AN ABSTRACT OF THE DISSERTATION OF

M. Quamar Salih for the degree of Doctor of Philosophy in Chemistry presented on May 1, 2014.

Title: Conformationally Chiral Diphenylethers and the Enantioselective Ullmann Etherification

Abstract approved:

Christopher M. Beaudry

Abstract

Since the discovery of molecular chirality in 1848, this notion has had a substantial impact on medicine, biology, and chemistry. Extensive effort has been directed towards the construction of chiral molecules that contain sp\(^3\) hybridized stereogenic centers. In contrast, less effort has been dedicated to molecules that are chiral by virtue of their conformation. Nevertheless, structures with restricted rotation of sigma bonds including biaryls, cyclophanes, allenes and strained cyclic alkenes have attracted plentiful attention as chiral ligands, catalysts, synthetic intermediates and targets of total synthesis.

We believe that conformational chirality is more prevalent than commonly believed and goes undetected in many natural products that do not contain sp\(^3\) hybridized stereogenic centers. This thesis contains a body of work that provides a better understanding of conformationally chiral molecules. The ability to identify the existence of conformational chirality in complex molecular architectures devoid of stereogenic centers along with methods to access them is described.
Toward this end, we sought to study a family of molecules with conserved molecular architectures, devoid of stereogenic centers, that sometimes (but not always) display chirality. The aim is to develop experimental tools to determine which members are chiral and achiral and to develop a structure chirality relationship. The diarylether heptanoid (DAEH) natural products fit these criteria, and they were selected as an excellent platform to study chirality in diphenylethers.

The exploration begins with the synthesis and chiral properties of the heptanone DAEHs. A unified route was developed to access all heptanone DAEH members. The synthetic material was used to measure their optical activities and free energy of activation for racemization. The natural enantiomers of myricatomentogenin, jugcathanin, galeon, and pterocarine were determined to have the same $\text{pR}$ absolute stereochemistry. Acerogenins L and C are achiral compounds.

The remaining DAEHs members, which are the garuganins and garugamblins were synthesized and their chiral properties were determined. Alkene stereoisomers, vinylogous ester regioisomers, and $\beta$-diketone congeners were also synthesized. The chiral properties and free energies of activation for racemization of the garuganin and garugamblin DAEHs and congeners were determined using dynamic NMR methods. A combination of techniques including coalescence measurements, lineshape analysis, and selective inversion experiments are used to measure racemization barriers. None of the garuganin or garugamblin diarylether heptanoids are chiral, despite being isolated as optically active compounds.

The first enantioselective Ullmann cross-coupling reactions to prepare diaryl ethers are reported. Upon completing the syntheses of the DAEHs and determining their chirality, we find only four members to be chiral. Our effort to access enantiopure
material was accomplished by rendering the Ullmann reaction enantioselective by using N-methyl proline as the chiral ligand. This reaction was used to prepare all the chiral diarylether heptanoid natural products, which are (−)-myricatomentogenin, (−)-jugcathanin, (+)-galeon, and (±)-pterocarine.

The first synthesis of russuphelol was accomplished, and its chiral properties were investigated. We have applied our knowledge of conformational chirality from the DAEH system to an acyclic triphenylether russuphelol. The synthesis of the natural product has been accomplished in six steps. Despite the optical activity reported upon isolation, we find russuphelol to have no element of chirality.

As a result of the work presented in this thesis we better understand conformational chirality in diphenylethers. Tools to examine, identify, and measure molecular chirality where no stereocenters are present were developed. This contribution will benefit the chemical community in many areas such as catalysis, natural product isolation and medicine. In conclusion, all fifteen members of the DAEH family have been synthesized, and determined which members of this family are chiral. This knowledge was then utilized in the investigation of chirality in the acyclic diphenylether russuphelol, which had a mistaken identity of chirality when isolated. Development of the first enantioselective Ullmann coupling reaction to construct C–O bonds and its use in the first enantioselective synthesis of all chiral DAEHs is reported. With all the knowledge we have created we hope to increase the understanding of molecular chirality in the greater scientific community.
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Conformationally Chiral Diphenylethers and the Enantioselective Ullmann Etherification

by
M. Quamar Salih

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I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

M. Quamar Salih, Author
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DEDICATION

To the Salih’s
CONFORMATIONALLY CHIRAL DIPHENYLEThERS AND THE ENANTIOSELECTIVE ULLMANN ETHERIFICATION
CHAPTER 1: INTRODUCTION

1.1 Introduction to Diphenylethers

Diphenylether containing molecules are important in medicine, catalysis and biology. For example, potent antibiotics such as vancomycin (1.1) and its derivatives are used to treat infections caused by bacteria, including methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis* (Figure 1.1).¹ Many diphenylethers are known anti-cancer agents.² The diphenylether motif is present in catalysts such as DPEphos (1.2) and xantphos.³ Thyroxine (1.3), a metabolism-regulating hormone produced in our bodies contains a diphenylether.⁴

![Figure 1.1. Diphenylether containing molecules](image)

Diphenylethers are a common motif in natural products.⁵ There are two classes of diphenylethers isolated: The first type is the acyclic diphenylether and the other is the macrocyclic diphenylether. Russuphelol (1.4) is a molecule that contains three diphenylether linkages and is an acyclic diarylether.⁶ Russuphelol was isolated from the toxic mushroom species *Russula subnigricans*. Galeon and cavicularin are two
members of the macrocyclic diphenylether category. Galeon (1.5)\textsuperscript{7} was isolated from myrtle species *Myrica gale*, and cavicularin (1.6)\textsuperscript{8} was isolated from the liverwort *Cavicularia densa*.

![Figure 1.2. Natural products that contain the diphenylether motif](image)

**Figure 1.2.** Natural products that contain the diphenylether motif

### 1.2 Conformational Chirality

Molecular chirality pervades all aspects of chemistry. Substantial effort has been devoted to preparing molecules that are chiral because of the presence of sp\textsuperscript{3} hybridized stereogenic centers. When molecules contain sp\textsuperscript{3} hybridized stereogenic centers, chirality is readily identified.

In contrast, less emphasis has been dedicated to molecules that are chiral by virtue of their conformation, which we refer to as conformational chirality. In molecules lacking stereogenic centers, chirality is not as easily identified. Furthermore, experimental determination of the presence or absence of chirality is not trivial, particularly when distinguishing between achiral molecules and racemic mixtures.

This thesis revolves around this concept of conformationally chiral diphenylethers. By developing new tools, a better understanding of chirality in many diphenylethers of...
both the acyclic and macrocyclic categories has been provided. A majority of diphenylethers studied had misunderstood chiral properties.

1.3 Conformationally Chiral Acyclic Diphenylethers

The first type of conformationally chiral diphenylether found in the literature is the non-macro cyclic type (Figure 1.3). McRae was the first to speculate on conformational behavior in diphenylether $1.8$. Based on the wooden model of $1.8$, McRae suggested a restricted rotation of the C–O bond due to steric hindrance of the ortho substituents. In 1968 Kessler quantified the activation energy to racemize diphenylether $1.9$, and found it to be 17.8 kcal/mol at 57 °C by variable temperature NMR.$^{10}$

![Figure 1.3](image_url)

**Figure 1.3.** Preliminary work to identify conformational chirality in diphenylethers

More recently, the Clayden group has studied the chirality of the non-macro cyclic type diphenylethers. They have developed a “rule of thumb” to identify if a diphenylether will have stable enantiomeric conformations. $^{11}$ To display conformational chirality, a diphenylether must have a significant barrier to the C–O bond rotation. In substituted diphenylethers such as $1.10$, large substituents at the ortho positions (W, X, Y, Z) may lead to molecular chirality (Figure 1.4). $^{12}$ Two distinct structural features lead to stable enantiomeric conformations of ether $1.10$. First, the substituents at the ortho positions cannot be identical (W≠X and Y≠Z). Second, one of
the ortho substituents needs to be a fully substituted sp³ carbon such as a tert-butyl group or a tertiary alcohol (Y or W ≥tBu).

![Chemical structure](attachment:image.png)

**Figure 1.4.** Predictive model for conformational stability

The Clayden group has developed an enzymatic method to access enantioenriched acyclic diphenylethers (Scheme 1.1). The bis-benzylic alcohol (1.12) can be oxidized with galactose oxidase (GOase) to obtain aldehyde (+)-1.13 in 80% yield and 94% ee. In a separate experiment, desymmetrization of the dialdehyde (1.14) with ketoreductase (KREDs) gives enantioenriched alcohol (−)-1.13 in 84% yield and 61% ee. Using two different enzymes and different substrates, Clayden is able to access both enantiomers of 1.13.

![Enzymatic desymmetrization](attachment:image2.png)

**Scheme 1.1.** Enzymatic desymmetrization to access enantioenriched diphenylethers
1.4 Conformationally Chiral Macro cyclic Diphenylethers: The Diarylether Heptanoid Natural Product Family

Diphenylethers that are constrained in a macrocyclic structure can also display chirality. To the best of our knowledge galeon (1.6) was the first reported chiral macrocyclic diphenylether (Figure 2). It was first isolated in 1976 by Hjortas from the extracts of Myrica gale and reported to be optically active \([\alpha]_D = -16\), \(\text{CHCl}_3\). Interestingly, galeon was reisolated from the same plant in 1997 by the Nagai group with nearly opposite specific rotation \([\alpha]_D = +24.6\), \(\text{CHCl}_3\). The absolute configuration of (+)-galeon was then determined by obtaining the x-ray structure of its \(p\)-bromobenzoate congener. It was determined to have \(pR\) absolute stereochemistry.

We desired a platform to study the chirality of macrocyclic diphenylethers, and we chose the diarylether heptanoids. This family has sixteen natural products that do not possess a stereocenter (Figure 1.5). Interestingly, some (not all) DAEHs were isolated as optically active compounds. The DAEH natural products were isolated from woody plants typically used for traditional medicine. These natural products display a range of biological activities and have attracted interest from synthetic chemists and biologists. The relationship between the DAEH structure and chirality has not been systematically investigated. Furthermore, there was no enantioselective synthesis of any DAEH natural product. We selected the DAEH natural products as ideal candidates for the investigation of conformational chirality and to develop a new enantioselective Ullmann ether coupling.
Figure 1.5. Diarylether heptanoid natural products that do not possess a stereocenter

The DAEHs (1.15–1.30) share a highly conserved molecular architecture containing a meta-para cyclophane. Specifically, the DAEH structure contains a meta-substituted A ring and a para-substituted B ring linked by a seven carbon ansa bridge and an oxygen atom (Figure 1.5). The individual DAEHs differ in the oxygenation of the A and B rings and the degree of unsaturation in the ansa bridge. As shown in Figure 1.5, nine of these compounds were reported to be optically active, suggesting that they are chiral non-racemic compounds. Four of these compounds were isolated with no mention of optical activity or chirality. It is unclear if these eight compounds are achiral, racemic, or chiral non-racemic molecules.

Conformational behavior can be inferred by examining the $^1$H NMR data in the isolation reports. In chiral molecules, geminal methylene protons appear as chemical shift inequivalent signals. This observation is suggestive of slow conformational exchange on the NMR time scale. Chemical shift inequivalent geminal methylene protons were reported in galeon, pterocarine, jugcathanin, myricatomentogenin, garuganin I, garuganin IV, garugamblin I, and II. Conversely, chemical shift equivalent
geminal methylene protons are suggestive of fast dynamic behavior on the NMR time scale. The geminal methylene protons in the acerogenins, garuganin III, 1,9'-didesmethylgaruganin III, 9'-desmethylgarugamblin I, ovalifoliolatin B and tederane A appear as chemical shift equivalent signals. This is suggestive of these molecules possessing fast racemization kinetics relative to the NMR time scale. Note that 1,9'-didesmethylgaruganin I and 9'-desmethylgarugamblin I were reported with non-zero specific rotation.

We considered the possibility that the optically inactive members of this class had been racemized during isolation. DAEHs are commonly isolated by Soxhlet extraction using hot solvents. Prolonged heating could lead to racemization of these conformationally chiral molecules. For example, garuganin I was isolated by continuous extraction of the dried plant powder with petroleum ether, DCM and finally with MeOH. Furthermore, we wondered if the vinylogous ester DAEHs were isolation artifacts arising from the corresponding diketone reacting with the hot acidic methanol. Prior to our work in this area a computational study of garuganin I suggested that racemization at room temperature was impossible.16

1.5 Overview of Previous Synthetic Strategies

The DAEHs have attracted interest from several synthetic groups.17 Two types of retrosynthetic disconnection have been used to prepare the DAEHs (Scheme 1.2). Disconnection of the ansa loop (path a) to give a benzaldehyde and a phosphonium salt was utilized in by Nogradi et al.17b More frequently, DAEHs are simplified by disconnection of the diphenylether (path b). This can be done by either disconnecting the para ring or the meta ring oxygen bond to give achiral halophenols (Figure 1.2b). The halophenols can be converted to the diarylethers by a metal-mediated oxidative
coupling, intramolecular $S_N^1$Ar reactions, or (most frequently) a copper-mediated Ullmann etherification.

Scheme 1.2. General retrosynthetic strategy for the DAEHs

The intramolecular Wittig reaction was used to construct the macrocycle in the synthesis of garugamblin I, garugamblin II and garuganin III.$^{17c}$ The Nogradi group used this strategy in their first synthesis of the DAEHs. This approach was found to be preferable to intramolecular aldol or Wurtz strategies. The intramolecular Wittig reaction of 1.31 promoted by butoxide, produced olefin 1.32 in 67% yield (Scheme 1.3). This is the only account of a DAEH macrocycle being constructed by the formation of its ansa loop.

Scheme 1.3. Construction of ansa loop to furnish the macrocycle

The copper-mediated Ullmann coupling is the most common method to construct the diarylether linkage. Three representative examples are shown in Scheme 1.4. In the synthesis of acerogenin C, the Nogradi group used a copper-mediated Ullmann cyclization of iodophenol 1.33.$^{17a}$ Jahng and coworkers used the CuO promoted Ullmann of bromophenol 1.34 in the synthesis the acerogenins, galeon and pterocarine.$^{17e}$ After failed attempts to furnish the macrocycle with RCM, Natarajan
and coworkers used CuO mediated Ullmann conditions to synthesize ovalifoliolatin B from bromophenol 1.35.\textsuperscript{17e}

![Chemical structures](image)

**Scheme 1.4.** Copper-mediated Ullmann couplings used in the syntheses of DAEHs

Zhu and coworkers utilized a $S_N$Ar reaction in the synthesis of the acerogenins.\textsuperscript{18} The base-promoted macrocyclization of 1.36 proceeded in 88% yield to provide 1.37 (Scheme 1.5). This compound was then advanced to acerogenin C, and a similar route was used to make acerogenin L. Realizing the product of the $S_N$Ar reaction (1.37) was a chiral racemic compound, a variety of chiral bases were screened to give non-racemic product starting from fluorophenol 1.38.\textsuperscript{19} The optimized conditions gave a 60% yield and 20 %ee of the cyclized product 1.39 with the use of chiral ammonium 1.40. The cyclophane 1.39 was not converted to any natural product. To the best of our knowledge, this was the only report in the literature to construct a macrocyclic diarylether in a non-racemic manner.
Scheme 1.5. Zhu’s asymmetric $S_N$Ar reaction to construct diphenylethers

Fujita and coworkers have proposed a biosynthetic hypothesis for the DAEHs. They conducted a $^{14}$C-labeled feeding study of the maple tree *Acer nikoense*. Based on the enrichment of the isotopic ratio, two $p$-coumarates and one malonate combine to give linear diaryl heptanoid 1.40 (Scheme 1.6). The bis-phenol 1.40 undergoes an oxidative phenolic coupling via diradical intermediate 1.41. This intermediate can either the form a C–C bond or the C–O bond containing macrocycle 1.42 or 1.43.

Scheme 1.6. The proposed biosynthesis of the DAEHs
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CHAPTER 2: SYNTHESIS AND CHIRAL PROPERTIES OF THE HEPTANONE DIARYLEETHER HEPTANOIDS

2.1 Introduction

This chapter closely followed the work published in *Organic Letters* in 2012. Chirality is of paramount importance to medicine, biology, and chemistry.\(^1\) Substantial effort has been devoted to preparing molecules that are chiral because of the presence of \(\text{sp}^3\) hybridized stereogenic centers. In contrast, less emphasis has been devoted to molecules that are chiral by virtue of their conformation. However, structures with restricted rotation of sigma bonds including biaryls, cyclophanes, and strained cyclic alkenes have attracted long-standing attention as chiral ligands, catalysts, and targets of total synthesis.\(^2\)

It is our contention that conformational chirality is more prevalent than commonly believed and goes unnoticed in many natural products. The long-term goal is to develop the ability to predict the existence of conformational chirality in complex molecular architectures devoid of stereogenic centers. Toward this end, we sought for study a family of molecules with conserved molecular architectures, devoid of stereogenic centers, that sometimes (but not always) display chirality. The aim is to establish which members are chiral, measure their free energy of activation for racemization, and determine their absolute stereochemistry. The diarylether heptanoid natural products fit these criteria, and they were chosen for study.

Diarylether heptanoids (DAEHs)\(^3\) are a class of natural products isolated from woody plants. These natural products display a range of biological activities\(^4\) and have
attracted interest from synthetic chemists. \(^5\) DAEHs are characterized by an oxa[1.7]metaparacyclophane architecture. Fifteen DAEHs do not possess a stereocenter (Figure 2.1), but interestingly, some (not all) DAEHs were isolated as optically active compounds. \(^6\) The relationship between DAEH structure and chirality has not been systematically investigated.

![Figure 2.1](image)

**Figure 2.1.** Diarylether heptanoid natural products that lack stereogenic centers with heptanone DAEHs highlighted

DAEHs can be divided into two distinct classes: 1. DAEHs with a heptanone *ansa* bridge (2.1–2.6); 2. DAEHs with multiple sp\(^2\)-hybridized carbons in the *ansa* bridge (2.7–2.16). Galeon (2.3) has been isolated on two separate occasions as both a levo- and dextrorotary compound. \(^7\) Jugcathanin (2.2) was isolated without mention of optical activity or chirality, and it was later isolated as an optically active molecule and named juglanin A. \(^8\) Seven other DAEHs were isolated as optically active compounds. \(^9_a,7_b,9\) Two DAEHs were reported to be optically inactive, \(^10\) and the remaining four DAEHs were isolated without mention of optical activity. \(^9_b,11\) It is unclear if the optically inactive members are achiral or are racemic mixtures. Similarly, it is unclear if the DAEHs with unreported optical activity are achiral, chiral racemic, or chiral non-racemic compounds. Although the more substituted members
of this class are commonly optically active (e.g. myricatomentogenin, 2.1), some molecules that have relatively little substitution (e.g. garuganin IV, 2.8) are also optically active. This chapter discloses the synthesis of the “heptanone-type” DAEHs (2.1–2.6) indicated with a box in Figure 2.1, determination of their free energy of activation for racemization, and absolute stereochemistry.

DAEHs are commonly isolated by Soxhlet extraction using hot solvents for hours or days. Elevated temperatures could lead to racemization of these conformationally chiral molecules. We considered the possibility that the optically inactive members of this class had been racemized during isolation.

Insight into the chiral properties of the DAEHs can be gleaned from data presented in the isolation reports. Inspection of the $^1$H NMR data of 2.1–2.4 reveals that the geminal methylene hydrogens are chemical-shift inequivalent. This observation is consistent with the presence of an element of chirality on the NMR timescale. All geminal methylene protons of 2.5 and 2.6 are chemical-shift equivalent, suggesting the natural products are achiral at RT on the NMR timescale.

2.2 Retrosynthetic Analysis

The heptanone DAEHs (2.1–2.6) were prepared to investigate their chiral properties. The retrosynthetic analysis of 2.1 and 2.2 simplifies the molecules by disconnection of the ether linkage to give achiral bromophenols 2.16 (Scheme 2.1). Positioning the phenolic functional group on the more electron-rich phenyl ring was anticipated to give a smoother cyclization than an alternative approach with an electron-rich bromide. Further simplification leads to aldehydes 2.17 and 2.18. Differentially
functionalized aldehyde $2.18$ was envisioned to arise from known coumarin $2.19$ which can be accessed from commercially available 7-hydroxycoumarin.

$$
\text{myricatomentogenin (2.1): } R = H \\
\text{jugcathanin (2.2): } R = \text{Me}
$$

$2.19$

![Scheme 2.1. Retrosynthesis of myricatomentogenin and jugcathanin](image)

2.3 Syntheses of All Heptanone DAEHs

The synthesis begins with $2.19$, which was prepared in 5 steps from 7-hydroxycoumarin. $^{12}$ Acylation under standard conditions provided 7-acetoxy coumarin ($2.19a$). Fries rearrangement promoted by AlCl$_3$ followed by protection of resulting phenol with benzyl bromide gives $2.19b$ (Scheme 2.2). Dakin oxidation of the acetate and concomitant hydrolysis yields a phenol that can be methylated to give a known compound $2.19$. Methanalysis and alkylation of $2.19$ gives ester $2.20$. A two-step oxidation state manipulation of ester $2.20$ produces aldehyde $2.18$. Horner–Wadsworth–Emmons reaction of $2.18$ with phosphonate $2.21$ followed by a reaction with Pearlman’s catalyst that saturates both alkenes and removes the benzyl ether in 83% over 2 steps to yield ketone $2.22$. Intramolecular Ullmann reaction followed by removal of the isopropyl ethers using BCl$_3$ completes the first synthesis of myricatomentogenin ($2.1$). $^{13}$ A similar strategy was used for the
synthesis of jugcathanin (2.2). Olefination of enal 2.18 with phosphonate 2.24 followed by hydrogenation gives ketone 2.25 in 71% over the two steps. Cyclization and deprotection completes the first synthesis of jugcathanin (2.2).

Scheme 2.2. Synthesis of myricatomentogenin and jugcathanin

A related strategy was used in an improved synthesis of 2.3, 2.4, and 2.5 (Scheme 2.3). Vanillin derivative 2.27\textsuperscript{se} undergoes condensation with phosphonate 2.21 to produce unsaturated ketone 2.28. Reduction of the two alkenes and deprotection of benzyl group with Pd(OH)\textsubscript{2} yields bromophenol 2.16c. Cyclization promoted by CuO gives cyclophane 2.29 in good yield. Deprotection with BCl\textsubscript{3} yields galeon (2.3). Removal of the methyl ether using AlCl\textsubscript{3} produces pterocarine (2.4). The synthesis of acerogenin L (2.5) begins with benzyl coumaraldehyde (2.30)\textsuperscript{14}, condensation with phosphonate 2.21 produces 2.31. Ketone 2.31 is reduced and deprotected to give bromophenol 2.16d. Cyclization proceeds under standard conditions to give diarylether 2.32. Deprotection completes the acerogenin L (2.5) synthesis. Finally, acerogenin C (2.6) was prepared using conditions from the literature.\textsuperscript{se} The syntheses
of 2.1–2.5 shown in Schemes 2.2 and 2.3 had combined overall yields of 25–62% and provided up to gram quantities of the natural products for further studies.

Scheme 2.3. Improved syntheses of galeon, pterocarine, and acerogenin L

The chiral properties of 2.1–2.6 were investigated. Some DAEHs have been isolated without optical activity data, and it has not been determined if optically inactive DAEHs are achiral or racemic. Compounds 2.1–2.4 were all found to be resolvable (i.e. chiral) by HPLC using a chiral stationary phase (Diacel, OD, hexanes:iPrOH). Analysis of 2.5 and 2.6 using chiral-phase HPLC showed a single sharp peak regardless of chiral columns or conditions. Moreover, geminal methylene protons of the acerogenins (2.5 and 2.6) were chemical shift equivalent in the $^1$H NMR spectra. These observations suggest that enantiomeric conformations of 2.5 and 2.6 are rapidly interconverting on the NMR timescale at RT.

2.4 Racemization Parameters for the Heptanone DAEHs
The racemization energies of the heptanone DAEHs were measured. To access enantiopure material, these compounds were simply resolved on preparative HPLC with a chiral stationary phase. Enantiopure DAEHs were subjected to elevated temperatures in dichlorobenzene in an isothermal bath. Surprisingly, (+)-2.3 and (+)-2.4 did not undergo racemization with any appreciable rate at the temperatures of Soxhlet extraction (80-110 °C). Racemization of (+)-2.3 occurred only slowly at 201 °C with a first-order rate constant ($k_{rac}$) of $5.20 \times 10^{-6}$ sec$^{-1}$ (approximate half-life of 8.5 h). This results in a free energy of activation for racemization ($\Delta G_{rac}^{\ddagger}$) of 39.6 ± 0.6 kcal/mol at 201 °C (Figure 2). Decomposition of (+)-2.4 occurred with no measureable racemization over a period of 9 h at 210 °C. Assuming first-order kinetics and a conservative half-life of at least 9 h gives a lower limit of $k_{rac} = 2.14 \times 10^{-5}$ sec$^{-1}$ and $\Delta G_{rac}^{\ddagger}$ greater than 39.1 kcal/mol at 210 °C.

![Figure 2.2. Free energies of racemization of DAEHs 2.1–2.6](image)

We then investigated the racemization energies of (−)-2.1 and (−)-2.2. Myricatomentogenin (2.1) decomposed without any measurable racemization at 220 °C over 6 h. Assuming a racemization half-life of more than 6 h gives a lower limit of $k_{rac} = 3.21 \times 10^{-5}$ sec$^{-1}$ and a $\Delta G_{rac}^{\ddagger}$ greater than 38.7 kcal/mol at 220 °C. Enantiopure
(-)-2.2 decomposed over 6 h with partial racemization (80% ee) at 225 °C. This gives a lower limit of $k_{\text{rac}} = 3.21 \times 10^{-5}$ sec$^{-1}$ and $\Delta G^\ddagger_{\text{rac}}$ greater than 39.9 kcal/mol at 225 °C. We hypothesized that the decomposition of the DAEHs was attributable to oxidative processes of the phenol functional group. Without rigorous exclusion of oxygen the decomposition was more rapid. We then investigated the racemization of (+)-2.1′ (diisopropylmyricatomentogenin) which lacks phenols. Racemization occurs at 230 °C with a first-order rate constant of $k_{\text{rac}} = 3.98 \times 10^{-6}$ sec$^{-1}$ and a $\Delta G^\ddagger_{\text{rac}}$ of 43.3 ± 0.5 kcal/mol at 230 °C.

Determination of $\Delta G^\ddagger_{\text{rac}}$ for the interconversion of enantiomeric conformations of the acerogenins was accomplished using low-temperature NMR methods. Specifically, acquisition of $^1$H NMR spectra at cryogenic temperatures induced decoalescence of geminal methylene protons. The coalescence temperature ($T_C$) was −60 °C and −75 °C for 5 and 6, respectively. The relationship $k_C = 2.22 \times \Delta v$ gives the rate constant for coalescence ($k_C$) where $\Delta v$ is the separation in Hz of the coalescing peaks at temperatures below coalescence.$^{16}$ Acquisition of NMR spectra at temperatures below coalescence was not possible for the acerogenins. We approximated $\Delta v$ using the width at half-height of the peak at coalescence.$^{17}$ For 2.5, our estimated $\Delta v = 33$ Hz giving an upper limit of $k_C = 73$ sec$^{-1}$ and $\Delta G^\ddagger_{\text{rac}}$ of 10.5 kcal/mol at −60 °C. For 2.6, our estimated $\Delta v = 31$ Hz giving an upper limit of $k_C = 93$ sec$^{-1}$ and $\Delta G^\ddagger_{\text{rac}}$ of 10.4 kcal/mol at −75 °C. Thus, the relative rate of racemization of the acerogenins compared to 2.1–2.4 is approximately $10^7$. More importantly, 2.5 and 2.6 undergo racemization at temperatures above −60 °C and 2.1–2.4 do not undergo racemization with any appreciable rate up to temperatures of 200 °C.

2.5 Absolute Stereochemistry of the chiral DAEHs
With enantiopure DAEHs in hand, their absolute stereochemistry was determined (Scheme 2.4). The absolute stereochemistry of (+)-2.3 (lit. \([\alpha]_D^{24} + 24.9; c 1.4, \text{CHCl}_3\)) was determined through x-ray crystallography of its p-bromobenzoate derivative.\(^7\) We find that (+)-2.3 (% ee = >99 by HPLC analysis) has \([\alpha]_D^{24} + 17.0 (c 1.4, \text{CHCl}_3)\). Demethylation of (+)-2.3 leads to (+)-2.4 (Scheme 2.4). Methylation of (+)-2.3 gives (+)-2.33 with no loss in enantiopurity by HPLC. Enantiopure (−)-2.2 was deoxygenated\(^{18}\) to give (+)-2.33, which matched (chiral HPLC) the sample prepared from (+)-2.3. Methylation of (−)-2.1 and (−)-2.2 gave the same enantiomer of (+)-2.34 (methylmyricatomentogenin). Thus, all the natural enantiomers of DAEHs 2.1–2.4 have the same pR absolute stereochemistry as shown in Scheme 2.4 and Figure 2.2.

2.6 Bioinspired Oxidative Coupling

Inspired by the biosynthesis and our interest to construct diaryl ethers, we have developed an oxidative phenolic coupling reaction to access the DAEH scaffold via construction of the ether bond. Synthesis of the substrate for the oxidative phenolic coupling reaction begins with functionalized methyl cinnamate derivative 2.35 (Scheme 2.5).\(^{19}\) Conversion of the ester to the aldehyde 2.37 proceeds in 83% over two steps. Phosphonate 2.36 synthesized in one step from methyl cinnamate 2.35 underwent an olefination reaction to give ketone 2.38. Reduction of double bonds and removal of protecting groups under hydrogenation conditions gives bisphenol
2.39. The convergent route along with a 66% overall yield over 4 steps allows rapid access of the bisphenol 2.39.

![Scheme 2.5. Synthesis of bisphenol used for oxidative phenolic coupling reaction](image)

With an efficient synthetic route to access the starting material, we explored various oxidants to carry out the oxidative cyclization. Based on literature precedent, we started with hypervalent iodine reagents to promote the reaction (Table 2.3).\(^\text{20}\) Bis(trifluoroacetoxy)iodo benzene (PIFA) and bis(acetoxy)iodo benzene (BAIB) under basic conditions, produced no desired cyclophane products. Selenium dioxide was used as an oxidant, even under elevated temperature and prolonged reaction times but no desired product was observed. The use of other inorganic oxidants such as KMnO\(_4\), MnO\(_2\), K\(_3\)Fe(CN)\(_6\) and FeCl\(_3\) only led to decomposition products that could not be identified. Ultimately, lead dioxide in acetic acid facilitated the cyclization to produce a mixture of two isomeric compounds. Based on 1D and 2D NMR data, we were able to identify the structures as 2.40 and 2.41. Increasing the equivalents of the oxidant only led to decomposition. With one and a half equivalents of PbO\(_2\) we were able to obtain a 22% yield of 2.40 and 3% yield of 2.41, while recovering 40% of our bisphenol starting material. In efforts to optimize the oxidative phenolic coupling reaction we examined alternative lead oxidant, Pb(OAc)\(_4\). When the reaction was run in acetic acid no cyclophane was produced, but in DCM about 5% of the mixture was seen by NMR. Catalytic oxidants such as salcomine under an atmosphere of oxygen or in stoichiometric amounts produced no cyclophane. Finally, a larger scale reaction
gave identical results as before. The acetate of the major product was cleaved under basic methanolic conditions to give pterocarine (2.4) in quantitative yield. The NMR data for pterocarine were identical to the synthetic material made previously and to the isolation data, further confirming the structure. These results support the biosynthetic route proposed by Fuji and coworkers, who claim that the linear diaryl heptanoids can be cyclized via an oxidative phenolic coupling reaction to produce cyclic DAEHs.

![Diagram showing reaction conditions and products]

Table 2.1 Oxidative phenolic coupling reaction to access the DAEHs

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<tr>
<th>Scale</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
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<td>BAIB, K₂CO₃, CF₃CH₂OH</td>
<td>0%</td>
</tr>
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<td>PIFA, K₂CO₃, CF₃CH₂OH</td>
<td>0%</td>
</tr>
<tr>
<td>15mg</td>
<td>SeO₂, K₂CO₃, Dioxane/H₂O</td>
<td>0%</td>
</tr>
<tr>
<td>15mg</td>
<td>PbO₂(1.5eq), K₂CO₃(3eq), HOAc</td>
<td>2.40 (15%) + 2.41 (~5%)</td>
</tr>
<tr>
<td>30mg</td>
<td>PbO₂(3eq), K₂CO₃(3eq), HOAC</td>
<td>Decomposed</td>
</tr>
<tr>
<td>15mg</td>
<td>PbO₂(1.5eq), HOAc, 6d</td>
<td>2.40 (22%) + 2.41 (3%) + sm (40%)</td>
</tr>
<tr>
<td>15mg</td>
<td>Pb(OAc)₄(1eq), HOAc</td>
<td>No cyclophane</td>
</tr>
<tr>
<td>15mg</td>
<td>Pb(OAc)₄(1eq), DCM</td>
<td>~5% of 1 by NMR</td>
</tr>
<tr>
<td>15mg</td>
<td>salcomine (1eq), MeOH, DMF</td>
<td>no reaction</td>
</tr>
<tr>
<td>120mg</td>
<td>PdO₂(1.5eq), HOAc</td>
<td>2.40 (20%) + 2.41 (7%) + sm (40%)</td>
</tr>
</tbody>
</table>

2.7 Experimental Section

General Experimental Details:
All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. Flash column chromatography was carried out with SiliaFlash P60, 60 Å silica gel.
Reactions and column chromatography were monitored with EMD silica gel 60 F254 plates and visualized with potassium permanganate, ceric ammonium molybdate, iodine, or vanillin stains. Tetrahydrofuran (THF), methylene chloride (CH₂Cl₂), acetonitrile (MeCN) and diethyl ether (Et₂O) were dried by passage through activated alumina columns. DMSO was stored over 3 Å molecular sieves. All other reagents and solvents were used without further purification from commercial sources.

Instrumentation: FT-IR spectra were obtained on NaCl plates with a PerkinElmer Spectrum Vision spectrometer. Proton and carbon NMR spectra (¹H NMR and ¹³C NMR) were recorded in deuterated chloroform (CDCl₃) unless otherwise noted on a Bruker 700 MHz Avance III Spectrometer with carbon-optimized cryoprobe and Bruker 400 MHz DPX-400 spectrometer and calibrated to residual solvent peaks to chloroform 7.28ppm for proton 77.0ppm for carbon resonance. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet. Melting points were determined with a Cole–Parmer instrument and are uncorrected.
(E)-methyl 3-(4-(benzyloxy)-2-hydroxy-3-methoxyphenyl)acrylate (2.51). To a solution of known 7-benzyloxy-8-methoxycoumarin 2.19 (2.68 g, 10 mmol) in MeOH (100 mL, 0.1 M) was added NaOMe (2.70 g, 50 mmol). The reaction mixture was heated to reflux for 13 h upon which time TLC indicated consumption of the coumarin. The reaction mixture was cooled to rt, quenched with H₂O, acidified with HCl to a pH of 3 and extracted with EtOAc (50 mL x 5). The organic layers were combined, washed with saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated. Purification by FCC (3:1 hexanes:EtOAc) to give 2.51 (1.73 g, 5.5 mmol, 55%) as a white solid.

Data for 2.51: Rf 0.25 (2:1 Hexanes:EtOAc); mp = 119–123 ºC; IR (thin film) 3344 (br), 2947, 1699, 1631, 1604 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, J = 16.4 Hz, 1 H), 7.33–7.45 (m, 5 H), 7.14 (d, J = 8.8 Hz, 1 H), 6.59 (d, J = 9 Hz, 1 H), 6.53 (d, J = 21 Hz, 1 H), 5.16 (s, 2 H), 3.96 (s, 3 H), 3.81 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 168.3, 152.8, 149.4, 140.2, 136.4, 135.8, 128.7, 128.2, 127.3, 124.8, 116.8, 115.3, 105.6, 70.7, 61.1, 51.5; HRMS (ESI) calcd for C₁₈H₁₈O₅ [M+H]: 315.1219, found 315.1232.

(E)-methyl-3-(4-(benzyloxy)-2-isopropoxy-3-methoxyphenyl)acrylate (2.20). To a solution of phenol 2.51 (1.30 g, 4.1 mmol) in DMF (20 mL, 0.2 M) were added K₂CO₃ (1.53 g, 12.3 mmol), TBAI (0.38 g, 1.0 mmol) and isopropyl bromide (1.16 mL, 12.3 mmol). The reaction was heated to 50 ºC for 24 h upon which time TLC indicated
consumption of the starting material. The reaction mixture was cooled to rt, quenched with H₂O, acidified with HCl to a pH of 3 and extracted with EtOAc (50mL x 3). The organic layers were combined, washed with H₂O, saturated aqueous NaCl, dried over MgSO₄, filtered and concentrated to give 2.20 (1.46 g, 4.1 mmol, 99%) as a white solid.

Data for 2.20: R₇ 0.5 (2:1 Hexanes:EtOAc); mp = 60–61 °C; IR (thin film) 2976, 1717, 1682 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.99 (d, J = 16.1 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 2 H), 7.42 (t, J = 7.4 Hz, 2 H), 7.36 (t, J = 7.4 Hz, 1 H), 7.26 (d, J = 8.8 Hz, 1 H), 6.75 (d, J = 8.8 Hz, 1 H), 6.27 (d, J = 16 Hz, 1 H), 6.39 (d, J = 7.4 Hz, 1 H), 5.18 (s, 2 H), 4.64 (sept, J = 6.1 Hz, 1 H), 3.90 (s, 3 H), 3.82 (s, 3 H), 1.34 (d, J = 6.1 Hz, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 168.0, 154.6, 151.4, 143.0, 140.5, 136.6, 128.7, 128.1, 127.3, 123.0, 122.4, 116.3, 109.1, 76.7, 70.8, 60.7, 51.6, 22.6; HRMS (ESI) calcd for C₂₁H₂₄O₅ [M+Na]: 379.1516, found 379.1512.

(E)–methyl–3–{(4–(benzyloxy)–2–isopropoxy–3–methoxyphenyl)acrylate (2.52). To a cooled (−78 °C) solution of ester 2.20 (800 mg, 2.24 mmol) in THF (23 mL, 0.1 M) was added DIBAL (5.2 mL, 1 M in toluene, 5.2 mmol). The reaction was done in 2h upon which time TLC indicated consumption of the starting material. The reaction mixture was quenched with of MeOH (2 mL) and of saturated Rochelle’s salt solution (2 mL), and warmed to rt. The mixture was diluted with H₂O, acidified with HCl to a pH of 5 and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with H₂O, saturated NaCl solution, dried over MgSO₄, filtered and concentrated. Purification by FCC (2:1 hexanes: EtOAc) gave 2.52 (726mg, 2.21 mmol, 99%) as a pale yellow wax.
Data for **S2**: R$_f$ 0.25 (2:1 Hexanes:EtOAc); IR (thin film) 3430 (br), 2974, 1594 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.47 (d, $J = 7.6$ Hz, 2 H), 7.41 (t, $J = 7.7$ Hz, 2 H), 7.35 (t, $J =$ 7.4 Hz, 1 H), 7.18 (d, $J = 8.6$ Hz, 1 H), 6.89 (d, $J = 16$Hz, 1 H), 6.72 (d, $J = 8.8$ Hz, 1 H), 6.27 (dt, $J =$ 16.0, 6.1Hz, 1 H), 5.15 (s, 2 H), 4.59 (sept, $J = 6.2$ Hz, 1 H), 4.33 (dd, $J =$ 6.1, 1.3 Hz, 2 H), 3.89 (s, 3 H), 1.32 (d, $J =$ 6.2 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 152.5, 149.6, 143.1, 137.0, 128.6, 127.9, 127.4, 127.3, 126.7, 125.1, 120.6, 109.4, 76.1, 70.9, 64.41, 60.6, 22.7; HRMS (ESI) calcd for C$_{20}$H$_{25}$O$_5$ [M+] : 329.1752, found 329.1753.

**(E)-3-(4-(benzylloxy)-2-isopropoxy-3-methoxyphenyl)acrylaldehyde (2.18)**. To a cooled (0 ºC) solution of alcohol **2.S2** (500 mg, 1.53 mmol) in DCM (15 mL, 0.1 M) were added NaHCO$_3$ (347 mg, 4.50 mmole) and the Dess–Martin periodionate (813 mg, 1.92 mmol). The reaction was warmed to rt after 15 min, 1h later TLC indicated consumption of the starting material. The reaction mixture was quenched with saturated aqueous NaHCO$_3$ solution. The mixture was extracted with DCM (30 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over Na$_2$SO$_4$, filtered and concentrated. Purification by FCC (8: 1 hexanes: EtOAc) yielded **2.18** (416 mg, 1.276 mmol, 83% yield) as a white solid.

Data for **2.18**: R$_f$ 0.3 (8:1 Hexanes: EtOAc); mp = 74–76 ºC; IR (thin film) 3031, 2972, 2832, 2801, 1680, 1599; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 9.68 (d, $J =$ 8.0 Hz, 1 H), 7.83 (d, $J =$ 16.0 Hz, 1 H), 7.47 (d, $J =$ 7.3 Hz, 2 H), 7.42 (d, $J =$ 7.4 Hz, 2 H), 7.38 (d, $J =$ 7.3 Hz, 1 H), 7.33 (d, $J =$ 8.8 Hz, 1 H), 6.79 (d, $J =$ 8.8 Hz, 1 H), 6.67 (dd, $J =$ 16.1, 8.0 Hz, 1 H), 5.20 (s, 2 H), 4.72 (sept, $J =$ 6.2Hz, 1 H), 3.91 (s, 3 H), 1.35 (d, $J =$ 6.2 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 194.4, 155.6, 151.6, 148.6, 142.9, 136.4, 128.7, 128.2, 127.3,
122.8, 122.5, 109.2, 76.8, 70.8, 60.71, 60.69, 22.68; HRMS (ESI) calcd for C\textsubscript{20}H\textsubscript{23}O\textsubscript{4} [M+H]: 327.1604, found 327.1596.

Dimethyl–(4–(3–bromo–4–isopropoxyphenyl)–2–oxobutyl)phosphonate (2.21). To a cooled (−78 °C) solution of dimethyl methylphosphonate (1.22 g, 9.75 mmol) in THF (23 mL, 0.14 M) was added MeLi (6 mL, 1.6 N in Et\textsubscript{2}O, 9.50 mmol). The mixture was stirred for 30 min after which known methyl ester 2.54 (1.00 g, 3.25 mmol) was added.\textsuperscript{22} The mixture was stirred for 15 min then warmed to rt for 2h upon which time TLC indicated consumption of starting material. The reaction mixture was quenched with saturated NH\textsubscript{4}Cl solution (5 mL). The mixture was diluted with H\textsubscript{2}O and extracted with EtOAc (25 mL x 4). The organic layers were combined, washed with H\textsubscript{2}O, saturated NaCl solution, dried over MgSO\textsubscript{4}, filtered and concentrated. Purification by FCC (100% EtOAc) yielded 2.21 (1.23 g, 3.13 mmol, 96%) as a yellow oil.

Data for 2.21: R\textsubscript{f} 0.15 (1:1 Hexanes: EtOAc); IR (thin film) 3344 (bs), 2947, 1699, 1631, 1604; \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) \(\delta\) 7.38 (d, \(J = 2.2\) Hz, 1 H), 7.07 (dd, \(J = 8.3\), 2.2 Hz, 1 H), 6.84 (d, \(J = 8.4\) Hz, 1 H), 4.51 (sept, \(J = 6.2\) Hz, 1 H), 3.87 (d, \(J = 11.3\) Hz, 6 H), 3.10 (d, \(J = 22.7\) Hz, 2 H), 2.94 (t, \(J = 7.3\) Hz, 2 H), 2.84 (t, \(J = 7.3\) Hz, 2 H), 1.38 (d, \(J = 6.2\) Hz, 6 H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) \(\delta\) 200.8 (d, \(J = 6.4\) Hz), 152.9, 134.4, 133.2, 128.3, 116.1, 113.7, 72.4, 53.1, 45.5, 41.5 (d, \(J = 128\) Hz), 28.1, 22.1; HRMS (TOF MS ESI+) calcd for C\textsubscript{15}H\textsubscript{22}O\textsubscript{5}BrP [M+Na]: 415.0271, found 415.0286.
Dimethyl (4–(3–bromo–4–methoxyphenyl)–2–oxobutyl)phosphonate (2.24). To a cooled (–78 ºC) solution of dimethyl methylphosphonate (3.72 g, 30 mmol) in THF (71 mL, 0.14 M) was added MeLi (18.1 mL, 1.6 N in Et₂O, 29 mmol). The mixture was stirred for 30 min after which known methyl ester 2.53 (2.72 g, 10 mmol) was added. The mixture was stirred for 15 min then warmed to rt for 2 h upon which time TLC indicated consumption of starting material. The reaction mixture was quenched with saturated NH₄Cl solution (10 mL). The mixture was diluted with H₂O and extracted with EtOAc (50 mL x 4). The organic layers were combined, washed with H₂O, saturated NaCl solution, dried over MgSO₄, filtered and concentrated. Purification by FCC (100% EtOAc) yielded 2.24 (3.41 g, 9.34 mmol, 94%) as a yellow oil.

Data for 2.24: Rₜ 0.2 (1:1 Hexanes: EtOAc); IR (thin film) 3344 (bs), 2947, 1699, 1631, 1604; ¹H NMR (700 MHz, CDCl₃) δ 7.38 (d, J = 2.2 Hz, 1 H), 7.07 (dd, J = 8.3, 2.2 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 4.51 (sept, J = 6.2 Hz, 1 H), 3.87 (d, J = 11.3 Hz, 6 H), 3.10 (d, J = 22.7 Hz, 2 H), 2.94 (t, J = 7.3 Hz, 2 H), 2.84 (t, J = 7.3 Hz, 2 H); ¹³C NMR (176 MHz, CDCl₃) δ 200.8 (d, J = 6.4 Hz), 154.2, 134.2, 133.1, 128.5, 111.9, 111.4, 56.2, 53.1, 45.4, 41.47 (d, J = 128 Hz), 41.1, 28.03; HRMS (TOF MS ES+) calcd for C₁₃H₁₈O₅BrP [M+Na]: 386.9964, found 386.9973.

4E,6E)–7–(4–(benzyloxy)–3–methoxyphenyl)–1–(3–bromo–4–isopropoxyphenyl)hepta–4,6–dien–3–one (2.28). To a solution of ketophosphonate
2.21 (1.00 g, 2.54 mmol) in THF (10 mL, 0.2 M) was added DBU (386 mg, 2.54 mmol). The mixture was stirred for 10 min after which known aldehyde 2.27 (546 mg, 2.04 mmol) was added. The reaction mixture was heated to 60 ºC for 6 h upon which time TLC indicated consumption of aldehyde. The reaction mixture was quenched with 2M HCl solution (2 mL). The mixture was diluted with H₂O and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with H₂O, saturated NaCl solution, dried over MgSO₄, filtered and concentrated. Purification by FCC (5:1 Hexanes:EtOAc) yielded 2.28 (916 mg, 1.71 mmol, 84%) as a bright yellow oil.

Data for 2.28: (Rf 0.6 (2:1 Hexanes: EtOAc); IR (thin film) 2976, 1678, 1583; \(^1^H\) NMR (700 MHz, CDCl₃) δ 7.46 (d, J = 7.4 Hz, 2 H), 7.43 (d, J = 2.0 Hz, 1 H), 7.40 (t, J = 7.4 Hz, 2 H), 7.35–7.31 (m, 2 H), 7.10 (dd, J = 2.1, 8.3 Hz, 1 H), 7.05 (d, J = 1.9 Hz, 1 H), 6.99 (dd, J = 1.9, 8.2 Hz, 1 H), 6.90–6.85 (m, 3 H), 6.76 (dd, J = 10.9, 15.5 Hz, 1 H), 6.26 (d, J = 15.3 Hz, 1 H), 5.21 (s, 2 H), 4.52 (sept, J = 6.1 Hz, 1 H), 3.96 (s, 3 H), 2.91 (m, 4 H), 1.39 (d, J = 6.1 Hz, 6 H); \(^{13}\)C NMR (176 MHz, CDCl₃) δ 199.1, 152.9, 149.8, 149.5, 143.2, 141.5, 136.7, 135.3, 133.2, 129.5, 128.6, 128.5, 128.3, 128.0, 127.2, 124.8, 121.3, 116.2, 113.8, 113.7, 109.7, 71.4, 70.9, 56.1, 42.2, 29.1, 22.1; HRMS (TOF MS ES+) calcd for C₃₀H₃₂O₅Br [M+H]: 535.1479, found 535.1484.

(4E,6E)-7-(4-{benzyloxy})-2-isopropoxy-3-methoxyphenyl)-1-(3-bromo-4-isopropoxyphenyl)hepta-4,6-dien-3-one (2.22). To a solution of ketophosphonate 2.21 (605 mg, 1.54 mmol) in THF (4 mL, 0.3 M) was added DBU (230 mg, 1.54 mmol). The mixture was stirred for 10 min after which aldehyde 2.18 (400 mg, 1.23 mmol) was added. The reaction mixture was heated to 60 ºC for 18 h upon which time TLC indicated consumption of aldehyde. The reaction mixture was quenched with 2M HCl
solution (2 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (5:1 Hexanes:EtOAc) yielded 2.22 (608 mg, 1.03 mmol, 83%) as a bright yellow oil.

Data for 2.22: $R_f$ 0.7 (2:1 Hexanes: EtOAc); IR (thin film) 2926, 1678, 1584; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.47 (d, $J = 7.06$ Hz, 2 H), 7.43–7.40 (m, 3 H), 7.36–7.35 (m, 2 H), 7.27 (d, $J = 5.8$ Hz, 1 H), 7.25 (s, 1 H), 7.11 (dd, $J = 2.2$, 8.4 Hz, 1 H), 6.87 (d, $J = 8.7$ Hz, 1 H), 6.80 (dd, $J = 11$, 15.7 Hz, 1 H), 6.74 (d, $J = 8.7$ Hz, 1 H), 6.24 (d, $J = 15.4$ Hz, 1 H), 5.17 (s, 2 H), 4.63 (sept, $J = 6.3$ Hz, 1 H), 4.52 (sept, $J = 6.1$ Hz, 1 H), 3.89 (s, 3 H), 2.91 (m, 4 H), 1.34 (d, $J = 6.1$ Hz, 6 H), 1.33 (d, $J = 6.2$ Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 199.2, 153.8, 152.9, 150.6, 144.0, 143.2, 137.1, 136.7, 135.3, 133.3, 128.6, 128.3, 128.2, 128.0, 127.3, 125.4, 124.6, 121.2, 116.2, 113.8, 109.4, 72.4, 70.4, 60.6, 42.1, 29.3, 29.0, 22.7, 22.1; HRMS (ESI) calcd for C$_{33}$H$_{37}$O$_5$Br [M+Na]: 595.1816, found 595.1824.

![Chemical structure](image)

(4$E$,6$E$)-7-(4-(benzyloxy)-2-isoproxy-3-methoxyphenyl)-1-(3-bromo-4-methoxyphenyl)hepta-4,6-dien-3-one (2.25). To a solution of ketophosphonate 2.24 (913 mg, 2.50 mmol) in THF (20 mL, 0.1 M) was added DBU (380 mg, 2.50 mmol). The mixture was stirred for 10 min after which aldehyde 2.18 (648 mg, 2.00 mmol) was added. The reaction mixture was heated to 55 $^\circ$C for 24 h upon which time TLC indicated consumption of aldehyde. The reaction mixture was quenched with 2M HCl solution (4 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with H$_2$O, saturated
NaCl solution, dried over MgSO₄, filtered and concentrated. Purification by FCC (6:1 Hexanes:EtOAc) yielded 2.25 (802 mg, 1.42 mmol, 71%) as a bright yellow oil.

Data for 2.25: Rf 0.5 (2:1 Hexanes: EtOAc); IR (thin film) 2973, 1680, 1581; ¹H NMR (700 MHz, CDCl₃) δ 7.48 (d, J = 7.3 Hz, 2 H), 7.44 (d, J = 2.1 Hz, 1 H), 7.43 (t, J = 7.8 Hz, 2 H), 7.37 (m, 2 H), 7.28 (d, J = 3.4 Hz, 1 H), 7.26 (d, J = 3.3 Hz 1 H), 7.16 (dd, J = 2.1, 8.3 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 1 H), 6.80 (dd, J = 11.1, 15.6 Hz, 1 H), 6.74 (d, J = 8.8 Hz, 1 H), 6.24 (d, J = 15.4 Hz, 1 H), 5.17 (s, 2 H), 4.64 (sept, J = 6.2 Hz, 1 H), 3.899 (s, 3 H), 3.897 (s, 3 H), 2.92 (m, 4 H), 1.33 (d, J = 6.2 Hz, 6 H); ¹³C NMR (176 MHz, CDCl₃) δ 199.2, 154.2, 153.8, 150.5, 144.1, 143.1, 137.1, 136.7, 135.1, 133.1, 128.7, 128.5, 128.2, 128.1, 127.3, 125.3, 124.6, 121.2, 111.9, 111.5, 109.3, 76.4, 70.8, 60.6, 56.3, 42.2, 29.0, 22.7; HRMS (ESI) calcd for C₃₁H₃₄O₅Br [M+H]: 565.1572, found 565.1566.

(4E,6E)-7-(4-(benzyloxy)phenyl)-1-(3-bromo-4-isopropoxyphenyl)hepta-4,6-dien-3-one (2.31). To a solution of ketophosphonate 2.21 (100 mg, 0.25 mmol) in THF (1 mL, 0.2 M) was added DBU (40 mg, 0.26 mmol). The mixture was stirred for 10 min after which aldehyde 2.30 (50 mg, 0.21 mmol) was added. The reaction mixture was heated to 50 °C for 24 h upon which time TLC indicated consumption of aldehyde. The reaction mixture was quenched with 2M HCl solution (1 mL). The mixture was diluted with H₂O and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with H₂O, saturated NaCl solution, dried over MgSO₄, filtered and concentrated. Purification by FCC (8:1 Hexanes:EtOAc) yielded 2.31 (87 mg, 0.17 mmol, 82%) as a bright yellow oil.

Data for 2.31: RF 0.7 (2:1 Hexanes: EtOAc); IR (thin film) 3031, 2976, 1679, 1587; ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.41 (m, 7 H), 7.38–7.32 (m, 2 H), 7.10 (dd, J = 2.2, 8.3
Hz, 1 H), 7.00 (d, J = 6.9 Hz, 2 H), 6.91 (d, J = 15.4 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H),
6.78 (ddd, J = 0.7, 10.9, 15.4 Hz, 1 H), 6.25 (d, J = 15.4 Hz, 1 H), 5.12 (s, 2 H), 4.52
(sept, J = 6.1 Hz, 1 H), 2.91 (bs, 4 H), 1.38 (d, J = 6.1 Hz, 6 H); \(^{13}\text{C} \text{NMR} \text{ (100 MHz,}
\text{CDCl}_3) \delta 199.1, 159.8, 152.9, 143.2, 141.3, 136.6, 135.3, 133.2, 129.1, 128.8, 128.7,
128.4, 128.3, 128.1, 127.5, 124.6, 116.3, 115.2, 113.8, 72.4, 70.1, 42.1, 29.1, 22.1;
HRMS (ESI) calcd for C\(_{29}\)H\(_{29}\)O\(_3\)Br [M+] : 505.1378, found 505.1396.

\[
\text{MeO} \quad \text{Br} \\
\text{HO} \quad \text{HO}
\]

**1–(3–bromo–4–isopropoxyphenyl)–7–(4–hydroxy–3–methoxyphenyl)heptan–3–one (2.55).** To a solution of 2.28 (900 mg, 1.68 mmol) in EtOAc (34 mL, 0.05 M) was
added Pearlman’s catalyst (180 mg, 20% Pd(OH)\(_2\) on carbon nominally 50% water,
20% w/w). The mixture was stirred vigorously under an atmosphere of hydrogen.
After 2 h TLC indicated consumption of starting material. The reaction mixture was
filtered through a silica gel/celite plug and concentrated to yield 2.55 (740 mg, 1.65
mmol, 98%) as a clear oil.

Data for 2.55: \(R_f\) 0.25 (3:1 Hexanes: EtOAc); IR (thin film) 3450 (br), 2931, 1709, 1604;
\(^1\text{H} \text{NMR} \text{ (700 MHz, CDCl}_3) \delta 7.37 \text{ (d, J = 2.2 Hz, 1 H)}, 7.05 \text{ (dd, J = 2.2, 8.4 Hz, 1 H)},
6.85–6.83 \text{ (m, 2 H)}, 6.69–6.66 \text{ (m, 2 H)}, 5.56 \text{ (bs, 1 H)}, 4.51 \text{ (sept, J = 6.1 Hz, 1 H)}, 3.89
(s, 3 H), 2.82 \text{ (t, J = 7.6 Hz, 2 H)}, 2.69 \text{ (t, J = 7.5 Hz, 2 H)}, 2.55 \text{ (t, J = 7.4 Hz, 2 H)}, 2.42 \text{ (t,}
J = 7.0 Hz, 2 H), 1.65–1.56(m, 4 H), 1.38 (d, J = 6.1 Hz, 6 H); \(^{13}\text{C} \text{NMR} \text{ (176 MHz, CDCl}_3)
\delta 209.9, 152.9, 146.4, 143.7, 135.0, 134.1, 133.1, 128.2, 120.9, 116.1, 114.2, 113.8,
111.0, 72.4, 55.9, 44.2, 42.9, 35.4, 31.3, 28.5, 23.4, 22.1; HRMS (ESI) calcd for
C\(_{23}\)H\(_{29}\)O\(_4\)Br [M+] : 449.1312, found 449.1327.
1-(3-bromo-4-isopropoxyphenyl)-7-(4-hydroxy-2-isopropoxy-3-methoxyphenyl)heptan-3-one (2.56). To a solution of 2.22 (900 mg, 1.68 mmol) in EtOAc (34 mL, 0.05 M) was added Pearlman’s catalyst (180 mg, (20% Pd(OH)$_2$ on carbon nominally 50% water), 20% w/w). The mixture was stirred vigorously under an atmosphere of hydrogen. After 2 h TLC indicated consumption of starting material. The reaction mixture was filtered through a silica gel/celite plug and concentrated to yield 2.56 (740 mg, 1.65 mmol, 98%) as a clear oil.

Data for 2.56: R$_f$ 0.25 (3:1 Hexanes: EtOAc); IR (thin film) 3450 (br), 2931, 1709, 1604; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.37 (d, $J$ = 2.2, 1 H), 7.06 (dd, $J$ = 2.2, 8.4 Hz, 1 H), 6.84 (d, $J$ = 8.4 Hz, 1 H), 6.78 (d, $J$ = 8.3 Hz, 1 H), 6.65 (d, $J$ = 8.3 Hz, 1 H), 5.60 (bs, 1 H), 4.54–4.48 (m, 2 H), 3.89 (s, 3 H), 2.82 (t, $J$ = 7.5 Hz, 2 H), 2.71 (t, $J$ = 7.6 Hz, 2 H), 2.55 (t, $J$ = 7.7 Hz, 2 H), 2.44 (t, $J$ = 7.3 Hz, 2 H), 1.65–1.53 (m, 4 H), 1.38 (d, $J$ = 6.1 Hz, 6 H), 1.29 (d, $J$ = 6.1 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 209.9, 152.9, 148.2, 147.6, 139.9, 135.1, 133.1, 128.3, 128.2, 124.2, 116.1, 113.8, 109.6, 74.5, 72.4, 60.4, 44.1, 42.9, 30.1, 29.3, 28.5, 23.7, 22.7, 22.1; HRMS (ESI) calcd for C$_{23}$H$_{29}$O$_4$Br [M+H]: 449.1312, found 449.1327.

1-(3-bromo-4-methoxyphenyl)-7-(4-hydroxy-2-isopropoxy-3-methoxyphenyl)heptan-3-one (2.57). To a solution of 2.25 (900 mg, 1.68 mmol) in EtOAc (34 mL, 0.05 M) was added Pearlman’s catalyst (180 mg, (20% Pd(OH)$_2$ on carbon nominally 50% water), 20% w/w). The mixture was stirred vigorously under an atmosphere of hydrogen. After 2 h TLC indicated consumption of starting material. The reaction mixture was filtered through a silica gel/celite plug and concentrated to yield 2.57 (740 mg, 1.65 mmol, 98%) as a clear oil.

Data for 2.57: R$_f$ 0.25 (3:1 Hexanes: EtOAc); IR (thin film) 3450 (br), 2931, 1709, 1604; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.37 (d, $J$ = 2.2, 1 H), 7.06 (dd, $J$ = 2.2, 8.4 Hz, 1 H), 6.84 (d, $J$ = 8.4 Hz, 1 H), 6.78 (d, $J$ = 8.3 Hz, 1 H), 6.65 (d, $J$ = 8.3 Hz, 1 H), 5.60 (bs, 1 H), 4.54–4.48 (m, 2 H), 3.89 (s, 3 H), 2.82 (t, $J$ = 7.5 Hz, 2 H), 2.71 (t, $J$ = 7.6 Hz, 2 H), 2.55 (t, $J$ = 7.7 Hz, 2 H), 2.44 (t, $J$ = 7.3 Hz, 2 H), 1.65–1.53 (m, 4 H), 1.38 (d, $J$ = 6.1 Hz, 6 H), 1.29 (d, $J$ = 6.1 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 209.9, 152.9, 148.2, 147.6, 139.9, 135.1, 133.1, 128.3, 128.2, 124.2, 116.1, 113.8, 109.6, 74.5, 72.4, 60.4, 44.1, 42.9, 30.1, 29.3, 28.5, 23.7, 22.7, 22.1; HRMS (ESI) calcd for C$_{23}$H$_{29}$O$_4$Br [M+H]: 449.1312, found 449.1327.
carbon nominally 50% water), 20% w/w). The mixture was stirred vigorously under an atmosphere of hydrogen. After 2 h TLC indicated consumption of starting material. The reaction mixture was filtered through a silica gel/celite plug and concentrated to yield 2.57 (740 mg, 1.65 mmol, 98%) as a clear oil.

Data for 2.57: Rf 0.25 (3:1 Hexanes: EtOAc); IR (thin film) 3450 (br), 2931, 1709, 1604; $^1$H NMR (700 MHz, CDCl$_3$) δ 7.38 (d, $J = 2.2$, 1 H), 7.10 (dd, $J = 2.2$, 8.4 Hz, 1 H), 6.83 (d, $J = 8.3$ Hz, 1 H), 6.78 (d, $J = 8.3$ Hz, 1 H), 6.65 (d, $J = 8.3$ Hz, 1 H), 5.60 (bs, 1 H), 4.50 (sept, $J = 6.2$ Hz, 1 H), 3.890 (s, 3 H), 3.886 (s, 3 H), 2.84 (t, $J = 7.5$ Hz, 2 H), 2.71 (t, $J = 7.6$ Hz, 2 H), 2.55 (t, $J = 7.7$ Hz, 2 H), 2.44 (t, $J = 7.4$ Hz, 2 H), 1.65–1.53 (m, 4 H), 1.29 (d, $J = 6.2$ Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 209.9, 154.2, 148.2, 147.6, 139.9, 134.8, 133.1, 128.4, 128.3, 124.2, 111.9, 111.5, 109.6, 74.5, 60.4, 56.3, 44.3, 42.9, 30.1, 29.3, 28.5, 23.7, 22.7; HRMS (ESI) calcd for C$_{23}$H$_{29}$O$_4$Br [M+H]: 449.1312, found 449.1327.

1-(3-bromo-4-isopropoxyphenyl)-7-(4-hydroxyphenyl)heptan-3-one (2.58). To a solution of 2.31 (900 mg, 1.68 mmol) in EtOAc (34 mL, 0.05 M) was added Pearlman’s catalyst (180 mg, (20% Pd(OH)$_2$ on carbon nominally 50% water), 20% w/w). The mixture was stirred vigorously under an atmosphere of hydrogen. After 2 h TLC indicated consumption of starting material. The reaction mixture was filtered through a silica gel/celite plug and concentrated to yield 2.58 (740 mg, 1.65 mmol, 98%) as a clear oil.

Data for 2.58: Rf 0.25 (3:1 Hexanes: EtOAc); IR (thin film) 3450 (br), 2931, 1709, 1604; $^1$H NMR (700 MHz, CDCl$_3$) δ 7.37 (d, $J = 2.0$ Hz, 1 H), 7.06 (dd, $J = 2.0$, 8.3 Hz, 1 H), 7.02 (d, $J = 8.3$ Hz, 1 H), 6.85 (d, $J = 8.3$ Hz, 1 H), 6.78 (dd, $J = 2.1$, 6.3 Hz, 2 H), 5.92 (bs, 1 H), 4.51 (sept, $J = 6.1$ Hz, 1 H), 2.82 (t, $J = 7.5$ Hz, 2 H), 2.71 (t, $J = 7.5$ Hz, 2 H),
2.54 (t, J = 7.5 Hz, 2 H), 2.43 (t, J = 7.2 Hz, 2 H), 1.64–1.54 (m, 4 H), 1.39 (d, J = 6.1 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 211.13, 153.90, 152.89, 134.97, 134.04, 133.11, 129.43, 128.26, 116.29, 115.25, 113.83, 72.53, 44.20, 42.99, 34.79, 31.18, 28.55, 23.36, 22.11; HRMS (ESI) calcd for C$_{23}$H$_{29}$O$_4$Br [M+H]: 449.1312, found 449.1327.

$^{*}$–Isopropyl galeon (2.29). To a solution of 2.55 (35 mg, 0.077 mmol) in pyridine (11 mL, 0.007 M) was added Cs$_2$CO$_3$ (62 mg, 0.19 mmol). The mixture was heated to 90 ºC for 10 min, CuO (15 mg 0.19 mmol) was added, and the mixture was heated to reflux. After 20 h TLC indicated consumption of starting material. The reaction mixture was cooled to rt and quenched with 2M HCl solution (1 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (4:1 Hexanes:EtOAc) yielded 2.29 (21 mg, 0.057 mmol, 73%) as opaque wax.

Data for 2.29: R$_f$ 0.65 (2:1 Hexanes: EtOAc); IR (thin film) 2933, 1713, 1584, 1502; $^1$H NMR (700 MHz, CDCl$_3$) δ 7.05–7.04 (m, 1 H), 6.90–6.88 (m, 2 H), 6.86 (d, J = 8.1 Hz, 1 H), 6.64 (dd, J = 2.2, 8.1 Hz, 1 H), 5.58 (d, J = 2.2 Hz, 1 H), 4.65 (sept, J = 6.1 Hz, 1 H), 3.74 (s, 3 H), 3.05 (dd, J = 10.5, 16.2 Hz, 1 H), 2.86 (td, J = 5.6, 13.3 Hz, 1 H), 2.73 (dd, J = 8.6, 16.3 Hz, 1 H), 2.65 (ddd, J = 5.4, 9.4, 13.8 Hz, 1 H), 2.40 (ddd, J = 1.5, 10.4, 16.9 Hz, 1 H), 2.28 (ddd, J = 1.3, 8.5, 16.9 Hz, 1 H), 2.07 (m, 1 H), 1.83 (m, 1 H), 1.67 (m, 1 H), 1.60–1.55 (m, 3 H), 1.43 (d, J = 6.1 Hz, 3 H), 1.41 (J = 6.1 Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 210.0, 152.3, 151.3, 144.5, 143.0, 139.6, 134.8, 124.3, 122.0, 121.2, 118.3, 115.3, 112.8, 72.2, 56.1, 46.1, 40.1, 36.0, 27.4, 27.1, 22.4, 22.3, 19.1; HRMS (ESI) calcd for C$_{23}$H$_{28}$O$_4$ [M+]: 368.19978, found 368.19876.
(±)-Isopropyl jugcathanin (2.26). To a solution of 2.57 (15 mg, 0.031 mmol) in pyridine (6.2 mL, 0.005 M) was added K₂CO₃ (11 mg, 0.078 mmol). The mixture was heated to 90 °C for 10 min, CuO (6 mg 0.078 mmol) was added, and mixture was heated to reflux. After 48 h TLC indicated consumption of starting material. The reaction mixture was cooled to rt and quenched with 2M HCl solution (1 mL). The mixture was diluted with H₂O and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with H₂O, saturated NaCl solution, dried over MgSO₄, filtered, and concentrated. Purification by FCC (6:1 Hexanes:EtOAc) yielded 2.26 (7.8 mg, 0.0196 mmol, 63%) as white solid.

Data for 2.26: Rₜ 0.5 (3:1 Hexanes: EtOAc); mp = 8587 °C; IR (thin film) 2939, 1734, 1582; ¹H NMR (700 MHz, CDCl₃) δ 6.97 (d, J = 8.4 Hz, 1 H), 6.84 (d, J = 8.2 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 1 H), 6.70 (dd, J = 2.1, 8.2 Hz, 1 H), 5.65 (d, J = 2.1 Hz, 1 H), 4.41 (sept, J = 6.2 Hz, 1 H), 3.96 (s, 3 H), 3.69 (s, 3 H), 3.15 (td, J = 5.7, 12.8 Hz, 1 H), 3.06 (ddd, J = 2.2, 9.2, 16.0 Hz, 1 H), 2.73 (ddd, J = 2.3, 7.9, 16.3 Hz, 1 H), 2.40–2.31 (m, 3 H), 2.15–2.09 (m, 1 H), 1.82–1.76 (m, 1 H), 1.76–1.70 (m, 1 H), 1.69–1.63 (m, 1 H), 1.57–1.52 (m, 2 H), 1.40 (d, J = 6.2 Hz, 3 H), 1.29 (J = 6.2 Hz, 3 H); ¹³C NMR (176 MHz, CDCl₃) δ 210.4, 150.6, 149.9, 147.6, 146.7, 146.6, 134.0, 133.4, 125.5, 121.5, 119.4, 113.3, 112.0, 75.4, 60.1, 56.3, 46.3, 41.1, 31.1, 27.2, 25.2, 23.1, 22.3, 19.1; HRMS (ESI) calcd for C₂₄H₃₀O₅ [M+Na]: 421.1950, found 421.1991.
(±)-Diisopropyl myricatomentogenin (2.23). To a solution of 2.56 (120 mg, 0.28 mmol) in pyridine (40 mL, 0.007 M) was added K$_2$CO$_3$ (99 mg, 0.71 mmol). The mixture was was heated to 90 °C for 10 min, CuO (56 mg 0.71 mmol) was added and mixture was heated to reflux. After 69 h TLC indicated consumption of starting material. The reaction mixture was cooled to rt and quenched with 2M HCl solution (3 ml). The mixture was diluted with H$_2$O and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (6:1 Hexanes:EtOAc) yielded (±)-2.23 (89 mg, 0.21 mmol, 74%) as white solid.

Data for 2.23: R$_f$ 0.66 (2:1 Hexanes: EtOAc); mp = 91–94 °C; IR (thin film) 2974, 1717, 1580; $^1$H NMR (700 MHz, CDCl$_3$) δ 6.96 (d, $J$ = 8.3 Hz, 1 H), 6.86 (d, $J$ = 8.1 Hz, 1 H), 6.78 (d, $J$ = 8.3 Hz, 1 H), 6.65 (dd, $J$ = 2.2, 8.1 Hz, 1 H), 5.64 (d, $J$ = 2.1 Hz, 1 H), 4.65 (sept, $J$ = 6.1 Hz, 1 H), 4.43 (sept, $J$ = 6.2 Hz, 1 H), 3.73 (s, 3 H), 3.16 (td, $J$ = 5.5, 12.9 Hz, 1 H), 3.07 (dd, $J$ = 9.9, 16.0 Hz, 1 H), 2.70 (ddd, $J$ = 1.5, 8.6, 16.1 Hz, 1 H), 2.40–2.30 (m, 3 H), 2.15 (ddd, $J$ = 6.0, 10.8, 19.2 Hz, 1 H), 1.80–1.75 (m, 1 H), 1.71–1.66 (m, 2 H), 1.56–1.50 (m, 2 H), 1.42 (t, $J$ = 6.0 Hz, 9 H), 1.23 (J = 6.1 Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 210.4, 151.6, 150.5, 147.8, 146.6, 144.6, 134.9, 133.2, 125.5, 121.5, 119.6, 117.6, 113.6, 75.3, 72.3, 60.2, 46.3, 41.0, 31.2, 27.2, 25.1, 23.2, 22.3, 22.2, 19.2; HRMS (ESI) calcd for C$_{26}$H$_{34}$O$_5$ [M+H]: 427.2486, found 427.2484.

(+)2.23. Racemic 2.23 was resolved using chiral HPLC with chiral stationary phase (Diacel, OD, 1:9, hex:iPrOH) to yield enantiopure (+)-2.23.

Data for (+)-2.23: mp = 92-94 °C; [α]$_D$ = +27.3 (c = 1.0, CHCl$_3$)
**Isopropyl acerogenin L (2.32).** To a solution of 2.58 (60 mg, 0.143 mmol) in pyridine (20 mL, 0.007 M) was added Cs$_2$CO$_3$ (116 mg, 0.357 mmol). The mixture was then heated to 90 °C for 10 min, then the CuO (28 mg, 0.357 mmol) was added and the mixture was heated to reflux. After 48 h TLC indicated consumption of starting material. The reaction mixture was cooled to rt and quenched with 2M HCl solution (3 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (40 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (5:1 Hexanes:EtOAc) yielded 2.32 (39 mg, 0.115 mmol, 81%) as white solid.

Data for 2.32: R$_f$ 0.8 (1:1 Hexanes: EtOAc); mp = 115–116 °C; IR (thin film) 2934, 1689, 1515; $^1$H NMR (700 MHz, CDCl$_3$) δ 7.29 (d, J = 8.4 Hz, 2 H), 7.02 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.2 Hz, 1 H), 6.65 (dd, J = 2.0, 8.2 Hz, 1 H), 5.50 (d, J = 2.0 Hz, 1 H), 4.60 (sept, J = 6.1 Hz, 1 H), 2.88 (t, J = 5.2 Hz, 2 H), 2.77 (t, J = 6.5 Hz, 2 H), 2.33 (t, J = 5.5 Hz, 2 H), 1.81 (t, J = 8.0 Hz, 2 H), 1.71–1.68 (m, 2 H), 1.61–1.57 (m, 2 H), 1.43 (d, J = 6.2 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 209.9, 154.8, 152.4, 144.7, 138.1, 134.6, 123.5, 121.3, 117.6, 114.4, 72.6, 46.1, 40.7, 35.4, 27.4, 27.1, 22.3, 19.0; HRMS (EI) calcd for C$_{22}$H$_{26}$O$_3$[M+] : 338.1870, found 338.1882.

**(-)-Galeon (2.3).** To a solution of 2.29 (400 mg, 1.08 mmol) in DCM (12 mL, 0.1 M) was added BCl$_3$ (3.25 mL, 1 M solution in THF, 3.25 mmol) at 0 °C. The mixture was
stirred for 10 min, and warmed to rt. After 10 min TLC indicated consumption of starting material. The reaction mixture was quenched with MeOH (3.6 mL). The mixture was stirred for 30 min and concentrated to yielded (±)-2.3 (349 mg, 1.06 mmol, 98%) as white solid.

Data for 2.3: Rf 0.5 (2:1 Hexanes: EtOAc); mp = 176–179 ºC; IR (thin film) 3407 (br), 2933, 1707, 1596; 1H NMR (700 MHz, CDCl3) δ 7.04 (d, J = 8.5 Hz, 1 H), 6.90 (m, 2 H), 6.85 (d, J = 8.1 Hz, 1 H), 6.64 (dd, J = 2.0, 8.1 Hz, 1 H), 5.66 (bs, 1 H), 5.58 (d, J = 2.0 Hz, 1 H), 3.75 (s, 3 H), 2.99 (dd, J = 10.2, 16.1 Hz, 1 H), 2.85 (td, J = 5.7, 13.1 Hz, 1 H), 2.74 (dd, J = 8.4, 15.9 Hz, 1 H), 2.67 (ddd, J = 5.5, 9.0, 13.0 Hz, 1 H), 2.38 (ddd, J = 1.5, 10.2, 16.5 Hz, 1 H), 2.27 (ddd, J = 1.5, 8.5, 16.5 Hz, 1 H), 1.98 (m, 1 H), 1.80 (m, 1 H), 1.66 (m, 1 H), 1.61–1.54 (m, 3 H); 13C NMR (176 MHz, CDCl3) δ 210.3, 152.2, 147.3, 143.2, 142.9, 140.2, 133.3, 124.1, 122.1, 122.0, 115.1, 112.3, 56.1, 46.4, 41.4, 36.0, 27.5, 27.4, 19.1; HRMS (ESI) calcd for C20H22O4 [M+H]: 327.1596, found 327/1608.

(+)·2.3. Racemic 2.3 was resolved using HPLC with chiral stationary phase (Diacel, OD, 1:9, hex:iPrOH) to yield enantiopure (+)-2.3.

Data for (+)-2.3: mp = 177-179 ºC; [α]D = +17.0 (c = 1.4, CHCl3)

(±)-Jugcathanin (2.2). To a solution of 2.23 (5 mg, 0.012 mmol) in DCM (1.2 mL, 0.01 M) was added BCl3 (0.08 mL, 1 M solution in THF, 0.08 mmol) at 0 ºC. The mixture was stirred for 10 min, and warmed to rt. After 10 min TLC indicated consumption of starting material. The reaction mixture was quenched with MeOH (3.6 mL). The mixture was stirred for 30 min and concentrated to yielded (±)-2.2 (4.5 mg, 0.012 mmol, 99%) as white solid.
Data for **2.2**: R$_f$ 0.4 (3:1 Hexanes: EtOAc); mp = 158–160 °C; IR (thin film) 3428 (br), 2935, 1710, 1586; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 6.93 (d, $J$ = 8.4 Hz, 1 H), 6.85 (d, $J$ = 8.3 Hz, 1 H), 6.72 (dd, $J$ = 2.1, 8.2 Hz, 1 H), 6.61 (d, $J$ = 8.4 Hz, 1 H), 5.98 (bs, 1 H), 5.58 (d, $J$ = 2.0 Hz, 1 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 3.19 (td, $J$ = 5.6, 13.0 Hz, 1 H), 3.02 (ddd, $J$ = 9.7, 8.4, 16.1 Hz, 1 H), 2.73 (dd, $J$ = 8.4, 16.1 Hz, 1 H), 2.44–2.37 (m, 2 H), 2.32 (ddd, $J$ = 1.3, 8.6, 16.9 Hz, 1 H), 2.11 (ddd, $J$ = 5.2, 11.2, 19.2 Hz, 1 H), 1.85–1.75 (m, 2 H), 1.70–1.54 (m, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 210.3, 149.0, 147.9, 146.5, 145.6, 139.8, 134.3, 126.1, 124.8, 121.7, 115.9, 113.0, 111.7, 61.7, 56.2, 46.2, 41.1, 29.9, 27.1, 24.6, 19.0; HRMS (El) calcd for C$_{21}$H$_{24}$O$_5$ [M+]: 356.16237, found 356.16218.

(–)-**2.2**. Racemic **2.2** was resolved using HPLC with chiral stationary phase (Diacel, OD, 1:9, hex:iPrOH) to yield enantiopure (–)**2.2**.

Data for (–)**2.2**: mp = 158-160 °C; $[\alpha]_D$ = -20.2 (c = 0.5, MeOH)

![Myricatumtogenin](image)

(±)-**Myricatumtogenin (2.1)**. To a solution of **2.23** (23 mg, 0.054 mmol) in DCM (0.6 mL, 0.1 M) was added BCl$_3$ (0.54 mL, 1 M solution in THF, 0.54 mmol) at 0 °C. The mixture was stirred for 10 min, and warmed to rt. After 15 min TLC indicated consumption of starting material. The reaction mixture was quenched with MeOH (2.0 mL). The mixture was stirred for 30 min and concentrated to yielded (±)**2.1** (19 mg, 0.054 mmol, 99%) as white solid.

Data for **2.1**: R$_f$ 0.2 (2:1 Hexanes: EtOAc); mp = 159–161 °C; IR (thin film) 3407 (br), 2935, 1706, 1596; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 6.93 (d, $J$ = 8.3 Hz, 1 H), 6.86 (d, $J$ = 8.2 Hz, 1 H), 6.66 (dd, $J$ = 2.0, 8.1 Hz, 1 H), 6.55 (d, $J$ = 8.4 Hz, 1 H), 6.05 (bs, 1 H), 5.61 (bs 1 H), 5.52 (d, $J$ = 2.0 Hz, 1 H), 3.94 (s, 3 H), 3.20 (td, $J$ = 5.7, 13.2 Hz, 1 H), 2.99 (dd, $J$ =
10.0, 16.2 Hz, 1 H), 2.77 (dd, J = 8.5, 16.1 Hz, 1 H), 2.43–2.41 (m, 2 H), 2.30 (ddd, J =
1.3, 8.8, 16.8 Hz, 1 H), 2.10 (ddd, J = 5.3, 11.3, 16.8 Hz, 1 H), 1.86–1.80 (m, 1 H), 1.79–
1.72 (m, 1 H), 1.72–1.66 (m, 1 H), 1.65–1.59 (m, 1 H), 1.59–1.52 (m, 1 H); 13C NMR
(176 MHz, CDCl3) δ 210.3, 148.1, 147.1, 145.2, 142.8, 140.0, 133.8, 126.4, 125.4,
122.4, 115.6, 115.2, 112.4, 61.8, 46.3, 41.1, 29.9, 27.2, 24.7, 19.0; HRMS (El) calcd for
C20H22O5 [M+] 342.14747, found 342.14672.

(--)-2.1. To a solution of (+)-2.23 (15 mg, 0.035 mmol) in DCM (3.5 mL, 0.01 M) was
added BCl3 (0.21 mL, 1 M solution in THF, 0.21 mmol) at 0 ºC. The mixture was stirred
for 10 min, and warmed to rt. After 15 min TLC indicated consumption of starting
material. The reaction mixture was quenched with MeOH (3.6 mL). The mixture was
stirred for 30 min and concentrated to yielded (±)-2.1 (12 mg, 0.035 mmol, 99%) as
white solid.
Data for (--)-2.1: mp = 159-161 ºC; [α]D = -12.0 (c = 0.1, CHCl3)

Acerogenin L (2.5). To a solution of 2.32 (25 mg, 0.074 mmol) in DCM (0.7 mL, 0.1 M)
was added BCl3 (0.22 mL, 1 M solution in THF, 0.22 mmol) at 0 ºC. The mixture was
stirred for 10 min, and warmed to rt. After 15 min TLC indicated consumption of
starting material. The reaction mixture was quenched with MeOH (3.6 mL). The mixture was
stirred for 30 min and concentrated to yielded 2.5 (21 mg, 0.071 mmol, 96%) as a off-white solid.

Data for 2.5: Rf 0.5 (2:1 Hexanes: EtOAc); mp = 184–185 ºC; IR (thin film) 3417 (br),
2936, 1699, 1595; 1H NMR (700 MHz, CDCl3) δ 7.32 (d, J = 8.4 Hz, 2 H), 7.20 (bs, 1 H),
7.03–7.01 (m, 2 H), 6.63 (dd, J = 2.1, 8.1 Hz, 1 H), 5.45 (d, J = 2.0 Hz, 1 H), 2.86 (t, J =
5.3 Hz, 2 H), 2.78 (t, J = 6.5 Hz, 2 H), 2.32 (t, J = 5.5 Hz, 2 H), 1.80 (t, J = 8.0 Hz, 2 H),
1.71–1.68 (m, 2 H), 1.60–1.55 (m, 2 H); 13C NMR (176 MHz, CDCl3) δ 210.2, 154.2,
148.5, 142.9, 138.9, 133.4, 131.4, 123.3, 121.9, 115.0, 113.2, 46.4, 41.0, 35.4, 27.4, 27.3, 19.0; HRMS (EI) calcd for C$_{19}$H$_{20}$O$_3$ [M$^+$]: 296.1419, found 296.1412.

(±)-Pterocarine (2.4). To a solution of galeon (2.3) (330 mg, 1.00 mmol) in DCM (10 mL, 0.1 M) was added AlCl$_3$ (1.33 g, 10.0 mmol). The mixture was heated to reflux. After 36 h TLC indicated consumption of starting material. The reaction mixture was quenched slowly with H$_2$O (10 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (3:1 Hexanes:EtOAc) yielded (±)-2.4 (237 mg, 0.76 mmol, 76%) as yellow solid.

Data for 2.4: R$_f$ 0.4 (2:1 Hexanes: EtOAc); mp = 142–146 ºC; IR (thin film) 3370 (br), 2932, 1702, 1596; $^1$H NMR (700 MHz, CDCl$_3$) δ 6.97 (d, $J$ = 2.0 Hz, 1 H), 6.91 (d, $J$ = 8.2 Hz, 1 H), 6.85 (d, $J$ = 8.1 Hz, 1 H), 6.84 (dd, $J$ = 2.0, 8.1 Hz, 1 H), 6.66 (dd, $J$ = 2.1, 8.1 Hz, 1 H), 5.77 (bs, 2 H), 5.60 (d, $J$ = 2.0 Hz, 1 H), 2.90 (ddd, $J$ = 2.1, 9.5, 16.2 Hz, 1 H), 2.84 (ddd, $J$ = 2.1, 8.8, 16.2 Hz, 1 H), 2.75–2.67 (m, 2 H), 2.39 (ddd, $J$ = 2.1, 9.5, 16.6 Hz, 1 H), 2.30 (ddd, $J$ = 2.1, 9.5, 16.6 Hz, 1 H), 1.96–1.91 (m, 1 H), 1.85–1.80 (m, 1 H), 1.75–1.70 (m, 1 H), 1.67–1.63 (m, 1 H), 1.60–1.56 (m, 2 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 210.6, 148.8, 146.8, 142.9, 140.6, 140.6, 134.0, 123.5, 122.9, 122.8, 118.0, 115.6, 112.6, 46.5, 41.2, 35.6, 27.3, 27.3, 19.0; HRMS (ESI) calcd for C$_{19}$H$_{20}$O$_4$ [M−H]: 313.1440, found 313.1448.

(+)-2.4. To a solution of (+)-2.3 (10 mg, 0.030 mmol) in DCM (2 mL, 0.06 M) was added AlCl$_3$ (30 mg, 0.23 mmol). The mixture was heated to reflux. After 36 h TLC indicated consumption of starting material. The reaction mixture was quenched
slowly with H$_2$O (5 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (3:1 Hexanes:EtOAc) yielded (+)-2.4 (8.5 mg, 0.027 mmol, 90%) as yellow solid.

Data for (+)-2.4: mp = 142-144 °C; [α]$_D$ = +27.3 (c = 1.0, CHCl$_3$)

(±)-Methylgaleon (2.33). To a solution of galeon (±)-2.3 (2 mg, 0.003 mmol) in MeCN (0.3 mL, 0.01 M) were added K$_2$CO$_3$ (0.4 mg, 0.006 mmol) and MeI (0.9 mg, 0.006 mmol). The mixture was heated to 40 °C and stirred. After 18 h TLC indicated consumption of starting material. The reaction mixture was cooled to rt and quenched with 2M HCl solution (1 mL). The mixture was diluted with H$_2$O and extracted with DCM (5 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated to yield (±)-2.33 (2 mg, 0.003 mmol, 98%) as white solid.

Data for 2.33: R$_f$ 0.66 (2:1 Hexanes: EtOAc); mp = 150–151 °C; IR (thin film) 2933, 1708, 1586; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.06 (d, $J$ = 8.5 Hz, 1 H), 6.90 (m, 2 H), 6.82 (d, $J$ = 8.3 Hz, 1 H), 6.68 (dd, $J$ = 1.6, 8.1 Hz, 1 H), 5.56 (d, $J$ = 1.6 Hz, 1 H), 3.95 (s, 3 H), 3.75 (s, 3 H), 3.05 (dd, $J$ = 10.5, 16.3 Hz, 1 H), 2.87 (td, $J$ = 5.6, 13.0 Hz, 1 H), 2.73 (td, $J$ = 8.3, 15.7 Hz, 1 H), 2.68–2.62 (m, 1 H), 2.39 (ddd, $J$ = 1.5, 10.0, 16.7 Hz, 1 H), 2.28 (ddd, $J$ = 1.7, 8.4, 16.8 Hz, 1 H), 2.12–2.02 (m, 1 H), 1.86–1.79 (m, 1 H), 1.75–1.67 (m, 1 H), 1.61–1.52 (m, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.0, 152.4, 149.3, 146.5, 142.5, 139.8, 133.9, 124.2, 122.0, 121.1, 115.2, 112.2, 111.9, 56.3, 56.1, 46.1, 41.2,
36.0, 27.4, 27.1, 19.2; HRMS (El) calcd for C\textsubscript{21}H\textsubscript{24}O\textsubscript{4} [M+]: 340.16746, found 340.16690.

\(\pm\)-2.33 from \(\pm\)-2.3. To a solution of galeon \(\pm\)-2.3 (2 mg, 0.003 mmol) in MeCN (0.3 mL, 0.01 M) were added K\textsubscript{2}CO\textsubscript{3} (0.4 mg, 0.006 mmol) and Mel (0.9 mg, 0.006 mmol). The mixture was heated to 40 °C and stirred. After 18 h TLC indicated consumption of starting material. The reaction mixture was cooled to rt and quenched with 2M HCl solution (1 mL). The mixture was diluted with H\textsubscript{2}O and extracted with DCM (5 mL x 3). The organic layers were combined, washed with H\textsubscript{2}O, saturated NaCl solution, dried over MgSO\textsubscript{4}, filtered and concentrated to yield \(\pm\)-2.33 (2 mg, 0.003 mmol, 98%) as white solid.

\(\pm\)-2.33 from \(\mp\)-2.2. To a solution of \(\mp\)-jugcathanin \(\mp\)-2.2 (1.5 mg, 0.0042 mmol) in DCM (0.8 mL, 0.005 M) were added pyridine (0.7 mg, 0.0084 mmol) and Tf\textsubscript{2}O (1.4 mg, 0.0050 mmol) at 0 °C. After 10 min TLC indicated consumption of starting material. The reaction mixture was quenched with saturated NaHCO\textsubscript{3} solution (1 mL). The mixture was diluted with H\textsubscript{2}O and extracted with DCM (5 mL x 3). The organic layers were combined, washed with H\textsubscript{2}O, saturated NaCl solution, dried over MgSO\textsubscript{4}, filtered and concentrated to yield 2.59 (2 mg, 0.003 mmol, 98%) as a yellow solid, which was used without further purification. To a solution of crude 2.59 (1.5 mg, 0.0042 mmol) in MeOH (0.4 mL, 0.01 M) were added NH\textsubscript{4}HCO\textsubscript{2} (1.3 mg, 0.021 mmol) and Pd/C (0.5 mg, 5% Pd/C, 25% w/w). The reaction mixture was heated to reflux. After 10 h TLC indicated consumption of starting material. The reaction mixture was filtered through a silica gel/celite plug and concentrated to yield \(\pm\)-2.33 (740 mg, 1.65 mmol, 98%) as a white solid.

Data for \(\pm\)-2.33: mp = 150-151 °C; \([\alpha]\)\textsubscript{D} = +21.1 (c = 1.0, CHCl\textsubscript{3})
(±)-Methyljugcathanin (2.34). To a solution of (±)-2.2 (1.5 mg, 0.0042 mmol) in MeCN (0.40 mL, 0.001 M) were added K₂CO₃ (1.7 mg, 0.0126 mmol) and Mel (1.8 mg, 0.0126 mmol). The mixture was stirred at rt. After 24 h TLC indicated consumption of starting material. The reaction mixture was quenched with 2M HCl solution (1 mL). The mixture was diluted with H₂O and extracted with DCM (10 mL x 3). The organic layers were combined, washed with H₂O, saturated NaCl solution, dried over MgSO₄, filtered and concentrated to yielded (±)-2.34 (1.5 mg, 0.0042 mmol, 99%) as white solid.

Data for 2.34: Rf 0.7 (2:1 Hexanes: EtOAc); mp = 105–107 °C; IR (thin film) 2930, 1713, 1582; ¹H NMR (700 MHz, CDCl₃) δ 6.97 (d, J = 8.3 Hz, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.70 (dd, J = 2.2, 8.4 Hz, 1 H), 5.61 (d, J = 2.2 Hz, 1 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 3.15 (td, J = 6.0, 12.8 Hz, 1 H), 3.00 (ddd, J = 2.4, 9.3, 16.3 Hz, 1 H), 2.76 (ddd, J = 2.3, 8.1, 16.4 Hz, 1 H), 2.42–2.31 (m, 3 H), 2.10–2.05 (m, 1 H), 1.80–1.73 (m, 2 H), 1.71–1.66 (m, 1 H), 1.59–1.55 (m, 2 H); ¹³C NMR (176 MHz, CDCl₃) δ 210.1, 152.6, 149.8, 147.7, 146.6, 146.2, 134.1, 132.2, 125.6, 121.6, 119.9, 113.1, 112.1, 61.0, 60.7, 56.3, 46.3, 41.0, 30.3, 27.1, 24.5, 19.0; HRMS (EI) calcd for C₂₂H₂₆O₅ [M+]: 370.17802, found 370.17636.

(+)–2.34 from (−)-2.1. To a solution of (−)-2.1 (1 mg, 0.003 mmol) in MeCN (0.3 mL, 0.001 M) were added K₂CO₃ (0.8 mg, 0.006 mmol) and Mel (1.3 mg, 0.009 mmol). The mixture was stirred at rt. After 19 h TLC indicated consumption of starting material. The reaction mixture was quenched with 2M HCl solution (1 mL). The mixture was diluted with H₂O and extracted with DCM (5 mL x 3). The organic layers were
combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated to yielded (+)-2.34 (1.1 mg, 0.003 mmol, 99%) as white solid.

**(+)-2.34 from (−)-2.2.** To a solution of (−)-2.2 (1 mg, 0.003 mmol) in MeCN (0.3 mL, 0.001 M) were added K$_2$CO$_3$ (0.8 mg, 0.006 mmol) and MeI (1.1 mg, 0.007 mmol). The mixture was stirred at rt. After 19 h TLC indicated consumption of starting material. The reaction mixture was quenched with 2M HCl solution (1 mL). The mixture was diluted with H$_2$O and extracted with DCM (5 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated to yielded (+)-2.34 (1.1 mg, 0.003 mmol, 99%) as white solid.

Data for (+)-2.34: mp = 105-107 °C; [α]$_D$ = +13.7 (c = 1.0, CHCl$_3$)

---

**dimethyl (4-(4-(benzylloxy)phenyl)-2-oxobutyl)phosphonate (2.36).** To a solution of Dimethyl methylphosphonate (1.16 g, 9.33 mmol) in THF (12.5 mL, 0.25 M) at −78 °C was added n-BuLi (3.90 ml, 9.33 mmol, 2.5 M in hexane). After stirring for 30 min, a THF solution (2.5 mL) of the known ester 2.35 was added slowly.$^{24}$ The reaction mixture was warmed to rt and TLC indicated complete consumption of the ester after 1h at rt. The reaction mixture was quenched with saturated NH$_4$Cl solution (5 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (25 mL x 4). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (100% EtOAc) yielded 2.36 (1.09 g, 3.01 mmol, 97%) as an oil.

Data for 2.36: R$_f$ 0.45 (1:1 hexanes: EtOAc); IR (thin film) 3034, 2955, 1714, 1512, 1244 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 7.44 (d, $J = 7.5$ Hz, 2 H), 7.39 (t, $J = 7.6$ Hz, 2 H), 7.34 (t, $J = 8.6$ Hz, 2 H), 6.91 (d, $J = 8.6$ Hz, 2 H), 5.05 (s, 2 H), 3.76 (d, $J = 11.3$ Hz, 6 H), 3.08 (d, $J = 22.7$ Hz, 2 H), 2.94 (t, $J = 7.2$ Hz, 2 H), 2.87 (t, $J = 7.2$ Hz, 2 H); $^{13}$C NMR
(176 MHz, CDCl$_3$) $\delta$ 201.1, 157.2, 137.1, 132.9, 129.4, 128.6, 127.9, 127.5, 114.9, 70.0, 53.05 (d, $J = 6.3$ Hz), 45.8, 41.55 (d, $J = 128.0$ Hz), 28.6; HRMS (TOF MS ES$^+$) calcd for C$_{19}$H$_{24}$O$_5$P[M+H$^+$]: 363.1357, found 363.1361.

(4E,6E)-1,7-Bis(4-(benzyloxy)phenyl)hepta-4,6-dien-3-one (2.38). To a solution of ketophosphonate 2.36 (420 mg, 1.16 mmol) in THF (4.7 mL, 0.20 M) was added DBU (184 mg, 1.21 mmol). The mixture was stirred for 20 min after which known aldehyde 2.37 (224 mg, 0.93 mmol) was added. The reaction mixture was heated to 60 °C for 18 h upon which time TLC indicated consumption of all aldehyde. To the reaction mixture 2 mL of hexane was added and cooled to rt and then to 0 °C and filtered to obtain yellow crystals. The mother liquor was recrystallized again with THF/hexane to obtain 2.38 (390 mg, 0.82 mmol, 88%).

Data for 2.38: $R_f$ 0.24 (4:1 hexanes: EtOAc); mp = 133-137 °C; IR (thin film) 3037, 2921, 1644, 1589, 1511 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.44 (m, 10 H), 7.35 (m, 3 H), 7.17 (d, $J = 8.6$, Hz, 2 H), 7.00 (d, $J = 8.8$ Hz, 1 H), 6.91 (d, $J = 15.4$ Hz, 1 H), 6.77 (dd, $J = 15.4$, 11.0 Hz, 1 H), 6.26 (d, $J = 15.4$ Hz, 1 H), 5.12 (s, 2 H), 5.07 (s, 2 H), 2.94 (m, 4 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 199.6, 159.7, 157.2, 143.2, 141.1, 137.2, 136.6, 133.7, 129.4, 129.1, 128.8, 128.7, 128.6, 128.55, 128.1, 127.9, 127.5, 124.7, 115.3, 114.9, 70.1, 42.5, 29.5; HRMS (TOF MS ES$^+$) calcd for C$_{33}$H$_{31}$O$_3$ [M+H$^+$]: 475.2273, found 475.2250.

1,7-Bis(4-hydroxyphenyl)heptan-3-one (2.39). To a solution of 2.38 (300 mg, 0.63 mmol) in EtOAc (6.3 mL, 0.1 M) was added Pearlman’s catalyst (60 mg, 20% Pd(OH)$_2$
on carbon nominally 50% water, 20% w/w). The mixture was stirred vigorously under an atmosphere of hydrogen. After 24 h TLC indicated consumption of starting material. The reaction mixture was filtered through a celite plug and concentrated. Purification by FCC (2:1 hexanes: EtOAc) yielded 2.39 (180 mg, 0.60 mmol, 96%) as an opaque wax that solidified in the freezer.

Data for 2.39: R<sub>f</sub> 0.25 (3:1 Hexanes: EtOAc); mp = 85-87 °C; IR (thin film) 3387 (br), 3024, 2929, 1696, 1514; <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>) δ 7.04 (dd, <i>J</i> = 14.7, 8.5 Hz, 4 H), 7.09 (dd, <i>J</i> = 8.5, 4.0 Hz, 4 H), 4.96 (bs, 2 H), 2.84 (t, <i>J</i> = 7.5 Hz, 2 H), 2.70 (t, <i>J</i> = 7.5 Hz, 2 H), 2.54 (t, <i>J</i> = 7.4 Hz, 2 H), 2.41 (t, <i>J</i> = 7.1 Hz, 2 H), 1.56 (m, 4 H); <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>) δ 210.8, 153.9, 153.6, 134.3, 133.2, 129.5, 115.3, 115.1, 44.5, 42.9, 34.8, 31.1, 29.0, 23.3; HRMS (ESI) calcd for C<sub>19</sub>H<sub>23</sub>O<sub>3</sub> [M+H]: 299.1650, found 299.1647

![Chemical structure of 3²-Hydroxy-8-oxo-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-1⁶-yl acetate (2.40) and 3²-hydroxy-6-oxo-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-1⁶-yl acetate (2.41).](image)

3²-Hydroxy-8-oxo-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-1⁶-yl acetate (2.40) and 3²-hydroxy-6-oxo-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-1⁶-yl acetate (2.41). To a solution of the bisphenol 2.39 (120 mg, 0.40 mmol) in HOAc (8 mL, 0.05 M) was added PbO<sub>2</sub> (144 mg, 0.60 mmol). The mixture was stirred vigorously. After 60 h the reaction mixture was filtered through a celite plug and concentrated. Purification by FCC (7:1 hexanes: EtOAc) yielded 2.40 (27 mg, 0.05 mmol, 20%), 2.41 (9 mg, 0.03 mmol, 7%) and bisphenol 2.39 (48 mg, 40%) was recovered.

Data for 2.40: R<sub>f</sub> 0.50 (2:1 Hexanes: EtOAc); mp = 190-192 °C; IR (thin film) 3404 (br), 3059, 2926, 1767, 1706, 1596, 1516, 1501; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.18 (dd, <i>J</i> = 8.2, 2.0 Hz, 1 H), 7.11 (d, <i>J</i> = 8.4 Hz, 1 H), 7.09 (d, <i>J</i> = 2.0 Hz, 1 H), 6.83 (d, <i>J</i> = 8.1 Hz, 1 H), 6.66 (dd, <i>J</i> = 8.1, 2.1 Hz, 1 H), 5.65 (d, <i>J</i> = 2.0 Hz, 1 H), 5.51 (bs, 1 H), 3.30 (dd, <i>J</i> = 16.5, 10.4 Hz, 1 H), 2.85 (dt, <i>J</i> = 13.1, 5.2 Hz, 1 H), 2.68 (m, 2 H), 2.45 (ddd, <i>J</i> = 16.7,
10.5, 1.7 Hz, 1 H), 2.27 (dd, \( J = 16.6, 7.4 \) Hz, 1 H), 2.18 (s, 3 H), 2.07 (m, 2 H), 1.80 (m, 2 H), 1.60 (m, 2 H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 210.4, 168.8, 147.1, 146.4, 143.4, 143.2, 140.0, 133.8, 128.8, 124.9, 124.7, 122.8, 115.1, 114.1, 46.3, 41.1, 35.5, 29.7, 27.3, 20.5, 18.8; HRMS (ESI) calcd for C\(_{21}\)H\(_{22}\)O\(_5\) [M+Na]: 377.1366, found 377.1365.

Data for \( \textbf{2.41} \): \( R_f \) 0.50 (2:1 Hexanes: EtOAc); mp = 168-172 °C; IR (thin film) 3392 (br), 3028, 2933, 1765, 1706, 1595, 1503; \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.14 (d, \( J = 8.4 \) Hz, 1 H), 7.07 (dd, \( J = 8.4, 2.1 \) Hz, 1 H), 6.99 (d, \( J = 2.1 \) Hz, 1 H), 6.87 (d, \( J = 7.7 \) Hz, 1 H), 6.70 (dd, \( J = 8.4, 2.1 \) Hz, 1 H), 5.85 (d, \( J = 2.1 \) Hz, 1 H), 5.86 (bs, 1 H), 2.99 (m, 2 H), 2.64 (m, 2 H), 2.53 (m, 1 H), 2.46 (m, 1 H), 2.22 (s, 3 H), 2.00 (m, 2 H), 1.41 (m, 2 H), 1.04 (m, 2 H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 211.9, 168.7, 148.6, 147.2, 143.42, 143.38, 138.9, 133.1, 127.9, 124.9, 124.5, 123.7, 117.1, 115.5, 46.3, 44.3, 32.0, 31.7, 27.2, 20.5, 20.4; HRMS (ESI) calcd for C\(_{21}\)H\(_{22}\)O\(_5\) [M+Na]: 377.1366, found 377.1365.
HPLC trace for (t)-2.3

Data File: C:\Chem3\DATA\QUAMA\mgp00105.D
Sample Name: galacosa-tac

Maximum Absorptivity: 254 nm (QUAMA:mgp00105.D)

Area Percent Report

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HPLC trace for (+)-2.3.

Sorted By : Signal
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Use Multiplier & Dilution Factor with ISTDs

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Total : 4046.34058 46.07596

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HPLC trace for (t)-2.4.

Sample Name: rac-pta

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Acq. Operator: qumar  Seq. Line: i
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Injection Date: 3/4/2012 2:54:31 PM  Inj: i
                Inj Volume: 25 µl
Acq. Method: C:\CHM332\METHODS\MQS-PPF-00M
Last changed: 3/4/2012 2:47:26 PM by subham
Analysis Method: C:\CHM332\METHODS\MQS-PPF-00M
Last changed: 6/6/2012 4:04:27 PM by Rhomson

VWD TA, Wavelength=284 nm (QUAMAR/MQ2000042.DI)

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Use Multiplier & Dilution Factor with ISTDs

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Instrument 1 6/3/2012 2:09:37 PM Rhomson
HPLC trace for (+)-2.4

Sample Name: + pto

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Seq. Line : 1
Acq. Instrument : HP1100
Location : Vial 1
Injection Date : 5/4/2012 7:19:48 PM
Inj Volume : 25 µl
Analyte Method : C:\CHM321\METHODS\DAHOG-09.DAT
Last changed : 4/3/2012 7:16:49 PM by quenar
Analysis Method : C:\CHM321\METHODS\DAHOG-09.DAT
Last changed : 6/7/2012 2:10:34 PM by Khoman
(modified after loading)

Fraction Information

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Area Percent Report

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Use Multiplier & Dilution Factor with \texttt{FFt}.

Signal 1: VWD1 A, Wavelength=254 nm

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Instrument 1 6/7/2012 2:13:32 PM Khoman
HPLC trace for (t)-2.33

Data File C:\CHEM32\DATA\QUAMA\MQ5000009.D
Sample Name: mps3002-r(mj)

HPLC trace for (t)-2.33

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Use Multiplier & Dilution Factor with ISDs

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Location: Vial 1
Injection Date: 5/2/2012 4:30:54 PM
Inj #: 1
Inj Volume: 50 µl

Analysis Method: C:\CH3H32\METHODS\MQ2240-03.PATH
Last changed: 5/2/2012 4:27:43 PM by Quanmax
Instrument: MQ2240-03
Last changed: 4/12/2012 3:28:14 PM by quanmax
Method Info: RP column, ml/min, 254 nm, FPA=REX 10:90,

--- Area Percent Report ---

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Use Multiplier & Dilution Factor with lstus

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Totals: 1624.15747  13.90309

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Instrument 1 6/7/2012 2:27:43 PM Khomson
HPLC trace for (+)-2.33 prepared from (-)-2.2

Data File: C:\CHMN32\DATA\GUAMAR\MQ2800000\nSample Name: mq28000002x(m).

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Flow Rate: 1.0000
Injection Volume: 50 µL
Injection Date: 5/2/2012 2:22:38 PM

No Fractions found.

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Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Use Multiplier & Dilution Factor with ISDFs

Signal 1: VWD1 A, Wavelength=254 nm

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Totals: 1548.29492 13.99866

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Intrametabolites Solution 6/7/2012 2:23:14 PM Khooson
HPLC trace for (t)-2.23

Sample Name: rac-imyr

Acq. Operator: qumar
Acq. Instrument: Instrument 1
Injection Date: 3/27/2012 12:31:35 PM
Inj.: 1
Rej. Volume: 10 µl

Acq. Method: C:\CHEMS2\1\METHODS\HQS-INTYR-00-ANAL.M

Last changed: 3/27/2012 12:30:21 PM by qumar (modified after loading)

Analysis Method: C:\CHEMS2\1\METHODS\HQS-INTYR-00-ANAL.M
Last changed: 6/7/2012 2:32:21 PM by Khomson (modified after loading)

Method Info: AD column, lml/min, 254 nm, IPA:HEX 10:90,

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Total: 2112.41516 29.5919%

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*** End of Report ***
HPLC trace for enantiopure (+)-2.23

Sample Name: IMYR-240-31h

Acq. Operator : quamar
Acq. Instrument : Instrument 1
Location : Vial 1
Injection Date : 3/29/2012 11:02:55 AM
Inj : 3
Inj Volume : 50 µL

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Last changed : 3/27/2012 1:33:48 PM by quamar
Analysis Method : C: \CHM331 \METHODS\MQE-JUG-AD.M
Last changed : 6/7/2012 2:42:53 PM by Khomson
(modified after loading)

Method Info : AD column, 1mL/min, 254 nm, IPA:HNXX 10:90

**: Area Percent Report

Sorted By : Signal
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Dilution : 1.0000
Use Multiplier & Dilution Factor with IS**

Signal 1: VN01 A, Wavelength=254 nm

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Totals : 2502.235671 38.29841

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HPLC trace for (t)-2.1

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Sample Name: myr000108.jpg

Acq. Operator: quanar
Acq. Instrument: Instrument 1
Location: Vial 1
Injection Date: 6/7/2012 3:55:38 PM
Inj.: 1
Injection Volume: 50 µL

Sequence File: C:\Chem32\SEQUENCE\MQR-3YR-OD-ANAL.P
Method: C:\Chem32\METHODS\MQR-MYR-OD-ANAL.P
Last changed: 6/7/2012 3:51:05 PM by quanar
Method Info: OD analytical, 1 mL/min, 254 nm, IPA:H2O 20:80

Area Percent Report

Signal 1: Wavelength=254 nm

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<td>2 27.856</td>
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Totals: 7061.36133 102.53972

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HPLC trace for (-)-2.1

Data File: C:\Chem32\DAPA\QUAMAR\mqg000100.d
Sample Name: (-)-MYR

Acq. Operator: quamar
Seq. Line: 1
Acq. Instrument: Instrument 1
Location: Vial 1
Injection Date: 6/7/2012 4:42:50 PM
Inj: 1
Injection Volume: 20 μL
Sequence File: C:\CHEM32\SEQ\RQ\RQ2-MYR-0D-AMAL.2
Method: C:\CHEM32\METHODS\RQ2-MYR-0D-AMAL.M
Last changed: 6/7/2012 3:54:05 PM by quamar
Method Info: OD analytical, 1 mL/min, 254 nm, IPA:MIX 20:80

Area Percent Report

Signal | Area | Height | Area
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Totals: 5694.01709 109.03002

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HPLC trace for (t)-2.2

Data File: C:\CHNH32\1\DATA\QUANAR\HQS00031.D
Sample Name: jug-rac

Acq. Operator: quanar
Acq. Instrument: Instrument 1
Location: Vial 1
Injection Date: 2/12/2012 3:53:36 PM
Inj. Time: 1
Inj Volume: 25 µl

Analysis Method: C:\CHNH32\1\METHODS\HQS02249-JDG_ANALY.M
Last Changed: 2/12/2012 3:50:16 PM by quanar

Analysis Method: C:\CHNH32\1\METHODS\HQS02249-JDG-AD.M
Last Changed: 6/7/2012 2:58:14 PM by Khomson

Method Info: AD column, 1mL/min, 364 nm, IPA/NEX 10:90,

Area Percent Report

Sorted By: Signal
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Dilution: 1.0000
Use Multiplier & Dilution Factor with INTDS

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Totals: 7413.56343 .77.69405

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HPLC trace for (-)-2.2

Data File: C:\CHEM321\DATA\QUAMAR\MQ5000032.D
Sample Name: jug-e9-210-2h

Injection Date: 5/28/2012 3:00:05 PM
Inj Volume: 50 µl

Acq. Operator: juan
Seq. Line: 1
Location: Vial 1

Acq. Method: C:\CHEM321\METHODS\MQ52249=JUG_ANALY.M
Last changed: 5/28/2012 2:57:21 PM by juan
Analysis Method: C:\CHEM321\METHODS\MQ5=JUG-AD.M
Last changed: 6/7/2012 3:06:08 PM by Khomson (modified after loading)

Method Info: AD column, 1mL/min, 254 nm, IPA:HEX 10:90,

Area Percent Report

Signal 1: W001 A, Wavelength=254 nm

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<tr>
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Totals: 1245.57569 14.64220

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HPLC trace for (±)-2.34

Data File: C:\Chem32\DATA\QUAR\mg900090.D
Sample Name: mg93044

Acq. Operator: Quamar  Seq. Line: 1
Acq. Instrument: Instrument 1  Location: Vial 1
Injection Date: 5/5/2012 2:17:34 PM  Inj.: 1
Inj. Volume: 50 µL
Sequence File: C:\Chem32\SEQ\QUAR\MG900090.D
Method: C:\Chem32\METHOD\MG900090.D
Last changed: 5/3/2012 10:29:39 AM by Quamar
Method Info: 0D column, 1ml/min, 254 nm, 2.5%IPA: H2O

VWD1 A, Wavelength=254 nm (QUAR/MG900090.D)

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HPLC trace for (+)-2.34 prepared from (-)-2.1

Data file: C:\Chem3\DATA\QUAMAR\mza000100.D
Sample Name: mza3093

Acq. Operator: Quasar
Acq. Instrument: Instrument 1
Injection Date: 5/5/2012 4:22:48 PM
Injection: 1
Location: Vial 1
Inj Volume: 50 µl
Sequence file: C:\\Chem32\\SEQUENCE\\MQR-0002.G
Method: C:\\Chem32\\METHODS\\MQR-MEJUC.M
Last changed: 5/3/2012 10:28:39 AM by Quasar
Method Info: 66 column, 1ml/min, 254 nm, 2.5%IPA: HEX

Area Percent Report

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<td>1.0000</td>
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Use Multiplier & Dilution Factor with 1STHs

Signal: WMD1 A, Wavelength=254 nm

Peak RetTime Type Width Area  Height  Area
[min] [min]   [mAU]  %
1 27.745 UV 1.5313 6251.93505  59.94905 100.0000

Totals: 6251.93505 59.94905

*** End of Report ***
HPLC trace for (+)-2.34 prepared from (-)-2.2

Data File: C:\Chem32\1\HPLC\QUAMARK\mqs000099.d
Sample Name: mqs000099

Acq. Operator: Quanar
Acq. Instrument: Instrument I
Seq. Line: 1
Injection Date: 5/5/2012 3:48:35 PM
Injection Volume: 50 µl
Method: C:\CHEM32\1\METHODS\QMS-5\QMS-5QOJUG.M
Last changed: 5/3/2012 10:29:39 AM by Quanar
Method info: 50 µl column, 1mL/min, 254 nm, 25% IPA: HRX

Plot:

Area: Signal
Multiplier: 1.0000
Dilution: 1.0000
Use Multiplier & Dilution Factor with rTMS

Signal 1: Wavelength=254 nm

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<th>Height</th>
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Totals: 7059.019655 67.00429

**End of Report**

Instrument 1 5/5/2012 4:18:56 PM Quanar

Page 1 of 1
Kinetics and Racemization Energies

Measurement for first-order rate constant and free energy of activation of racemization.¹

\[ A \xrightleftharpoons[k_r]{k_f} B \]

A = enantiomer A
B = enantiomer B

\( k \) = rate constant for forward (and reverse) reactions

\( x \) = mole fraction of the major enantiomer that has reacted

\( x_e \) = mole fraction of the major enantiomer that has reacted when equilibrium is reached (i.e. 50)

\( a \) = initial concentration of A
\( b \) = initial concentration of B

\( t \) = time in seconds,

Then the rate of the reaction is expressed by:

\[ \frac{dx}{dt} = k_f (a - x) - k_r (b - x) \]

After rearranging the integrating, the expression becomes:

\[ \ln \frac{x_e}{x_e - x} = 2kt \]

Below we tabulate \( t \) and \( x \), we set \( x_e \) to 50 and plot the linear relationship above. The slope of the line is \( 2k_{rac} \). The equation below relates the rate constant with the free energy of activation for racemization.

\[ k_{rac} = \frac{k_b}{h} e^{\frac{-\Delta G_{rac}^\dagger}{RT}} \]

Rearranging for \( \Delta G_{rac}^\dagger \) gives,

\[ \Delta G_{rac}^\dagger = -RT \ln \frac{hk_{rac}}{k_b T} \]

Finally, to convert an approximate half-life \( (t_{1/2}) \) to an estimated \( k_{rac} \), we use the equation below, and convert \( k_{rac} \) to \( \Delta G_{rac}^\dagger \) as described above
Kinetics data for galeon (2.3) obtained at 201 °C.

\[
k_{\text{rac}} \frac{\ln 2}{t_{1/2}}
\]

<table>
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<tr>
<th>Time (s)</th>
<th>Ent 2</th>
<th>Ent 1</th>
<th>( x )</th>
<th>( x_e/x_e-x )</th>
<th>Ln ( (x_e/x_e-x) )</th>
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<td>0.2</td>
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<td>14.5</td>
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<td>37.3</td>
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\[
y = 0.00001039x + 0.24625112
\]

\[
R^2 = 0.97508287
\]

\[
k_{\text{rac}} = 5.20E-06
\]

\[
\Delta G^\ddagger_{\text{rac}} = 39.6 \pm 0.6 \text{ kcal/mole}
\]
Kinetics data for iPr-myricatomentogenin (2.23) obtained at 240 °C.

<table>
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<th>x</th>
<th>$x_e/x_e-x$</th>
<th>$\ln (x_e/x_e-x)$</th>
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<td>0.1</td>
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<td>3.3</td>
<td>3.3</td>
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$k_{\text{rac}} = 3.98 \times 10^{-6}$

$\Delta G_{\text{rac}} = 43.3 \pm 0.5$ kcal/mole
VT–NMR stack plot of acerogenin C
VT-NMR stack plot of acerogenin L
CD spectrum for (+)-2.3

![Graph showing CD spectrum with peaks at specific wavelengths]

**Measurement Information**
- Instrument Name: Jasco CD 365
- Model Number: 365
- Serial No.: 1030509168
- Accessory: Standard
- Accessory No.: 8600381168
- Cell Length: 1 mm
- Measurement date: 7/6/2012 2:09 PM

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- Vertical axis: OD (relative)
- Start: 210 nm
- End: 600 nm
- Data interval: 0.1 nm
- Data points: 2001
CD spectrum for (+)-2.4
CD spectrum for (+)-2.33

[Graph showing CD spectrum with data points and wavelength on the x-axis and CD in mdeg on the y-axis.]
CD spectrum for (+)–2.23
CD spectrum for (-)-2.1
CD spectrum for (-)-2.2

[Measurement Information]
Instrument Name: Jasco-CD
Serial No.: 4856614
Accessory: Standard
Wavelength: 1 mm

[Detailed Information]
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Vertical axis: CD [deg]
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[Graph]
CD spectrum for (+)–2.34
References Cited

1 Eliel, E. L.; Wilen, S. H.; Mander, L. N. Stereochemistry of Organic Compounds

2 For reviews, see: a) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Chem.


B.; Keserü, G. M.; Mezey–Vándor, G.; Nógrádi, M.; Tóth, G. Tetrahedron 1993, 49,

6 Costantino, V.; Fattorusso, E.; Mangoni, A.; Perinu, C.; Teta, R.; Panza, E.; Ianaro, A.

820.

2008, 74, 754.

9 a) Liu, H. B.; Cui, C. B.; Cai, B.; Gu, Q. Q.; Zhang, D. Y.; Zhao, Q. C.; Guan, H. S. Chin.


13 Ullmann, F.; Sponagel, P. *Ber.* **1905**, *38*, 2211.


17 Using values for Δν ranging from 1 Hz to the full spectral width (4000 Hz) resulted in less than 2 kcal/mol variation in ΔG‡rac.


22 Audic, N; Herve, C; Marc, M; Jean–Claude, G. *J. Am. Chem. Soc,* **2003**, *125*, 9248

CHAPTER 3: SYNTHESES AND CHIRALITY OF THE GARUGANINS AND GARUGAMBLINS

3.1 Introduction

The previous chapter describes the synthesis, free energies of activation for racemization, and absolute stereochemistry of the DAEHs that display a heptanone ansa bridge, specifically 3.1–3.6. With this knowledge and with the help of postdoctoral scholar Dr. Zhi-Qiang Zhu, we aimed to synthesize the garuganin and garugamblin DAEHs and determine their chiral properties. The material in this chapter follows the work we published in *Journal of Organic Chemistry* in 2013.

**Figure 3.1.** All DAEHs members with garuganin and garugamblin DAEHs highlighted.
The garuganin and garugamblin DAEHs (3.7–3.14) share a highly conserved molecular architecture. These compounds differ only in the substitution pattern at C2–C4 and the methylation pattern of the 1,3-diketone. Of the multiple numbering systems for the DAEHs used in the literature, we choose to use the system adopted by Nagai (Scheme 3.1). As shown in Figure 3.1, five of these compounds were reported to be optically active, suggesting that they are chiral non-racemic compounds. Three of these compounds were isolated without mention of optical activity or chirality, and it is unclear if they are achiral, racemic, or chiral non-racemic molecules. Nogradi and coworkers synthesized garuganin III, garugamblin I, and garugamblin II using a Wittig macrocyclization approach. We desired a more general approach to access the garuganin and garugamblins.

3.2 Retrosynthetic Analysis

![Scheme 3.1. Retrosynthetic analysis of the garuganin and garugamblin DAEHs](image)

We decided to prepare 3.7–3.14 to investigate their chiral properties. We envisioned the vinylogous ester DAEHs, exemplified by general structures 3.17 or 3.18, arising from the corresponding vinylogous acid 3.19 (Scheme 3.1). Although this strategy would require regio- and stereoselective vinylogous ester formation,
it would allow a unified strategy for the formation of all the garuganins and garugamblins, and it could provide access to isomeric DAEH structures for investigation. Moreover, we considered the possibility that the vinylogous esters had formed upon isolation of the vinylogous acids by hot methanolic extraction, and that they were the thermodynamically favored isomer or “stabilomer” (vide infra).

Simplification of the macrocycle by way of an intramolecular Ullmann coupling leads to bromophenols 3.20. Positioning the phenol functional group on the more electron-rich phenyl ring was anticipated to give a smoother cyclization than an alternative approach with an electron-rich bromoarene. The β-diketone functional group present in 3.20 suggested that it could be prepared via an aldol addition with subsequent oxidation, thus beginning with aldehyde 3.21 and methyl ketone 3.22.5
3.3 Syntheses of the Garuganins and Garugamblins

Scheme 3.2. Synthesis of the Ullmann substrates

The synthesis of garugamblin I (3.10) began with hydrocinnamaldehyde derivative 3.23 (Scheme 3.2). Addition of 3.23 to the lithium enolate derived from 3.22 resulted in formation of aldol product 3.24. Oxidation of the β-hydroxy ketone using IBX gave β-diketone 3.25. Debenzylation gave the Ullmann coupling substrate 3.26 in good yield. Compounds 3.27–3.31 were prepared using an analogous 3-step sequence. Note that Ullmann substrate 3.28 has the position of...
the bromide and the phenol reversed relative to its congeners. The remaining bromophenols were obtained in 44-53% over the three-step sequence.

Table 3.1. Ullmann cyclizations
With the Ullmann substrates in hand, we then investigated the key macrocyclization (Table 3.1). Cyclization occurred using stoichiometric CuO in pyridine at elevated temperatures. The yields for the Ullmann reaction were good and quite sufficient for material throughput. Previously, this type of cyclization was predicted to be problematic.\textsuperscript{3a} The formation of 3.12 represents the synthesis of 9′-desmethylgarugamblin I. Spectroscopic data for this compound matched those reported in the literature.\textsuperscript{2g} Cleavage of the isopropyl ether of 3.34 gave the structure reported for 1,9′-didesmethylgaruganin III (3.10), which does not have spectral data consistent with that published for the natural compound, indicating that the structure of the natural product has been misassigned.
Table 3.2. Synthesis of the garuganin and garugamblin DAEHs
We next investigated the methylation of the vinylogous acids 3.12, 3.32, 3.33, 3.35, and 3.36. Methylation with (trimethylsilyl)diazomethane was quantitative, giving a 1:1 mixture of vinylogous ester regioisomers with Z-configuration (see general structures 3.37 and 3.38, Table 3.2). These conditions trap the dominant thermodynamic Z conformation of the vinylogous acid tautomer, leading to the Z-vinylogous esters. If desired, the regioisomeric Z-vinylogous esters can be separated by column chromatography, isolated, and observed by NMR in anhydrous base-treated CDCl₃. In practice, the Z-vinylogous esters were typically not isolated because quantitative isomerization to the E-configured esters (general structures 3.39 and 3.40) is induced by treatment with weak acid (e.g. CSA, acetic acid, proline).

A convenient method for inducing quantitative and rapid isomerization involves dissolving the Z-configured ester in dry CDCl₃ that has not been treated with base. If desired, any of the E- and Z-configured esters can be recycled by hydrolysis to the corresponding diketones by treatment with aqueous acid. Note that natural products 3.7, 3.8, 3.11, and 3.13 are exemplified by generic structure 3.39, and garuganin III (3.9) is exemplified by generic structure 3.40. All of the spectral data for the DAEHs matched those data reported for the natural samples, except for garuganin IV (3.8), and we believe the structure of garuganin IV has been misassigned. The correct structures for garuganin IV and 1,9’-didesmethylgaruganin III were described by Zhu and Beaudry in a separate report.
3.4 Artifacts of Isolation

![Chemical reaction](image)

**Table 3.3.** Diketones in hot acidic methanol to access vinylogous ester DAEHs

DAEHs are commonly isolated by Soxhlet extraction with methanol, and we wondered if the vinylogous ester DAEHs were isolation artifacts arising from the corresponding diketone. To this end, we subjected 3.12 to hot acidic methanolic
conditions (Table 3.3). After 72 h, the reaction mixture contained a 1:1 ratio of 
3.12 and garugamblin I (3.11) as a single regio- and stereoisomer. These reaction 
conditions also gave a single regio- and stereoisomer of garuganin I (3.7), the 
reported structure of garuganin IV (3.8), and garugamblin II (3.13) in chemical 
yields of 17%, 14%, and 12%, respectively. The mass balance contained only 
unreacted starting material. Interestingly, treatment of 3.35 with acidic methanol 
led to the regioisomer of garuganin III (3.44) in 16% yield. Garuganin III (3.9) 
was not observed in the reaction mixture. This suggests that garuganin III is not an 
artifact of the isolation process.

Garuganin VI (3.14) displays geminal methyl groups, and was prepared from 3.32 
by methylation with Mel in hot basic THF (Eq. 1). Using the strategy discussed 
above, 10–100 mg quantities of the garuganins and garugamblins (3.7–3.14) were 
prepared to study their chiral properties.

3.5 Racemization Parameters of the Garuganins and Garugamblins

Figure 3.2. Garuganin and garugamblin structure types
With 3.7–3.14 and regiosomers 3.41–3.45 in hand, we attempted to determine which have stable isolable enantiomeric conformations. Note that all of the cyclophane molecules discussed in this study can be grouped into one of six structure types (type A through E, and garuganin VI; Figure 3.2). Analytical HPLC of 3.7–3.14 and 3.41–3.45 using chiral stationary phases showed a single peak regardless of chiral columns (OD, ODH, AY, OZ, IC), solvents, flow rate, or temperature (0 °C to rt). Of course, a single peak is consistent with a compound with enantiomeric conformations that interconvert rapidly on the HPLC timescale, or a compound with two stable enantiomers that have coincident retention times.

![Figure 3.3. $^1$H NMR spectra for 3.32, 3.7, 3.41, and 3.14](image)

The 1D $^1$H NMR spectra of 3.7–3.14 and congeners can be used to obtain qualitative information regarding the rate of interconversion of enantiomeric
conformations. Figure 3.3 shows the room temperature $^1$H NMR spectra of the garuganin I series of compounds (i.e. 3.32, 3.7, 3.41, and 3.14). Only the spectrum of garuganin I (3.7), which displays the $E$-configured $C_9$-oxo structure (structure type B) shows chemical shift inequivalent geminal methylene protons. Furthermore, symmetry-related protons $H_{15}/H_{19}$ and $H_{16}/H_{18}$ show chemical shift inequivalence in 3.7 only. The vinylogous acid 3.32 (structure type A), isomer 3.41 (structure type C), and garuganin VI (3.14) exhibit chemical shift equivalent geminal methylene (and symmetry-related phenyl) protons. This observation holds in the other garuganin and garugamblin series as well: only DAEHs of structure type B have chemical shift inequivalent geminal methylene and phenyl protons. The chemical shift equivalence in structure types A and C–E suggests that enantiomeric conformations are interconverting rapidly at rt.¹¹

![Figure 3.4. Low temperature $^1$H NMR spectra of 3.32 (d$_9$-toluene, 400 MHz), *Indicates resonance used to determine T_c](image)

Variable temperature (VT) NMR was next used to investigate the rate of interconversion of enantiomeric forms. Low temperature NMR spectra of molecules with structure type A (i.e. 3.12, 3.32, 3.33, 3.35, and 3.36), structure
type C (3.41–3.43, 3.9, and 3.45), and garuganin VI (3.14) were used to determine approximate rates of interconversion of enantiomeric conformations at cryogenic temperatures (see data for 3.32, Figure 3.4). At low temperatures, racemization becomes slow relative to the NMR timescale, and decoalescence occurs. In two-site equally populated cases, the relationship \( k_C = 2.22 \times \Delta v \) gives the rate constant for coalescence \( k_C \) where \( \Delta v \) is the separation in Hz of the coalescing peaks at temperatures below coalescence.\(^{12}\) We used this relationship to estimate the rate of conformational exchange in DAEHs that have coalescence temperatures below rt. For 3.32, our estimated \( \Delta v = 106 \) Hz giving \( k_C = 236 \) s\(^{-1}\), an approximate \( \Delta G^\ddagger_{\text{rac}} = 9.0 \) kcal/mol at \(-80 \) °C, and a half-life of 0.003 s at \(-80 \) °C. All molecules with structure type A had nearly identical values (Table 3.4).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure Type</th>
<th>( \Delta v ) (Hz)</th>
<th>( T_C ) (K)</th>
<th>( k_C )</th>
<th>( \Delta G ) (kcal/mole)</th>
<th>( t_{1/2} ) (s)</th>
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<tr>
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<td>169</td>
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<td>157</td>
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<td>3.43</td>
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Table 3.4. Half-lives of molecules with structure types A, C, and garuganin VI (3.14) at cryogenic temperatures

For structure 3.41, we observed \( T_C = -10 \) °C and \( \Delta v = 76 \) Hz giving \( k_C = 169 \) s\(^{-1}\), an approximate \( \Delta G^\ddagger_{\text{rac}} = 12.7 \) kcal/mol, and a half-life of 0.0041 s at \(-10 \) °C. All molecules with structure type C had nearly identical values (Table 3.4). Garuganin VI (3.14) showed \( T_C = -50 \) °C and \( \Delta v = 31 \) Hz giving \( k_C = 68 \) s\(^{-1}\), an approximate \( \Delta G^\ddagger_{\text{rac}} = 11.1 \) kcal/mol, and a half-life of 0.0102 s at \(-50 \) °C. Thus, DAEHs with
structure types A, C, and garuganin VI (3.7) are achiral molecules, despite any reported non-zero specific rotation values at room temperature.

Chemical shift inequivalence in structure type B indicates that the interconversion of enantiomeric conformations is slow on the NMR timescale at rt. However, since the NMR timescale is faster than the laboratory timescale, this observation does not demonstrate that enantiomeric conformations of structure type B could be resolved at rt.

**Figure 3.5.** High Temperature NMR Spectra of 3.7 (d_6-DMSO, 400 MHz), *Indicates Resonance Used to Determine T_C

The $^1$H NMR spectra of compounds with structure type B (i.e. 3.7, 3.11, 3.13, 3.44, 3.8) were recorded at elevated temperatures (data for 3.7 is shown in Figure 4.5). Coalescence of the geminal methylene protons and of the symmetry-related phenyl protons occurs at 90 °C. The coalescence temperature ($T_C$) and the separation between coalescing peaks below $T_C$ can be used to determine $k_C$. For 3.7, $\Delta v = 180$ Hz, giving a value of $k_C = 400$ s$^{-1}$. This results in an approximate free energy of activation for racemization ($\Delta G^\ddag_{\text{rac}}$) of 17 kcal/mol at 90 °C. Of course, the free energy of activation for racemization at elevated temperatures does not give the half-life of an enantiomeric conformation at rt.
Lineshape analysis using simulated spectra gives the rate of interconversion of enantiomers at temperatures below coalescence and is more accurate than using coalescence measurements. In collaboration with Professor Alex Bain we were able to obtain simulated data for line shape analysis. Figure 3.6 shows experimental and simulated spectra for garuganin l (3.7). Analysis of these spectra gives values of $k = 5, 25, 60$ and $110$ s$^{-1}$ at $35, 45, 55$, and $65$ °C, respectively. Extrapolation of the data using Eyring analysis gives a value of $k = 2.4$ s$^{-1}$ at $25$ °C, which corresponds to an approximate half-life of $0.29$ s for each enantiomeric conformation. The calculated half-lives based on lineshape analysis of compounds with structure type B were all quite similar (see Table 3.6, below).

### Table 3.5. Half-lives of molecules with structure types B at elevated temperatures

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure Type</th>
<th>$\Delta v$ (Hz)</th>
<th>$T_c$ (K)</th>
<th>$k_c$</th>
<th>$\Delta G$ (kcal/mol)</th>
<th>$t_{1/2}$ (s)</th>
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<td>363</td>
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<td>363</td>
<td>419</td>
<td>17.0</td>
<td>0.0017</td>
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<tr>
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<tr>
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<td>426</td>
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</tr>
<tr>
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<td>150</td>
<td>363</td>
<td>333</td>
<td>17.2</td>
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</table>

**Figure 3.6.** Experimental and simulated $^1$H NMR spectra of 3.7
Selective Inversion Recovery (SIR) describes a two-pulse NMR technique that can be used to obtain rates of processes that occur slowly on the NMR timescale. Using this technique, selectively inverting one site leads to relaxation to equilibrium by normal T1 mechanisms and exchange with the non-inverted site. The non-inverted site shows a characteristic negative transient. These relaxations can be analyzed exactly, and the analysis results in accurate values of the interconversion rate. Use of SIR in combination with lineshape analysis gives a very accurate measurement of rate.

![Figure 3.7. Selective Inversion Recovery (SIR) experiments Using 3.7](image)

- = Data for H\textsubscript{15}; X = Data for H\textsubscript{19}

SIR experiments were performed on the molecules with structure type B. In these spectra, the signal for H\textsubscript{15} was sufficiently well resolved to enable selective inversion using a soft pulse. The delay between pulses was varied between 0.001 and 10 s, and magnetization transfer to H\textsubscript{19} was observed (see data for 3.7, Figure 3.7). Mathematical analysis of the delay-dependent integration of H\textsubscript{15} and H\textsubscript{19} was used to obtain the rate of exchange at rt. Using SIR, we found that the rate of interconversion of enantiomeric conformations of 3.7 is $k_{\text{rac}} = 3.5 \text{ s}^{-1}$, giving a half-life of 0.20 s at 25 °C. This value corresponds well to the value obtained using
lineshape analysis (0.29 s). Moreover, we found half-lives for enantiomeric conformations of compounds with structure type B at rt as determined from SIR experiments were quite similar, and agreed well with the values obtained from lineshape analysis (Table 3.6).

<table>
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<tr>
<th>Compound</th>
<th>t_{1/2} (s) from lineshape analysis</th>
<th>t_{1/2} (s) from SIR experiments</th>
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<td>3.7</td>
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<td>0.20</td>
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<td>3.8</td>
<td>0.38</td>
<td>0.18</td>
</tr>
<tr>
<td>3.11</td>
<td>0.51</td>
<td>0.30</td>
</tr>
<tr>
<td>3.13</td>
<td>0.54</td>
<td>0.63</td>
</tr>
<tr>
<td>3.44</td>
<td>0.23</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 3.6. Room temperature half-lives of enantiomeric conformations of molecules with structure Type B

### 3.6 Mechanism of Racemization for the DAEHs

In collaboration with the Cheong group (OSU) the mechanism of racemization has been computed using SCS-MP2 \(^{16}\) /def2-\(∞\) \(^{17}\) // B3LYP \(^{18}\) /6-31G* \(^{19}\) /PCM (dichlorobenzene) \(^{20}\) level of theory. \(^{21}\) The local symmetry of ring B and the E/Z configuration of the vinylogous acid/ester are critical in determining the presence of chirality in the DAEH natural product family. If ring B does not contain local symmetry such as in galeon, the rate determining step in the racemization event is the rotation of the B ring through the macrocycle as shown in Figure 3.8. The rotation causes trans-annular interactions between aryl hydrogens (H\(_{18}\) and H\(_{19}\)) and the ansa loop hydrogens (H\(_{11}\)) and A ring hydrogen (H\(_{6}\)), this barrier amounts to 45 kcal/mol.
If the B ring contains local symmetry the rate-limiting step is the movement of the ansa loop. The barrier for this process is computed to be between 9-18 kcal/mole, rendering the garuganins and garugamblins achiral. The activation energy barriers obtained computationally are in good agreement with the values obtained experimentally. With this method we are able to predict if a DAEH member can be isolated as a stable enantiomer under ambient conditions. A predictive rule-of-thumb has been developed based on the characteristic of the structures; this is shown in Figure 3.9 and it can be used to predict which of the DAEHs will have stable isolable enantiomeric conformations.
3.7 Experimental Section

General Experimental Details:
All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. External bath temperatures were used to record all reaction mixture temperatures. Flash column chromatography was carried out with SiliaFlash P60 silica gel. Tetrahydrofuran (THF), methylene chloride (CH₂Cl₂) and acetonitrile (MeCN) were dried by passage through activated alumina columns. DMF and DMSO were stored over 3 Å molecular sieves. Pyridine (C₆H₅N) and diisopropylamine were distilled from CaH. All other reagents and solvents were used without further purification from commercial sources. FT-IR spectra were obtained as thin films on NaCl plates. Proton and carbon NMR spectra (¹H NMR and ¹³C NMR) were recorded in deuterated chloroform (CDCl₃) unless otherwise
noted at 700 MHz or 400 MHz as indicated. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet. Melting points are uncorrected.

**3-(5-(Benzyloxy)-2,4-dimethoxyphenyl)propanal (3.23).** To a solution of ethyl 3-(2,4-dimethoxyphenyl)propanoate\(^{24}\) (1.191 g, 5 mmol) in CH\(_2\)Cl\(_2\) (20 mL, 0.25 M) at 0 °C were added acetyl chloride (535 mL, 7.5 mmol) and AlCl\(_3\) (2 × 500 mg, 7.5 mmol).\(^1\) After stirring for 2 h at 0 °C, the reaction mixture was poured into a mixture of ice (50 g) and aqueous HCl (10 mL, 1 M). The organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with MgSO\(_4\). Evaporation of the solvent gave ethyl 3-(5-acetyl-2,4-dimethoxyphenyl)propanoate (3.51, 1.334 g, 4.76 mmol, 95% yield) as a white solid. Data for 3.51: R\(_f\) 0.41 (3:2 hexanes:EtOAc); mp = 90-92 °C, IR (thin film) 1723, 1656, 1605, 1570, 1262, 1234, 1208, 1171, 1020 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.68 (s, 1 H), 6.42 (s, 1 H), 4.13 (q, \(J = 7.1\) Hz, 2 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 2.88 (t, \(J = 7.8\) Hz, 2 H), 2.57 (s, 3 H), 2.56 (t, \(J = 7.8\) Hz, 2 H), 1.26 (t, \(J = 7.1\) Hz, 3 H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\), HSQC, DEPT) \(\delta\) C 197.6, 173.1, 162.2, 160.2, 121.1, 119.9; CH 132.1, 94.5, CH\(_2\) 60.3, 34.3, 25.2; CH\(_3\) 55.6, 55.5, 31.9, 14.2; HRMS (TOF MS ES+) calcd for C\(_{15}\)H\(_{20}\)O\(_5\)Na [M+Na]: 303.1208, found 303.1211.

To a solution of 3.51 (1.682 g, 6 mmol) in CH\(_2\)Cl\(_2\) (14 mL, 0.25 M) at 0 °C were added TsOH (52 mg, 0.3 mmol) and a solution of mCPBA (70%, 2.071 g, 8.4 mmol) in CH\(_2\)Cl\(_2\) (10 mL) over a period of 30 min. The reaction mixture was stirred for 30 min at 0 °C and 4 h at rt. Subsequently, aqueous Na\(_2\)S\(_2\)O\(_3\) (5 mL, 1 M) was added and the suspension was stirred for 15 min at rt. Aqueous saturated NaHCO\(_3\) was added until aqueous phase had pH 7. The organic phase was separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 30 mL). The combined organic
phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave ethyl 3-(5-acetoxy-2,4-dimethoxyphenyl)propanoate (3.52, 1.25 g, 4.22 mmol, 70% yield) as a light yellow solid. Data for 3.52: R$_f$ 0.42 (2:1 hexanes:EtOAc); mp = 33-35 °C, IR (thin film) 2939, 1764, 1732, 1619, 1515, 1371, 1319, 1197, 1034, 913 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.83 (s, 1 H), 6.51 (s, 1 H), 4.12 (q, $J$ = 7.1 Hz, 2 H), 3.82 (s, 6 H), 2.85 (t, $J$ = 7.7 Hz, 2 H), 2.56 (t, $J$ = 7.7 Hz, 2 H), 2.28 (s, 3 H), 1.24 (t, $J$ = 7.1 Hz, 3 H); $^{13}$C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) $\delta$ C 173.2, 169.4, 155.8, 150.0, 132.6, 120.8; CH 123.8, 96.8, CH$_2$ 60.2, 34.2, 25.2; CH$_3$ 56.1, 55.7, 20.6, 14.2; HRMS (TOF MS ES+) calcd for C$_{15}$H$_{20}$O$_6$Na [M+Na]: 319.1158, found 319.1151.

To a solution of 3.52 (296 mg, 1 mmol) in EtOH (10 mL, 0.1 M) was added K$_2$CO$_3$ (415 mg, 3 mmol) at rt. The mixture was heated to 70 °C. After 2 h, BnBr (178 mL, 1.5 mmol) was added. The mixture was maintained at 70 °C for another 2 h. The mixture was cooled to rt and quenched by the addition of saturated aqueous NH$_4$Cl (20 mL). The resultant mixture was extracted with EtOAc (4 x 20 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 6:1) gave ethyl 3-(5-(benzyloxy)-2,4-dimethoxyphenyl)propanoate (3.53, 323 mg, 0.94 mmol, 94% yield) as a light yellow solid. Data for 3.53: R$_f$ 0.57 (2:1 hexanes:EtOAc); mp = 41-43 °C, IR (thin film) 2937, 1731, 1614, 1513, 1455, 1374, 1208, 1034, 865 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51-7.29 (m, 5 H), 6.79 (s, 1 H), 6.54 (s, 1 H), 5.08 (s, 2 H), 4.13 (q, $J$ = 7.1 Hz, 2 H), 3.90 (s, 3 H), 3.83 (s, 3 H), 2.85 (t, $J$ = 7.8 Hz, 2 H), 2.55 (t, $J$ = 7.8 Hz, 2 H), 1.26 (t, $J$ = 7.1 Hz, 3 H); $^{13}$C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) $\delta$ C 173.4, 152.4, 149.2, 141.8, 137.6, 120.6; CH 128.4, 127.8, 127.6, 118.1, 98.0, CH$_2$ 72.5, 60.2, 34.6, 25.5; CH$_3$ 56.5, 56.0, 14.3; HRMS (TOF MS ES+) calcd for C$_{20}$H$_{25}$O$_5$ [M+H]: 345.1702, found 345.1686.
To a solution of 3.53 \( (482 \text{ mg, } 1.4 \text{ mmol}) \) in \( \text{CH}_2\text{Cl}_2 \) \( (14 \text{ mL, } 0.1 \text{ M}) \) at \(-78 \, ^\circ\text{C}\) was added DIBAL-H \( (1.4 \text{ mL, } 1.68 \text{ mmol, } 1.2 \text{ M in toluene}) \) over a period of 30 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle’s salt \( (30 \text{ mL}) \) at \(-78 \, ^\circ\text{C}\). The mixture was warmed to rt. The organic phase was separated and the inorganic phase was extracted with EtOAc \( (3 \times 30 \text{ mL}) \). The combined organic phases were dried with \( \text{MgSO}_4 \). Purification by flash column chromatography \( (\text{hexanes}:\text{EtOAc} = 5:1) \) gave 3.23 \( (366 \text{ mg, } 1.22 \text{ mmol, } 87\% \text{ yield}) \) as white solid. Data for 3.23: \( R_f \) 0.33 \( (5:2 \text{ hexanes}:\text{EtOAc}) \); mp = 80-82 \, ^\circ\text{C}, \text{IR} \,(\text{thin film}) \, 2936, \, 1713, \, 1607, \, 1519, \, 1462, \, 1402, \, 1310, \, 1219, \, 1027 \, \text{cm}^{-1}; \, ^1\text{H} \text{NMR} \,(400 \text{ MHz, CDCl}_3) \delta \, 9.77 \,(s, \, 1 \text{ H}), \, 7.51-7.29 \,(m, \, 5 \text{ H}), \, 6.75 \,(s, \, 1 \text{ H}), \, 6.54 \,(s, \, 1 \text{ H}), \, 5.08 \,(s, \, 2 \text{ H}), \, 3.91 \,(s, \, 3 \text{ H}), \, 3.82 \,(s, \, 3 \text{ H}), \, 2.85 \,(t, \, J = 7.2 \text{ Hz}, \, 2 \text{ H}), \, 2.66 \,(t, \, J = 7.2 \text{ rHz}, \, 2 \text{ H}); \, ^{13}\text{C} \text{NMR} \,(101 \text{ MHz, CDCl}_3, \text{ HSQC, DEPT}) \delta \, \text{C} \, 152.2, \, 149.4, \, 141.8, \, 137.6, \, 120.1; \, \text{CH} \, 202.5, \, 128.5, \, 128.7, \, 127.6, \, 118.2, \, 98.0; \, \text{CH}_2 \, 72.6, \, 44.2, \, 22.9; \, \text{CH}_3 \, 56.5, \, 55.9; \, \text{HRMS} \,(\text{TOF MS ES}+) \text{ calcd for } \text{C}_{18}\text{H}_{20}\text{O}_4\text{Na} \, [\text{M+Na}] : \, 323.1259, \text{ found } 323.1263.

7-(5-(Benzyloxy)-2,4-dimethoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (3.24). To a solution of diisopropylamine \( (363 \text{ mg, } 3.59 \text{ mmol}) \) in THF \( (12 \text{ mL, } 0.1 \text{ M}) \) at 0 \, ^\circ\text{C} \) was added \( n\)-BuLi \( (2.24 \text{ mL, } 3.59 \text{ mmol, } 1.6 \text{ M in hexane}) \) over a period of 10 min. After stirring at 0 \, ^\circ\text{C} \) for 30 min, the mixture was cooled to \(-78 \, ^\circ\text{C}\). A solution of 3.22 \( (782 \text{ mg, } 3.44 \text{ mmol}) \) in THF \( (8 \text{ mL}) \) was added over a period of 1 h. After stirring at \(-78 \, ^\circ\text{C} \) for 30 min, a solution of 3.23 \( (862 \text{ mg, } 2.87 \text{ mmol}) \) in THF \( (9 \text{ mL}) \) was added over a period of 1 h. After stirring for 2 h, the reaction was quenched with saturated aqueous \( \text{NH}_4\text{Cl} \) \( (30 \text{ mL}) \). The organic phase was separated and the aqueous phase was extracted with EtOAc \( (3 \times 30 \text{ mL}) \). The combined organic phases were dried with \( \text{MgSO}_4 \). Purification by flash column chromatography \( (\text{hexanes}:\text{EtOAc} = 5:1 \text{ to } 5:2) \) gave 3.24 \( (1.146 \text{ g, } 2.17 \text{ mmol, } 76\% \text{ yield}) \).
yield) as a white solid. Data for 3.24: Rf 0.20 (2:1 hexanes:EtOAc); mp = 75–78 °C, IR (thin film) 3512 (br), 2933, 1708, 1511, 1454, 1404, 1315, 1203, 1072, 1035 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.28 (m, 7 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.74 (s, 1 H), 6.53 (s, 1 H), 5.08 (s, 2 H), 3.94 (m, 1 H), 3.90 (s, 3 H), 3.81 (s, 3 H), 3.00 (br s, 1 H), 2.86 (t, J = 7.3 Hz, 2 H), 2.78-2.44 (m, 6 H), 1.75-1.53 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT) δ C(210.2, 152.1, 149.0, 142.1, 139.9, 137.6, 121.5, 119.9; CH 131.6, 130.2, 128.5, 127.8, 127.6, 118.1, 98.2, 66.9; CH₃ 72.4, 49.4, 44.8, 37.1, 28.8, 25.4; CH₃ 56.5, 56.3; HRMS (TOF MS ES+) calcd for C₂₈H₃₂BrO₅ [M+H⁺]: 527.1433, found 527.1442.

1-(5-(Benzyloxy)-2,4-dimethoxyphenyl)-7-(4-bromophenyl)heptane-3,5-dione (3.26). To a solution of 3.24 (106 mg, 0.2 mmol) in EtOAc (2 mL, 0.1 M) at rt was added IBX (168 mg, 0.6 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude b-diketone 3.25, which was used directly without further purification.

To a stirred solution of 3.25 (0.2 mmol, from previous step) in CH₂Cl₂ (4 mL, 0.05 M) were added pentamethylbenzene (89 mg, 0.6 mmol) and BCl₃ (0.8 mL, 0.8 mmol, 1 M in DCM) at −78 °C over a period of 10 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (1 mL) at −78 °C. The resultant mixture was allowed to warm to rt. Diluted aqueous NaHCO₃ was added until the aqueous phase had pH 6. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 3.26 (59 mg, 0.136 mmol, 68% yield, 2 steps) as a light yellow solid. Data for
3.26: R\textsubscript{f} 0.40 (2:1 hexanes:EtOAc); mp = 69-71 °C, IR (thin film) 3455 (br), 2939, 1612, 1513, 1201, 1034 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), enol tautomer) \(\delta\) 15.44 (br s, 1 H), 7.41 (d, \(J = 8.1\) Hz, 2 H), 7.08 (d, \(J = 8.1\) Hz, 2 H), 6.73 (s, 1 H), 6.49 (s, 1 H), 5.45 (s, 1 H), 5.24 (br s, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 2.95-2.71 (m, 4 H), 2.63-2.46 (m, 4 H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\), HSQC, DEPT, enol tautomer) \(\delta\) C 193.5, 192.8, 150.9, 145.1, 139.7, 139.2, 121.4, 120.0; CH 131.5, 130.1, 115.8, 99.5, 96.7; CH\(_2\) 39.8, 38.6, 30.8, 25.8; CH\(_3\) 56.3, 56.2; HRMS (TOF MS ES+) calcd for C\(_{21}\)H\(_{24}\)BrO\(_5\) [M+H]: 435.0807, found 435.0816.

4,6-Dimethoxy-2-oxatricyclo[13.2.2.1\(^{3,7}\)]icosa-1(17),3,5,7(20),15,18-hexene-10-12-dione (3.32). To a sealed tube were added 3.26 (21.8 mg, 0.05 mmol), CuO (9.9 mg, 0.125 mmol) and K\(_2\)CO\(_3\) (13.8 mg, 0.1 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (10 mL, 0.005 M). The tube was then sealed and heated to 120 °C. After 36 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool to rt. After evaporation of the solvent, aqueous HCl (1 mL, 1 M) and H\(_2\)O (5 mL) were added. The mixture was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried with MgSO\(_4\). Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave 3.32 (7.9 mg, 0.0223 mmol, 45% yield) as a light yellow solid. Data for 3.32: R\textsubscript{f} 0.52 (2:1 hexanes:EtOAc); IR (thin film) 2939, 1604, 1520, 1504, 1392, 1318, 1209, 1030, 868 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 15.13 (br s, 1 H), 7.17 (d, \(J = 8.4\) Hz, 2 H), 6.99 (d, \(J = 8.4\) Hz, 2 H), 6.53 (s, 1 H), 5.67 (s, 1 H), 4.98 (s, 1 H), 3.99 (s, 3 H), 3.82 (s, 3 H), 3.04 (t, \(J = 6.8\) Hz, 2 H), 2.89 (m, 2 H), 2.46 (t, \(J = 6.8\) Hz, 2 H), 2.39 (m, 2 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\), HSQC, DEPT) \(\delta\) C 197.3, 188.5, 155.6, 151.7, 146.8, 144.8, 136.2, 121.1; CH 130.6, 123.0, 115.2, 103.0, 97.3; CH\(_2\) 39.5, 36.8, 32.3, 20.8; CH\(_3\) 56.6, 56.2; HRMS (TOF MS ES+) calcd for C\(_{21}\)H\(_{23}\)O\(_5\) [M+H]: 355.1545, found 355.1555.
Garuganin I (7) and \((10\text{E})-4,6,12\text{-Trimethoxy-2-oxatricyclo[13.2.2.1}^{3,7}\text{]icosa-}\)1(17),3,5,7(20),10,15,18-heptaen-12-one (3.41). To a solution of 3.32 (28.4 mg, 0.08 mmol) in CH\(_3\)CN and MeOH (8 mL, 0.01 M, 10:1 v/v) was added TMSCHN\(_2\) (0.4 mL, 0.8 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 3.37a (14.1 mg, 0.0383 mmol, 48% yield, white solid, more polar) and 3.38a (13.9 mg, 0.0377 mmol, 47% yield, white solid, less polar) in 1:1 regioselectivity. Treating 3.37a and 3.38a with dry acidic CDCl\(_3\) (“old” CDCl\(_3\) dried by 3 Å MS) at rt (approximately 5 minutes) gave garuganin I (3.7) and 3.41, respectively in >95% yield. Data for garuganin I (7): white solid, R\(_f\) 0.46 (2:1 hexanes:EtOAc); IR (thin film) 2928, 1684, 1587, 1512, 1204, 1097, 1035 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.37 (dd, \(J = 8.3, 1.8\) Hz, 1 H), 7.01 (dd, \(J = 8.3, 2.3\) Hz, 1 H), 6.91 (dd, \(J = 8.1, 2.3\) Hz, 1 H), 6.86 (dd, \(J = 8.1, 1.8\) Hz, 1 H), 6.48 (s, 1 H), 5.34 (s, 1 H), 5.28 (s, 1 H), 4.01 (td, \(J = 12.9, 3.3\) Hz, 1 H), 3.98 (s, 3 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.99 (dt, \(J = 12.9, 3.8\) Hz, 1 H), 2.88 (td, \(J = 12.9, 2.9\) Hz, 1 H), 2.83 (dd, \(J = 15.9, 11.6\) Hz, 1 H), 2.70 (dd, \(J = 16.0, 6.8\) Hz, 1 H), 2.57 (dd, \(J = 17.8, 6.8\) Hz, 1 H), 2.41 (dd, \(J = 18.2, 11.5\) Hz, 1 H), 2.32 (dt, \(J = 12.8, 3.8\) Hz, 1 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\), HSQC, DEPT) \(\delta\) C 197.2, 172.8, 156.0, 151.2, 146.3, 145.7, 137.8, 122.0; CH 131.1, 130.0, 124.4, 122.3, 117.1, 101.0, 97.5; CH\(_2\) 44.4, 33.9, 33.0, 19.1; CH\(_3\) 56.6, 56.5, 55.2; HRMS (TOF MS ES+) calcd for C\(_{22}\)H\(_{25}\)O\(_5\) [M+H]: 369.1702, found 369.1693.

Data for 3.41: white solid, R\(_f\) 0.25 (2:1 hexanes:EtOAc); IR (thin film) 2928, 1664, 1562, 1515, 1504, 1441, 1394, 1203, 1034 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.27 (m, 2 H), 6.98 (d, \(J = 8.5\) Hz, 2 H), 6.51 (s, 1 H), 5.26 (s, 1 H), 5.20 (s, 1 H), 3.99 (s, 3 H), 3.81 (s, 3 H), 3.45 (s, 3 H), 3.10 (t, \(J = 7.0\) Hz, 2 H), 3.08-2.40 (m, 6 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\), HSQC, DEPT) \(\delta\) C 198.9, 174.2, 154.5, 151.4, 145.7, 145.2,
Garuganin VI (3.14). To a solution of 3.32 (8 mg, 0.0226 mmol) in THF (2 mL, 0.0113 M) was added K$_2$CO$_3$ (3.12 mg, 0.226 mmol). After stirring at rt for 30 min, CH$_3$I (42 mL, 0.678 mmol) was added. The mixture was heated to reflux. After 24 h, another 42 mL of CH$_3$I was added. After refluxing for another 24 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt and filtered through a short pad of Celite. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave 3.14 (5 mg, 0.0131 mmol, 58% yield) as a light yellow solid. Data for 3.14: \( R_f \) 0.31 (3:1 hexanes:EtOAc); IR (thin film) 2925, 1691, 1606, 1453, 1318, cm$^{-1}$; \(^1\)H NMR (700 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J = 8.5$ Hz, 2 H), 6.97 (d, $J = 8.5$ Hz, 2 H), 6.47 (s, 1 H), 4.92 (s, 1 H), 3.98 (s, 3 H), 3.78 (s, 3 H), 3.04-2.92 (m, 4 H), 2.63 (t, $J = 5.4$ Hz, 2 H), 2.54 (br s, 2 H), 1.40 (s, 6 H); \(^{13}\)C NMR (176 MHz, CDCl$_3$, HSQC, DEPT) $\delta$ C 207.6, 207.4 155.5, 151.2, 146.2, 145.9, 138.4, 121.1, 62.7; CH 131.1, 123.4, 115.7, 97.3; CH$_3$ 41.4, 37.3, 28.8, 19.2; CH$_3$ 56.6, 56.4, 22.8; HRMS (TOF MS ES+) calcd for C$_{23}$H$_{26}$O$_5$Na $[M+Na]$: 405.1678, found 405.1691.

1-(3-(Benzylloxy)-4-methoxyphenyl)-7-(4-bromophenyl)heptane-3,5-dione (3.27). To a solution of diisopropylamine (468 mg, 4.62 mmol) in THF (15 mL, 0.1 M) at 0 °C was added n-BuLi (2.89 mL, 4.62 mmol, 1.6 M in hexane) over a period of 10 min. After stirring at 0 °C for 30 min, the mixture was cooled to $-78$ °C. A solution of 3.22 (1.01 g, 4.44 mmol) in THF (11 mL) was added over a period of 30 min. After stirring at $-78$ °C for 30 min, a solution of 3-(3-(benzylloxy)-4-methoxyphenyl)propanal$^{25}$ (1 g, 3.7 mmol) in THF (11 mL) was added over a
period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH₄Cl (40 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(3-(Benzyloxy)-4-methoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (3.S4, 1.325 g, 2.66 mmol, 72% yield) as white solid. Data for 3.S4: Rᵣ 0.29 (2:1 hexanes:EtOAc); mp = 96-98 °C, IR (thin film) 3504 (br), 2931, 1707, 1514, 1258, 1138, 1011 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.50-7.28 (m, 7 H), 7.06 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 8.0 Hz, 1 H), 6.79-6.71 (m, 2 H), 5.15 (s, 2 H), 3.99 (m, 1 H), 3.88 (s, 3 H), 2.91 (d, J = 3.4 Hz, 1 H), 2.86 (t, J = 7.4 Hz, 2 H), 2.77-2.47 (m, 6 H), 1.81-1.54 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT) δ C 210.5, 148.1, 148.0, 139.7, 137.3, 134.3, 120.0; CH 131.6, 130.1, 128.5, 127.8, 127.4, 121.0, 114.9, 112.1, 66.8; CH₂ 71.1, 49.3, 44.7, 38.1, 31.2, 28.8; CH₃ 56.2; HRMS (TOF MS ES+) calcd for C₂₇H₃₀BrO₄ [M+H]: 497.1327, found 497.1327.

To a solution of 3.S4 (199 mg, 0.4 mmol) in EtOAc (4 mL, 0.1 M) at rt was added IBX (336 mg, 1.2 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 6 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude 3.S5, which was used directly without further purification.

To a solution of 3.S5 (0.4 mmol, from previous step) in CH₂Cl₂ (8 mL, 0.05 M) were added pentamethylbenzene (178 mg, 1.2 mmol) and BCl₃ (1.6 mL, 1.6 mmol, 1 M in DCM) over a period of 10 min at −78 °C. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (1 mL) at −78 °C. The resultant mixture was allowed to warm to rt. Diluted aqueous NaHCO₃ was added until aqueous phase had pH 6. The organic phase was separated and the aqueous phase was extracted with
EtOAc (3 x 20 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 3.27 (105 mg, 0.26 mmol, 65% yield, 2 steps) as a light yellow solid. Data for 3.27: R$_f$ 0.41 (2:1 hexanes:EtOAc); mp = 54-56 °C, IR (thin film) 3445 (br), 2933, 1592, 1513, 1489, 1442, 1273, 1129, 1011 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$, enol tautomer) δ 15.42 (br s, 1 H), 7.42 (d, $J = 8.4$ Hz, 2 H), 7.08 (d, $J = 8.4$ Hz, 2 H), 6.81-6.75 (m, 2 H), 6.68 (dd, $J = 8.2$, 2.1 Hz, 1 H), 5.61 (br s, 1 H), 5.44 (s, 1 H), 3.89 (s, 3 H), 2.90 (t, $J = 7.8$ Hz, 2 H), 2.85 (t, $J = 7.8$ Hz, 2 H), 2.60-2.54 (m, 4 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC, DEPT, enol tautomer) δ C 193.0, 192.8, 145.5, 145.0, 139.6, 133.9, 120.0; CH 131.6, 130.1, 119.7, 114.4, 110.6, 99.7; CH$_2$ 40.0, 39.8, 30.9, 30.8; CH$_3$ 56.0; HRMS (EI+) calcd for C$_{20}$H$_{21}$BrO$_4$: 404.0623, found 404.0610.

9'-Desmethylgarugamblin I (3.12). To a sealed tube were added 3.27 (20.3 mg, 0.05 mmol), CuO (9.9 mg, 0.125 mmol) and K$_2$CO$_3$ (13.8 mg, 0.1 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (10 mL, 0.005 M). The tube was then sealed and heated to 120 °C. After 24 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool to rt. After evaporation of the solvent, aqueous HCl (1 mL, 1 M) and H$_2$O (5 mL) were added. The mixture was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 5:1) gave 3.12 (8.3 mg, 0.0256 mmol, 51% yield) as a light yellow solid. Data for 3.12: R$_f$ 0.54 (2:1 hexanes:EtOAc); IR (thin film) 2922, 2850, 1589, 1515, 1505, 1440, 1262, 1228, 1128 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 15.27 (br s, 1 H), 7.21 (d, $J = 8.5$ Hz, 2 H), 7.03 (d, $J = 8.5$ Hz, 2 H), 6.84 (d, $J = 8.3$ Hz, 1 H), 6.72-6.68 (m, 1 H), 5.63 (d, $J = 2.2$ Hz, 1 H), 4.98 (s, 1 H), 3.97 (s, 3 H), 3.07 (t, $J = 6.8$ Hz, 2 H), 2.95 (m, 2 H), 2.49 (t, $J$
Garugamblin I (11) and (10E)-4,10-Dimethoxy-2-oxatricyclo[13.2.2.1]3,7-icosa-1(17),3,5,7(20),10,15,18-heptaen-12-one (3.42). To a solution of 3.12 (13 mg, 0.04 mmol) in a mixed solvent of CH₃CN and MeOH (4 mL, 0.01 M, 10:1 v/v) was added TMSCHN₂ (0.2 mL, 0.4 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 3.37b (6.5 mg, 0.0192 mmol, 48% yield, more polar) and 3.38b (6.4 mg, 0.0189 mmol, 47% yield, less polar) in 1:1 ratio. Treating 3.37b and 3.38b with dry acidic CDCl₃ (“old” CDCl₃ dried by 3 Å MS) at rt (approximately 5 minutes) gave garugamblin I (3.11) and 3.42, respectively in >99% yield. Data for garugamblin I (3.11): Rf 0.50 (2:1 hexanes:EtOAc); IR (thin film) 2933, 1681, 1589, 1515, 1432, 1259, 1210, 1128, 1097 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.40 (d, J = 8.5 Hz, 1 H), 7.11-7.06 (m, 1 H), 6.90-6.86 (m, 2 H), 6.76 (d, J = 8.1 Hz, 1 H), 6.63 (dd, J = 8.1, 2.1 Hz, 1 H), 5.34 (s, 1 H), 5.29 (d, J = 2.1 Hz, 1 H), 4.05 (td, J = 12.9, 3.4 Hz, 1 H), 3.95 (s, 3 H), 3.71 (s, 3 H), 3.23 (dd, J = 14.8, 11.6 Hz, 1 H), 3.00 (dt, J = 12.8, 4.0 Hz, 1 H), 2.92 (td, J = 12.9, 3.1 Hz, 1 H), 2.59-2.52 (m, 1 H), 2.49-2.42 (m, 1 H), 2.37-2.32 (m, 1 H), 2.30 (dd, J = 15.1, 7.0 Hz, 1 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 197.2, 173.1, 155.1, 151.6, 146.3, 138.2, 135.0; CH 130.8, 130.5, 124.5, 122.3, 120.6, 115.4, 111.0, 101.2; CH₂ 45.4, 33.9, 33.0, 26.7; CH₃ 56.1, 55.2; HRMS (EI+) calcd for C₂₁H₂₂O₄ [M]+: 338.1518, found 338.1520.

Data for 3.42: Rf 0.26 (2:1 hexanes:EtOAc); IR (thin film) 2929, 1668, 1566, 1515, 1504, 1442, 1266, 1226, 1127 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.33-7.27 (m, 2
H), 6.99 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.2 Hz, 1 H), 6.68 (dd, J = 8.2, 2.1 Hz, 1 H), 5.29 (d, J = 2.1 Hz, 1 H), 5.22 (s, 1 H), 3.96 (s, 3 H), 3.46 (s, 3 H), 3.11 (t, J = 7.0 Hz, 2 H), 3.08-2.40 (m, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC, DEPT) δ C 198.9, 174.0, 154.3, 151.1, 145.7, 137.5, 133.3; CH 131.3, 123.6, 121.0, 112.6, 111.7, 102.1; CH$_2$ 44.3, 31.2, 28.6, 26.0; CH$_3$ 56.2, 55.7; HRMS (TOF MS ES+) calcd for C$_{21}$H$_{23}$O$_4$ [M+H]: 339.1596, found 339.1582.

1-(4-Bromophenyl)-7-(7-hydroxybenzo[d][1,3]dioxol-5-yl)heptane-3,5-dione (3.28). To a slurry of NaH (312 mg, 7.8 mmol) in THF (10 mL, 0.195 M) at 0 °C was slowly added ethyl 2-(diethoxyphosphoryl)acetate (1.55 mL, 7.8 mmol) over a period of 10 min. After stirring at 0 °C for 30 min, a solution of 7-(benzyloxy)benzo[d][1,3]dioxol-5-carbaldehyde$^{26}$ (1.0 g, 3.9 mmol) in THF (10 mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. The reaction was quenched with saturated NH$_4$Cl solution (30 mL). The organic phase was then separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) gave (E)-Ethyl 3-(7-(benzyloxy)benzo[d][1,3]dioxol-5-yl)acrylate (3.56, 1.27 g, 3.89 mmol, >99% yield) as a white solid. Data for 3.56: $R_f$ 0.51 (4:1 hexanes:EtOAc); mp = 115-118 °C, IR (thin film) 1698, 1511, 1434, 1279, 1235, 1130, 1090, 1034 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, J = 15.9 Hz, 1 H), 7.49-7.30 (m, 5 H), 6.76 (s, 2 H), 6.26 (d, J = 15.9 Hz, 1 H), 6.02 (s, 2 H), 5.20 (s, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 1.35 (t, J = 7.1 Hz, 3 H); $^{13}$C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) δ C 167.1, 149.6, 142.6, 137.8, 136.4, 129.2; CH 144.3, 128.7, 128.2, 127.6, 116.8, 111.6, 101.4; CH$_2$ 101.9, 71.6, 60.4; CH$_3$ 14.4; HRMS (TOF MS ES+) calcd for C$_{19}$H$_{19}$O$_5$ [M+H]: 327.1232, found 327.1229.
To a solution of 3.56 (1.7 g, 5.21 mmol) in THF (40 mL, 0.065 M) were added 40 mL H₂O, NaOAc (1.71 g, 20.84 mmol) and a solution of TsNHNH₂ (4.85 g, 26.05 mmol) in THF (40 mL) over a period of 30 min at 80 °C. After 24 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave Ethyl 3-(7-(benzyloxy)benzo[d][1,3]dioxol-5-yl)propanoate (3.57, 1.7 g, 5.18 mmol, >99% yield) as a colorless solid. Data for 3.57: Rₚ 0.55 (4:1 hexanes:EtOAc); mp = 51-53 °C, IR (thin film) 2933, 1731, 1632, 1509, 1437, 1373, 1190, 1126, 1086, 1043 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.48-7.32 (m, 5 H), 6.45 (d, J = 1.4 Hz, 1 H), 6.42 (d, J = 1.4 Hz, 1 H), 5.96 (s, 2 H), 5.19 (s, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.86 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 172.8, 149.1, 142.5, 136.8, 135.1, 134.0; CH 128.6, 128.1, 127.6, 109.7, 102.7; CH₂ 101.2, 71.5, 60.5, 36.2, 31.0; CH₃ 14.3; HRMS (TOF MS ES+) calcd for C₁₉H₂₁O₅ [M+H]: 329.1389, found 329.1405.

To a solution of 3.57 (328 mg, 1 mmol) in CH₂Cl₂ (10 mL, 0.1 M) at −78 °C was added DIBAL-H (1 mL, 1.2 mmol, 1.2 M in toluene) over a period of 15 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle’s salt (20 mL) at −78 °C. The mixture was allowed to warm to rt. The organic phase was separated and the inorganic phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(7-(benzyloxy)benzo[d][1,3]dioxol-5-yl)propanal (3.58, 261 mg, 0.92 mmol, 92% yield) as a light yellow oil. Data for 3.58: Rₚ 0.58 (2:1 hexanes:EtOAc); IR (thin film) 2925, 1722, 1632, 1509, 1436, 1192, 1127, 1087, 1043 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.80 (t, J = 1.3 Hz, 1 H),
7.48-7.31 (m, 5 H), 6.42 (d, J = 1.3 Hz, 1 H), 6.40 (d, J = 1.3 Hz, 1 H), 5.96 (s, 2 H), 5.19 (s, 2 H), 2.86 (t, J = 7.4 Hz, 2 H), 2.72 (t, J = 7.4 Hz, 2 H); $^{13}$C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) δ C 149.2, 142.5, 136.8, 134.8, 134.1; CH 201.4, 128.6, 128.1, 127.6, 109.9, 102.7; CH$_2$ 101.2, 71.6, 45.4, 28.1; HRMS (TOF MS ES+) calcd for C$_{17}$H$_{17}$O$_4$ [M+H]: 285.1127, found 285.1124.

To a solution of diisopropylamine (223 mg, 2.2 mmol) in THF (8 mL, 0.1 M) was added n-BuLi (1.38 mL, 2.2 mmol, 1.6 M in hexane) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. A solution of 3.22 (479 mg, 2.11 mmol) in THF (5 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of 3.58 (500 mg, 1.76 mmol) in THF (5 mL) was added over a period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH$_4$Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(7-(benzylxyloxy)benzo[d][1,3]dioxol-5-yl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (3.59, 511 mg, 1 mmol, 57% yield) as a white solid. Data for 3.59: Rf 0.26 (3:1 hexanes:EtOAc); mp = 113-115 °C, IR (thin film) 3468 (br), 2928, 1707, 1631, 1508, 1489, 1436, 1191, 1125, 1073, 1042 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 7.48-7.32 (m, 7 H), 7.07 (d, J = 8.4 Hz, 2 H), 6.43 (d, J = 1.2 Hz, 1 H), 6.41 (d, J = 1.2 Hz, 1 H), 5.95 (s, 2 H), 5.19 (s, 2 H), 4.02 (m, 1 H), 2.95 (br s, 1 H), 2.87 (t, J = 7.5 Hz, 2 H), 2.74 (t, J = 7.5 Hz, 2 H), 2.73-2.67 (m, 1 H), 2.62-2.49 (m, 3 H), 1.79-1.72 (m, 1 H), 1.65-1.58 (m, 1 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC, DEPT) δ C 210.5, 149.0, 142.4, 139.7, 136.9, 136.2, 133.8, 120.0; CH 131.6, 130.1, 128.6, 128.0, 127.6, 109.9, 102.8, 66.6; CH$_2$ 101.2, 71.5, 49.3, 44.7, 38.1, 31.7, 28.8; HRMS (TOF MS ES+) calcd for C$_{27}$H$_{28}$BrO$_5$ [M+H]: 511.1120, found 511.1125.
To a solution of 3.59 (199 mg, 0.39 mmol) in EtOAc (4 mL, 0.1 M) at rt was added IBX (328 mg, 1.17 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 6 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude 3.510, which was used directly without further purification.

To a solution of 3.510 (approximately 0.39 mmol, from previous step) in CH₂Cl₂ (8 mL, 0.05 M) were added pentamethylbenzene (173 mg, 1.17 mmol) and BCl₃ (0.78 mL, 0.78 mmol, 1 M in DCM) over a period of 10 min at –78 °C. After addition is completed, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (2 mL) at –78 °C. The resultant mixture was allowed to warm to rt. Diluted aqueous NaHCO₃ was added until the aqueous phase had pH 6. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 1-(4-Bromophenyl)-7-(7-hydroxybenzo[d][1,3]dioxol-5-yl)heptane-3,5-dione (3.28, 125 mg, 0.3 mmol, 76% yield, 2 steps) as a light yellow solid. Data for 3.28: Rf 0.38 (2:1 hexanes:EtOAc); mp = 89-91 °C, IR (thin film) 3400 (br), 2925, 1621, 1488, 1446, 1070 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, enol tautomer) δ 15.37 (s, 1 H), 7.42 (d, J = 8.1 Hz, 2 H), 7.07 (d, J = 8.1 Hz, 2 H), 6.33 (s, 2 H), 5.94 (s, 2 H), 5.43 (s, 1 H), 5.22 (br s, 1 H), 2.94-2.74 (m, 4 H), 2.62-2.50 (m, 4 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT, enol tautomer) δ C 193.0, 192.8, 148.8, 139.6, 139.1, 135.3, 132.5, 120.0; CH 131.6, 130.1, 110.6, 101.9, 99.8; CH₂ 101.3, 40.0, 39.7, 31.3, 30.9; HRMS (TOF MS ES+) calcd for C₂₀H₂₀BrO₅ [M+H]: 419.0494, found 419.0486.
2,5,7-Trioxatetracyclo[16.2.2.1^{3,10}.0^{4,8}]tricosa-1(20),3,8,10(23)18,21-hexaene-3,15-dione (3.33). To a sealed tube were added 3.28 (21.8 mg, 0.05 mmol), CuO (9.9 mg, 0.125 mmol) and K$_2$CO$_3$ (13.8 mg, 0.1 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (10 mL, 0.005 M). The tube was then sealed and heated to 130 °C. After 24 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool to rt. After evaporation of the solvent, aqueous HCl (1 mL, 1 M) and H$_2$O (5 mL) were added. The mixture was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave 3.33 (6.4 mg, 0.0189 mmol, 38% yield) as a light yellow solid. Data for 3.33: R$_f$ 0.63 (2:1 hexanes:EtOAc); IR (thin film) 1635, 1600, 1504, 1435, 1210, 1192, 1064 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 15.19 (br s, 1 H), 7.21 (d, $J = 8.5$ Hz, 2 H), 7.04 (d, $J = 8.5$ Hz, 2 H), 6.33 (m, 1 H), 6.03 (s, 2 H), 5.21 (m, 1 H), 4.96 (s, 1 H), 3.06 (t, $J = 6.8$ Hz, 2 H), 2.91 (m, 2 H), 2.48 (t, $J = 6.8$ Hz, 2 H), 2.37 (m, 2 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC, DEPT) $\delta$ C 197.0, 188.7, 154.1, 148.9, 144.8, 137.0, 135.4, 133.1; CH 130.6, 123.0, 107.7, 103.1, 102.8; CH$_2$ 101.6, 39.4, 38.0, 32.2, 28.0; HRMS (EI+) calcd for C$_{20}$H$_{18}$O$_5$ [M]: 338.1154, found 338.1138.

Garugamblin II (13) and (13E)-13-methoxy-2,5,7-trioxatetracyclo[16.2.2.1^{3,10}.0^{4,8}]tricosa-1(20),3,8,10(23),13,18,21-heptaen-15-one (3.43). To a solution of 3.33 (13.5 mg, 0.04 mmol) in a mixed solvent of CH$_3$CN and MeOH (4 mL, 0.01 M, 10:1 v/v) was added TMSCHN$_2$ (0.2 mL, 0.4 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 3.37c (6.7 mg, 0.019 mmol, 48% yield, white solid, more polar) and 3.38c (6.8 mg, 0.0193 mmol, 48% yield, white solid, less polar) in 1:1 ratio.
Treating 3.37c and 3.38c with dry acidic CDCl$_3$ (“old” CDCl$_3$ dried by 3 Å MS) at rt (approximately 5 minutes) gave garugamblin II (3.13) and 3.43, respectively in >99% yield. Data for garugamblin II (3.13): R$_f$ 0.58 (2:1 hexanes:EtOAc); IR (thin film) 2932, 1681, 1634, 1587, 1505, 1438, 1192, 1097, 1061 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.39 (dd, $J$ = 8.3, 2.0 Hz, 1 H), 7.08 (dd, $J$ = 8.3, 2.3 Hz, 1 H), 6.90 (dd, $J$ = 8.1, 2.3 Hz, 1 H), 6.87 (dd, $J$ = 8.1, 2.0 Hz, 1 H), 6.27 (m, 1 H), 6.02-5.99 (m, 2 H), 5.33 (s, 1 H), 4.90 (br s, 1 H), 4.03 (td, $J$ = 12.9, 3.5 Hz, 1 H), 3.72 (s, 3 H), 3.21 (dd, $J$ = 15.1, 11.3 Hz, 1 H), 3.00 (dt, $J$ = 12.8, 4.0 Hz, 1 H), 2.91 (td, $J$ = 12.9, 3.1 Hz, 1 H), 2.57-2.51 (m, 1 H), 2.49-2.42 (m, 1 H), 2.36-2.32 (m, 1 H), 2.25 (dd, $J$ = 15.4, 6.9 Hz, 1 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC, DEPT) $\delta$ C 197.0, 173.1, 154.8, 148.4, 145.6, 138.5, 136.4, 132.5; CH 130.8, 130.3, 124.3, 122.1, 109.7, 102.6, 101.2; CH$_2$ 101.4, 45.4, 33.9, 33.0, 27.2; CH$_3$ 55.3; HRMS (TOF MS ES+) calcd for C$_{21}$H$_{21}$O$_5$ [M+H]: 353.1389, found 353.1373.

Data for 3.43: R$_f$ 0.33 (2:1 hexanes:EtOAc); IR (thin film) 2919, 1667, 1636, 1567, 1504, 1440, 1190, 1064 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.33-7.27 (m, 2 H), 7.00 (d, $J$ = 8.6 Hz, 2 H), 6.29 (d, $J$ = 1.2 Hz, 1 H), 6.01 (s, 2 H), 5.21 (s, 1 H), 4.87 (br s, 1 H), 3.46 (s, 3 H), 3.11 (t, $J$ = 6.9 Hz, 2 H), 3.08-2.40 (m, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC, DEPT) $\delta$ C 198.8, 173.9, 153.8, 148.9, 145.0, 137.8, 134.9, 132.2; CH 131.2, 123.4, 106.5, 102.2, 102.1; CH$_2$ 101.4, 44.3, 31.2, 28.6, 26.8; CH$_3$ 55.7; HRMS (TOF MS ES+) calcd for C$_{21}$H$_{21}$O$_5$ [M+H]: 353.1389, found 353.1374.

1-(4-Bromophenyl)-7-(3-hydroxy-4-isopropoxy-5-methoxyphenyl)heptane-3,5-dione (3.29). To a solution of 3-(benzyloxy)-4-hydroxy-5-methoxybenzaldehyde$^{27}$ (1.162 g, 4.5 mmol) in DMF (45 mL, 0.1 M) was added K$_2$CO$_3$ (933 mg, 6.75 mmol) and 2-bromopropane (634 mL, 6.75 mmol) at 80 °C. After 1 h, TLC indicated complete consumption of the starting material. The reaction mixture was allowed to cool to rt and poured into 100 mL H$_2$O. The resultant mixture was extracted
with Et₂O (4 x 50 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 6:1) gave 3-(Benzyloxy)-4-isopropoxy-5-methoxybenzaldehyde (3.511, 1.334 g, 4.44 mmol, 99% yield) as a white solid. Data for 3.511: Rₜ 0.43 (3:1 hexanes:EtOAc); mp = 57-
59 °C, IR (thin film) 2976, 1693, 1585, 1493, 1429, 1383, 1326, 1233, 1119 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.85 (s, 1 H), 7.50-7.31 (m, 5 H), 7.20 (d, J = 1.7 Hz, 1 H),
7.16 (d, J = 1.7 Hz, 1 H), 5.18 (s, 2 H), 4.60 (sept, J = 6.2 Hz, 1 H), 3.92 (s, 3 H), 1.34
(d, J = 6.2 Hz, 6 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT) δ C 154.6, 153.3,
142.7, 136.6, 131.5; CH 191.1, 128.6, 128.0, 127.3, 109.1, 106.6, 76.1; CH₂ 71.2;
CH₃ 56.2, 22.6; HRMS (TOF MS ES⁺) calcd for C₁₉H₂₁O₄ [M+H⁺]: 301.1440, found
301.1441.

To a slurry of NaH (276 mg, 6.9 mmol) in THF (10 mL, 0.3 M) at 0 °C was added
ethyl 2-(diethoxyphosphoryl)acetate (1.37 mL, 6.9 mmol) over a period of 10 min.
After stirring at 0 °C for 30 min, a solution of 3.511 (1.382 g, 4.6 mmol) in THF (5
mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. The
reaction was quenched with saturated aqueous NH₄Cl (30 mL). The organic phase
was then separated and the aqueous phase was extracted with EtOAc (3 x 30 mL).
The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) gave (E)-ethyl 3-(3-(benzyloxy)-4-isopropoxy-5-methoxyphenyl)acrylate (3.512, 1.7 g, 4.59 mmol,
>99% yield) as a colorless solid. Data for 3.512: Rₜ 0.47 (3:1 hexanes:EtOAc); mp =
66-68 °C, IR (thin film) 2977, 1710, 1636, 1579, 1500, 1425, 1274, 1246, 1175,
1156, 1116 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 15.9 Hz, 1 H), 7.51-7.30
(m, 5 H), 6.82 (d, J = 1.5 Hz, 1 H), 6.79 (d, J = 1.5 Hz, 1 H), 6.33 (d, J = 15.9 Hz, 1 H),
5.14 (s, 2 H), 4.50 (sept, J = 6.2 Hz, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 1.39-
1.30 (m, 9 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT) δ C 167.0, 154.3, 153.1,
139.1, 136.9, 129.6; CH 144.7, 128.5, 127.9, 127.3, 117.2, 107.8, 105.5, 75.8; CH₂
71.2, 60.5; CH$_3$ 56.1, 22.6, 14.4; HRMS (TOF MS ES+) calcd for C$_{22}$H$_{27}$O$_5$ [M+H]: 371.1858, found 371.1842.

To a solution of 3.512 (1.482 g, 4 mmol) in THF (20 mL, 0.1 M) were added H$_2$O (20 mL), NaOAc (1.312 g, 16 mmol) and a solution of TsNHNH$_2$ (2.235 g, 12 mmol) in THF (20 mL) over a period of 40 min at 80 °C. After 18 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave ethyl 3-(3-(benzyloxy)-4-isopropoxy-5-methoxyphenyl)propanoate (3.513, 1.49 g, 4 mmol, >99% yield) as a colorless oil. Data for 3.513: R$_f$ 0.40 (5:1 hexanes:EtOAc); IR (thin film) 2976, 1732, 1588, 1502, 1454, 1428, 1375, 1236, 1117, 936 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50-7.29 (m, 5 H), 6.50 (d, J = 1.3 Hz, 1 H), 6.46 (d, J = 1.3 Hz, 1 H), 5.10 (s, 2 H), 4.39 (sept, J = 6.2 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.84 (s, 3 H), 2.89 (t, J = 7.8 Hz, 1 H), 2.61 (t, J = 7.8 Hz, 1 H), 1.31 (d, J = 6.2 Hz, 6 H), 1.26 (t, J = 7.1 Hz, 3 H); $^{13}$C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) $\delta$ C 172.9, 154.0, 152.9, 137.4, 135.8, 135.4; CH 128.4, 127.7, 127.3, 107.7, 105.9, 75.3; CH$_2$ 71.2, 60.4, 36.0, 31.3; CH$_3$ 56.1, 22.6, 14.2; HRMS (TOF MS ES+) calcd for C$_{22}$H$_{29}$O$_5$ [M+H]: 373.2015, found 373.2025.

To a solution of 3.513 (1.594 g, 4.28 mmol) in CH$_2$Cl$_2$ (43 mL, 0.1 M) at −78 °C was added DIBAL-H (4.28 mL, 5.14 mmol, 1.2 M in toluene) over a period of 1 h. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle’s salt (100 mL) at −78 °C. The mixture was allowed to warm to rt. The organic phase was separated and the inorganic phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(3-(benzyloxy)-4-isopropoxy-5-
methoxyphenyl)propanal (3.514, 1.14 g, 3.47 mmol, 81% yield) as a white solid. Data for 3.514: R_f 0.50 (2:1 hexanes:EtOAc); mp = 60-62 °C, IR (thin film) 2974, 1723, 1587, 1503, 1454, 1428, 1235, 1117, 933 cm^{-1}; ^1H NMR (400 MHz, CDCl$_3$) δ 9.81 (m, 1 H), 7.50-7.29 (m, 5 H), 6.47 (d, J = 1.8 Hz, 1 H), 6.44 (d, J = 1.8 Hz, 1 H), 5.10 (s, 2 H), 4.39 (sept, J = 6.2 Hz, 1 H), 3.84 (s, 3 H), 2.89 (t, J = 7.4 Hz, 2 H), 2.76 (t, J = 7.4 Hz, 2 H), 1.31 (d, J = 6.2 Hz, 6 H); ^13C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) δ C 154.1, 153.0, 137.4, 135.6, 135.4; CH$_2$ 71.2, 45.3, 28.4; CH$_3$ 56.1, 22.6; HRMS (TOF MS ES+) calcd for C$_{20}$H$_{25}$O$_4$ [M+H]: 329.1753, found 329.1755.

To a solution of diisopropylamine (253 mg, 2.5 mmol) in THF (8 mL, 0.1 M) was added n-BuLi (1.56 mL, 2.5 mmol, 1.6 M in hexane) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. A solution of 3.22 (545 mg, 2.4 mmol) in THF (6 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of 3.514 (657 mg, 2 mmol) in THF (6 mL) was added over a period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH$_4$Cl (30 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(3-(benzylxyloxy)-4-isopropoxy-5-methoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (3.515, 891 mg, 1.6 mmol, 80% yield) as a colorless oil. Data for 3.515: R_f 0.26 (2:1 hexanes:EtOAc); IR (thin film) 3490 (br), 2932, 1708, 1588, 1503, 1454, 1431, 1236, 1115, 935 cm^{-1}; ^1H NMR (400 MHz, CDCl$_3$) δ 7.50-7.29 (m, 7 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.48 (d, J = 1.5 Hz, 1 H), 6.44 (d, J = 1.5 Hz, 1 H), 5.10 (s, 2 H), 4.39 (sept, J = 6.2 Hz, 1 H), 4.05 (m, 1 H), 3.83 (s, 3 H), 3.02 (br s, 1 H), 2.87 (t, J = 7.4 Hz, 2 H), 2.80-2.47 (m, 6 H), 1.86-1.58 (m, 2 H), 1.31 (d, J = 6.2 Hz, 6 H); ^13C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) δ C 210.5, 154.0, 152.8, 139.7, 137.5, 137.0, 135.1,
120.0; CH 131.6, 130.1, 128.4, 127.7, 127.3, 107.9, 106.0, 75.3, 66.9; CH$_2$ 71.2, 49.4, 44.7, 38.1, 32.1, 28.8; CH$_3$ 56.1, 22.6; HRMS (TOF MS ES+) calcd for C$_{30}$H$_{36}$BrO$_5$ [M+H]: 555.1746, found 555.1749.

To a solution of **3.515** (805 mg, 1.45 mmol) in EtOAc (14.5 mL, 0.1 M) at rt was added IBX (1.218 g, 4.35 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4–8 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel and concentrated. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 1-(3-(benzylloxy)-4-isopropoxy-5-methoxyphenyl)-7-(4-bromophenyl)heptane-3,5-dione (**3.516**, 640 mg, 1.16 mmol, 80% yield) as a light yellow oil. Data for **3.516**: R$_f$ 0.67 (2:1 hexanes:EtOAc); IR (thin film) 2973, 1590, 1489, 1453, 1232, 1117, 1011, 931 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, enol tautomer) δ 15.44 (br s, 1 H), 7.50-7.30 (m, 7 H), 7.07 (d, $J$ = 8.3 Hz, 2 H), 6.48 (d, $J$ = 1.6 Hz, 1 H), 6.43 (d, $J$ = 1.6 Hz, 1 H), 5.41 (s, 1 H), 5.10 (s, 2 H), 4.40 (sept, $J$ = 6.2 Hz, 6 H); $^{13}$C NMR (101 MHz, CDCl$_3$, HSQC, DEPT, enol tautomer) δ C 192.9, 192.8, 154.0, 152.9, 139.6, 137.4, 135.8, 135.4, 120.0; CH 131.6, 130.1, 128.4, 127.8, 127.3, 107.8, 105.9, 99.8, 75.3; CH$_2$ 71.2, 40.0, 39.7, 31.9, 30.8; CH$_3$ 56.1, 22.6; HRMS (TOF MS ES+) calcd for C$_{30}$H$_{33}$BrO$_5$Na [M+Na]: 575.1409, found 575.1415.

To a solution of **3.516** (166 mg, 0.3 mmol) in EtOAc (15 mL, 0.02 M) was added 20% Pd/C (16.6 mg, 10% w/w). Hydrogen gas was applied (balloon), and the mixture was stirred at rt until complete consumption of the starting material (carefully monitored by TLC, approximately 30 min–2 h). The reaction was quenched by filtering through a short pad of silica gel. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 8:1) gave 1-(4-bromophenyl)-7-(3-hydroxy-4-isopropoxy-5-methoxyphenyl)heptane-3,5-dione (**3.29**, 95 mg, 0.205 mmol, 68% yield) as a yellow oil. Data for **3.29**: R$_f$ 0.39 (3:1 hexanes:EtOAc); IR
(thin film) 3445 (br), 2974, 1704, 1508, 1489, 1459, 1357, 1197, 1107, 1011, 929 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, enol tautomer) δ 15.42 (br s, 1 H), 7.41 (d, J = 8.2 Hz, 2 H), 7.07 (d, J = 8.2 Hz, 2 H), 6.45 (d, J = 1.6 Hz, 1 H), 6.30 (d, J = 1.6 Hz, 1 H), 5.82 (br s, 1 H), 5.43 (s, 1 H), 4.53 (sept, J = 6.2 Hz, 1 H), 3.82 (s, 3 H), 2.93-2.75 (m, 4 H), 2.62-2.51 (m, 4 H), 1.31 (d, J = 6.2 Hz, 6 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT, enol tautomer) δ C 192.9, 192.8, 152.3, 150.0, 139.6, 136.5, 120.0; CH 131.6, 130.1, 107.4, 104.2, 99.7, 75.1; CH₂ 39.9, 39.7, 31.6, 30.8; CH₃ 55.8, 22.6; HRMS (TOF MS ES⁺) calcd for C₂₃H₂₆BrO₄ [M+H-H₂O]: 445.1014, found 445.1006.

5-Methoxy-4-(propan-2-yloxy)-2-oxatricyclo[13.2.2.13,7]icos-1(17),3,5,7(20),15,18-hexaene-10,12-dione (3.34). To a sealed tube were added 3.29 (23.2 mg, 0.05 mmol), CuO (9.9 mg, 0.125 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (10 mL, 0.005 M). The tube was then sealed and heated to 130 °C. After 72 h, the reaction mixture was allowed to cool to rt. After evaporation of the solvent, aqueous HCl (1 mL, 1 M) and H₂O (5 mL) were added. The mixture was extracted with EtOAc (4 x 10 mL). The combined organic phase was dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave 3.34 (7.1 mg, 0.0186 mmol, 37% yield) as a light yellow solid. Data for 3.34: Rf 0.41 (3:1 hexanes:EtOAc); IR (thin film) 3450 (br), 2973, 1590, 1505, 1433, 1216, 1092, 934 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 15.17 (br s, 1 H), 7.18 (d, J = 8.5 Hz, 2 H), 6.99 (d, J = 8.5 Hz, 2 H), 6.33 (d, J = 1.9 Hz, 1 H), 5.26 (d, J = 1.9 Hz, 1 H), 4.98 (s, 1 H), 4.50 (sept, J = 6.2 Hz, 1 H), 3.84 (s, 3 H), 3.05 (t, J = 6.8 Hz, 2 H), 2.95 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.39 (m, 2 H), 1.41 (d, J = 6.2 Hz, 6 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 197.2, 188.6, 155.5, 155.0, 153.7, 136.4, 136.0, 134.0; CH₁ 130.5, 123.2, 106.9, 105.5, 103.2, 75.6; CH₂ 39.4, 37.6, 32.3, 28.1; CH₃
56.1, 22.6; HRMS (TOF MS ES+) calcd for C_{23}H_{27}O_{5} [M+H]: 383.1858, found 383.1865.

**Reported Structure of 1,9'-Didesmethylgaruganin III (3.10).** To a solution of 3.34 (5 mg, 0.013 mmol) in DCM (1 mL, 0.013 M) was added BCl₃ (39 uL, 0.039 mmol) at 0 °C. The mixture was allowed to warm to rt. After 5 min, TLC indicated consumption of starting material. The reaction was then quenched with MeOH (1 mL) and stirred for 10 min. The solvent was evaporated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 3.10 (3.2 mg, 0.0097 mmol, 74% yield) as a light yellow solid. Data for 3.10: Rₓ 0.20 (3:1 hexanes:EtOAc); IR (thin film) 3441 (br), 2939, 1603, 1454, 1436, 1213, 1083, 860 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 15.19 (br s, 1 H), 7.20 (d, J = 8.4 Hz, 2 H), 7.02 (d, J = 8.4 Hz, 2 H), 6.34 (br s, 1 H), 5.53 (s, 1 H), 5.28 (d, J = 1.7 Hz, 1 H), 4.97 (s, 1 H), 3.90 (s, 3 H), 3.06 (t, J = 6.8 Hz, 2 H), 2.93 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.38 (m, 2 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 197.0, 188.8, 154.7, 148.9, 147.2, 136.8, 132.6, 132.0; CH 130.6, 123.2, 106.7, 105.0, 103.2; CH₂ 39.5, 37.9, 32.2, 28.0; CH₃ 56.3; HRMS (TOF MS ES+) calcd for C_{20}H_{22}O_{5} [M+H]: 341.1389, found 341.1380.

**1-(4-Bromophenyl)-7-(3-hydroxy-4,5-dimethoxyphenyl)heptane-3,5-dione (3.30).** To a slurry of NaH (360 mg, 9 mmol) in THF (10 mL, 0.3 M) was added ethyl 2-(diethoxyphosphoryl)acetate (1.79 mL, 9 mmol) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, a solution of 3-(benzyloxy)-4,5-dimethoxybenzaldehyde (1.634 g, 6 mmol) in THF (10 mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. The reaction was quenched with saturated aqueous NH₄Cl (30 mL). The organic phase was then separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic
phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) gave (E)-Ethyl 3-((benzyl oxy)-4,5-dimethoxyphenyl)acrylate (3.517, 2.038 g, 5.95 mmol, >99% yield) as a white solid. Data for 3.517: Rf 0.51 (3:1 hexanes:EtOAc); mp = 67-69 °C, IR (thin film) 2940, 1709, 1636, 1581, 1504, 1425, 1275, 1176, 1152, 1120, 1005 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 15.9 Hz, 1 H), 7.49-7.31 (m, 5 H), 6.81 (d, J = 1.8 Hz, 1 H), 6.78 (d, J = 1.8 Hz, 1 H), 6.32 (d, J = 15.9 Hz, 1 H), 5.15 (s, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 1.35 (t, J = 7.1 Hz, 3 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT) δ C 166.9, 153.6, 152.5, 140.8, 140.8, 136.8, 129.9; CH 144.5, 128.6, 128.0, 127.3, 117.5, 107.7, 105.4; CH₂ 71.2, 60.5; CH₃ 61.0, 56.2, 14.4; HRMS (TOF MS ES+) calcd for C₂₀H₂₃O₅ [M+H]: 343.1545, found 343.1528.

To a solution of 3.517 (1.883 g, 5.5 mmol) in THF (28 mL, 0.1 M) were added H₂O (28 mL), NaOAc (1.805 g, 22 mmol) and a solution of TsNHNH₂ (3.072 g, 16.5 mmol) in THF (27 mL) over a period of 1 h at 80 °C. After 24 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave Ethyl 3-((benzyl oxy)-4,5-dimethoxyphenyl)propanoate (3.518, 1.88 g, 5.46 mmol, >99% yield) as a colorless oil. Data for 3.518: Rf 0.39 (4:1 hexanes:EtOAc); IR (thin film) 2940, 1732, 1590, 1508, 1454, 1429, 1239, 1120, 1011 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.49-7.31 (m, 5 H), 6.50 (d, J = 1.8 Hz, 1 H), 6.46 (d, J = 1.8 Hz, 1 H), 5.14 (s, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.89 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 7.8 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 172.9, 153.3, 152.3, 137.2, 137.1, 136.3; CH 128.5, 127.9, 127.3, 107.5, 105.6; CH₂ 71.1, 60.5, 36.0, 31.3; CH₃ 60.9, 56.1, 14.3; HRMS (TOF MS ES+) calcd for C₂₀H₂₅O₅ [M+H]: 345.1702, found 345.1699.
To a solution of 3.518 (344 mg, 1 mmol) in CH₂Cl₂ (10 mL, 0.1 M) at −78 °C was added DIBAL-H (1 mL, 1.2 mmol, 1.2 M in toluene) over a period of 15 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle’s salt (20 mL) at −78 °C. The mixture was warmed to rt. The organic phase was separated and the inorganic phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(3-(benzyloxy)-4,5-dimethoxyphenyl)propanal (3.519, 246 mg, 0.82 mmol, 82% yield) as a colorless oil. Data for 3.519: Rf 0.49 (2:1 hexanes:EtOAc); IR (thin film) 2937, 1722, 1589, 1507, 1453, 1429, 1239, 1119, 1008 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.80 (br s, 1 H), 7.49-7.29 (m, 5 H), 6.47 (d, J = 1.6 Hz, 1 H), 6.44 (d, J = 1.6 Hz, 1 H), 5.13 (s, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.88 (t, J = 7.4 Hz, 2 H), 2.74 (t, J = 7.4 Hz, 2 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT) δ C 153.4, 152.4, 137.3, 137.2, 136.0; CH 201.5, 128.5, 127.9, 127.3, 107.7, 105.8; CH₂ 71.2, 45.3, 28.4; CH₃ 60.9, 56.1; HRMS (TOF MS ES⁺) calcd for C₁₈H₂₁O₄ [M+H]: 301.1440, found 301.1449.

To a solution of diisopropylamine (190 mg, 1.88 mmol) in THF (6 mL, 0.1 M) was added n-BuLi (1.17 mL, 1.88 mmol, 1.6 M in hexane) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. A solution of 3.22 (409 mg, 1.8 mmol) in THF (4 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of 3.519 (451 mg, 1.5 mmol) in THF (5 mL) was added over a period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH₄Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(3-(Benzyloxy)-4,5-dimethoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (3.520, 554 mg,
1.05 mmol, 70% yield) as a colorless oil. Data for 3.520: Rf 0.21 (2:1 hexanes:EtOAc); IR (thin film) 3500 (br), 2934, 1707, 1590, 1505, 1489, 1330, 1239, 1118, 1010 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.50-7.29 (m, 7 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.48 (br s, 1 H), 6.45 (br s, 1 H), 5.13 (s, 2 H), 4.04 (m, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.06 (br s, 1 H), 2.86 (t, J = 7.3 Hz, 2 H), 2.80-2.47 (m, 6 H), 1.84-1.57 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT) δ C 210.5, 153.3, 152.3, 139.7, 137.4, 137.3, 137.0, 120.0; CH 131.6, 130.1, 128.5, 127.8, 127.3, 107.8, 105.9, 66.8; CH₂ 71.1, 49.4, 44.7, 38.1, 32.0, 28.8; CH₃ 60.9, 56.1; HRMS (TOF MS ES⁺) calcd for C₂₈H₃₂BrO₅ [M+H]: 527.1433, found 527.1429.

To a solution of 3.520 (448 mg, 0.85 mmol) in EtOAc (8.5 mL, 0.1 M) at rt was added IBX (714 mg, 2.55 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4–8 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude 3.521, which was used directly without further purification.

To a solution of 3.521 (approximately 0.85 mmol, from previous step) in CH₂Cl₂ (17 mL, 0.05 M) were added pentamethylbenzene (378 mg, 2.55 mmol) and BCl₃ (3.4 mL, 3.4 mmol, 1 M in DCM) over a period of 10 min at −78 °C. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (2mL) at −78 °C. The resultant mixture was allowed to warm to rt. Diluted aqueous NaHCO₃ was added until the aqueous phase had pH 6. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 1-(4-Bromophenyl)-7-(3-hydroxy-4,5-dimethoxyphenyl)heptane-3,5-dione (3.30, 263 mg, 0.604 mmol, 71% yield, 2 steps) as a light yellow solid. Data for 3.30: Rf 0.39 (2:1 hexanes:EtOAc); mp = 60-63 °C, IR (thin film) 3432 (br),
2934, 1594, 1511, 1489, 1356, 1202, 1106, 1010 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, enol tautomer) δ 15.41 (br s, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.08 (d, J = 8.2 Hz, 2 H), 6.45 (d, J = 1.7 Hz, 1 H), 6.31 (d, J = 1.7 Hz, 1 H), 5.74 (br s, 1 H), 5.44 (s, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.94-2.76 (m, 4 H), 2.63-2.53 (m, 4 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT, enol tautomer) δ C 192.9, 192.7, 152.3, 149.2, 139.6, 136.9, 133.9, 120.0; CH 131.6, 130.1, 107.7, 104.3, 99.7; CH₂ 39.9, 39.7, 31.6, 30.8; CH₃ 61.0, 55.8; HRMS (TOF MS ES⁺) calcd for C₂₁H₂₄BrO₅ [M+H]: 435.0807, found 435.0791.

4,5-Dimethoxy-2-oxatricyclo[13.2.2.1³,7]icosa-1(17),3,5,7(20),15,18-henaene-10,12-dione (3.35). To a sealed tube were added 3.30 (21.8 mg, 0.05 mmol), CuO (9.9 mg, 0.125 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (10 mL, 0.005 M). The tube was then sealed and heated to 130 °C. After 48 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool to rt. After evaporation of the solvent, aqueous HCl (1 mL, 1 M) and H₂O (5 mL) were added. The mixture was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 5:1) gave 3.35 (9 mg, 0.0254 mmol, 51% yield) as a light yellow solid. Data for 3.35: Rᶠ 0.53 (2:1 hexanes:EtOAc); IR (thin film) 2932, 1589, 1507, 1454, 1432, 1215, 1096, 1003 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 15.16 (br s, 1 H), 7.19 (d, J = 8.4 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 2 H), 6.35 (d, J = 1.8 Hz, 1 H), 5.29 (d, J = 1.8 Hz, 1 H), 4.97 (s, 1 H), 4.00 (s, 3 H), 3.88 (s, 3 H), 3.06 (t, J = 6.8 Hz, 2 H), 2.95 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.39 (m, 2 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 196.9, 188.7, 154.9, 154.8, 153.1, 136.6, 136.5, 136.1; CH 130.6, 123.1, 107.0, 105.6, 103.2; CH₂ 39.4, 37.6, 32.2, 28.1; CH₃
61.2, 56.1; HRMS (TOF MS ES+) calcd for C_{21}H_{23}O_{5} [M+H]: 355.1545, found 355.1539.

(11E)-4,15,12-trimethoxy-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1(17),3,5,7(20),11,15,18-heptaen-10-one (3.44) and garuganin III (3.9). To a solution of 3.35 (21.3 mg, 0.06 mmol in a mixed solvent of CH_{3}CN and MeOH (6 mL, 0.01 M, 10:1 v/v) was added TMSCHN\_2 (0.3 mL, 0.6 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 3.37d (10.6 mg, 0.0288 mmol, 48% yield, white solid, more polar) and 3.38d (10.6 mg, 0.0288 mmol, 48% yield, white solid, less polar) in 1:1 ratio. Treating 3.37d and 3.38d with dry acidic CDCl\_3 (“old” CDCl\_3 dried by 3 Å MS) at rt (approximately 5 minutes) gave 3.44 and garuganin III (3.9), respectively in >99% yield. Data for garuganin III (3.9): R\_f 0.25 (2:1 hexanes:EtOAc); IR (thin film) 2925, 1667, 1589, 1568, 1506, 1451, 1271, 1214, 1093 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\_3) \(\delta\) 7.32-7.26 (m, 2 H), 6.97 (d, \(J = 8.6\) Hz, 2 H), 6.30 (d, \(J = 1.7\) Hz, 1 H), 5.22 (s, 1 H), 4.92 (d, \(J = 1.7\) Hz, 1 H), 4.00 (s, 3 H), 3.86 (s, 3 H), 3.47 (s, 3 H), 3.11 (t, \(J = 7.0\) Hz, 2 H), 3.08-2.40 (m, 6 H); \(^{13}\)C NMR (176 MHz, CDCl\_3, HSQC, DEPT) \(\delta\) C 198.8, 173.8, 155.2, 154.5, 153.1, 137.4, 136.1, 135.3; CH\_3 131.2, 123.4, 106.0, 105.0, 102.1; CH\_2 44.3, 31.1, 28.5, 26.9; CH\_3 61.2, 56.0, 55.7; HRMS (TOF MS ES+) calcd for C_{22}H_{25}O_{5} [M+H]: 369.1702, found 369.1686.

Data for 3.44: R\_f 0.41 (2:1 hexanes:EtOAc); IR (thin film) 2935, 1682, 1589, 1506, 1432, 1261, 1210, 1147, 1096, 1007 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\_3) \(\delta\) 7.38 (dd, \(J = 8.2, 1.4\) Hz, 1 H), 7.04 (dd, \(J = 8.2, 1.9\) Hz, 1 H), 6.90-6.84 (m, 2 H), 6.30 (d, \(J = 1.8\) Hz, 1 H), 5.33 (s, 1 H), 4.94 (d, \(J = 1.8\) Hz, 1 H), 4.02 (td, \(J = 12.9, 3.4\) Hz, 1 H), 4.00 (s, 3 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 3.24 (dd, \(J = 14.7, 11.4\) Hz, 1 H), 2.99 (dt, \(J = 12.8, 4.0\) Hz, 1 H), 2.91 (td, \(J = 12.9, 3.1\) Hz, 1 H), 2.57-2.51 (m, 1 H), 2.48 (dd, \(J =
17.5, 11.0 Hz, 1 H), 2.34 (dt, J = 12.8, 3.8 Hz, 1 H), 2.28 (dd, J = 15.6, 6.7 Hz, 1 H); 
$^{13}$C NMR (176 MHz, CDCl$_3$, HSQC, DEPT) δ C 196.8, 173.0, 155.6, 155.5, 152.8, 
138.1, 137.4, 135.7; CH 130.8, 130.2, 124.4, 122.2, 108.9, 105.5, 101.2; CH$_2$ 45.0, 
33.9, 33.0, 27.5; CH$_3$ 61.2, 56.2, 55.2; HRMS (TOF MS ES+) calcd for C$_{22}$H$_{25}$O$_5$ 
[M+H]: 369.1702, found 369.1692.

1-(3-Bromo-5-methoxyphenyl)-7-(4-hydroxyphenyl)heptane-3,5-dione (3.31). To 
a slurry of NaH (540 mg, 13.5 mmol) in THF (15 mL, 0.3 M) was added ethyl 2- 
(diethoxyphosphoryl)acetate (2.68 mL, 13.5 mmol) over a period of 10 min at 0 
°C. After stirring at 0 °C for 30 min, a solution of 3-bromo-5- 
methoxybenzaldehyde$^{28}$ (1.935 g, 9 mmol) in THF (15 mL) was added. The mixture 
was warmed to rt and stirred at rt for 30 min. The reaction was quenched with 
saturated aqueous NH$_4$Cl (50 mL). The organic phase was then separated and the 
aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic 
phases were dried with MgSO$_4$. Purification by flash column chromatography 
(hexanes:EtOAc = 10:1 to 5:1) gave (E)-Ethyl 3-(3-bromo-5- 
methoxyphenyl)acrylate (3.522, 2.541 g, 8.91 mmol, 99% yield) as a colorless 
solid. Data for 3.522: $R_f$ 0.41 (5:1 hexanes:EtOAc); mp = 43-45 °C, IR (thin film) 
2981, 1713, 1641, 1565, 1456, 1422, 1270, 1178, 1050 cm$^{-1}$; $^1$H NMR (700 MHz, 
CDCl$_3$) δ 7.56 (d, J = 16.0 Hz, 1 H), 7.27 (t, J = 1.3 Hz, 1 H), 7.07 (t, J = 2.0 Hz, 1 H), 
6.96 (t, J = 1.7 Hz, 1 H), 6.42 (d, J = 16.0 Hz, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 3.83 (s, 3 
H), 1.35 (t, J = 7.1 Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC) δ C 166.5, 160.5, 
137.2; CH 142.9, 123.3, 120.0, 118.7, 112.5; CH$_2$ 60.7; CH$_3$ 55.6, 14.3; HRMS (TOF 
MS ES+) calcd for C$_{12}$H$_{14}$BrO$_3$ [M+H]: 285.0126, found 285.0138.

To a solution of 3.522 (2.024 g, 7.1 mmol) in THF (36 mL, 0.1 M) were added H$_2$O 
(36 mL), NaOAc (2.33 g, 28.4 mmol) and a solution of TsNHNH$_2$ (3.967 g, 21.3 
mmol) in THF (35 mL) over a period of 1 h at 80 °C. After 24 h, TLC indicated the
complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 8:1) gave Ethyl 3-(3-bromo-5-methoxyphenyl)propanoate (3.523, 2.04 g, 7.1 mmol, >99% yield) as a colorless oil. Data for 3.523: Rf 0.55 (3:1 hexanes:EtOAc); IR (thin film) 2939, 1724, 1598, 1568, 1459, 1430, 1153, 1055 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 6.97 (t, J = 1.5 Hz, 1 H), 6.92 (d, J = 2.0 Hz, 1 H), 6.70 (m, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 2.91 (t, J = 7.7 Hz, 2 H), 2.62 (t, J = 7.7 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 172.6, 160.4, 143.8, 122.7; CH 123.8, 114.9, 113.4; CH₂ 60.6, 35.5, 30.7; CH₃ 55.4, 14.2; HRMS (EI+) calcd for C₁₂H₁₅BrO₃ [M]: 286.0205, found 286.0201.

To a solution of 3.523 (2.01 g, 7 mmol) in CH₂Cl₂ (70 mL, 0.1 M) at −78 °C was added DIBAL-H (7 mL, 8.4 mmol, 1.2 M in toluene) over a period of 1 h. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle’s salt (100 mL) at −78 °C. The mixture was warmed to rt. The organic phase was separated and the inorganic phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(3-Bromo-5-methoxyphenyl)propanal (3.524, 1.38 g, 5.68 mmol, 81% yield) as a light yellow oil. Data for 3.524: Rf 0.41 (3:1 hexanes:EtOAc); IR (thin film) 2981, 1713, 1641, 1565, 1456, 1422, 1270, 1178, 1050 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 9.83 (t, J = 1.2 Hz, 1 H), 6.95 (t, J = 1.5 Hz, 1 H), 6.92 (t, J = 2.0 Hz, 1 H), 6.69 (m, 1 H), 3.79 (s, 3 H), 2.91 (t, J = 7.5 Hz, 2 H), 2.81-2.77 (m, 2 H); ¹³C NMR (176 MHz, CDCl₃, HSQC, DEPT) δ C 160.4, 143.6, 122.9; CH 200.9, 123.7, 114.8, 113.5; CH₂ 44.9, 27.8; CH₃ 55.5; HRMS (EI+) calcd for C₁₀H₁₁BrO₂ [M]: 241.9942, found 241.9940.
To a solution of diisopropylamine (481 mg, 4.75 mmol) in THF (20 mL, 0.1 M) was slowly added n-BuLi (2.97 mL, 4.75 mmol, 1.6 M in hexane) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. A solution of 4-(4-(benzylxyloxy)phenyl)butan-2-one$^{29}$ (1.16 g, 4.56 mmol) in THF (9 mL) was added over a period of 1 h. After stirring at −78 °C for 30 min, a solution of 3.524 (924 mg, 3.8 mmol) in THF (9 mL) was added over a period of 1 h. After stirring for 2 h, the reaction was quenched with saturated aqueous NH$_4$Cl (30 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 1-(4-(Benzyloxy)phenyl)-7-(3-bromo-5-methoxyphenyl)-5-hydroxyheptan-3-one (3.525, 1.377 g, 2.77 mmol, 73% yield) as a light yellow solid. Data for 3.525: R$_f$ 0.25 (2:1 hexanes:EtOAc); mp = 80-82 °C, IR (thin film) 3371 (br), 2929, 1705, 1605, 1566, 1512, 1454, 1237, 1154, 817 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.49-7.30 (m, 5 H), 7.10 (d, $J$ = 8.6 Hz, 2 H), 6.95 (br s, 1 H), 6.94-6.87 (m, 3 H), 6.69 (br s, 1 H), 5.06 (s, 2 H), 4.03 (m, 1 H), 3.79 (s, 3 H), 3.09 (d, $J$ = 3.1 Hz, 1 H), 2.92-2.46 (m, 8 H), 1.84-1.59 (m, 2 H); $^{13}$C NMR (101 MHz, CDCl$_3$, HSQC, DEPT) δ C 211.2, 160.4, 157.3, 145.1, 137.1, 132.9, 122.7; CH 129.2, 128.6, 127.9, 127.4, 123.9, 115.0, 114.5, 113.5, 66.6; CH$_2$ 70.1, 49.2, 45.2, 37.6, 31.5, 28.7; CH$_3$ 55.4; HRMS (TOF MS ES$^+$) calcd for C$_{27}$H$_{30}$BrO$_4$ [M+H]: 497.1327, found 497.1310.

To a solution of 3.525 (497 mg, 1 mmol) in EtOAc (10 mL, 0.1 M) at rt was added IBX (840 mg, 3 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4–8 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give crude 3.526, which was used directly without further purification.
To a stirred solution of 3.526 (approximately 1 mmol, from previous step) in CH₂Cl₂ (20 mL, 0.05 M) were added pentamethylbenzene (445 mg, 3 mmol) and BCl₃ (4 mL, 4 mmol, 1 M in DCM) over a period of 10 min at −78 °C. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (2mL) at −78 °C. The resultant mixture was allowed to warm to rt. Diluted aqueous NaHCO₃ was added until the aqueous phase had pH 6. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with MgSO₄. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 1-(3-Bromo-5-methoxyphenyl)-7-(4-hydroxyphenyl)heptane-3,5-dione (3.31, 291 mg, 0.72 mmol, 72% yield, 2 steps) as a light yellow solid. Data for 3.31: Rₚ 0.49 (2:1 hexanes:EtOAc); mp = 54-57 °C, IR (thin film) 3402 (br), 2936, 1724, 1699, 1600, 1569, 1515, 1456, 1266, 1054, 828 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, enol tautomer) δ 15.39 (br s, 1 H), 7.05 (d, J = 8.3 Hz, 2 H), 6.95 (br s, 1 H), 6.92 (t, J = 1.9 Hz, 1 H), 6.77 (d, J = 8.3 Hz, 2 H), 6.67 (br s, 1 H), 5.44 (s, 1 H), 5.26 (br s, 1 H), 3.79 (s, 3 H), 2.92-2.72 (m, 4 H), 2.62-2.51 (m, 4 H); ¹³C NMR (101 MHz, CDCl₃, HSQC, DEPT, enol tautomer) δ C 193.02, 193.0, 160.4, 154.1, 143.8, 132.6, 122.8; CH 129.4, 123.8, 115.4, 114.9, 113.4, 99.8; CH₂ 40.2, 39.6, 31.1, 30.8; CH₃ 55.5; HRMS (TOF MS ES+) calcd for C₂₀H₂₂BrO₄ [M+H]: 405.0701, found 405.0709.

5-Methoxy-2-oxatricyclo[13.2.2.1³,⁷]isoca₁(17),3,5,7(20),15,18-hexaene-10,12-dione (3.36). To a sealed tube were added 3.31 (40.5 mg, 0.1 mmol), CuO (19.9 mg, 0.25 mmol) and K₂CO₃ (27.6 mg, 0.2 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (20 mL, 0.005 M). The tube was then sealed and heated to 130 °C. After 72 h, the reaction mixture was allowed to cool to rt. After evaporation of the solvent, aqueous HCl (2 mL, 1 M) and H₂O (10 mL) were added. The mixture was extracted with EtOAc (4 x 20 mL).
The combined organic phases were dried with MgSO$_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave 3.36 (13 mg, 0.04 mmol, 40% yield) as a light yellow solid. Data for 3.36: R$_f$ 0.63 (2:1 hexanes:EtOAc); IR (thin film) 2939, 1599, 1505, 1461, 1434, 1342, 1294, 1218, 1137, 1059 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 15.20 (br s, 1 H), 7.20 (d, $J = 8.4$ Hz, 2 H), 6.99 (d, $J = 8.4$ Hz, 2 H), 6.60 (t, $J = 2.2$ Hz, 1 H), 6.34 (m, 1 H), 5.21 (m, 1 H), 4.97 (s, 1 H), 3.82 (s, 3 H), 3.06 (t, $J = 6.8$ Hz, 2 H), 2.96 (m, 2 H), 2.48 (t, $J = 6.8$ Hz, 2 H), 2.38 (m, 2 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC) $\delta$ C 197.0, 188.8, 162.9, 160.6, 154.6, 143.3, 136.7; CH 130.6, 123.1, 107.8, 105.7, 103.2, 100.3; CH$_2$ 39.4, 37.7, 32.2, 28.4; CH$_3$ 55.4; HRMS (TOF MS ES+) calcd for C$_{20}$H$_{21}$O$_4$ [M+H]: 325.1440, found 325.1456.

Reported Structure of Garuganin IV (3.8) and (10E)-5,10-dimethoxy-2-oxatricyclo[13.2.2.1$^{3,7}$]isoca-1(17),3,5,7(20),10,15,18-heptaen-12-one (3.45). To a solution of 3.36 (26 mg, 0.08 mmol) in a mixed solvent of CH$_3$CN and MeOH (8 mL, 0.01 M 10:1 v/v) was added TMSCHN$_2$ (0.4 mL, 0.8 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 3.37e (13.3 mg, 0.0393 mmol, 49% yield, white solid, more polar) and 3.38e (13 mg, 0.0384 mmol, 48% yield, white solid, less polar) in 1:1 ratio. Treating 3.37e and 3.38e with dry acidic CDCl$_3$ (“old” CDCl$_3$ dried by 3 Å MS) at rt (approximately 5 minutes) gave garuganin IV (3.8) and 3.45, respectively in >99% yield. Data for garuganin IV (3.8): white solid, R$_f$ 0.57 (2:1 hexanes:EtOAc); IR (thin film) 2932, 1682, 1591, 1503, 1462, 1434, 1212, 1136, 1098 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.38 (d, $J = 8.3$ Hz, 1 H), 7.04 (dd, $J = 8.3$, 1.8 Hz, 1 H), 6.90-6.83 (m, 2 H), 6.56 (t, $J = 2.2$ Hz, 1 H), 6.28 (br s, 1 H), 5.33 (s, 1 H), 4.86 (br s, 1 H), 4.03 (td, $J = 12.9$, 3.4 Hz, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.26 (dd, $J = 14.5$, 11.7 Hz, 1 H), 2.99 (dt, $J = 3.4$ Hz, 1 H), 2.38 (m, 2 H), 2.32 (br s, 3 H), 1.38 (br s, 3 H), 1.12 (br s, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$, HSQC) $\delta$ C 197.0, 188.8, 162.9, 160.6, 154.6, 143.3, 136.7; CH 130.6, 123.1, 107.8, 105.7, 103.2, 100.3; CH$_2$ 39.4, 37.7, 32.2, 28.4; CH$_3$ 55.4; HRMS (TOF MS ES+) calcd for C$_{20}$H$_{21}$O$_4$ [M+H]: 325.1440, found 325.1456.
12.6, 3.9 Hz, 1 H), 2.92 (td, \( J = 12.9, 3.0 \text{ Hz}, 1 \text{ H} \)), 2.57-2.50 (m, 1 H), 2.47 (dd, \( J = 17.8, 11.2 \text{ Hz}, 1 \text{ H} \)), 2.34 (dt, \( J = 12.9, 3.8 \text{ Hz}, 1 \text{ H} \)), 2.30 (dd, \( J = 15.2, 7.0 \text{ Hz}, 1 \text{ H} \));

\(^{13}\text{C} \) NMR (176 MHz, CDCl\(_3\), HSQC, DEPT) \( \delta \) C 196.9, 173.0, 163.6, 160.4, 155.4, 144.2, 138.2; CH 130.7, 130.3, 124.4, 122.2, 107.6, 107.4, 101.3, 99.5; CH\(_2\) 45.0, 33.9, 32.9, 27.6; CH\(_3\) 55.4, 55.2; HRMS (TOF MS ES+) calcd for C\(_{21}\)H\(_{23}\)O\(_4\) [M+H]: 339.1596, found 339.1584.

Data for 3.45: white solid, \( R_f \) 0.31 (2:1 hexanes:EtOAc); IR (thin film) 2917, 1668, 1589, 1567, 1505, 1458, 1440, 1267, 1215, 1133 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\) \( \delta \) 7.32-7.26 (m, 2 H), 6.96 (d, \( J = 8.6 \text{ Hz}, 2 \text{ H} \)), 6.55 (t, \( J = 2.3 \text{ Hz}, 1 \text{ H} \)), 6.30 (m, 1 H), 5.21 (s, 1 H), 4.87 (m, 1 H), 3.80 (s, 3 H), 3.46 (s, 3 H), 3.11 (t, \( J = 7.0 \text{ Hz}, 2 \text{ H} \)), 3.08-2.40 (m, 6 H); \(^{13}\text{C} \) NMR (176 MHz, CDCl\(_3\), HSQC, DEPT) \( \delta \) C 198.7, 173.9, 163.2, 160.4, 154.4, 142.8, 137.5; CH 131.1, 123.5, 107.1, 104.7, 102.0, 99.6; CH\(_2\) 44.3, 31.2, 28.3, 27.1; CH\(_3\) 55.6, 55.3; HRMS (TOF MS ES+) calcd for C\(_{21}\)H\(_{23}\)O\(_4\) [M+H]: 339.1596, found 339.1601.

Garugamblin I (3.11). To a solution of 3.12 (1.5 mg, 4.63 mmole) in dry MeOH (0.46 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 mmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 x 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and garugamblin I (3.11) (50% yield).

Garuganin I (3.7). To a solution of 3.32 (2.0 mg, 5.65 mmole) in dry MeOH (0.57 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 mmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 x 2 mL) and concentrated. Analysis of the crude material by NMR
indicated that it was a mixture of unreacted starting material and garuganin I (3.7) (17% yield).

**Reported structure of Garuganin IV (3.8).** To a solution of 3.37 (1.8 mg, 5.55 µmole) in dry MeOH (0.56 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 mmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 x 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and reported structure of garuganin IV (3.8) (14% yield).

**Garugamblin II (3.13).** To a solution of 3.34 (1.5 mg, 4.44 mmole) in dry MeOH (0.44 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 mmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 x 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and garugamblin II (3.13) (12% yield).

**(11E)-4,15,12-trimethoxy-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1(17),3,5,7(20),11,15,18-heptaen-10-one (3.44).** To a solution of 3.30 (2.2 mg, 6.21 mmole) in dry MeOH (0.62 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 mmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 x 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and (11E)-4,15,12-trimethoxy-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1(17),3,5,7(20),11,15,18-heptaen-10-one (3.44) (16% yield).
ZQZ-1126 C13

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PROCNO 1

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AQ 1.3664756 sec
RI 6502
DM 20.850 us
DE 6.00 us
TR 299.2 s
T2 0.28000000 sec
g 0.03000000 sec
DR13 0.10000000 sec
TDD 1

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P1 8.30 us
PL1 3.00 dB
SF1 100.6555216 MHz

--- CHANNEL f2 -------
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MC2 1H
PC/D2 90.00 us
PL2 -3.00 dB
FL1 15.00 dB
FL13 15.00 dB
SF2 400.6263013 MHz

F2 - Processing parameters:
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SF 100.645570 MHz
MEQ 0
SSB 0
LB 1.00 Hz
GB 0
FC 1.40
2Q8-1137

![Compound Structure]

Current Data Parameters
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EXPNO 1
PROCHD 1

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FDRES 0.195625 H
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RG 90.3
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DE 6.00 u
tE 299.2 K
D1 2.00000000 s
D2 1

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PL1 1.40 d
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F2 - Processing parameters:
SI 32768
SP 400.2600000 MHz
WOW EW
SUB 0
LS 0.30 H
GB 0
PC 1.00
195

ZQZ-1160 C13

MeO

O

24

Br

MeO

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PROCNO: 1

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POLAR:筥
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SGLVBT: CDC13
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DS: 4
GWM: 23980.814 Hz
FIDRMS: 0.365918 Hz
AQ: 1.3664756 sec
RG: 18190.4
DW: 20.850 us
DE: 6.00 us
TE: 299.2 K
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D11: 0.03000000 sec
DELTA: 0.10000000 sec
TDG: 1

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PL: 1.00 dB
FGF: 100.655502 MHz

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BB: 1.00 Hz
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P: 1.49
ZQZ-Ed2041

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PROCBO: 1
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Time: 14:45
IPMHRM: rokinson
PRMABN: 5 mm PABBO HU-
POLPNQ: zg30
TD: 32768
SOLVENT: CDCl3
NS: 8
IS: 2
SNH: 711.908 Hz
FIDRS: 0.219235 Hz
AQ: 2.2807028 ppm
RG: 114
DN: 69.600 um
DS: 6.50 um
TB: 298.2 K
DI: 2.0000000 ppm
TD0: 1

NMCl: IN
PI: 11.20 us
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SI: 12768
SP: 400.1400000 MHz
WIN: EX
USB: 0
LR: 0.30 Hz
SR: 0
FC: 1.00

15.5 ppm
1,8'-didesmethylgarugain III (10)
(reported structure)
ZQZ-2015 C13

---

S17

MeO

MeO

OEt

---

NMR: ZQS-2015
EXPERIMENT: 2
PROTOCOL: 1
Date: 20120428
Time: 18.26
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PULPROG: sppq30
TD: 65136
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NS: 180
DS: 4
SNR: 33980.81 Hz
FIDRES: 6.365918 Hz
AQ: 1.3664756 sec
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DW: 6.50 use
TH: 298.5 K
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DD: 1

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PL13: 17.00 dB
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SP: 100.615281 MHz
WDN: RM
SUS: 0
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PROCNR: 1
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SR: 12768
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DSB: 0
TH: 0.30 Hz
GH: 0
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**TIME**      16.50
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**FLEXSP**    nq10
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**FIDRES**    0.219235 Hz
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PROCISO: 1
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Time: 16:36
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R9: 128
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DK: 6.50 us
TE: 360.0 K
TD0: 2.000000000 s

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J4 0.0000 MHz
J5 32768
J6 400.1400000 MHz
J7 0
J8 0.30 Hz
J9 0
PC 1.00
ZQZ-2033 C13

$\text{MeO} - \text{O} - \text{Br}$

259

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**Name**: ZQZ-2033

**Sample**: 2

**Compound**: 2

**Date**: 2012/06/04

**Time**: 17:41

**Instrument**: robinson

**Proton NMR**: 5 mm PABRO HS-FULPHRO

**T0**: 61536

**Solvent**: CDCl3

**DS**: 521

**FS**: 23980.814 Hz

**Phases**: 0.365918 Hz

**AQ**: 1.3664756 sec

**BS**: 18190.4

**IS**: 20.850 use

**DS**: 6.50 use

**TE**: 300.0 K

**DI**: 0.0000000 sec

**D1**: 0.03900000 sec

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**CHANNEL f1**

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P1: 9.00 use

L1: -2.00 dB

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**CHANNEL f2**

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HAC2: 1H

PCPD2: 90.00 use

PL2: 0.00 dB

PL12: 16.16 dB

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2T: 100.6152830 MHz

WDM: NM

DB: 0

LB: 1.00 Hz

CH: C

DC: 1.40
ZGZ-2049

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PROCNO   1
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T0       3

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GB    0
FC    1.00
Low Temperature NMR Data for 10, 12, 32, 33, 35, and 36 – VT-Stacks
9'-desmethylgarugamblin I (12)
1,9'-didesmethylgaruganin III (10) (reported structure)
High Temperature NMR Data for 7, 8, 11, 13, and 44 – VT-Stacks

garuganin I (7)
The image contains a graph with multiple sets of data points, each labeled with temperatures ranging from 10K to 75K. The graph is divided into columns, with each column representing a different temperature. The x-axis is labeled with values from 1 to 7.5, while the y-axis is labeled with values from 1 to 7K.

Below the graph, there is a chemical structure labeled with the number 44. The structure includes multiple oxygen atoms labeled with MeO, and there is a small depiction of a molecule with the same labeling.
garuganin IV (8)
(reported structure)
garugamblin I (11)
Low Temperature NMR Data for 9, 14, 41, 42, 43, and 45 – VT-stacks
Lineshape Analysis Data

65 °C, Experimental

55 °C, Experimental

45 °C, Experimental

35 °C, Experimental

3

5 ºC, Experimental

3

5 ºC, Simulated

4

5 ºC, Simulated

6

5 ºC, Simulated

garuganin I (7)
65 °C, Simulated
65 °C, Experimental
55 °C, Simulated
55 °C, Experimental
45 °C, Simulated
45 °C, Experimental
garuganin IV (8)
(report structure)
garugamblin I (11)
7. SIR Experiments – Tabulated data

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<th>( t_{1/2} ) (sec)</th>
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7. SIR Experiments – SIR Plots

SIR Data for Garuganin I (7)

SIR data for 44
6. Lineshape Analysis Data

### Eyring plot for Garuganin I (7)

![Eyring plot for Garuganin I](image)

- $y = 0.1015x - 1.6685$
- $R^2 = 0.95151$

### Eyring plot for 44

![Eyring plot for 44](image)

- $y = 0.1007x - 2.2006$
- $R^2 = 0.99728$

### Eyring plot for Garuganin IV (reported) (8)

![Eyring plot for Garuganin IV](image)

- $y = 0.1007x - 2.2613$
- $R^2 = 0.99728$

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<td>65.00</td>
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<tr>
<td>25.00</td>
<td>1.29</td>
<td>0.26</td>
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</tbody>
</table>
1 Salih, M. Q.; Beaudry, C. M. Org. Lett. 2012, 14, 4026.

Furthermore, natural garuganin IV was hydrolyzed to the corresponding diketone, which does not have the same NMR shifts as synthetic 37 prepared in this report.

10 Molecules of structure type D and E were prepared from structure type A as described above and in the experimental section. They showed chemical shift equivalent geminal methylene protons in their 1H NMR. However, they were converted to structure types B and C, respectively, without full characterization.

11 Note that the chemical shift equivalence could, in principle, be the unlikely result of accidental equivalence of all geminal methylene and symmetry-related phenyl protons.


22 Pattawong, O.; Salih, M. Q.; Rosson, N. T.; Beaudry C. M.; Cheong, P. Org. Biomol. Chem., 2014, Accepted Manuscript DOI: 10.1039/C3OB42550A


CHAPTER 4: DEVELOPMENT OF THE ENANTIOSELECTIVE ULLMANN ETHERIFICATION

1.1 Introduction

The Ullmann ether coupling\(^1\) is a versatile reaction that is used to prepare diarylethers and other types of ethers that cannot be accessed by the Williamson\(^2\) method. Classic Ullmann conditions require high temperatures, stoichiometric copper reagents, and often proceed in modest yields. However, modern improvements to this reaction have increased reactivity, chemical yields, and lowered reaction temperatures.\(^3\) Such improvements to the Ullmann coupling use ligands to accelerate the reaction and improve efficiency of the Cu catalyst.\(^4\) Many of the ligands that accelerate the Ullmann reaction happen to be chiral; although, they are often used in racemic form because the product diarylethers are usually achiral.\(^5\) This chapter follows work published in *Organic Letters* in 2013.

We hypothesized that use of non-racemic ligands in the presence of Cu salts would render the Ullmann reaction enantioselective, and we decided to evaluate such conditions in the syntheses of the conformationally chiral cyclophane natural products (−)-myricatomentogenin, (−)-jugcathanin, (+)-galeon, and (+)-pterocarine (Figure 1).\(^6\),\(^7\) To the best of our knowledge, there were no examples of an enantioselective Ullmann ether synthesis. However, desymmetrization reactions forming C–N and C–O bonds were recently reported by the same group.\(^8\) The C–N variant is promoted by CuI with BINOL type chiral ligands (equation 4.1).\(^8a\) The C–O
variant is a palladium-mediated reaction that utilizes a chiral phosphine ligand (equation 4.2). \(^8\text{b}\)

\[
\text{R} \quad \text{NH} \quad \text{I} \quad \text{CuI, Cs\textsubscript{2}CO\textsubscript{3}, rt}
\]
\[
\text{Yield} \quad 16-90\%
\]
\[
\% \text{ ee} \quad 40-96
\]

\[
\text{R} \quad \text{OH} \quad \text{OH}
\]
\[
Pd(OAc)\textsubscript{2}, \text{Cs\textsubscript{2}CO\textsubscript{3}, 90 \degree C}
\]
\[
\text{Yield} \quad 5-65\%
\]
\[
\% \text{ ee} \quad 0-80%
\]

Enantioselective Ullmann couplings could find applications in reagent-controlled syntheses of atropodiasteromeric ether substructures in molecules such as vancomycin. \(^9\) Finally, substituted diarylethers can be chiral depending on their substitution pattern and an enantioselective Ullmann reaction would find application in the syntheses of such molecules. \(^10\)

![Figure 4.1. Chiral diarylether heptanoids lacking stereocenters](image)

### 4.2 Exploration of Ligands

Our interest in the DAEHs arises from their chiral properties. \(^11\) In the previous two chapters we have shown that of the sixteen DAEHs that do not possess a stereocenter, only four DAEHs are chiral: \((-\)-myricatomentogenin, \((-\)-jugcathanin, \((+\)-galeon, \((+\)-pterocarine
jugcathanin,\textsuperscript{13} (+)-galeon,\textsuperscript{12,14} and (+)-pterocarine.\textsuperscript{15} These chiral DAEHs all possess the same $\text{Pr}^\text{R}$ absolute configuration (Figure 4.1).\textsuperscript{11a} Our syntheses of the racemic DAEHs involves an intramolecular Ullmann ether coupling of bromophenols $4.1$, $4.2$, and $4.3$ to give chiral cyclophanes $4.4$, $4.5$, and $4.6$, respectively (Scheme 4.1). Such reactions convert an achiral starting material to a chiral product, employ a metal catalyst, and are ligand accelerated. These factors suggest the Ullmann ether synthesis could be rendered enantioselective.

Scheme 4.1. Racemic syntheses of chiral diarylether heptanoids lacking stereocenters

Ullmann substrate $4.7$ was prepared using conditions developed in our previous galeon synthesis, and we knew from previous studies that the cyclopane product $4.8$ was a common intermediate for a galeon and pterocarine synthesis (Figure 4.2).\textsuperscript{17} The intramolecular coupling was evaluated using enantiopure ligands known to accelerate the Ullmann reaction and some other privileged ligand structures. Note that racemization of the chiral DAEHs (and alkylated congeners) does not occur at the temperature of the Ullmann cyclization as seen in chapter 2.\textsuperscript{11a}
BINOL-type ligands have been used in Cu-catalyzed cross-coupling reactions.\textsuperscript{5b,8} We found that use of such ligands in the coupling gave some of the cyclophane product with modest enantioselectivities (Figure 4.2). Perhaps unsurprisingly, the chemical yields were low, because a significant amount of the phenolic ligand coupled with the bromide functionality of 4.7.

![Diagram of BINOL-type ligands](image)

**Figure 4.2.** Evaluation of binapthol-type ligands in the Ullmann coupling of 4.7

Diamines including \textit{N,N}-dimethylcyclohexylidiamine have been used to accelerate Cu-catalyzed cross-coupling reactions.\textsuperscript{18} However, use of diamines did not lead to appreciable amounts of the desired product (Figure 4.2). Similarly, Taillefer has used a chiral Schiff-base ligand to increase the rate of the Ullmann reaction.\textsuperscript{5a} A moderate yield of the product was observed when Schiff-base ligands were used; however, the enantioselectivity was low. Other privileged ligand classes that have been used in

<table>
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<th>Yield\textsuperscript{a}</th>
<th>\text{er}</th>
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<td>5%</td>
<td>44:56</td>
</tr>
<tr>
<td>OH</td>
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<td>55:45</td>
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<td>OH</td>
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<td>OH</td>
<td>18%</td>
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<td>CF\textsubscript{3}</td>
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</table>

\textsuperscript{a} All reactions were carried out at 0.007M for 48h on 0.10 mmol scale. Isolated yields are based on recovered starting material.

\begin{tabular}{|c|c|c|}
\hline
Ligand        & Yield\textsuperscript{a} & \text{er} \textsuperscript{} \n\hline
\text{er}       & 0%                       & 47:53      \\
\text{er}       & 19%                      & 52:48      \\
\text{er}       & 20%                      & 52:48      \\
\text{er}       & 0%                       & 50:50      \\
\hline
\end{tabular}
carbon-heteroatom bond formations were evaluated including chiral phosphines,\textsuperscript{19} bisoxazolines,\textsuperscript{20} salen,\textsuperscript{21} and Trost ligands\textsuperscript{22}, but yields of the coupling were low and the product was not appreciably enantioenriched.

\[ \text{Ligand (40 mol\%)} \]
\[ \text{Cul (20 mol\%)} \]
\[ \text{Cs$_2$CO$_3$ (2 equiv.)} \]
\[ \text{dioxane, 90 °C} \]

Figure 4.3. Evaluation of amino acid-derived ligands in the Ullmann coupling of 4.7

Gratifyingly, we found that use of $N$-methyl proline in the reaction did lead to increased product yield and encouraging levels of enantioselectivity (Figure 4.4).\textsuperscript{23} Proline and a variety of analogs were then investigated in the reaction. Variation in the $N$-alkyl group, ring size, and the carboxylic acid functionality did not markedly improve the yield or enantioselectivity of the reaction. Use of dipeptides or other $N,N$-dimethyl amino acids did not improve the selectivity.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield$^a$</th>
<th>$\text{er}^{b}$</th>
<th>Yield$^a$</th>
<th>$\text{er}^{b}$</th>
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<td>52:48</td>
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\textsuperscript{a}All reaction were carried out at 0.007M for 48h on 0.10 mmol scale. Isolated yields are based on recovered starting material.
\textsuperscript{b}Isolated yield (average of three runs)
4.3 Reaction Optimization

Upon finding a suitable ligand other variables were examined. Increasing the copper and ligand loading did not improve the reaction outcome. Reducing the temperature to 70 °C yielded no isolable cyclophane even after 2 weeks. Increasing the equivalence of base did not enhance the yield.

| Copper Source | Cu(OTf)$_2$ | CuBr.DMS | CuTC | Cu(MeCN)$_2$BF$_4$ | Cu(OTf).PhMe | Cu(TMEDA) Cl$_2$
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<td>13%</td>
<td>26%</td>
<td>10%</td>
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<tr>
<td>er</td>
<td>57:43</td>
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<th>K$_2$CO$_3$</th>
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<td>72:28</td>
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</table>

**Table 4.1.** Optimization of reaction conditions

We then selected $N$-methylproline as the preferred ligand and investigated the other reaction variables (Table 4.1). Variation of the solvent did not improve the yield or selectivity compared with our standard conditions, nor did variation of the Cu source. Finally, we surveyed a variety of inorganic and organic bases in the Ullmann coupling and found that use of K$_3$PO$_4$ gave the product with a higher enantiomeric ratio without significant decrease in chemical yield.

We next examined chiral copper complexes. Copper (I) BINAP, copper(I)salen and copper(I) proline and 1,10-phenanthroline complex were prepared and used as the
chiral metal complex. Unfortunately, we did not see any improvement in the selectivity of the cyclophane product.

4.4 Completion of the Enantioselective Syntheses of Chiral DAEHs

With our optimized conditions we completed the first enantioselective synthesis of a DAEH natural product. Dimethyl cyclophane 4.8 was recrystallized to obtain material that was enantioenriched (92:8 er) (Scheme 4.2). It was then converted to a 1:1 mixture of (+)-galeon and (+)-pterocarine in 46% and 45% yield respectively without any measurable loss in enantiopurity.

Scheme 4.2. Synthesis of (+)-galeon and (+)-pterocarine

Diisopropyl-substituted bromophenol 4.9 was prepared following the same general strategy used for 4.7. Cyclization using the optimized conditions gave 4.10 in moderate yield and enantioselectivity (Scheme 4.3). Cyclophane 4.10 could be further purified by recrystallization to give material that was enantioenriched (82:18 er). Treatment of 4.10 with BCl₃ gave a 1:1 mixture of (−)-myricatomentogenin and the product of removal of the more accessible isopropyl ether (4.11) in nearly quantitative yield and no loss in enantioenrichment. Methylation and subsequent deprotection of 4.11 gave (−)-jugcathanin with no loss in enantiomeric ratio.
Scheme 4.3. Synthesis of (−)-myricatomentogenin and (−)-jugcathanin

4.5 Stereochemical Model and Rationale for Selectivity

The mechanism of the C–O bond formation has recently been investigated by Houk and Buchwald, and it may proceed by the general sequence in Scheme 5. Coordination of the heteroatom nucleophile (ROH) to the Cu-ligand complex 4.12 gives intermediate 4.13. Halogen atom transfer produces radical intermediate 4.14. The authors propose that 4.14 is a caged radical pair that reacts rapidly before adventitious reactions (such as radical cage separation) can occur. Combination of the radical pair results in complex 4.15. Dissociation then releases the product.

Scheme 4.4. Proposed mechanics for C–O bond formation
Our syntheses employed substrate 4.7 and when (S)-N-methylproline was used we found that the pR enantiomer of 4.8 is formed selectively. The stereochemical model in Figure 4.4 can be used to provide a basis for the selectivity observed. Following the mechanism proposed in Scheme 4.4, we arrive at the intermediate 4.14. The chiral nature of the complex provides four possible diastereomeric intermediates, shown in Figure 4.4. The phenyl radical approaching cis to the amine on the copper complex (4.16 and 4.17) is disfavored because of the steric interaction between the methoxy group of the substrate and the N-methyl on the ligand. Intermediate 4.18 illustrates a steric interaction between the methoxy group and the N-methyl group of the ligand, that can be avoided by positioning the methoxy group away from the N-methyl group as shown in 4.19. Combination of radicals and dissociation of intermediate 44 gives cyclophane with pR absolute stereochemistry.

**Figure 4.4.** Diastereomeric copper intermediates
4.6 Experimental Section

General Experimental

All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. Flash column chromatography (FCC) was carried out with SiliaFlash P60, 60 Å silica gel. Reactions and column chromatography were monitored with EMD silica gel 60 F254 plates and visualized with vanillin stains. Dichloromethane (DCM) and acetonitrile (MeCN) were dried by passage through activated alumina columns. Dioxane was dried with CaH₂ and distilled onto 3 Å molecular sieves. All other reagents and solvents were used without further purification from commercial sources.

Instrumentation: FT-IR spectra were obtained on NaCl plates with a PerkinElmer Spectrum Vision spectrometer. Proton and carbon NMR spectra (¹H NMR and ¹³C NMR) were recorded in deuterated chloroform (CDCl₃) unless otherwise noted on a Bruker 700 MHz Avance III Spectrometer with carbon-optimized cryoprobe and Bruker 400 MHz DPX-400 spectrometer and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet. Melting points were determined with a Cole–Parmer instrument and are uncorrected.
1-(3-Bromo-4-methoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptan-3-one (4.7).

To a solution of ketophosphonate 4.S2 (915 mg, 2.51 mmol) in THF (10 mL, 0.20 M) was added DBU (380 mg, 2.50 mmol). The mixture was stirred for 10 min after which aldehyde 4.S1 (536 mg, 2.00 mmol) was added. The reaction mixture was heated to 60 °C for 18 h upon which time TLC indicated consumption of 4.S1. The reaction mixture was quenched with 2M HCl solution (2 mL). The mixture was diluted with H$_2$O and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered through silica gel and concentrated. The bright yellow oil (819 mg) was used in the next step without further purification.

To a solution of the bright yellow oil (819 mg) in EtOAc (34 mL, 0.05 M) was added Pearlman’s catalyst (165 mg, 20% Pd(OH)$_2$ on carbon nominally 50% water, 20% w/w). The mixture was stirred vigorously under an atmosphere of hydrogen. After 1 h TLC indicated consumption of starting material. The reaction mixture was filtered through a celite plug and concentrated. Purification by FCC (3:1 Hexanes:EtOAc) yielded 4.7 (580 mg, 1.38 mmol, 73%) as an opaque wax. Data for 4.7: R$_f$ 0.25 (3:1 Hexanes:EtOAc); IR (thin film) 3428 (br), 3009, 2935, 1709, 1601; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38 (d, $J = 2.3$ Hz, 1 H), 7.09 (dd, $J = 2.2$, 8.4 Hz, 1 H), 6.82 (t, $J = 8.1$ Hz, 1 H), 6.66 (m, 2 H), 5.51 (br s, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 2.83 (t, $J = 7.4$ Hz, 2 H), 2.69 (t, $J = 7.4$ Hz, 2 H), 2.55 (t, $J = 6.9$ Hz, 2 H), 2.41 (t, $J = 7.0$ Hz, 2 H), 1.60 (m, 4 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 209.7, 154.2, 146.3, 143.7, 134.8, 134.1, 133.0, 128.4, 120.9, 114.2, 111.9, 111.5, 110.9, 56.3, 55.9, 44.2, 42.9, 35.4, 31.2, 28.5, 23.4; HRMS (ESI) calcd for C$_{21}$H$_{26}$O$_4$Br [M+H]: 421.1014, found 421.1024
(pR)–4.8. To a solution of CuI (4 mg, 0.02 mmol), K$_3$PO$_4$ (42 mg, 0.20 mmol) and L-N-methyl proline (6 mg, 0.04 mmol) in dioxane (14 ml, 0.007 M) was added bromophenol 7 (42 mg, 0.10 mmol). The mixture was heated to 90 ºC. After 3 d, the reaction mixture was cooled to rt and quenched by slowly adding 2N HCl (4 ml). The mixture was diluted with H$_2$O and extracted with EtOAc (30 ml x 3). The organic layers were combined, washed with H$_2$O, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated. Purification by FCC (4:1 Hexanes:EtOAc) yielded (pR)–4.8 (13.3 mg, 0.039 mmol, 39%, er = 72:28) as white solid. Recrystallization of the white solid (DCM and hexane, layering) gave racemic needle like crystals; concentration of the mother liquor gave enantioenriched (er = 92:8) (pR)–4.8. The enantiomeric excess was determined using chiral HPLC by an analytical Chiralcel OD-H column (I.D = 5 mm, length = 250 mm), 80:20 hexanes:IPA (1.0 mL/min), (pR)–4.8: 35-36 min, (pS)–4.8: 16-17 min. See data traces below. Data for (pR)–4.8 matched that previously reported.$^1$
(+)-Galeon and (+)-Pterocarine. To a solution of (pR)– 4.8 (3.4 mg, 0.01 mmol) in DCM (0.4 ml, 0.025 M) at −40 °C was added BBr₃ (1 M in DCM, 0.02 ml, 0.022 mmol). The reaction mixture was quenched after 45 min by slowly adding MeOH (0.4 mL) and warmed to rt. The quenched reaction was stirred at rt for 10 min and concentrated. Purification by FCC (3:1 Hexanes:EtOAc) yielded (+)-galeon (1.4 mg, 0.0043 mmol, 46%, er = 92:8) as white solid and (+)-pterocarine (1.4 mg, 0.0045 mmol, 45%, er = 92:8) as a off-white solid that matched literature data.¹
(pR)– 4.10. To a solution of Cul (4 mg, 0.02 mmol), K₃PO₄ (42 mg, 0.20 mmol) and L-N-methyl proline (6 mg, 0.04 mmol) in dioxane (14 ml, 0.007 M) was added known bromophenol 9 (42 mg, 0.10 mmol).¹ The mixture was then heated to 90 ºC. The reaction mixture was quenched after 3 d by slowly adding 2N HCl (4 mL). The quenched reaction mixture was diluted with H₂O and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with H₂O, saturated NaCl solution, dried over MgSO₄, filtered and concentrated. Purification by FCC (7:1 Hexanes:EtOAc) yielded (pR)– 4.10 (9.8 mg, 0.023 mmol, 24%, er = 67:33) as white solid. Recrystallization of the white solid (DCM and hexane, layering) gave racemic needle like crystals; concentration of the mother liquor gave enantioenriched (er = 82:18) (pR)– 4.10. The enantiomeric excess was determined using chiral HPLC by an analytical Chiralcel OD-H column (I.D = 5 mm, length = 250 mm), 98:2 hexanes:IPA (0.5 mL/min), (pR)– 4.10: 18-19 min, (pS)– 4.10: 14-15 min. See data traces below.

Spectral data for (pR)– 4.10 matched that previously reported.¹

(–)-Myricatomentogenin and (pR)– 4.11. To a solution of (pR)– 4.10 (3.0 mg, 0.007 mmol) in DCM (0.7 ml, 0.01 M) at –10 ºC was added BCl₃ (1 M in DCM, 0.02 ml, 0.022 mmol). The reaction was monitored by TLC. The reaction mixture was quenched after 25 min by slowly adding MeOH (0.4 mL) and warmed to rt. The quenched reaction was stirred at rt for 10 min and concentrated. Purification by FCC (5:1 Hexanes:EtOAc) yielded (–)-myricatomentogenin (1 mg, 0.0031 mmol, 44%, er = 82:18) as white solid that matched the literature data and (pR)– 4.11 (1.5 mg, 0.0039
mmol, 56%) as a white solid. Data for (pR)-**4.11**. Rf 0.45 (2:1 Hexanes: EtOAc); mp = 101-103 ºC; IR (thin film) 3411 (br), 2933, 1708, 1586; \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\)

\[
\begin{align*}
6.99 (d, J = 8.5 \text{ Hz}, 1 \text{ H}), 6.88 (d, J = 8.2 \text{ Hz}, 1 \text{ H}), 6.82 (d, J = 8.3 \text{ Hz}, 1 \text{ H}), 6.66 (dd, J = 2.1, 8.2 \text{ Hz}, 1 \text{ H}), 5.70 (d, J = 2.0 \text{ Hz}, 1 \text{ H}), 5.68 \text{(br s, 1 H)}, 4.41 \text{(sept, J = 6.3 \text{ Hz}, 1 \text{ H})}, \\
3.54 \text{(s, 3 H)}, 3.15 \text{(dt, J = 5.8, 13.0 \text{ Hz}, 1 \text{ H})}, 3.03 \text{(ddd, J = 2.5, 9.4, 16.6 \text{ Hz}, 1 \text{ H})}, 2.71 \text{(ddd, J = 1.8, 8.5, 15.9 \text{ Hz}, 1 \text{ H})}, 2.35 \text{(m, 3 H)}, 2.07 \text{(m, 1 H)}, 1.76 \text{(m, 1 H)}, 1.65 \text{(m, 3 H)}, 1.53 \text{(m, 2 H)}, 1.40 \text{(d, J = 6.2 \text{ Hz}, 3 \text{ H})}, 1.23 \text{(d, J = 6.2 \text{ Hz}, 3 \text{ H})}; \\
13\text{C NMR (100 MHz, CDCl}\_3) \delta 210.3, 150.8, 148.2, 148.0, 146.4, 143.4, 134.0, 133.5, 125.6, 122.5, 119.1, 115.3, 113.4, 75.4, 59.9, 46.6, 41.3, 31.1, 27.4, 25.3, 23.0, 22.2, 19.1; \text{HRMS (EI) calcd for C}_{23}\text{H}_{29}\text{O}_5 [M+H]: 385.2015, found 385.2034. \\
\end{align*}
\]

(-)-Jugcathanin. To a solution of (pR)-**4.11** (1.5 mg, 0.0039 mmol) in MeCN (1 ml, 0.004 M) was added K\(_2\)CO\(_3\) (1.1 mg, 0.008 mmol) and MeI (1 mg, 0.008 mmol). The reaction was monitored by TLC (vanillin stain). After 18 h 2 N HCl (0.2 mL) was added. The mixture was diluted with H\(_2\)O and extracted with DCM (10 mL x 3). The organic layers were combined, washed with saturated NaCl solution, dried over MgSO\(_4\), filtered and concentrated. The crude material was used without further purification.

To a solution of the crude mixture from above in DCM (0.4 ml, ~0.0039 mmol) at 0 ºC was added BCl\(_3\) (1 M in DCM, 0.013 ml, 0.013 mmol). The reaction mixture was quenched after 25 min by slowly adding MeOH (0.4 mL) and warmed to rt. The mixture was stirred at rt for 10 min and concentrated. Purification by FCC (3:1
Hexanes:EtOAc) yielded (−)-jugcathanin (1.1 mg, 0.0032 mmol, 84%, er = 82:18) as white solid that matched the literature data.¹
3. HPLC Data

HPLC trace for (+)-4.8

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Dilution: 1.0000
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Method Info: gal - DO NOT CHANGE

10% IPA:hex, 1 ml/min, OD anal

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Area Percent Report

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Dilution: 1.0000
Use Multiplier & Dilution Factor with ISTDs

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HPLC for (+)-pterocarline produced from (pR)--4.8
HPLC trace for (±)-4.10

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Use Multiplier & Dilution Factor with ISTBDs

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Acq. Instrument : Instrument 1  Location : Vial 1
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Injection Volume : 50 μl
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Last changed : 7/17/2013 7:45:41 PM by QUANAR
Method Info : OD-H analytical, 0.5mL/min, 254 nm, IPA:HEX 2:98, imyr

Area Percent Report

Signal 1: VW01 A, Wavelength=254 nm

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HPLC data for (pR)– 4.10 after recrystallization

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Sample Name: 4032-1-RE

Acq. Operator : QUANAR  
Acq. Instrument : Instrument 3  
Location : Vial 1  
Injection Date : 7/17/2013 8:21:37 PM  
Volume : 50 µl

Seq. Line : 1
Method : C:\Chem32\METHODS\MQS-IMTR-OD-H-ANAL.M
Last changed : 7/17/2013 7:45:41 PM by QUANAR

Method Info : OD-H analytical, 0.5mL/min, 254 nm, IPA:HEX 2:1; 10 µL

--- Area Percent Report ---

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Totals : 2.81422e6 364.07845

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HPLC trace for (±)-myricatomentogenin

Sample Name: zsg-myr

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Data File: C:\CHEM32\LUMIN\G4-ANAL.M
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Injection: 1
Inj Volume: 50 µL
Location: Vial 1
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Last changed: 7/20/2013 4:29:40 PM by qumar
Method Info: OD analytical, 1mL/min, 254 nm, TFA:HEX 20:80

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**Use Multiplier & Dilution Factor with LSTDs**

**Signal 1:** Wavelength=254 nm

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Instrument 1 7/20/2013 7:38:12 PM qumar
HPLC trace for (−)-myricatomentogenin produced from (pR)- 4.10

**Area Percent Report**

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*** End of Report ***
HPLC trace for (±)-jucathanin

Data file C:\chem32\1\ADATA\QUAMRR\mps000035.D
Sample Name: mmc-jug

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Acq. Instrument : Instrument 1  Location : Vial 1
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Inj Volume : 50 µl
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Method : C:\CHEM32\METHODS\WGD-2UG-AD.M
Last changed : 7/22/2013 10:01:51 AM by guamar
Method Info : AD column, 1ml/min, 254 nm, IPA 15%

Area Percent Report

Signal 1: VWD1 A, Wavelength=254 nm

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*** End of Report ***
HPLC data for (−)-Jucathanin produced from (pR)- 4.10

Data File: C:\Chem32\1\DATA\QUAMR\mgp00236.D
Sample Name: 4084-1

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Acq. Instrument: Instrument 1  Location: Vial 1
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Method: C:\CHEM32\\METHODS\WDS-2US-AD.M
Last changed: 7/22/2013 10:01:51 AM by quanar

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**Area Percent Report**

Sorted By: Signal
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Dilution: 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

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Totals: 3296.54401 36.80499

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*** End of Report ***
1 Ullmann, F.; Sponagel, P. *Ber.* **1905**, *38*, 2211.


17 With the use of BBr$_3$ in previous work which was not reported.


CHAPTER 5: SYNTHESIS AND CHIRALITY OF RUSSUPHELOL

1.1 Introduction

The genus *Russula* comprises many common, moderately large, often colorful mushrooms. Individual *Russula* species can be delicious, such as the shrimp russula (*R. xerampilina*)\(^1\), sickening (*R. emetica*)\(^2\), or fatally toxic (*R. subnigricans*). Molecules with various biological activities have been isolated from *Russula* species.\(^3\) Investigations of the secondary metabolites of *R. subnigricans* resulted in the discovery of a family of chlorinated hydroquinone oligomers that have cytotoxic properties (Figure 5.1).\(^4\) In 1995, Nozoe and coworkers isolated russuphelol (5.1), a tetracyclic member of this family, from the mushroom *Russula subnigricans*\(^5\).

We became interested in russuphelol because it was reported to be a chiral molecule. Specifically, the natural russuphelol sample was optically active ([\(\alpha\)]\(_D\) = −3.2) and had reported Cotton effects \((\text{MeOH} \ \lambda_{\text{ext}} 347 \ \text{nm (\Delta}e 0.086), 311 (+0.063), 302 (−0.073), 273 (+0.11), 227 (−0.98))\}. Nozoe interpreted this optical activity to indicate that an “asymmetric phase” resulted from the steric size of the B–C–D ring system.

Diphenylethers that are not part of a macrocyclic ring can possess stable single enantiomer conformations at room temperature.\(^6\) Chirality in diphenylethers of the type 5.4 requires all four substituents adjacent to the C–O–C linkage of the diphenylether to be non-hydrogen (\(R^1, R^2, R^3, R^4 \neq H\)) and at least one of \(R^1–R^4\) to be large (i.e. a fully-substituted sp\(^3\) carbon, such as a tert-butyl group).\(^7\)
The molecular architecture of russuphelol contains four non-hydrogen substituents adjacent to the C–B diphenylether linkage and the B–D linkage; however, the substituents are oxygen and chlorine atoms and are not particularly large. Therefore, russuphelol does not fit the structure type of known chiral diphenylethers.

We considered two possibilities to reconcile the structural considerations discussed above and the reported optical activity of the sample. The first possibility is that the russuphelol sample from natural sources was contaminated with non-racemic impurities that gave a false-positive optical activity. Alternatively, if russuphelol has chiral conformations, it may be the result of “gearing” of the B–C–D ring system, where interconversion of enantiomers requires a precise positioning of the rings and simultaneous movement of the C and D rings. Such a situation may result in a large entropic cost for the alignment of several functional groups.

The identification of chirality in molecules that lack stereogenic sp\(^3\)-hybridized carbon atoms (i.e. stereocenters) is not trivial, and molecules that lack such stereocenters often have misunderstood chiral properties.\(^8\) Chemical synthesis and derivatization is often the only way to determine if a molecule is chiral or achiral. We decided to prepare russuphelol to determine if it was a chiral molecule.
5.2 Retrosynthetic Analysis

We envisioned russuphelol arising from quinone 5.5. This strategy would require selective methylation of the oxygen at C4’ on the B ring. Noticing the symmetry in this intermediate allows us to further simplify to tricyclic quinone 5.6. Symmetric intermediate 5.6 would be the product of a three-component coupling of dichloroquinone 5.7 and two equivalents of phenol 5.8.
Our synthesis began with the addition of two equivalents of phenol 5.8 to dichloroquinone 5.7 to form quinone 5.6 in 72% yield (Scheme 5.2). Similar transformations have been reported in the literature, but have been performed in two sequential steps.9 Bromination of the quinone B-ring was accomplished using pyridinium tribromide, which proceeds in 98% yield to produce bromoquinone 5.10.10 Addition of phenol 5.11 to bromoquinone 5.10 proceeded smoothly to give quinone 5.5. The structure of quinone 5.5 was confirmed by x-ray crystallographic analysis.
Scheme 5.2. Synthesis and X-ray structure of quinone 5.5

Our first strategy for the conversion of 5.5 to russuphelol depended on a phenol methylation. First, quinone 5.5 was reduced to the corresponding hydroquinone 5.12. Methylation of 5.12 was not straightforward. Treatment of 5.12 with basic conditions led to oxidation to quinone 5.5. Presumably, the corresponding phenoxide is quite electron-rich, and undergoes oxidation with adventitious oxygen. Moreover, hydroquinone 5.12 is slowly oxidized to quinone 5.5 on standing. Methylation of 5.12 with trimethylsilyldiazomethane was modestly selective; at partial conversion, the desired mono-methylated compound (5.13) could be isolated along with the dimethyl hydroquinone 5.14. Intermediate 5.13 was subjected to BCl3 to remove the isopropyl protecting groups and complete the synthesis of russuphelol. The 1H and 13C NMR chemical shifts for the synthetic material matched the chemical shifts reported for the natural sample.
The methylation of 5.12 allowed us to complete the synthesis of russuphelol and verify the structure of the natural product. However, the overall chemical yield was only modest, and the chemical yields of 5.13 were highest at partial conversion. These factors caused the production of 5.13 to be operationally tedious, and a smoother transformation of quinone 5.5 to russuphelol was desired.

Quinones are known to undergo reductive alkylation with trialkylphosphites to give mono-alkylated hydroquinones. We subjected 5.5 to triisopropylphosphite, which delivered alkylation product 5.15. Presumably, the regioselectivity in this reaction results from a steric preference for attack with the less hindered quinone carbonyl. Hydrolysis of the phosphonate ester followed by methylation under standard conditions gave triisopropyl russuphelol (5.16). Removal of the isopropyl groups gave the natural product.
Scheme 5.5. Reductive alkylation route to russuphelol

5.4 Experimental Determination of Chirality

With russuphelol in hand, we turned our attention to determining if it is chiral. Distinguishing chiral racemic samples and achiral samples is not trivial. If russuphelol is a chiral molecule with stable enantiomeric conformations it could be resolved using chiral stationary phase HPLC. We examined various columns (OD-H, AD and AS-H) and multiple solvent systems times only to observe a single peak for russuphelol. Attempted resolution of 5.13, 5.14, and 5.16 was similarly unsuccessful. This observation is consistent with the enantiomers of these four compounds having coincidentally one peak on chiral HPLC or the enantiomeric conformations of the compounds are rapidly interconverting on the HPLC timescale.

We examined the UV-Vis spectrum of russuphelol. Upon isolation the UV maximum was reported to be 280 nm. We have found the UV maximum to be 294 nm. The $\lambda_{\text{max}}$
corresponds to cotton effects in the CD spectrum. The CD spectrum of russuphelol has five cotton effects reported, at 227, 273, 302, 311, 347 nm. There appears to be no cotton effect at 280 or 294 nm. This suggests that the compound responsible for the cotton effect is a result of a chiral non-racemic impurity in the sample. This would also explain the sample having a non-zero optical activity.

Inspection of the $^1$H and $^{13}$C NMR data can provide qualitative information about chirality in molecules. If an element of chirality is present we would expect to observe two signals for the symmetry related methyl groups of the isopropyl ether both in the $^1$H and $^{13}$C NMR spectra. Examination of the NMR data for compounds 5.5, 5.13, 5.14, 5.15, and 5.16 (which all contain isopropyl groups) revealed no chemical shift inequivalent isopropyl proton or carbon signals. This suggests that the barrier for interconversion at room temperature is low, and the enantiomeric forms are rapidly interconverting on the NMR timescale.

Variable temperature NMR can be used to study the rate of interconversion of enantiomeric conformations. The rate of racemization can be obtained at the coalescence temperature. In our previous work we have used this method to measure the racemization energy barriers of compounds that have fast conformational dynamics at room temperature. Low temperature NMR data for compounds 5.13, 5.14, and 5.16 were recorded. No decoalescence of any symmetry related methyl group (of the isopropyl methyls) was seen at temperatures as low as $–100$ °C. A coalescence temperature ($T_c$) below $–100$ °C gives an upper limit for the racemization barrier. The upper limit for the barrier of racemization is 8.8 kcal/mol with a rate ($k_c$) of 600 sec$^{-1}$ at $–100$ °C. Observation of such rates at cryogenic temperatures is consistent with a molecule that has rapidly interconverting enantiomeric conformations, suggesting that russuphelol is an achiral molecule.
5.5 Experimental Section

General Experimental Details

All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. Flash column chromatography (FCC) was carried out with SiliaFlash P60, 60 Å silica gel. Reactions and column chromatography were monitored with EMD silica gel 60 F254 plates and visualized with vanillin stains. Dichloromethane (DCM) and acetonitrile (MeCN) were dried by passage through activated alumina columns. Dioxane was dried with CaH and distilled onto 3 Å molecular sieves. All other reagents and solvents were used without further purification from commercial sources.

Instrumentation: FT-IR spectra were obtained on NaCl plates with a PerkinElmer Spectrum Vision spectrometer. Proton and carbon NMR spectra ($^1$H NMR and $^{13}$C NMR) were recorded in deuterated chloroform (CDCl$_3$) unless otherwise noted on a Bruker 700 MHz Avance III Spectrometer with carbon-optimized cryoprobe and Bruker 400 MHz DPX-400 spectrometer and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet. Melting points were determined with a Cole–Parmer instrument and are uncorrected.
2,6-Bis(2,6-dichloro-4-isopropoxyphenoxy)cyclohexa-2,5-diene-1,4-dione (5.6). To a solution of phenol 5.8 (663 mg, 3.00 mmol) in DMF (12 mL, 0.25 M) was added NaH (132 mg, 3.30 mmol, 60% in mineral oil). The mixture was stirred for 15 min after which dichloroquinone 5.7 (292 mg, 1.65 mmol) was slowly added. The reaction mixture was stirred for 16 h upon which time TLC indicated consumption of all quinone starting material. The reaction mixture was carefully quenched with 2M HCl solution (2 mL). The mixture was diluted with H2O and extracted with DCM (30 mL x 3). The organic layers were combined, washed with H2O, saturated NaCl solution, dried over MgSO4, and concentrated. Purification by FCC (10:1 Hexanes:EtOAc) yielded 5.6 (644 mg, 1.19 mmol, 72%) as a yellow solid.

Data for 5.6: Rf 0.15 (8:1 Hexanes: EtOAc); IR (thin film) 3091, 2980, 1701, 1647, 1602; 1H NMR (700 MHz, CDCl3) δ 6.95 (s, 4 H), 5.59 (s, 2 H), 4.53 (sept, J = 6.1 Hz, 2 H), 1.38 (d, J = 6.1 Hz, 12 H); 13C NMR (176 MHz, CDCl3) δ 186.1, 174.2, 156.4, 154.8, 138.0, 128.6, 116.4, 110.7, 71.4, 21.8; HRMS (ESI) calcd for C24H21O6Cl [M+H]: 545.0100, found 545.0092.

2-Bromo-3,5-bis(2,6-dichloro-4-isopropoxyphenoxy)cyclohexa-2,5-diene-1,4-dione (5.10). To a solution of quinone 5.6 (335 mg, 0.618 mmol) in (1:1) HOAc/DCM (6.18 mL, 0.10 M) was added PyrHBr3 (198 mg, 0.618 mmol). The reaction mixture was stirred for 1 h upon which time TLC indicated consumption of all quinone starting material. The reaction mixture was quenched with 2M HCl solution (10 mL). The mixture was diluted with H2O and extracted with DCM (20 mL x 4). The organic layers
were combined, washed with 2M HCl solution (10 mL), H₂O, saturated NaCl solution, 
dried over MgSO₄, and concentrated to yield 5.6 (378 mg, 0.605 mmol, 98%) as a red 
solid.

Data for 5.10: Rf 0.45 (6:1 Hexanes: EtOAc); IR (thin film) 3008, 2978, `1691, 1656, 
1639, 1596; ¹H NMR (700 MHz, CDCl₃) δ 6.93 (s, 2 H), 6.90 (s, 2 H), 5.80 (s, 1 H), 4.50 
(m, 2 H), 1.38 (d, J = 6.1 Hz, 6 H), 1.37 (d, J = 6.1 Hz, 6 H); ¹³C NMR (176 MHz, CDCl₃) δ 
179.1, 172.1, 156.5, 155.0, 154.3, 152.8, 141.8, 137.8, 128.4, 126.9, 118.4, 116.4, 
116.2, 109.9, 71.5, 71.3, 21.9, 21.8; HRMS (ESI) calcd for C₂₄H₂₀O₆Cl₄Br [M+H]: 
622.9197, found 622.9210

3,5-Bis(2,6-dichloro-4-isopropoxyphehenoxy)-2-(2,6-dichloro-4-
methoxyphenoxy)cyclohexa-2,5-diene-1,4-dione (5.5). To a solution of phenol 5.11 
(21 mg, 0.11 mmol) in DMF (2 mL, 0.05 M) was added Cs₂CO₃ (36 mg, 0.11 mmol). 
The mixture was stirred for 15 min after which bromoquinone 5.10 (63 mg, 0.10 
mmol) was added. The reaction mixture was stirred for 14 h (in the dark) upon which 
time TLC indicated consumption of all quinone starting material. The reaction 
mixture was quenched with 2M HCl solution (10 mL). The mixture was diluted with 
H₂O and extracted with DCM (25 mL x 3). The organic layers were combined, washed 
with H₂O, saturated NaCl solution, dried over MgSO₄, and concentrated. Purification 
by FCC (10:1 Hexanes:EtOAc) yielded 5.5 (49 mg, 0.066 mmol, 66.6%) as a red wax. 
This material was dissolved in CHCl₃ (1 ml) and crystalized by vapor diffusion (pentane / CHCl₃) solution to obtain a single crystal suitable for diffraction.
Data for 5.5: Rf 0.33 (7:1 Hexanes: EtOAc); IR (thin film) 3007, 2978, 1737, 1685, 1661, 1607; $^1$H NMR (700 MHz, CDCl$_3$) δ 6.92 (s, 2 H), 6.805 (s, 2 H), 6.803 (s, 2 H), 5.45 (s, 1 H), 4.51 (sept, $J = 6.0$ Hz, 1 H), 4.45 (sept, $J = 6.0$ Hz, 1 H), 3.77 (s, 3 H), 1.37 (d, $J = 6.0$ Hz, 6 H), 1.32 (d, $J = 6.0$ Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 180.4, 174.8, 156.4, 156.1, 154.6, 154.3, 142.4, 141.9, 139.8, 139.1, 138.0, 128.5, 126.88, 126.85, 116.4, 116.2, 114.2, 107.8, 71.4, 71.3, 55.9, 21.83, 21.79; HRMS (ESI) calcd for C$_{31}$H$_{25}$O$_8$Cl$_6$ [M+H]: 734.9681, found 734.9688.

3,5-Bis(2,6-dichloro-4-isopropoxyphenoxy)-2-(2,6-dichloro-4-methoxyphenoxy)benzene-1,4-diol (5.12). To a solution of quinone 5.5 (61 mg, 0.083 mmol) in THF (0.8 mL, 0.1 M) was added saturated Na$_2$S$_2$O$_4$ solution drop wise (0.08 mL). The mixture was goes from orange to clear in 10 min. Upon which time TLC indicated consumption of all quinone starting material. The reaction mixture was quenched with 2M HCl solution (1 mL). The mixture was diluted with H$_2$O and extracted with DCM (10 mL x 3). The organic layers were combined, dried over MgSO$_4$, and concentrated to yield 5.12 (61 mg, 0.066 mmol, 99%) as a white solid.

Data for 5.12: Rf 0.30 (7:1 Hexanes: EtOAc); IR (thin film) 3128 (br), 2976, 1684, 1660, 1605; $^1$H NMR (700 MHz, CDCl$_3$) δ 6.91 (s, 2 H), 6.83 (s, 2 H), 6.76 (s, 2 H), 6.01 (s, 1 H), 5.46 (br s, 1 H), 4.96 (br s, 1 H), 4.51 (sept, $J = 6.2$ Hz, 1 H), 4.44 (sept, $J = 6.2$ Hz, 1 H), 3.77 (s, 3 H), 1.38 (d, $J = 6.0$ Hz, 6 H), 1.33 (d, $J = 6.2$ Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 155.8, 155.5, 153.7, 143.6, 142.6, 141.2, 140.7, 140.6, 135.7, 130.7, 130.1, 129.8, 128.3, 127.0, 116.4, 115.8, 114.5, 96.0, 71.3, 71.0, 56.0, 21.95, 21.86; HRMS (ESI) calcd for C$_{21}$H$_{26}$O$_4$Br [M+H]: 421.1014, found 421.1024.
3,5-Bis(2,6-dichloro-4-isopropoxyphenoxy)-2-(2,6-dichloro-4-methoxyphenoxy)-4-methoxyphenol (5.13). To a solution of hydroquinone 5.12 (42 mg, 0.057 mmol) in (3:1) DCM/MeOH (0.57 mL, 0.01 M) was added TMSCHN$_2$ (57 mL, 0.114 mmol, 2M solution in hexane). The reaction mixture was stirred at rt for 2 h upon which time TLC indicated multiple spots. The reaction mixture was quenched with saturated Na$_2$S$_2$O$_4$ solution (1 mL). The mixture was diluted with H$_2$O and extracted with DCM (10 mL x 3). The organic layers were combined, dried over Na$_2$SO$_4$, and concentrated. Purification by FCC (10:1 Hexanes: EtOAc) yielded dimethyl 5.14 (1 mg, 0.0013 mmol, 3%), monomethyl 5.13 (13 mg, 0.0173 mmol, 31%) and recovered 5.12 (23 mg, 0.0312 mmol, 55%).

Data for 5.13: $R_f$ 0.30 (10:1 Hexanes: EtOAc); IR (thin film) 3087, 2976, 1684, 1660, 1605; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 6.93 (s, 2 H), 6.83 (s, 2 H), 6.78 (s, 2 H), 5.87 (s, 1 H), 5.71 (br s, 1 H), 4.51 (sept, $J$ = 6.1 Hz, 1 H), 4.43 (sept, $J$ = 6.0 Hz, 1 H), 3.77 (s, 3 H), 3.53 (s, 3 H), 1.38 (d, $J$ = 6.2 Hz, 6 H), 1.33 (d, $J$ = 6.2 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 155.8, 155.3, 153.6, 147.3, 143.9, 143.6, 142.8, 141.1, 139.9, 132.3, 129.9, 129.8, 129.4, 128.4, 126.6, 116.6, 116.5, 116.4, 116.2, 116.0, 114.4, 95.1, 71.3, 71.2, 71.1, 61.5, 56.0, 21.91, 21.88, 21.84, 21.76; HRMS (ESI) calcd for C$_{32}$H$_{29}$O$_8$Cl$_6$ [M+H]: 750.9994, found 751.0024

Data for 5.14: $R_f$ 0.33 (10:1 Hexanes: EtOAc); IR (thin film) 2976, 1597, 1562, 1498; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.94 (s, 2 H), 6.81 (s, 2 H), 6.79 (s, 2 H), 5.78 (s, 1 H), 4.52 (sept, $J$ = 6.1 Hz, 1 H), 4.44 (sept, $J$ = 6.1 Hz, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.56 (s, 3 H), 1.38 (d, $J$ = 6.0 Hz, 6 H), 1.33 (d, $J$ = 6.0 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$
Russuphelol (5.1). To a solution of 5.13 (12 mg, 0.016 mmol) in DCM (0.16 mL, 0.1 M) was added BCl₃ (0.1 ml, 0.10 mmol, 1 M in DCM solution). The mixture was stirred for 15 min after which dichloroquinone 5.7 (292 mg, 1.65 mmol) was slowly added. The reaction mixture was stirred for 4 h at rt upon which time TLC indicated consumption of all quinone starting material. The reaction mixture was slowly quenched with MeOH (2 mL), stirred for 30 min and concentrated. Purification by FCC (2:1 Hexanes: EtOAc) yielded russuphelol (6.9 mg, 0.0103 mmol, 64%) as a white solid, which matched reported data.

Data for 5.1: Rf 0.1 (3:1 Hexanes: EtOAc); IR (thin film) 3365 (br), 2925, 2853, 1604, 1469, 1435, 1212; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 2.3 Hz, 1 H), 7.09 (dd, J = 2.2, 8.4 Hz, 1 H), 6.82 (t, J = 8.1 Hz, 1 H), 6.66 (m, 2 H), 5.51 (br s, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 2.83 (t, J = 7.4 Hz, 2 H), 2.69 (t, J = 7.4 Hz, 2 H), 2.55 (t, J = 6.9 Hz, 2 H), 2.41 (t, J = 7.0 Hz, 2 H), 1.60 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 209.7, 154.2, 146.3, 143.7, 134.8, 134.1, 133.0, 128.4, 120.9, 114.2, 111.9, 111.5, 110.9, 56.3, 55.9, 44.2, 42.9, 35.4, 31.2, 28.5, 23.4; HRMS (ESI) calcd for C₂₁H₂₆O₄Br [M+H]: 421.1014, found 421.1024
2,6-Bis(2,6-dichloro-4-isopropoxyphenoxy)-3-(2,6-dichloro-4-methoxyphenoxy)-4-isopropoxyphenyl diisopropyl phosphate (5.15). To a solution of quinone 5.5 (56 mg, 0.075 mmol) in benzene (0.75 mL, 0.1 M) was isopropylphosphite (47 mg, 0.225 mmol). The mixture was stirred vigorously for 48 h after which time TLC indicated consumption of all quinone starting material. The reaction mixture was directly loaded on to a column and purified (4:1 Hexanes:EtOAc) to yield 5.15 (44 mg, 0.0466 mmol, 62%) as an yellow oil.

Data for 5.15: Rf 0.15 (8:1 Hexanes: EtOAc); IR (thin film) 2977, 2932, 1595, 1459; $^1$H NMR (700 MHz, CDCl$_3$) δ 6.92 (s, 2 H), 6.79 (s, 2 H), 6.71 (s, 2 H), 5.00 (m, 2 H), 4.51 (sept, J = 6.0 Hz, 1 H), 4.42 (sept, J = 6.0 Hz, 1 H), 3.99 (sept, J = 6.2 Hz, 1 H), 1.37 (m, 12 H), 1.32 (d, J = 6.1 Hz, 6 H), 1.29 (d, J = 6.1 Hz, 6 H), 0.80 (d, J = 5.8 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 155.3, 155.1, 154.7, 153.6, 144.6, 144.0, 143.9, 143.7, 141.31, 141.29, 140.6, 133.3, 130.0, 127.6, 126.6, 116.6, 116.4, 113.9, 96.2, 73.3 (d, j = 7.1 Hz), 71.25, 71.24, 70.6, 55.9, 23.8 (d, j = 2.1 Hz), 21.9, 21.8, 20.9; HRMS (ESI) calcd for C$_{40}$H$_{46}$O$_{11}$PCl$_6$ [M+H]: 943.0863, found 943.0909.

2,2'-(4-(2,6-dichloro-4-methoxyphenoxy)-5-isopropoxy-2-methoxy-1,3-phenylene)bis(oxy))bis(1,3-dichloro-5-isopropoxybenzene) (5.16). (i) To a solution
of 5.15 (38 mg, 0.040 mmol) in IPA (0.4 mL, 0.1 M) was added KOH (22 mg, 0.40 mmol). The reaction mixture was stirred vigorously for 16 h upon which time TLC indicated consumption of all starting material. The reaction mixture was quenched with 2M HCl solution (2 mL). The mixture was diluted with H₂O and extracted with DCM (10 mL x 3). The organic layers were combined, dried over Na₂SO₄, and concentrated. The crude material was carried over to the next reaction.

(ii) To a solution of crude phenol (~0.040 mmol) in acetone (0.4 mL, 0.1 M) were added K₂CO₃ (22 mg, 0.16 mmol) and MeI (23 mg, 0.16 mmol). The reaction mixture was stirred for 18 h upon which time TLC indicated consumption of all starting material. The reaction mixture was quenched with 2M HCl solution (0.5 mL). The mixture was diluted with H₂O and extracted with DCM (10 mL x 3). The organic layers were combined, dried over MgSO₄, and concentrated. Purification by FCC (10:1 Hexanes:EtOAc) yielded triisopropyl russuphelol 5.16 (22 mg, 0.0277 mmol, 70%) as a clear oil.

Data for 5.16: Rf 0.50 (6:1 Hexanes: EtOAc); IR (thin film) 2977, 2931, 1597, 1563, 1494, 1464; ¹H NMR (400 MHz, CDCl₃) δ 6.93 (s, 2 H), 6.84 (s, 2 H), 6.78 (s, 2 H), 5.72 (s, 1 H), 4.52 (sept, J = 6.1 Hz, 1 H), 4.46 (sept, J = 6.1 Hz, 1 H), 4.10 (sept, J = 6.1 Hz, 1 H), 3.764 (s, 3 H), 3.761 (s, 3 H), 1.37 (d, J = 6.0 Hz, 6 H), 1.33 (d, J = 5.9 Hz, 6 H), 0.94 (d, J = 6.1 Hz, 6 H); ¹³C NMR (176 MHz, CDCl₃) δ 155.1, 154.9, 153.6, 146.1, 144.5, 144.1, 143.8, 142.4, 140.2, 133.8, 133.4, 129.9, 127.4, 127.3, 116.5, 116.4, 114.1, 96.1, 71.3, 71.2, 70.8, 61.5, 55.9, 21.9 (2C), 21.2; HRMS (ESI) calcld for C₃₅H₃₄O₈Cl₆ [M+H]: 793.0385, found 793.0379.

Russuphelol (5.1). To a solution of 5.16 (20 mg, 0.025 mmol) in DCM (0.25 mL, 0.1 M) was added BCl₃ (0.25 mL, 0.25 mmol, 1M solution in DCM). The reaction mixture was stirred for 2 h upon which time TLC indicated consumption of all starting material. The reaction mixture was quenched with MeOH (0.25 mL), stirred for 15 min and concentrated. Purification by FCC (2:1 Hexanes:EtOAc) yielded 5.1 (11.6 mg, 0.0173
mmol, 69%) as a white solid, with spectroscopic data identical the material synthesized previously.

$^1$H NMR data of isolated and synthetic russuphelol in $d$-MeOD

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$^{13}$C data for isolated and synthetic russuphelol in $d$-MeOD

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CHAPTER 6: CONCLUSION AND FUTURE DIRECTION

6.1 Conclusion

In 1848 Louis Pasteur discovered molecular chirality by crystallization of racemic sodium ammonium tartrate tetrahydrate from aqueous solution. Since then, the concept of chirality has had an enormous impact in various disciplines of science. Considerable effort has been dedicated to synthesizing molecules that are chiral because of sp³ hybridized stereogenic centers. In contrast, less emphasis has been put towards molecules that are chiral by their conformation. However, compounds with restricted rotation of sigma bonds including biaryls, cyclophanes, strained cyclic alkenes and allenes have attracted long-standing attention as chiral ligands, synthetic intermediates, catalysts, and targets of total synthesis.

Conformational chirality is more widespread than commonly believed and goes unnoticed in many molecules. This thesis is a body of work that provides a better understanding of conformational chirality in molecules. The ability to identify the existence of conformational chirality in complex molecular architectures devoid of stereogenic centers along with methods to access them is described.

Chapter 2 describes the syntheses of all known heptanone DAEHs. The first syntheses of myricatomentogenin and jugcathanin were completed. The same synthetic strategy was used in an improved synthesis of galeon, pterocarine, and acerogenin L. With synthetic DAEHs in hand we determined definitively which of these compounds were chiral, and measured their optical activities. We measured racemization energies of these natural products by heating the synthetic material and using kinetics to determine their energies of racemization. Low-temperature NMR was
used to determine the $\Delta G^\ddagger_{\text{rac}}$ for interconversion of enantiomeric conformations of the acerogenins. We have found that the acerogenins were not racemized upon Soxhlet extraction, but rather they are achiral at RT. Furthermore, the remaining heptanone DAEHs were not racemized during isolation temperatures (80 – 110 °C). The natural enantiomers of the chiral members have the same $pR$ absolute stereochemistry. Finally, we have demonstrated that the heptanone DAEH molecular architecture can be constructed by a bioinspired oxidative coupling.

In Chapter 3 the garuganin and garugamblin DAEHs were synthesized using a key Ullmann bond-forming reaction to build the cyclophane molecular architecture of the natural products. Selective methylation of the vinylogous acid DAEHs (e.g. 9′-desmethylgarugamblin I) occurred in hot acidic methanol and produced a single isomer of the vinylogous ester DAEHs (e.g. garugamblin I). An unselective methylation using (trimethylsilyl)diazomethane, followed by acid-catalyzed isomerization also gave access to the natural products along with their corresponding regio– and stereoisomers. The overall syntheses proceeded with yields of 8–12%.

The racemization barriers of the garuganin and garugamblin DAEH natural products and congeners were measured. DAEHs that belong to the same structural class (see Figure 3.2) have nearly identical racemization barriers. Compounds with structure types A and C (e.g. 9′-desmethylgarugamblin I, garuganin III, and 1,9′-didesmethylgaruganin III) undergo racemization at cryogenic temperatures with half-lives on the order of milliseconds. Enantiomeric conformations of garuganin VI have an approximate half-life of 0.01 s at – 50 °C and cannot be resolved at rt. DAEHs with structure type B (e.g. garugamblin I, garugamblin II, garuganin I, and the reported structure of garuganin IV) have relatively higher barriers of racemization; however, resolution of enantiomeric conformations is not possible at rt. Lineshape analysis and selective inversion recovery (SIR) experiments indicate that the half-life of
enantiomeric conformations of DAEHs with structure type B are less than 1 s at rt. Finally, all garuganin and garugamblin DAEHs are achiral, and they are not optically active.

The mechanism of racemization was examined using computational methods. Two important structural features in the DAEHs lead to chirality. Local symmetry in the B ring leads to the ansa loop rotation barrier being the rate-limiting step (9-18 Kcal/mol). If there is no symmetry in the B ring the rotation of the B ring is the rate-limiting step (~45 kcal/mol). The flow chart created (Figure 3.9) predicts if a given DAEH has stable enantiomeric conformations under ambient conditions.

The first enantioselective Ullmann reaction was developed and used in the syntheses of all chiral DAEHs. We found that the use of non-racemic ligands renders the Ullmann ether synthesis enantioselective. This is the first example of an enantioselective Ullmann ether coupling. In a survey of a variety of ligands known to accelerate the Ullmann reaction, N-methyl proline was the best ligand in terms of chemical yield and enantioselectivity. The non-racemic cyclophane product could be enriched by recrystallization, and the enantioenriched material was used in the first enantioselective syntheses of (−)-myricatomentogenin, (−)-jugcathanin, (+)-galeon, and (+)-pterocarine.

In Chapter 5 we used the tools and knowledge developed in the context of macrocyclic diphenylethers and applied it in the synthesis of an acyclic diphenylether-containing molecule, russuphelol. Russuphelol was isolated as an optically active molecule. The synthesis utilizes the symmetry in the structure of the natural product. Addition of the D-ring to the bromoquinone and a quinone reductive alkylation are highlights of the synthesis. The synthesis is six steps and approximately 15% in overall yield. The chiral properties of russuphelol have been studied.
Observation of a single peak on chiral stationary phase HPLC (regardless of conditions), comparison to known chiral diphenyl ether structures, chemical shift equivalent $^1$H and $^{13}$C NMR signals and coalescence at –100 °C suggest that russuphelol is an achiral molecule. The barrier to rotation at –100 °C is below 9 kcal/mol. Despite previous reports, russuphelol is an achiral molecule under ambient conditions.

6.2 Future Directions

We have started to explore the biological properties of the DAEHs and derivatives. The NCI-60 cancer cell line screen has been performed for 66 compounds. We are collaborating with H3 biomedicine to develop structure activity relationships for the DAEHs that have significant activity. Furthermore, we are collaborating with Prof. Robert Tanguay at OSU to explore the biological activity of the DAEHs in zebrafish. We have submitted two 96-well plates of DAEHs and related compounds for screening and have received the preliminary data for these compounds. Efforts to determine the mode of action and the binding sites during the zebrafish development process of these molecules in underway.

We would like to develop a better understanding of the chirality-activity relationship for molecules with conformational chirality. Upon isolation many of these molecules studied had mistaken chiral properties, and the ability to further our understanding of conformationally chiral molecules in biological systems is necessary. We are uniquely positioned to launch this investigation because we have all the DAEH racemic molecules, their enantiopure molecules, and derivatives. Not surprisingly, in
the preliminary data from both zebra fish and the NCI-60 screen a different biological profile is seen for enantiomers.

We can further extend our knowledge of conformational chirality with the tools and techniques established in this thesis. There are still many classes of molecules with conformational chirality that have gone unnoticed. A recent report from the Baran group reported a new method to dimerize carbazoles and carbolines by forming a N–N bond and completed the synthesis of dixiamycin.\(^1\) In this report, four compounds (with general structure 6.1) that have the requirements to display conformational chirality, yet no mention of this was reported (Figure 6.1). Eriocauline (6.2) an optically active dimeric naphthopyranone was isolated in 2007.\(^3\) Similar to russuphelol this molecule is an acyclic diarylether, which possibility contains a higher barrier of racemization. This can be verified thought synthesis and conducting a racemization study.

![Figure 6.1. Conformationally chiral natural products of interest](image)

Current efforts in the group to explore conformational chirality in various molecular architectures are underway. Arundamine (6.3) and related natural products contain a C–N bond with hindered rotation.\(^4\) Similar to the chiral DAEHs the enantiomers can be resolved and the racemization parameters can be obtained. Macroyclic BisBibenzyls (MBBs) can also display conformational chirality. Asterelin A (6.4) is a natural product that contains chemical shift-inequivalent protons, which is a consistent with an element of chirality present in the molecule. Synthetic efforts toward the asterelin A are underway. Finally, conformational chirality has been
overlooked in natural products, the work done in this thesis is an effort to raise awareness of this concept, and in the future make it trivial to identify this phenomenon in any given molecule.