2000

Total synthesis of the natural furanones

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Total synthesis of the natural furanones

by

Zhiwen Wan

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Major Professor: George A. Kraus

Iowa State University

Ames, Iowa

2000

Graduate College

Iowa State University

This is to certify that the doctoral dissertation of

Zhiwen Wan

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

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For the Major Program

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For the Graduate College

DEDICATION

To

my Savior,

my wife, Jie Deng,

my mother, Jiayin Zhang,

and the memory of my father, Maoyin Wan,

who have inspired me

by their

patience,

understanding,

and

love.

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ABSTRACT

Organic synthesis is a highly-developed, useful, and interdisciplinary branch of natural science. Modern synthetic chemistry has provided complex molecules and new materials with unique properties. This study focused on creating new methodology, or new routes, to achieve a biologically active, natural product synthesis.

A new methodology to generate 2,4-diacylfuran compounds has been developed and discussed. The synthesis of two natural 2,4-diacylfuran compounds, hibiscone C, and halenaquinone, has been achieved. The new route to hibiscone C features an efficient ring formation and rearrangement. Halenaquinone analogues have been synthesized by Michael addition, annulation, and palladium catalyzed reaction. The new route provides a new lead in the discovery of anticancer reagents like halenaquinone.

A first approach towards building a BCD ring system for aquayamycin via intramolecular anion reaction is described. The approach could eventually provide a route to achieve the total synthesis of aquayamycin, a new antibiotic which might eventually be used to treat cancer.

GENERAL INTRODUCTION

Organic synthesis is a natural science that is highly developed and useful. Modern synthesis chemistry has provided complex molecules and new materials with unique properties. A large number of such synthetic compounds have already contributed to modern medicine. In order to enable organic synthesis to be more broadly used in large quantity production, new synthetic routes need to be developed and refined for efficiency, economical, and environmental concerns. This study focuses on creating new methodologies, or new routes, to achieve biologically active natural product synthesis.

Two research studies are described. One is the synthesis of furanone natural compounds. In this study, a new route has been developed to generate 2,4-diacylfuran skeletons, and was used to synthesize hibiscone C and halenaquinone analogues.

The second study focused on building an ABC ring system in aquayamycin, one of the biologically active quinones with a unique structure, by intramolecular anion reaction. This methodology could potentially enable the first total synthesis of aquayamycin.

Dissertation Organization

This dissertation is comprised of four publishable articles in different refereed journals. Therefore, the numbering scheme adopted for the compounds and the references are independent for each paper. A general summary follows the fourth paper. The first author for each paper is the major professor who also is the correspondent for publication. The second author is myself, the doctoral candidate who carried out the research under the guidance of the major professor.

CHAPTER 1. FURAN SYNTHESIS VIA A 4 + 1 RING - BUILDING STRATEGY- AN APPROACH TO 2,4-DIACYLFURANS

A paper, a portion of which was published in *Synlett*

George A. Kraus and Zhiwen Wan

Introduction

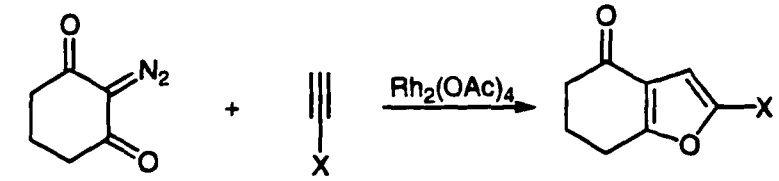
Furan, a five-member heterocyclic compound, was first discovered by Scheele in 1780, by dry distillation of mucic acid, now known as furan-2-carboxylic acid. Furan itself has also been called tetrophenol.[1] Furan derivatives were commercially insignificant until about 1920. The commercial importance of furan gained significance due to its role as a precursor of the very widely used solvent tetrahydrofuran. Now furan is manufactured by the gas phase decarbonylation of furan-2-carbaldehyde (furfural), which is obtained from vegetable waste.[2]

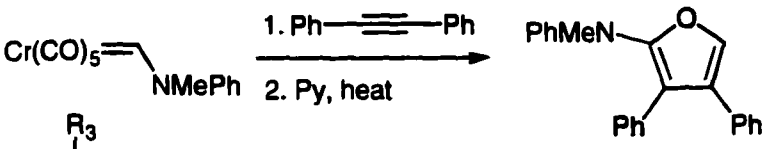
Furan

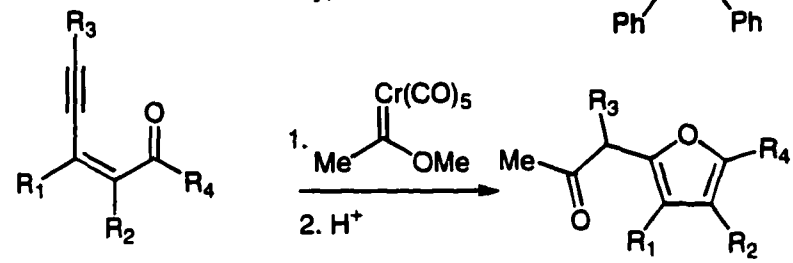
The furan ring system is found in many naturally-occurring compounds. Several reviews have listed the natural furan compounds.[3] Most of the naturally-occurring furan compounds are terpenes. In the past few decades, substitution furan ring synthesis has attracted much interest because of the biologic activity of naturally-occurring furans. Dunlop[4] reviewed the classic syntheses of furans. Russian researchers published a survey of methods for preparing β-substituted furans in 1969.[5] Dean[6], and Donnelly and Meegan[7] reviewed the synthesis of furans. Friedrichsen[8] reviewed the literature from 1984 to 1995. In 1994, Allen[9] provided a detailed review of furanosesquiterpene synthesis.

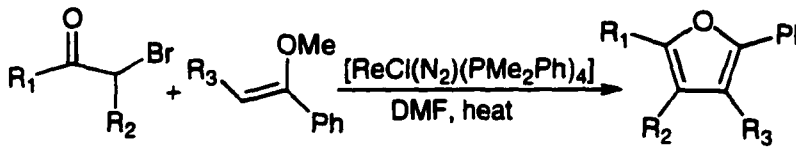
Since 1996, many new methodologies for furan synthesis have been reported. Several of these new furan syntheses involve organometallic chemistry. Pirrug[10] described a new route to furans by a rhodium reagent catalyzed reaction of diazo-compounds and alkynes

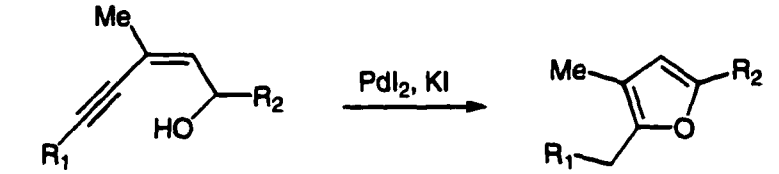
(Equation 1). Chromium compounds have been used by Rudler (Equation 2),[11] and Herndon (Equation 3)[12] to react with alkynes to generate furans. Other routes to furans, which make use of transition metallic coupling and cyclization, have been reported by Narasaka (Equation 4),[13] Gabriele (Equation 5),[14] and Cacchi (Equation 6).[15] Mikami,[16] Asouti[17] and Sha [18] have described a photo-rearrangement of enones to generate furans (Equation 7).

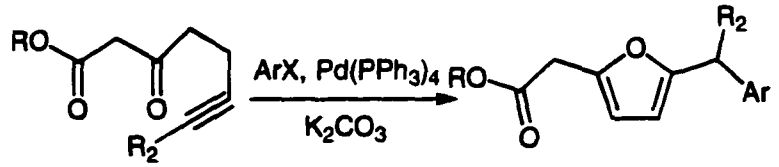


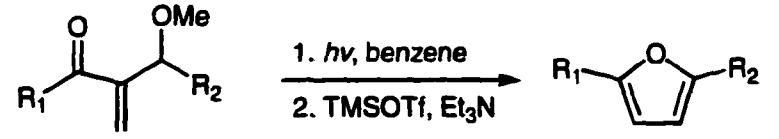




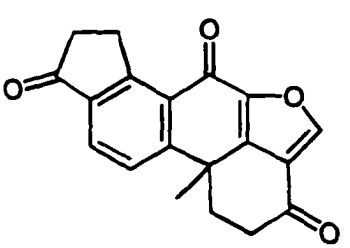




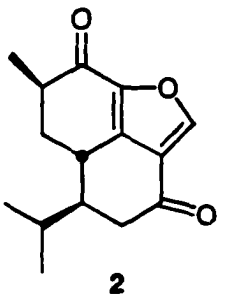




Recently, a new group of natural furans has been isolated with a 2,4-diacylfuran skeleton, such as the virindin family (**1**),[19] hibiscone C (**2**),[20] halenaquinone (**3**),[21] and pterophyllin (**4**).[22] Their biological activities have attracted many chemists to synthesize them. In this study, we developed a direct route to 2,4-diacylfurans present in this group of natural furans.



1



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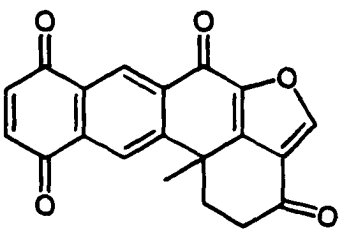

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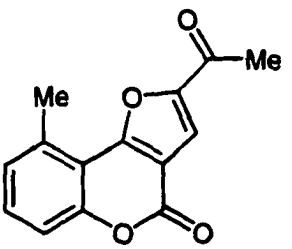

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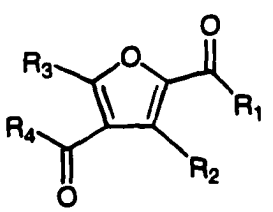
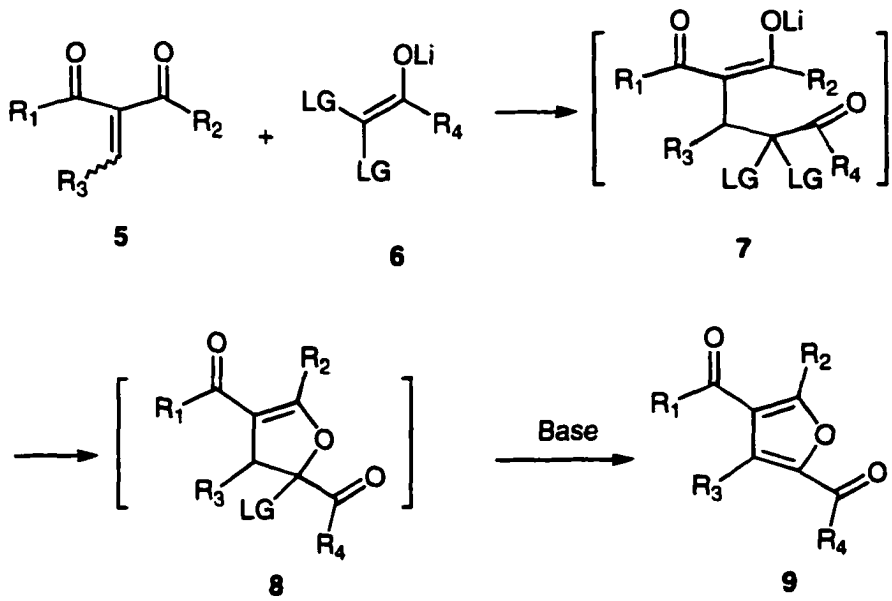


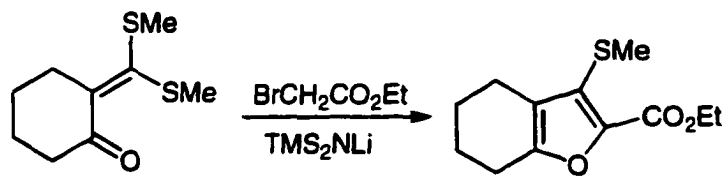
2,4-Diacylfuran

The strategy to form furans is illustrated below (Scheme 1). It begins with a Michael addition reaction of enolate **6** to α-acyl alkenones **5**. The resulting enolate **7** displaces one of the leaving groups to form dihydrofuran intermediate **8**. Base elimination generates the furanone.



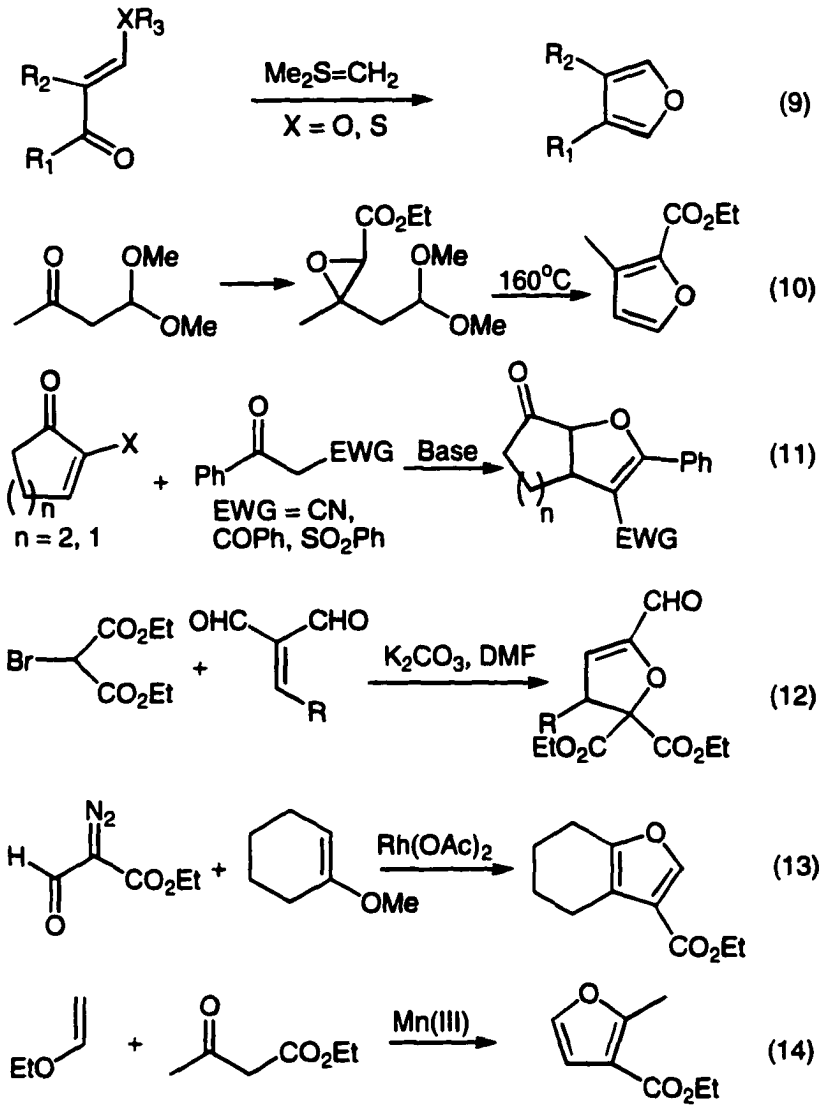
Scheme 1

The reaction of an enone with an enolate unit to generate furans was described by Datta (Equation 8)[23] in 1989. In his methodology, β,β-bis(methylthio)-α,β-unsaturated ketones react with ethyl bromoacetate in the presence of a base to give 3-(methylthio)furans via an oxirane intermediate.



(8)

In a similar sequence, an enone with a donor group in the β-position reacted with sulfonium ylides, generating 3,4-disubstituted furans (Equation 9).[24] The epoxidation of mono-protected 1,3-dicarbonyl compounds, followed by pyrolysis, generates furans (Equation 10).[25] Similar Michael-reaction sequences have also been used to form dihydrofurans by Arai (Equation 11)[26] and Arnold (Equation 12).[27] Other similar tandem reactions to generate furans, such as a carbene reaction (Equation 13)[28] and a radical reaction (Equation 14)[29] are shown as follows.



Results and Discussion

To achieve the synthesis of 2,4-diacylfurans, we used a dichloroacetate enolate as a Michael donor and enediones as Michael acceptors (Equation 15). The results are shown in Table 1. In the beginning of this research, we used one equivalent of LDA and one equivalent of dichloroacetate, and found a great quantity of starting material remained with low yields of products (with the exception of cases **13** and **14**). In subsequent reactions, when we used two equivalents of LDA and two equivalents of dichloroacetate, and let the reactions warm to room temperature, we obtained 2,4-diacylfurans directly.

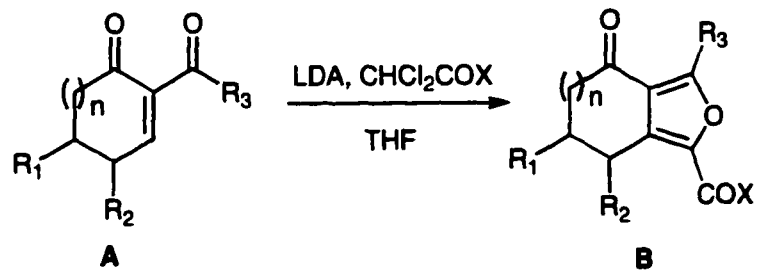
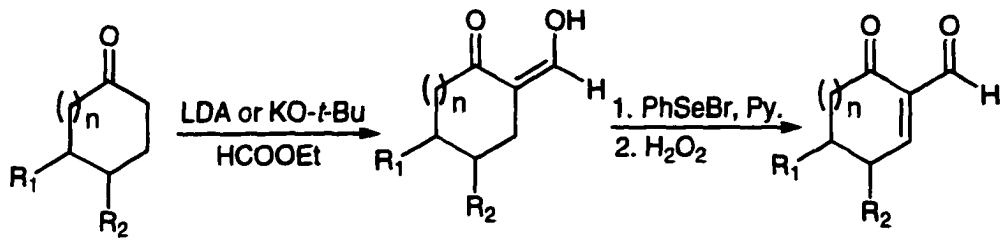


Table 1. Synthesis of Bicyclic Furans from Cyclic Enediones (Equation 15)

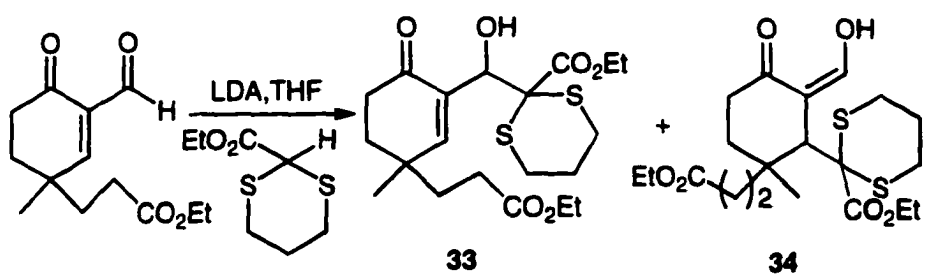
A	n	R_1	R_2	R_3	X	B	% yield
10	0	H	H	H	OEt	25	50
11	1	H	H	H	OEt	26	70
12	1	H	H	Me	OEt	27	86
13	1	*i*-Pr	H	H	OEt	28	63
14	1	H	Me	H	OEt	29	30
15	1	*i*-Pr	$CH_2CH_2CO_2Et$	H	OEt		0
16	1	H	Me, Me	H	OEt		0
17	1	H	t-Bu	H	OEt		0
18	1	H	Me, $CH_2CH_2CO_2Et$	H	OEt		0
19	1	H	H, $CH_2CH_2CO_2Et$	H	OEt		0
20	1	H	H, Allyl	H	OEt		0
21	1	*i*-Pr	Allyl	H	OEt		0
22	1	H	H	Me	Me	30	70
23	2	H	H	H	OEt	31	52
24	2	H	H	H	Me	32	55

For cases **13** and **14**, the intermediates were isolated. To form furans, we carried out the reaction and then treated the crude intermediates with excess DBU in acetonitrile at room temperature for one hour to obtain the products with good yields. Starting materials for these reactions were made by Liotta's procedure[30] (Scheme 2). These acylcycloalkenones could not be purified and needed to be used freshly due to tautomerization.



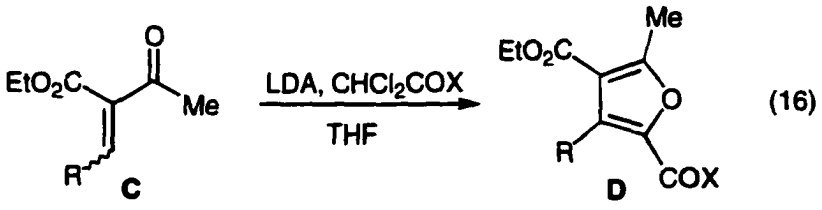
Scheme 2

From the results above, this reaction has been shown to be very sensitive to the steric effect of R_2. The ketones in cases **12** and **22** exhibited high yields of Michael addition to form furans. To examine this effect, we used the more stable anion of ethyl -1,3-dithiane-2-carboxylate to react with the hindered Michael acceptor **18** and isolated the products (Scheme 3). The ^{1}H NMR spectrum of the mixtures showed more aldehyde aldol product **33** than the Michael addition product **34**.



Scheme 3

Acyclic keto ester **C**, a good Michael acceptor, also reacted well under the same reaction condition used for cyclic enediones to generate furans (Equation 16). The starting materials **C** were available by a known procedure from Lehnert.[31] Table 2 shows the results of this reaction. When compared to cyclic analogues, the acyclic keto esters gave the better results.

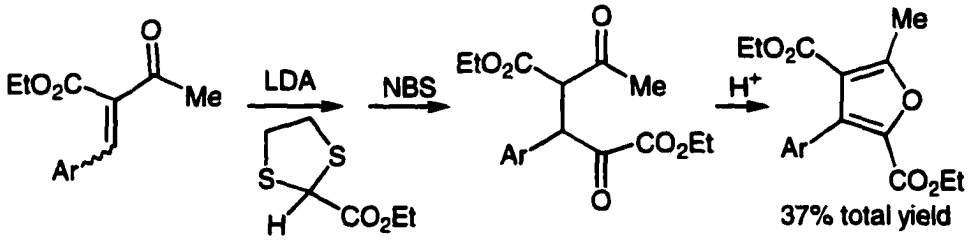


(16)

Table 2. Synthesis of 2,4-Diacylfurans from Enedicarbonyl Compounds (Equation 16)

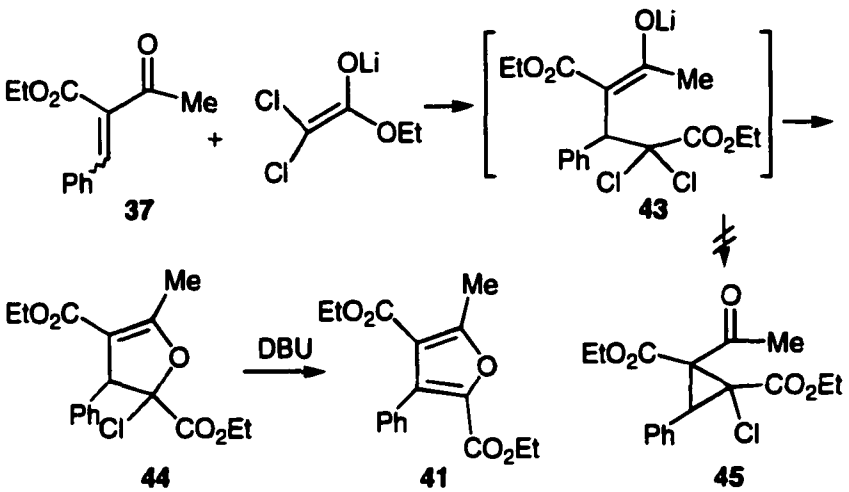
C	R	X	D	% yield
35	Me	OEt	39	68
36	Me	Me	40	62
37	Ph	OEt	41	75
38	Ph	Me	42	57

Similar products were also reported by Taylor[32] in 1989 via a multistep procedure (Scheme 4). From the results shown in Table 2, both ethyl dichloroacetate and dichloroacetone were used to generate anion under low temperature to form furans. However, α,α-dichloroacetophenone resulted in complex products.

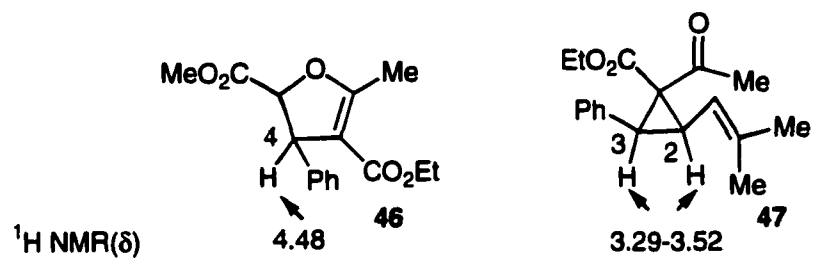


Scheme 4

In order to better understand the course of this reaction, we tried the reaction shown in Scheme 5. One equivalent of the lithium enolate of ethyl dichloroacetate was used to react with keto ester **37** at –78°C. The reaction was quenched at the same temperature after one hour with acetic acid in dichloromethane. The crude product showed no peak between 3 ppm and 4 ppm in ^{1}H NMR spectrum. Several singlet peaks have been found between 4.60 ppm and 4.69 ppm, which were integrated to approximately one proton.



Scheme 5



From references and experiments, we found that for dihydrofuran **46**,[33] the proton on carbon-4 was approximately 4.5 ppm, and for cyclopropane **47**,[34] the proton on carbon-3 was approximately 3.5 ppm. We concluded that the intermediate in this reaction was a dihydrofuran. This intermediate was treated with DBU to produce furan.

Conclusion

Two types of furan compounds have been generated. The ready availability of the starting materials and the mild reaction conditions employed in the 4+1 cyclization reaction make this furan synthesis a useful complement to existing methodology.

Experiments

Unless otherwise noted, the materials used in the experiments for this research were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene, dichloromethane,

acetonitrile, toluene, diisopropylamine were distilled from calcium hydride. The reactions were conducted in a nitrogen atmosphere and the organic extracts were dried with magnesium sulfate. The melting point was determined on a Fisher-Johns apparatus and was not corrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer and nuclear magnetic resonance spectra were determined on a Nicolet Magnetics Corporation NMR-1280 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), and m (multiplet). The addition of br indicates a broadened pattern.

The glass apparatus were flame-dried and cooled under the steam of nitrogen. Flash column chromatography was conducted using Neutral or Basic Aluminium (Brockmann) standard grade (150 mesh) from Aldrich Chemical Company and Silica Gel (EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F254 prepared plates with a thickness of 0.25 mm. High resolution MS was obtained from Kratos Model MS-50 spectrometer and low resolution MS was obtained from a Finnegan 4023 Mass spectrometer.

General procedure for 2,4-diacylfuran syntheses

N-BuLi (2.5 M, 4 mL, 10 mmol) in hexane was added to diisopropylamine (1.8mL, 12 mmol) in THF (30 mL) in a dry flask at –78°C under nitrogen. After warming the solution to 0°C, it was stirred for at least 45 minutes, then cooled to –78°C. Ethyl dichloroacetate or dichloroacetone (10 mmol) in THF (10 mL) was added dropwise to the solution. The solution was stirred at –78°C for 1 hour. The Michael acceptor (5 mmol in 10 mL THF) was then added and the solution was stirred at –78°C for 3 hours and allowed to warm to room temperature. Saturated ammonium chloride (30mL) solution was added and the solution was partitioned between ether and water. The ether layer was dried and purified by flash column chromatography using a mixture of hexanes and ethyl acetate.

Ethyl 1-methyl-4,5-dihydro-6-oxo-cyclopenta[c]furan-3-carboxylate (25)

50% yield. ^{1}H NMR ($CDCl_3$, δ): 4.36 (q, J = 7 Hz, 2H), 3.07 (t, J = 7 Hz, 2H), 2.94 (t, J = 7 Hz, 2H), 2.55 (s, 3H), 1.37 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 198.1,158.4, 154.1, 146.1, 135.8, 127.7, 61.0, 42.95, 19.7, 14.5, 14.0. IR (neat) cm^{-1}: 2983, 1716, 1617, 1013.

Ethyl 4, 5, 6, 7-tetrahydro-7-oxo-3-isobenzofurancarboxylate (26)

70% yield. ^{1}H NMR ($CDCl_3$, δ): 8.07 (s, 1H), 4.40 (q, J = 7 Hz; 2H), 3.02 (t, J = 7 Hz, 2H), 2.55 (t, J =7 Hz, 2H), 2.12 (m, 2H), 1.40 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 195.1, 159.5, 145.4, 140.0, 139.5, 123.6, 61.4, 35.4, 25.6, 22.1, 14.2. IR (neat) cm^{-1}: 3150, 2985, 1721, 1505. MS m/z (CI-NH_3): 208.

Ethyl 1-methyl-4, 5, 6, 7-tetrahydro-7-oxo-3-isobenzofurancarboxylate (27)

86% yield. ^{1}H NMR ($CDCl_3$, δ): 4.36 (q, J = 7 Hz, 2H), 2.97(t, J = 7 Hz, 2H), 2.65 (s, 3H), 2.47 (t, J = 7Hz, 2H), 2.06(m, 2H), 1.38 (t, J=7Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 195.1, 160.6, 159.0, 136.9, 135.2, 120.1, 60.8, 39.6, 23.4, 21.8, 14.4, 14.3. IR (neat) cm^{-1}: 2986, 1716, 1683, 1598, and 1276.

3-Acetyl-1-methyl-4, 5, 6, 7-tetrahydro-7-oxo-isobenzofuran (30)

70% yield. ^{1}H NMR ($CDCl_3$, δ): 3.2(t, J = 7 Hz, 2H), 2.5 (t, J = 7 Hz, 2H), 2.67 (s, 3H), 2.47 (s, 3H), 2.08 (quintet, J = 7 Hz, 2H). ^{13}C NMR ($CDCl_3$, δ): 195.2, 188.0, 159.9, 145.6, 134.6, 120.6, 39.5, 26.9, 23.4, 22.1, 14.4. IR (neat) cm^{-1}: 3325, 2955, 1693, 1548, 908.

Ethyl 4, 5, 6, 7-tetrahydro-8-oxo-cyclohepta[c]furan-3-carboxylate (31)

52% yield. ^{1}H NMR ($CDCl_3$, δ): 4.39 (q, J = 7 Hz, 2H), 3.21 (t, J = 7 Hz, 2H), 2.73(t, J = 7 Hz, 2H), 1.9-2.0(m, 4H), 1.4(t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 197.8, 159.2, 148.5, 140.8, 132.9, 130.3, 61.1, 42.6, 25.5, 23.8, 22.1, 14.3. IR (neat) cm^{-1}: 3160, 2985, 1712, 1681, 1593, 1282.

3-Acetyl-4, 5, 6, 7-tetrahydro-8-oxo-cyclohepta[c]furan (32)

55% yield. ^{1}H NMR ($CDCl_3$, δ): 3.24 (t, J = 7 Hz, 2H), 3.71 (t, J = 7 Hz, 2H), 2.49 (s, 3H), 1.80-1.90 (m, 4H). ^{13}C NMR ($CDCl_3$, δ): 198.1, 189.71, 148.0, 145.2,131.9,130.9, 43.1, 27.4, 25.6, 24.2, 22.2. IR (neat) cm^{-1}: 3118, 2950, 1670, 1574, 1392, 1136.

Diethyl 3, 5-dimethyl-2, 4-furandicarboxylate (39)

68% yield. ^{1}H NMR ($CDCl_3$, δ): 4.25-4.41 (m, 4H), 2.62 (s, 3H), 2.53(s, 3H), 1.35-1.41 (m, 6H). ^{13}C NMR ($CDCl_3$, δ): 163.8, 162.2, 159.5, 139.0, 132.1, 115.9, 60.8, 60.4, 14.8, 14.4, 14.3, 11.0. IR (neat) cm^{-1}: 2982, 1719, 1608, 1077.

Ethyl 2-acetyl-3, 5-dimethyl-4-furancarboxylate (40)

62% yield. ^{1}H NMR ($CDCl_3$, δ): 4.31 (q, J = 7 Hz; 2H), 2.60 (s, 3H), 2.45 (s, 3H), 2.44(s, 3H), 1.36 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 188.9, 163.8, 161.6, 147.2, 131.2, 116.5, 60.4, 27.3, 14.9, 14.3, 11.0. IR (neat) cm^{-1}: 2981, 1709, 1676, 1592, 1242. MS m/z (CI-NH_3): 210.

Diethyl 5-methyl-3-phenyl-2.4-difurancarboxylate (40)

75% yield. ^{1}H NMR ($CDCl_3$, δ): 7.2-7.4 (m, 5H), 4.17 (q, J = 7 Hz, 2H), 4.06 (q, J = 7 Hz, 2H), 2.69(s, 3H), 1.10 (t, J = 7 Hz, 3H), 1.01 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$) ppm: 163.2, 162.0, 158.7, 138.8, 134.6, 131.8, 129.5, 127.9, 127.8, 127.3, 60.8, 60.3, 14.6, 13.9, 13.7. IR (neat) cm^{-1}: 3010, 2982, 1721, 1594, 1410, 1254, 1178.1089. MS m/z (CI-NH_3): 320.

Ethyl 2-acetyl-5-methyl-3-phenyl-4-furancarboxylate (41)

57% yield. ^{1}H NMR ($CDCl_3$, δ): 7.27-7.41 (m, 5H), 4.07 (q, J = 7 Hz, 2H), 2.71 (s, 3H), 2.08(s, 3H), 1.00 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 186.8, 163.0, 162.2, 146.7, 134.1,132.1,129.3, 128.2, 127.9,116.4, 60.3, 27.9, 14.6, 13.6. IR (neat) cm^{-1}: 3059, 2982, 1711, 1673, 1590, 1445, 1240, 1174.

General procedure for 13 and 14:

N-BuLi (2.5 M, 4 mL, 10 mmol) in hexane was added to diisopropylamine (1.8 mL, 12 mmole) in THF (30 mL) in a dry flask at –78°C under nitrogen. After warming to 0°C, the solution was stirred for at least 45 minutes, then cooled to –78°C. A solution of ethyl dichloroacetate or dichloroacetone (10 mmol) in THF (10 mL) was added dropwise to this solution. The solution was stirred at –78°C for 1 hour. The Michael acceptor (10 mmol in 20 mL THF) was then added, and the solution was stirred at –78°C for 3 hours and allowed to warm to room temperature. Saturated ammonium chloride solution (30 mL) was added and then the solution was partitioned between ether and water. The ether layer was dried and the solvent was removed under reduced pressure. The crude product was dissolved in acetonitrile (30 mL). To this solution DBU (4.5 mL, 30 mmol) was added and stirred for 1 hour. Saturated ammonium chloride solution (30 mL) was added and the solution was partitioned between ether and water. The ether layer was dried and purified by flash column chromatography using a mixture of hexanes and ethyl acetate.

Ethyl 5-isopropyl-4, 5, 6, 7-tetrahydro-7-oxo-3-isobenzofurancarboxylate (28)

63% yield. ^{1}H NMR ($CDCl_3$, δ): 8.07 (s, 1H), 4.40 (q, J = 7 Hz; 2H), 3.2-3.3(m, 1H); 2.55-2.65 (m, 2H), 2.25-2.35 (m, 1H), 1.9-2.1 (m, 1H), 1.7-1.8(m, 1H), 1.41(t, J = 7 Hz; 3H), 1.0 (d, J = 7 Hz, 6H). ^{13}C NMR ($CDCl_3$, δ): 194.9, 158.9, 146.1, 140.0, 134.2, 125.7, 61.2, 43.1, 43.2, 31.7, 24.9, 19.6, 19.5, 14.4. IR (neat) cm^{-1}: 3175, 2987, 1715, 1235.

Ethyl 4-methyl-4, 5, 6, 7-tetrahydro-7-oxo-3-isobenzofurancarboxylate (29)

30% yield. ^{1}H NMR ($CDCl_3$, δ): 8.01 (s, 1H); 4.3-4.5 (m, 2H); 3.5-3.6 (m, 1H); 1.9-2.7 (m, 4H); 1.38 (t, J = 7 Hz, 3H); 1.33(d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 194.2, 158.6, 146.4, 139.8, 138.9, 124.7, 61.2, 34.4, 29.9, 25.4, 18.8, 14.3. IR (neat) cm^{-1}: 3143, 2990, 1720, 1278.

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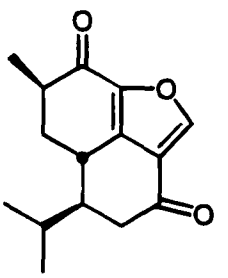
CHAPTER 2. TOTAL SYNTHESIS OF HIBISCONE C

A paper, a portion of which was accepted by *Synlett*

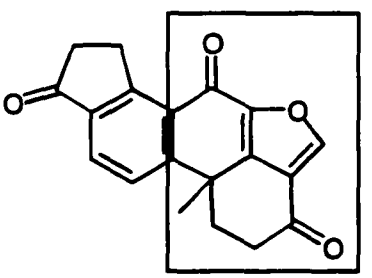
George A. Kraus and Zhiwen Wan

Introduction

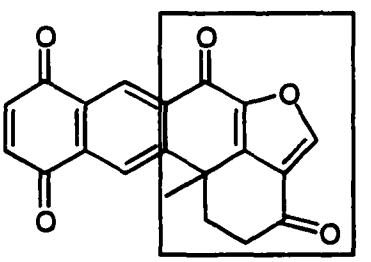
Hibiscone C was originally isolated as gmelofuran from *Gmelina aborea* in 1978.[1] Because it also is found in *Hibiscus* sp., the nation tree of Jamaica, the name was changed to hibiscone C.[2] Hibiscone C contains a furan ring as part of a bicyclo [4. 4. 0] decane system. The key architectural feature of this family, namely the trisubstituted furan ring skeleton, also appears as a central structural unit in the viridin family[3] and halenaquinone family.[4]



Hibiscone C (Gmelofuran) (**1**)

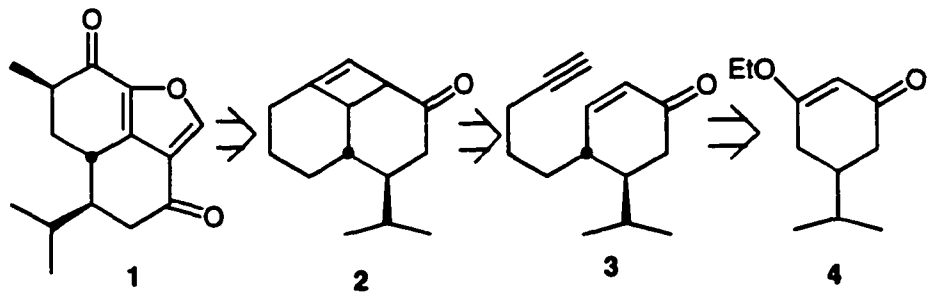


Virindin



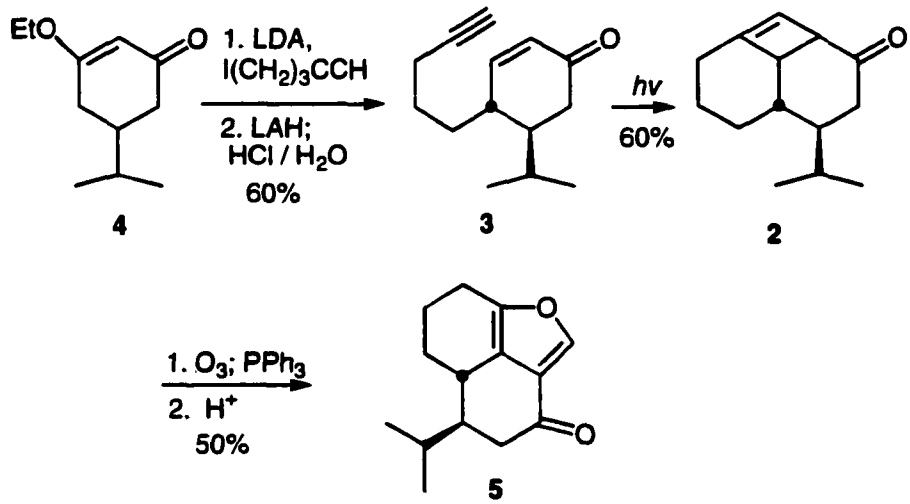
Halenaquinone

The only total synthesis of hibiscone C was reported by Smith[5] in 1984. He developed an intramolacular alkyne-enone photocycloaddition to form a cyclobutene, followed by ozonolysis and acidic cyclization to provide the furan. The retrosynthetic analysis is shown in Scheme 1.



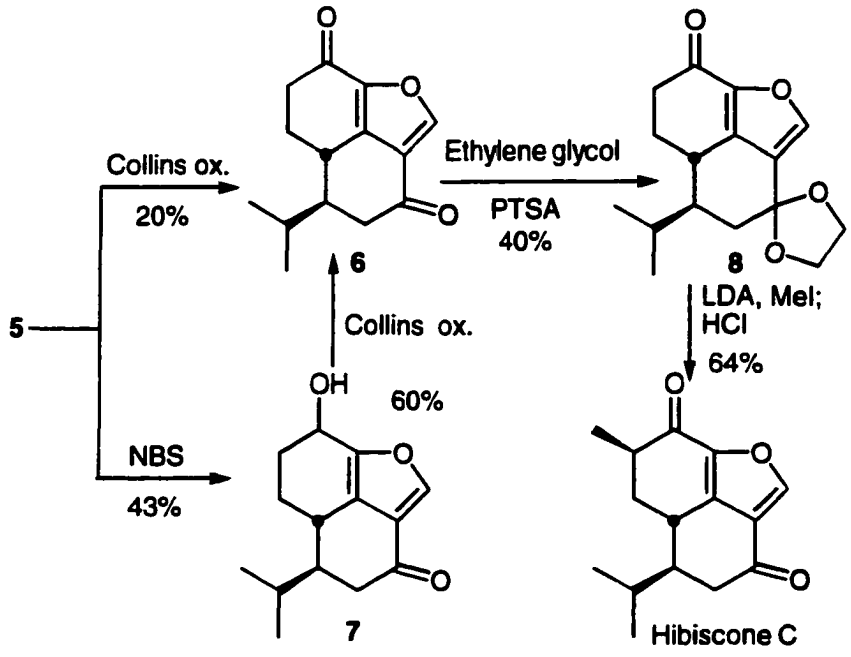
Scheme 1

His synthesis started with the alkylation of **4**, followed by LAH reduction and acid work-up to give alkyne **3** in a total yield of 60% (Scheme 2). Irradiation of **2** in hexane under argon for 24 hours gave **2** in 60% yield. Ozonolysis of **2**, followed by acidic cyclization, led to furan **5** in 50% yield.



Scheme 2

To generate the second carbonyl, Smith[5] first tried to oxidize **5** with Collins reagent, giving **6** in 20% yield. He then used NBS in water to oxidize **5** and isolated alcohol **7** in 60% yield. Oxidation of **7** with Collins reagent afforded **6** in 40% yield. Monoprotected **8** was used to make hibiscone C (Scheme 3).



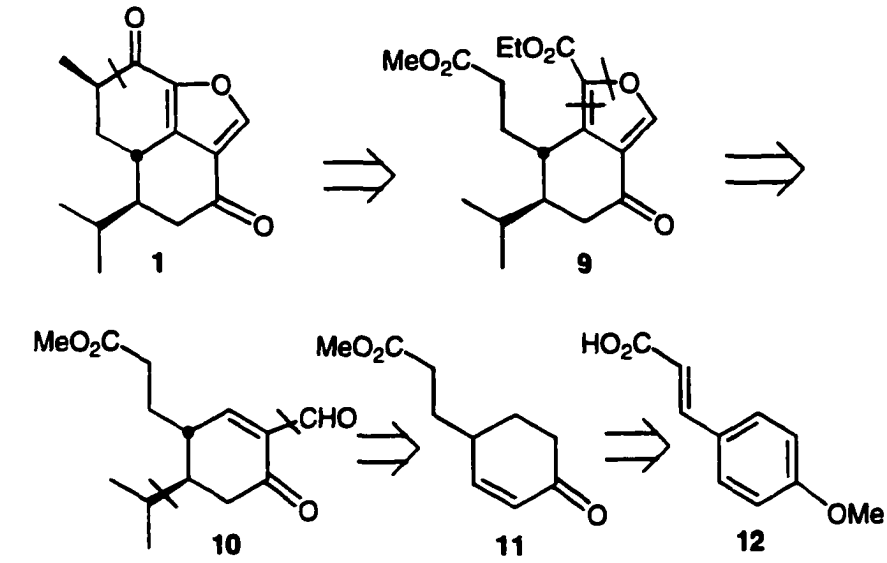
Scheme 3

The route discussed above has a novel furan synthesis. However, the last several steps proceed in low yield and are not efficient.

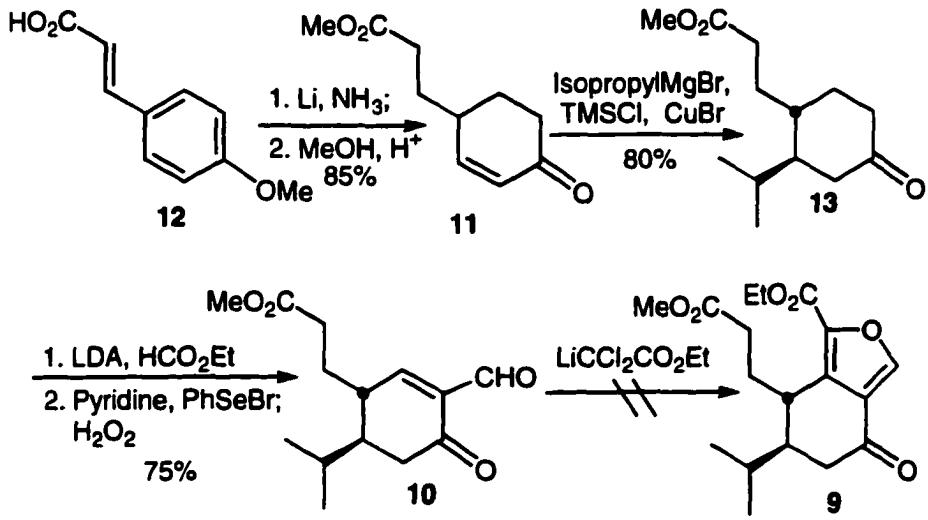
Results and Discussion

As a part of a study to make natural 2,4-diacylfurans, we wanted to use the methodology we developed[6] to prepare hibiscone C. The retrosynthetic analysis is shown in Scheme 4. Hibiscone C was planed to be generated from **9** via Dieckmann condensation. Reaction of the enolate of ethyl dichloroacetate with **10** is expected to provide furan **9**. Formyl cyclohexenone **10** could be obtained from **11** by literature procedures.

We reduced 4-methoxycinnamic acid (**11**) using lithium in liquid ammonia. The reduction product was treated with PTSA to afford cyclohexenone **12** in 85% yield.[7] Compound **12** was treated with isopropyl magnesium bromide, CuBr and four equivalents of TMSCl to afford **13** in 80% yield.[8] Reaction of the enolate of **13** with ethyl formate, followed by Liotta's procedure[9], gave **10** in 75% yield (Scheme 5). However, the reaction of the enolate of ethyl dichloroacetate with **10** did not give furan **9**. The reason for this failure could be attributed to steric hindrance and the high acidity of the allylic methylene proton.

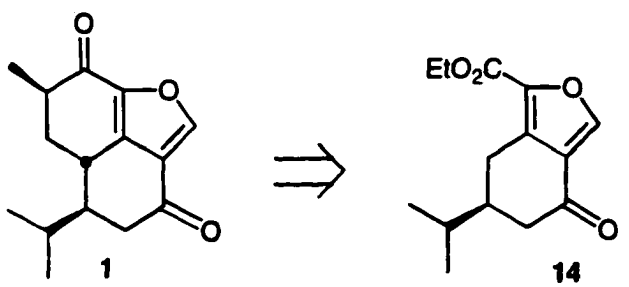


Scheme 4



Scheme 5

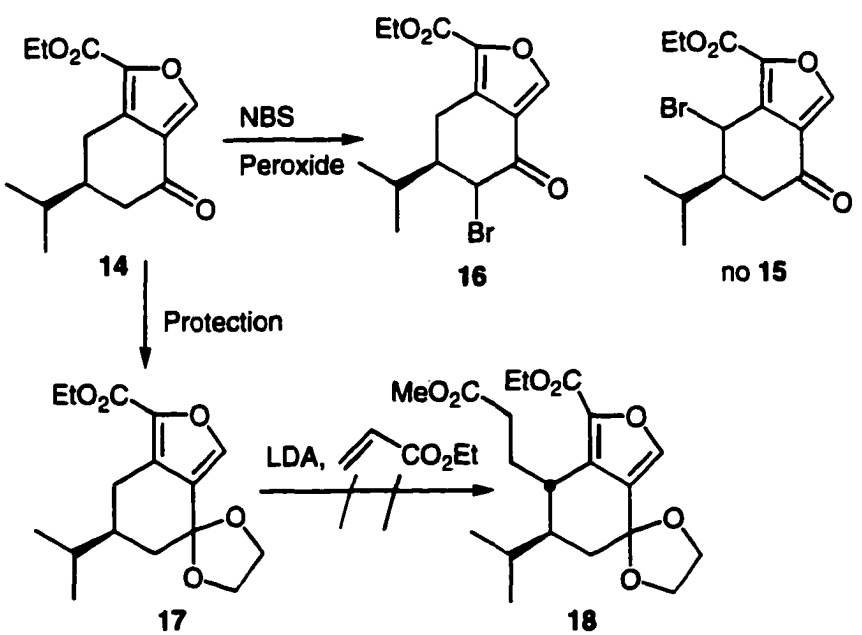
At this point, we tried to use furan **14**[6] to prepare **1** from keto ester **14** by reaction at the allylic methylene group of **14**(Scheme 6). There are two ways to achieve this strategy. One is to generate a radical at C-7 and react with acrylate to form **9**. Another strategy was to generate an anion to form **9**.



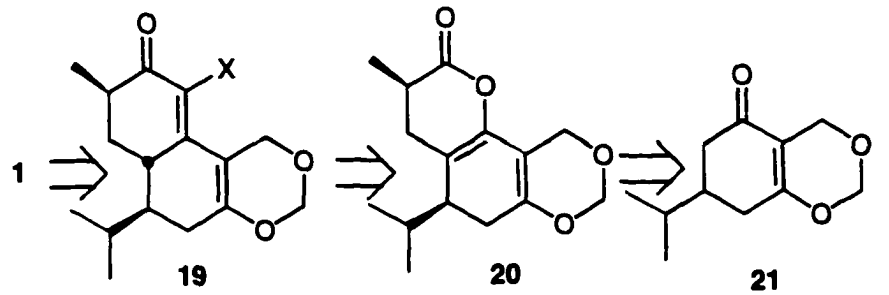
Scheme 6

When **14** was brominated with NBS and dibenzoyl peroxide, **16** was obtained as the only product (Scheme 7). Because of the undesired regioselectivity of bromination, we evaluated the anion strategy. The ketone carbonyl in **14** was protected as ketal. Ketal **17** was treated with LDA followed by ethyl acrylate. However, this sequence did not give diester **18.**

We next decided to focus on a different approach. The retrosynthetic analysis is shown in Scheme 8. We envisioned that the furan ring in hibiscone C could be formed from a precursor such as **19.** The new chemistry would involve a tandem Wittig reaction from enol ester **20,** which would be prepared from **21**[10] by alkylation.



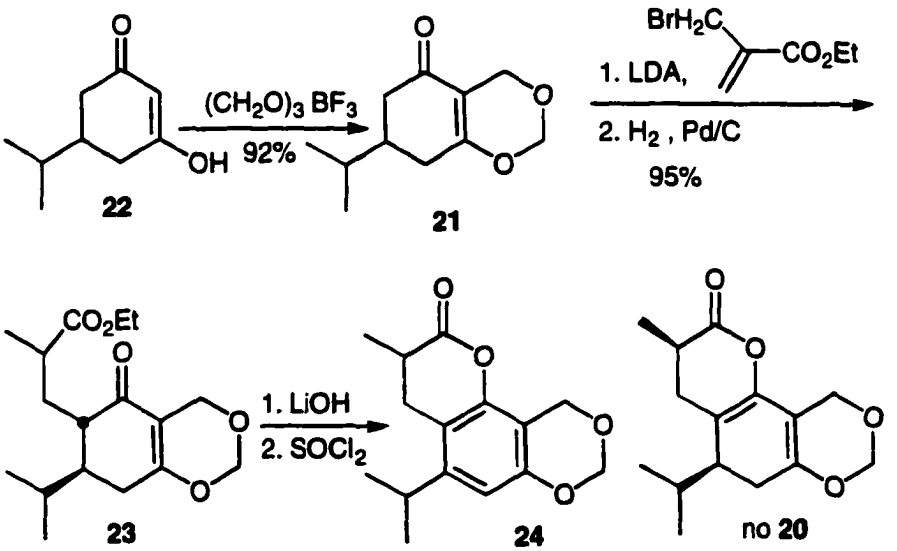
Scheme 7



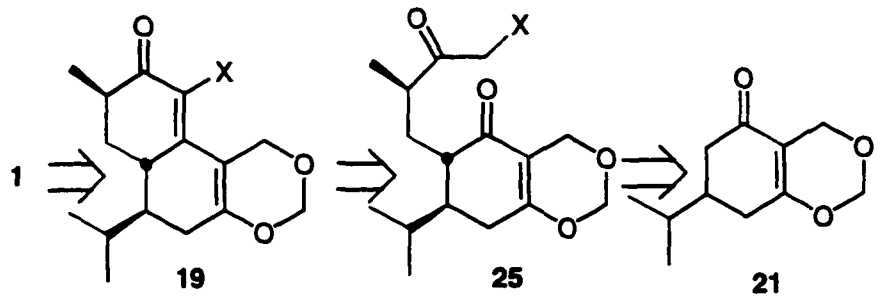
Scheme 8

Starting with commercially available 5-isopropyl-1,3-cyclohexanedione (**22**), we prepared **21** in 92% yield by Smith's procedure[10] (Scheme 9). Because of the bulky isopropyl group, Michael addition of **21**with acrylate failed. However, the alkylations of **21** with LDA and allyl bromide, allyl iodide and 2-methyl allyl iodide were successful. Alkylation of **21** with ethyl 2-bromomethylacrylate followed by hydrogenation provided **23** in 95 % yield. Treatment of **23** with LiOH in water provided an acid. The reaction of the acid with thionyl chloride did not give **20**. Compound **24** was the only stable product.

We then decided to generate **19** from **25**. The retrosynthetic analysis is shown in Scheme 10. Compound **25** might be obtained from **21** via a Michael addition reaction.

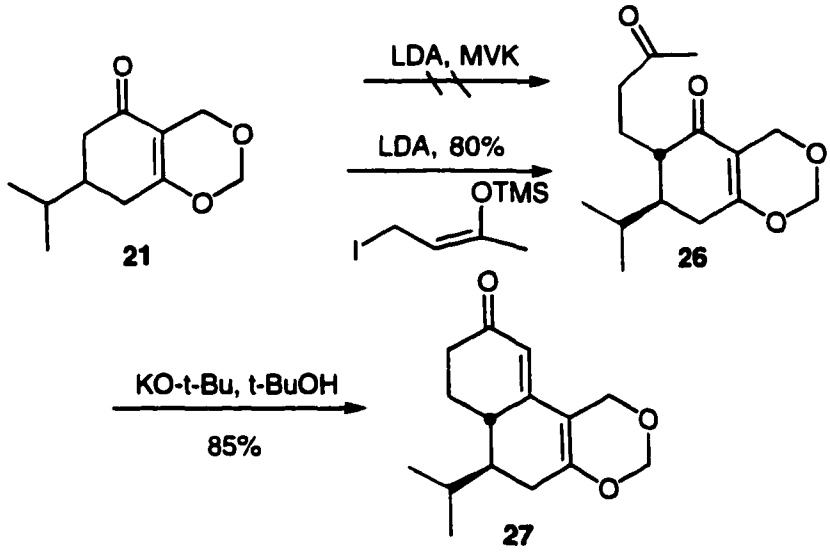


Scheme 9



Scheme 10

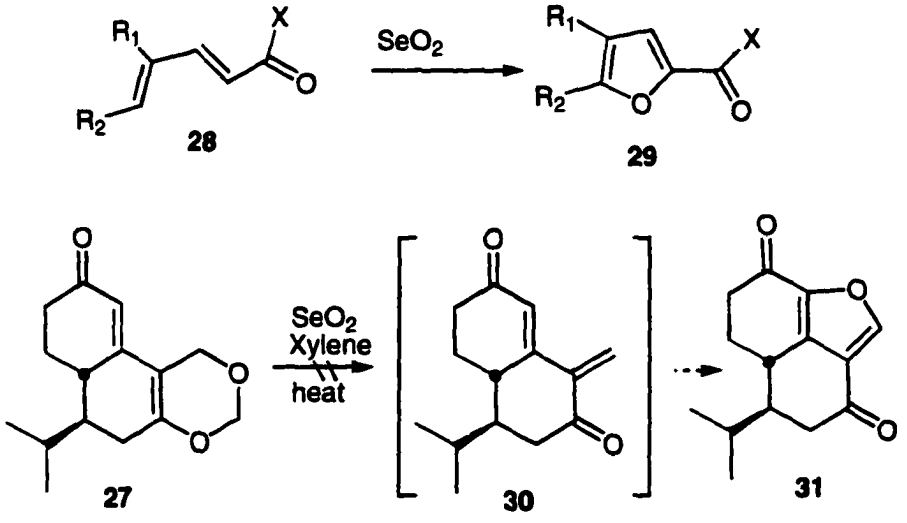
The reaction of **21** with LDA followed by methyl vinyl ketone led to recovered starting material. Because the alkylation had worked, we looked for an alkylating reagent that was an MVK equivalent. We used the procedure reported by Hamiton[11] to prepare **26** in 80% yield (Scheme 11). With **26** in hand, we evaluated the annulation reaction. KH in mineral oil was added to a solution of **26** in *tert*-BuOH. The solution was stirred overnight at room temperature to generate **27** in 85% yield.



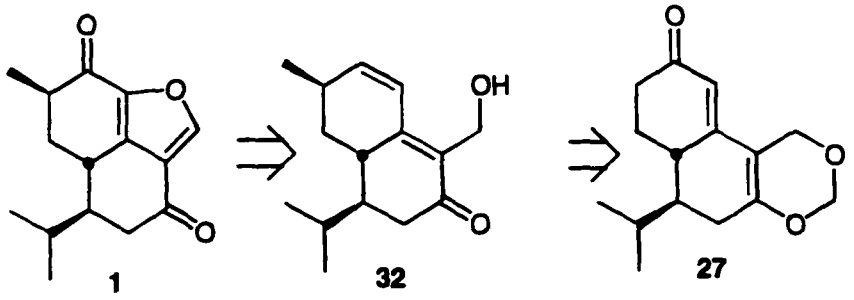
Scheme 11

The last key step was the generation of a heteroatom group on α-carbon of the enone **19**. There were two ways to achieve this plan. One was to put the heteroatom group on the methyl vinyl ketone equivalent then try the alkylation and annulation to generate **19**. Another route was to start with **27** to generate the heteroatom group. With **27** in hand, we were ready to attempt the second procedure. At first, we tried the oxidation reaction developed by No[12] reported. He used selenium dioxide to convert dienone **28** into furan **29** in good yield. We predicted that **27** could give **30** via a retro-Diels-Alder reaction. The reaction of **30** with selenium dioxide could generate furan **31** by selenium dioxide. Unfortunately, the reaction did not give **31** (Scheme 12).

At this point, we reconsidered our approach to hibiscone C from **27**. The precursor to the furan in hibiscone C could be obtained from **31** by selective oxidation of the remote double bond. Reduction of **27** followed by acid catalyzed rearrangement might produce **31**(Scheme 13).

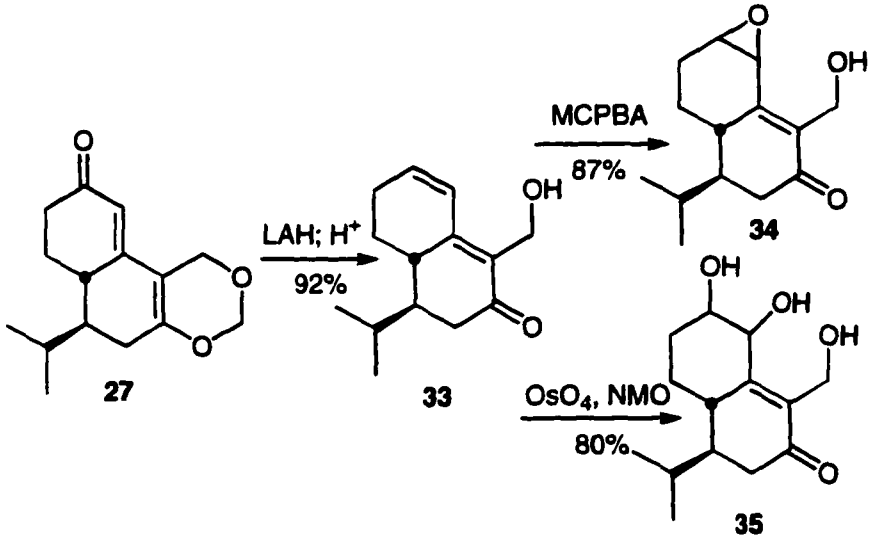


Scheme 12



Scheme 13

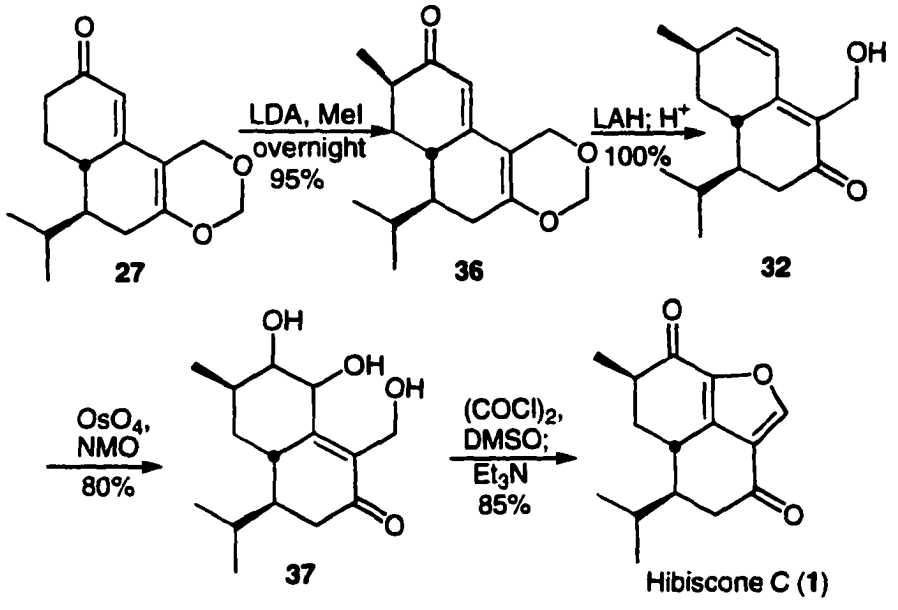
Treatment of **27** with lithium aluminum hydride followed by acidification and rearrangement gave **33** in 92% yield. Then we tried the selective oxidations using MCPBA epoxidation or osmium tetraoxide dihydroxylation (Scheme 14). MCPBA epoxidation generated **34** in 87% yield. The dihydroxylation reaction generated triol **35** in 80% yield. We did not study the stereoselectivity of this reaction.



Scheme 14

At the same time, we reacted **27** with 1 equivalent of LDA followed by MeI to generate **36** as the only product based oh the proton NMR spectrum in 95% yield (Scheme 15). However, if this reaction was quenched in 3 hours, a mixture of **36** and a by-product was obtained. Compound **36** did not need further purification for the next step. The reduction of **36** with LAH followed by acid catalyzed rearrangement gave **32** in almost

quantitative yield. We then used the dihydroxylation procedure to obtain triol **37** in 80% yield. We needed two equivalents of the Swern reagentan oxidant to generate two carbonyl groups. We treated the triol **37** with 2.5-3 equivalents of Swern oxidant and obtained hibiscone C in 85 % yield.



Scheme 15

Conclusion

The synthesis of hibicone C was achieved in seven steps. The key steps were the reduction and rearrangement of dioxenone **36** and the Swern oxidation to generate the furan. This strategy could be applicable to the synthesis of other furans.

Experiments

Unless otherwise noted, the materials used in the experiments for this research were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene, dichloromethane, acetonitrile, toluene, diisopropylamine were distilled from calcium hydride. The reactions were conducted in a nitrogen atmosphere and the organic extracts were dried with magnesium sulfate. The melting point was determined on a Fisher-Johns apparatus and was not corrected. Infrared spectra were obtained on a Perkin-Elmer model 1320

spectrophotometer and nuclear magnetic resonance spectra were determined on a Nicolet Magnetics Corporation NMR-1280 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), and m (multiplet). The addition of br indicates a broadened pattern.

The glass apparatus were flame-dried and cooled under the steam of nitrogen. Flash column chromatography was conducted using Neutral or Basic Aluminium (Brockmann) standard grade (150 mesh) from Aldrich Chemical Company and Silica Gel (EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F254 prepared plates with a thickness of 0.25 mm. High resolution MS was obtained from Kratos Model MS-50 spectrometer and low resolution MS was obtained from a Finnegan 4023 Mass spectrometer.

4,6,7,8-Tetrahydro-7-isopropyl-5H-1, 3-benzodioxin-5-one (21)

A solution of 5-isopropyl-cyclohexanedione (3.1 g, 20 mmol) in 50mL of methylene chloride was added dropwise at room temperature over 5 hours to a solution of 1,3,5-trioxane (12.8 g, 12 mmol) and boron trifluoride etherate (7.38 mL, 60 mmol) in dry methylene chloride 1L at room temperature. After addition, the solution was stirred further for 36 hours. The reaction was quenched slowly with saturated sodium bicarbonate solution (50 mL). The organic layer was separated and aqueous phase was extracted with methylene chloride. The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in a vacuum. The residue was purified by flash chromatography (eluting with 5:1 hexane/ethyl acetate) to give 3.6g of light yellow oil **21** (92% yield). ^{1}H NMR ($CDCl_3$, δ): 5.21(d, J = 6 Hz, 1H), 5.06 (d, J = 6 Hz, 1H), 4.3-4.5 (m, 2H), 1.7-2.5 (m, 5H), 1.6 (Septet, J = 7 Hz, 1H), 0.93(d, J = 7 Hz, 6H). ^{13}C NMR ($CDCl_3$, δ): 196.9, 170.5, 111.5, 91.8, 63.1, 40.8, 39.8, 32.1, 31.7, 19.8, 19.7. IR cm^{-1}: 2985, 1691, 1310. MS m/z: 196.

4,6,7,8-Tetrahydro-7-isopropyl-6- (3-oxo-1- butyl)-5H-1,3-benzodioxin-5-one (26)

A solution of n-BuLi (4.5 mL of 2.5M solution in hexane) was added to diisopropylamine (1.8 mL, 12 mmol) in THF (30 mL) at 0°C. The resulting solution was stirred for 45 minutes. Then the mixture was cooled to –78°C and **21** (1.9g, 10 mmol) in 10mL of THF was added over 10 min. The resulting solution was stirred for 1 hour. At the same time, fresh MVK (2.5 mL, 30mmol) in 30 mL methylene chloride was cooled to –78°C and to this solution, freshly distilled TMSI (4.3 mL, 30 mmol) was added and stirred for 2 hours at the same temperature. The resulting solution was transferred to the **21** anion solution. The resulting mixture was stirred for another 4 hours and then quenched with water. The organic layer was separated and washed with dilute HCl (10 mL), saturated sodium bicarbonate (10 mL) and brine (10 mL), and dried with magnesium sulfate. Removing the solvent gave a crude product, which was purified by flash column chromatography (5:1 hexanes: ethyl acetate), giving 2.1g of **26** as light yellow oil (80% yield). ^{1}H NMR ($CDCl_3$, δ): 5.10 (dd, J = 6 Hz; 2 Hz, 2H), 4.36 (m, 2H), 2.4-2.5 (m, 3H), 2.2-2.3 (m, 2H), 2.10 (s, 3H), 1.9-2.05 (m, 1H), 1.7-1.85(m, 3H), 0.92 (d, J = 7 Hz, 3H), 0.85 (d, J = 7Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 208.7, 198.2, 168.5, 110.6, 91.5, 62.8, 47.3, 42.3, 40.5, 30.1, 28.3, 16.9, 22.1, 20.9, 17.9.

5,6,7,8-tetrahydro-6-isopropyl- (1H)-naphtho[2,1-d][1,3]dioxin-8-one (27)

A solution of KH in mineral oil (30%, 0.5 mL) was added to **26** (1.33g, 5 mmol) in t-BuOH (15 mL) under nitrogen. The resulting solution was stirred overnight, then quenched with ammonium chloride solution (10 mL). The product was extracted with ethyl acetate (20 mL x 3), then washed with brine (20 mL) and dried with magnesium sulfate. The solvent was removed under vacuum, followed by flash column chromatography purification, which generated 1.0g of **27** (85% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$, δ): 5.45 (s, 1H), 5.20 (d, J = 6 Hz, 1H), 5.00(d, J = 6 Hz, 1H), 4.3-4.4 (m, 2H), 2.0-2.6 (m, 7H), 1.5-1.7 (m, 2H), 0.96(d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 199.0, 160.3, 157.8, 116.6, 106.6, 90.9, 63.8, 43.5, 37.9, 37.2, 26.8, 26.2, 26.1, 20.9, 14.5. MS m/z (CI-NH_3): 248.

7-Methyl-5,6,7,8-tetrahydro-6-isopropyl- (1H)-naphtho[2,1-d][1,3]dioxin-8-one (36)

A solution of **27** (1.25 g, 5 mmol) in 10 mL of THF was added to LDA (6 mmol, from n-BuLi and diisopropylamine) in 50 mL THF solution at –78°C under nitrogen. The resulting solution was stirred for 1 hour and methyl iodide (0.8 mL, 6 mmol) was added. The resulting solution was warmed overnight to room temperature. Water (10 mL) was added to quench the reaction. The product was extracted with ethyl acetate (30 mL x 3), washed with brine and dried with magnesium sulfate. Removal of the solvent generated 1.3g oil **36** which was pure enough for the next step. ^{1}H NMR ($CDCl_3$, δ): 5.35 (s, 1H), 5.20 (d, J = 6 Hz, 1H), 5.01 (d, J = 6 Hz, 1H), 4.30-4.42 (m, 2H), 1.95-2.6 (m, 6H), 1.6-1.8 (m, 2H), 1.17 (d, J = 7 Hz, 3H), 0.96(d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 202.5, 160.2, 156.8, 115.2, 106.6, 90.8, 63.8, 43.1, 39.5, 32.7, 32.5, 26.9, 26.0, 20.8, 16.4, 14.3.

1-Hydroxymethy-4-isopropyl-6-methy-2,3,4,5,6,10-hexahydro-2-oxo-naphthalene (32).

A solution of **36** (0.52 g, 2 mmol) in THF (10 mL) was added to the suspension of LAH (20 mg, 5.2 mmol) in 30mL THF at room temperature under nitrogen. The solution was stirred at 0°C for 3 hours, and then water (1 mL) was added to quench the reaction. The solution was acidified with HCl (6N) to pH 1 and stirred for another hour. The product was extracted with ethyl acetate (30 mLx3), washed with saturated sodium bicarbonate (20 mL) and brine (40 mL), and dried with magnesium sulfate. After removal of the solvent, a 0.46g of pure yellow oil product **32** was obtained. ^{1}H NMR ($CDCl_3$, δ): 6.58(d, J = 6 Hz, 1H), 6.31 (dd, J = 3 Hz; 6Hz, 1H), 4.42 (dd, J = 9 Hz; 2Hz, 2H), 2.7 (m, 1H), 2.4-2.6 (m, 3H), 2.0-2.2 (m, 2H, OH), 1.91 (m, 1H), 1.7-1.8 (m, 1H), 1.4-1.5 (m, 1H), 1.11 (d, J = 7 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 0.80 (d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 202.1, 154.2, 145.4, 130.9, 123.1, 56.3, 44.2, 37.0, 33.5, 31.9, 29.6, 26.1, 20.8, 18.5, 15.0. IR (neat) cm^{-1}: 3396, 1666, 1558, 1472, 1012. MS m/z (CI-NH_3): 234. HRMS: 234.16198 (cal. 234.16226).

1-Hydroxymethy-7, 8-dihydroxy-4-isopropyl-6-methy-2,3,4,5,6,7,8,10-decahydro-2-oxo-naphthalene (37)

OsO_4 in t-BuOH (5 mg/mL, 0.2 mL), and after 5 minutes, 4-methylmorpholine N-oxide (NMO, 60 mg, 0.55 mmol) was added to the solution of **32** (0.12 g, 0.5 mmol) in acetone (5 mL) with water (1 mL). Then sodium thiosulfate (10%, 5 mL) was added to

quench the reaction after 18 hours. The product was extracted with ethyl acetate (15 mL x 3), filtered by celite, then washed with brine and dried with magnesium sulfate. After removal of the solvent, the product was obtained and purified with FCC (1:1 Ethyl acetate: Hexane) (0.11g as oil, 80% yield). ^{1}H NMR ($CDCl_3$, δ): 4.68 (d, J = 12 Hz, 1H), 4.62 (d, J=3Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 3.68 (dd, J = 3 Hz; 6Hz, 1H), 1.6-2.5 (m, 8H), 1.16 (d, J = 7 Hz, 3H), 0.92 (d, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 200.3, 162.8, 134.5, 77.3, 72.5, 55.2, 44.4, 36.5, 36.3, 33.3, 32.6, 27.6, 21.2, 18.5, 16.7. MS m/z (CI-NH_3): (M-OH) 251. HRMS (M-OH): 251.164719 (cal. M: 268.167459).

Hibiscone C

A solution of oxalyl chloride (0.043 mL, 0.5 mmol) was added to DMSO (0.1mL, 1.4 mmol) solution in methylene chloride at –78°C under nitrogen. Then, after 5 minutes, **37** (0.054 g, 0.2 mmol) in methylene chloride (3 mL) was added. The resulting solution was stirred for 15 minutes, and then triethyl amine (0.5 mL) was added. After 15minutes, the solution was warmed to room temperature. Water (2 mL) was added, and the product was extracted with methylene chloride (10 mLx3), washed with HCl (1N, 10 mL), saturated sodium bicarbonate (10 mL) and brine (10 mL), and dried with magnesium sulfate. After removal of the solvent, pure hibiscone C (40 mg, 85% yield) was obtained by preparative TLC (2:1 Hexane: Ethyl acetate). ^{1}H NMR ($CDCl_3$, δ): 8.10 (s, 1H), 3.04 (ddd, J = 5 Hz; 11 Hz; 11 Hz, 1H), 2.78-2.83 (m, 1H), 2.60 (dd, J = 3 Hz; 17 Hz, 1H), 2.36 (dd, J = 13 Hz; 17 Hz, 1H), 2.17-2.23 (m, 1H), 2.0-2.1 (m, 1H), 1.85-1.94 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): 193.5, 188.7, 147.8, 145.0, 144.5, 123.3, 48.0, 42.8, 40.1, 36.0, 30.1, 26.7, 20.9, 16.4, 15.5. IR (neat) cm^{-1}: 1717, 1646, 1457. MS m/z (CI-NH_3): 246. HRMS: 246.1260 (calculate for $C_{15}H_{18}O_3$: 46.1256).

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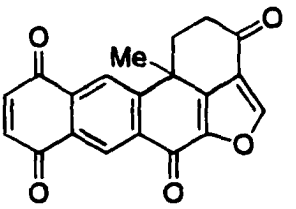
CHAPTER 3. SYNTHETIC APPROACH TO NATURAL ANALOGUES OF HALENAQUINONE

A paper, a portion of which will be submitted to *J. Org. Chem.*

George A. Kraus and Zhiwen Wan

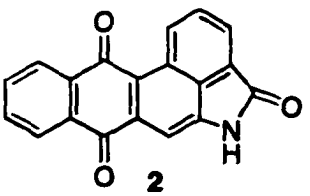
Introduction

In recent years, marine natural compounds have attracted much interest because of their biological activities and structural variety. Many novel biologically active compounds have been isolated from marine sponges. In 1983, Clardy and co-workers reported a most unusual quinone from a tropical sponge collected in a Western Carolina Island[1].



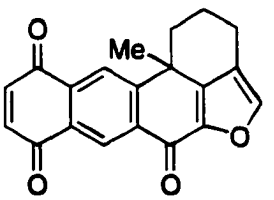
Halenaquinone (**1**)

Clardy[1] gave the name halenaquinone to the structure. A study of the biological activity of halenaquinone (**1**) by Clardy showed that halenaquinone possessed *in vitro* antibiotic activity against *Staphyococcus aureus* and *Bacillus subtilis*. At that time, the closest literature analogue was quinone **2**. The structure of halenaquinone was later determined by X-ray crystallographic structure analysis and its absolute stereochemistry was determined by Harada[2] in 1989.

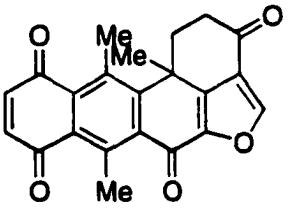


2

In 1985, Nakamura[3] reported another biologically active metabolite from the Okinawan sea sponge *Xestospongia sapra*. He called it xestoquinone (**3**). The structure was similar to halenaquinone. He found that xestoquinone showed powerful cardiotonic activity and a marked inotropic action. It also caused a concentration-dependent inhibitory effect on Na, K-ATPase isolated from pig cerebral cortex. Xestoquinone was the first example of a marine natural product having parallelism between the inotropic action and Na, K-ATPase inhibition. More recently, Schmitz and a co-worker isolated furanone compounds including **3** from a marine sponge, *Adocia sp.* From Truk Lagoon[4]. They also revealed that some of the novel marine natural products showed cytotoxicity.

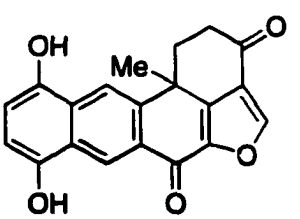


Xestoquinone (**3**)

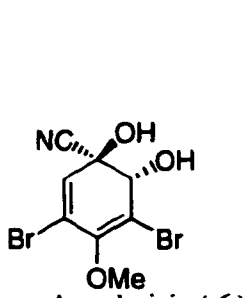


11, 18-dimethyl-9-hydroxyhalenaquinone (**4**)

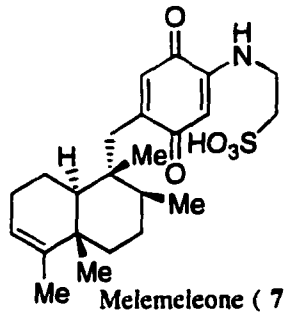
In 1998, Scheuer and co-workers examined a sample of an undescribed species of *Xestospongia* from Derawan Island in Indonesia, and found 11,18-dimethyl-9-hydroxylhalenaquinone (**4**)[5]. By studying the effects of halenaquinone (**1**), xestoquinone (**3**), and some non-natural analogues as protein tyrosine kinase inhibitors, Lee and co-workers found that halenaquinone was a potent irreversible inhibitor of PTKs.[6] Halenaquinol **5**, the corresponding hydroquinone, was also as potent as the quinone.[7] They are among the most potent kinase inhibitors reported to date. In fact, only two other compounds, aeroplysin (**6**) and melemelone (**7**), have shown similar PTK activity.[6] Surprisingly, xestoquinone showed less PTK activity.



Halenaquinol (**5**)



Aeroplysinin (**6**)



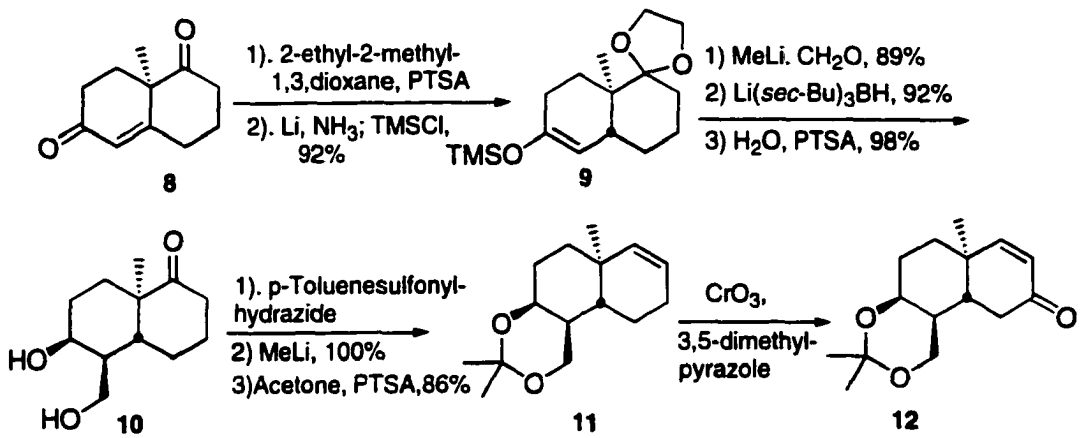
Melemeleone (**7**)

In 1993, Tsuji and co-workers discovered that halenaquinone (**1**) and xestoquinone (**3**) were potent inhibitors of topoisomerase I purified from the nuclei of the mouse leukemic cell L1210.[8] Topoisomerase I and topoisomerase II are important targets for antitumor agents. In last few years, three total syntheses have been reported and a few approaches have been communicated.

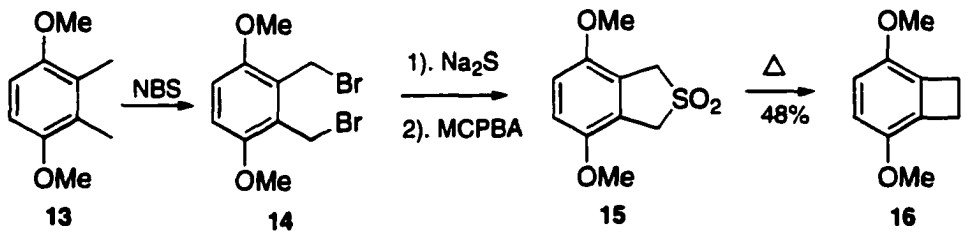
Harada's synthesis[9]

Harada began his synthesis with enantiomerically pure Wieland-Miescher ketone **8** (Scheme 1). The carbonyl group at C-1 was selectively protected. Reduction in liquid ammonia and TMSCl quenching afforded trimethylsilyl enol ether **9**. The anion generated by treating **9** with MeLi reacted with gaseous formaldehyde to give a hydroxy ketone. Lithium tri-*sec*-butylborohydride reduction and deprotection of carbonyl groupgave keto diol **10**. Formation of the hydrazone of **10** followed by treatment with MeLi, and glycol protection gave acetonide **11**. Allylic oxidation afforded enone **12**.

The second part of the work was synthesis ofthe diene (Scheme 2). The bromination of **13** under radical condition gave dibromide **14**. Treatment of **14** with sodium sulfide followed by MCPBA oxidation afforded sulfone **15**. Sulfone **15** was heated at 305 °C-310 °C to give **16** in 48% yield.

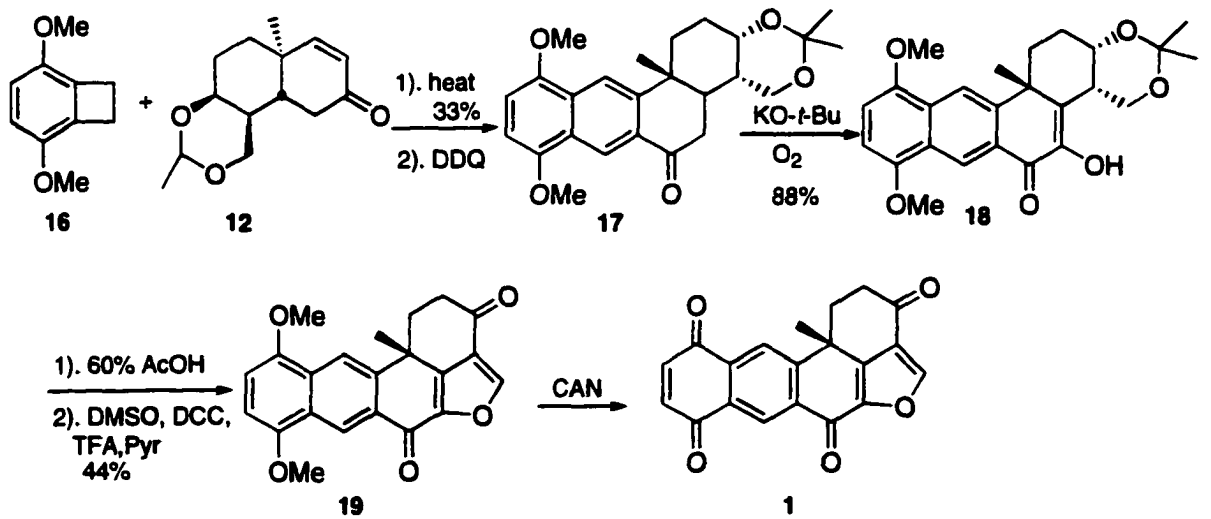


Scheme 1



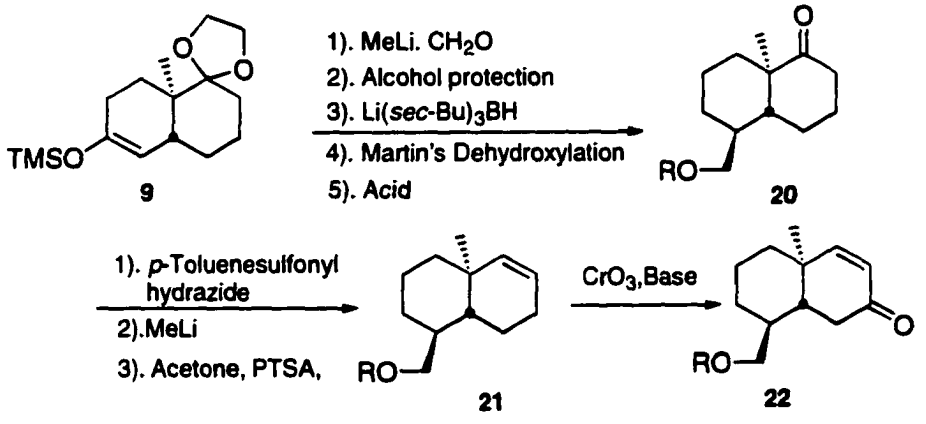
Scheme 2

Compounds **16** and **12** were heated a sealed tube at 210 °C for 20 hours (Scheme 3). DDQ oxidation gave **17** in 30% yield. Ketone **17** in *tert*-BuOH with KO-*tert*-Bu and air to give **18** in 80 % yield. Deprotection of the acetonide in **18** and Swern oxidation afforded **19**. Halenaquinone was obtained by oxidation of **19**.

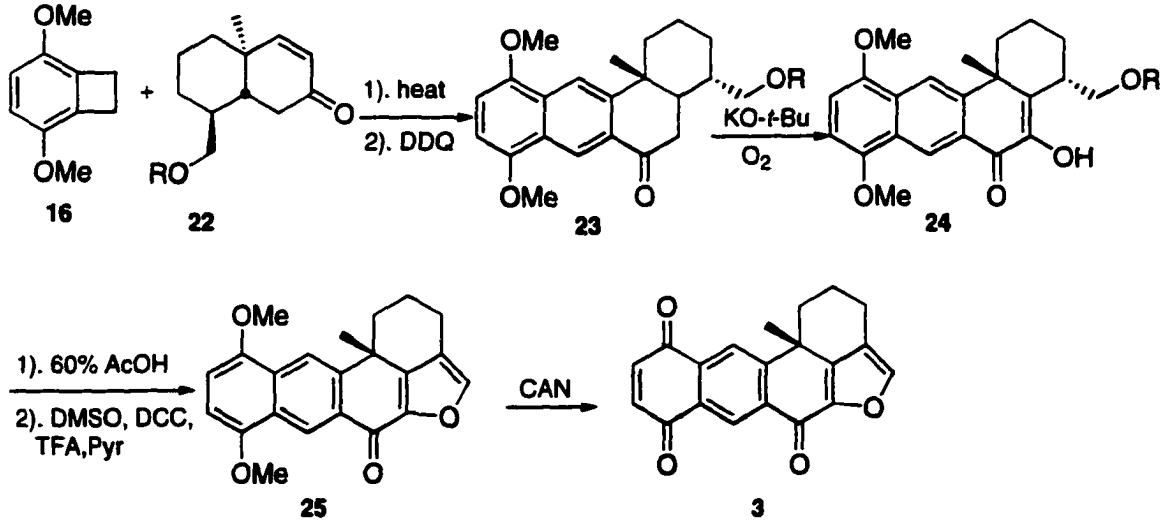


Scheme 3

Xestoquinone was also synthesized by Harada.[10] Treatment of **9** with MeLi and gaseous formaldehyde gave a β-hydroxyketone (Scheme 4). Protection of the alcohol, reduction of the carbonyl group, dehydroxylation, and deprotection gave ketone **20**. The same procedures used to generate enone**12** were then used to generate **22**.
Compounds **16** and **22** were heated for 10 hours (Scheme 5). DDQ oxidation gave **23** in 32% overall yield. Ketone **23** was oxidized to afford **24**. Deprotection of the acetonide of **24** and Swern oxidation generated **25**. It was oxidized to produce xestoquinone (**3**).



Scheme 4



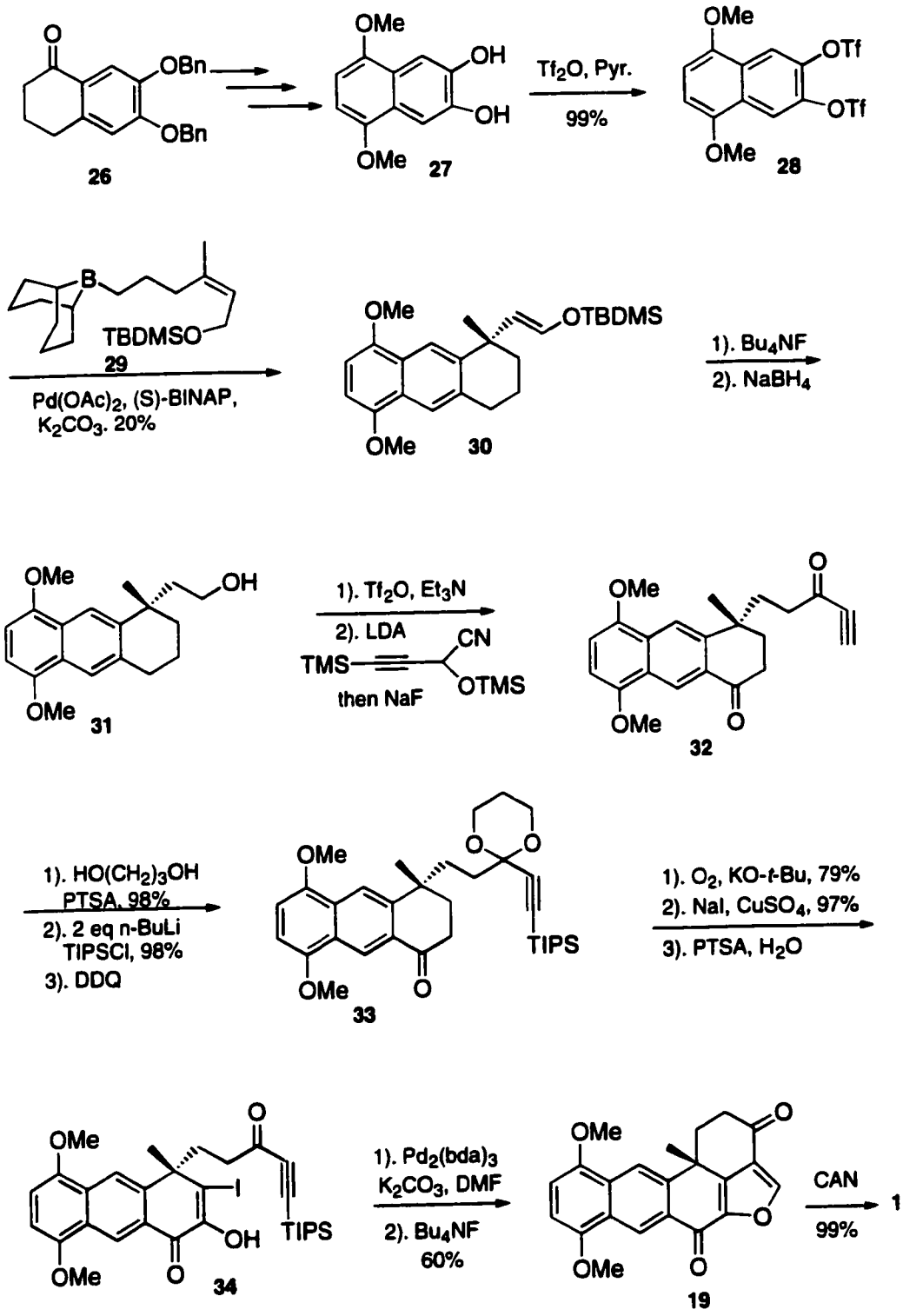
Scheme 5

Shibasaki's synthesis[11]

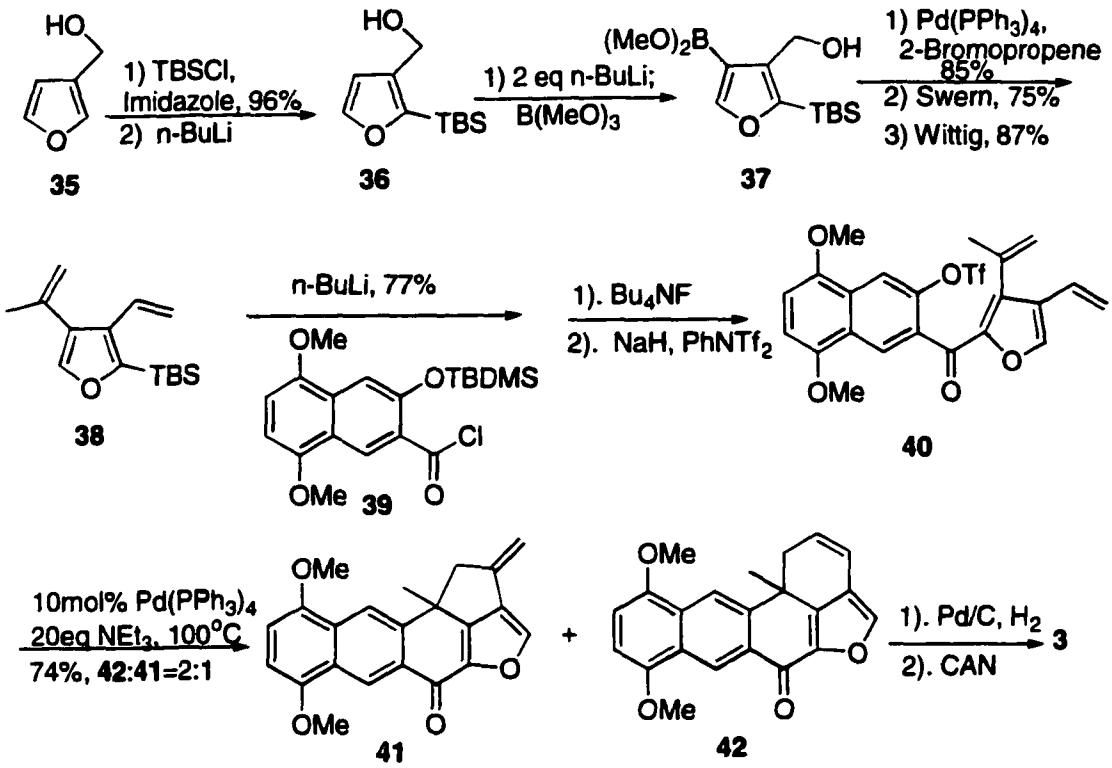
In 1998, Shibasaki and co-workers described an asymmetric total synthesis of halenaquinone via a Suzuki cross-coupling and an asymmetric Heck reaction. The synthesis (Scheme 6) started with the catechol **27**, which was obtained from tetralone **26** in 4 steps. Compound **27** was converted into **28** in 99% yield. Product **30** was obtained from bistriflate **28** and **29** via a tandem Suzuki coupling and Heck reaction in 20 % yield with 85% ee. With large quantities of **30** in hand, they were ready to pursue a catalytic asymmetric synthesis of **1**. Compound **30** was converted into an aldehyde. Sodium borohydride reduction gave alcohol **31**. Compound **31** was transformed into a triflate. It was converted into ketone **32**. After protection of the carbonyl group and silylation of acetylene, **32** was oxidized to give **33**. The reaction of **33** with oxygen in presence of a base followed by iodination and deprotection gave **34**. Treatment of **34** with a palladium reagent followed by desilylation afforded **19** in 60% yield. Compound **19** was converted into **1** by oxidation.

Keay's synthesis[12]

In 1996, Keay and co-workers reported another asymmetric palladium catalyzed synthesis of the pentacyclic ring system. The synthesis started with furan **35** (Scheme 7). Treatment of **35** with TBDMSCl and imidazole followed by BuLi treatment gave **36**. The dianion from **36** was quenched with trimethylborate gave **37**. Suzuki coupling, Swern oxidation and Wittig olefination generated **38**. The anion from **38** reacted with **39** to give a ketone. Desilylation and triflate formation, provided **40**. Compound **40** was cyclized in the presence of (S)-(+)-BINAP to give **42** and **41** in a 2 to 1 ratio. Compound **42** converted into **3** by hydrogenation and oxidation.


OBn
OBn
26
OMe
OH
OH
OMe
27
Tf2O, Pyr.
99%
OMe
OTf
OTf
OMe
28
B
TBDMSO
29
Pd(OAc)2, (S)-BINAP,
K2CO3. 20%
OMe
OTBDMS
OMe
30
1). Bu4NF
2). NaBH4
OMe
OH
OMe
31
1). Tf2O, Et3N
2). LDA
CN
TMS
OTMS
then NaF
O
OMe
O
OMe
32
1). HO(CH2)3OH
PTSA, 98%
2). 2 eq n-BuLi
TIPSCl, 98%
3). DDQ
O
O
OMe
TIPS
OMe
O
33
1). O2, KO-t-Bu, 79%
2). NaI, CuSO4, 97%
3). PTSA, H2O
O
OMe
I
OH
TIPS
OMe
O
34
1). Pd2(bda)3
K2CO3, DMF
2). Bu4NF
60%
O
OMe
O
OMe
O
19
CAN
99%
1

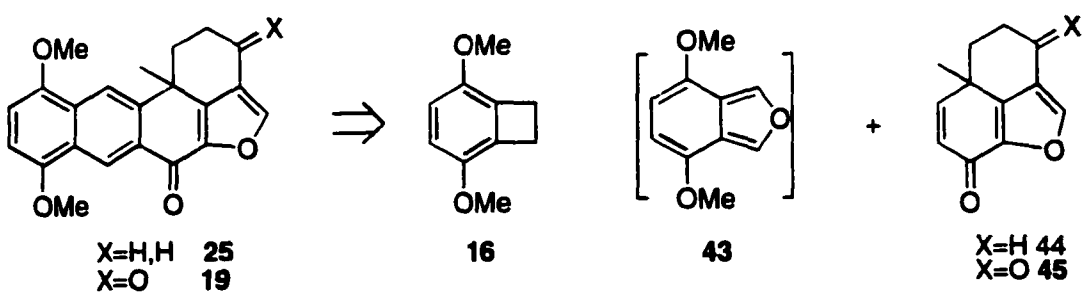
Scheme 6



Scheme 7

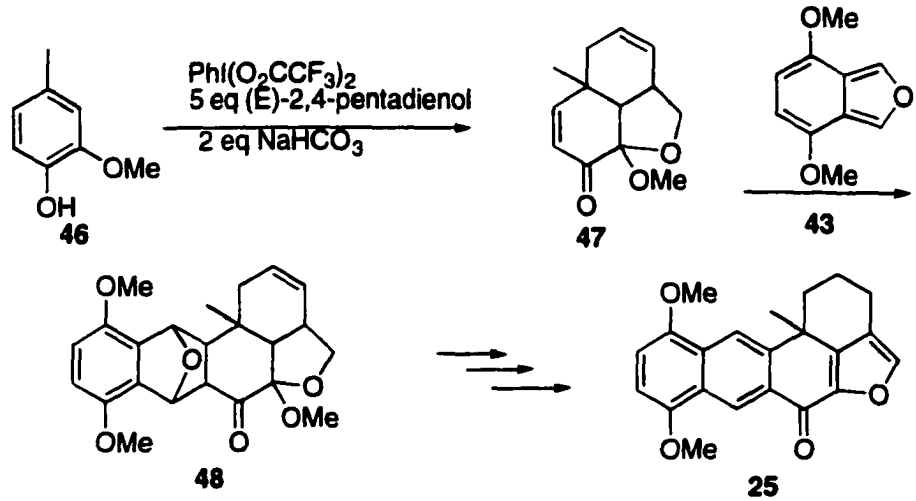
Synthetic approaches to halenaquinone

Several synthetic approaches have been reported in the past few years. Most of the approaches have focused on the development of the Diels-Alder precursors **44** and **45** (Scheme 8). The halenaquinone skeleton was constructed by the Diels-Alder reaction of either diene **16** or benzofuran **43**.



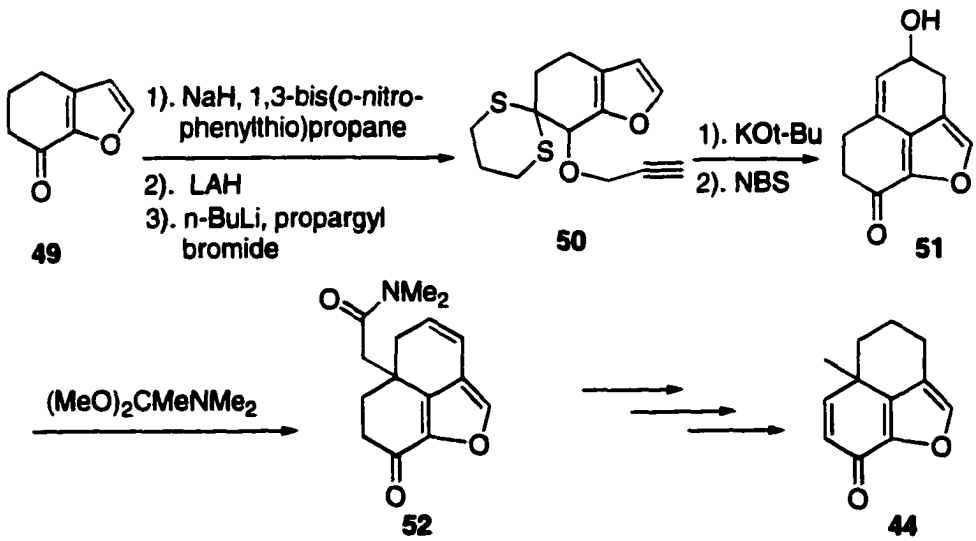
Scheme 8

One of the approaches was reported by Carlini and co-workers in 1997 (Scheme 9).[13] Oxidation of phenol **46** in the presence of an excess of 2,4-pentandien-1-ol gave the Diels-Alder product **47**. Compound **47** reacted with **43** to give **48**. Xestoquinone was obtained from **48** by standard procedures.



Scheme 9

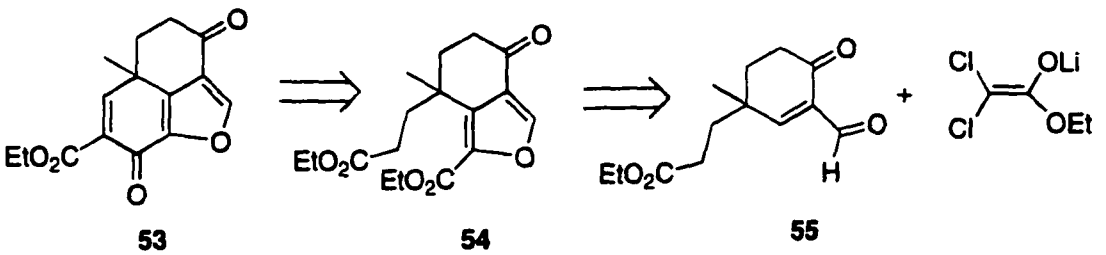
Another unique strategy was described by Kanematsu and co-workers in 1991.[14] They developed a furan synthesis for synthesis of halenaquinone (Scheme 10). Oxidation of **49** by a known procedure followed by LAH reduction and ether formation generated **50**. Rearrangement of **50** provided **51**. The Claisen rearrangement of **51** provided **52**. Ketone **52** was transformed into ketone **44**.



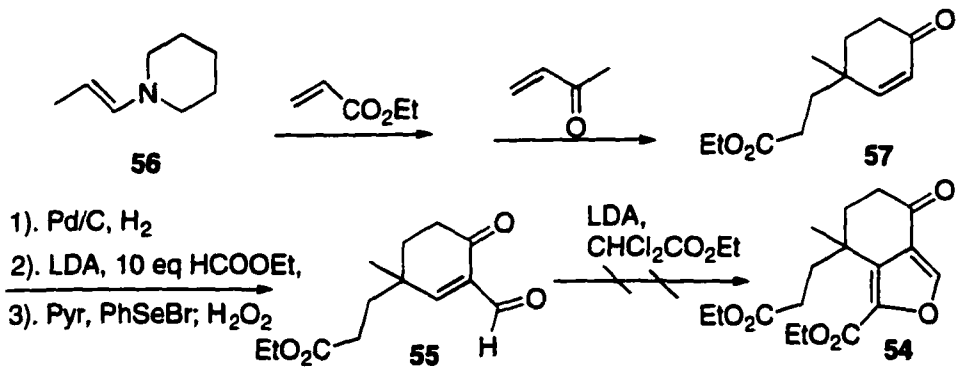
Scheme 10

Results and Discussion

Our retrosynthetic analysis is shown in Scheme 11. To examine this strategy, we generated cyclohexenone **57** *via* one-pot double Michael addition and cyclization (Scheme 12).[15] The precursor **55** was prepared from **57** by a sequence of reactions involving hydrogenation, aldehyde formation and alkene formation. Unfortunately, the reaction of cyclohexenone **55** with the anion of ethyl dichloroacetate did not give furan **54**. The failure may be attributed to steric hindrance.



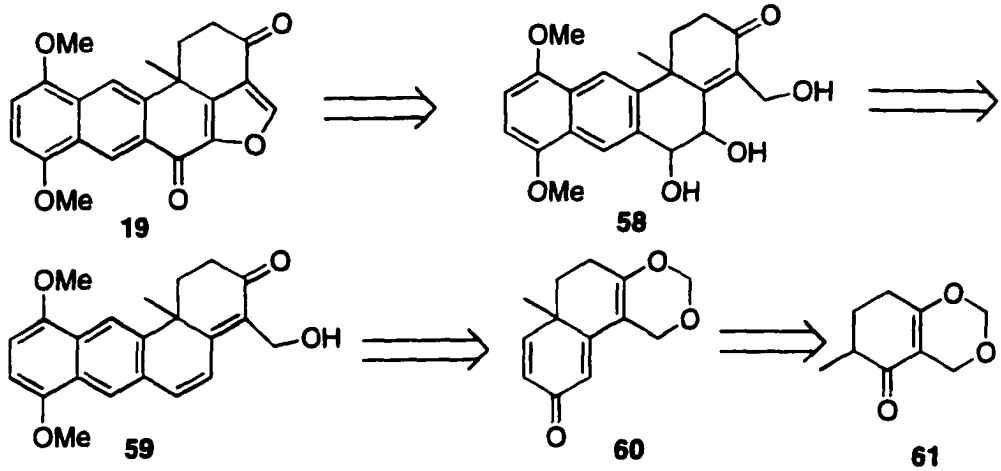
Scheme 11



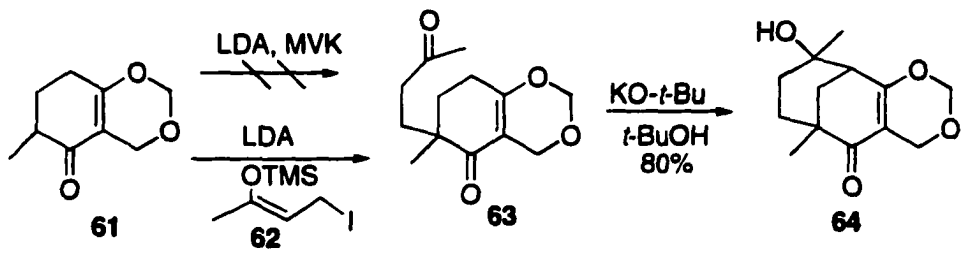
Scheme 12

The next retrosynthetic analysis is shown in Scheme 13. Triol **58** was a key intermediate. Compound **59** was planned to come from **60**.

The synthesis started with the known compound **61**.[16] Although Robinson annulation reaction with methyl vinyl ketion (Scheme 14), the alkylation of **61** with **62**[17] gave **63** in 80% yield. Following the same procedure as in the synthesis of hibiscone C, **63** was treated with excess potassium tert-butoxide in *tert*-BuOH to give **64**.

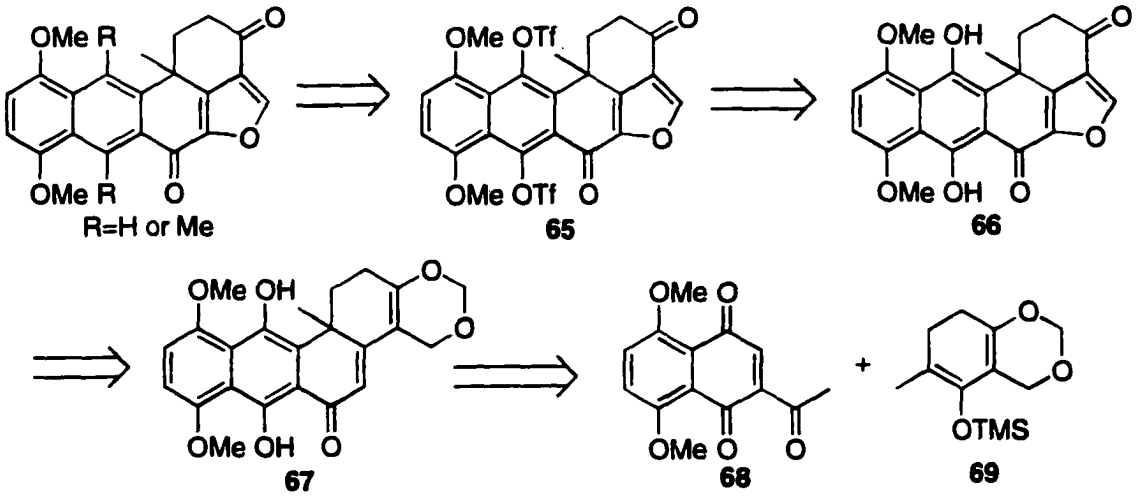


Scheme 13



Scheme 14

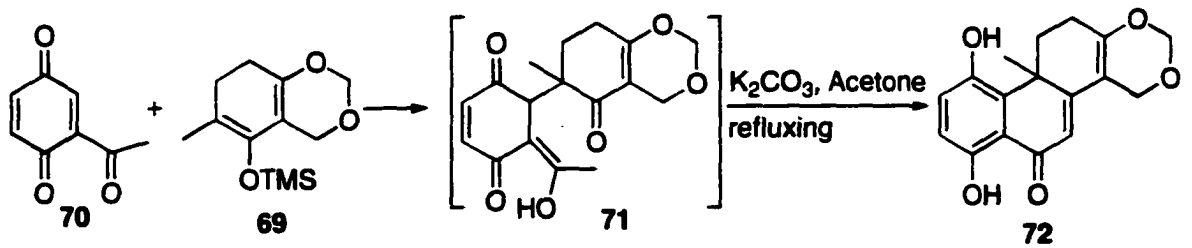
The next retrosynthetic analysis is shown in Scheme 15. The reaction sequence involving Michael addition followed by annulation was utilized by our group to make 3-deoxyrabelomycin.[18] Quinone **68** and silyl enol ether **69** could react to give the required cyclization product **67**. A procedure similar to that employed for the synthesis of hibiscone C would then be used to generate furan **66**. The triflate chemistry would then be used to convert the dihydroxy group to R = H or R = Me.



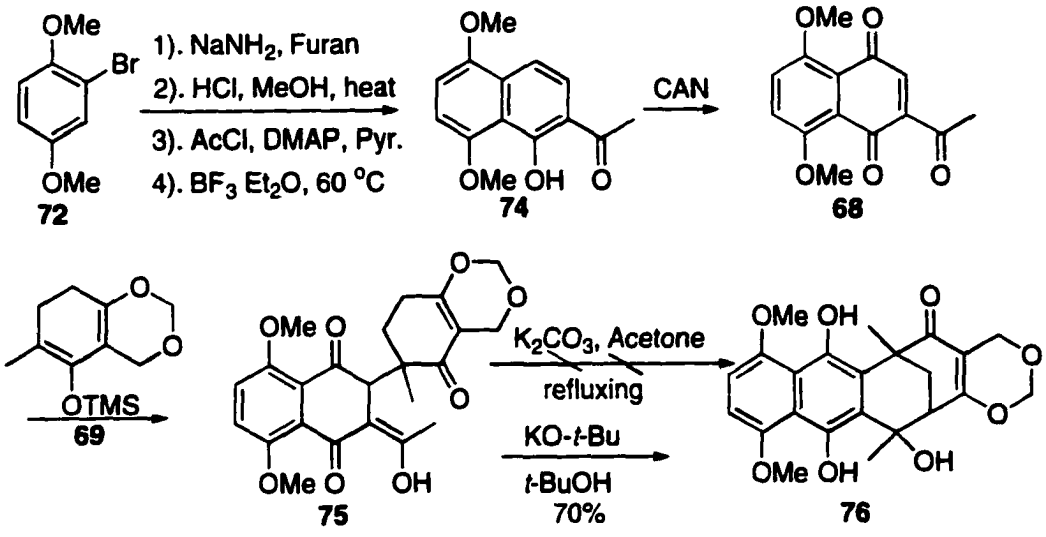
Scheme 15

To evaluate this strategy, we started with a simple model system. Readily available quinone **70**[19] was selected for this purpose. The reaction of silyl enol ether **69** reacted with **70** in methylene chloride gave intermediate **71**. Aromatization of **71** with potassium carbonate in acetone resulted in the generation of the cyclization product **72** (Scheme 16).

With this successful cyclization, we started the synthesis of halenaquinone. Naphthoquinone **68**[20] was prepared in modest yield by oxidation of **74**, which, in turn, was prepared *via* a Diels-Alder reaction, aromatization, phenol acetate formation and Fries rearrangement (Scheme 17). Quinone **68** reacted with enol silyl ether **69**, giving Michael addition intermediate **75**. The model system procedure was used for the aromatisation or cyclization of **75**. Unfortunately, **75** was recovered after boiling with potassium carbonate in acetone. When potassium *tert*-butoxide in t-BuOH was used instead of potassium carbonate, cyclization product **76** was isolated as the only product.

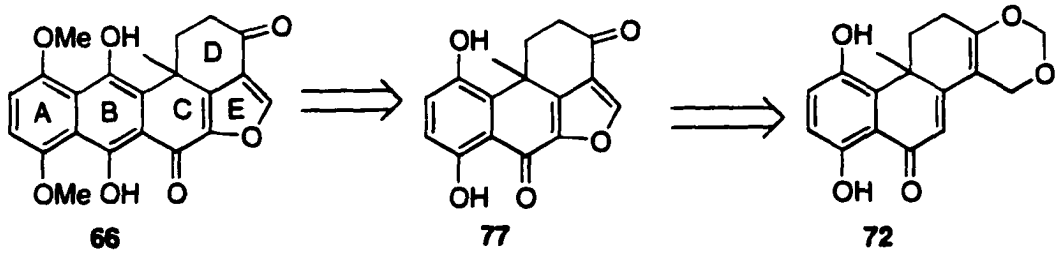


Scheme 16

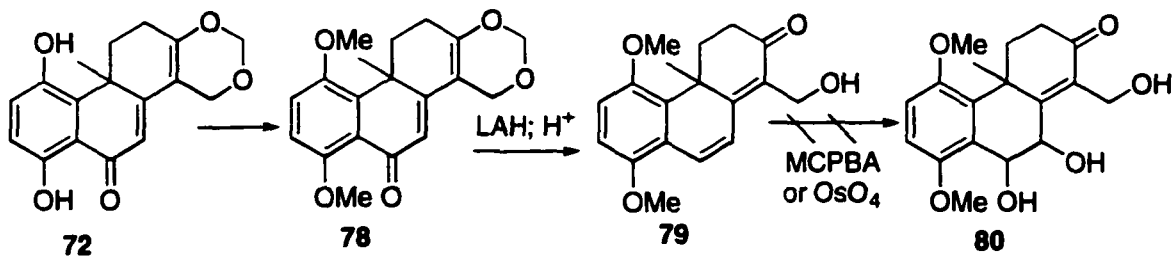


Scheme 17

We then dedicated to add the A ring *via* a Diels-Alder reaction. The retrosynthetic analysis is shown in Scheme 18. Before we started to study the Diels-Alder reaction, we needed to test the strategy for making the furan. We tried to generate furan **77** from **72** by the procedure used to synthesized hibiscone C. Compound **72** wasconverted into ether **78** (Scheme 19). The reduction of **78** with LAH followed by acid mediated rearrangement gave **79**. However, the γ,δ-double bond could not be oxidized with either osmium tetraoxide or MCPBA.



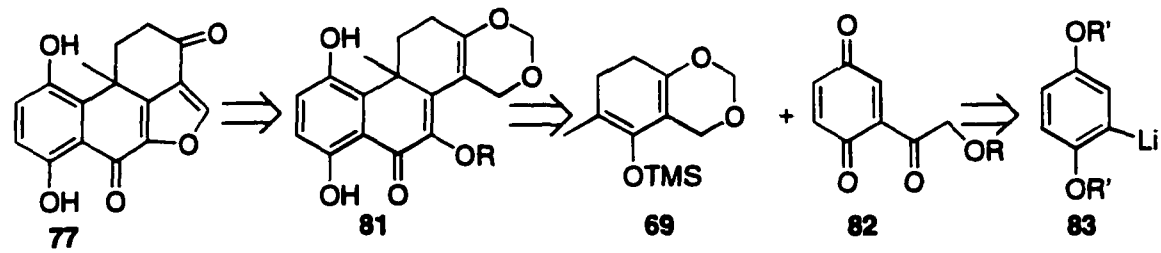
Scheme 18



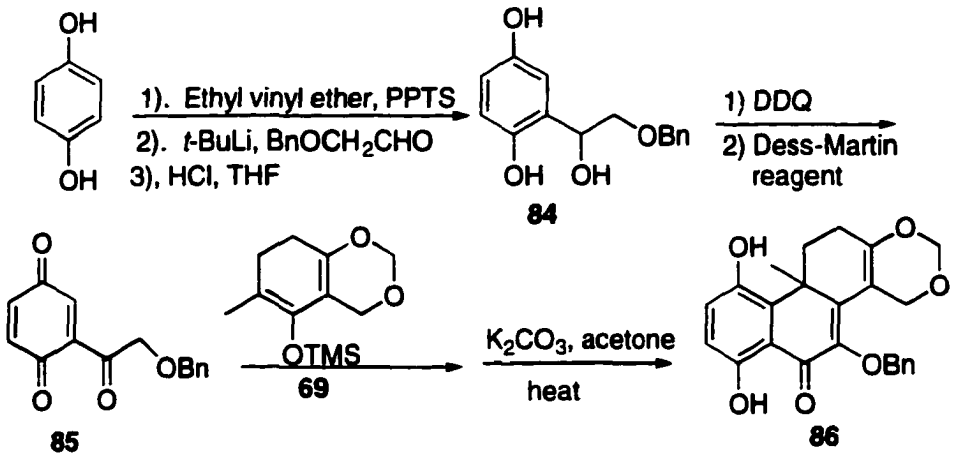
Scheme 19

We next decide to introduce the alkoxy group onto quinone. Compound **82** could be prepared from anion **83** (Scheme 20).

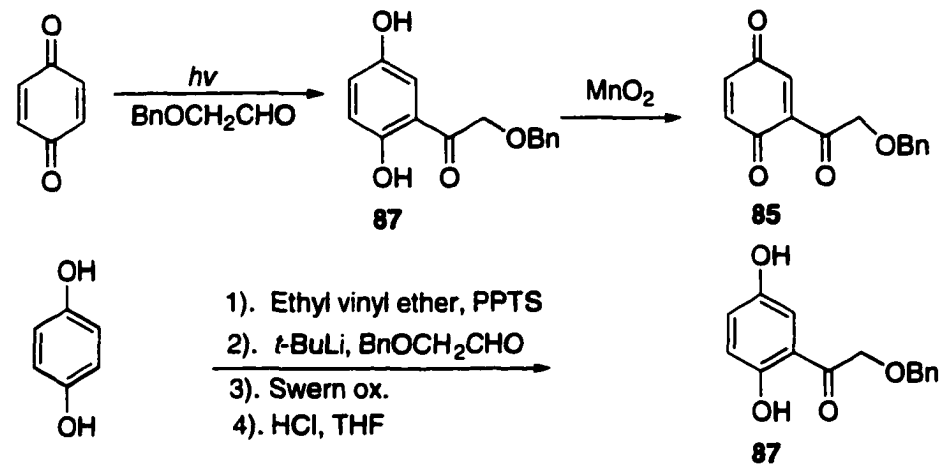
We generated the side chain *via* an anion of a protected hydroquinone. Protected hydroquinones were deprotonated by *tert*-BuLi.[21] Hydroquinone **84** was obtained from a sequence of reactions involving protection of hydroquinone with ethyl vinyl ether and PPTS, anion generation, anion quenching with α-benzyloxylacetaldehyde,[22] and deprotection with acid. Quinone **85** was prepared by two-step oxidation. Both MnO_2 and DDQ oxidation of **84** gave a hydroxyquinone.[23] The Dess-Martin oxidation provided quinone **85**. Two equivalents of the Dess-Martin reagent oxidized **84** to **85**, but the yield was poor. The sequence of DDQ and Dess-Martin oxidation provided the best yield of **85**. With **85** in hand, the tetracyclic product **86** was obtained by Michael addition followed by base-induced cyclization (Scheme 21). Compound **85** was also obtained *via* a photochemical reaction (Scheme 22).[24] Irradiation of benzoquinone and α-benzyloxylacetaldehyde afforded **87** in good yield based on ^1H NMR.



Scheme 20

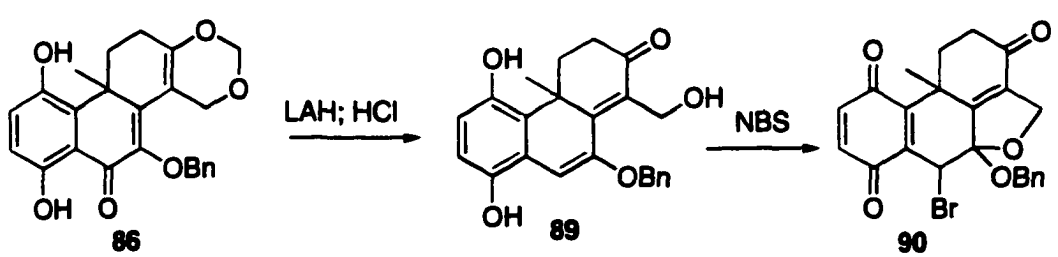


Scheme 21



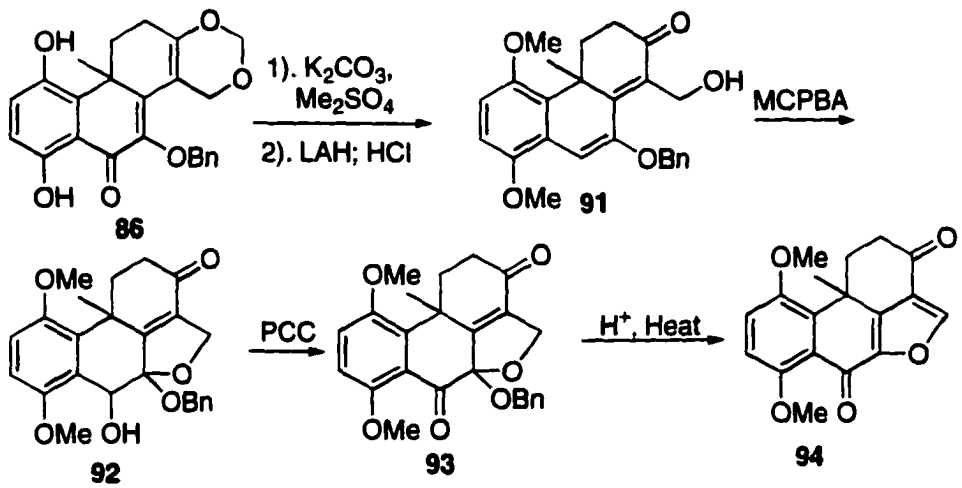
Scheme 22

The reduction of **86** with excess LAH in THF followed by rearrangement produced stable enol ether **89**. Treatment of **89** with 3 equivalents of NBS in acetonitrile gave bromoquinone **90** (Scheme 23). However, the reaction of **90** with 1-trimethylsilyloxybutadiene or 1,1,4-trimethoxybutadiene[25] gave low yields.



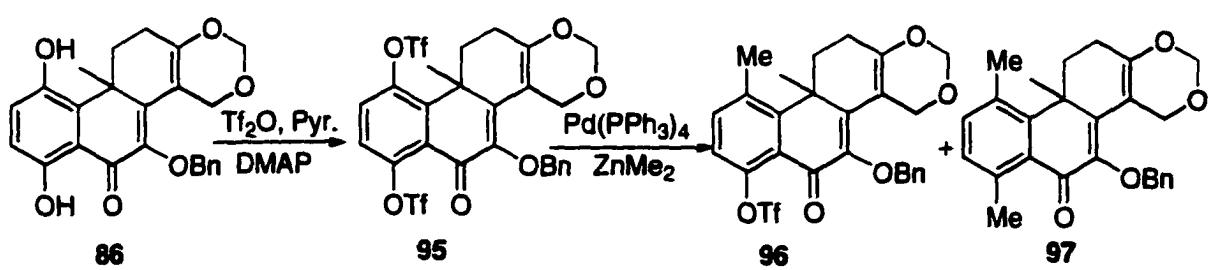
Scheme 23

Hydroquinone **86** was the protected. Treatment of the protected compound with LAH followed by acidic rearrangement afforded enol ether **91** in almost quantitative yield. MCPBA oxidation of **91** provided alcohol **92**. Alcohol **92** was oxidized with PCCto afforded ketal **93**. Finally, furan **94** was obtained by boiling **93** with concentrated HCl in MeOH (Scheme 24).



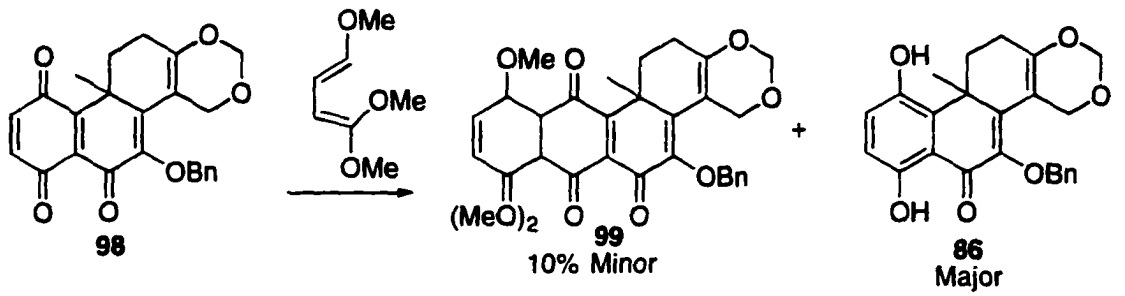
Scheme 24

After the successful preparation of a furan, we evaluated the conversion of the hydroquinone unit into a xylene unit. Compound **86** was used to examine this strategy (Scheme 25). Compound **86** was treated with excess Tf_2O, pyridine and DMAP to give **95**. Treatment of **95** with a palladium catalyst and excess dimethyl zinc in boiling benzene afforded a mixture of **96** and **97**.[26] The yield of **97** was improved by a longer reaction time.



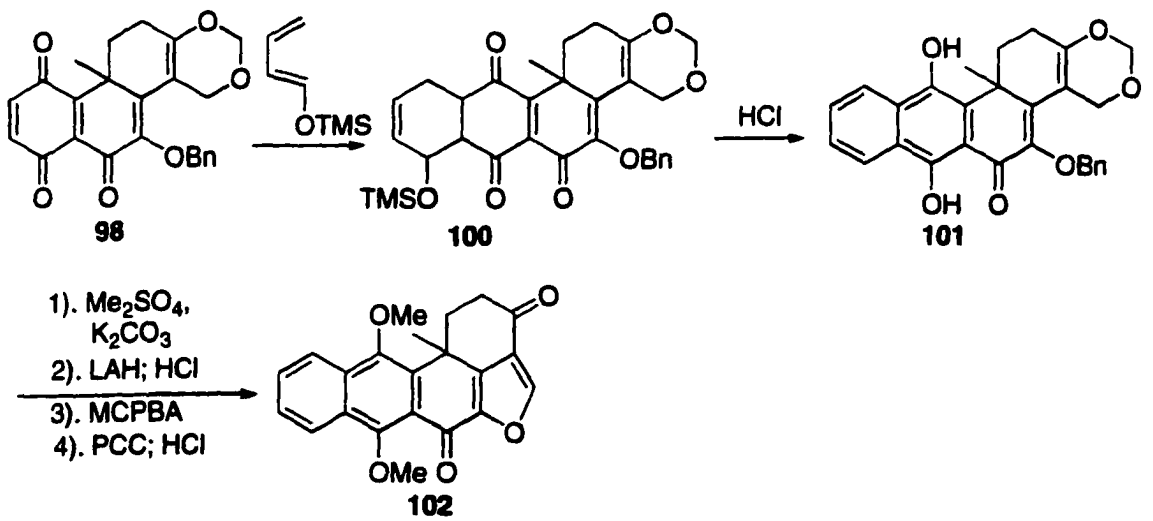
Scheme 25

The next problem we faced was the Diels-Alder reaction to generate the A ring.. Quinone **98**, which was obtained by oxidization of **86** with MnO_2, reacted with 1,1,4-trimethoxylbutadiene. The major product was the reduced product **86**. The Diels-Alder product **99** was produced in less than 10% yield (Scheme 26).



Scheme 26

However, treatment of **98** with 1-trimethysilyloxybutadiene produced the regioselective Diels-Alder product **100**. Treatment of **100** with acid provided hydroquinone **101**. Furan **102** was obtained by phenol protection, LAH reduction, acid rearrangement, MCPBA oxidation, PCC oxidations, and acid treatment (Scheme 27).

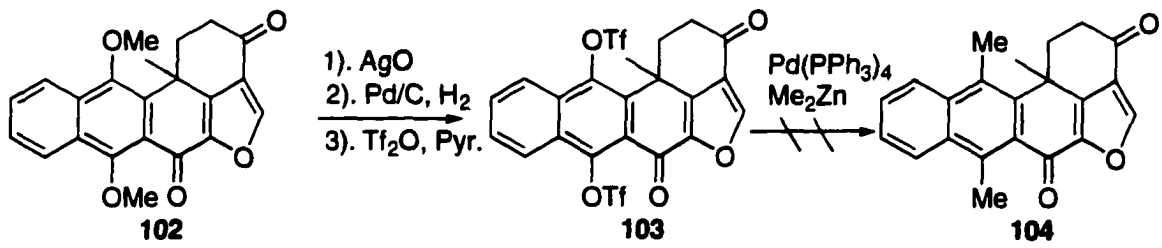


Scheme 27

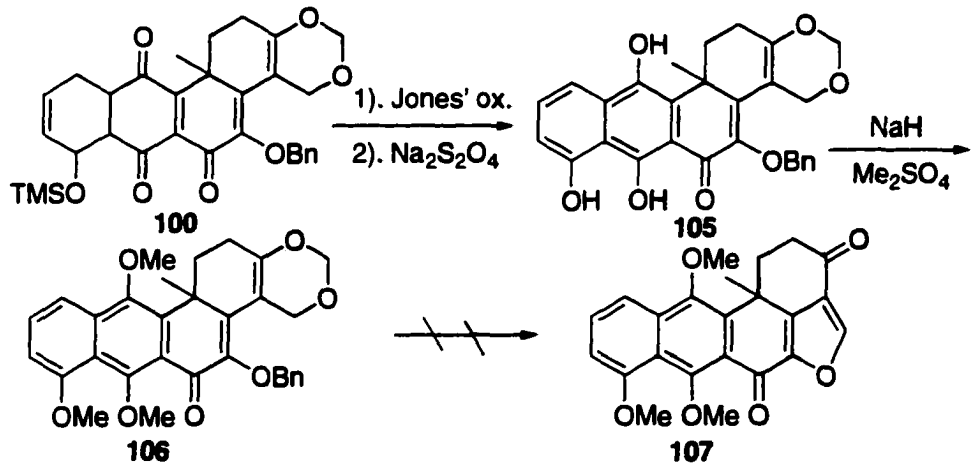
With **102** in hand, we were able to examine the bis-triflate strategy in this pentacyclic system. Compound **102** was demethylated by a two-step reaction sequence involving oxidation with silver(II) oxide and nitric acid to a quinone and then hydrogenation to the hydroquinone. The hydroquinone was converted into a bis-triflate **103** with

trifluoromethanesulfonic acid anhydride, pyridine and DMAP. However, bis-triflate **103** did not give the dimethyl product **104**. It decomposed upon treatment with dimethyl zinc and a palladium catalyst (Scheme 28).

We next studied the oxidation of the A ring to a quinone. Treatment of adduct **100** with Jones' reagent at 0 °C followed by sodium hydrosulfite reduction, gave triol **105**.[27] Protection of **105** with excess sodium hydride and dimethyl sulfate gave product **106**. However, **106** could not be transformed into furan **107**. The MCPBA oxidation led to demethylation, which interfered with the PCC oxidation (Scheme 29).

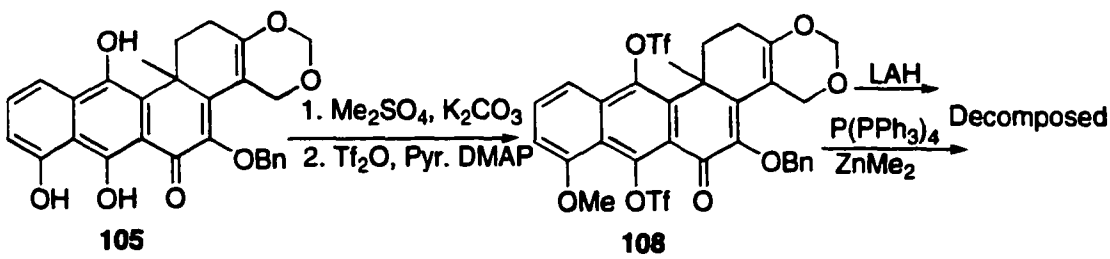


Scheme 28



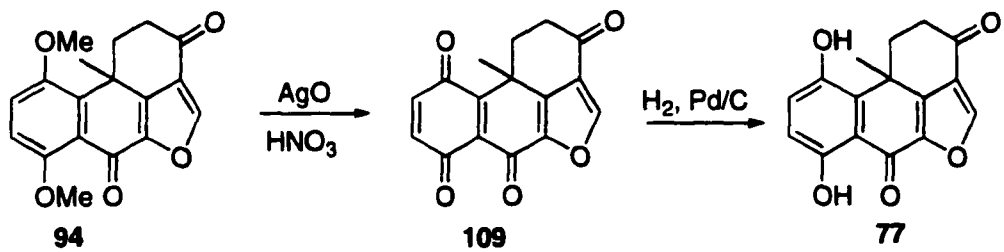
Scheme 29

we decided to convert the hydroquinone unit into the xylene unit. Compound **105** was prepared with 1.2 equivalents of dimethyl sulfate and potassium carbonate. The intermediate was treated with excess Tf_2O and pyridine to afford bis-triflate **108**. Unfortunately, it decomposed during LAH reduction or reaction with dimethyl zinc with a palladium catalyst (Scheme 30).



Scheme 30

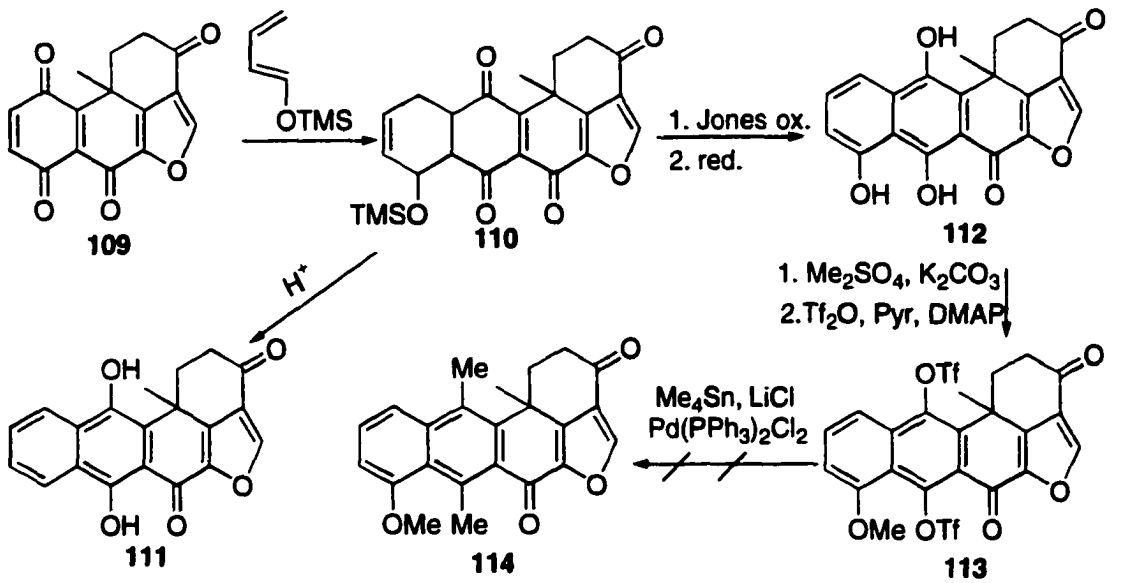
We then returned to furan **94** and hoped that the furan would be more stable. Treatment of **94** with silver(II) oxide and 6 N nitric acid followed by hydrogenation produced hydroquinone **77**. Compound **77** will be tested to understand the structure-activity relationships in the halenaquinone system(Scheme 31).



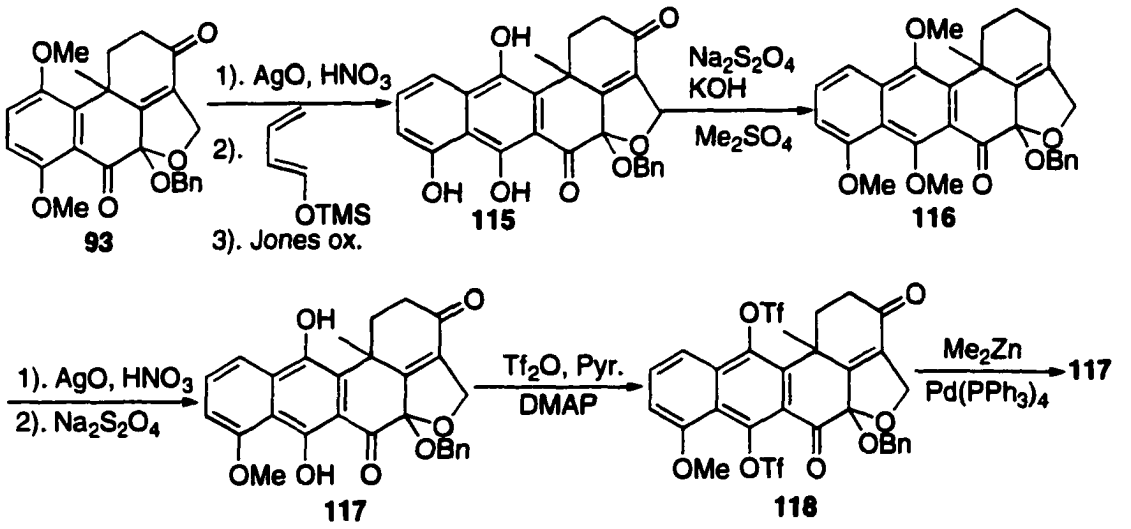
Scheme 31

Quinone **109** was treated with trimethylsilyloxybutadieneto give **110.** Treatment of **110** with acid gave **111**(Scheme 32), which also will be tested to develop the structure-activity relationships. When Jones' reagent was used instead of acid, triol **112** was obtained. Monoprotection of **112** followed by treatment with excess Tf_2O and pyridine produced ditriflate **113.** However, treatment of **113** with $Pd(PPh_3)_2Cl_2$, tetramethyl tin and lithium chloride did not generate methylation product **114.**[28] The crude product had no furan proton.

The best opportunity to achieve the synthesis had been the route starting with the furan precursor **93.** The ketal structure might be stable to the methylation reaction (Scheme 33). Triol **115** was obtained by a Diels-Alder reaction and a Jones' oxidation of **93.** Methylation of **114** *via* a procedure for the reductive methylation of hydroxy quinones generated triether **116.**[29] Oxidation of **116** with AgO followed by the reduction with $Na_2S_2O_4$ in pH 7 buffer solution provided **117.** With **117** in hand, bis-triflate **118** was prepared. Unfortunately, **117** was obtained when **118** was heated in benzene with dimethyl zinc and a palladium catalyst.



Scheme 32



Scheme 33

Conclusion

We have demonstrated a unique pathway to the furan skeleton of halenaquinone *via* a sequence of reactions involving Michael addition, cyclization and Diels-Alder reaction. In addition, analogs of halenaquinone were produced for a structure-activity relationship study of this anti-cancer reagent. The intermediates generated here have the potential for eventual transformation into halenaquinone.

Experimental

Unless otherwise noted, the materials used in the experiments for this research were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene, dichloromethane, acetonitrile, toluene, diisopropylamine were distilled from calcium hydride. The reactions were conducted in a nitrogen atmosphere and the organic extracts were dried with magnesium sulfate. The melting point was determined on a Fisher-Johns apparatus and was not corrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer and nuclear magnetic resonance spectra were determined on a Nicolet Magnetics Corporation NMR-1280 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), and m (multiplet). The addition of br indicates a broadened pattern.

The glass apparatus were flame-dried and cooled under the steam of nitrogen. Flash column chromatography was conducted using Neutral or Basic Aluminium (Brockmann) standard grade (150 mesh) from Aldrich Chemical Company and Silica Gel (EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F254 prepared plates with a thickness of 0.25 mm. High resolution MS was obtained from Kratos Model MS-50 spectrometer and low resolution MS was obtained from a Finnegan 4023 Mass spectrometer.

1-(2, 5-dihydroxyphenyl)-2-benzyloxyethanol (84).

PPTS (0.1 g) and ethyl vinyl ether (100 mL, 1.1 mol) was added to hydroquinone (22 g, 200 mmol) in methylene chloride (200 mL). The resulting solution was stirred overnight. Water (100 mL) was added, and the organic layer was separated and washed with sodium hydroxide (1N, 100 mL) and brine (100 mL), then dried with magnesium sulfate. After removal of the solvent, the pure 2,5-di (1-ethoxyethoxyl) benzene[21] was obtained by distillation under reduced pressure.

N-BuLi (1.7 M in hexane, 40 mL, 68 mmol) was added dropwise to 2,5-di (1-ethoxyethoxyl) benzene (12.7 g, 50 mmol) in dry diethyl ether solution at 0 °C under nitrogen. After 3 hours, the resultant light yellow solution was cooled to –78°C and α-benzoxyacetaldehyde[22] (10.5 g, 70 mmol) in diethyl ether (50 mL) was added in 5 minutes. The solution was then stirred for 6 hours and slowly warmed to 0°C. Water (50 mL) was added and the solution was acidified to pH 1 with hydrochloric (6 N). It took about 1 hour to completely remove the EVE protection group, which was monitored with TLC. Brine (100 mL) was then added and the organic layer was separated. The aqueous solution was extracted with ethyl ether (100 mL x 4). The organic layers were combined and washed with sodium bicarbonate (10%, 100 mL) and brine (100 mL), then dried with magnesium sulfate. After removal of the solvent, **84** (10.0 g, 80% yield) was obtained from flash column chromatography eluted with a mixture of ethyl acetate and hexanes (1:1). It was transferred to quinone at once. ^{1}H NMR ($CDCl_3$, δ): 7.70 (br, 1 H), 7.20-7.35 (m, 5 H), 6.67 (d, J = 6 Hz, 1H); 6.59 (dd, J = 6 Hz; 1 Hz, 1H), 6.44 (d, J = 1 Hz, 1H), 4.69 (br, 1H), 4.89 (dd, J = 6 Hz; 1Hz, 1H), 4.54 (dd, J = 9 Hz; 9 Hz; 2H), 3.55-3.65 (m, 2H), 3.41 (br, 1H). ^{13}C NMR ($CDCl_3$, δ): 149.3, 148.9, 137.2, 128.7, 128.2, 128.1, 124.2,118.2,116.2, 114.3, 73.6, 73.7, 73.5.

2-(2-Benzyloxy-1-hydroxyethyl)-1,4-benzoquinone

The 2,3-dichloro-5, 6-dicyano-1,4-benzoquinone (DDQ) (4.6g, 20 mmol) was added to the solution of **84** (5.2 g, 20 mmol) in methylene chloride (100 mL). After 1 hour, the solution was filtered and the filtrate was concentrated. A 2-(2-Benzyloxyl-1-hydroxyethyl)-1,4-benzoquinone was obtained after flash column chromatography (5.0 g, 99% yield). ^{1}H NMR ($CDCl_3$, δ): 7.28-7.39 (m, 5H), 6.92 (s, 1H), 6.74 (dd; J = 7 Hz, 2H), 4.9-5.0 (m, 1H), 4.57 (dd, J = 12 Hz, 2H), 3.79 (dd, J = 9 Hz; 3Hz, 1H), 3.43 (dd, J = 9Hz; 6Hz, 1H), 2.90 (d; J = 3 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ): 187.5, 187.1, 146.9, 137.4, 136.7, 136.5, 132.7, 128.6, 128.1, 127.9, 73.4, 72.9, 67.1. HRMS m/z: 258.0896, for $C_{15}H_{14}O_4$ calculated. 258.0892.

α-Benzyloxyacetyl-1, 4-benzoquinone (85).

A solution of Dess-Martin reagent (9.4 g, 22 mmol) in methylene chloride was added to the solution of 2-(2-Benzyloxyl-1-hydroxyethyl)-1,4-benzoquinone (5.2 g, 20mmol) in

methylene chloride (40 mL) under nitrogen. The reaction was monitored and completed in about 30 minutes. The solution was put on a short silicon gel column (3.5 cm x 5 cm) and flushed with a mixture of hexanes and ethyl acetate (3:1). The pure **85** was collected as an orange crystal (3.6 g, 71% yield), which was used at once in the next step. ^{1}H NMR ($CDCl_3$, δ): 7.3-7.4 (m, 5H), 7.02(d, J = 3 Hz, 1H), 6.84(dd, J = 9 Hz; 3Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 4.61 (s, 2H), 4.55 (s, 2H). ^{13}C NMR ($CDCl_3$, δ): 196.9, 186.8, 185.2, 142.1, 136.9, 136.6, 136.5, 135.9, 128.6, 128.3, 128.2, 75.6, 73.9.

6-Methyl-5-trimethylsiloxy-2,4,7,8-tetrahydrobenzo-1,3-dioxane (69)

Compound **60** (3.4g, 20 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol from BuLi and diisopropylamine) in THF (30 mL) at –78°C under nitrogen. The reaction was stirred at –78 °C for 1 hour and chlorotrimethylsilane (2.5 g, 23 mmol) was added to the reaction mixture. After 4 hours at –78 °C, pentane (100 mL) was added, and the resultant solution was washed with pH 7 buffer (30 mL) and dried with magnesium sulfate. Removal of the solvent produced the pure compound **68** (4.6 g, 92% yield), which was used at once. ^{1}H NMR ($CDCl_3$, δ): 0.95 (s, 2H), 1.0 (s, 2H), 2.20-2.25 (m, 4H), 1.62 (s. 3H), 0.20 (s; 9H). ^{13}C NMR ($CDCl_3$, δ): 148.5, 140.3, 106, 105.9, 90.5, 64.0, 27.9, 25.7, 16.3, 0.5.

5-Benzyloxy-7, 10-dihydroxy-10*b*-menthyl-2,4, 6, 10*b*, 11,12 -hexahydro-6-oxo-phenanthro [2,1-*d*]-1,3-dioxin (86)

A solution of **84** (3.4 g, 14 mmol) in methylene chloride (40 mL) was added dropwise to a solution of **69** from 3.4 g **61** in methylene chloride (30 mL) at –78 °C under nitrogen. The resultant solution was stirred overnight and slowly warmed up, then concentrated to give a dark residue. The dark residue was dissolved in dry acetone (100 mL), and flashed with nitrogen. Potassium carbonate (20 g, 180 mmol) was added to this acetone solution. The resulting solution was refluxed for12 hours and then concentrated. The residue was dissolved in water, neutralized carefully with HCl (6 N) and extracted with ethyl acetate (50 mL x 3). The organic layers were combined and washed with brine then dried with magnesium sulfate. Removal of the solvent, followed by flash column chromatography, provided **86** as a yellow crystal (3.7g, 65% yield). ^{1}H NMR ($CDCl_3$, δ): 13.1 (s, 1H), 7.25-7.50 (m, 5H), 6.78 (d, J = 6 Hz, 1H), 6.76 (d, J = 6 Hz, 1H), 5.84 (s, 1H), 5.15 (d, J = 3 Hz,

1H), 9.00 (d, J = 3 Hz, 1H), 4.95 (s, 2H), 4.86 (d, J = 12 Hz, 1H), 4.27 (d, J = 12 Hz, 1H), 3.35 (dd, J = 9 Hz; 3Hz, 1H); 2.45-2.50 (m, 1H), 2.20 (dd, J = 9 Hz; 3Hz, 1H), 1.56 (s, 3H), 1.40-1.55 (m, 1H). ^{13}C NMR ($CDCl_3$, δ): 185.7, 156.2,156.1, 149.7, 142.2, 136.6, 134.1, 128.8, 128.5, 128.3, 124.2, 115.9, 115.7, 105.7, 90.9, 74.2, 67.4, 40.1, 27.3, 25.0, 22.2. HRMS m/z: 406.1420, for $C_{23}H_{22}O_6$ calculated: 406.1416.

10-benzyloxy-5, 8-dimethoxy-1-hydroxymethyl-4a-methyl-2-oxo-2,3,4,4a-tetrahydrophenanthrene (90):

A solution of **86** (2 g, 5 mmol), potassium carbonate (20 g, 150 mmol) and dimethyl sulfate (5 mL, 50 mmol) in acetone (100 mL) was boiled under nitrogen for 36 hours. Then the acetone was removed under vacuum, and the residue was dissolved in water (50 mL) and stirred forl hour to decompose the dimethyl sulfate. Compound **90** was extracted with ethyl acetate (30 mL x 3), washed with brine and then dried with magnesium sulfate. Removal of solvent, followed by flash column chromatography, produced dimethylated **86** (2.15 g, 98 % yield). ^1H NMR ($CDCl_3$, δ): 7.46 (d, J = 6 Hz, 2H), 7.2-7.4 (m, 3H), 7.05 (d, J = 9 Hz, 1H), 6.93 (d, J = 9 Hz, 1H), 5.11 (d, J = 6 Hz, 1H), 4.98 (d, J = 9 Hz, 1H), 4.97 (d, J = 6 Hz, 1H), 4.92 (d, J = 9 Hz, 1H), 4.81 (d, J = 12 Hz, 1H), 4.25 (d, J = 12 Hz; 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.18 (dd, J = 9 Hz; 6 Hz, 1H), 2.4-2.5 (m, 1H), 2.17 (dd, J = 15 Hz; 6 Hz, 1H), 1.52 (s, 3H), 1.4-1.5 (m, 1H). ^{13}C NMR ($CDCl_3$, δ): 180.3, 154.5, 153.9, 150.9, 144.1, 143.2, 139.1, 137.3, 128.9, 128.3, 128.0, 122.1,116.3,111.5,105.6,90.8,73.6,67.6, 56.9, 55.8, 39.7, 28.4, 25.1, 22.3.

Dimethylated **86** (2.15 g, 4.9 mmol) solution in THF (10 mL) was added to the suspension of LAH (300 mg, 7.9 mmol) in THF (50 mL) at 0 °C. After 3 hours, the reaction was quenched with water (2 mL) and acidified to pH 1 by HCl (6 N). The resultant yellow solution was stirred for 20 minutes. Brine (20 mL) and ethyl acetate (30 mL) was added and the organic layer was separated, and then the aqueous layer was extracted with ethyl acetate (30 mL x 2). The organic layers were combined and washed with saturated sodium bicarbonate (30 mL), brine (30 mL) and dried with magnesium sulfate. After removal of the solvent, **91** was obtained pure enough (1.95 g) for the next step. ^1H NMR ($CDCl_3$, δ): 7.3-7.5 (m, 5H), 6.73 (s, 1H), 6.52 (s, 1H), 5.11 (d, J = 12 Hz, 1H), 5.02 (d, J = 12 Hz, 1H), 4.4-

4.6 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.45-3.55 (m, 1H), 2.45-2.70 (m, 3H), 2.0-2.15 (m, 1H), 1.49 (s, 3H).

5*a*-Benzyloxy-7, 10-dimethoxy-6-hydroxy-10*b*-menthyl-3-oxo-2, 3, 4,5*a*, 6, 10*b* - hexahydro-phenanthro[4, 4*a*-6]furan (92)

MCPBA (68%, 1.9 g, 7.5 mmole) was added to the solution of **91** (1.95g, 4.8 mmol) in methylene chloride (50 mL). The solution was stirred overnight. Sodium thiosulfate (10%, 10 mL) was added to quench the reaction, the organic layer was separated and washed with sodium hydroxide (3N, 50 mL), brine (50 mL), and then dried with magnesium sulfate. Removal the solvent under vacuum provided **92** (2.0 g, total yield 98%). ^{1}H NMR ($CDCl_3$, δ): 7.2-7.3 (m, 5H), 6.88 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 5.28 (s, 1H), 5.04 (d, J = 12 Hz, 1H), 4.87(d, J = 12 Hz, 1H), 4.65 (d, J = 12 Hz, 1H), 4.41 (d, J = 12 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 3.1-3.2 (m, 1H), 2.75-2.9 (m, 1H), 2.5-2.6 (m, 1H), 2.05-2.2 (m, 1H), 1.78 (s, 3H). ^{13}C NMR ($CDCl_3$, δ): 195.9, 158.7, 152.6, 152.4, 138.0, 134.5, 130.8, 128.3, 127.5, 127.4, 125.1, 112.9, 112.7, 110.1, 73.5, 67.7, 65.2, 56.3, 55.7, 38.6, 35.8, 35.7, 21.8.

5*a*-Benzyloxy-7, 10-dimethoxy-10*b*-methyl-3, 6-dioxo-2, 3, 4, 5*a*, 6, 10*b*-hexahydrophenanthro[4, 4*a*-6]furan (93)

PCC (2.0 g, 9.4 mmol) was added to a solution of **92** (2.0 g, 4.7 mmol) in methylene chloride (50 mL). The resultant solution was stirred overnight. Then the solution was filtered through Celite which was washed with methylene chloride (20 mL x 5). The filtrate was washed with saturated ammonium chloride (50 mL) and brine (50 mL), and then dried with magnesium sulfate. Removal of the solvent, followed by flash column chromatography, provided **93** (1.7g, 85% yield). ^{1}H NMR ($CDCl_3$, δ): 7.15-7.3 (m, 5H), 7.09 (d, J = 6 Hz, 1H), 6.88 (d, J = 6 Hz, 1H), 5.05 (d, J = 12 Hz, 1H), 4.88 (d, J = 12 Hz, 1H), 4.71 (d, J = 9 Hz, 1H), 4.56 (d, J = 9 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.1-3.2 (m, 1H), 2.75-2.85 (m, 1H), 2.45-2.55 (m, 1H), 1.95-2.05 (m, 1H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, δ): 194.7, 190.3, 157.9, 154.5, 151.5, 137.4, 135.6, 135.1, 128.2, 127.6, 127.5, 122.5, 118.3, 112.2, 109.1, 72.7, 66.7, 56.8, 55.9, 38.7, 35.7, 35.5, 21.4.

7, 10-Dimethoxyl-10*b*-menthyl-3, 6-dioxo-2, 3, 6, 10*b*-tetrahydrophenanthro[4, 4a-6]furan (94)

Concentrated HCl (10 mL) was added to a solution of **93** (2.1 g, 5 mmol) in methanol (20 mL). The resultant solution was boiled for 3 hours. Then the solution was concentrated under vacuum and the residue was dissolved in ethyl acetate (100 mL), which was washed with saturated sodium bicarbonate (15 mL) and brine (20 mL), and then dried with magnesium sulfate. Removal of the solvent, followed by flash column chromatography, produced **94** (1.2 g, 77% yield). ^{1}H NMR ($CDCl_3$, δ): 8.11 (s, 1H), 7.13 (d, J = 6 Hz, 1H), 7.00 (d, J = 6 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.45-3.5 (m, 1H), 2.85-2.95 (m, 1H), 2.60-2.70 (m, 1H), 1.95-2.05 (m, 1H), 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$, δ): 193.1, 172.9, 156.5, 151.9, 147.5, 145.4, 144.6, 138.4, 123.4, 122.2, 117.4, 113.1, 57.1, 56.0, 36.9, 36.4, 32.5, 25.6. MS m/z (CI-NH_3): 312.

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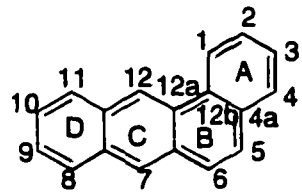
CHAPTER 4. A SYNTHETIC APPROACH TO AQUAYAMYCIN

A paper, a portion of which was published in *Tetrahedron Letter*

George A. Kraus and Zhiwen Wan.

Introduction

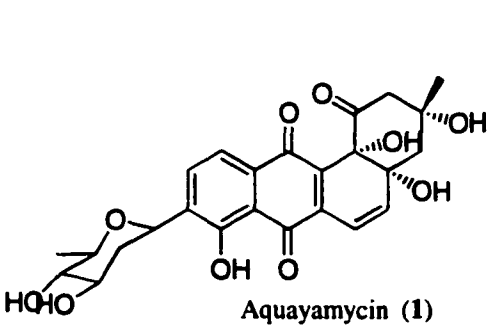
The angucyclines[1] are a relatively new group of antibiotics with antitumor, enzyme inhibitory, antiviral, and antifungal activity. This novel type of microbial natural product bearing a tetracyclic ring frame was first described in 1966.[2] The name came from the characteristic four-ring frame of the aglycone moiety which is assembled in an angular manner.[3] The classification of the angucyclines is related to the tetracyclic benzo[a]anthracene system and its derived compounds.



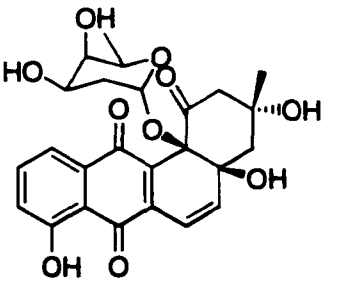
The tetracyclic benz[*a*]anthracene frame

Aquayamycin (**1**)[4] and sakyomycin D (**2**)[5], our target molecules, are two members of the angucyclines. They inhibit the proliferation of HIV *in vitro*. Aquayamycin was first described in 1968.[6] The structure was later determined in 1970.[4]

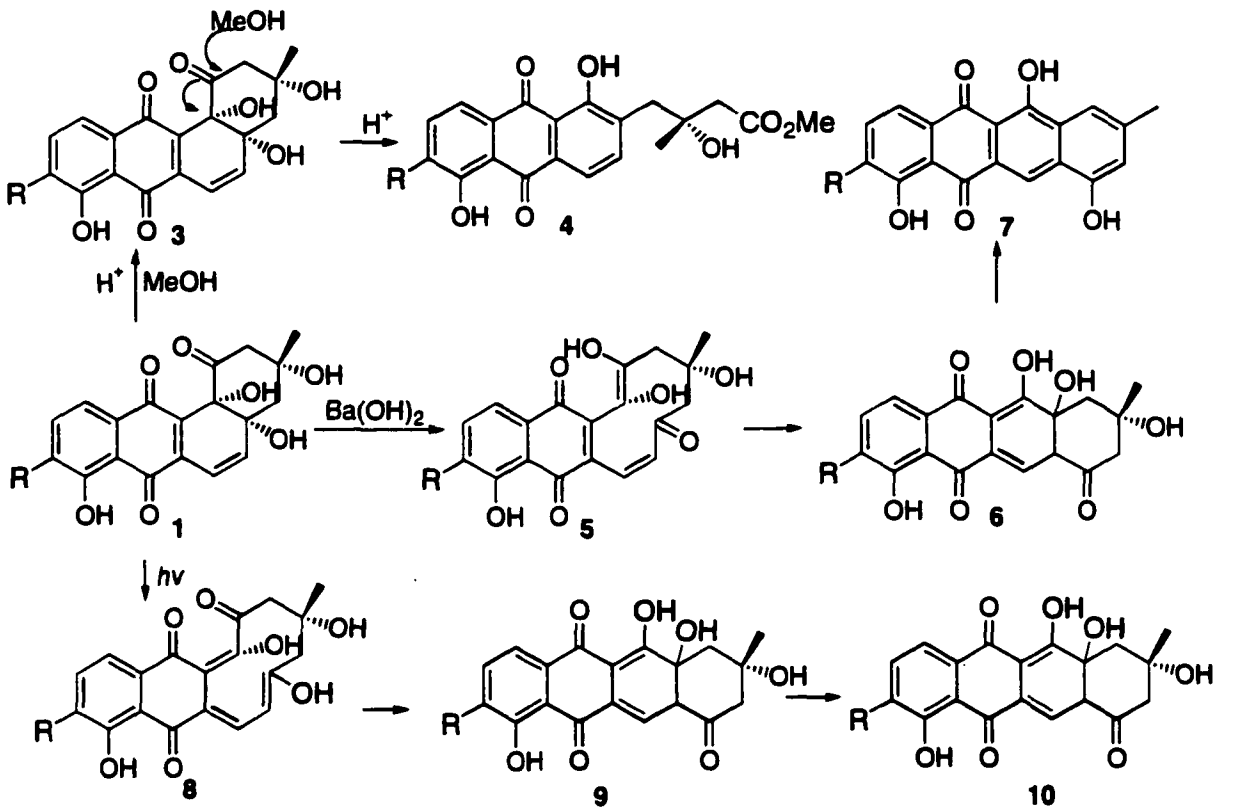
A study of its chemistry[4] showed that aquayamycin is sensitive to acid, base, and light. Acidic treatment of **1** in methanol yielded a tricyclic ring system (**4**). The mechanism is shown in Scheme 1. The initiation step of this reaction was suggested to be the attack of methanol at C-1 catalyzed by acid followed by a cleavage of the C-12b/C-1 bond. The product was also found as a methyl ester of a natural product, namely of vineomycinone B_2 (fridamycin A).[7]



Aquayamycin (1)



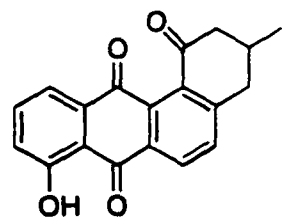
Sakyomycin D (2)



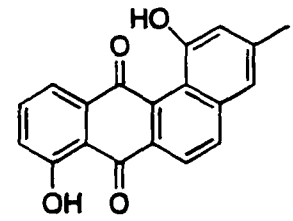
Scheme 1

When **1** was treated with weak bases (e.g., $Ba(OH)_2$ or heat), the cleavage of the C12b/C4a bond followed by rearrangement occurred to give the linear tetracyclic compound **7**. Irradiation of **1** with light resulted in the linear derivative **10**. The reaction mechanism involves conrotatory ring opening, isomerization, and conrotatory cyclization.

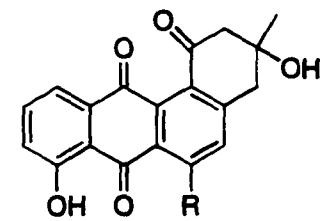
In past few decades, the synthesis of angucycline antibiotics[8] focused on the development of skeleton and some simple members, such as ochromycin (**11**),[9] tetrangulol (**12**),[2] tetrangomycin (**13**)[2] and rabelomycin (**14**).[10]



Ochromycin (**11**)

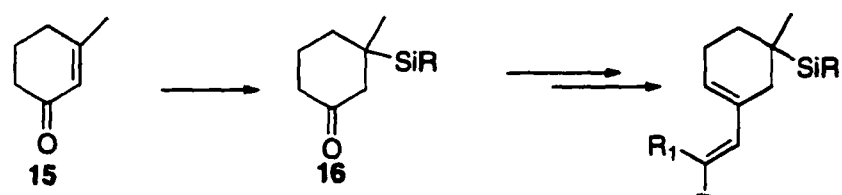


Tetrangulol (**12**)



R=H Tetrangomycin (**13**)
R=OH Rabelomycin (**14**)

Three methodologies were used to generate the 3-hydroxy group. The first methodology featured the silyl group as the precursor for the hydroxyl group. It was developed by Krohn.[11] The Diels-Alder reaction of diene **17** (Scheme 2) and a naphthaquinone gave the angucycline skeleton. The oxidation of the silyl group produced the hydrox group. The diene was made by Michael addition of a silane with cyclohexenone **15**.

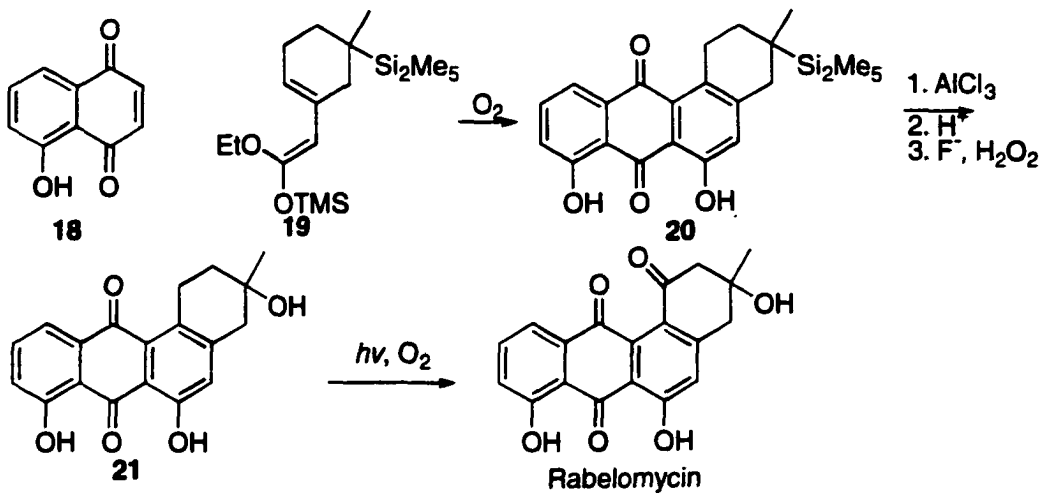


R=Me, Me, Ph; Me, Me, TMS

R1, R2 = H, H; H, OTMS; OEt, OTMS

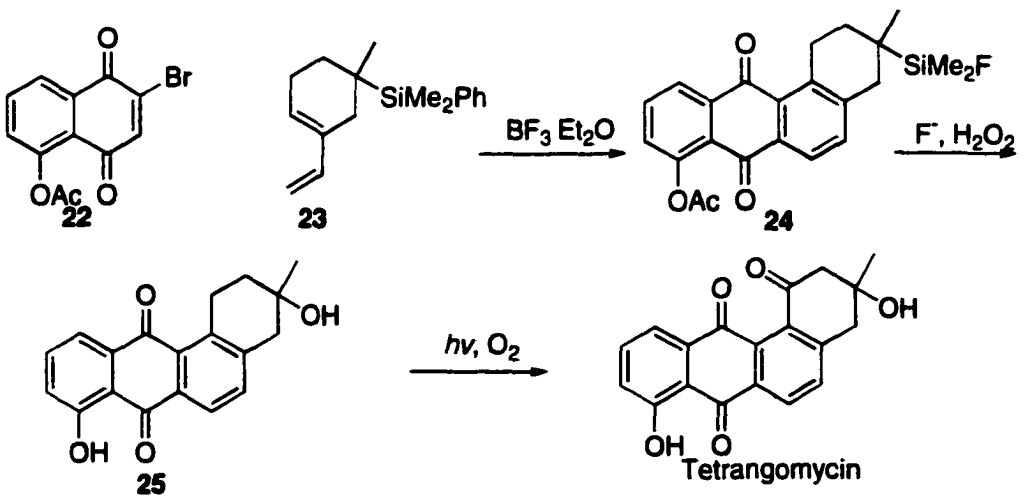
Scheme 2

The above strategy was used in syntheses of **13** and **14**. The synthesis of racemic rabelomycin was outlined in Scheme 3.[11] The Diels-Alder reaction of quinone **18** and diene **19** gave quinone **20**. The silyl group was converted to a hydroxyl group by $AlCl_3$ cleavage of the Si-Si bond followed by H_2O_2 oxidation in presence of fluoride to give **21**. The carbonyl group at C-1 was introduced by photooxidation.



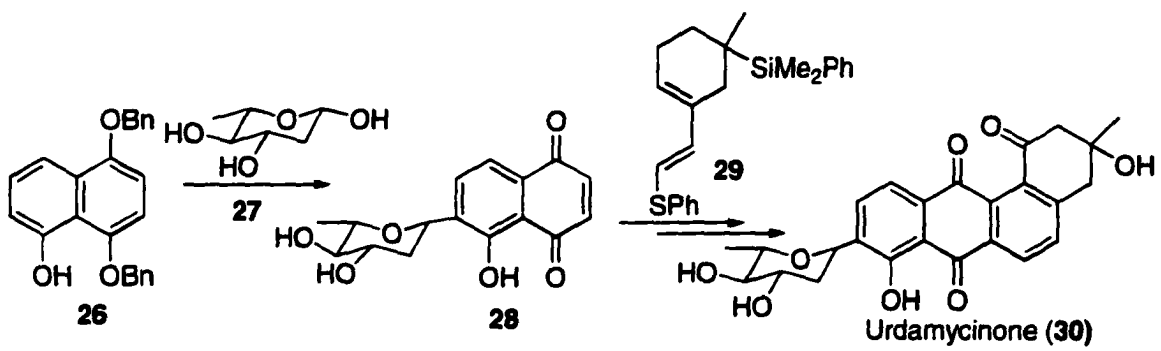
Scheme 3

Later, the dimethylphenylsilyl group was used. It was converted into a hydroxyl group under milder conditions. Krohn[12] used the dimethylphenylsilyl group for the synthesis of tetrangomycin (Scheme 4). A regioselective Diels-Alder reaction of bromoquinone **22** with the diene **23** followed by elimination of HBr and the treatment with a Lewis acid produced the product **24**. Oxidation of **24** generated tetrangomycin.



Scheme 4

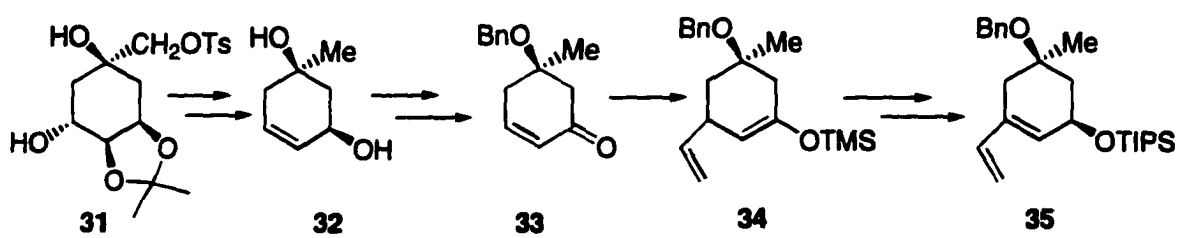
Toshima[13] used also the dimethylphenylsilyl group in a synthesis of urdamycinone B. He coupled the olivose **27** with naphthol **26** using trimethylsilyl triflate as the Lewis acid to generate a C-glycoside. Removal of the benzyl ethers and air oxidation gave **28**. The regioselective Diels-Alder reaction of quinone **28** and diene **29** followed by elimination of thiophenol and oxidation yielded urdamycinone B (Scheme 5).



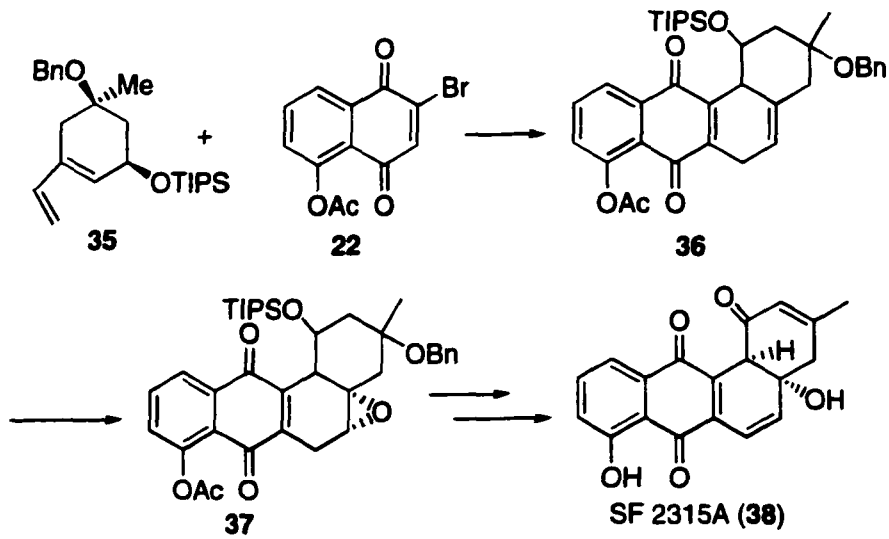
Scheme 5

A different methodology was developed by Boyd and Sulikowski.[14] Starting from (-)-quinic acid they employed a sequence of reactions analogous to that reported by Steglick[15] (Scheme 6). The epoxide resulting from **31** was reduced to a diol. The secondary hydroxyl group was mesylated. Reductive fragmentation gave alcohol **32**. They prepared the diene **34** *via* Michael addition and DDQ oxidation of the silyl enol ether.

The Diels-Alder adduct **36** was epoxided with dimethyldioxiranto give **37**. Rearrangement of **37** with TBAF followed by elimination yielded SF2315 A (**38**) (Scheme 7).[16]

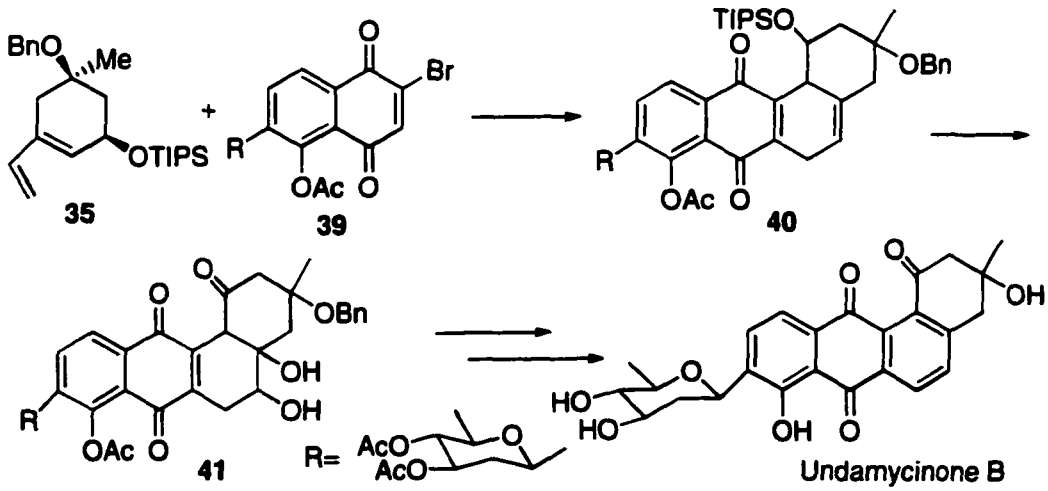


Scheme 6



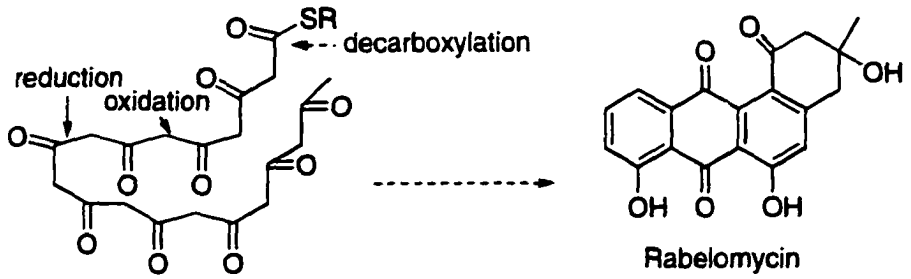
Scheme 7

A similar strategy was also used to complete the first enantioselective synthesis of undamycinone B.[14] Regioselective Diels-Alder reaction of bromoquinone **39** and diene **35** followed by the elimination of HBr yielded quinone **40**. Oxidation to cis-diol **41** followed by deprotection, oxidation, and aromatisation gave undamycinone B (Scheme 8).



Scheme 8

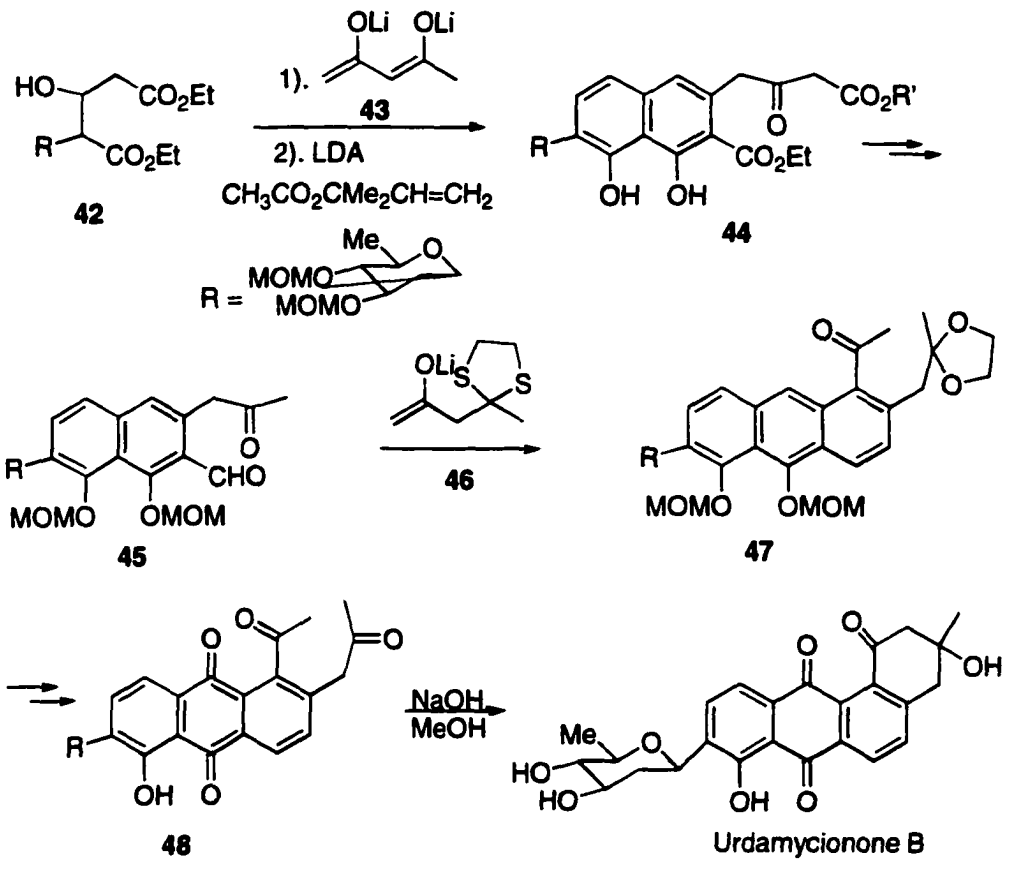
The third route was a biomimetic-type synthesis. Biosynthesis is presumed to occur *via* a hypothetical decaketide (Scheme 9).[1] Rohr[17] recently presented a folding analysis of polyketides in terms of sequential (E)- or (Z)-enolate. However, it should be mentioned that Gould[18] recently presented an alternative mechanism for PD 116198 involving a skeletal rearrangement.



Scheme 9

The first biomimetic–type synthesis of urdamycinone B was realized by Yamaguchi.[19] Starting with ester **42**, they prepared the naphthalenediol **44** by successive condensation of **42** with acetoacetate dianion **43** and acetate anion. Aldehyde **45** was prepared by dealkoxydecarbonylation, base-catalyzed ring closure, alcohol protection, and DIBAL reduction. Enolate of **46** reacted with the aldehyde, giving a diketoalcohol which spontaneously cyclized with concomitant aromatisation to **47**. Deprotection, base-catalyzed air oxidation to an anthraquinone, and removal of the dithiane then generated the crucial diketone **48**. Base-catalyzed cyclization yielded undamycinone B (Scheme 10).

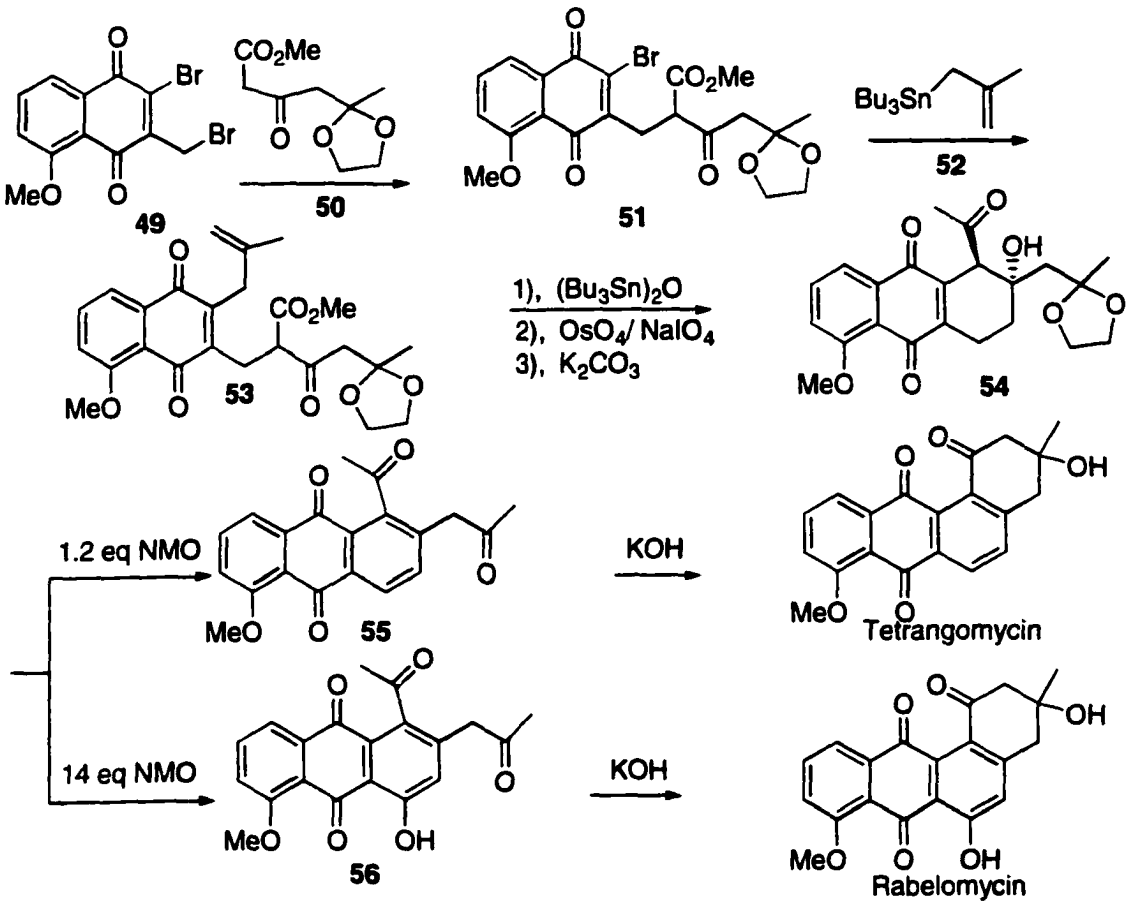
Krohn[20] reported another biomimetic synthesis (Scheme 11). Starting with bromoquinone **49**, he prepared quinone **51** by alkylation of the benzylic bromide with the ketoester **50**. The second chain was introduced by a Stille reaction of **52**. Decarbomethoxylation of **53** under neutral conditions followed by the cleavage of the side chain and base-catalyzed cyclization gave **54**. Compound **54** was oxidized with NMO. Phenol **55** was isolated as the major product using 1.2 equivalents of NMO. Phenol **56** was the major product using 14 equivalents of NMO. Base-catalyzed cyclization of **55** and **56** gave tetrangomycin and rabelomycin, respectively.



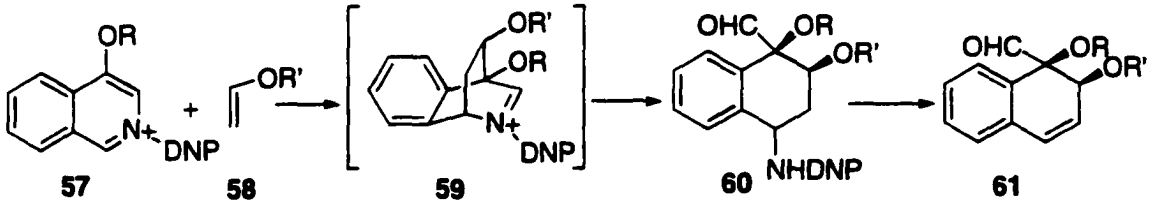
Scheme 10

However, angucyclines in which ring A is not aromatic present a great challenge for chemical synthesis. The most difficult aspect of the total synthesis of the more complex angucyclines such as aquayamycin is the construction of the *cis*-AB ring junction with diol functionality. This motif exhibits a marked propensity towards skeletal rearrangement under basic, acidic, and photochemical conditions.[4]

Nicolas and Frank[21] first addressed the problem of establishing the two *cis*-hydroxyl groups. They used the Bradsher cycloaddition reaction to construct the ring system (Scheme 12). The iminium salt **57** reacted with enol ether **58** to form the aldehyde **60** *via* intermediate **59**. The protected enediol **61** was prepared by elimination of the amine.



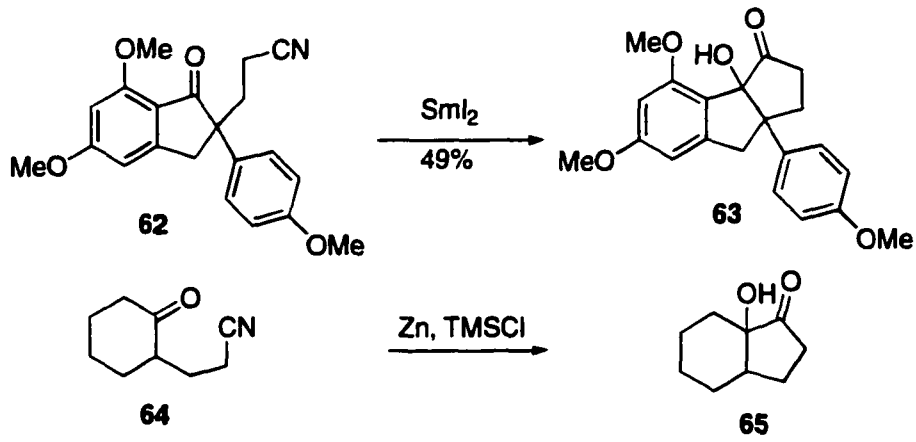
Scheme 11



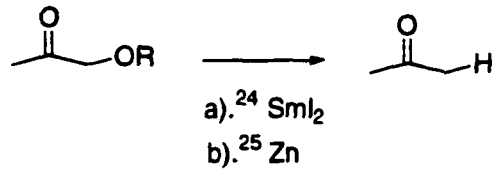
Scheme 12

Results and Discussion

To construct the C-1, C-4a and C-12b functionalities, we focused on the construction of the α-hydroxy ketone. In 1989 our group developed the methodology to achieve this goal *via* the keto nitrile cyclization by samarium iodide reduction.[22] Corey[23] reported a related methodology to prepare α-hydroxy ketones from keto nitriles by zinc and chlorotrimethylsilane.

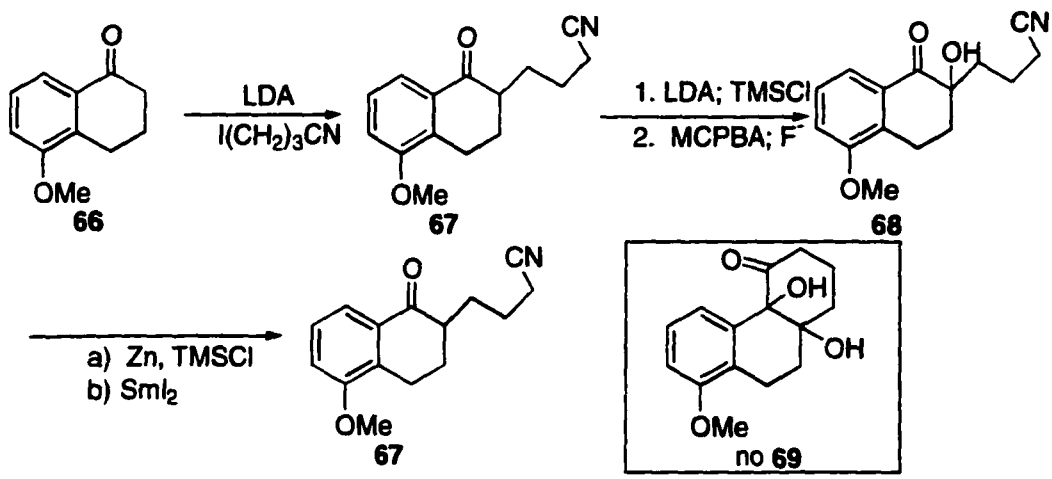


Both of these methodologies constructed five-member rings. To use these methodologies to construct the AB ring junction of aquayamycin, we needed to determine whwether the reductive cleavage of α-alkoxy groups (Scheme 13) reported by Molander [24] and Rosenfeld[25] would interfere.



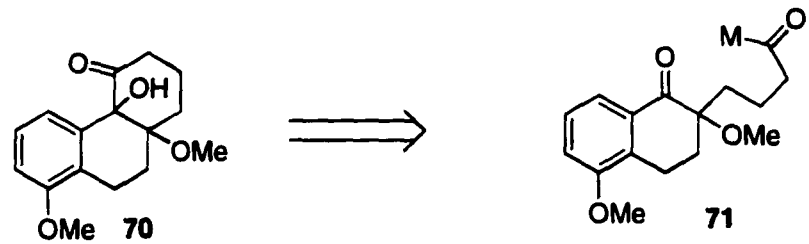
Scheme 13

We converted tetralone **66** into ketonitrile **67** to determine whether reductive cyclization was favored over cleavage of an α-substituent (Scheme 14). Alkylation of tetralone **66** with LDA and 4-iodobutyronitrile required the addition of hexamethylphosphoric triamide (HMPA) for a reproducible 50% yield of **67**. Ketone **68** was prepared from **67** in 72% overall yield *via* oxidation of an enol silyl ether with MCPBA.[26] Unfortunately, both SmI_2 and Zn/TMSCl gave deoxygenation product **67**. No cyclization product **69** was isolated.

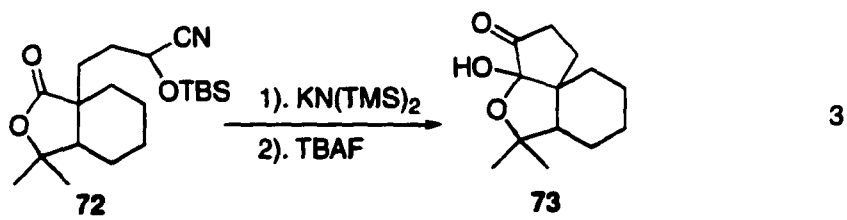


Scheme 14

The next strategy we evaluated was an intramolecular cyclization of an acyl carbanion equivalent (Scheme 15). Intermolecular alkylation of acyl carbanion equivalents are well documented, however, only a few intramolecular reactions have been reported.[27] A recent example described by Paquette.[28]



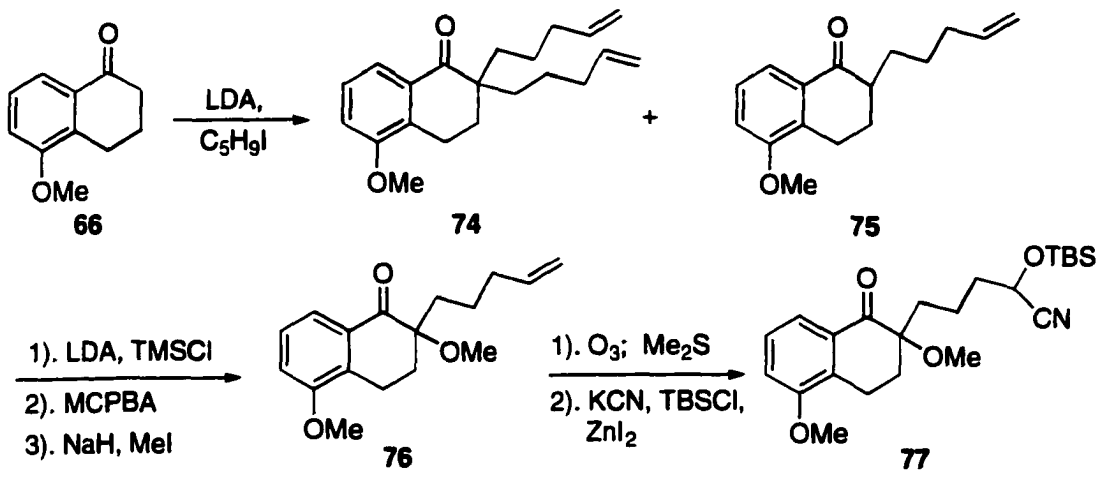
Scheme 15



3

To examine this strategy, we started with tetralone **66**. The alkylation of tetralone **66** with LDA and 5-bromo-1-pentene gave a mixture of mono- and dialkylated products (Scheme 16). The yield of the mono-alkylated product **75** was improved to 55% by using $NaN(TMS)_2$. Installation of methoxyl group was accomplished using a three-step reaction

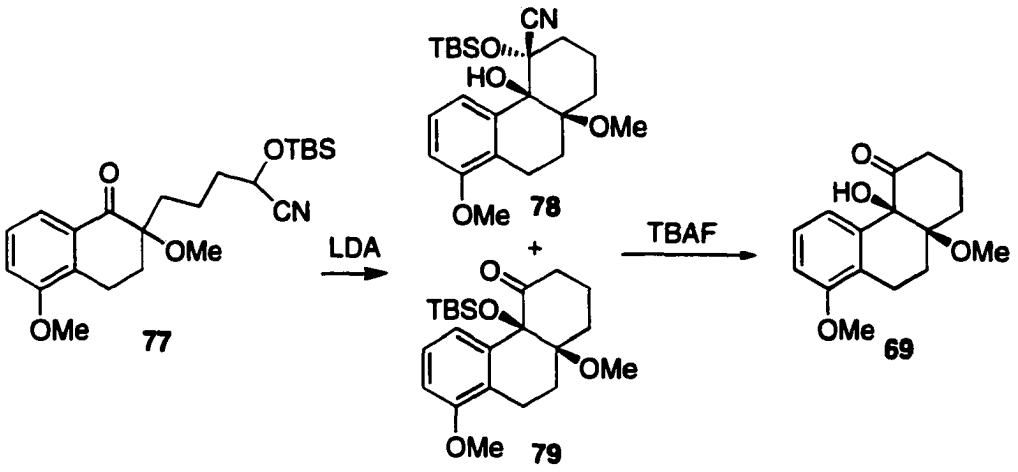
sequence involving enol silyl ether formation with LDA and TMSCl, MCPBA oxidation,[26] fluoride desilylation, and methylation with NaH and MeI in DMF. Oxidation of alkene **75** with ozone generated an aldehyde. Treatment of the aldehyde with TBDMSCl, ZnI_2, and KCN in dry acetonitrile gave **77** in 72% yield.[29]



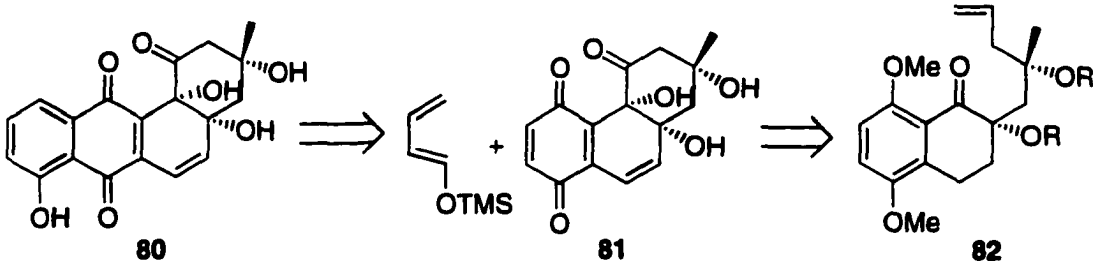
Scheme 16

Treatment of **77** with LDA at –78 °C yielded nitrile **78** and hydroxy ketone **79** (Scheme 17). The relative stereochemistry of **78** is tentatively assigned based on the NMR spectrum of **78**. It contained a methyl resonance at –0.4 ppm. This corresponds to a methyl group attached to silicon which has been deshielded by the aromatic ring and would be possible only with the OTBS group in an endo-configuration. Treatment of the unpurified mixture of **78** and **79** with TBAF yielded ketone **69** in 73% overall yield. The *cis*-stereochemistry of the hydroxyl and methoxyl groups was confirmed by x-ray structure determination.

This chemistry provided a convenient approach to the ABC ring system containing a selectively protected cis-4a, 12b diol. To fit this strategy to the synthesis of aquayamycin, we proposed a retrosynthetic analysis shown in Scheme 18. The regioselective Dials-Alder reaction of the ketoquinone **81** had been reported by our group.[30]



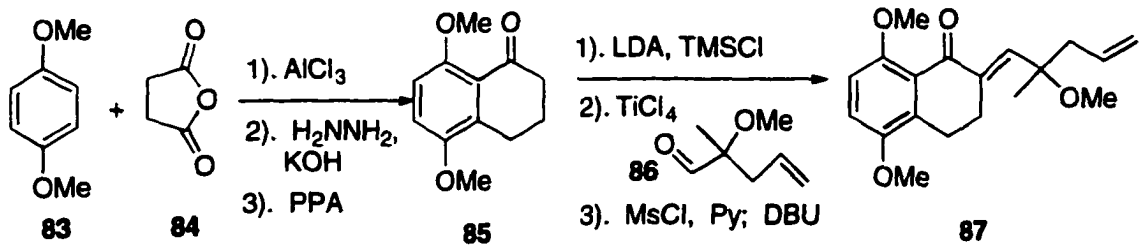
Scheme 17



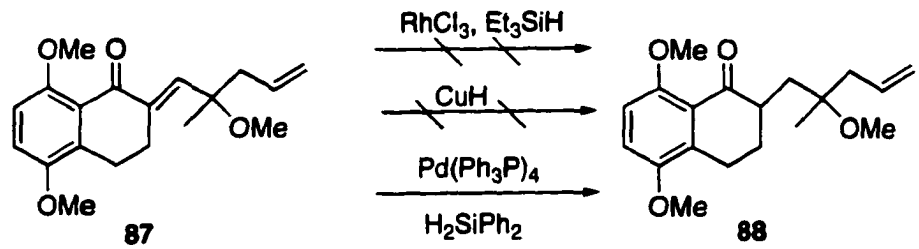
Scheme 18

We next started with **83**. Tetralone **85** was prepared from **83** by a known procedure (Scheme 19).[31] Using an aldol reaction, we introduced the side chain.[32] An aldol reaction with LDA resulted in recovered starting material. However, the silyl enol ether of **85** reacted with aldehyde **86** to give the aldol product.[33] Mesylate elimination then afforded enone **87** in good yield.

To selectively reduce the enone double bond, we tried a rhodium-catalyzed reaction, but recovered **87**.[34] CuH reagent also failed.[35] Fortunately, a palladium-meidiated silane reduction gave the reduction product **88** (Scheme 20).[36]

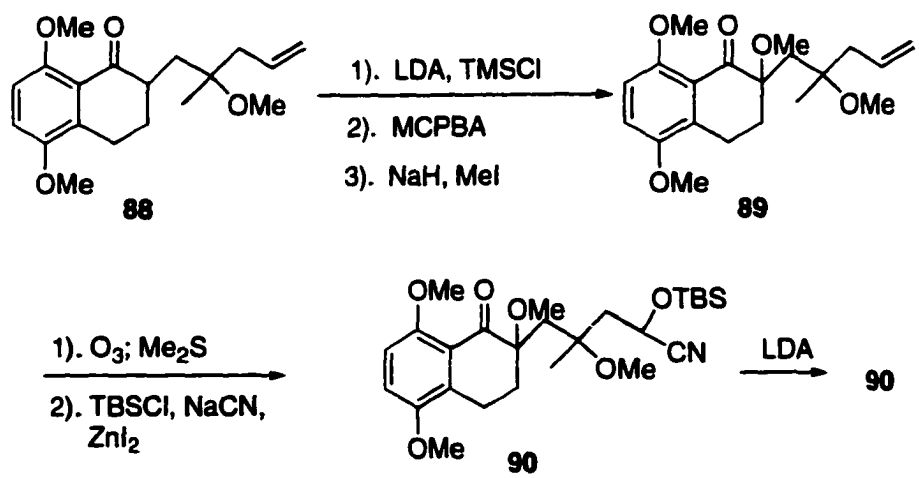


Scheme 19



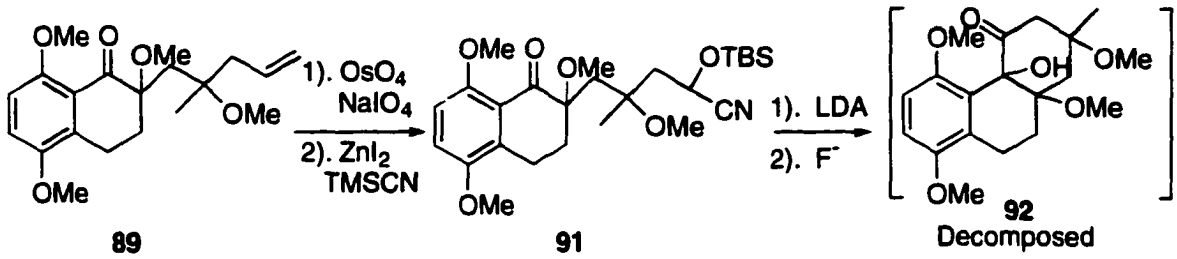
Scheme 20

Ketone **88** was silylated, oxidized and methlated to make ketone **89** (Scheme 21). However, **89** was a mixture of diastereomers. Compound **89** was converted into the cyanohydrin **90**.[29] Treatment of **90** with LDA returned recovered starting material. We cyanohydrin may be too bulky to react with the hindered carbonyl group.



Scheme 21

The smaller thimethylsilyl cyanohydrin was made using TMSCN and ZnI_2 (Scheme 22).[37] This cyanohydrin is difficult to purify. Treatment of **91** with LDA gave a new product. From the ^1H NMR spectrum, the cyanohydrin proton at 4.5 ppm had disappeared and the two aromatic protons at 6.92 ppm and 6.77 ppm had become a singlet at 6.75 ppm. Unfortunately, this product decomposed upon treatment with tetrabutylammonium fluoride.



Scheme 22

Conclusion

We developed an approach to the ABC ring system of aquayamycin. The C-3 hydroxyl group was introduced by an aldol-enone reaction. With minor changes, the total synthesis of aquayamycin might be possible.

Experiments

Unless otherwise noted, the materials used in the experiments for this research were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene, dichloromethane, acetonitrile, toluene, diisopropylamine were distilled from calcium hydride. The reactions were conducted in a nitrogen atmosphere and the organic extracts were dried with magnesium sulfate. The melting point was determined on a Fisher-Johns apparatus and was not corrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer and nuclear magnetic resonance spectra were determined on a Nicolet Magnetics Corporation NMR-1280 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), and m (multiplet). The addition of br indicates a broadened pattern.

The glass apparatus were flame-dried and cooled under the steam of nitrogen. Flash column chromatography was conducted using Neutral or Basic Aluminium (Brockmann) standard grade (150 mesh) from Aldrich Chemical Company and Silica Gel (EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F254 prepared plates with a thickness of 0.25 mm. High resolution MS was obtained from Kratos Model MS-50 spectrometer and low resolution MS was obtained from a Finnegan 4023 Mass spectrometer.

5-Methoxy-2-(3-cyanopropyl)-1-tetralone (67).

Compound **66** (1.76 g, 10 mmol) in THF (10 mL) at –78 °C was added under nitrogen to LDA (12 mmol from 4.5 mL of 2.5 M BuLi and 1.8 mL of diisopropylamine) in THF (50 mL) solution. This solution was stirred for 1 hour. HMPA (2.7mL, 15 mol) and 4-iodobutyronitrile (2.4 g, 12 mmol) were added and the resultant solution was stirred overnight. Saturated ammonium chloride (20 mL) was added, and the product was extracted with ethyl acetate (30 mL x 3), washed with brine (30 mL), and then dried with magnesium sulfate. After removal of the solvent, 1.2 g of **67** was obtained from flash column chromatography purification (50% yield). ^{1}H NMR ($CDCl_3$, δ): 7.62 (d, J = 6 Hz, 1H), 7.27 (t, J =6 Hz, 1H), 7.01 (q, J = 6 Hz, 1H), 3.86 (s, 3H), 1.6-3.2 (m, 11H). ^{13}C NMR ($CDCl_3$, δ): 199.8, 156.8, 133.4, 132.8, 127.0, 119.7, 118.9, 114.2, 55.74, 46.4, 29.0, 28.0, 23.3, 22.1, 17.5. IR (neat) cm^{-1}: 3003, 2937, 2360, 1681, 1582, 1471, 1260. MS m/z (CI-NH_3): 243.

5-Methoxy- 2-hydroxy-2-(3-cyanopropyl)-1-tetralone (68).

Compound **67** (0.5 g, 2 mmol) in THF (5 mL) at –78°C was added under nitrogen to LDA (2.5 mmol) in THF (20 mL) solution. This solution was stirred for 1 hour, then TMSCl (0.32 mL, 2.6 mmol) was added. The resultant solution was stirred at –78 °C for 4 hours and pentane (50 mL) was added. The solution was warmed to room temperature, washed by pH 7.00 buffer solution (30 mL), and then dried with magnesium sulfate. After removal of the solvent, the oily residue was dissolved in methylene chloride (30 mL), and cooled in an ice bath. MCPBA (68% pure, 0.62 g, 2.5 mmol) was added to this solution. After the solution

was stirred for 30minutes, sodium thiosulfate (10 %, 5 mL) was added. The organic lay was separated and washed with sodium bicarbonate (20 mL) and brine (20 mL). After removal of the solvent under vacuum, the remaining oil was dissolved in THF (10 mL) and treated with HF (48%, 0.5 mL) for 1 hour. Then water (10 mL) was added. The product was extracted with ethyl acetate (20 mLx3), and washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), and then dried with magnesium sulfate. After removal of the solvent, 0.4g of the pure product was obtained after flash column chromatography (72% yield). ^{1}H NMR ($CDCl_3$, δ): 7.60 (d, J = 6 Hz, 1H), 7.58 (t, J = 6 Hz, 1H), 7.07 (d, J = 6 Hz, 1H), 3.88 (s, 3H), 2.9-3.2 (m, 1H), 2.6-2.9 (m, 1H), 1.6-2.4 (m, 8H). ^{13}C NMR ($CDCl_3$, δ): 201.6, 157.0, 132.2,130.8, 127.8, 119.4, 119.3, 115.1, 75.1, 55.7, 34.3, 33.5, 20.8, 19.6, 17.4. IR (neat) cm^{-1}: 3400, 3021, 2360, 1682, 1581, 1260. MS m/z (CI-NH_3): 277.

5-Methoxy-2-(4-pentenyl)-1-tetralone (74)

Compound **66** (1.76 g, 10 mmol) in THF (10 mL) at –78 °C was added under nitrogen to $NaN(TMS)_2$ (1N in THF, 12 mL, 12 mmol) in THF (50 mL) solution. Then this solution was stirred for 1 hour, 5-bromo-1-pentene (1.75 g, 12 mmol) was added, and the resultant solution was stirred overnight. Saturated ammonium chloride (20 mL) was added, and the product was extracted with ethyl acetate (30mL x 3), washed with brine (30 mL), and then dried with magnesium sulfate. After removal of the solvent, 1.34 g of **74** were obtained from flash column chromatography purification (55 %). ^{1}H NMR ($CDCl_3$, δ): 7.63 (dd, J =6 Hz; 1Hz, 1H), 7.25 (t, J = 6 HZ, 1H), 6.99 (dd, J = 6 Hz; 1Hz, 1H), 5.7-5.9 (m, 1H), 4.9-5.1 (m, 2H), 3.86 (s, 3H), 3.0-3.1 (m, 1H), 2.7-2.8 (m, 1H), 2.4-2.5 (m, 1H), 1.8-2.2 (m, 5H), 1.3-1.5 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 200.6, 156.8, 138.8, 133.6, 132.9, 126.8, 119.0, 114.6, 113.9, 55.7, 46.96, 34.0, 28.9, 27.6, 26.5, 21.8.

2,5-Dimethoxy-2-(4-pentenyl)-1-tetralone (75)

Compound **74** (0.5 g, 2 mmol) in THF (5 mL) at –78 °C was added under nitrogen to LDA (2.5 mmol) in THF (20 mL) solution. This solution was stirred for 1 hour, then TMSCl (0.32 mL, 2.6 mmol) was added. After 4 hours, pentane (50 mL) was added, and the solution warmed to room temperature, washed by pH 7.00 buffer solution (30 mL) and brine (30 mL), and then dried with magnesium sulfate. After removal the solvent, the oily residue was

dissolved in methylene chloride (30 mL), and cooled in an ice bath. MCPBA (68%, 0.62g, 2.5 mmol) was added to this solution. After 30minutes, sodium thiosulfate (10 %, 5 mL) was added, and the organic layer was separated and washed with brine. After removal of the solvent under vacuum, the remaining oil was dissolved in THF (10 mL) and treated with HF (48%, 0.5 mL) for 1 hour. Water (10 mL) was then added. The product was extracted with ethyl acetate (20 mLx3), washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), and then dried with magnesium sulfate. After removal of the solvent, 0.47 g of the pure product was obtained after flash column chromatography (85% yield) as 5-methoxy-2-hydroxy-2-(4-pentenyl)-1-tetralone. ^{1}H NMR ($CDCl_3$, δ): 7.61 (dd, J = 6 Hz; 1Hz, 1H); 7.30 (t, J = 6 HZ, 1H), 7.04 (dd, J = 6 Hz; 1 Hz, 1H), 5.7-5.9 (m, 1H), 4.9-5.1 (m, 2H), 3.86 (s, 3H), 3.0-3.15 (m, 1H), 2.65-2.8 (m, 1H), 2.3-2.4 (m, 1H), 1.9-2.15 (m, 3H), 1.30-1.75 (m, 4H). ^{13}C NMR ($CDCl_3$, δ): 202.2, 156.9, 138.3, 132.4, 131.2, 127.5, 119.4, 114.8, 114.7, 75.5, 55.7, 35.0, 33.8, 33.3, 22.3, 20.9.

NaH (60% in mineral oil, 50 mg) was added under nitrogen to the solution of hydroxytetralone in DMF (10 mL). After 30 minutes, MeI (0.4 mL) was added and the resultant solution was stirred overnight. Water (20mL) was added, and the product was extracted with ethyl acetate (30 mL x3). The organic solution was washed with water (20 mL x3) and brine (20 mL x3), and then dried with magnesium sulfate. After removal of the solvent, **75** (0.49 g) was obtained as oil, which was pure enough for next step. ^{1}H NMR ($CDCl_3$, δ): 7.65 (dd, J = 6 Hz; 1Hz, 1H), 7.28 (t, J = 6 HZ; 1H), 7.01 (dd, J = 6 Hz; 1 Hz, 1H), 5.7-5.9 (m, 1H), 4.9-5.1 (m, 2H), 3.87 (s, 3H), 3.2 (s, 3H), 3.0-3.15 (m, 1H), 2.75-2.9 (m, 1H), 2.35-2.45 (m, 1H), 2.0-2.1 (m, 3H), 1.4-1.9 (m, 4H). ^{13}C NMR ($CDCl_3$, δ): 197.5, 156.7, 138.5, 132.9, 132.4, 127.1, 119.6, 114.9, 114.1, 79.2, 55.68, 51.3, 34.1, 31.3, 30.6, 22.2, 19.9.

2,5-Dimethoxy-2-(4-t-butyldimethylsiloxy -4-cyanobutyl)-1-tetralone (76)

Ozone was bubbled through the solution of **75** (0.3 g 1.1 mmol) in methylene chloride (15 mL) at –78 °C until the solution became light blue. Then the solution was decolorized with argon for 15minutes. Dimethylsufide (0.2 mL, 2.7 mmol) was added and the solution warmed and stirred for 12 hours. Then the solution was washed with brine (10 mL) and

dried with magnesium sulfate. The aldehyde was obtained as oil after removal of the solvent, which was pure enough for the next step.

ZnI_2 (10 mg), TBDMSCl (0.23 g, 1.5 mmol) and KCN (0.13 g, 2.0 mmol) were added to the solution of the aldehyde in dry acetonitrile (15 mL). The resultant solution was stirred overnight. Then water (10 mL) was added to quench the reaction. The products were extracted with ethyl acetate (20 mL x3), washed with brine (20 mL), and then dried with magnesium sulfate. Removal of the solvent, followed by FCC purification, yielded 0.41 g **76** in 85% yield. ^{1}H NMR ($CDCl_3$, δ): 7.64 (dd, J=6 Hz; 1Hz, 1H), 7.29 (t, J = 6 HZ, 1H), 7.03 (dd, J = 6 Hz; 1Hz, 1H); 4.44 (t, J = 7 Hz, 1H), 3.86 (s, 3H), 3.20 (s, 3H), 3.0-3.15 (m, 1H), 2.75-2.9 (m, 1H), 2.3-2.5 (m, 1H), 1.5-2.1 (m, 7H), 0.9 (two s', 9H), 0.17 (dd) and 0.18 (dd) (total 6H). ^{13}C NMR ($CDCl_3$, δ): (diastereomers) 197.23, 197.18, 156.71, 132.74, 132.70, 132.68, 132.37, 132.33, 127.18, 127.11, 120.07, 120.02, 119.58, 119.55, 114.27, 114.26, 114.19, 78.96, 78.92, 61.90, 61.87, 55.69, 51.34, 42.98. 36.68, 36.16, 31.27, 31.22, 31.11, 30.51, 30.44, 25.72, 25.63, 26.57, 25.36, 19.81, 19.74, 18.68, 18.29, 18.21, 18.09, -5.08, -5.29, -4.76. MS m/z (CI-NH_3): 417.

(*cis*)-1, 8*a*-Dimethoxy-4*b*-hydroxy-4, 6, 7, 8, 9, 10, 4*b*, 8*a*-octahydro-5-oxo-phenathrene (69)

LDA (1N, 0.6 mL, 0.6 mol) was added under nitrogen to a solution of **76** (0.2 g, 0.48 mmol) in THF (10 mL) at –78 °C under nitrogen. The solution was stirred at –78 °C for 3 hours, then saturated ammonium chloride (10 mL) was added to quench the reaction. The product was extracted with ethyl acetate (20 mL x 3), washed with brine, and then dried with magnesium sulfate. The crude intermediate was obtained as light oil after removal of the solvent. Tetrabutylammonium fluoride (1N in methylene chloride, 1 mL) was added under nitrogen to the solution of the intermediate in methylene chloride (15 mL). After 3 hours the reaction was quenched with saturated ammonium chloride (10 mL). The product was extracted with ethyl acetate (20 mL x 3), washed with brine, and then dried with magnesium sulfate. Removal of the solvent, followed by flash column chromatography purification, gave **69** as a white crystal (95 mg, 73% yield). A single crystal was obtained for x-ray structure[38] determination from recrystallization in the mixture of methylene chloride and

hexanes. ^{1}H NMR ($CDCl_3$, δ): 7.14 (t, J = 6 Hz, 1H), 6.77 (dd, J = 6 Hz; 1 Hz, 1H), 6.45 (dd, J = 6 Hz; 1 Hz, 1H), 4.08 (s, 1H, OH, disappeared with D_2O), 3.83 (s, 3H), 3.26 (s, 3H), 3.08 (dd, J = 15 Hz, 6 Hz, 1H), 2.3-2.7 (m, 3H), 1.7-2.2 (m, 6H). ^{13}C NMR ($CDCl_3$, δ): 211.9,157.6, 127.8, 124.3, 119.7, 114.7, 109.6, 82.2, 81.2, 55.4, 48.6, 38.2, 26.3, 24.1, 21.8, 21.4. IR (neat) cm^{-1}: 3496, 2942, 1717,1585, 1467, 1261, 1091. MS m/z (CI-NH_3): 276.

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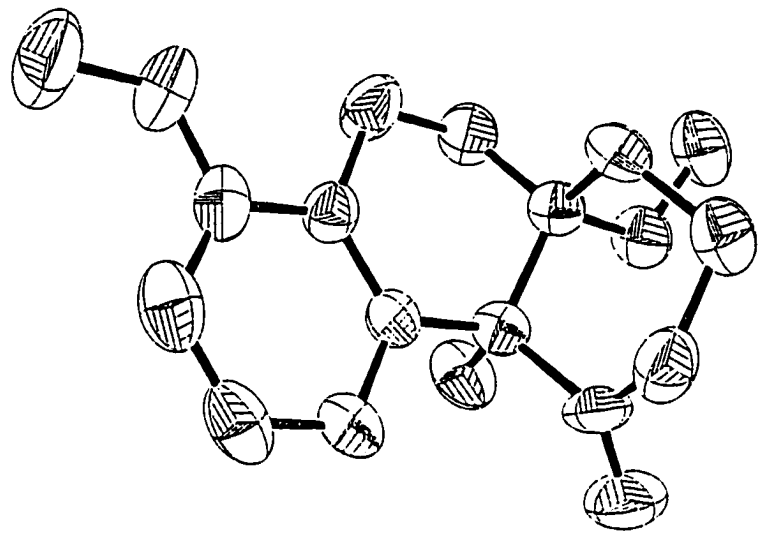
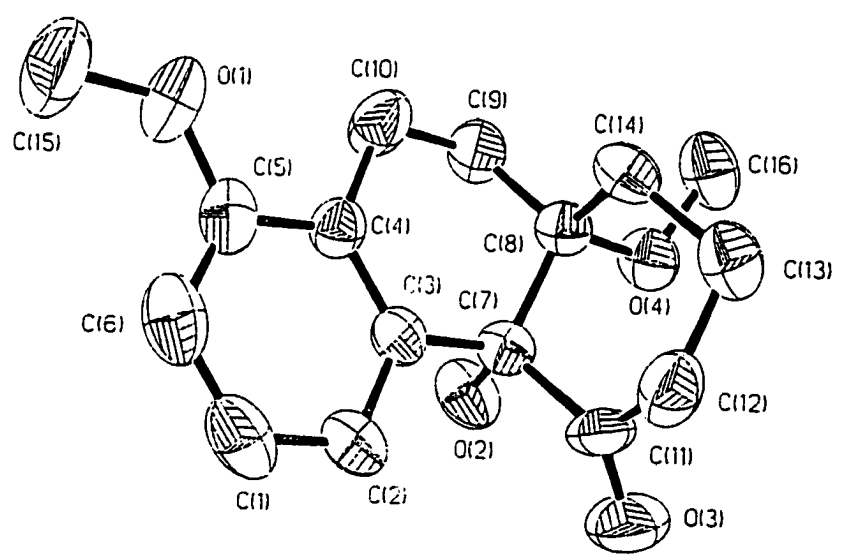
38. X-ray structure of **68**:





GENERAL CONCLUSION

Different methodologies were used to achieve the synthesis of natural furan. These strategies could be used to construct more complex antitumor antibiotics. A synthesis of hibiscone C was achieved in seven steps. Halenaquinone analogs were prepared *via* Michael addition, annulation, and a Diels-Alder reaction. In the final project, we developed convenient method to construct the *cis*- fused BCD ring system in aquayamycin.

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