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Connective methodologies for natural product synthesis

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Connective methodologies

for natural product synthesis

by

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Graduate College

Iowa State University

This is to certify that the Master's thesis of

Qunying Dai

has met the thesis requirements of Iowa State University

Signatures have been redacted for privacy

DEDICATION

To my parents, brother and Hualong.

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GENERAL INTRODUCTION

Introduction

Organic synthesis is a highly developed and interdisciplinary branch of the natural sciences. It remains as one of the most challenging fields of chemistry. The ultimate goal of the synthetic natural product chemist is to synthesize complex molecules that mimic the natural product's biological activity as efficiently as possible. Synthetic chemistry relies on imagination, creativity and solid knowledge of the previous work in the field to solve complex molecular puzzles.

The purpose of this research was to develop efficient syntheses of molecules with biological activity that are beneficial to human beings. The first project covers a direct synthetic approach to a potential anti-coccidial compound. The second project concerns the synthetic approaches to glycinoeclepin A. We have developed a new methodology for forming two new carbon-carbon bonds using [(phenylsulfonyl)-methylene]dilithium. In the third project, we have worked toward the total synthesis of eleutherobin, a new cytotoxin that mimics paclitaxel (taxol) by stabilizing microtubules. Isolated from a rare marine soft coral, it is not easily available from natural sources.

Thesis organization

This thesis is divided into three chapters. Each chapter is presented in the form of a journal paper. The numbering schemes adopted for the compounds and the references are independent for each chapter. At the end of this thesis is a general summary which highlights the importance of the research reported.

CHAPTER I

SYNTHETIC APPROACHES TO ANTICOCCIDIAL COMPOUNDS

A work to be reported in the future as part of a larger review[a]

George A. Kraus and Qunying Dai

Introduction

The protozoan disease coccidiosis is a major intestinal disease of poultry primarily caused by intestinal parasites in the genus *Eimeria.* It has global distribution and has caused serious economic losses to the commercial poultry industry. Due to the intensive rearing practices of the modern poultry industry, the disease is one of the most commonly occurring diseases today. In the United States the disease is largely controlled through management and chemotherapeutic agents administered in the feed. However, because of the widespread resistance of coccidia to anticoccidial feed additives developed decades ago, the discovery and research of new anticoccidials remains active.

The following naphthoquinone compounds (Figure 1) are expected to be potential anticoccidials due to the structure similarity toward one of the

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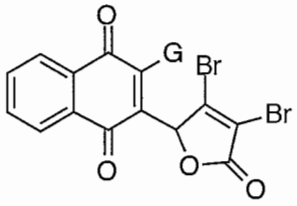
[a] This will be submitted to Studies in natural products chemistry, 2000. A contribution from Professor Don Reynolds will be added.

anticoccidials. This fact makes them interesting targets of organic synthesis.



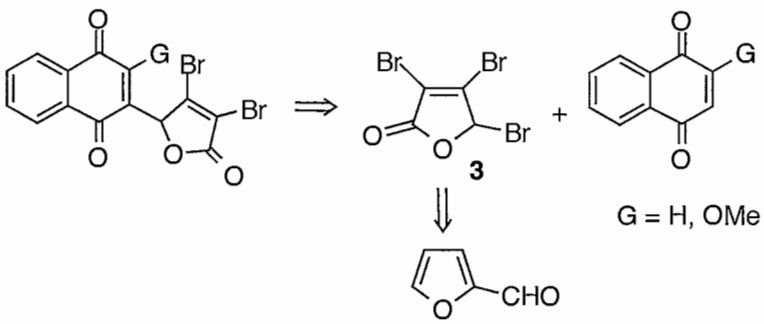
1: G= H; **2**: G= OMe

Figure 1. Potential anticoccidial compounds

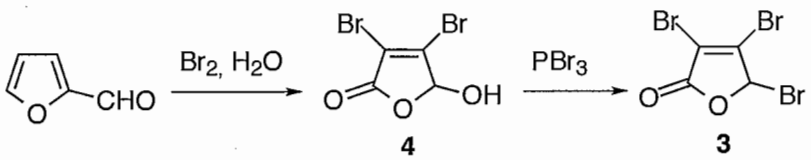
Results and discussion

We broke the compound into two fragments, the lactone part and the naphthoquinone part. The retrosynthesis is outlined in Scheme 1, starting from commercially available furfural and 1,4-naphthoquinone. The preparation of the requisite 2,3,4-tribromobut-2-en-4-olide (**3**) is shown in Scheme 2.[1,2]

Scheme 1

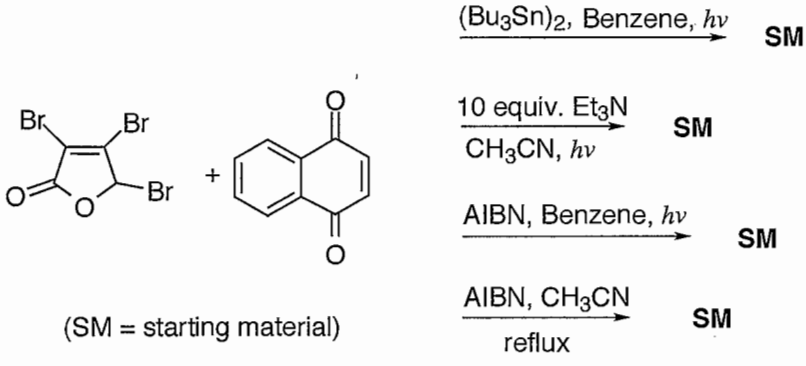


Scheme 2

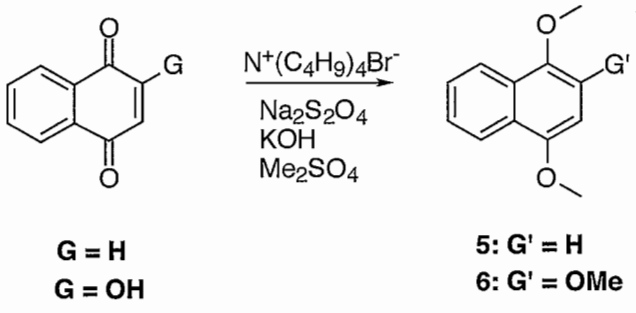


Believing that it is feasible to generate an allylic radical under suitable conditions, we attempted a classical radical addition to 1,4-naphthoquinone (Scheme 3). Much to our surprise, these reaction conditions returned the two starting materials. Therefore, we turned to ionic chemistry. The preparation of compounds **5** and **6** is shown in Scheme 4 using the reductive methylation method developed within the group.[3] First we tried the electrophilic substitution of **5** using the Lewis acid tin(IV) chloride. However, we got the two starting materials back untouched. Then we used silver triflate which gave us the desired result. Following ceric ammonium nitrate oxidation, we obtained the quinone **1** (Scheme 5).

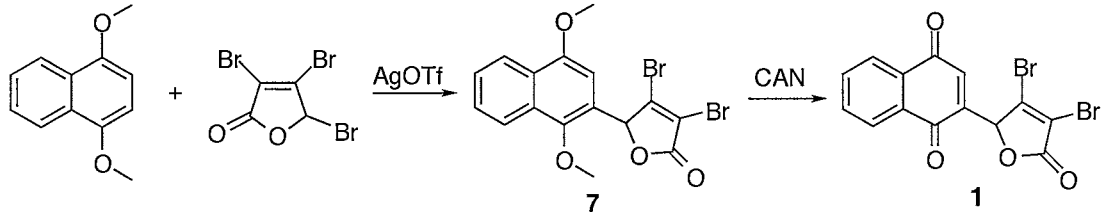
Scheme 3



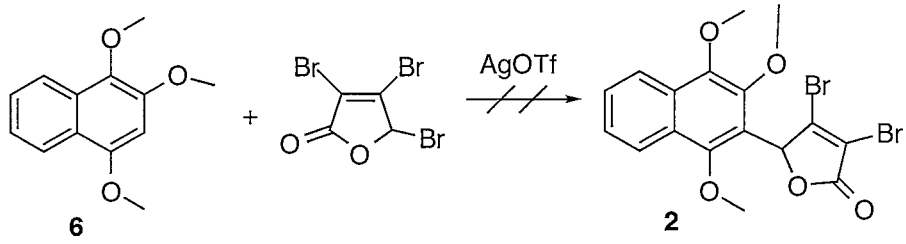
Scheme 4



Scheme 5



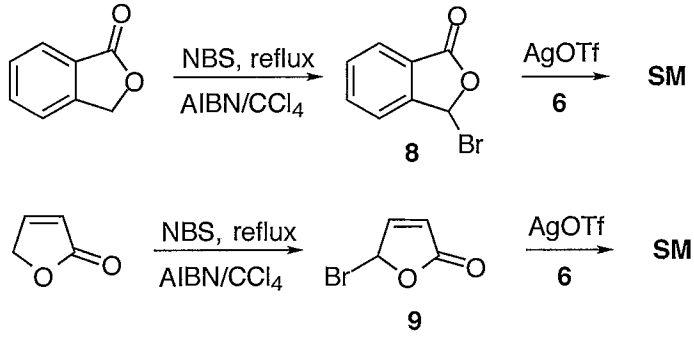
Scheme 6



With compound **1** in hand, we attempted to synthesize compound **2** from 2-hydroxy-1,4-naphthoquinone using the same route (Scheme 6). Surprisingly, we didn't get the desired product this time. Nuclear magnetic resonance spectra, infrared specctra and mass spectra of the purified product showed that due to steric hindrance, the lactone reacted at C-6 or C-7 of the naphthalene. In order to solve the steric problem, we tried two bromides which we believed to be less crowded. Their preparation and the result of the reactions with **6** are shown below in Scheme 7.

We were discouraged by this turn of events. Compounds **8** and **9** are too "big" to squeeze into the desired position between the methoxy groups of **6**.

Scheme 7



Conclusion

We have synthesized compound **1** in five steps from commercially available furfural and 1,4-naphthoquinone. However, the synthesis of **2** was not successful due to steric hindrance of the neighboring two methoxy groups present in compound **6**. A different approach is needed to overcome this problem.

Experimental

Unless otherwise noted, material was obtained from commercial suppliers and was used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methylene chloride and acetonitrile were purified by distillation from calcium hydride. The apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 h and cooled under a stream of argon or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was

performed using Aldrich TLC plates (silica gel 60) with a thickness of 0.25 mm. The solvent system was suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sg represents silica gel. Infrared spectra were obtained on a Bio-Rad FTS-7 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetic Corporation NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ABQ (AB quartet), and m (multiplet). The br prefix indicates a broadened pattern. Carbon-13 spectra were obtained on a Nicolet Magnetic Corporation NT-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm). Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The purity of all title compounds was determined to be >95% by 300 MHz proton NMR spectroscopy.

αβ-Dibromo-β-formylacrylic Acid (4)[1]: A mixture of furfural (17.36 g, 0.18 mol) and water (174 mL) was stirred vigorously in a three-necked round-bottomed flask equipped with a dropping funnel and a thermometer. The flask was immersed in an ice bath and 50 mL of bromine was added, while the temperature was kept below 5 °C. After the addition was complete, the thermometer was replaced by a refluxing condenser, and the mixture was stirred and boiled for 30 minutes. The

reflux condenser was replaced by a still head and condenser, and excess bromine was removed by distilling the liquid until the distillate was almost colorless. Then the reaction mixture was evaporated, using a trap cooled in ice to condense the hydrobromic acid. The solid residue was cooled in an ice bath and triturated with 10 mL of ice water. A few grams of $NaHSO_3$, dissolved in water, were added to discharge a slight yellow discoloration. The cold mixture was filtered with suction to separate crude product, which was washed with two small portions of ice water. The crude product was dissolved in about 40 mL of boiling water, cooled to 0-5 °C. Colorless crystals of **4** were separated from the filtrate, then filtered and dried by vacuum. The yield was 25%. ^{1}H NMR ($CDCl_3$) δ 6.06 (d, J = 9 Hz, 1H), 3.73 (d, J = 9 Hz, 1H).

2,3,4-Tribromobut-2-en-4-olide (3)[2]: The acid **4** (dried in *vacuo* over calcium chloride) (1.3929 g, 5.4 mmol) was dissolved in 10 mL of diethyl ether and treated with a solution of phosphorus tribromide (0.1857 mL, 2.0 mmol) in 5 mL of diethyl ether at 20 °C. The solvent was removed under reduced pressure at 35 °C, and the reaction mixture heated with exclusion of moisture at 100 °C for 1.5 h. After cooling of the mixture, ice water was added and the mixture was well shaken. After 24 h at 20 °C the crystalline product was filtered off, well washed with cold water, dried ($CaCl_2$), and recrystallized from ethanol to give tribromolactone **4**: m.p. 57 °C; The yield was 71%. ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 1H); ^{13}C NMR: δ 162.96 (s, C=O),

147.14 (s, =C-Br), 116.80 (s, =C-Br, adjacent to C=O), and 77.79 ppm (s, >CHBr).

General procedure for the reductive methylation[3]: To 2 mmol of naphthoquinone and 75 mg of *n*-Bu_4NBr in 5 mL of THF and 2 mL of H_2O were added 12 mmol of aqueous $Na_2S_2O_4$. After 15 min at ambient temperature, 46 mmol of aqueous KOH was added. After 5 min, 4 mL of Me_2SO_4 was added and the mixture was stirred for 10 h. The product was isolated by partitioning between water and methylene chloride, and the organic layer washed with KOH, water and brine successively. The crude product was purified by silica gel chromatography. The following compounds were prepared using the general procedure.

1,4-Dimethoxynaphthalene (5): 1,4-Naphthoquinone was used as the starting material. The yield was 66%. ^1H NMR ($CDCl_3$) δ 8.20 (m, 2H), 7.50 (m, 2H), 6.70 (s, 2H), 4.00 (s, 6H).

1,2,4-Trimethoxynaphthalene (6): 2-Hydroxy-1,4-naphthoquinone was used as the starting material. The yield was 51%. ^1H NMR ($CDCl_3$) δ 8.17-8.12 (m, 1H), 8.07-8.02 (m, 1H), 7.49 (m, 1H), 7.35 (m, 1H), 6.65 (s, 1H). 4.01 (s, 3H), 4.00 (s, 3H), 3.93 (s, 3H).

2-(3,4-Dibromo-5-oxo-2,5-dihydrofuran-2-yl)-1,4-dimethoxynaphthalene

(**7**): To the mixture of 1,4-dimethoxynaphthalene (1.0820 g, 3.37 mmol) and 2,3,4-tribromobut-2-en-4-olide (0.6404 g, 3.37 mmol) in methylene chloride solution at 0 °C was added silver triflate (0.8661 g, 3.37 mmol). The solution was stirred overnight at ambient temperature. It was worked up by filtering through Celite, and the dark violet solution was washed with $NaHCO_3$, water and brine. The yield was 42%. ^1H NMR ($CDCl_3$) δ 8.30-8.23 (m, 1H), 8.13-8.06 (m, 1H), 7.65-7.53 (m, 2H), 6.55 (s, 1H), 6.21 (s, 1H), 4.01 (s, 3H), 3.94 (s, 3H).

2-(3,4-Dibromo-5-oxo-2,5-dihydrofuran-2-yl)-1,4-naphthoquinone (**1**): To **7** (0.0414 g, 0.0963 mmol) dissolved in a mixture of acetonitrile (2 mL) and water (2 mL), a cooled solution of ceric ammonium nitrate (0.1320 g, 0.24 mmol) in a mixture of 0.34 mL of acetonitrile and 0.14 mL of water was slowly added with stirring at 0 °C for 30 min. The reaction mixture was stirred at room temperature for 20 min, poured into a separatory funnel, extracted four times with methylene chloride, washed with water and brine, and then dried over Na_2SO_4. The yield was 98%. ^1H NMR ($CDCl_3$) δ 8.08-8.17 (m, 2H), 7.79-7.85 (m, 2H), 6.93 (s, 1H), 6.21 (s, 1H).

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1. Shoppee, C.W. *J. Chem. Soc., Perkin Trans. I* **1985**, 45.
2. Rabjohn, Norman. *Organic Synthesis* Collective Volume 4, 688.
3. Kraus, G. A.; Man, T. O., *Synth. Commun.* **1986**, *16*, 1037.

CHAPTER II

STUDIES TOWARD SYNTHESIS OF GLYCINOECLEPIN A

A work to be communicated in the future as part of a broader study

Introduction

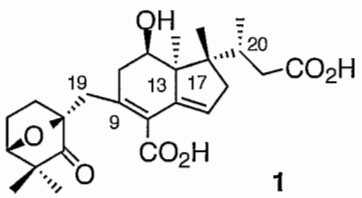
Soybean cyst nematode (SCN), also known as *Heterodera glycines*, is one of the most widely distributed and economically devastating soybean pests. Imported probably from the Far East, SCN first appeared in the United States in North Carolina in 1954.[1] Ever since then, SCN has been a substantial national problem. As the use of soybeans for more valuable products has increased, the significance of the SCN problem has also increased.

SCN survives in the soil as eggs contained within protective cysts. Many of the eggs contain fully developed second-stage juveniles, which will hatch under the proper conditions.[2] The hatched worm will invade the root and draw off nutrients from the soybean until the end of its life cycle. The adult females continue to grow and eventually will break through the surface of the root.[3] After fertilization, an adult female begins to deposit eggs externally and later will retain the remainder of the eggs within the body cavity, which will become a tough protective covering after its death. The cyst, an egg-filled body of a dead female, is easily dislodged from the root

and encysted eggs can remain viable in the soil for eleven years or more. The control of SCN remains difficult due to its short life cycle (24-30 days), its durability and its longevity.

Recently, there has been more interest in the possible development of herbicides that affect the hatch of SCN.[4] Herbicides, which stimulate the hatch in the absence of a host plant, and herbicides, which inhibit the hatch during the growing season could be used to manage SCN populations.

The isolation and structural elucidation of glycinoeclepin A (Figure 1) has revealed a compound with an unusual molecular structure and significant biological activity. At concentrations as low as 10^{-12} g/ml, it is capable of initiating hatch of the SCN eggs.[4] Glycinoeclepin A is a degraded triterpenoid isolated from kidney bean roots, but only milligram quantities can be obtained from kilograms of roots.[4] Since it is a naturally occurring compound, it should be readily biodegradable. These characteristics, combined with the lack of a satisfactory natural source, make it an attractive and challenging synthetic target.



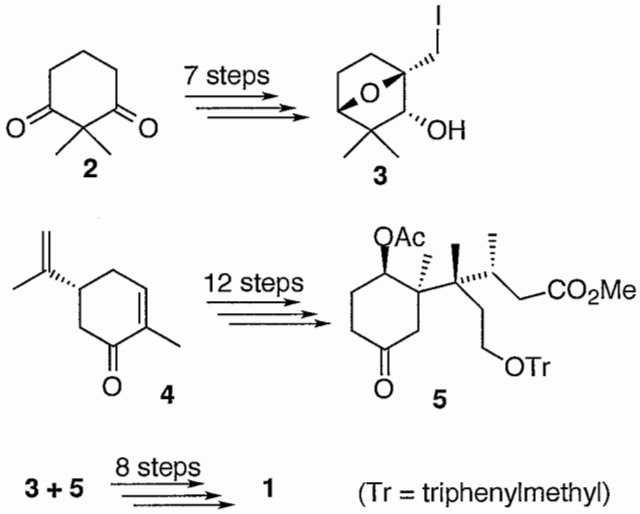
1

Figure 1 Glycinoeclepin A (1)

The first synthesis of **1** was completed by Akio Murai and co-workers in

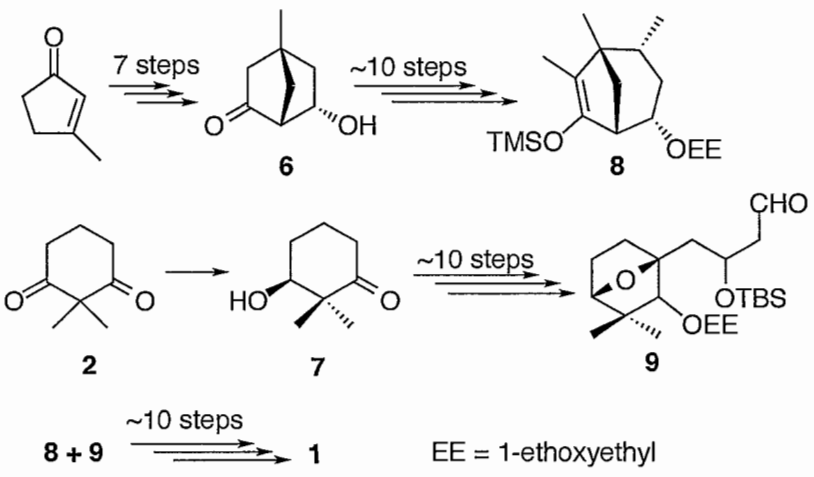
1988.[5] Murai started with 2,2-dimethylcyclohexane-1,3-dione (**2**) and obtained **1** in 27 steps (as shown in Scheme 1).

Scheme 1



In 1989 Kenji Mori succeeded in completing a second synthetic route to glycinoeclepin A.[6] He exploited two chiral building blocks of microbial origin, **6** and **7**, as shown in Scheme 2.

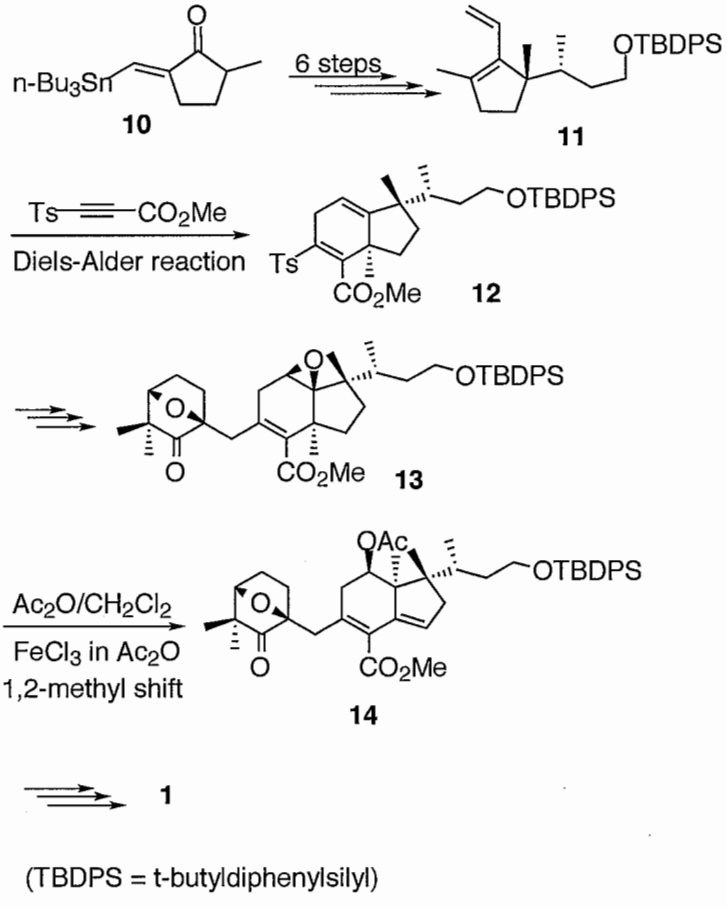
Scheme 2



With 32 steps and 3% overall yield from **2**, Mori's synthesis was not much of an improvement over Murai's. It was still not a feasible method for the production of large quantities of glycinoeclepin A due to its length and complexity.

In 1990, E. J. Corey completed a third total synthesis of glycinoeclepin A, which involved a Diels-Alder reaction and an interesting 1,2-methyl shift (Scheme 3).[7] At over 20 steps from **10**, Corey's is by far the most direct of the three syntheses.

Scheme 3



(TBDPS = t-butyldiphenylsilyl)

In 1994, Corey developed a biosynthetic route using the naturally occurring compound abietospiran (**15**), which is obtained from the bark of the common white fir tree, *Abies alba*.[8] He made desoxyglycinoeclepin **16** in 21 steps (Figure 2).

However, at over 20 steps, there is room for improvement. That is the reason why we continue our effort to construct a more efficient synthesis of glycinoeclepin A. Studying the structure of glycinoeclepin A, we decided to focus on construction of the fused 5,6-membered ring system first. In order to form two carbon-carbon bonds in one step, we came up with a dianion strategy.

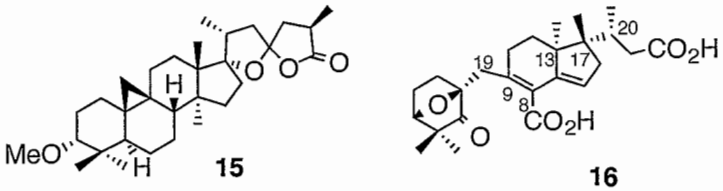


Figure 2. The structures of abietospiran (**15**) and desoxyglycinoeclepin (**16**)

Many carbon-based reactive intermediates, such as carbocations, carbanions, carbenes and radicals, are used routinely in organic synthesis. Dianions, which are molecules that bear two anionic centers, have become increasingly popular in organic synthesis, particularly in novel carbon-carbon bond-forming reactions. Among the dianions prepared from bis-deprotonations of certain organic molecules, there are four major types named C,C-dianions, O,C-dianions, N,C-dianions and S,C-dianions, which vary only in the nature of the first deprotonation. For example, a C,C-dianion results from deprotonation occurring at two C-H positions, whereas a N,C-dianion

results from first deprotonation at an N-H functional group, followed by deprotonation at a C-H (Figure 3).

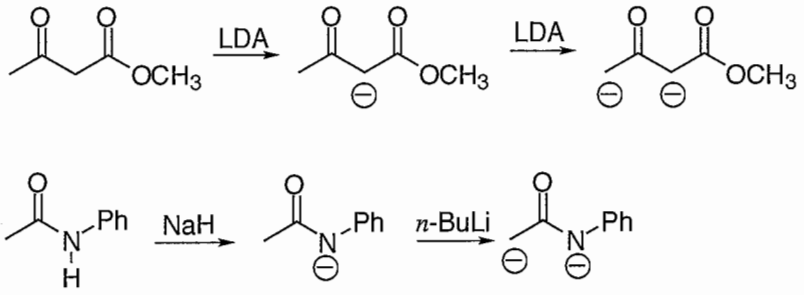
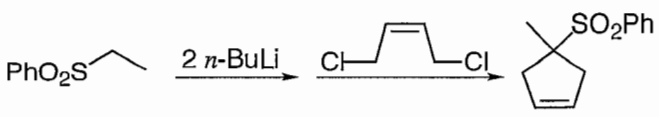


Figure 3. Comparison of C,C- and N,C-dianions

For our convenience in the construction of the fused [4.3.0] ring system, we chose a 1,1-(C,C)-dianion (in other words a geminal or α,α-dianion). We hoped to develop an intermediate which is capable of reacting twice with a bifunctional electrophile leading to novel ring-constructing processes. There are four types of well-known geminal dianions according to the carbanion-stabilizing group appended namely, (halo)carbonyl-, nitrile-, nitro-, and sulfonyl-stabilized dianions. Geminal dianions may be viewed as having a high degree of coulombic repulsion. A representative geminal(1,1)-dianion is shown in Figure 4.[9] Among the four types of geminal dianions, sulfonyl-stabilized dianions have been found to undergo bis-reactions at the α-site with simple electrophiles. An example is shown in Scheme 4.[10]

Scheme 4



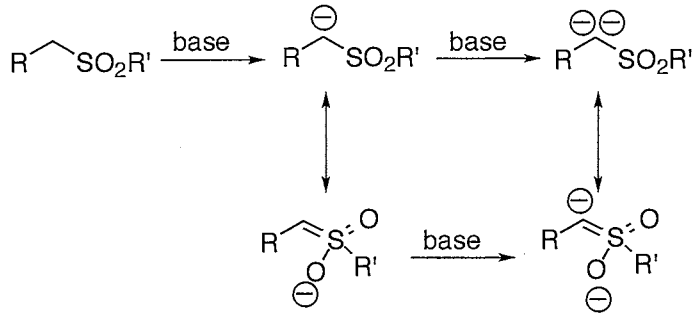
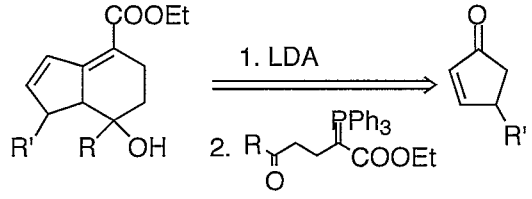


Figure 4 Reorganization to 1,3-dianion (R' is a non-enolizable substituent.)

Results and discussion

We initiated a route featuring an aldol condensation and a Wittig reaction in one pot. The retrosynthesis is outlined in Scheme 5.

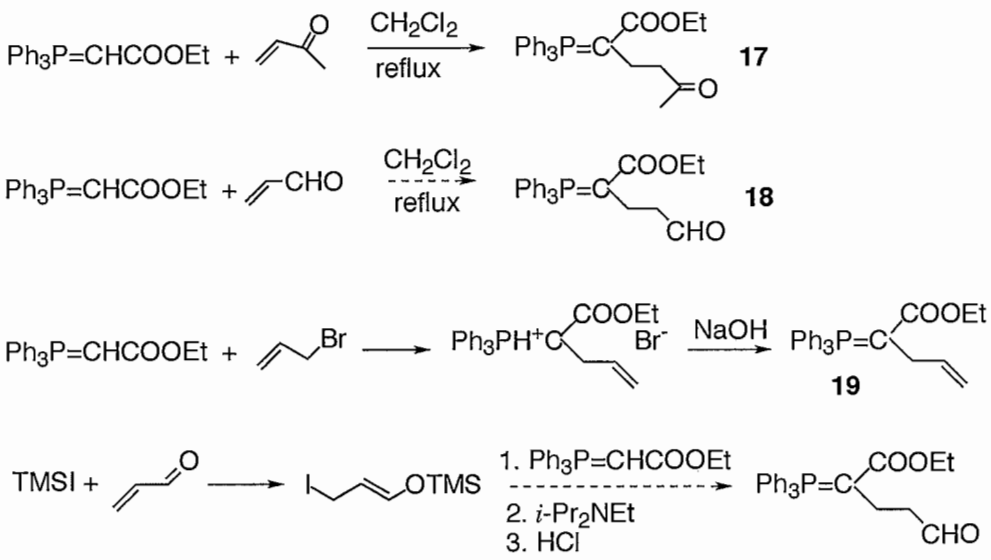
Scheme 5



The triphenylphosphorane reagent is the essential building block which would make two new carbon-carbon bonds possible in one step. According to the structure of glycinoeclepin A, R should be H. We attempted to make **18** as shown in Scheme 6. We found that compound **17** could be prepared from the Michael-addition of carboalkoxytriphenylphosphorane to methyl vinyl ketone in polar solvents like dichloromethane.[11] Therefore, we utilized the same conditions with acrolein.

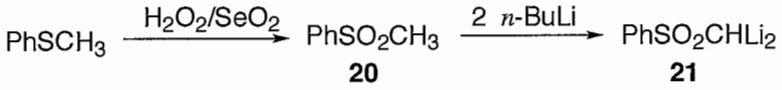
However, ethyl 2,4-pentadienoate was what we obtained, not the desired compound **18**. Then we attempted another pathway using an enol silyl ether. Since compound **19** was obtainable from an ylid and allyl bromide,[12] we wanted to take advantage of this reaction to transform acrolein to an enol silyl ether and then submit it to reaction with the ylid. However, the result was not promising at all. We didn't get **18**.

Scheme 6

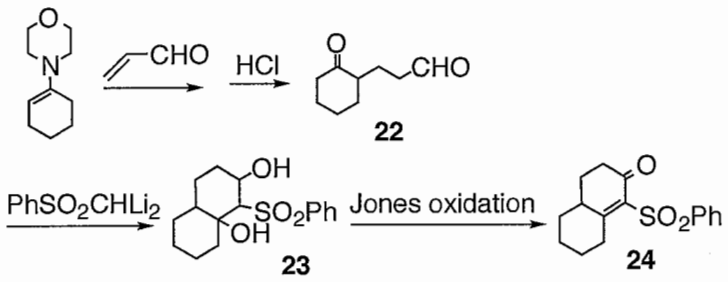


Since compound **18** is not easily obtainable, we turned to another approach with the same idea----namely making two carbon-carbon bonds in one step. The only difference is that we want to utilize a compound with two carbonyl groups and a suitable dianion. We made the sulfone from thioanisole (Scheme 7)[13]. Treatment of methyl phenyl sulfone (**20**) in dry THF with 2 mol equivalents of *n*-butyllithium in hexane under argon gave an insoluble precipitate of **21**.[14,15]

Scheme 7

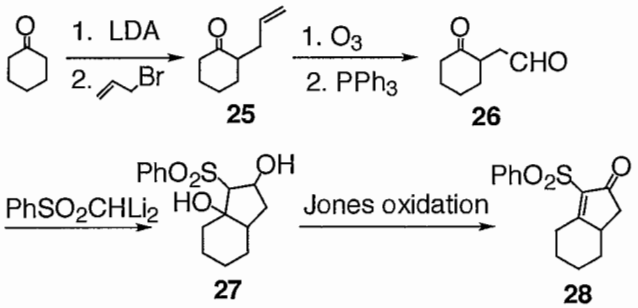


Scheme 8

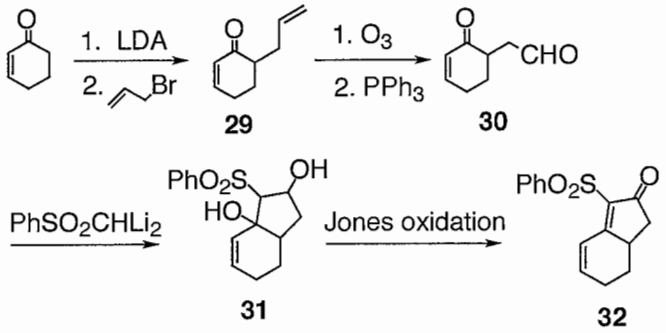


The first attempt to utilize dianion **21** is shown in Scheme 8. Starting from 1-morpholino-1-cyclohexene, we made the 1,5-dicarbonyl compound **22**.[16,17] Its reaction with the dilithio derivative of methyl phenyl sulfone (**20**) was successful. To extend the use of this geminal dilithioalkyl sulfone, we tried other bifunctional organic substrates. These 1,4-dicarbonyl compounds were made from reactions with ozone.[18] The attempts are shown in Schemes 9 and 10 and we got **28** and **32**.

Scheme 9

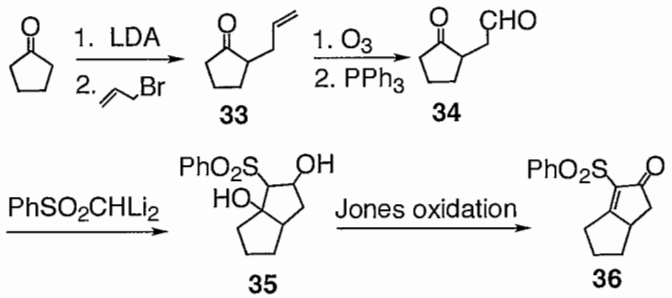


Scheme 10

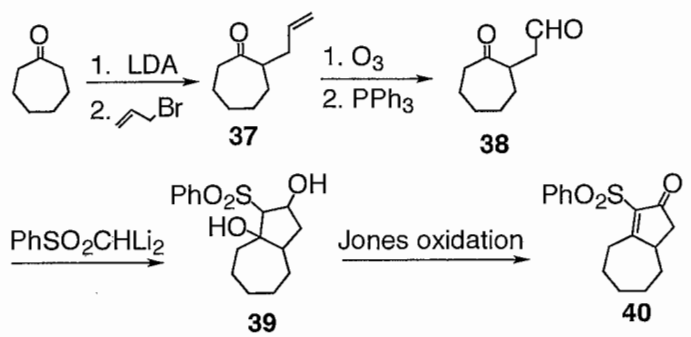


Besides the construction of fused ring systems starting from six-member ring compounds, we have also made five and seven-membered ring compounds (shown in Schemes 11 and 12).

Scheme 11



Scheme 12



Conclusion

We have developed an efficient synthetic methodology to form bicyclic compounds via a sulfonyl-stabilized dianion. The new route promises to open up an entirely new approach to the total synthesis of glycinoeclepin A.

Experimental

Unless otherwise noted, material was obtained from commercial suppliers and used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methylene chloride and acetonitrile were purified by distillation from calcium hydride. The apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12h and cooled under a stream of argon or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using Aldrich TLC plates (silica gel 60) with a thickness of 0.25 mm. The solvent system was suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sg represents silica gel. Infrared spectra were obtained on a Bio-Rad FTS-7 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetic Corporation NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated

as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ABQ (AB quartet), and m (multiplet). The br prefix indicates a broadened pattern. Carbon-13 spectra were obtained on a Nicolet Magnetic Corporation NT-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm). High-resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low-resolution mass spectra (MS) were obtained on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The purity of all title compounds was determined to be >95% by 300 MHz proton NMR spectroscopy.

Ethyl 5-oxo-2-(triphenylphosphoranylidene)hexanoate (17): A solution of methyl vinyl ketone (0.1 mL, 1.20 mmol) and ethoxycarbonylmethylene-(triphenyl)phosphorane (0.4177 g, 1.12 mmol) in methylene chloride was boiled for 36 h. MP: 104 °C. IR (nujol) 1706/1615 cm^{-1} (lit.[11] 1700/1620 cm^{-1}). ^1H NMR ($CDCl_3$) δ 7.65-7.41 (m, 15H), 3.68 (q, J = 7 Hz, 2H), 2.50 (t, J = 8 Hz, 2H), 2.30-2.12 (m, 2H), 2.02 (s, 3H), 0.43 (t, J = 7 Hz, 3H).

(1-Ethoxycarbonylbut-3-enylidene)triphenylphosphorane (19): A mixture of (ethoxycarbonylmethylene)triphenylphosphorane (3.48 g, 10 mmol) and allyl bromide (3.02 g, 25 mmol) in dry chloroform (20 mL) was refluxed for 8 h and the solvent was removed under reduced pressure. Ether (20 mL) was added to the oily

residue and the mixture was cooled to 0 °C. It was then scratched to get a white solid which was filtered and washed with benzene. The solid was recrystallized from chloroform-hexane to give the bromide salt. The yield was 94% (mp 150-151 °C). The salt dissolved in water (150 mL) and benzene (100mL) was added to it. It was then made alkaline (at 25 °C) with 2 N NaOH. The benzene layer was separated and the aqueous layer was extracted with benzene (100 mL). The combined benzene layer was dried (Na_2SO_4) and the solvent removed uner reduced pressure to get a crude product. This compound was recrystallized from benzene-hexane to furnish **19**. The yield was 78%; m p 122 °C. ^{1}H NMR ($CDCl_3$) δ 7.71-7.40 (m, 15H), 5.90-5.74 (m, 1H), 4.67 (d, J = 10 Hz, 1H), 4.52 (d, J = 17 Hz, 1H), 4.00 (q, J = 7 Hz), 3.70 (q, J = 7 Hz), 2H, 2.73 (d, J = 7 Hz, 1H), 2.68 (d, J = 7 Hz, 1H), 1.08 (t, J = 7 Hz), 0.43 (t, J = 7 Hz), 3H.

Methyl phenyl sulfone (20): Methyl phenyl sulfide (10 mL, 0.09 mol) and SeO_2 (12.6 g, 0.11 mol) were dissolved in 50 mL of methanol at 0°C. H_2O_2 (64 mL, 0.6 mol)was added dropwise since the oxidation was exothermic. After the reaction mixture was stirred for one hour, water and $NaHCO_3$ were added (checking with KI/starch paper). Then partial evaporation of methanol was done before workup. The mixture was extracted with CH_2Cl_2. The organic layers were combined and washed with $NaHCO_3$ if the solution was acidic, then with water and brine. The

organic layers were dried over $MgSO_4$. The yield was 100%. ^1H NMR ($CDCl_3$) δ 7.98-7.93 (m, 2H), 7.70-7.62 (m, 1H), 7.60-7.55 (m, 2H), 3.05 (s, 3H).

[(Phenylsulfonyl)methylene]dilithium (21): A solution of methyl phenyl sulfone (1.50 g, 9.6 mmol) in 30 mL of anhydrous THF was cooled to 0 °C under nitrogen and treated dropwise with a solution of *n*-butyllithium in hexane (14 mL, 21.1 mmol). Upon addition, a yellow suspension began to form and was stirred for a further hour at 0 °C before reacting with various bifunctional organic substrates.

2-Oxocyclohexanepropanal (22): To 1-morpholino-1-cyclohexene solution (168 mL, 1 mole) in 150 mL of anhydrous ether, freshly distilled acrolein (67 mL, 1 mole) dissolved in 150 mL of anhydrous ether was added dropwise. After 3 h at ambient temperature, the reaction was stopped by cooling and 550 mL of 2 N hydrochloric acid was added. The hydrolysis took about 2 days at room temperature. After separation of the layers, sodium chloride was added to the water layer. Then the reaction mixture was extracted with ether. Combined etheral solutions were dried over $MgSO_4$, then solvent was evaporated and product was distilled. The yield was 70% (BP 139-143 °C/19 mm Hg). ^1H NMR ($CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1H). 2.62-2.44 (m, 2H), 2.43-2.22 (m, 3H), 2.16-1.94 (m, 3H), 1.93-1.78 (m, 1H), 1.77-1.49 (m, 3H), 1.48-1.32 (m, 1H).

General procedure for the reaction of dicarbonyl compounds with 21: The suspended reagent **21** (1 mmol) was treated dropwise with a solution of 1 mmol of dicarbonyl compound in 10 mL of anhydrous THF at 0°C. The reaction mixture was stirred for 30 min at 0 °C and then allowed to warm to room temperature. Quenching with water and workup with an ether-water mixture gave an organic layer that was separated, dried over anhydrous $MgSO_4$, evaporated *in vacuo*, and subjected to column chromatography on silica gel.

General procedure for Jones oxidation: To an acetone solution of diol was added dropwise 8 N CrO_3 reagent until the orange color persisted for 1 min. The mixture was then poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layers were combined and washed with water, brine, then dried over anhydrous $MgSO_4$.

4,4a,5,6,7,8-Hexahydro-3H-naphthalen-1-(phenylsulfonyl)-2-one (24): The yield was 45%. ^{1}H NMR ($CDCl_3$) δ 7.90-7.85 (m, 2H), 7.72-7.50 (m, 3H), 3.62-3.18 (m, 2H), 2.88-2.20 (m, 3H), 1.96-1.28 (m, 8H). IR (nujol) 1733, 1306, 1149, 1085, 1018, 723, 688, 465 cm^{-1}. HRMS m/z calculated for $C_{16}H_{18}SO_3$: 290.0977, measured: 290.0982.

General procedure for reaction of ketone and allyl iodide: Ketone

(10 mmol) was treated with LDA (11 mmol) at –78 °C. After the mixture was stirred for one hour at the same temperature, allyl iodide (1 mL, 11 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ether. The combined ether layers were washed with water and brine, and dried over anhydrous $MgSO_4$. The crude product was subjected to chromatography on silica gel using hexane and ethyl acetate.

General procedure for ozonolysis: Ozone was passed through a solution of allylcycloalkanone (0.1 mmol) in methylene chloride solution at –78 °C until the solution turned purple-blue color. Ozone was stopped and the reaction mixture was flushed with argon until the blue color disappeared. PPh_3 (0.0525 g, 0.2 mmol) was added and the reaction mixture was stirred overnight. The solvent was removed by vacuum and the crude product was subjected to chromatography on silica gel.

2-Allylcyclohexanone (25): The cyclohexanone used was freshly distilled over $MgSO_4$. The yield was 8%. ^1H NMR ($CDCl_3$) δ 5.82-5.60 (m, 1H), 5.60-4.98 (m, 2H), 2.59-2.46 (m, 1H), 2.46-2.23 (m, 3H), 2.17-1.91 (m, 3H), 1.91-1.79 (m, 1H), 1.79-1.60 (m, 2H), 1.43-1.24 (m, 1H). (Spectral characteristics are identical to those previously reported.[19])

2-Oxo-cyclohexane-acetaldehyde (26): The yield was 98%. ^{1}H NMR ($CDCl_3$) δ 9.80 (t, J = 1.5 Hz, 1H), 3.01-2.89 (m, 2H), 2.47-2.34 (m, 2H), 2.34-2.17 (m, 1H), 2.17-2.06 (m, 2H), 1.93-1.83 (m, 1H), 1.80-1.55 (m, 2H), 1.48-1.34 (m, 1H). (Spectral characteristics are identical to those previously reported.[20])

1,2,3,6,7,7a-Hexahydro-inden-3-(phenylsulfonyl)-2-one (28): ^{1}H NMR ($CDCl_3$) δ 7.97-7.77 (m, 2H), 7.73-7.48 (m, 3H), 3.57-3.06 (m, 2H), 2.86-2.07 (m, 2H), 1.98-1.12 (m, 7H). IR (nujol) 1733, 1306, 1149, 1085, 1019, 723, 688, 465 cm^{-1}. MS (CI, m/z) 277($M+H^+$); HRMS m/z calculated for $C_{15}H_{16}SO_3$: 276.082017, measured: 276.0822902; $M+H^+$: calculated: 277.0904, measured: 277.0898.

6-Allyl-2-cyclohexene-1-one (29): The yield was 16%. ^{1}H NMR ($CDCl_3$) δ 6.92 (dt, J = 4, 10 Hz, 1H), 6.01 (dt, J = 2, 10 Hz, 1H), 5.86-5.70 (m, 1H), 5.10-5.00 (m, 2H), 2.67-2.58 (m, 1H), 2.40-2.30 (m, 3H), 2.18-2.05 (m, 2H), 1.80-1.65 (m, 1H). (Spectral characteristics are identical to those previously reported.[21])

2-Oxo-3-cyclohexene-1-acetaldehyde (30): Trace amount of Sudan Red 7B was added and TLC was used to monitor the reaction. The yield was 98%. ^{1}H NMR ($CDCl_3$) δ 9.85 (t, J = 1.5 Hz, 1H), 7.02-6.95 (m, 1H), 6.07-6.02 (m, 1H), 3.07-2.92 (m, 2H), 2.57-2.34 (m, 3H), 2.14-2.05 (m, 1H), 1.88-1.73 (m, 1H).

3,3a,4,5-Tetrahydro-1-(phenylsulfonyl)-2-indenon (32): ^{1}H NMR ($CDCl_3$) δ 7.93-7.77 (m, 2H), 7.70-7.40 (m, 3H), 6.79-6.72 (m, 1H), 5.96-5.90 (m, 1H), 3.32-2.86 (m, 2H), 2.67-2.06 (m, 3H), 1.62-1.28 (m, 2H). IR (nujol) 1733, 1306, 1151, 1047, 723, 689, 464 cm^{-1}. MS (EI, m/z) 280, 278, 277, 274 (M^+); HRMS m/z calculated for $C_{15}H_{14}SO_3$: 274.0664, measured: 274.0669.

2-Allylcyclopentanone (33): Purified by distillation under reduced pressure. The yield was 49%. ^{1}H NMR ($CDCl_3$) δ 5.8-5.6 (m, 1H), 5.08-4.98 (m, 2H), 2.81-2.40 (m, 1H), 2.32-1.94 (m, 4H), 1.94-1.75 (m, 2H), 1.75-1.63 (m, 1H), 1.61-1.40 (m, 1H). (Spectral characteristics are identical to those previously reported.[22])

2-Oxo-cyclopentaneacetaldehyde (34): ^{1}H NMR ($CDCl_3$) δ 9.79 (t, J = 1 Hz, 1H), 2.97-2.88 (m, 1H), 2.59-2.48 (m, 2H), 2.42-2.14 (m, 4H), 1.93-1.77 (m, 1H), 1.63-1.48 (m, 1H). (Spectral characteristics are identical to those previously reported.[20])

4,5,6,6a-Tetrahydro-1H-pentalen-3-(phenylsulfonyl)-2-one (36): ^{1}H NMR ($CDCl_3$) δ 7.98-7.92 (m, 2H), 7.69-7.54 (m, 3H), 3.50-3.10 (m, 2H), 3.00-2.04 (m, 3H), 1.95-1.30 (m, 4H). IR (nujol) 1732, 1305, 1149, 1085, 1019, 746, 724, 689, 464 cm^{-1}. MS (EI, m/z) 262(M^+), 155, 141. HRMS m/z calculated for $C_{14}H_{14}SO_3$: 262.0664, measured: 262.0667.

2-Allylcycloheptanone (37): Purified by distillation under reduced pressure. The yield was 47%. ^{1}H NMR ($CDCl_3$) δ 5.80-5.60 (m, 1H), 5.06-4.97 (m, 2H), 2.60-2.27(m, 4H), 2.12-2.00 (m, 1H), 1.90-1.78 (m, 4H), 1.70-1.53 (m, 1H), 1.48-1.22 (m, 3H). (Spectral characteristics are identical to those previously reported.[23])

2-Oxocylcoheptaneacetaldehyde (38): ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 3.20-3.11 (m, 1H), 3.07-2.97 (m, 1H), 2.72-2.62 (m, 1H), 2.50-2.36 (m, 2H), 1.95-1.66 (m, 4H), 1.65-1.30 (m, 4H).

4,5,6,7,8,8a-Hexahydro-1H-azulen-3-(phenylsulfonyl)-2-one (40): The yield was 37%. ^{1}H NMR ($CDCl_3$) δ 7.97-7.87 (m, 2H), 7.68-7.50 (m, 3H), 3.63-3.10 (m, 2H), 2.71-2.60 (m, 1H), 2.59-2.18 (m, 2H), 1.96-1.32 (m, 8H). IR (nujol) 1733, 1305, 1149, 1085, 1018, 723, 688, 464 cm^{-1}. MS (EI, m/z) 292, 290(M^+), 225,183, 151, 77; MS (CI, m/z) 328, 308, 291($M+H^+$), 174. HRMS m/z calculated for $C_{16}H_{18}SO_3$: 290.0977, measured: 290.0982.

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CHAPTER III

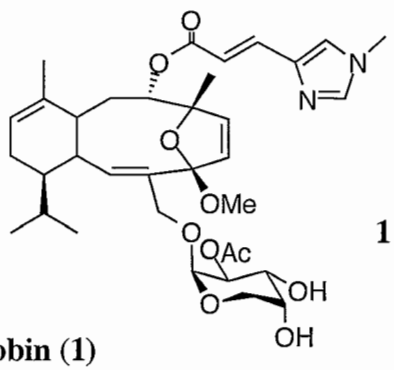
SYNTHETIC APPROCHES TO ELEUTHEROBIN

A paper to be submitted to Synlett

George A. Kraus and Qunying Dai

Introduction

Eleutherobin (Figure 1) is a new diterpene glycoside isolated from a rare kind of marine soft-corals (identified as an *Eleutherobia* species) near Western Australia in 1995.[1] This compound possesses significant cytotoxicity against a wide variety of cancer cells. In subsequent testing, eleutherobin was shown to be a potent cancer cell inhibitor with an IC_{50} range of 10-15 nM *in vitro* against a diverse panel of tumor tissue cell lines. Eleutherobin was also found to stabilize microtubules by competing for the paclitaxel (taxol) binding site on the microtubule polymer. The tumor tissue selectivity of eleutherobin showed an approximate 100-fold increased potency toward selected breast, renal, ovarian, and lung cancer cell lines.[1] This makes it one of the most promising antitumor agents isolated from nature in recent years.

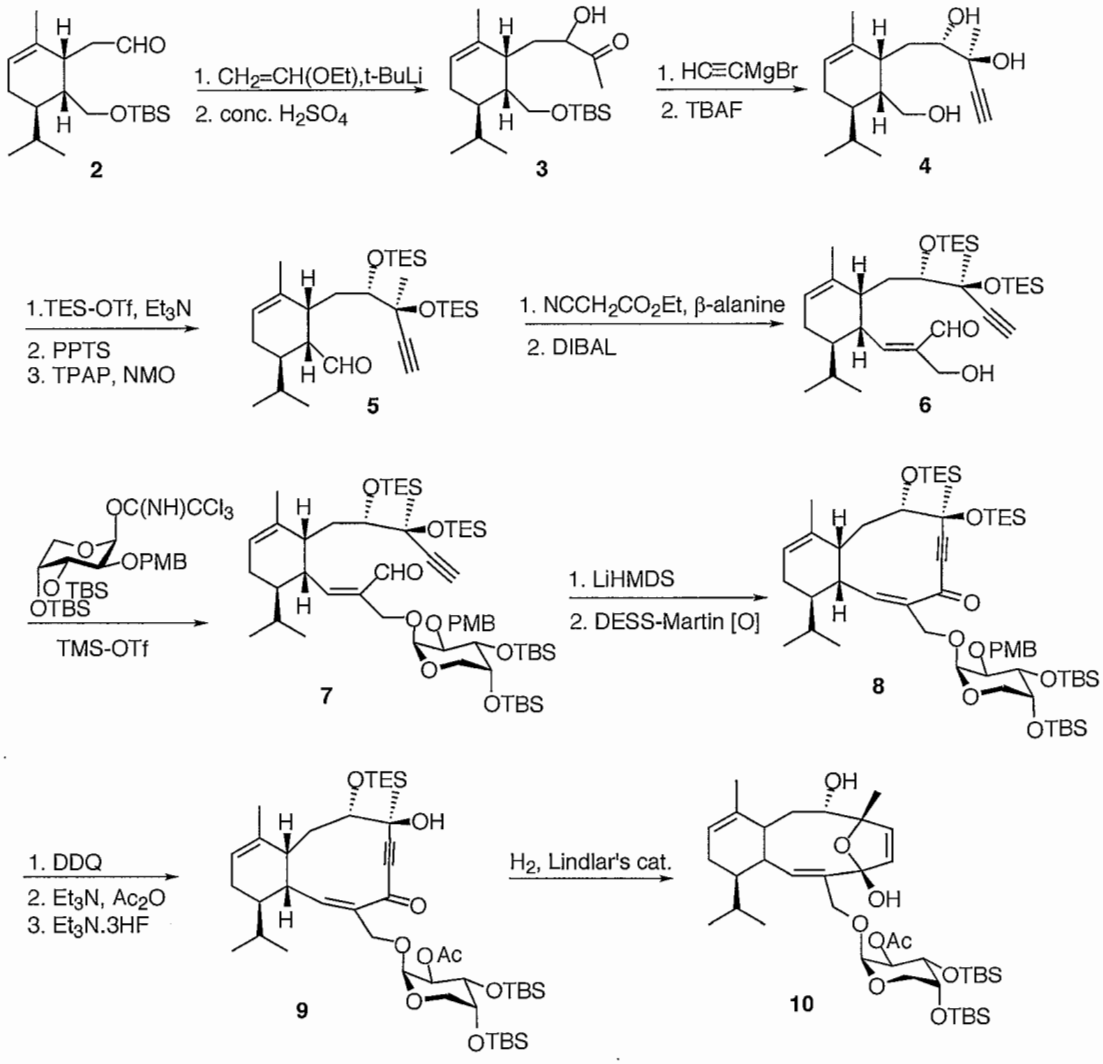


1

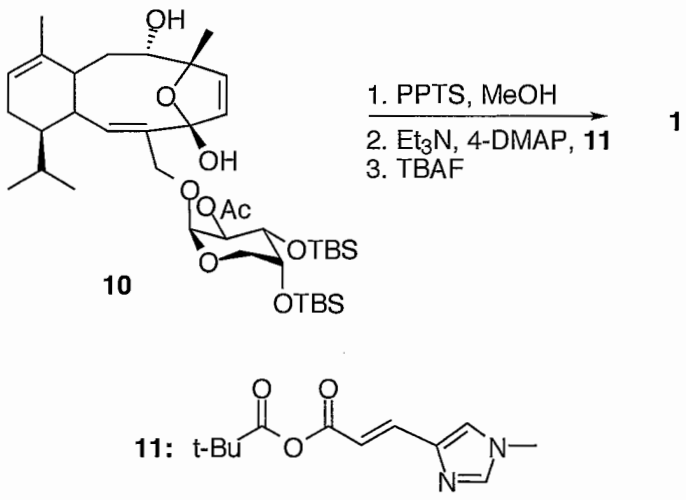
Figure 1 Eleutherobin (1)

With its considerably interesting biological data, its unique structure and the difficult availability from nature, eleutherobin became the challenging target of chemical synthesis. The first total synthesis of eleutherobin (Scheme 1) was achieved by Nicolaou group in 1997.[2,3] The 10-membered ring alcohol **8** was furnished by the action of LiHMDS. Following Lindlar hydrogenation gave the desired 5-membered ring lactol **10**.

Scheme 1

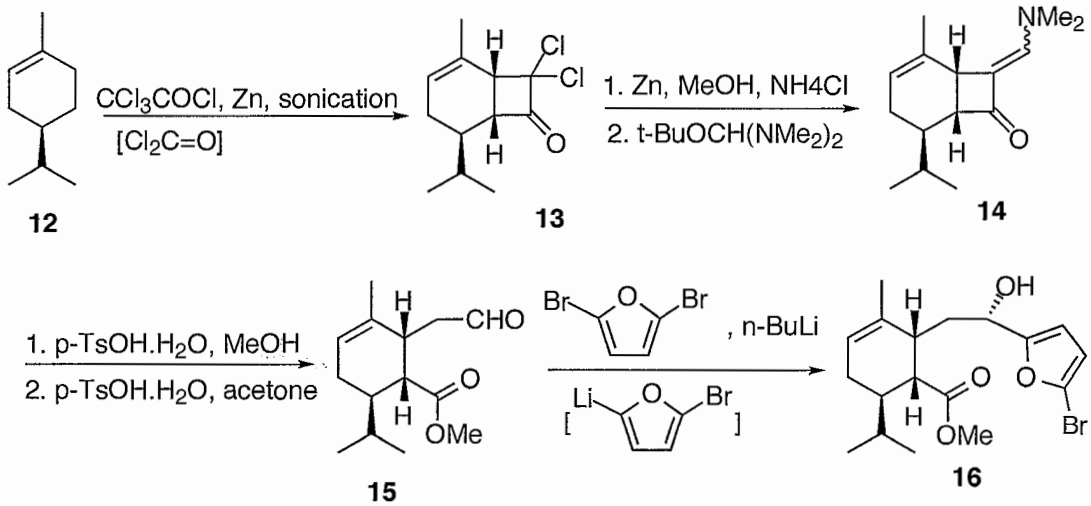


Scheme 1 Continued

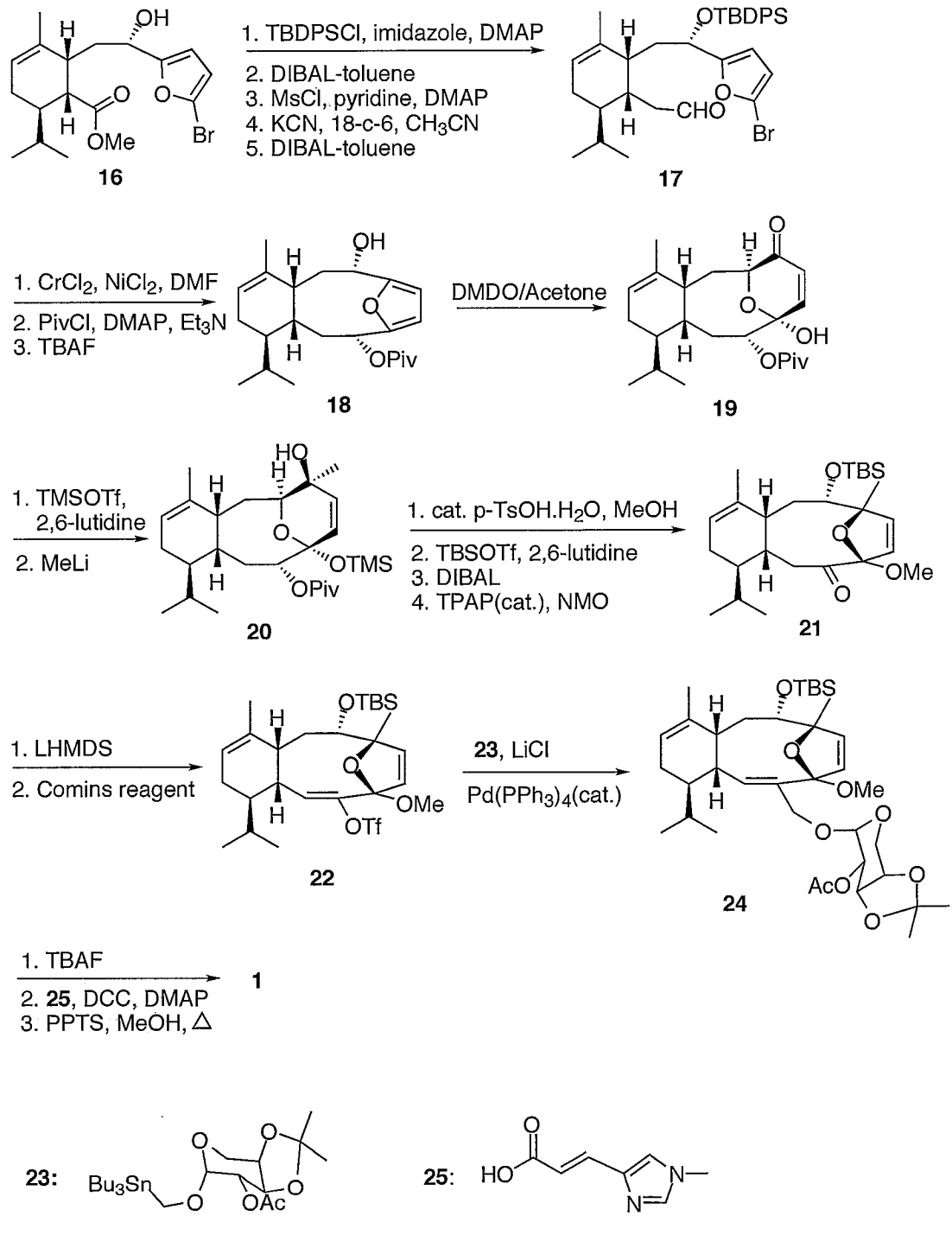


In 1998, Danishefsky group started to release their accomplishment on the total synthesis of eleutherobin which involved a Nozaki-Kishi reductive cyclization of bromoaldehyde **17** and an efficient pyranose (**20**) to furanose (**21**) interconversion.[4] They started from commercially available ®-(-)-α-phellandrene (**12**).[5] The total synthesis is shown below in Scheme 2.

Scheme 2



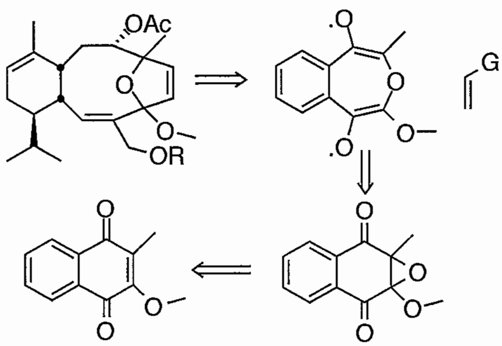
Scheme 2 Continued



Result and discussion

Their synthetic routes are long. We attempted to find an efficient way to make the unusual skeleton of eleutherobin. Our original strategy is shown in Scheme 3. Believing that it is feasible to have carbon-carbon bond fission of the oxirane ring, generate a diradical and have [2+3] photocycloaddition, we could furnish the ring structure directly from an epoxynaphthoquinone.[6] **27** was chosen as model system. Naphthoquinone **26** was our first synthetic target (Scheme 4).[7] We made phthiocol from 2-methyl-1,4-naphthoquione by oxidation with H_2O_2 and isomerization with concentrated sulfuric acid. Addition of diazomethane gave a high yield of **26**.

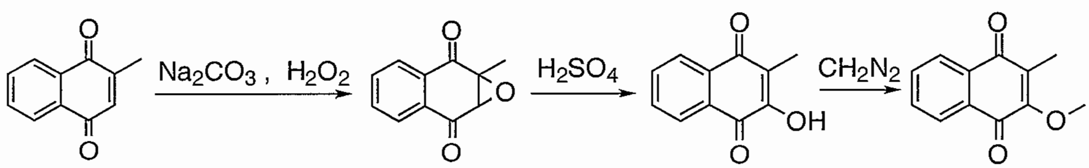
Scheme 3



26 **27**

G: electron-withdrawing group

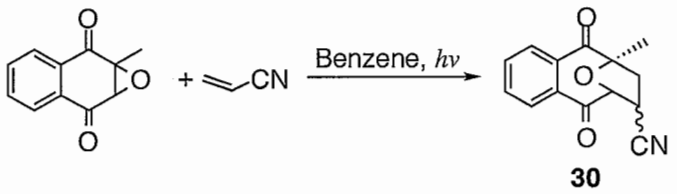
Scheme 4



28 **29** **26**

It is known that the photoreactions of epoxynaphthoquinone are highly dependent upon the substitution pattern at the C2 and C3 position.[6] We wanted to study the reaction types of the diradical generated from the epoxynaphthoquinone included in our study. First, we tried photochemistry of the simple epoxynaphthoquinone **28** with acrylonitrile (Scheme 5) and got a promising result from it. Then we started to make the epoxide from **26**. However, the oxidation method which worked perfectly with 2-methyl-1,4-naphthoquinone didn't work well with **26**. To overcome this problem, we made dimethyldioxirane (DMDO).[8] It gave the desired epoxide in excellent yield (Scheme 6).

Scheme 5



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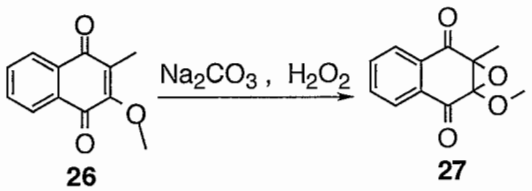
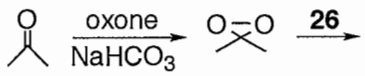
Scheme 6



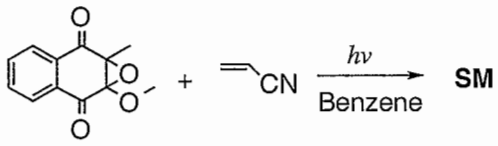
26 **27**



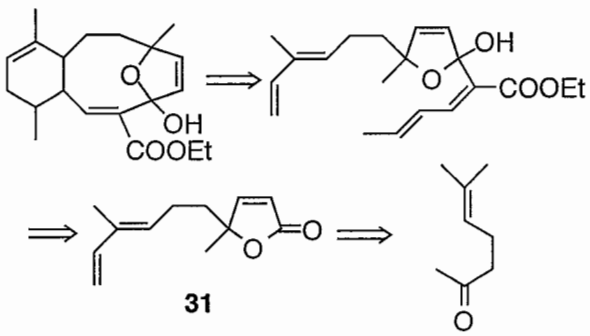
90%

With enough material in hand, we submitted it for the next step—photo-addition (Scheme 7). However, it didn't give any products. We changed the solvents and UV light sources, but still got the starting material back. We assume that it is more difficult to generate diradical from **27** compared with that from **28**.

Scheme 7



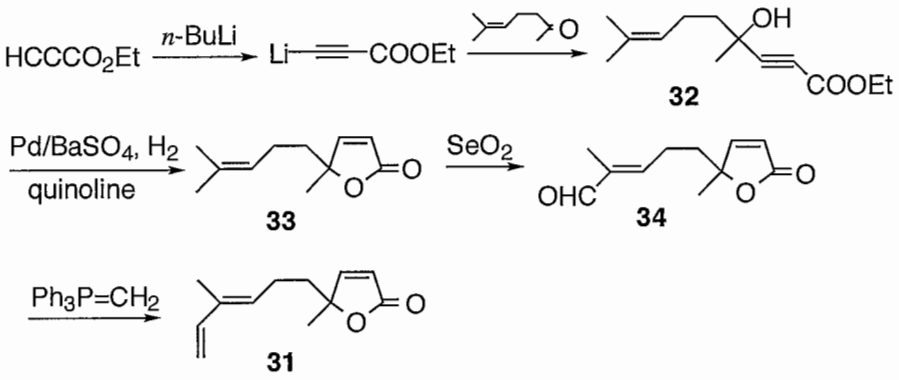
Scheme 8



At this point, we came up with the second idea. As shown in Scheme 8, we expected to have an intramolecular Diels-Alder reaction to furnish two fused rings in one step. We started from a commercial available ketone, 6-methyl-5-hepten-2-one and ethyl propiolate. The preparation of **31** is shown in Scheme 9. The anion of ethyl propiolate reacted with the ketone to get the tertiary alcohol **32**.[9] Saponification of **32** followed by hydrogenation[10] gave **33** in poor yield. Therefore, we tried

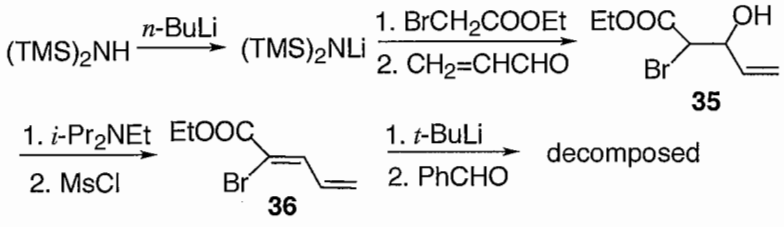
hydrogenation of **32** directly and got **33** in nice yield. A SeO_2 oxidation[11] and Wittig reaction furnished the diene **31**.

Scheme 9



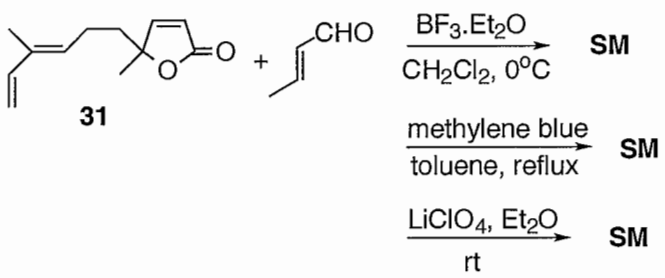
Another fragment we need to synthesize is the bromodiene which could undergo bromine-lithium exchange and react with the lactone. The preparation of the bromopentadienoate **36** is shown in Scheme 10. We used benzaldehyde for a model study and the result is shown below. To our surprise, we didn't succeed in converting vinylic bromide into the corresponding lithium compound by reaction with a twofold molar excess of *tert*-butylithium.

Scehme 10



Studying the structure of **31**, we came up with the idea of having the Diels-Alder reaction first and ring closure later. Following this thought, we tried a Diels-Alder reaction with crotonaldehyde under different conditions;[12] however, none of them gave the positive result (Scheme 11).

Scheme 11



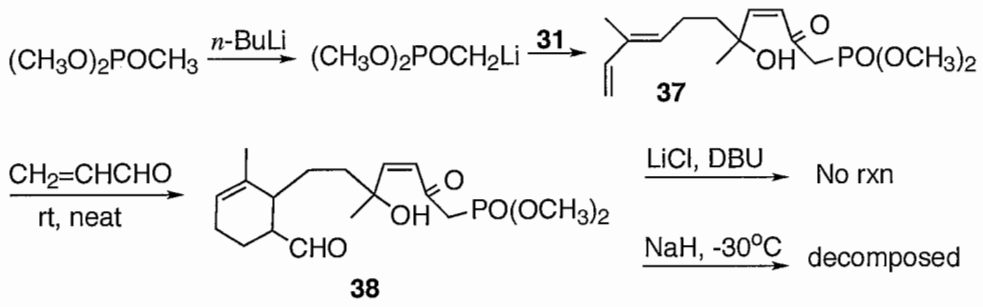
31

We assumed that the double bond within the lactone has some effect on the Diels-Alder reaction. One solution is to have some anion attack the lactone so that the double bond would be less electron deficient. Our attempt is shown below in Scheme 12. Compound **37** was made smoothly.[13] From NMR we found out that the lactone ring had opened. When we tried a Diels-Alder reaction with acrolein, we got **38**. The last step is the formation of a macrocyclic ring. We hoped to have intramolecular ketophosphonate-aldehyde condensation to furnish the 10-membered ring. However, the two conditions we chose didn't work. With LiCl and DBU,[14] we got the starting material; With NaH at low temperature,[15] we got **37** instead of ring closure product.

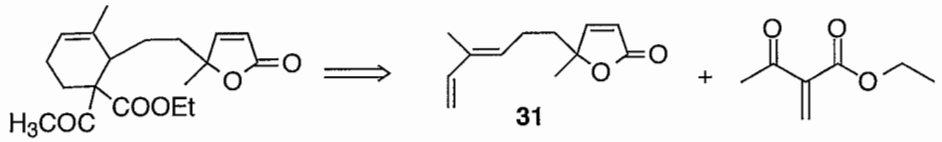
Then we thought to make dienophile more electron deficient. We tried a Diels-Alder reaction using an unstable dienophile which was made *in situ*.[16] The

retrosynthetic analysis is shown in Scheme 13. In Scheme 14, **39** was made and oxidized by MCPBA. The oxidation product was used *in situ* to react with diene. It turned out to be successful. **40** and **41** were made without any problem.

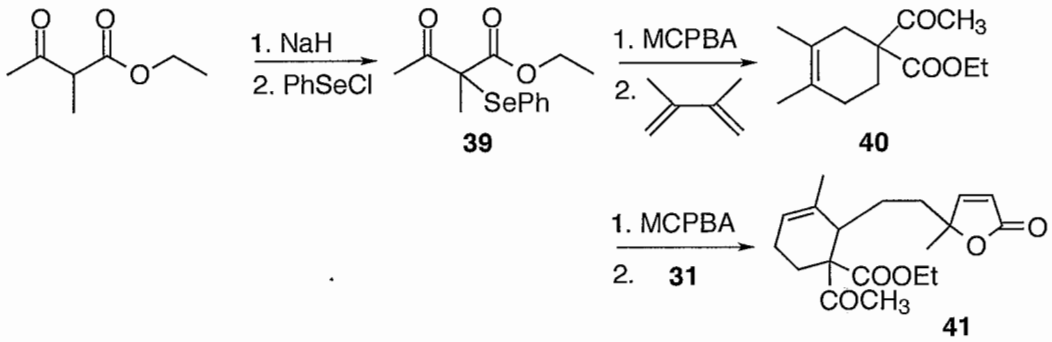
Scheme 12



Scheme 13



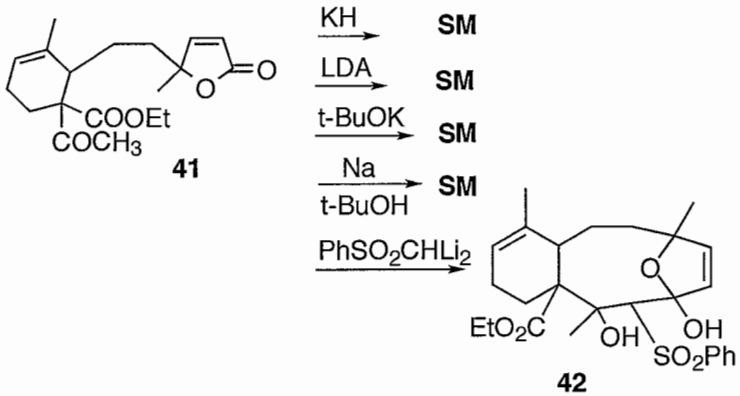
Scheme 14



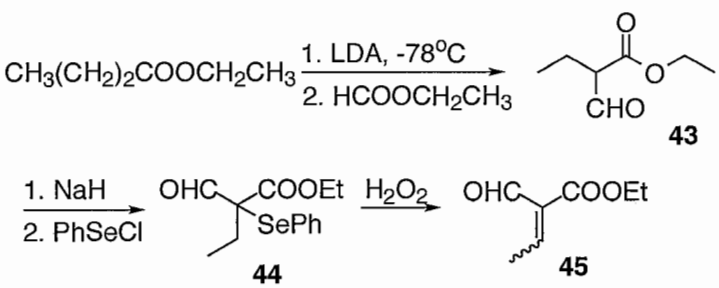
With compound **41** in hand, we attempted a cyclization. Within its structure, only the methyl ketone was enolizable. KH is known to metalate a wide range of

ketones with little or no self-condensation or reduction in THF. Solutions of highly reactive potassium enolates are formed quantitatively in minutes at 20 °C. We tried the ring closure first with KH[17] and hoped that the enolate would react with the lactone to furnish the skeleton of eleutherobin. However, starting material was all we recovered. We also tried other bases, such as LDA, potassium t-butoxide, sodium in t-butanol and none of them worked. Then the dianion of methyl phenyl sulfone was used. This formed the ten membered ring.

Scheme 15

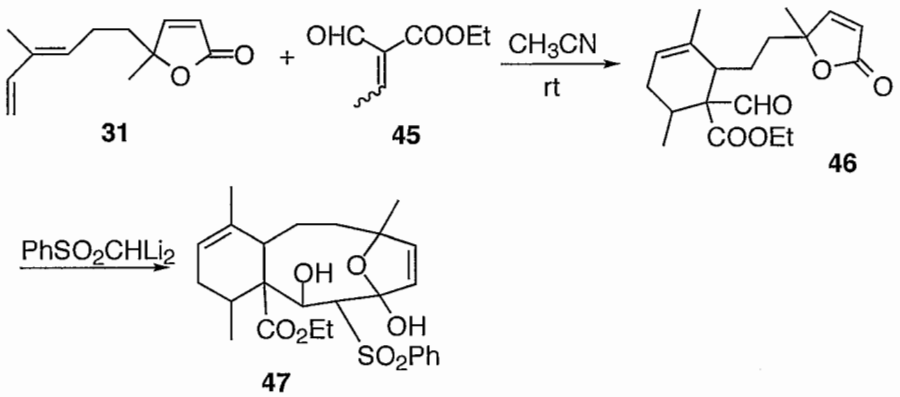


Scheme 16



We made substrate **46** to react with the dianion. The preparation of dienophile[18] **45** was shown in Scheme 16. It was a mixture of *cis*, *trans* isomers. The Diels-Alder reaction of **31** with **45** went smoothly since the latter is quite electron deficient (Scheme 17). To our delight, the next reaction with the dianion turned out to be promising.

Scheme 17



31 **45** **46** **47**

Conclusions

During this investigation, we have succeeded in synthesizing the skeleton of eleutherobin in six steps. It is hopeful that this route could be used in the near future for the total synthesis of eleutherobin.

Experimental

Unless otherwise noted, material was obtained from commercial suppliers and was used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum

hydride. Methylene chloride and acetonitrile were purified by distillation from calcium hydride. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12h and cooled under a stream of argon or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using Aldrich TLC plates (silica gel 60) with a thickness of 0.25 mm. The solvent system was suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sg represents silica gel. Infrared spectra were obtained on a Bio-Rad FTS-7 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetic Corporation NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ABQ (AB quartet), and m (multiplet). The br prefix indicates a broadened pattern. Carbon-13 spectra were obtained on a Nicolet Magnetic Corporation NT-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm). High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra (MS) were obtained on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The purity of all title compounds was determined to be >95% by 300 MHz proton NMR spectroscopy.

2-Methyl-1,4-naphthoquinone-2,3-epoxide (28): 2-Methyl-1,4-naphthoquinone (1 g, 6.32 mmol) was dissolved in 10 mL of ethanol by warming. The solution was allowed to stand while the second reagent was prepared by dissolving 0.2 g of anhydrous Na_2CO_3 in 5 mL of water and adding 30% H_2O_2 (1 mL, 8.82 mmol). The quinone was cooled under the tap till crystallization began. The peroxide solution was added at once. The mixture was cooled and the yellow color of quinone was at once discharged, giving a color of pale yellowish solution. On addition of about 100 mL of water and cooled in ice, target compound was separated as colorless crystals. The yield was 89%; M.P. 93.5-94.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 1H), 7.95 (m, 1H), 7.75 (m, 2H), 3.86 (s, 1H), 1.74 (s, 3H).

2-Hydroxy-3-methyl-1,4-naphthoquinone (29): Epoxide **28** (0.5525 g, 2.94 mmol) was treated with 3 mL of concentrated H_2SO_4 (without cooling) and the mixture was stirred to produce a homogeneous deep red solution. After 10 minutes the reaction mixture was cooled in ice and slowly diluted with 10 mL of water. The precipitated **29** was filtered, washed and crystallized by dissolving it in methanol (13 mL) containing 3 drops of concentrated HCl. The yield was 84%. M.P. 172-173 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 2H), 7.72 (m, 2H), 7.29 (s, 1H), 2.11 (s, 3H).

2-Methoxy-3-methyl-1,4-naphthoquinone (26): To the stirred solution of **29** in ethyl ether with ice bath was added diazomethane dropwise. TLC was used to

monitor the reaction process. The solvent was evaporated to give the relatively pure product. M.P. 190 °C. The yield was 100%. ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 2H), 7.70 (m, 2H), 4.12 (s, 3H), 2.10 (s, 3H).

Dimethyldioxirane: A 2-L, three-necked, round-bottomed flask containing a mixture of water (80 mL), acetone (50 mL, 0.68 mol), and sodium bicarbonate (96 g), is equipped with a magnetic stirring bar and a pressure-equalizing addition funnel containing water (60 mL) and acetone (60 mL, 0.82 mol). A solid addition flask containing Oxone (180 g, 0.29 mol) is attached to the reaction vessel via a rubber tube. An air condenser (20 cm length) loosely packed with glass wool is attached to the reaction vessel. The outlet of the air condenser is connected to a 75x350-mm Dewar condenser filled with dry ice-acetone that is connected to a receiving flask (100 mL) cooled in a dry ice-acetone cold trap, a trap containing a KI solution, and a drying tube. A gas inlet tube is connected to the reaction flask and a stream of nitrogen gas is bubbled through the reaction mixture. The Oxone is added in portions (10-15 g) while the acetone-water mixture is simultaneously added dropwise. The reaction mixture is stirred vigorously throughout the addition of reagents (ca. 30 min). A yellow solution of DMDO in acetone collects in the receiving flask. Vigorous stirring is continued for an additional 15 min while a slight vacuum (ca. 30 mm, water aspirator) is applied to the cold trap. The yellow DMDO solution (62-76 mL) is dried over sodium sulfate, filtered and stored in the freezer (-25 °C) over sodium sulfate.

Generally concentrations in the range of 0.07-0.09 m are obtained.

2-Methoxy-3-methyl-2,3-epoxy-1,4-naphthoquinone (27): To the stirred solution of **26** in acetone at room temperature was added DMDO dropwise till there was no change indicated by TLC. The crude product was subjected to chromatography on silica gel. The yield was 90%. ^{1}H NMR ($CDCl_3$) δ 8.04 (m, 2H), 7.75 (m, 2H), 3.83 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.0, 184.2, 134.7, 134.3, 132.2, 131.7, 127.6, 127.2, 85.9, 67.8, 56.9, 10.4.

5,6,7,8,9,10-Hexahydro-7-cyano-9-methyl-6,9-epoxybenzocyclooctene-5,10-dione (30): The solution of **28** (0.1671g, 0.89 mmol) and acrylonitrile (0.1 mL, 1.52 mmol) in benzene was put under u. v. irradiation under argon overnight using a pyrex filter at room temperature. Evaporation of the solvent gave the crude product. The yield was 19%. ^{1}H NMR ($CDCl_3$) δ 7.98-7.94 (m, 1H), 7.79-7.68 (m, 3H), 5.09 (dd, J = 6, 7 Hz, 1H), 3.60 (dd, J = 2, 8 Hz, 1H), 3.00-2.92 (m, 1H), 2.43-2.35 (m, 1H), 1.77 (s, 3H); MS (CI, m/z) 243, 242, 241(M^+).

Ethyl 4-hydroxy-4,8-dimethyl-2-nonynoate (32): The reaction flask was charged with 10 mL of THF and ethyl propiolate (0.4905 g, 5 mmol). The solution was cooled to –78 °C, and *n*-butyllithium (2 mL, 5 mmol) was added. The solution was stirred for 10 min, and then 6-methyl-5-hepten-2-one (0.6310 g, 5 mmol) was

added. The mixture was stirred for 10 min, and then the bath was removed and the mixture was allowed to warm up slightly. Acetic acid, 1 mL, was added and the solution warmed to room temperature. Ethyl ether was added and the mixture was washed with saturated sodium bicarbonate. The ether layer was dried with potassium carbonate and the ether was removed on a rotary evaporator. The crude compound was purified by chromatography on silica gel. The yield was 98%. ^{1}H NMR ($CDCl_3$) δ 5.19-5.12 (m, 1H), 4.23 (q, J = 7 Hz, 2H), 2.32-2.10 (m, 2H), 1.74 (t, J = 8 Hz, 2H), 1.68 (s, 3H), 1.64 (s, 3H), 1.51 (s, 3H), 1.29 (t, J = 7 Hz, 3H).

5-(4-Methyl-3-pentenyl)-5-methylbutenolide (33): To a solution of **32** (0.5569 g, 2.48 mmol) in 140 mL of methanol was added 5% Pd/$BaSO_4$ (10.8 mg) and quinoline (10 mg). Reaction was placed on hydrogenator and after taking up theoretical amount of hydrogen, the reaction mixture was filtered and evaporated. The resulting oil was dissolved in ether and shaken in a separatory funnel with concentrated HCl. Then it was washed with water, saturated $NaHCO_3$, brine, dried over $MgSO_4$, evaporated to give crude product which was purified by chromatography on silica gel. The yield was 63%. ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 6 Hz, 1H), 6.00 (d, J = 6 Hz, 1H), 5.05-4.98 (m, 1H), 2.00-1.72 (m, 4H), 1.67 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H).

5-(4-Methyl-6-oxo-3-pentenyl)-5-methylbutenolide (34): A slolution of SeO_2 (0.3050 g, 2.75 mmol) in 15 mL 97% aqueous ethanol was added dropwise to **33** (0.1832 g, 1.02 mmol) dissolved in 20 mL 97% aqueous ethanol at 55 °C. The mixture was boiled for 17 hours with stirring. When the solution was cooled, the selenium was removed by filtration. After ethanol was removed by vacuum, the residue was taken up in ether, washed with $NaHCO_3$ and brine, dried over $MgSO_4$. The yield was 36%. ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1H), 7.36 (d, J = 6 Hz, 1H), 6.42-6.34 (m, 1H), 6.06 (d, J = 6 Hz, 1H), 2.42-2.20 (m, 2H), 2.12-2.00 (m, 1H), 1.93-1.82 (m, 1H), 1.70 (s, 3H), 1.51 (s, 3H).

5-(4-Methyl-3,5-hexadienyl)-5-methylbutenolide (31): To the THF solution of Ph_3PCH_3Br (3.5724 g, 10 mmol) at 0 °C was added *n*-BuLi (4 mL, 10 mmol) dropwise. After stiring for 10 min, it was then allowed to warm to ambient temperature and stir for another 20 min. Then **34** (1.9400 g, 10 mmol) was added to the reaction mixture at -78 °C. The reaction mixture was allowed to warm up gradually and stir for another two hours at ambient temperature. Then it was quenched with ammonium chloride, extracted with ether, washed with water and brine, dried over $MgSO_4$. The yield was 60 %. ^{1}H NMR ($CDCl_3$) δ 7.33 (d, J = 6 Hz, 1H), 6.32-6.23 (dd, J = 11, 17 Hz, 1H), 5.97 (d, J = 6 Hz, 1H), 5.33 (t, J = 1 Hz, 1H), 5.05 (d, J = 17 Hz, 1H), 4.90 (d, J = 11Hz, 1H), 2.23-2.00 (m, 2H), 1.98-1.85 (m, 1H), 1.83-1.73 (m, 1H), 1.70 (s, 3H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.5, 160.2,

141.2, 135.0, 131.0, 120.8, 111.5, 88.8, 38.0, 24.3, 22.8, 11.8. MS (EI, m/z): 192 (M^+), 155, 127, 98, 55, 43; HRMS m/z calculated for $C_{12}H_{16}O_2$: 192.1150, measured: 192.1154.

Ethyl 2-bromo-3-hydroxy-4-pentenoate (35): To the THF solution of 1,1,1,3,3,3-hexamethyldisilazane (2.53 mL, 12 mmol) at 0 °C was added *n*-BuLi (4.8 mL, 12 mmol). After stirring for 20 min, ethyl bromoacetate (1.1 mL, 10 mmol) was added to the mixture at -78 °C. One hour later, acrolein (0.73 mL, 11 mmol) was added and the reaction mixture was stirred for 20 min. Then acetic acid (1.26 mL, 22 mmol) was used to quench to reaction at -78 °C. Water and ether were used to work up the reaction. The reaction mixture was extracted several times with ether and the ether layers were combined, dried over $MgSO_4$. The crude product was purified by chromatography on silica gel. The yield was 58%. ^{1}H NMR ($CDCl_3$) δ 5.89-5.79 (m, 1H), 5.44 (d, J = 17 Hz, 1H), 5.32 (d, J = 11 Hz, 1H), 4.55-4.48 (m, 1H), 4.26 (q, J = 7 Hz, 2H), 2.86-2.79 (m, 1H), 1.29 (t, J = 7 Hz, 3H).

Ethyl 2-bromo-2,4-pentadienoate (36): To the methylene chloride solution of **35** (1 g, 4.48 mmol) at 0 °C was added N,N-diisopropylethylamine (0.78 mL, 4.48 mmol) and mesyl chloride (0.35 mL, 4.52 mmol) with stirring. The crude product was subjected to chromatography on silica gel. The yield was 17%. ^{1}H NMR

($CDCl_3$) δ 7.63 (d, J = 11 Hz, 1H), 6.74 (dt, J = 10, 17 Hz, 1H), 5.76 (d, J = 17 Hz, 1H), 5.67 (d, J = 10 Hz 1H), 4.28 (q, J = 7 Hz, 2H), 1.35 (t, J = 7 Hz, 3H).

Dimethyl (5-hydroxy-5,9-dimethyl-2-oxo-3,8,10-undecatrienyl)phosphonate (37): Dimethyl methyl phosphonate (0.3321 g, 2.7 mmol) in THF was treated with *n*-BuLi (1.08 mL, 2.7 mmol) at -78 °C. After 10 min, **31** (0.5175 g, 2.7 mmol) in THF was added dropwise and the mixture was stirred at -78 °C for 1 h. 6N HCl was added to quench the reaction and the reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined and washed with saturated $NaHCO_3$, water and brine, dried over $MgSO_4$. The crude product was subjected to chromatography on silica gel. The yield was 43%. ^{1}H NMR ($CDCl_3$) δ 7.02 (d, J = 6 Hz, 1H), 6.58 (d, J = 6 Hz, 1H), 6.32 (dd, J = 11, 17 Hz, 1H), 5.40 (t, J = 1 Hz, 1H), 5.08 (d, J = 17 Hz, 1H), 4.92 (d, J = 11 Hz, 1H), 4.58 (d, J = 8 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 2.12-2.03 (m, 2H), 1.92-1.71 (m, 2H), 1.69 (s, 3H), 1.41 (s, 3H).

Dimethyl {7-(6-formyl-1-methyl-1-cyclohexenyl)-5-hydroxy-5-methyl-2-oxo-3-heptenyl}phosphonate (38): The mixture of **37** and freshly distilled acrolein (excess) was stirred overnight at room temperature without solvent. The yield was 31%. ^{1}H NMR ($CDCl_3$) δ 9.60 (s, 1H), 7.05-6.98 (m, 1H), 6.58-6.52 (m, 1H), 5.49-

5.38 (m, 1H), 4.62-4.55 (d, J = 8 Hz, 1H), 3.72-3.69 (m, 3H), 3.69-3.65 (m, 3H), 2.10-1.56 (m, 12H), 1.40 (s, 3H).

Ethyl 2-methyl-2-phenylselenenyl acetoacetate (39): To the stirred suspension of NaH (0.2303 g, 9.60 mmol) in THF under Argon at 0 °C was added dropwise a solution of ethyl 2-methylacetoacetate (0.5526 g, 3.84 mmol) in THF. A solution of PhSeCl in methylene chloride was added. The reaction mixture was added into 50% ether-pentane, 2.5 mL of saturated $NaHCO_3$ and some ice. The aqueous layer was washed with ether-pentane. The combined organic layers were washed with brine, dried and evaporated, the crude product was subjected to chromatography on silica gel. The yield was 83%. ^{1}H NMR ($CDCl_3$) δ 7.53-7.48 (m, 2H), 7.43-7.37 (m, 1H), 7.33-7.27 (m, 2H), 4.25 (q, J = 5 Hz, 2H), 2.39 (s, 3H), 1.58 (s, 3H), 1.29 (t, J = 5 Hz, 3H).

General procedure for Diels-Alder reaction using MCPBA: m-chloro-perbenzoic acid (0.3625 g, 2.1 mmol) in methylene chloride was added to a stirred solution of phenylseleno compound (0.2990 g, 1mmol) in methylene chloride. After 5 min 1 mmol of diene was added and the stirring was continued for 30 min. The solution was diluted with ether, washed with $NaHCO_3$ solution and water, dried and evaporated. Chromatography of the residual oil over silica gave the desired product.

Ethyl 2-(2,3-dimethyl-2-cyclohexenyl)acetoacetate (40): Compound **39** and 2,3-dimethyl-1,3-butadiene were used. The yield was 66%. ^{1}H NMR ($CDCl_3$) δ 4.16 (q, J = 7 Hz, 2H), 2.49-2.27 (q, J = 17 Hz, 2H), 2.16 (s, 3H), 2.15-1.92 (m, 4H), 1.65 (s, 3H), 1.57 (s, 3H), 1.23 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.3, 172.2, 125.0, 122.9, 61.3, 60.0, 35.8, 28.8, 27.4, 25.9, 19.1, 18.8, 14.1. MS (CI, m/z): 242 ($M+NH_4^+$), 225 ($M+H^+$); MS (EI, m/z): 225 ($M+H^+$), 181, 150, 134, 107, 91.

5-{2-(1-Ethoxycarbonyl-1-methyloxo-5-methyl-4-cyclohexenyl)}-5-methylbutenolide (41): Compound **31** and **39** were used. The yield was 53%. ^{1}H NMR ($CDCl_3$) δ 7.28 (d, J = 3 Hz, 1H), 6.04-5.98 (m, 1H), 5.45-5.21 (m, 1H), 4.15 (q, J = 7 Hz, 2H), 2.17-2.12 (m, 5H), 1.98-1.80 (m, 3H), 1.74 (s, 3H), 1.66-1.49 (m, 3H), 1.47 (d, J = 3 Hz, 1H), 1.41 (d, J = 2 Hz, 3H), 1.23 (t, J = 7 Hz, 3H). MS (CI, m/z): 352 ($M+NH_4^+$), 335 ($M+H^+$); MS (EI, m/z): 334 (M^+), 291, 288, 245, 192, 179, 163, 143, 105, 91, 77.

General procedure for the reaction of dicarbonyl compounds with 21: The suspended reagent **21** (1 mmol) was treated dropwise with a solution of 1 mmol dicarbonyl compound in 10 mL of anhydrous THF. The reaction mixture was stirred for 30 min at 0 °C and then allowed to attain room temperature. Quenching with water and workup with an ether-water mixture gave an organic layer that was

separated, dried over anhydrous $MgSO_4$, evaporated *in vacuo*, and subjected to column chromatography on silica gel.

(42): MS (CI, m/z): 491, 490 (M^+), 473, 448, 352, 310, 293, 216, 174; HRMS m/z calculated for $C_{26}H_{34}SO_7$: 490.2025, measured: 490.2033; For $[M-H_2O]^+$ calculated: 472.1920, measured: 472.1923.

Ethyl 2-formylbutyrate (43): LDA was made from *n*-BuLi (20.4 mL, 51 mmol) and diisopropylamine (7 mL, 50 mmol) at 0 °C. The mixture was cooled to -78 °C and ethyl butyrate (6.7 mL, 50 mmol) was added and stirred for 1 h. Then ethyl formate (4.2 mL, 50 mmol) was added and the reaction mixture was allowed to warm up gradually and stirred overnight. It was quenched with NH_4Cl and extracted with ether, dried over $MgSO_4$. The crude product was subjected to distillation under reduced pressure. ^1H NMR ($CDCl_3$) ald-form: δ 9.71 (d, J = 2 Hz, 1H), 4.25 (m, 2H), 3.18 (dt, J = 2, 7Hz, 1H), 1.92 (dq, J = 7, 7 Hz, 2H), 1.31 (q, J = 7 Hz, 3H), 0.98 (t, J = 7 Hz, 3H); enol-form: δ 11.40 (d, J = 12 Hz, 1H), 7.00 (dt, J = 1, 13 Hz, 1H), 4.25 (m, 2H), 2.10 (dq, J = 1, 7 Hz, 2H), 1.30 (t, J = 7 Hz, 3H), 1.03 (t, J = 7 Hz, 3H).

Ethyl 2-formyl-2-(phenylselenenyl)butyrate (44): To the stirred suspension of NaH (0.3624 g, 15.1 mmol) in THF under Argon at 0 °C was added dropwise a solution of **43** (0.8697 g. 6.04 mmol) in THF. A solution of PhSeBr in methylene

chloride was added rapidly until a pale brown color persisted. Stirring was continued for 15 min. The reaction mixture was washed in turn with water, 10% HCl, saturated $NaHCO_3$ and brine, then dried and evaporated. The crude product was subjected to chromatography on silica gel. ^1H NMR ($CDCl_3$) δ 9.62 (s, 1H), 7.58-7.54 (m, 2H), 7.45-7.38 (m, 1H), 7.38-7.35 (m, 2H), 4.16 (q, J = 7 Hz, 2H), 1.95 (q, J = 7 Hz, 2H), 1.25 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H).

Ethyl 2-formyl 2-butenoate (45): To the stirred solution of **44** (0.4785 g, 1.6 mmol) in methylene chloride was added gradually H_2O_2 (0.45 mL, 4.0mmol), temperature was kept between 20-30 °C. After stirring for an additional 10 minutes at 25 °C, the reaction mixture was poured into 25 mL of methylene chloride and 10 mL 10% Na_2CO_3 with stirring. The aqueous layer was washed with methylene chloride. Combined organic layer was washed with brine and dried over $MgSO_4$. Two isomers: *Cis*: ^1H NMR ($CDCl_3$) δ 9.68 (s, 1H), 7.20 (q, J = 7 Hz, 1H), 4.34 (q, J = 7 Hz, 2H), 2.21 (d, J = 7 Hz, 3H), 1.38 (t, J = 7 Hz, 3H); *Trans*: ^1H NMR ($CDCl_3$) δ 10.13 (d, J = 3 Hz, 1H), 7.53 (dq, J = 3, 7 Hz, 1H), 4.30 (q, J = 7 Hz, 2H), 2.30 (d, J = 8 Hz, 3H), 1.32 (t, J = 7 Hz, 3H).

5-{2-(1-Ethoxycarbonyl-1-formyl-2,5-dimethyl-4-cyclohexenyl)}-5-methylbutenolide (46): The mixture of **31** (0.0956 g, 0.5 mmol) and **45** (0.0707 g, 0.5 mmol) in 1 mL of acetonitrile at room temperature was stirred overnight. The

solvent was evaporated and the crude oil was subjected to chromatography on silica gel. ^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1H), 7.30 (t, J = 6 Hz, 1H), 6.00 (d, J = 6 Hz, 1H), 5.40-5.10 (m, 1H), 4.22 (t, J = 7 Hz, 2H), 2.58-2.12 (m, 3H), 2.03-1.75 (m, 5H), 1.71 (s, 3H), 1.44 (s, 3H), 1.24 (t, J = 7 Hz, 3H), 1.02 (d, J = 7 Hz, 3H). MS (CI, m/z): 352 ($M+NH_4^+$), 335 ($M+H^+$). HRMS m/z calculated for $C_{19}H_{26}O_5$: 334.1780, measured: 334.1785.

(47): MS (CI, m/z): 490 (M^+), 461, 324, 307, 174, 160; HRMS m/z calculated for $C_{26}H_{34}SO_7$: 490.2025, measured: 490.2022.

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GENERAL SUMMARY

In the first part of this research, a direct synthetic approach to a potential anti-coccidial compound was achieved by using electrophilic substitution and CAN oxidation as its key steps. In the second part of this thesis, we developed a new methodology of forming two new carbon-carbon bonds using sulfonyl-stabilized dianion which led to a number of fused ring compounds. Hopefully, a total synthesis of glycinoeclapin A based on this work will be completed in the near future. Finally, in the third project, we have developed a synthetic pathway to the skeleton of eleutherobin. As the synthetic approach is very direct, it could enable medicinal researchers to synthesize diverse analogs of eleutherobin.

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