide compound 9,10-dimethoxy-1,3-bis(methoxymethoxy)anthracene **72** (0.16 g, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8 Hz, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.39 (d, *J* = 2.5 Hz, 1H), 6.87 (d, *J*= 2.5 Hz, 1H), 5.42 (s, 2H), 5.36 (s, 2H), 4.05 (s, 3H), 4.03 (s, 3H), 3.64 (s, 3H), 3.56 (s, 3H).

2-Bromo-1,3-dihydroxyanthracene-9,10-dione (75)

First dioxane-bromine complex in dioxane was prepared by adding bromine (0.88 g, 10 mmol) to dioxane at 0 ^oC. The solution was warmed to room temperature. This solution was used for the bromination reaction. This reagent was always freshly prepared and used immediately.

To the stirred solution of 1,3-dihydroxyanthracene-9,10-dione **67** (0.24 g, 0.26 mL, 1 mmol) in THF (10 mL), the freshly prepared dioxane-bromine solution was added (2 mL, 2 mmol) at 0 ^oC. The solution was warmed to room temperature and stirred for four hours. After this the solvent was removed and crude product was used for the next reaction without further purification. It can be purified by silica gel flash column chromatography (EtOAc/hexanes, 1:3) to give 2-bromo-1,3-dihydroxyanthracene-9,10-dione **75** (0.26 g, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J*= 8 Hz, 1H), 8.25 (d, *J* = 8 Hz, 1H), 7.96 – 7.93 (m, 2H), 7.45 (s, 1H).

2-Bromo-1,3-dimethoxyanthracene-9,10-dione (76)

To a stirred solution of 2-bromo-1,3-dihydroxyanthracene-9,10-dione **75** (0.31 g, 1 mmol) in acetone (20 mL) were added cesium carbonate (1.3 g, 4 mmol) and dimethyl sulfate (0.38 g, 0.3 mL, 3 mmol). The reaction mixture refluxed for six hours and cooled to room temperature. The solvent was removed and the crude product was taken directly for the

next reaction. The crude product could be crystallized from acetone to give pure 2-bromo-1,3-dimethoxyanthracene-9,10-dione **76**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 - 8.11 (m, 2H), 7.96 – 7.93 (m, 2H), 7.67 (s, 1H), 4.16 (s, 3H), 3.96 (s, 3H).

2-Bromo-1,3,9,10-tetramethoxyanthracene (77)

To the crude 2-bromo-1,3-dimethoxyanthracene-9,10-dione **76** prepared by the above procedure, solid tetrabutylammonium bromide (35 mg, 0.1 mmol), 10 mL of THF and 4 mL of water were added. To this stirred solution was added aqueous solution of sodium dithionite (1 g, 6 mmol) in 5 mL water. After 30 minutes of stirring at room temperature potassium hydroxide (1.6 g, 28 mmol) in 5 mL water was added. After 15 minutes dimethyl sulfate (2.66 g, 2 mL, 21 mmol) was added. The mixture was stirred for six hours and diluted with 50 mL of dichloromethane. This was washed with 50 mL of sodium chloride solution and the organic layer was separated. It was dried over anhydrous $MgSO_4$, the solvent was removed, and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:4) to provide 2-bromo-1,3,9,10-tetramethoxyanthracene **77** (0.26 g, 69% yield over three steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J*= 8 Hz, 1H), 8.20 (d, *J* = 8 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.38 (s, 1H), 4.08 (s, 6H), 4.04 (s, 3H), 4.00 (s, 3H), 3.96 (s, 3H).

1-(1,3,9,10-Tetramethoxyanthracen-2-yl)ethanol (78)

To the stirred solution of 2-bromo-1,3,9,10-tetramethoxyanthracene **77** (0.3 g, 0.8 mmol) in 8 mL THF, *n*-BuLi (2.5 M solution in hexane, 0.35 mL, 0.87 mmol) was added at -78 ^{o}C. This was stirred for 30 minutes at -78 ^{o}C and then the solution of acetaldehyde (0.7 g, 0.9 mL, 16 mmol) in 2 mL THF was added. The solution was warmed to room temperature and diluted with 50 mL dichloromethane and washed with 50 mL of ammonium chloride solution. The organic layer separated, dried with $MgSO_4$, concentrated and the crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:2) to provide **1**-(1,3,9,10-tetramethoxyanthracen-2-yl)ethanol **78** (0.21g, 79% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J*= 8 Hz, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.37 (s, 1H), 5.55 (m, 1H), 4.07 (s, 6H), 3.99 (s, 3H), 3.94 (s, 3H), 1.69 (d, J = 7, 3H).

2-(2-Methyl-1,3-dioxolan-2-yl)acetaldehyde (81)

A solution of ethyl acetoacetate (10 g, 77 mmol), ethylene glycol (14 g, 230 mol), and PTSA (0.65 g, 3.4 mmol) in 100 mL benzene was refluxed for five hours with continuous azeotropic water separation (Dean-Stark). The mixture was then cooled to room temperature, washed sequentially with sat. aq. NaHCO3 (2 x 100 mL) and brine (100 mL), dried with $MgSO_4$, filtered and concentrated to afford the ketal ester (12 g, 90% yield) as a colorless oil. This material was for the next reaction without purification.

A solution of the above ketal ester (4.5 g, 26 mmol) in 10 mL THF was added to a stirred suspension of LAH (1 g, 28.5 mmol) at 0 ^{o}C. The suspension was stirred at the same temperature for three hours. The solution was quenched with 100 mL of sodium tartarate solution. The solution was extracted with 2x100 mL of ether, the organic layers were combined and washed with brine. The organic layer was separated, dried with $MgSO_4$ and the solvent was removed to give the alcohol (3.1 g, 91% yield).

To a solution of oxalyl chloride (1.27 g, 0.87 mL, 9.9 mmol) in 30 mL dichloromethane, dry DMSO (0.78 g, 0.7 mL, 9.9 mmol) was added at -78 ^{o}C. This mixture was stirred for 15 minutes and the solution of above alcohol (1 g, 7.6 mmol) in 5 mL dichloromethane was added dropwise. This solution was stirred for one more hour and triethylamine (3 g, 4 mL, 30 mmol) was added at -78 ^{o}C. The solution was warmed to room temperature and diluted with 50 mL of dichloromethane. This solution was washed successively with 50 mL of ammonium chloride and then with 50 mL of brine. The organic layer was separated, dried with $MgSO_4$, concentrated to give the aldehyde **81** (0.9 g, 91% yield) which was pure enough to be used for further reactions.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 3.99 – 3.98 (m, 4H), 2.70 – 2.69 (m, 2H), 1.41 (s, 3H).

Compound 82

To the stirred solution of 2-bromo-1,3,9,10-tetramethoxyanthracene **77** (0.1 g, 0.27 mmol) in 5 mL THF, *n*-BuLi (2.5 M solution in hexane, 0.12 mL, 0.3 mmol) was added at -78 ^{o}C. This was stirred for 30 minutes at -78 ^{o}C and then the solution of aldehyde **81** (0.65 g, 5 mmol) in 2 mL THF was added. The solution was warmed to room temperature and diluted with 50 mL dichloromethane and washed with 50 mL of ammonium chloride solution. The organic layer was separated, dried with $MgSO_4$, concentrated and the crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:2) to provide the benzyl alochol **82** (0.07 g, 63% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J*= 7.5 Hz, 1H), 8.19 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.35 (s, 1H), 5.73 (m, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 3.86 (s, 3H), 3.73 (s, 3H), 3.93 – 3.85 (m, 4H), 2.31 – 2.1 (m, 2H), 1.42 (d, *J* = 7 Hz, 3H).

Compound 83

To a stirred solution of the dess-martin periodinane (0.3 g, 0.7 mmol) in 10 mL of dichloromethane, the solution of benzyl alcohol **82** (0.1 g, 0.23 mmol) in 3 mL of dichloromethane was added. The solution was stirred for six hours and the resulting mixture was diluted with 50 mL ether. This suspension was treated with 10 mL of dil. NaOH solution and the layers separated. The organic layer was washed with 50 mL of brine solution, dried with $MgSO_4$ and the solvent was removed. The crude product was purified by silica gel flash column chromatography to give pure ketone **83** (0.07 g, 76% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J*= 7.5 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.31 (s, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.91 – 3.86 (m, 4H), 3.53 (m, 2H), 1.61 (d, *J* = 7, 3H).

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CHAPTER 3

An approach to the synthesis of rubianine

Introduction

Rubia is a genus of the family Rubiaceae that has about sixty species of plants which are present in Africa, Asia and America. These plants are commonly known as madder. The three best examples of these plants are *Rubia tinctorum* (common madder), *Rubia peregrine* (wild madder) and *Rubia cordifolia* (indian madder).[1]

It was used as a natural dye for leather, cotton, wool and silk. The dye is fixed to the cloth with the help of a mordant, most commonly alum. Early evidence of dyeing came from India where a piece of cotton dyed with madder was recovered from the archaeological site at Mohenjodaro (third millennium BCE). From the Viking age, remains of both woad (a natural blue dye) and madder had been excavated. The oldest European textiles dyed with madder came from the grave of the Merovingian queen in a place near Paris which was dated between 565 and 570 CE.[2]

By the nineteenth century madder became an important dye and imports into the United Kingdom reached 1.25 million pounds per year. The main advantages of madder dye were the following:

1. It was capable of producing a wide variety of colors and shades from black to pink to bright red, depending upon the mordant used.
2. It had little affinity towards the fiber, but had great affinity towards the mordant, making it possible to get just a white color in part of the cloth where mordant was not applied.
3. The color was very stable and hence it was possible to treat with different reagents to improve or to modify the shade.

The main component of madder was isolated, identified and named as alizarin (1,2-dihyroxyanthraquinone). Several other minor compounds were also isolated and identified.

Seven of the anthraquinone compounds isolated by Schunck from the roots of *Rubia tinctorum* were rubiretene, rubiagine, rubiacine, rubianine, chlorubian, chlorubiadine, perchlororubian.[3] Farrar analyzed these compounds and suggested that rubianine could be a C-glycoside which was unique in madder. Vaidyanathan ascertained the correct structure of the compound as shown in Figure 1.[4]

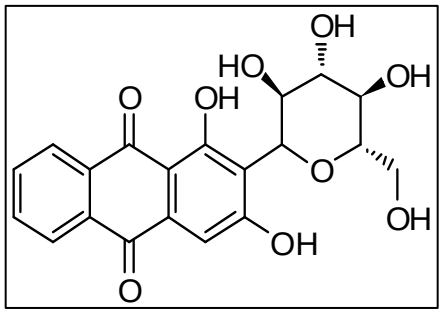


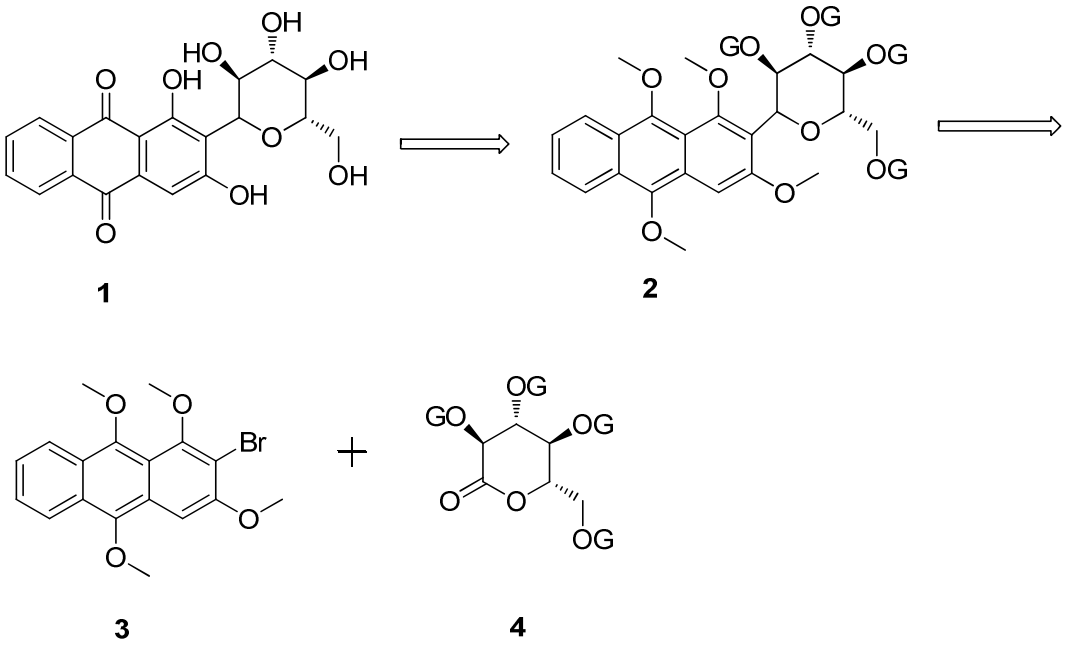
Figure 1: Rubianine (1)

Rubianine belongs to the class of compounds called C-glycosides which are derivatives of carbohydrates. Carbohydrates are of interest not only due to their abundance in nature but also due to the synthetic challenges they pose because of their polyhydroxylated structures as well as their tendency to hydrolyze easily at the glycosidic bond. The discovery of C-glycoside compounds in nature started the development of a new generation of carbohydrate based products.[5] C-glycosides could be made by the replacement of exo-glycosidic bond of an O-glycoside by a carbon atom. In recent years many C-glycosides have been isolated from nature. The aryl C-glycosides exhibit many interesting biological activities such as antiviral, cytotoxic and DNA binding activities, making them attractive synthetic targets for organic chemists.[6]

Results and Discussion

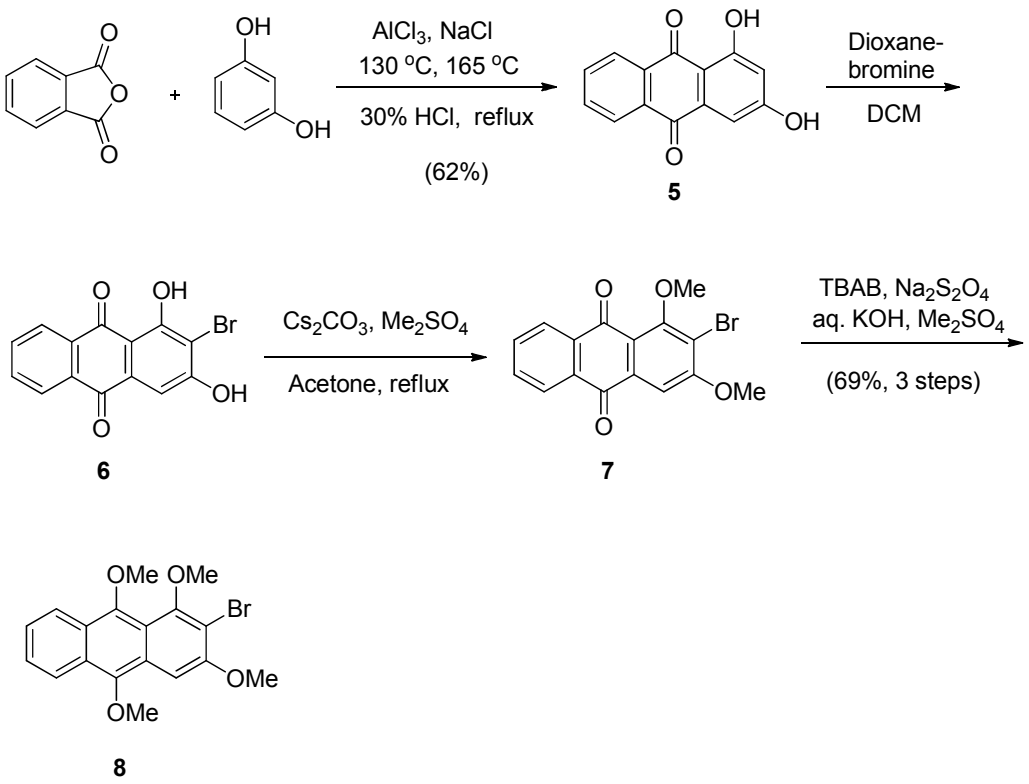
The total synthesis of rubianine has not yet been reported. The intriguing biological activity and unique structural features prompted us to undertake a synthetic study of this aryl C-glycoside. The synthesis was envisioned as the C-glycosylation at the 2 position of 1,3-dihydroxy-9,10-anthraquinone.

Scheme 1



Our first synthetic strategy for rubianine is depicted in Scheme 1. Rubianine **1** could be prepared by reaction of the anion, made by the metal-halogen exchange of bromotetramethoxyanthracene **3,** on the protected gluconic acid lactone **4**. The bromotetramethoxyanthracene **3** could be made by the same procedure used in the approach to topopyrone-D which is shown in Scheme 2.

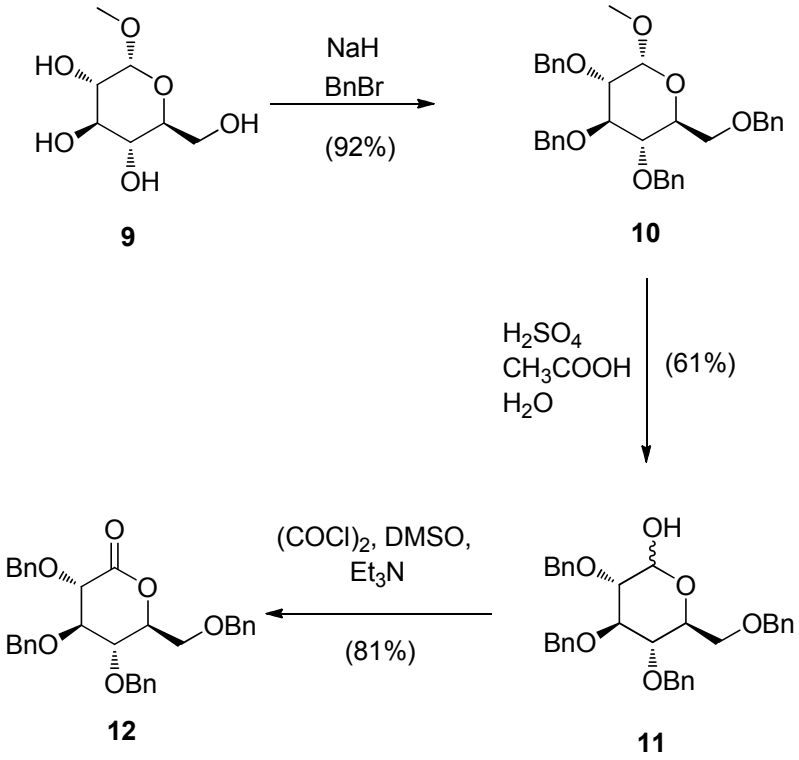
Scheme 2



1,3-Dihydroxyanthraquinone **5** was prepared by the Friedel-Crafts reaction of phthalic anhydride and resorcinol. This was selectively brominated at the 2-position to give bromodihydroxyanthraquinone **6**.[7] The hydroxyl groups were protected by methyl groups to give bromodimethoxyanthraquinone **7**. This was then converted to bromotetramethoxy-anthracene **8** by a reductive methylation reaction.[8]

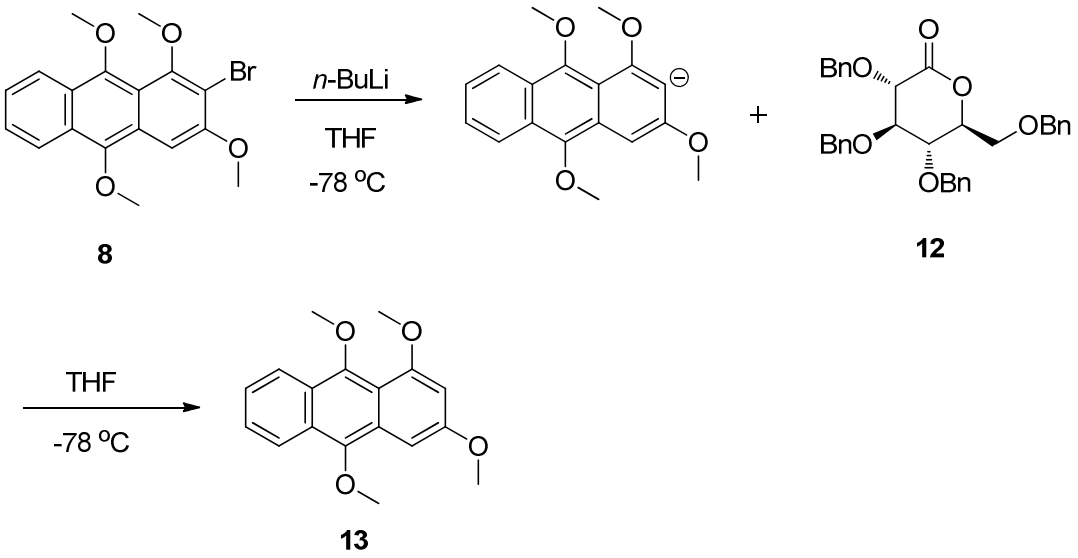
The benzyl protected gluconic acid lactone was prepared as shown in Scheme 3. The hydroxyl groups of methyl-α-D-glucopyranoside **9** were protected with benzyl groups to give compound **10**. This compound was hydrolyzed to give glucopyranose **11**.[9] This was then oxidized by Swern oxidation to give benzyl-protected gluconic acid lactone **12**.[10]

Scheme 3



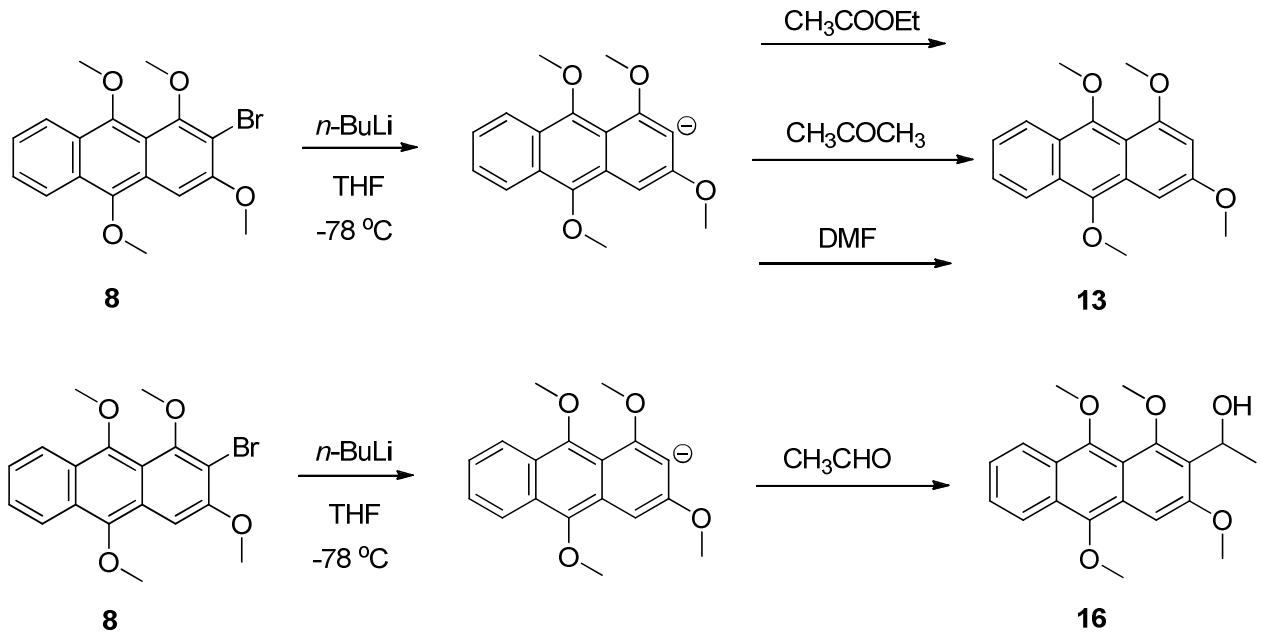
With the gluconic acid lactone **12** in hand, the reaction with the anion formed by the metal-halogen exachange of bromotetramethoxyanthracene **8** was tried by using the standard conditions as shown in Scheme 4. It was observed that the dehalogenated compound was obtained as the major product.

Scheme 4



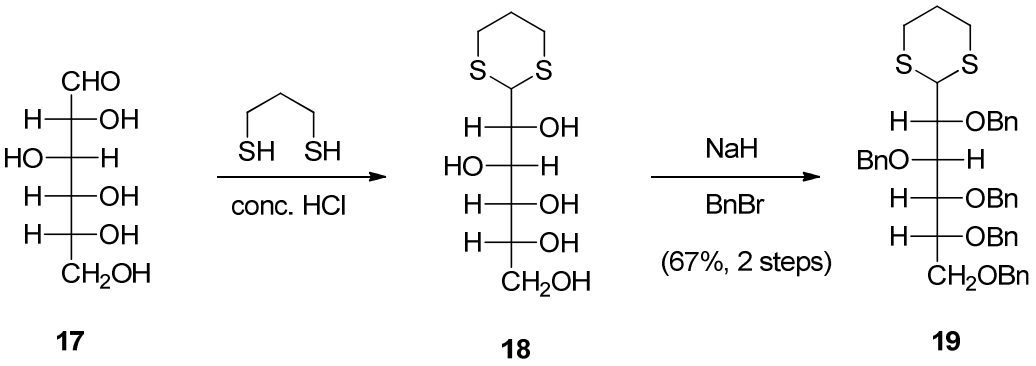
It was known earlier from the synthesis of topopyrone-D that the anion formed from bromoanthracene **8** reacted with aldehydes but not with anhydrides. To find out if the anion formed above would react with other electrophiles, it was treated with DMF, acetone and ethyl acetate. In all cases it gave only the debrominated compound **13**. However, it reacted with acetaldehyde as found during the synthesis of topopyrone-D.

Scheme 5



Since the anion formed from bromoanthracene **8** reacted with aldehydes, it was decided to treat it with pentabenzyl D-glucose. The aldehyde group of D-glucose was protected by treating with 1,3-propanedithiol to form the cyclic dithioacetal **18**. Then the hydroxyl groups were protected with benzyl groups to give the protected D-glucose **19**.[11]

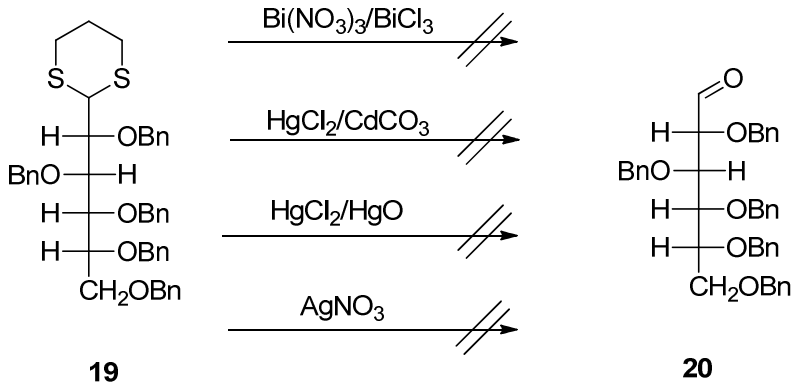
Scheme 6



17 **18** **19**

The deprotection of the cyclic dithioacetal group in **19** was then tried by different methods. In all cases only complex mixtures were obtained.

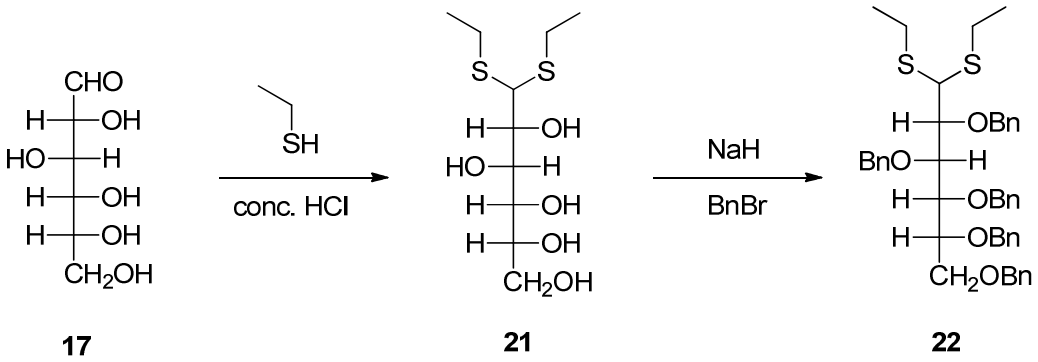
Scheme 7



19 **20**

The deprotection of compound **19** was difficult which could be because of the cyclic dithioacetal group. It could be because the cyclic protecting groups are more stable as compared to open chain groups. Hence, it was decided to do the protection with an open chain dithioacetal group as shown in Scheme 8. The aldehyde group of D-glucose was protected by treating with ethanethiol to form the dithioacetal **21**. The hydroxyl groups were then protected with benzyl groups to give protected D-glucose **22**.[12]

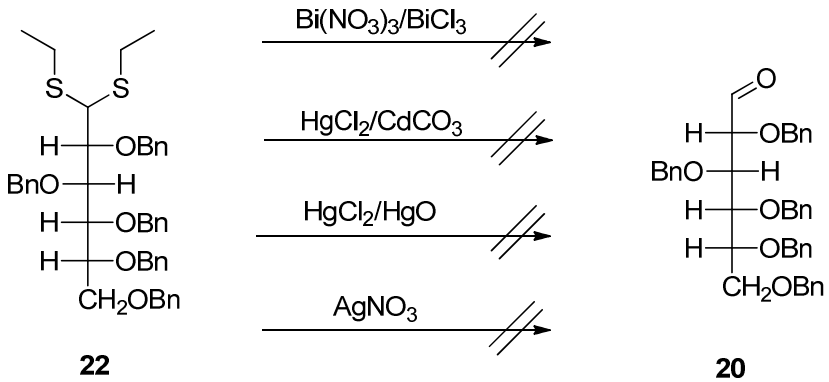
Scheme 8



17 **21** **22**

The deprotection of the open chain dithioacetal group was tried by different methods. In these cases also only complex mixtures were obtained.

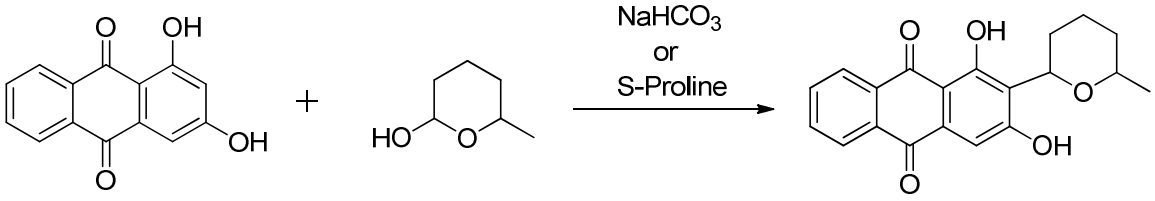
Scheme 9



22 **20**

Since the anion reactions were not successful, other types of reactions were explored to make the carbon-carbon bond between the anthraquinone moiety and the glucose moiety. Electrophilic aromatic substitution reactions were tried. As shown in Scheme 10, a coupling reaction was reported in the literature for 6-methyltetrahydropyran-2-ol.[13, 14]

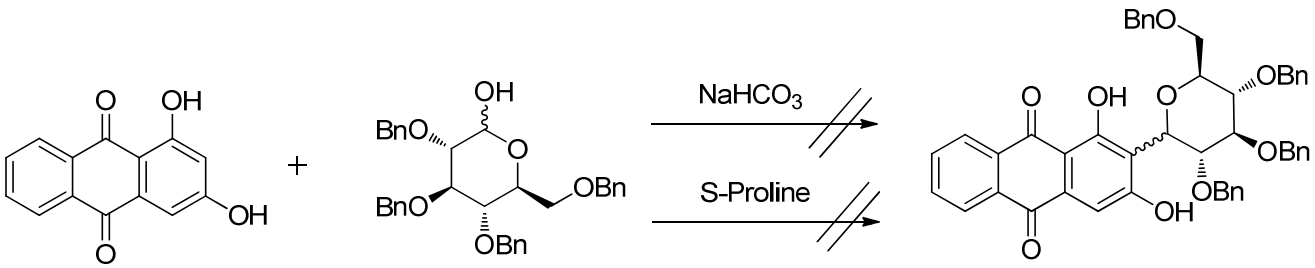
Scheme 10



13 **23** **24**

Since hemiacetal **11** was readily available, the reaction was attempted using both sodium bicarbonate and S-proline. In both cases the reactions failed to give the desired product.

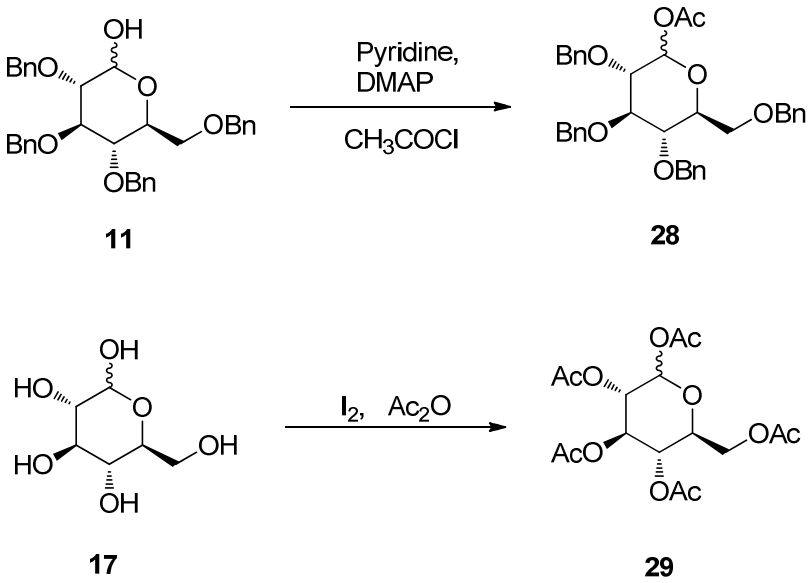
Scheme 11



13 **11**

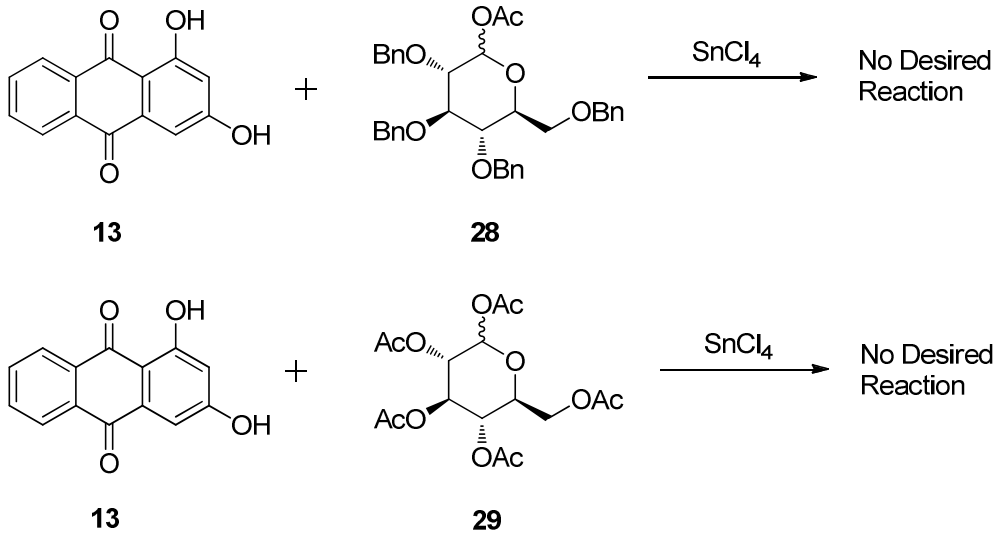
Next, Friedel-Crafts type reactions were tried. These types of reactions had been reported with similar substrates.[15] The required glucose derivatives were prepared as shown in Scheme 12.

Scheme 12



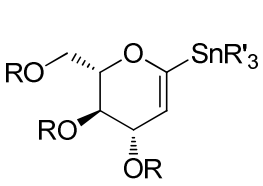
Pentaacetate **29** and tetrabenzylmonoacetate **28** were then subjected to a Friedel-Crafts reaction as reported in the literature with similar substrates. However, in both cases the desired product could not be obtained despite variations in temperature and solvent.

Scheme 13

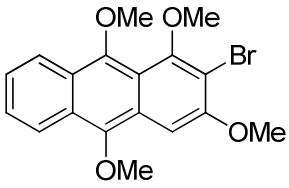


The failure of the reactions to make the carbon-carbon bond between the anthraquinone and glucose moiety could be because of the steric hindrance. Hence, it was decided to use a glucal. Quite a few reactions are known in the literature in which Stille coupling was used to form C-glycosides.[16] Hence, Stille coupling reactions of stannylated D-glucal and bromoanthracene **8** were tried.

Figure 2



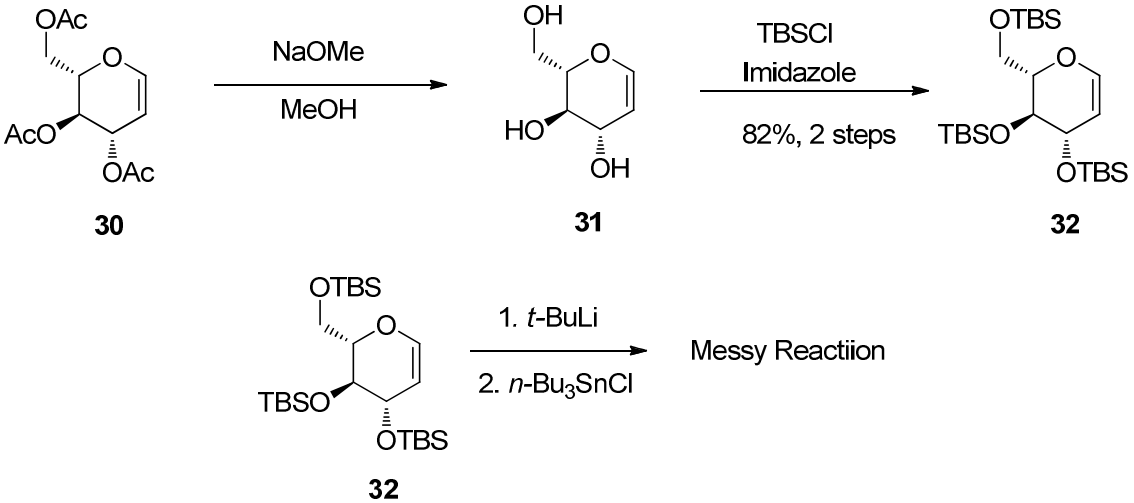
Stannylated glucal



8

Preparation of stannylated D-glucal was attempted by the method shown in Scheme 14. The commercially available D-glucal triacetate **30** was hydrolyzed with sodium methoxide to form D-glucal **31**. The hydroxy groups were then protected with TBS groups to form the trisilyl ether **32**. This was then stannylated using the standard procedure.[17]

Scheme 14

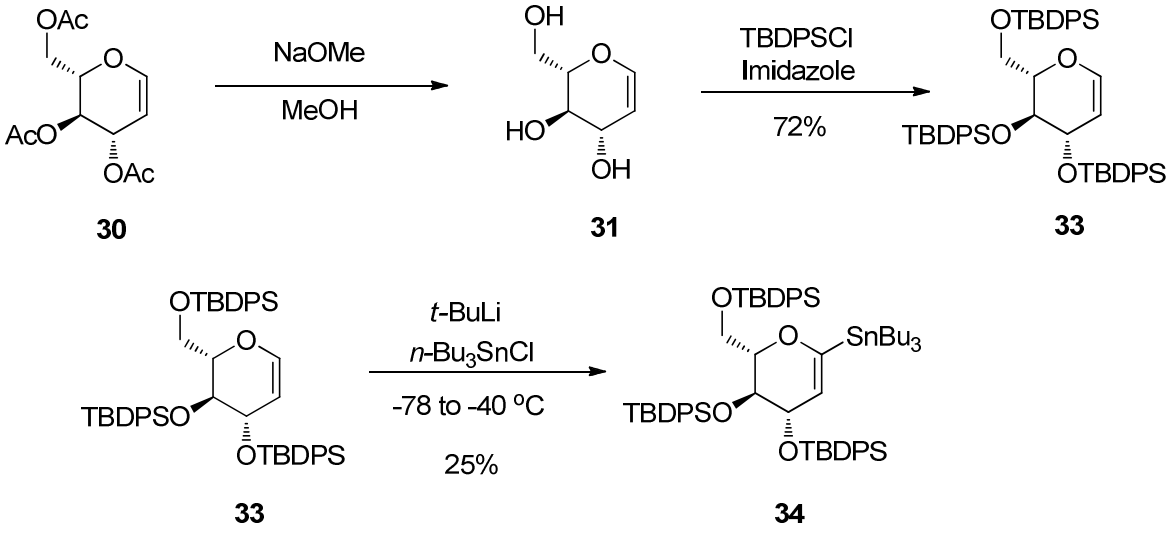


30 **31** **32**

32

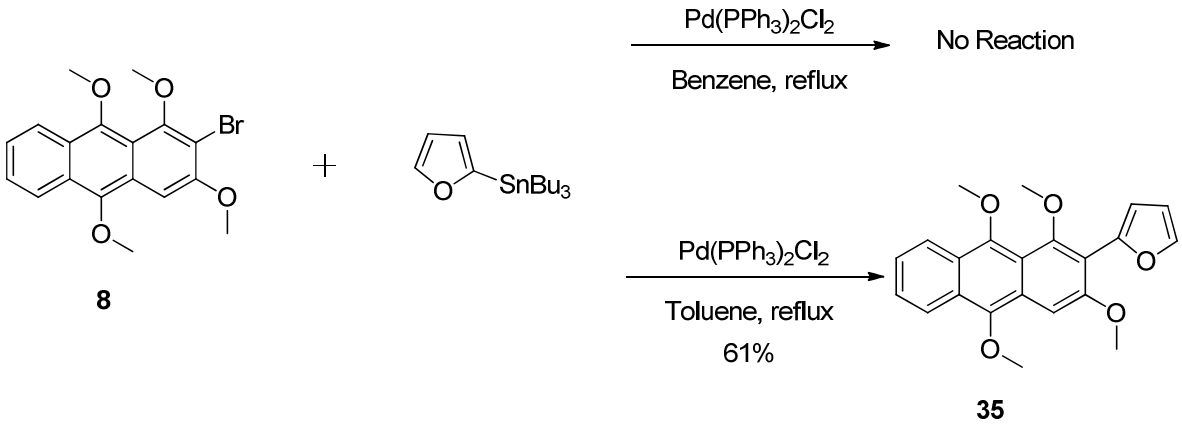
Initially, the anion was formed from protected glucal **32** at -78 ^{o}C by adding *t*-BuLi and quenching with tributyltin chloride at the same temperature. Then the reaction was warmed to room temperature and worked up. Since this resulted in a messy reaction, the reaction was warmed only to 0 ^{o}C. This also did not result in a successful reaction. It had been reported in the literature that when the TBS protected glucal **32** was treated with *t*-BuLi, deprotonation at C-1 and alpha to silicon occurred.[18] To prevent the formation of α-silyl carbanions, the protecting groups were changed from TBS to TBDPS groups. With this glucal, the stannylation worked well. However, there were some non-polar impurities which were difficult to remove. This could be because *t*-BuLi could react with THF above -40 ^{o}C. To avoid this, the reaction was stopped at -40 ^{o}C. This resulted in lower yields, but a purer product. These results are summarized in Scheme 15.

Scheme 15



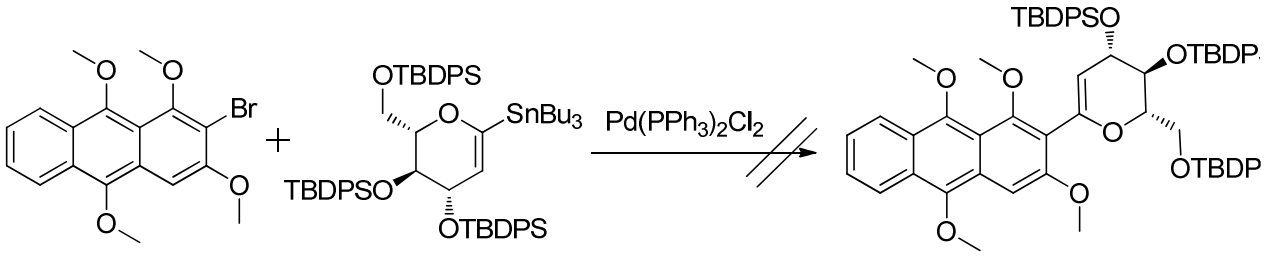
Before trying the Stille coupling of stannylated glucal **34** with bromoanthracene **8**, coupling with commercially available 2-(tri-*n*-butylstannyl)furan was performed to standardize the reaction conditions. Initially the reaction was tried with bis(triphenylphosphine)palladium dichloride as the catalyst and benzene under reflux conditions which was not successful. However, the reaction worked well with toluene as the solvent under reflux conditions.[17]

Scheme 16



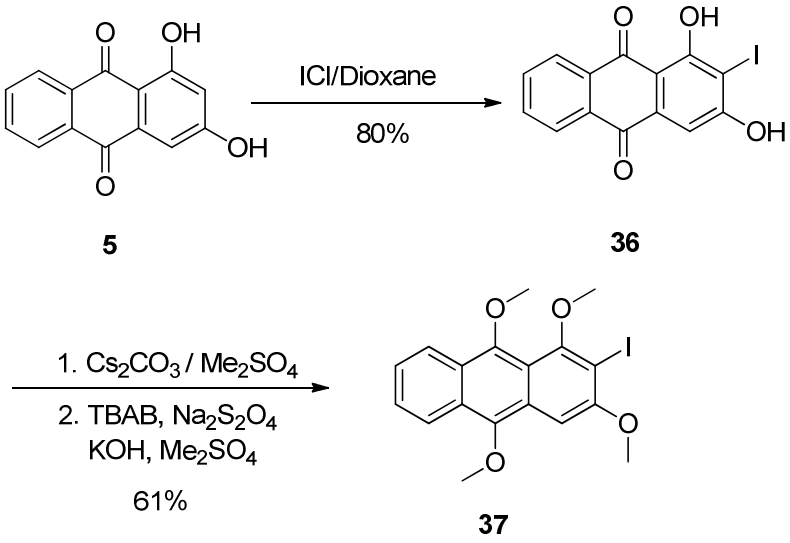
When the Stille coupling was attempted with stannylated glucal **34**, the reaction failed. Use of different solvents and different temperature conditions did not result in a successful reaction.

Scheme 17



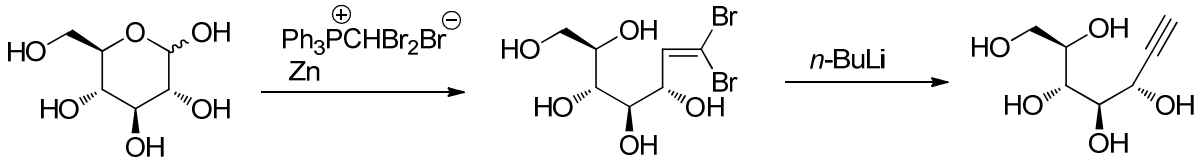
Since the Stille coupling with bromoanthracene **8** failed, the Stille coupling of iodoanthracene **37** with stannylated glucal **34** was attempted as iodine is more reactive than bromine for Stille coupling reactions. The iodoanthracene **37** was prepared as shown in Scheme 18. Iodination of dihydroxyanthraquine failed with iodine in dioxane. However, this reaction worked well with iodine monochloride in dioxane to give iodoanthraquinone **36**.[19] Stille coupling of iodoanthracene **37** with glucal **34** also failed to produce the desired product.

Scheme 18



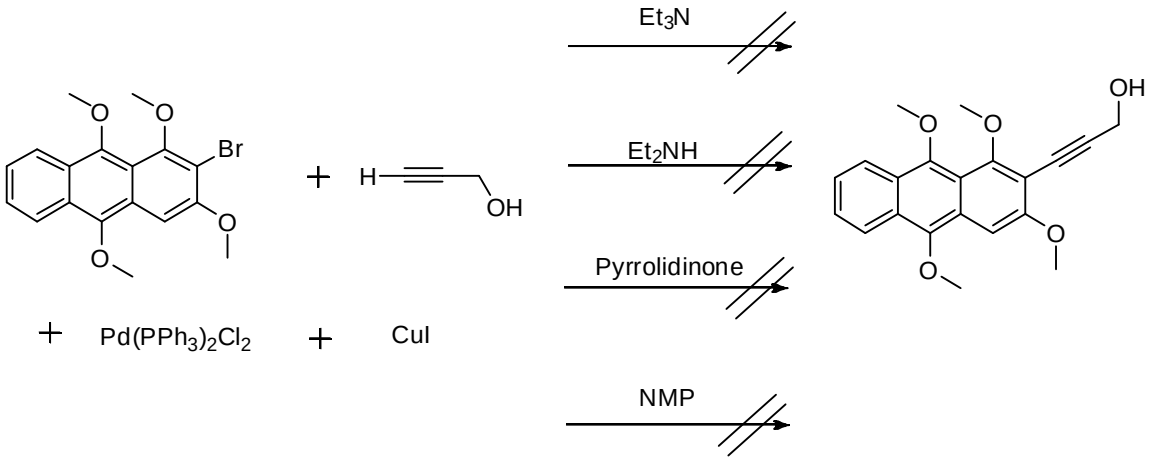
According to a literature procedure, glyco-1-ynitol could be produced from protected or unprotected aldoses by a two-step pathway shown in Scheme 19.[20] If these terminal alkynes could be made, then they could be reacted with bromoanthracene **8** by a Sonogashira reaction.

Scheme 19



Before making these glyco-1-ynitols, the Sonogashira reaction was tried with propargyl alcohol because that would be the simplest alkynol and would help to standardize the Sonogashira reaction conditions.[21] However, this reaction failed under different solvent and temperature conditions as shown in Scheme 20.

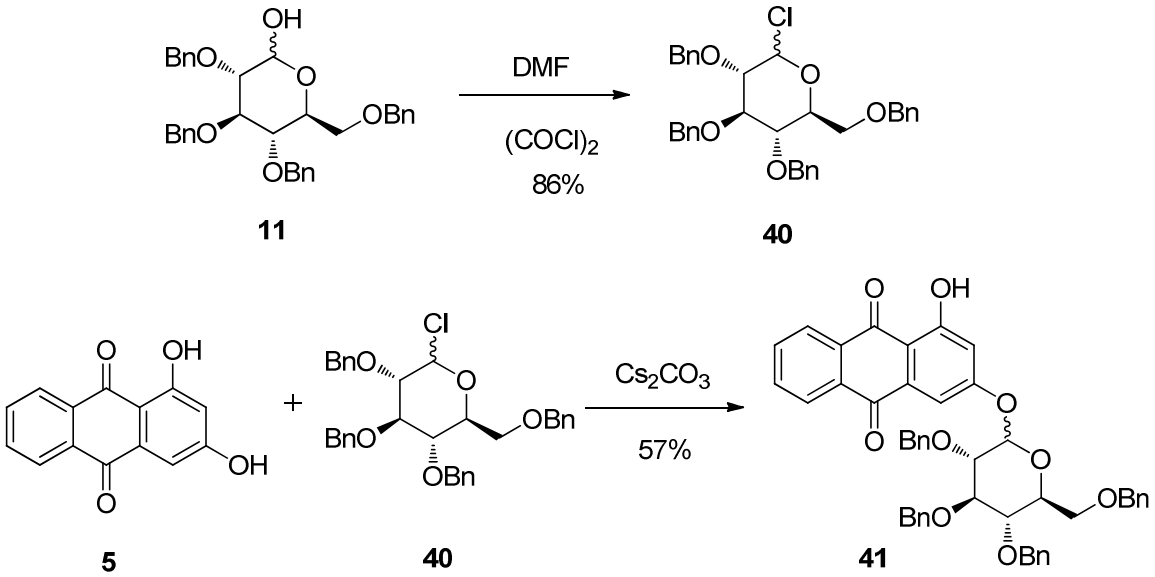
Scheme 20



Since many of the intermolecular reactions failed, the next plan was to try the intramolecular reactions. It is known from the literature that O-glycosides could be converted to C-glycosides by using Lewis acid catalysts.[22] To try this reaction on our substrate, the O-glycoside **41** was made as shown in Scheme 21.

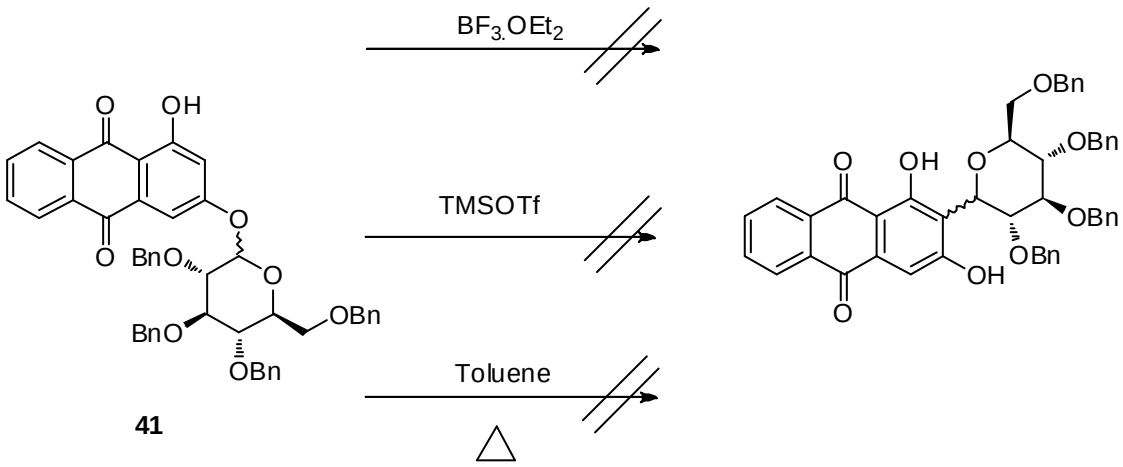
Benzyl protected glucopyranosyl chloride **40** was prepared from the glucopyranose **11**.[23] This then was treated with dihydroxyanthraquinone **5** to give the mono-O-glycoside **41**.

Scheme 21



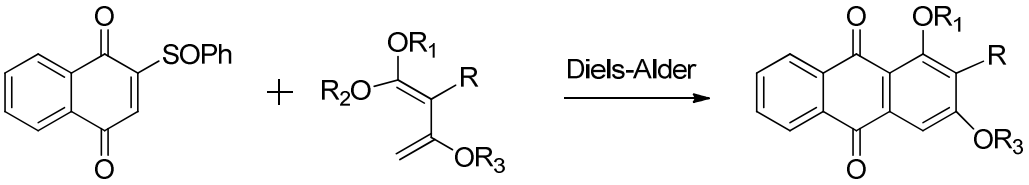
The O-glycoside **41** was treated with Lewis acids according to the literature procedures. The thermal rearrangement was also tried by heating **41** in toluene from 100-200 ^{o}C.[24] The isomerization from O-glycoside to C-glycoside failed to take place under these conditions.

Scheme 22



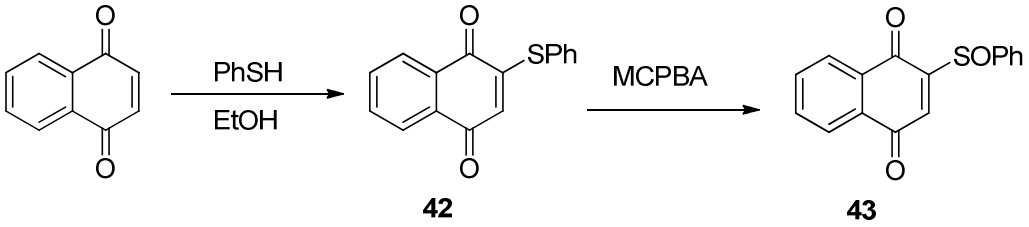
Since many reactions to make the carbon-carbon bond between the anthraquinone and glucose moiety failed, it was time to re-think our strategy. Our new plan was to make the carbon-carbon bond between the carbon of a diene and the anomeric carbon of the glucose moiety first and then assemble the anthraquinone moiety by a Diels-Alder reaction. The following Diels-Alder reaction was developed and reported by Kraus and Woo.[25]

Scheme 23



The method shown in Scheme 23 could be applied for the preparation of rubianine if R was the glucose moiety. Sulfinylquinone **43** was prepared as shown in Scheme 24. The nucleophilic substitution of naphthoquinone by thiophenol gave the sulfide[26] **42**, which on oxidation with MCPBA gave the sulfinylquinone **43**.[27]

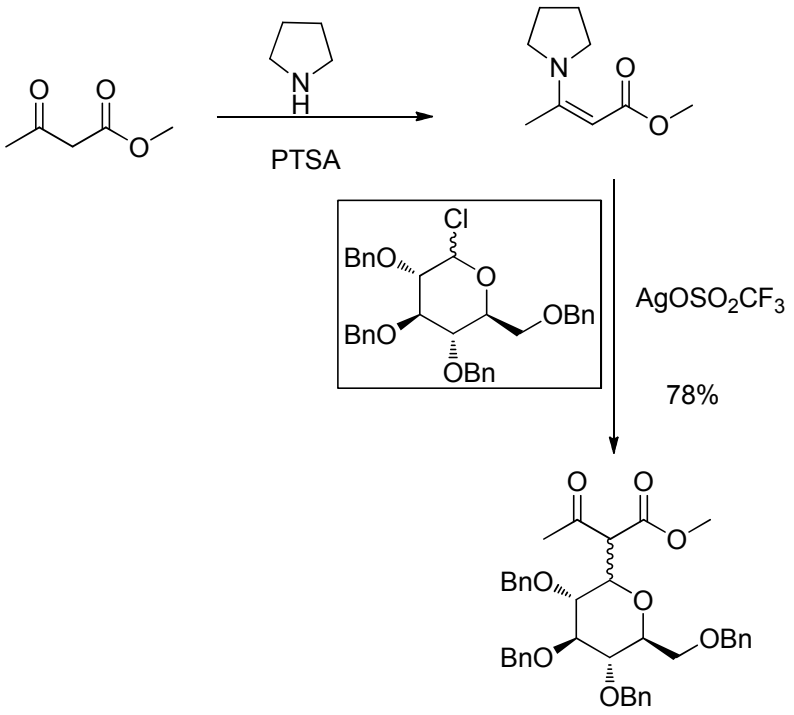
Scheme 24



42 **43**

The methyl acetoacetate with the protected glucose unit at the 2-position was prepared as shown in Scheme 25. Methyl acetoacetate was converted to the enamine, which on treatment with glucopyranosyl chloride **40** in the presence of silver triflate gave the keto ester **44**.[28]

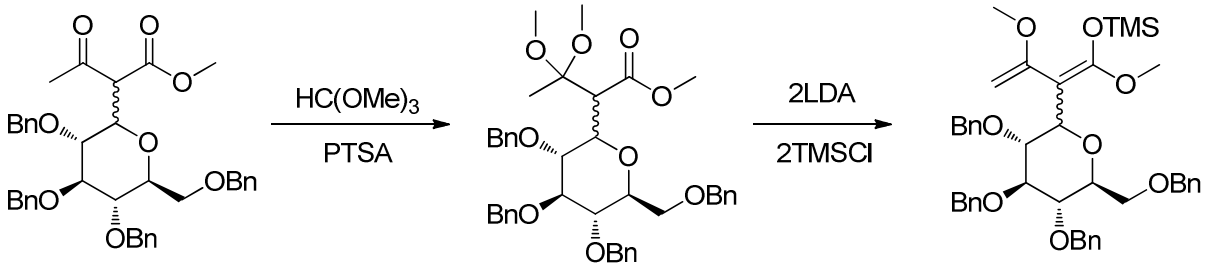
Scheme 25



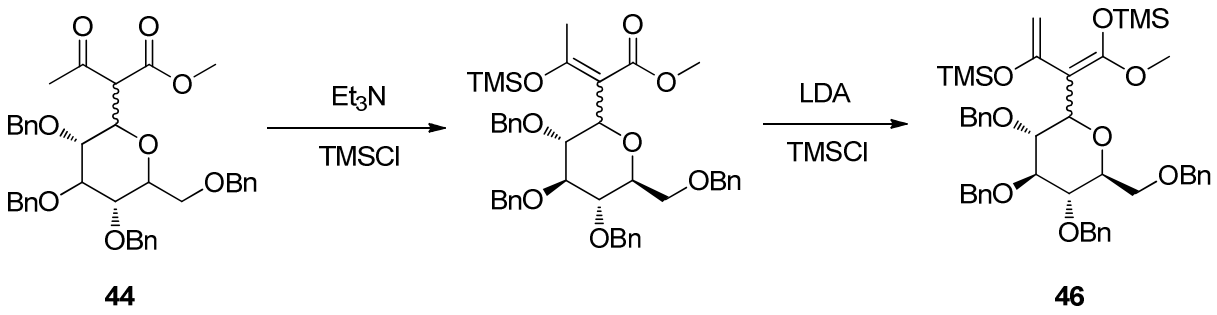
44

Compound **44** was converted to two types of dienes, the dimethoxy diene and the bis-silyloxy diene as shown in Scheme 26. The intermediates were not characterized. During the preparation of diene **45** the monoene is shown as a ketal because according to a literature procedure the 2-substitued methyl acetoacetate gave a ketal on treatment with trimethyl orthoformate, which on treatment with two equivalents of LDA gave the desired diene **45**.[29]

Scheme 26



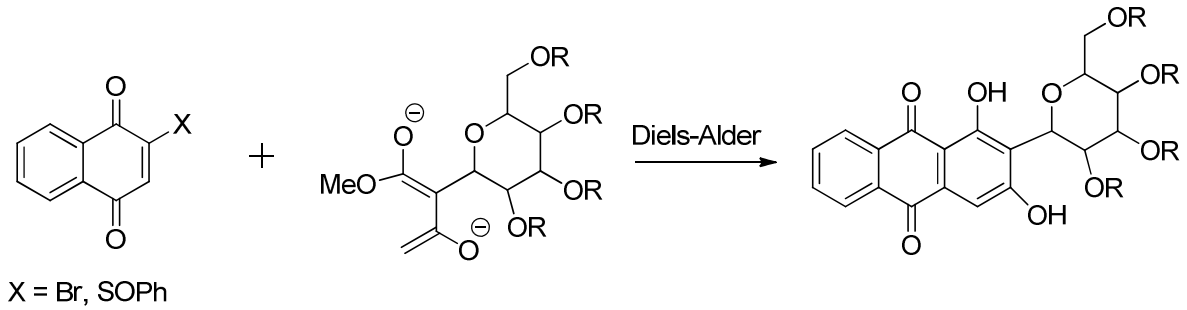
44 **45**

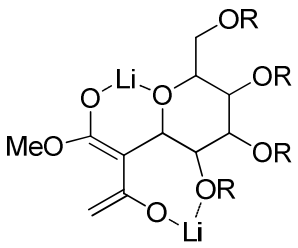


44 **46**

Diels-Alder reactions were tried with these two dienes and sulfinylquinone **43** under different conditions, which were unsuccessful. The major drawback was that the dienes were unstable. To overcome this, the Diels-Alder reaction with the dianion, from compound **44** was tried. The dianion could be stabilized by the oxygen atoms in the glucose ring as shown in Scheme 27.

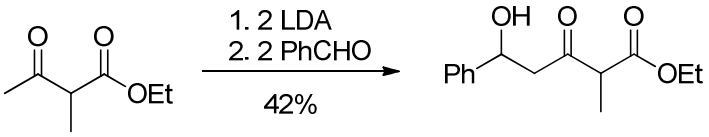
Scheme 27





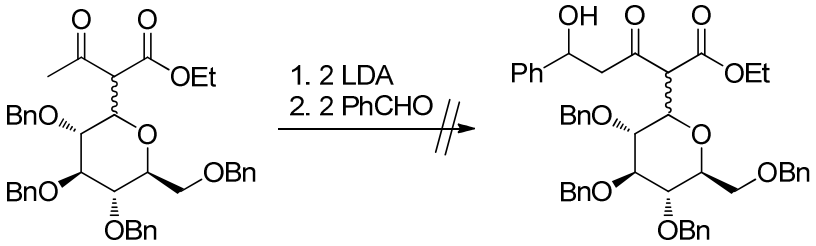
Before trying the Diels-Alder reaction with the dianion, it was necessary to identify optimal conditions for dianion formation. Thus, 2-methyl methylacetoacetate was treated with two equivalents of LDA and quenched with benzaldehyde. ^{1}H NMR spectrum of the reaction showed that the aldol reaction had occurred, confirming dianion formation.

Scheme 28



The Diels-Alder reactions were tried with 2-bromonaphthoquinone and 2-phenylsulfinylnaphthoquinone. However, the reaction decomposed as soon as the dienophile was added to the dianion. Even though this reaction failed, the Diels-Alder reaction with the dianion formed from compound **44** might work, because it could be stabilized by the oxygen atoms in the glucose ring as shown in Scheme 27. Hence, the aldol reaction was tried first to standardize conditions for dianion formation, which failed. This suggested that dienes **44** and **45** might not have been formed.

Scheme 29

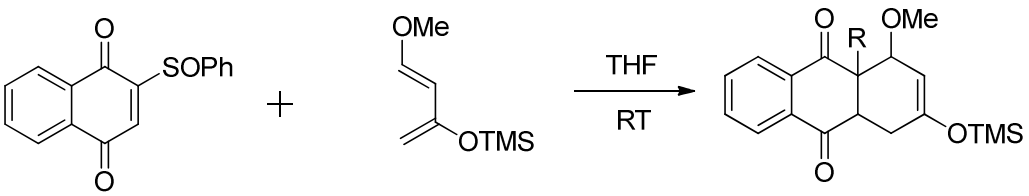


44

Hence, it was once again necessary to change the strategy. Since the substitution of glucose unit at the two position of methyl acetoacetate was successful, this could be used to

make the required C-glycoside bond. The treatment of sulfinylquinone **43** with the Danishefsky diene **47**[30] would give the enol silyl ether **48**. This intermediate could be treated with glucopyranosyl chloride **40** in the presence of silver triflate to produce the required glucose-substituted tricyclic system.

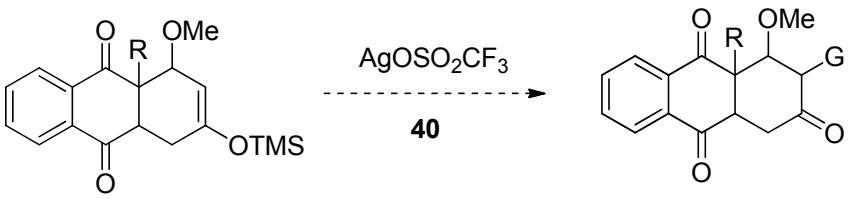
Scheme 30



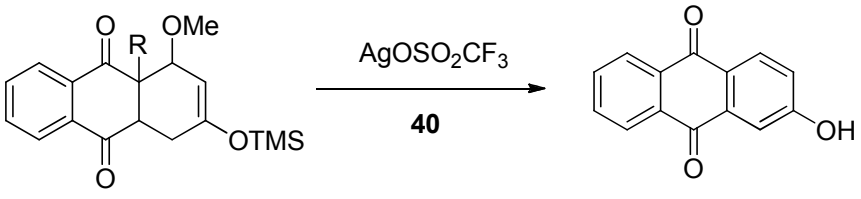
43 **47** **48** (R = SOPh)

However, when this reaction was tried, only 3-hydroxyanthraquinone was obtained. The expected reaction (as depicted by a broken arrow) and the obtained reaction (as depicted by a solid arrow) are shown in Scheme 31. This could be because the intermediate **48** was unstable and formed the enone which aromatized easily to the anthraquinone.

Scheme 31



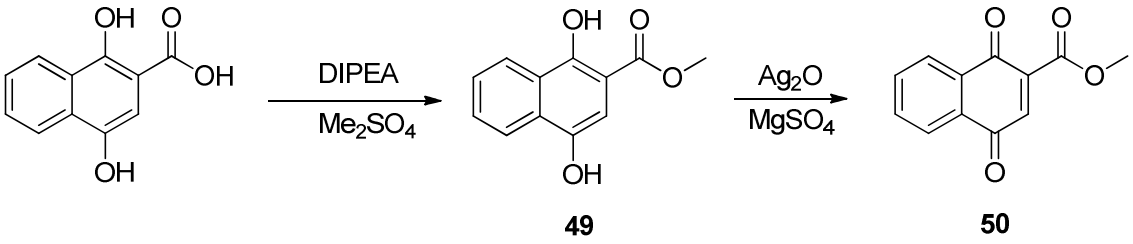
48 (R = SOPh)



48 (R = SOPh)

The Diels-Alder adduct shown in Scheme 30 was unstable, which could be because the phenylsulfinyl group is a very good leaving group. If that was replaced by a carboxyl group, the adduct could be stable enough for the substitution to occur. The naphthoquinone was prepared as shown in Scheme 32. The carboxynaphthalene **49** was oxidized with silver(I) oxide to give the naphthoquinone **50**.[31]

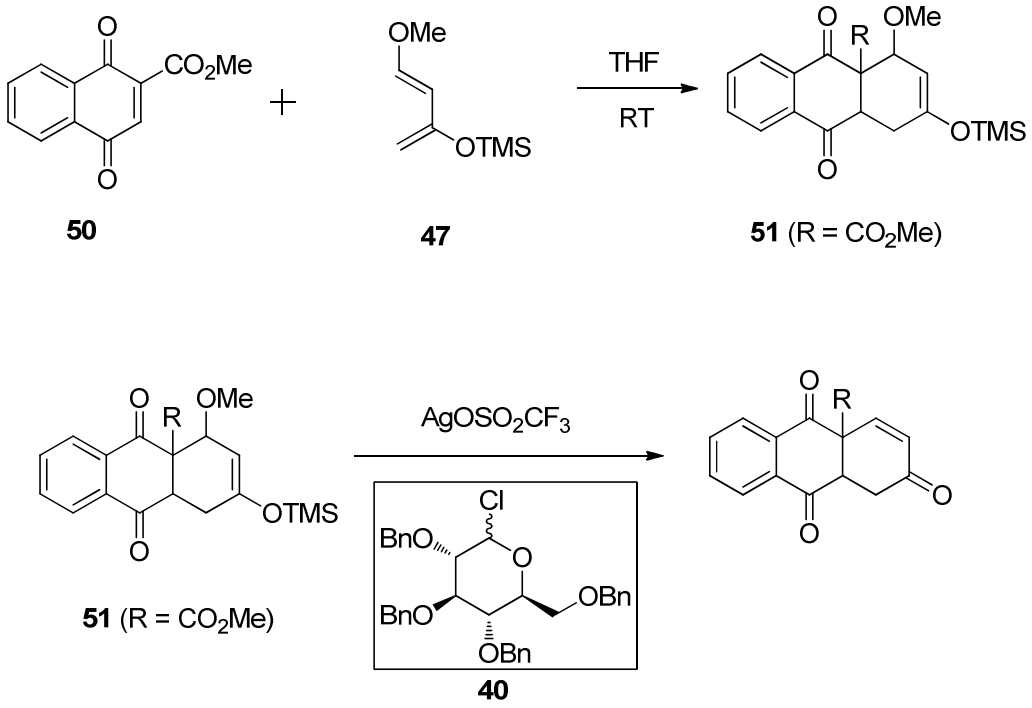
Scheme 32



49 **50**

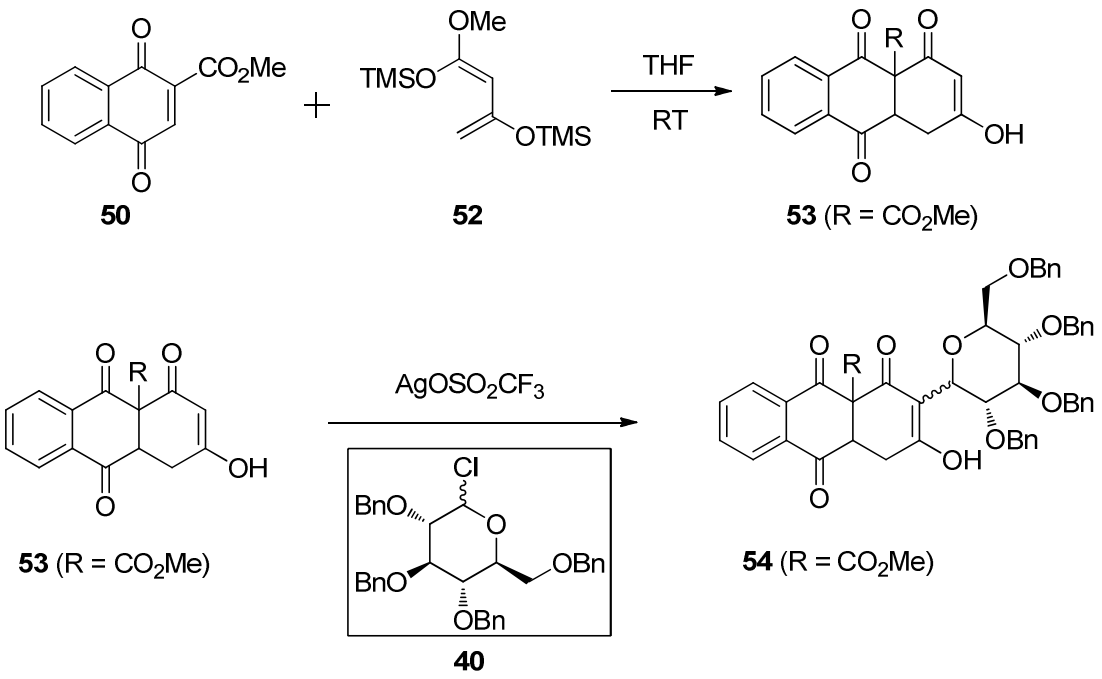
With the dienophile **50** in hand, the Diels-Alder reaction with the Danishefsky diene and subsequent reaction of the intermediate with glucopyranosyl chloride were tried. However, this reaction produced only the enone and not the substitution product. This showed that the elimination of the methoxy group occurred before the substitution could take place.

Scheme 33



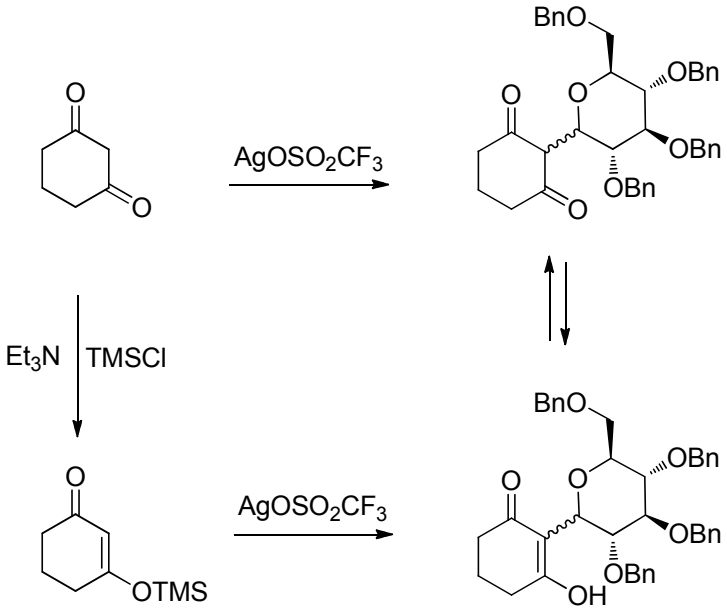
Since the intermediates from the Diels-Alder reactions of the dienophiles **43** and **50** with the Danishefsky diene fell apart before the desired substitution, it would be better to treat the dienophile with butadiene **52**. This would solve the problems we faced with the intermediates of the Diels-Alder reaction with the Danishefsky diene. When this reaction was tried as shown in Scheme 34, it was successful. Proton NMR and HRMS showed that the desired product was formed.

Scheme 34



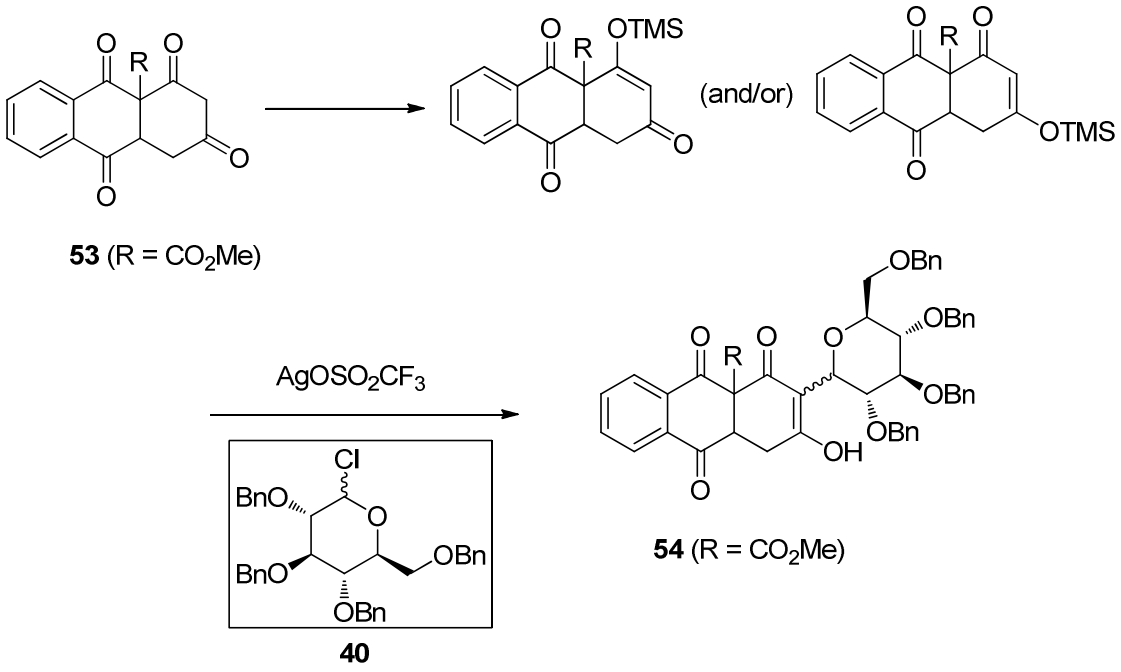
However, the intermediate **53** shown in Scheme 34 could undergo either C-glycosylation or O-glycosylation and it would be very difficult to differentiate these two compounds. To find out which product was formed, the reaction was tried with 1,3-cyclohexanedione as well as with the enol silyl ether of 1,3-cyclohexanedione. The enol silyl ether would give only the C-glycosylated product and the dione could give both. The products formed from these reactions were purified and analyzed. These reactions formed the same type of products. However, the reaction with enol silyl ether was clean and was easy to purify. These reactions are summarized in Scheme 35.

Scheme 35



To confirm the product of the reaction shown in Scheme 34, the enol silyl ether of intermediate **53** was prepared. This was reacted with glucopyranosyl chloride **40**. The products of these two reactions were the same as confirmed by ^{1}H NMR spectroscopy. Hence, this showed that we successfully achieved the desired C-glycosylation as shown in Scheme 36.

Scheme 36



Thus the carbon skeleton of rubianine could be made by treating the Diels-Alder adduct **53** with glucopyranosyl chloride **40** in presence of silver triflate. Decarboxylation and then debenzylation reactions would result in the formation of rubianine **1.**

Experimental Section

Methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (10)

To a solution of methyl- α-D-glucopyranoside **9** (2 g, 10 mmol) in DMF (50 mL) at 0 ^{o}C, NaH (60%, 0.8 g, 20 mmol) was added. After 15 minutes, benzyl bromide (3.4 g, 2.5 mL, 20 mmol) was added at 0 ^{o}C and the mixture was stirred for one hour at room temperature. After this, NaH and benzyl bromide (same amounts as above) were added and again the mixture was stirred for one more hour. This step was repeated two more times and finally the reaction mixture was allowed to stir for six hours at room temperature. The reaction mixture was quenched by adding to 200 mL of ice-cold water and extracted with 200 mL ether. The ether layer was washed with 3x200 mL brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel flash column

chromatography (EtOAc/hexanes, 1:4) to provide methyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside **10** (5.1 g, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 20H), 4.99 (d, *J* = 14 Hz, 1H), 4.84 – 4.78 (m, 3H), 4.69 – 4.59 (m, 3H), 4.5 – 4.46 (m, 2H), 3.99 (t, *J* = 10 Hz, 1H), 3.74 – 3.58 (m, 5H), 3.38 (s, 3H).

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (11)

To a solution of methyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside **10** (2.5 g, 4.5 mmol) in 100 mL acetic acid, 25 mL of 1 M sulfuric acid was added. The reaction mixture was boiled at 125 ^{o}C for five hours. It was then cooled to room temperature and allowed to stand for six hours. The solid product crystallized out which was separated by filtration. The solids were again dissolved in 250 mL dichloromethane and washed with 250 mL of dilute sodium bicarbonate solution and then with 250 mL of brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The product was purified by recrystallization from hexane : ethyl acetate (2:1) mixture to give 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside **11** (1.5 g, 62% yield). However, the product before crystallization was pure enough to be taken for the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 20H), 5.32 (d, *J* = 4 Hz, 1H), 5.00 – 4.40 (m, 8H), 4.21 – 4.17 (m, 2H), 4.00 – 3.90 (m, 2H), 3.67 – 3.50 (m, 2H).

3,4,6-Tri-*O*-*tert*-butyldiphenylsilyl-D-glucal (33)

To a solution of 3,4,6-tri-O-acetyl-D-glucal (2 g, 7.35 mmol) in 20 mL methanol was added sodium methoxide solution in methanol (25% solution, 0.05 g, 0.18 mmol) at room temperature and stirred for four hours. At the end of this reaction time the solvent was removed to give crude D-glucal **31** which was taken for the next reaction without further purification.

The crude D-glucal **31** obtained as above was dissolved in 50 mL DMF and imidazole (3 g, 44 mmol) was added to it and stirred for 10 minutes. After this, *tert*-butyldiphenylsilyl chloride (12 g, 11 mL, 44 mmol) was added dropwise at room temperature with stirring. The

reaction was allowed to stir at 50 ^{o}C for overnight. At the end of the reaction time the reaction mixture was cooled, diluted with ether and washed with 300 mL water three times. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:9) to provide pure 3,4,6-tri-O-*tert*-butyldiphenylsilyl-D-glucal **33** (4.6 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.18 (m, 30H), 6.27 (d, 8.5 Hz, 1H), 4.43 – 4.39 (t, *J* = 8 Hz, 1H), 4.24 – 4.12 (m, 2H), 3.95 (d, *J* = 2.4 Hz, 1H), 3.74 – 3.70 (m, 2H), 1.02 (s, 9H), 0.91 (s, 9H), 0.73 (s, 9H).

3,4,6-Tri-O -(*tert* -butyldiphenylsilyl)-1-(tributyl-Stannyl)-D-glucal (34)

To a solution of 3,4,6-tri-O-*tert*-butyldiphenylsilyl-D-glucal **33** (1 g, 1.2 mmol) in 20 mL THF, *t*-BuLi solution (1.7 M in pentane, 3.5 mL, 6 mmol) was added at -78 ^{o}C. This was stirred for one hour at -78 ^{o}C and then the solution of tributylstannyl chloride (1.9 g, 1.6 mL, 6 mmol) in 5 mL THF was added. This reaction mixture was warmed to -40 ^{o}C and then quenched by adding to 100 mL of ice-cold water and extracted with 200 mL of ether. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:20) to provide pure 3,4,6-tri-O-(*tert* -butyldiphenylsilyl)-1-(tributyl-Stannyl)-D-glucal **34**. (0.35 g, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.18 (m, 30H), 4.49 (d, *J* = 2.4 Hz, 1H), 4.13 – 3.98 (m, 2H), 3.97 (s, 1H), 3.77 – 3.75 (d, *J* = 8 Hz, 1H), 3.65 (d, *J* = 2.8 Hz, 1H), 1.57 – 1.45 (p, *J* = 8 Hz, 6H), 1.35 -1.23 (p, *J* = 8 Hz, 6H), 0.99 (s, 9H), 0.95 – 0.89 (m, 6H), 0.91 (s, 9H), 0.76 (s, 9H).

2-(1,3,9,10-Tetramethoxyanthracen-2-yl)furan (35)

To a solution of bromotetramethoxy anthracene **8** (1 g, 2.6 mmol) in 2 mL toluene was added 2-tributylstannylfuran (1.8 g, 1.6 mL, 5 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.09 g, 0.13 mmol) and the mixture was boiled for six hours. After this the solvent removed and crude product was purified by silica

gel flash column chromatography (EtOAc/hexanes, 1:3) to give pure 2-(1,3,9,10-tetramethoxyanthracen-2-yl)furan **35** (0.58 g, 61% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9 Hz, 1H), 8.21 (d, *J* = 9 Hz, 1H), 7.65 (m, 1H), 7.52 – 7.44 (m, 2H), 7.39 (s, 1H), 6.72 (d, *J* = 3 Hz, 1H), 6.59 (dd, *J* = 1.5 Hz and *J* = 3 Hz, 1H), 4.09 (s, 3H), 4.04 (s, 3H), 3.99 (s, 3H), 3.81 (s, 3H).

1,3-Dihydroxy-2-iodoanthracene-9,10-dione (36)

Iodine monochloride solution in dioxane was prepared first, by adding ICl (1 M solution in DCM, 10 mL, 10 mmol) to 10 mL dioxane at 0 ^{o}C. The solution was warmed to room temperature and used for the iodination reaction. This reagent was always freshly prepared and used immediately.

To the stirred solution of 1,3-dihydroxyanthracene-9,10-dione **5** (0.24 g, 1mmol) in 10 mL THF, the freshly prepared ICl solution in dioxane was added (4 mL, 2 mmol) at 0 ^{o}C. The solution was warmed to room temperature and stirred for four hours. After this the solvent was removed and the crude product was used as such for the next reaction. It can also be purified by silica gel flash column chromatography (EtOAc/hexanes, 1:3) to give 1,3-dihydroxy-2-iodoanthracene-9,10-dione **36** (0.25 g, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8, 1H), 8.24 (d, *J* = 8, 1H), 7.97 – 7.93 (m, 2H), 7.41 (s, 1H).

2-Iodo-1,3,9,10-tetramethoxyanthracene (37)

To a stirred solution of 1,3-Dihydroxy-2-iodoanthracene-9,10-dione **36** (0.37 g, 1 mmol) in 20 mL acetone were added cesium carbonate (1.3 g, 4 mmol) and dimethyl sulfate (0.38 g, 0.3 mL, 3 mmol). The reaction mixture was refluxed for six hours and cooled to room temperature. The solvent was removed and the crude product was taken directly for the next reaction.

To the crude 2-iodo-1,3-dimethoxyanthracene-9,10-dione, solid tetrabutylammonium bromide (35 mg, 0.1 mmol), 10 mL of THF and 4 mL of water were added. To this stirred

solution was added an aqueous solution of sodium dithionite (1 g, 6 mmol) in 5 mL water. After 30 minutes of stirring at room temperature, potassium hydroxide (1.6 g, 28 mmol) in 5 mL water was added. After 15 minutes, dimethyl sulfate (2.66 g, 2 mL, 21 mmol) was added. The mixture was stirred for six hours and diluted with 50 mL of dichloromethane. This was washed with 50 mL of sodium chloride solution and the organic layer was separated. It was dried over anhydrous $MgSO_4$, concentrated, and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:4) to provide 2-iodo-1,3,9,10-tetramethoxyanthracene **77** (0.26 g, 61% yield over two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J*= 8 Hz, 1H), 8.20 (d, *J* = 8 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.32 (s, 1H), 4.08 (s, 6H), 4.06 (s, 3H), 4.02 (s, 3H), 3.97 (s, 3H).

2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl chloride (40)

To a solution of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside **11** (1 g, 1.8 mmol) in 20 mL dichloromethane, DMF (0.36 mL) was added and the reaction mixture was cooled to 0 ^{o}C. To this oxalyl chloride (0.69 g, 0.46 mL, 3 mmol) was added dropwise at 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for two more hours. At the end of this reaction time, the solvent was removed and the crude product was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:4) to give 2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl chloride **40** (0.86 g, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.21 (m, 20H), 6.07 (d, *J* = 4 Hz, 1H), 4.98 (d, *J* = 12 Hz, 1H), 4.83 (m, 2H), 4.71 (d, *J* = 4 Hz, 2H), 4.51 (d, *J* = 12 Hz, 1H), 4.45 (t, *J* = 12 Hz, 2H), 4.07 – 4.01 (m, 2H), 3.76 – 3.71 (m, 3H), 3.64 (d, *J* = 12 Hz, 1H).

2-(Phenylsulfinyl)naphthalene-1,4-dione (43)

To a solution of 1,4-naphthoquinone (1.58 g, 10 mmol) in 10 mL ethanol, benzenethiol (1.1g, 10 mmol) was added the mixture was heated to 100 ^{o}C in a sealed tube for overnight. At the end of this reaction time, the reaction mixture was cooled and the solvent was removed. The crude product was purified by silica gel flash column

chromatography (EtOAc/hexanes, 1:3) to give 2-(phenylthio)naphthalene-1,4-dione (1.6 g, 61% yield).

To a solution of 2-(phenylthio)naphthalene-1,4-dione (1 g, 3.5 mmol) in 10 mL dichloromethane was added a solution of MCPBA (0.67 g, 3.9 mmol) in 5 mL dichloromethane at 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for two more hours. After this, it was diluted with 200 mL dichloromethane and washed with 200 mL water. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:2) to provide pure 2-(phenylsulfinyl)naphthalene-1,4-dione **43**. (0.91 g, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8 Hz, 1H), 8.00 (d, *J* = 8 Hz, 1H), 7.85 (m, 2H), 7.76 (m, 2H), 7.65 (s, 1H), 7.49 (m, 3H).

Compound 44

The enamine was prepared first. To a solution of methyl acetoacetate (1.16 g, 10 mmol) in 50 mL benzene, piperidine (0.7 g, 1.6 mL, 10 mmol) and PTSA (0.05 g) was added. This solution was refluxed and water was removed continuously by using Dean-Stark apparatus for five hours. The reaction mixture was cooled to room temperature and the solvent was removed. The crude enamine was used as such for the next reaction.

To a solution of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl chloride **40** (2 g, 3.6 mmol) in dichloromethane, dry 4A^{o} molecular sieves (approx 0.5 g) and a solution of the above enamine (10 mmol) in dichloromethane were added. After this solid silver triflate (1.9 g, 7.2 mmol) was added and the reaction mixture was stirred in the dark for one hour. The reaction mixture was filtered through celite and the solvent was removed. Finally, the crude product was purified by silica gel column chromatography to give the anomeric mixture (α and β) of the compound **44** (1.8 g, 78% yield).

MS: m/e: 675 (M + Na^{+}), 653, 562, 455, 412, 408, 346, 181, 91. HRMS: m/e calc 652.304, m/e found: 652.306.

2-Methoxycarbonyl-1,4-naphthoquinone (50)

To a solution of 1,4-dihydroxy-2-naphthoicacid (2 g, 10 mmol) in 20 mL THF, diisopropylethylamine (1.4 g, 1.96 mL, 11 mmol) and dimethyl sulfate (2.8 g, 2 mL, 22 mmol) were added and the mixture heated to 50 ^{o}C for four hours. The mixture was cooled to room temperature and diluted with 200 mL of ethyl acetate. The organic layer was washed with 200 mL of sodium bicarbonate solution and then 200 mL of brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:2) to provide methyl 1,4-dihydroxynaphthalene-2-carboxylate (1.9 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 12 Hz, 1H), 8.21 (d, *J* = 12 Hz, 1H), 7.69 (t, *J* = 7 Hz, 1H), 7.63 (t, *J* = 7 Hz, 1H), 7.19 (s, 1H), 3.98 (s, 3H).

To a solution of 1,4-dihydroxynaphthalene-2-carboxylate (1.3 g, 6 mmol) in 20 mL THF, silver(I) oxide (2.8 g, 12 mmol) and magnesium sulfate (1.3 g) were added and the reaction mixture was stirred at room temperature for one hour. At the end of this reaction time, the reaction mixture was filtered and the filtrate was concentrated. The crude 2-methoxycarbonyl-1,4-naphthoquinone **50** was unstable for further purification and used as such for further reactions. (1.2 g, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 2H), 7.92 – 7.90 (m, 2H), 7.25 (s, 1H), 3.89 (s, 3H).

Compound 54

To a solution of 2-methoxycarbonyl-1,4-naphthoquinone **50** (0.4 g, 1.85 mmol) in 10 mL THF, a solution of 1,3-bissilyloxy-1-methoxy-1,3-butadiene (0.72 g, 2.8 mmol) in 5 mL THF was added at -78 ^{o}C. This mixture was warmed to 0 ^{o}C in 2 hours and then 2 mL of 1% HCl solution in water was added and stirred for one more hour. At the end of this reaction time, the reaction mixture was diluted with 100 mL of ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The residue

was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:1) to provide the intermediate **53** (0.23 g, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.8 (s, 1H), 8.36 (d, *J* = 8 Hz, 1H), 8.86 (d, *J* = 8 Hz, 1H), 7.59 (t, *J* = 7 Hz, 1H), 7.49 (t, *J* = 8 Hz, 1H), 5.59 (s, 1H), 4.11 (q, *J* = 7 Hz, 1H), 3.97 (s, 3H), 3.65 (d, *J* = 16 Hz, 1H), 3.51 (d, *J* = 16 Hz, 1H), 3.03 (q, *J* = 10 Hz, 2H).

The intermediate **53** (0.08 g, 0.27 mmol) prepared as above, was dissolved in 5 mL THF and to this solution 2,3,4,6-tetra-O-benzyl-D-glucopyranosyl chloride **40** (0.3 g, 0.54 mmol) in 2 mL THF and silver triflate (0.14 g, 0.54 mmol) were added and the mixture stirred for 1 hour at room temperature in the dark. The reaction mixture was filtered and the solvent was removed. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes, 1:1) to give the product **54** (0.13 g, 62% yield).

MS: m/e: 861 (M + K^+), 845 (M + Na^+), 822, 566, 556, 417, 384, 319, 252. . HRMS: m/e calc 822.865, m/e found: 822.868.

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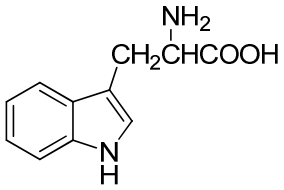
CHAPTER 4

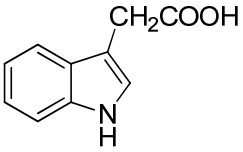
A flexible synthesis of indoles from ortho-substituted anilines

Introduction

Indoles have been an important topic of research for over a century. The syntheses and activities of indole derivatives appear in the chemical literature every year. The reason for this prolonged interest in indole derivatives is mainly because of their profound biological activity.[1] The indole ring appears in many natural products. An indole ring is present in the amino acid tryptophan **(1)**, which is very important for both plants and animals. Indole-3-acetic acid **(2)** is a plant growth hormone and serotonin **(3)** is the key neurotransmitter in animals. The indole ring also appears in many natural products like alkaloids, fungal metabolites and marine natural products. Some examples among the many important indole derivatives which are used as drugs are indomethacin **(4)** - a non-steroidal anti-inflammatory agent, sumatriptan **(5)** - a drug for migraine headache and pindolol **(6)** - a β-adrenerrgic blocker.[2]



1



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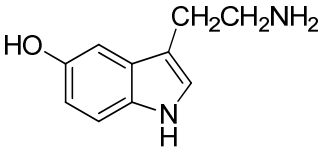

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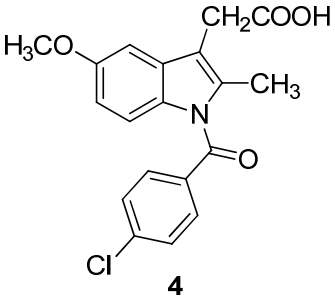

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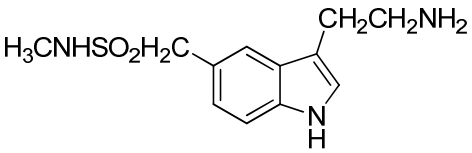

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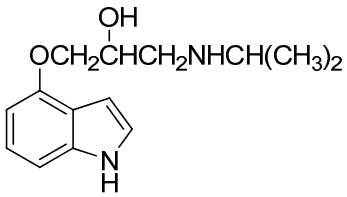
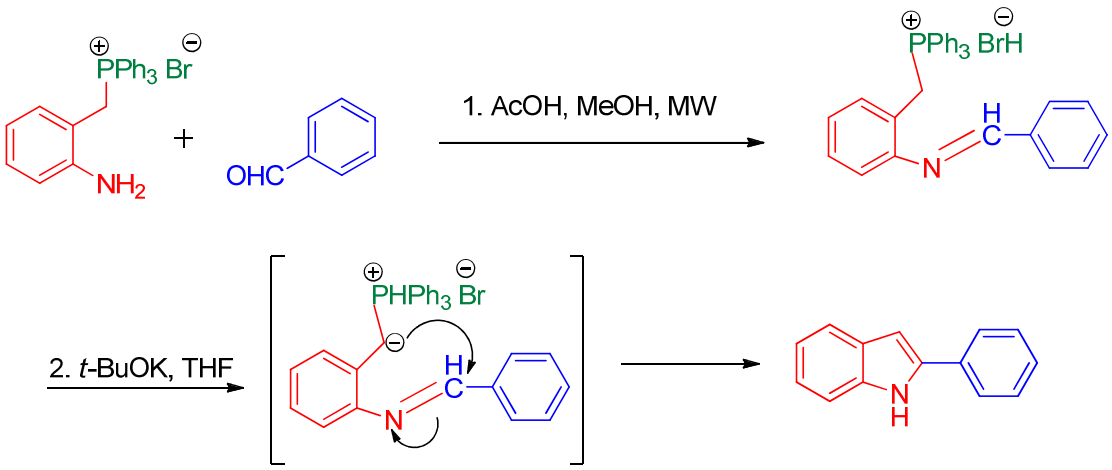


6

The first synthetic preparation for indole was reported by Fischer in 1883. Since, then many methods for the preparation of indoles were reported in the literature. The notable among them are from Bartoli, Bischler, Hemetsberger, Julia, Larock, Medelung, Nenitzescu, Reissert and Sundberg.[3] Although, these reactions are synthetically useful, they suffer from one or more of the following disadvantages: i. high temperatures and long reaction times, ii. use of expensive transition metal catalysts, iii. methods involving multistep reactions which resulted in moderate yields and iv. use of reagents which are highly sensitive to moisture.

Recently Kraus and Guo reported an efficient method for the preparation of indoles which is shown in Scheme 1.[4, 5] This method involved the condensation of an aromatic aldehyde with (2-aminobenzyl)triphenylphosphonium bromide to form an intermediate imine. This, on treatment with a base, underwent electrocyclic ring closure to form the indole.

Scheme 1



This method was very versatile and tolerant to both electron-withdrawing and electron-donating substituents on both the amine and the aldehyde compounds. However, the main disadvantages of this method are listed below.

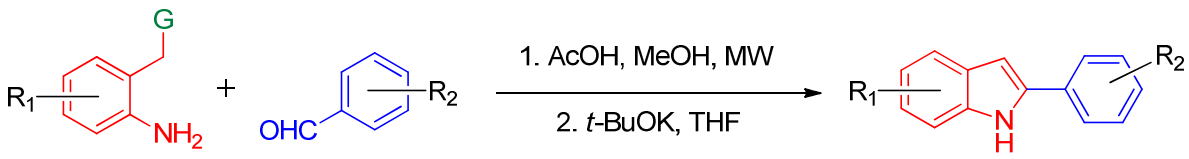
1. The starting material contains both an amino group as well as a phosphonium group. Depending on the substrate used, potentially both of these groups could react with the aldehyde group and could lower the overall yield of the reaction.
2. The starting material used was a salt. This resulted in poor solubility in many organic solvents.
3. The starting phosphonium salt compounds are expensive.

Due to these reasons it was important to evaluate other leaving groups which could work as effectively as the triphenylphosphonium group without the above discussed disadvantages.

Results and Discussion

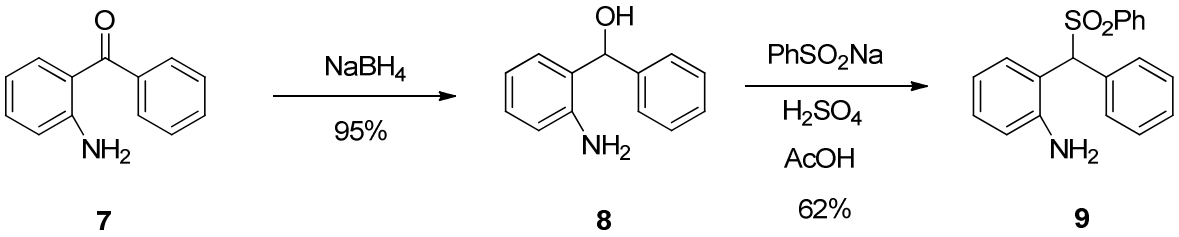
The general scheme for the formation of indoles is shown below. R_1 and R_2 could be electron-releasing or electron-withdrawing groups. G could be any leaving group which also could assist the formation of a carbanion.

Scheme 2



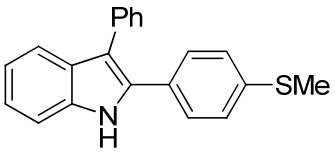
The first alternative substrate tried was aminophenylsulfone **9,** in which the G was the sulfone group. This could be made easily from the commercially available 2-aminobenzophenone **7** in two steps, as shown in Scheme 3. This appears to be a reasonably general method for aminobenzyl sulfone synthesis.[6] The starting amino compound is more soluble than the previously used phosphonium salt, and therefore would permit a wider range of reaction conditions for the imine formation step.

Scheme 3

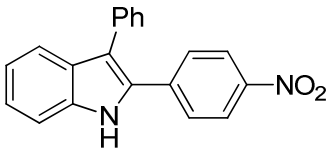


7 **8** **9**

With the phenylsulfone **9** in hand, indole formation was attempted with some representative aldehydes using the procedure reported by Kraus and Guo. These reactions proceeded smoothly to form the corresponding indoles in good to excellent yields. These results are summarized in Table 1. The exceptions to this method were 4-thiomethylbenzaldehyde and 4-nitrobenzaldehyde. In the former case, the thiomethylindole **10** had the same R_f value as the phenylsulfone **9**. Hence, it was very difficult to purify this compound. In the latter case, the nitrophenylindole **11** formed from the nitrobenzaldehyde was unstable to purification.

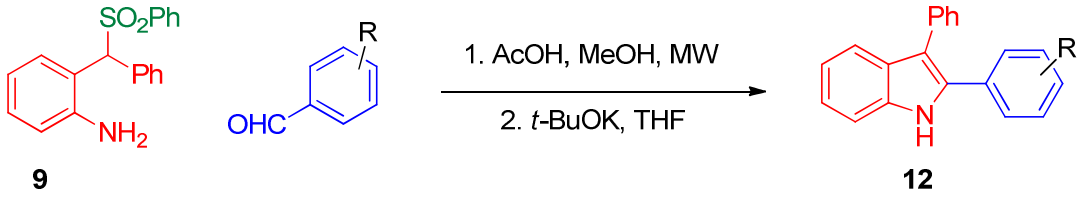


10

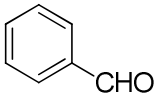
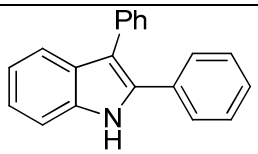
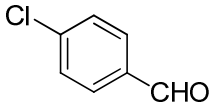
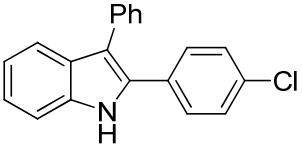
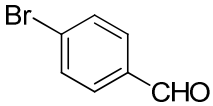
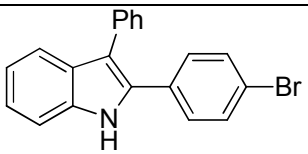
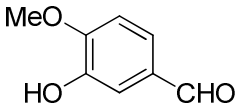
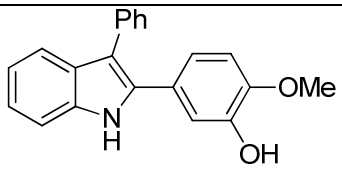
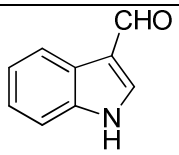
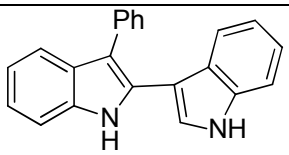
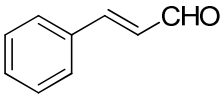
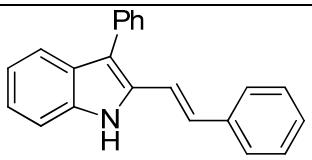


11

Table 1: Reaction of **9** with aldehydes to generate indoles.

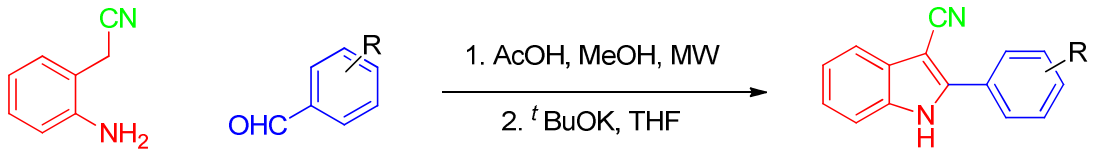


9 **12**

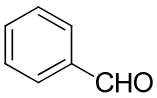
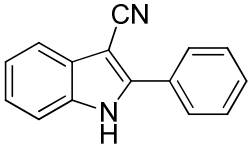
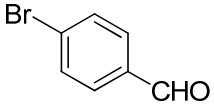
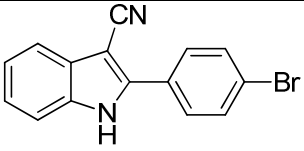
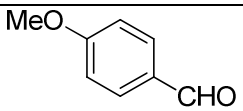
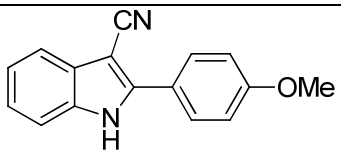
Entry	Aldehyde	Product		Yield (%)
1			**12a**	85
2			**12b**	81
3			**12c**	68
4			**12d**	71
5			**12e**	74
6			**12f**	68

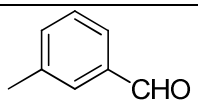
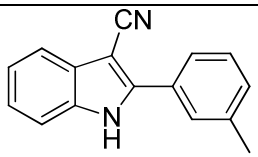
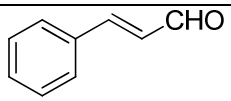
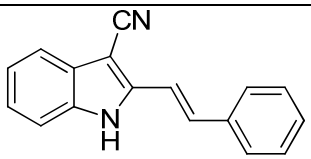
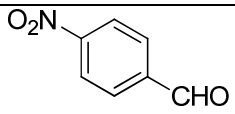
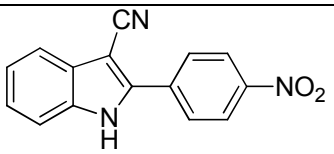
Commercially available 2-cyanomethylaniline **13** was studied next, with some representative aldehydes using the usual procedure. These reactions formed the corresponding cyanoindoles in good to excellent yields. Thus in these cases, instead of the elimination of the cyanide, oxidation to a 3-cyanoindole occurred, presumably via deprotonation of the benzylic hydrogen with the base, followed by aromatization. Hence, the atom economy of these reactions turned out to be excellent as the cyano group stayed, and only water was lost to form the indoles. These results are summarized in the following table.

Table 2: Reaction of **13** with aldehydes to generate indoles.



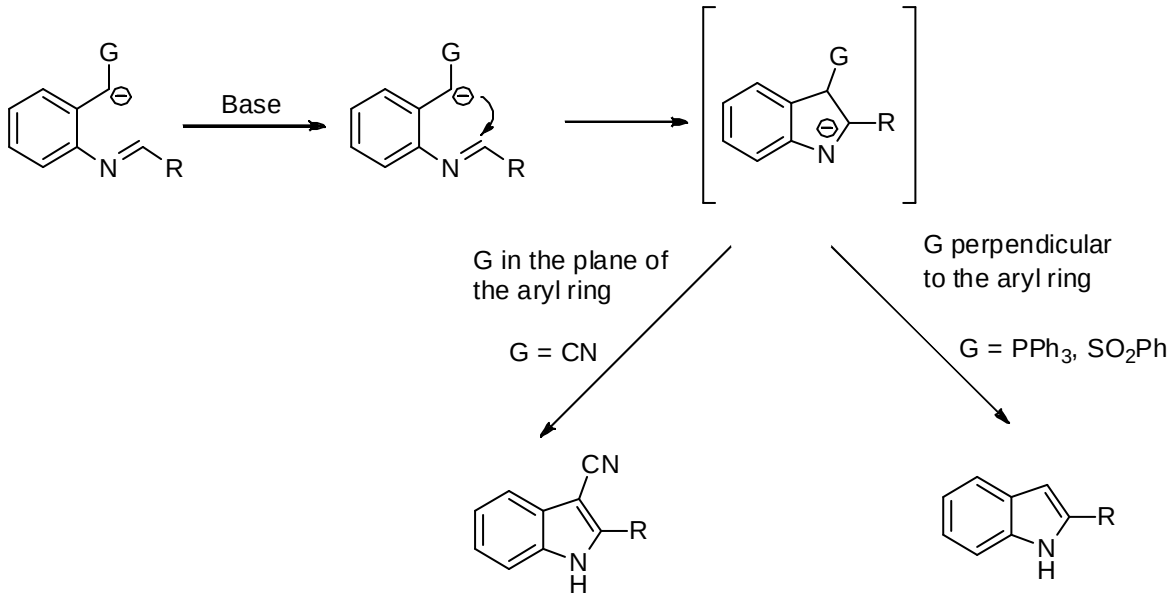
13 **14**

Entry	Aldehyde	Product		Yield (%)
1			**14a**	93
2			**14b**	83
3			**14c**	78

4			**14d**	87
5			**14e**	69
6			**14f**	85

The reason for the difference in reactivity between the bulky substituents (G = SO_2Ph and $P^{(+)}Ph_3Br^{(-)}$) and smaller substituents (G = CN) could be due to the steric effect exerted by them on the cyclization of the imine intermediate. This is shown in Scheme 4. If G is bulky, then it might orient itself in the plane perpendicular to the plane of the aromatic ring to avoid any non-bonded interactions. From this orientation it could easily undergo elimination to form the final indole. However, if G is small group, then it might orient in the plane of the aromatic ring. The benzylic hydrogen alpha to the nitrile would be acidic, allowing deprotonation and oxidation to form the 3-cyanoindole.

Scheme 4



Thus, use of cyano group in the starting material helped to improve the atom efficiency of this indole preparation method. Also, the cyano group at the 3-position of the indole could be used as a handle for further reactions.

Experimental Section

2-(Phenyl(phenylsulfonyl)methyl)aniline (9)

To a stirred solution of (2-aminophenyl)phenylmethanol **8** (2 g, 10 mmol) in 20 mL acetic acid and 10 mL ethanol, sodium benzenesulfinate (2 g, 12 mmol) was added. To this solution concentrated sulfuric acid (4 g, 4 mmol) was added and the mixture was heated to 100 ^{o}C for 12 hours. At the end of this reaction time, the reaction mixture was cooled to room temperature and diluted with water and the product was extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:3) to provide pure 2-(phenyl(phenylsulfonyl)methyl)aniline **9** (2 g, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 12 Hz, 2H), 7.61 (d, *J* = 12 Hz, 2H), 7.50 – 7.47 (m, 4H), 7.38 – 7.35 (m, 3H), 7.11 (t, *J* = 8 Hz, 1H), 6.81 (t, *J* = 8 Hz, 1H), 6.76 (d, *J* = 12 Hz, 1H), 5.73 (s, 1H).

General procedure for the synthesis of indoles

In a 10 mL microwave reaction vessel (CEM Discover System) equipped with a magnetic stir bar, the 2-substituted aniline (0.5 mmol), the aldehyde (0.5 mmol) and glacial acetic acid (11.4 μL, 0.2 mmol) were added to 5 mL of distilled methanol. The vial was capped properly and placed in the microwave. Microwave irradiation was carried out at 80 ºC for 10 min (temperature fixed). After cooling the vial to room temperature, methanol was removed under vacuum. Methanol must be completely removed before the next step. THF (4 mL) weas added to the mixture and 0.8 mL of a 1 M *t*-BuOK solution in THF was added dropwise. The resulting mixture was stirred at 25 ºC under the argon for one hour. Then saturated NH_4Cl solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined and washed with brine (2 x 10 mL). The organic layer was separated, dried with $MgSO_4$ and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate and hexanes as the eluent.

Compounds **12a** to **12f** were made by a different method and reported by Kraus and Guo.[5]

2,3-Diphenyl-*1H*-indole (12a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.48 – 7.38 (m, 7H), 7.35 – 7.25 (m, 5H), 7.18 (t, *J* = 7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6, 135.2, 134.2, 132.8, 130.3, 128.9, 128.8, 128.6, 128.3, 127.8, 126.3, 122.8, 120.5, 119.8, 115.1.

HRMS: m/e calc, 269.1205; m/e found, 269.1209.

2-(4-Chlorophenyl)-3-phenyl-*1H*-indole (12b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.50 – 7.43 (m, 5H), 7.40 – 7.30 (m, 6H), 7.24 (t, *J* = 8 Hz, 1H).

2-(4-Bromophenyl)-3-phenyl-*1H*-indole (12c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.50 – 7.43 (m, 5H), 7.40 – 7.36 (m, 6H), 7.24 (t, *J* = 8 Hz, 1H).

2-(3-Hydroxy-4-methoxyphenyl)-3-phenyl-*1H*-indole (12d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 7 Hz, 2H), 7.45 – 7.19 (m, 5H), 7.09 (d, *J* = 2 Hz, 1H), 6.92 – 6.90 (m, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H).

3-Phenyl-*1H,1'H*-2,3'-biindole (12e)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 11.30 (s, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.50 – 7.39 (m, 5H), 7.31 (t, *J* = 8 Hz, 2H), 7.20 – 7.05 (m, 5H), 6.85 (t, *J* = 7 Hz, 1H).

(E)-3-Phenyl-2-styryl-*1H*-indole (12f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.62 – 7.17 (m, 11H), 6.90 (d, *J* = 16 Hz, 1H).

3-Cyano-2-phenyl-*1H*-indole (14a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.89 (d, *J* = 8 Hz, 2H), 7.78 (d, *J* = 8 Hz, 1H), 7.55 – 7.45 (m, 4H), 7.34 – 7.28 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 136.4, 135.9, 128.9, 128.2, 128.1, 124.6, 124.1, 123.8, 122.8, 119.2, 115.9, 112.9, 54.3.

MS: m/e, 218, 190, 164, 96, 83, 71, 69, 57, 52. HRMS: m/e calc, 218.084; m/e found, 218.084.

3-Cyano-2-(4-bromophenyl)-*1H*-indole (14b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.98 (d, *J* = 8 Hz, 2H), 7.73 (d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 8 Hz, 1H), 7.32 (t, *J* = 8 Hz, 1H), 7.27 (d, *J* = 8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 149.5, 135.7, 132.2, 130.9, 129.6, 129.3, 129.1, 127.0, 126.3, 125.8, 118.4, 118.1, 65.2.

MS: m/e, 298, 296, 219, 190, 165, 143, 116, 89. HRMS: m/e calc, 295.995; m/e found, 295.995.

3-Cyano-2-(4-methoxyphenyl)-*1H*-indole (14c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.84 (d, *J* = 8 Hz, 2H), 7.74 (d, *J* = 8 Hz, 2H), 7.43 (d, *J* = 8 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.04 (d, *J* = 8 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 145.1, 135.1, 129.1, 128.5, 122.1, 119.6, 115.1, 111.6, 67.5, 60.1, 55.7.

MS: m/e, 248, 233, 205, 178, 151, 124, 105, 86, 84, 49. HRMS: m/e calc, 248.096; m/e found, 248.095.

3-Cyano-2-(3-methylphenyl)-*1H*-indole (14d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.77 (d, *J* = 8 Hz, 1H), 7.69 (d, *J* = 8 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.32 – 7.29 (m, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 139.5, 135.1, 129.6, 127.6, 122.6, 119.8, 116.9, 111.8, 67.2, 21.7.

MS: m/e, 232, 204, 190, 115. HRMS: m/e calc, 232.100; m/e found, 232.100.

3-Cyano-2-styryl-*1H*-indole (14e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.43 – 7.24 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 135.6, 135.5, 133.2, 129.5, 129.2, 128.4, 127.3, 125.0, 122.6, 119.7, 116.2, 115.5, 115.3, 111.6, 86.6.

MS: m/e, 244, 243, 231, 217, 191, 189, 115, 105, 84, 56, 49, . HRMS: m/e calc, 244.100; m/e found, 244.101.

3-Cyano-2-(4-nitrophenyl)-*1H*-indole (14f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.49 (d, *J* = 8 Hz, 2H), 8.30 (d, *J* = 8 Hz, 2H), 7.75 (d, *J* = 8 Hz, 1H), 7.62 (d, *J* = 8 Hz, 1H). 7.40 (t, *J* = 8 Hz, 1H), 7.35 (t, *J* = 8 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 137.6, 135.1, 130.1, 129.5, 129.0, 127.2, 124.3, 122.3, 118.9, 116.5, 112.6, 57.0.

MS: m/e, 264, 263, 247, 241, 217, 211, 190, 163, 150, 123, 102. HRMS: m/e calc, 263.069; m/e found, 263.069.

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GENERAL CONCLUSIONS

In this dissertation, direct and concise strategies for the synthesis of natural products have been studied. Also, a flexible synthetic methodology for indoles has been developed.

Chapter one describes an efficient method for the total synthesis of littorachalcone. This was the first synthetic pathway reported for littorachalcone. Our route is significantly more direct and operationally more convenient than the methods described for structurally similar verbenachalcone, because, we started from commercially available *para*-tolyl ether, thus avoiding the protection and deprotection steps necessary in those methods. One more structurally similar compound, the phenoxydicarboxylic acid was also synthesized. Biological activity of littorachalcone and its intermediates were studied. One of its intermediates, the dialdehyde showed a potent antibacterial activity.

Chapter two outlines a synthetic approach towards topopyrone-D. Metal-hydrogen exchange reactions on an anthracene moiety were investigated. Since they were unsuccessful, they were replaced by selective and efficient metal-halogen exchange reactions and this was applied for the synthesis of topopyrone-D. Synthesis of a model compound for topopyrone-D was completed.

Chapter three presents a synthetic strategy towards the synthesis of rubianine which is a C-glycoside. A complex Diels-Alder adduct was used effectively to introduce the glucose unit onto the anthraquinone carbon skeleton.

Chapter four reports the effect of different substituents at the *ortho*-position of the starting aniline compound. Bulky substituents like phosphonium salts and phenylsulfones tend to be lost to produce the final indole molecule. Small substituents like the cyano group stay in the final product and only water was lost to form the final indole molecule. This makes the method more atom economical and more environmental friendly than the previously reported methods.

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