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BOSTON UNIVERSITY

GRADUATE SCHOOL OF ARTS AND SCIENCES

Dissertation

STUDIES TOWARD THE TOTAL SYNTHESIS OF TETRAMETHYLDIHYDROXANTHENE NATURAL PRODUCTS

by

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B.S., Ecole Nationale Supérieure de Chimie de Montpellier, 2007

Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

2014

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2014

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"Experience has shown, and a true philosophy

will always show, that a vast, perhaps the larger

portion of the truth arises from the seemingly irrelevant."

Edgar Allan Poe

To my parents Gilles and Sylvie,

and to my sister Eva for offering me everything;

To those present in every important moments of

my life for challenging, loving and supporting me

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STUDIES TOWARD THE TOTAL SYNTHESIS OF TETRAMETHYLDIHYDROXANTHENE NATURAL PRODUCTS

ANAIS GERVAIS

Boston University Graduate School of Arts and Sciences, 2014

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ABSTRACT

Tetramethyldihydroxanthenes constitute a large class of natural products wherein a 6member ring triketone moiety is linked to an aromatic moiety. Progress toward the syntheses of six biologically active natural products isolated from these genus species; rhodomyrtone A, rhodomyrtosones A and B, tomentosones A and B, and bullataketals A and B, are described. These compounds possess challenging structures and interesting bioactivities making them attractive targets. Isolation, structure elucidation and biosyntheses of rhodomyrtone A, rhodomyrtosone A and B, tomentosones A and B, and bullataketals A and B are discussed. To accomplish their total syntheses, several new methodologies have been developed. A nickelmediated catalytic 1,4-conjugate addition was developed. Literature precedents showcasing the use of nickel-mediated 1,4-conjugate addition and previously reported nickel-mediated enantioselective catalytic systems are presented herein along with our work. The challenges met during the development of a regioselective dehydrative cyclization for the syntheses of rhodomyrtone A and rhodomyrtosone B are discussed and strategies designed to overcome this synthetic challenge are presented in detail. Our studies to develop a flow photochemistrymediated process to access endoperoxides, as well as generation and trapping of active vinyloxocarbenium intermediates are presented along with relevant literature precedents.

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LIST OF ABBREVIATIONS

| 4Å MS | 4Å molecular sieves |
|-----------------------------------|--|
| [α] | specific rotation |
| μΜ | micromolar |
| Ac | acetyl |
| AcOH | acetic acid |
| aq. | aqueous |
| ACT | artemisinin combined therapy |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BINOL | 1,1'-bi-2-naphtol |
| Bn | benzyl |
| Bu | butyl |
| cat. | catalytic |
| CF ₃ SO ₃ H | triflic acid |
| CH ₂ Cl ₂ | dichloromethane |
| CH ₃ CN | acetonitrile |
| ChiralCel-OD | cellulose tris (3,5-dimethylphenylcarbamate) |
| cm ⁻¹ | wavenumber |
| CoA | coenzyme A |
| conc. | concentrated |
| CuI | copper iodide |
| DBFox | (<i>R</i> , <i>R</i>)-4,6-Dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) |
| DCE | dichloroethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |

| DFT | density functional theory |
|-------------------|---|
| DIBAL-H | diisobutylaluminum hydride |
| DMF | N,N-dimethylformamide |
| EDF2 | empirical density functional 2 |
| EtOH | ethanol |
| EtOAc | ethyl acetate |
| dr | diastereomeric ratio |
| ee | enantiomeric excess |
| equiv | equivalents |
| Et | ethyl |
| Et ₃ N | triethylamine |
| FTIR | Fourier transform infrared spectroscopy |
| δ | chemical shift |
| h | hour(s) |
| H ₂ | hydrogen |
| HCl | hydrochloric acid |
| HF | hydrofluoric acid |
| HFIP | 1,1,1,3,3,3-hexafluoro-2-propanol |
| HMBC | heteronuclear multiple bond correlation |
| НОМО | highest occupied molecular orbital |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectroscopy |
| HSQC | heteronuclear single quantum coherence |
| Hz | hertz |

| hν | irradiation |
|--------------------------------|--|
| IBX | 2-iodoxybenzoic acid |
| <i>i</i> -Pr | isopropyl |
| IR | infrared |
| [Ir(cod)Cl] ₂ | bis(1,5-cyclooctadiene)diiridium(I) dichloride |
| JohnPhos | (2-Biphenyl)di-tert-butylphosphine |
| K ₂ CO ₃ | potassium carbonate |
| КОН | potassium hydroxide |
| LUMO | lowest unoccupied molecular orbital |
| Me | methyl |
| MeOH | methanol |
| MIC | minimum inhibitory concentration |
| min | minutes |
| MMFF | merck molecular force field |
| mmol | millimole |
| mol | mole |
| mp. | melting point |
| NaH | sodium hydride |
| NaOH | sodium hydroxide |
| NHTf ₂ | bis(trifluoromethane) sulfonamide |
| Ni(acac) ₂ | nickel (II) acetylacetonate |
| nM | nanomolar |
| NMR | nuclear magnetic resonance |
| $Pd(OAc)_2$ | palladium diacetate |

| Pd(PPh ₃)Cl ₂ | bistriphenylphsophine palladium (II) dichloride |
|---------------------------------------|---|
| Ph | phenyl |
| PKS | polyketide synthase |
| PhMe | toluene |
| PPh ₃ | triphenylphosphine |
| p-TsOH | <i>p</i> -toluenesulfonic acid |
| ppm | parts per million |
| Pr | propyl |
| PSI | pounds per square inch |
| PyBox | bisoxazoline |
| Q-TOF | quadrupole time-of-flight |
| r.t. | room temperature |
| Rh(PPh ₃) ₃ Cl | rhodium (I) tris-triphenylphosphine chloride |
| SAM | S-adenosyl methionine |
| S. aureus | staphylococcus aureus |
| SiO ₂ | silica gel |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMSOTf | trimethylsilyl trifluoromethanesulfonate |
| UPLC | ultra performance liquid chromatography |
| ЦV | ultra viol |

Chapter 1

Introduction to the Tetramethyldihydroxanthene Natural Products.

1.1 Tetramethyldihydroxanthenes: Definition, Origin, and Isolation

Tetramethyldihydroxanthenes constitute a diverse family of natural products. Although their core structures contain a triketone moiety attached to an acylated phloroglucinol by an alkyl bridge, numerous variations can be found around this core. This structural diversity leads to a rich set of biological activities for these compounds. Thus we became interested in gathering and understanding data and information regarding this family of natural products structural diversity, isolation, and biosynthesis reported by the several research groups. These data are presented herein and provided us with insights to design efficient biomimetic syntheses for this class of natural products.

1.1.1 Definition, Origin, and Isolation

As previously mentioned, tetramethyldihydroxanthenes contain a triketone moiety attached to an acylated phloroglucinol by an alkyl linkage. This linkage varies in length: an isopropyl group for **1.8-1.14**, an isobutyl group for **1.1-1.4**, **1.16**, **1.18-1.20**, and an ethyl benzyl group for **1.17** (**Figure 1.1-1.7**). The acylated phoroglucinol moiety is also diverse with either isovaleryl, isobutyryl, and hexanoyl substituents. The alkyl bridge and acyl substituents usually bear the same chain except for **1.14-1.16**. Tetramethyldihydroxanthenes can be either fully cyclized (e.g **1.1, 1.2, 1.9, 1.12, 1.19, 1.20**) or hydrated (e.g. **1.3, 1.8, 1.11, 1.13-1.18**). Additionally, some members of the family are trimeric compounds containing one aromatic moiety and two triketone moieties. Trimers can be fully cyclized (e.g. **1.4, 1.12**), fully hydrated (e.g. **1.10, 1.14, 1.15**), or partially cyclized (e.g. **1.11, 1.13**). They usually bear the same acyl and alkyl chains except for compounds **1.14** and **1.15**. Some members of the family possess more complex aromatic moieties bearing, both acyl and methyl groups such as **1.16-1.17**, substituted flavones such as compound **1.18**, or dihydrochalcone moieties such as **1.19** and **1.20** (Figure 1.1-1.7).

Rhodomyrtosone A **1.5** and tomentosones A **1.6** and B **1.7** do not possess an alkyl linkage. In these family members, the aromatic moiety is linked to the triketone moiety by a bicyclic ketal where the proton and isopropyl group at the ring junctures are *cis* to each other. This structurally diverse family possesses equally diverse origins and bioactivities. Rhodomyrtone A **1.1** was isolated in 2002 by Sargent and coworkers from the leaves of the *Rhodomyrtus tomentosa* plant as a racemic mixture (**Figure 1.1**).¹ Rhodomyrtosone B **1.2**, **1.3**, rhodomyrtosone A **1.5**, rhodomyrtosone C **1.4** were isolated in 2008 by Mahabusarakam and coworkers also from the leaves of the plant *Rhodomyrtus tomentosa*.² This plant grows in Indonesia and Thailand and has been extensively used in folk medicine. Extraction of the leaves with hexanes and ethyl acetate led to the identification and isolation of these five tetramethydihydroxanthenes along with other compounds. Plant extracts have shown anti-hepatitis properties, blood platelet aggregation inhibition properties, and calcium antagonist activities. Rhodomyrtone A **1.1** has shown some potent antibiotics activities against several strains of *Staphylococcus* and *Streptococcus*.





Dichloromethane extracts of the leaves provided tomentosones A **1.6** and B **1.7** which were identified in 2012 by Mahabusarakam and coworkers (**Figure 1.2**).³ These compounds exhibited the ability to inhibit the growth of chloroquinine-resistant and chloroquinine-sensitive strains of the malaria parasite *Plasmodium falciparum* in the micromolar range.

Figure 1.2. Tomentosones A and B.



Myrtucommulones B **1.9** and A **1.10** were first isolated in 1971 by Kashman and coworkers (**Figure 1.3**).⁴ They were isolated from the methanolic extracts of the plant *Myrtus communis*, which grows in the Mediterranean area and has been used in folk medicine to treat several ailments. Several studies have later found antibacterial, anti-inflammatory, anti-hyperglycemic, and antioxidant activities in various extracts of this plant.⁵

Figure 1. 3. Myrtucommulones A and B, and Semi-myrtucommulone.



1.10 myrtucommulone A



Semi-myrtucommulone 1.8 was isolated in 2002 by Appendino and coworkers from an acetone extract of the plant leaves.⁶ During their studies, Appendino and coworkers proposed that semimyrtucommulone 1.8 may exist as two atropisomers. They were able to measure a coalescence temperature for 1.8 and upon cyclization under acidic conditions, 1.8 yielded two regioisomers **1.8A** and **1.8B** in 30 % yield and a 1:1 ratio (Figure 1.3, *Inset*).

Myrtucommulone D 1.11, myrtucummulone E 1.12, and myrtucommulone C 1.13 were isolated in 2006 by Shaheen and cowokers also from the methanolic extract of the plant.⁷ In their studies, Shaheen and coworkers were able to show that both myrtucommulones D 1.11 and E 1.12 possessed antibiotics activities against *Staphylococcus aureus* strains (Figure 1.4).

Figure 1.4. Myrtucommulones C, D, and E.





Myrtucommulones F **1.14** and H **1.15** were isolated in 2008 by Quinn and coworkers from the ground seeds of the tree *Corymbia scabrida* growing in Australia (**Figure 1.5**). In their studies, Quinn and coworkers demonstrated that myrtucommulone A **1.10**, D **1.11**, F **1.14** and H **1.15** exhibited substantial binding affinity for the thyrotropin-releasing hormone (TRH) receptor-2 in rats.⁸ THR is found in the central and peripheral nervous system and may be involved in pain control. They also revised the structure for myrtucommulone D **1.11** that had been mistakenly assigned as its epimer at the hemiketal carbon by Shaheen and coworkers.

Figure 1.5. Myrtucommulones F and H.



Quinn and coworkers also isolated corymbone A **1.16** and B **1.17**, and **1.18** in 2008 from the flowers of the australian tree *Corymbia peltata* (Figure 1.6).⁹



Both corymbones A **1.16** and B **1.17** also showed binding affinity for the TRH receptor in rats (IC₅₀ 23 μ M and 19 μ M respectively). In their work, Quinn and coworkers found that the strong hydrogen-bond network existing within the compounds structure was affecting their behavior on

TLC plate by rendering them less polar than expected. They also proposed that due to this strong hydrogen-bond network, the compounds may exist in several stable or semi-stable conformations. They also ventured that in nature different conformational compositions may exist for the same compounds which may explain why the optical activities recorded by Shaheen and coworkers for myrtcucommulone A **1.10** greatly differ from their measurement. These observations corroborated Appendino observations about semi-myrtucommulone **1.8** which was proposed to exist as an atropisomeric mixture.

Finally, kunzeanones A **1.19** and B **1.20** were isolated from the acetone extract of the plant *Kunzea ambigua* which grows in New Zealand, and has been used in folk medicine for the treatment of diarrhea, cold, and inflammation (**Figure 1.7**).¹⁰ Kunzeanones A **1.19** and B **1.20** have also been reported to possess a strong hydrogen bond network within their structures. They have been reported to co-crystallize by forming a single unit cell due to a very strong intermolecular hydrogen-bond network existing between the two isomers. This case of co-crystallization is particularly interesting as it is the first case of such behavior observed to date (**Figure 1.7**, **Xray**).





Xray of 1.19 and 1.20

Isolation studies were insightful as they provided us with some information about the possible atropisomeric character of non-cyclized, tetramethyldihydroxanthene family members. The structural diversity around the aromatic core also provided a better understanding of the challenges that may arise during our synthetic studies of rhodomyrtone A **1.1** and related natural products.

1.1.2 Structure Elucidation

The strong biological activity of the rhodomyrtones, rhodomyrtosones, and tomentosones as well as their challenging structural features led us to focus our studies on this set of compounds.

1.1.2.a Rhodomyrtone A 1.1, Rhodomyrtosone B 1.2, and Rhodomyrtosone C 1.4

We turned our attention to rhodomyrtone A **1.1** and rhodomyrtosone B **1.2**, which are isomers. The structure determination of rhodomyrtone A **1.1** was conducted by Sargent and coworkers by analyzing mass spectrometry data.¹ High-resolution mass spectrometry data for **1.1** displayed a peak (m/z 443.2434), which is consistent with the molecular formula $C_{26}H_{34}O_6$. ¹³C NMR data (**Table 1.1**) supported the molecular formula and DEPT NMR spectroscopy indicated the presence of eight methyl, two methylene, four methane, and 12 fully-substituted carbons.

Table 1. 1.¹H NMR and ¹³C NMR Data for 1.1.



| C# | ¹³ C NMR (ppm) | ¹ H NMR (ppm, mult, J Hz) |
|----|---------------------------|--------------------------------------|
| 1 | 198.56 | |
| 2 | 56.05 | |
| 3 | 212.16 | |
| 4 | 47.23 | |
| 4a | 167.65 | |

| 4b | 155.63 | |
|------|--------|--|
| 5 | 94.74 | 6.19 (s) |
| 6 | 158.70 | |
| 7 | 107.63 | |
| 8 | 162.84 | |
| 8a | 106.30 | |
| 9 | 25.19 | 4.3 (t, 5.5, 5.5) |
| 9a | 114.26 | |
| 10 | 24.21 | 1.39 (s) |
| 11 | 24.58 | 1.42 (s) |
| 12 | 24.72 | 1.44 (s) |
| 13 | 24.72 | 1.56 (s) |
| 1' | 206.75 | |
| 2' | 53.18 | 2.97 (dd, 6.8, 15.5); 3.03(dd, 6.8, 15.5) |
| 3' | 25.15 | 2.28 (m) |
| 4' | 22.74 | 0.98 (d, 6.3) |
| 5' | 22.81 | 0.98 (d, 6.3) |
| 1" | 45.82 | 1.48 (m) |
| 2" | 25.10 | |
| 3" | 22.53 | 0.84 (d, 5.9) |
| 4" | 23.16 | 0.87 (d, 5.9) |
| 6-OH | | 8.08 (s) |
| 8-OH | | 13.39 (s) |

IR data allowed three of the quaternary carbons to be assigned as keto-groups. D₂O exchange experiments identified two hydroxyl groups. The remaining oxygen was therefore attributed to an ether linkage. DQF-COSY, HMQC, and HMBC data revealed the presence of an aromatic ring and the presence of an attached isovaleryl group. An additional isobutyl was identified to be consistent with the base peak of the mass-spectroscopy data. Two structures were initially proposed for rhodomyrtone A **1.1** which only differed in the position of the isovaleryl substituent. HMBC data distinguished between the two regioisomeric structures. A three–bond coupling with H-9 allowed the assignment of carbon C-10a, which showed a two-bond coupling with H-5, subsequently allowing the correct position of the isovaleryl substituent to be assigned to C-7. This assignment was confirmed by single crystal X-ray data (**Figure 1.8**).

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Figure 1.8. Xray of Rhodomyrtone A.



The structure determination of rhodomyrtosone B **1.2**, which is the regioisomer of rhodomyrtone A **1.1** and only differs by the position of the isovaleryl group, started with the analysis of the mass spectrometry data.² High-resolution mass spectrometry data displayed a peak (m/z 442.2352) consistent with a molecular formula of $C_{26}H_{34}O_6$ with ten degrees of unsaturation. The ¹H NMR data (**Table 1.2**) supported the presence of a chelated hydroxyl group, a free hydroxyl group, an aromatic proton an isopentyl group, an isovaleryl group, and four singlet methyl groups corresponding to a β -triketone moiety. These data supported the hypothesis that **1.2** was a structural isomer of rhodomyrtone A **1.1**. Slight differences in chemical shifts were observed for the chelated hydroxyl group at C-6 and for the non-equivalent methylene protons at C-2' of the isovaleryl group substituent, consequently the isovaleryl group was placed at C-5 rather than at C-7. HMBC data confirmed this initial assignment with H-7 having a two bond coupling with C-6 and C-8 and three-bond coupling with C-8a (**Table 1.2**).

Table 1. 2.¹H NMR, ¹³C NMR Data for 1.2.



| C# | ¹³ C NMR (ppm, mult) | ¹ H NMR (ppm, mult, J Hz) |
|----|---------------------------------|--------------------------------------|
| 1 | 197.6 s | |
| 2 | 56.1 s | |

| 3 | 211.7 s | |
|----------|---------|---|
| 4 | 47.2 s | |
| 4a | 166.9 s | |
| 4b | 153.3 s | |
| 5 | 105.9 s | |
| 6 | 159.0 s | |
| 7 | 100.3 d | 6.23 (s) |
| 8 | 159.0 s | |
| 8a | 105.9 s | |
| 9 | 25.1 d | 4.25 (t, 6.0, 6.0) |
| 9a | 114.5 s | |
| 10 | 24.3 q | 1.39 (s) |
| 11 | 24.4 q | 1.42 (s) |
| 12 | 24.8 q | 1.63 (s) |
| 13 | 25.4 q | 1.47 (s) |
| 1' | 204.0 s | |
| 2' | 53.6 t | 3.18 (dd, 17.0, 6.5);2.96 (dd 17.0, 6.5) |
| 3' | 24.5 d | 2.37 (m, 6.5) |
| 4' | 22.9 q | 1.04 (d, 6.5) |
| 5' | 22.6 q | 1.01 (d, 6.5) |
| 1" | 46.9 t | 1.38 |
| 2" | 24.9 d | 1.38 |
| 3" | 23.4 q | 0.89 (d, 6.5) |
| 4" | 23.1 q | 0.87 (d, 6.5) |
| 6- OH | | 13.43 (s) |
| 8- OH | | 6.40 (br s) |

1.1.2.b Rhodomyrtosone A 1.5, Tomentosone A 1.6, and Tomentosone B 1.7

The structure elucidation for rhodomyrtosone A **1.5** was based on initial analysis of mass spectrometry data.² High-resolution mass spectrometry data displayed a molecular ion peak at m/z 456.2133, consistent with a molecular formula of $C_{26}H_{32}O_7$ with 11 degrees of unsaturation. IR spectrometry data indicated the presence of a hydroxyl group, a non-conjugated carbonyl and a conjugated carbonyl groups. ¹³C NMR and DEPT spectroscopy data (**Table 1.3**) suggested the presence of three carbonyls, ten fully substituted, four methine, one methylene, and eight methyl

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carbons. HMBC data showed correlations for both H-12 and H-13 with carbonyl carbon C-3 vinylic carbon C-4a, whereas both H-10 and H-11 showed correlations to carbonyl carbons C-1 and C-3. This suggested the presence of a β -triketone moiety. The ¹³C NMR data displayed a low field chemical shift of C-4a suggesting that the β triketone moiety was connected to the oxygen of a furan ring. The ¹H NMR signals of the two hydroxyl groups, one aromatic proton, and an isovaleryl group were proposed to be derived from a di-C-substituted phloroglucinol moiety. The ¹H NMR data also display a methine proton and an isopropyl group. HMBC data indicated a fused-ring bearing the isopropyl group. Protons at 6-OH and 8-OH displayed three-bond coupling to the aromatic methine carbon C-7 and from 6-OH to C-5 indicating that the aromatic proton was located in between two hydroxyl groups (C-7). Consequently the isovaleryl group was then placed at C-5. NOESY data indicated correlations of methine proton H-9 to the isopropyl, which allowed the assignment of a *cis* relative stereochemistry for the *bis*-furan fused ring system.

Table 1. 3.¹H NMR, ¹³C NMR and HMBC NMR Data for 1.5.



| C# | ¹³ C NMR (mult, ppm) | ¹ H NMR (mult, ppm, J Hz) | HMBC (H→C) |
|----|---------------------------------|--------------------------------------|------------------------|
| 1 | 198.3 s | | |
| 2 | 55.1 s | | |
| 3 | 211.1 s | | |
| 4 | 45.6 s | | |
| 4a | 179.7 s | | |
| 4b | 159.8 s | | |
| 5 | 101.7 s | | |
| 6 | 166.7 s | | |
| 7 | 99.6 d | 6.11 (s) | C-5, C-6, C-8, C-8a |
| 8 | 159.6 s | | |
| 8a | 104.2 s | | |

| | | | C-4a, C-4b, C- |
|------|---------|----------------------------|-------------------------|
| 9 | 45.0 d | 4.50 (s) | 8, C-8a, C-9a, |
| | | | C-2″ |
| 9a | 113.2 s | | |
| 10 | 24.4 q | 1.52 (s) | C-1, C-2, C-3, C-11 |
| 11 | 24.1 q | 1.42 (s) | C-1, C-2, C-3, C-10 |
| 12 | 23.1 q | 1.34 (s) | C-3, C-4, C-4a, C-13 |
| 13 | 25.9 q | 1.41 (s) | C-3, C-4, C-4a, C-12 |
| 1' | 203.7 s | | |
| 21 | 5154 | 2.96 (dd, 14.7, 6.6), 2.76 | C-1', C-3', C-4', |
| Z | 51.5 t | (dd, 14.7, 6.6) | C-5′ |
| 3' | 25.8 d | 2.17 (m, 6.6) | C-2′, C-4′, C-5′ |
| 4' | 22.8 q | 1.01 (d, 6.6) | C-2', C-3', C-5' |
| 5' | 22.7 q | 0.99 (d, 6.6) | C-2′, C-3′, C-4′ |
| 1″ | 129.4 s | | |
| 2″ | 35.4 d | 2.40 (hept, 6.9) | C-1", C-3", C- 4" |
| 3″ | 15.7 q | 1.11 (d, 6.9) | C-1", C-2", C- 4" |
| 4″ | 15.6 q | 1.09 (d, 6.9) | C-1", C-2", C- 3" |
| 6-OH | | 13.27 (s) | C-5, C-6, C-7 |
| 8-OH | | 9.78 (s) | C-7, C-8 |
| | | | |

The structure elucidation for tomentosone A **1.6** began with an analysis of the mass spectrometry data.³ High-resolution mass spectrometry data displayed a molecular ion peak at m/z 688.3610 corresponding to the molecular formula of $C_{41}H_{52}O_9$. UV spectroscopy data were consistent with the IR spectrometry data indicating the presence of a hydroxyl, conjugated carbonyl and non-conjugated carbonyl groups. ¹H NMR data suggested the presence of eight tertiary methyl groups, six secondary methyl groups, two methylene groups, five methine protons and one hydrogen-bonded hydroxyl proton (**Table 1.4**). COSY data showed correlations that helped to assign the isopropyl, isobutyl, and isopentyl moieties. ¹³C NMR and DEPT data indicated the presence of five carbonyl carbons, ten sp2 hybridized fully substituted carbons, four

sp-3 hybridized quaternary carbons, five methine carbons, two methylene carbons, and 14 methyl carbons. HMBC data displayed correlations for the eight methyl singlets, which corresponded to the presence of two 1,1,3,3-tetramethyl β -triketone moieties. Additional HMBC data showed correlations from H-7^{'''} to C-6, C-8, C-1^{'''}, and C-5^{'''} indicating that the isopentyl group was attached to one of these β -triketones. The presence of a phloroglucinol moiety was deduced from correlations between H-7^{'''} and C-6, C-8, from H-9 to C-4a, C-8 and C-8a' and from 6-OH to C-5, C-6 and C-7. HMBC correlations from the methine proton H-9 to C-4a, C-9a and C-2^{''} as well as that of the methyl protons of the isopropyl group to C-1^{''} (δ C 128.8) indicated that the second β -triketone was attached to the phloroglucinol moiety via a *bis*-furan fused-ring bearing the isopropyl group as for rhodomyrtosone A **1.5**. An isovaleryl group was indicated to be present in the molecule due HMBC correlations from the isobutyl protons H-2' and H-3' to the only remaining unassigned carbonyl carbon C-1'.

Table 1. 4.¹H NMR, ¹³C NMR Data for 1.6.



| С # | ¹³ C NMR (mult, ppm) | ¹ H NMR (mult, ppm, J Hz) |
|-----|---------------------------------|--------------------------------------|
| 1 | 192.0 s | |
| 2 | 56.1 s | |
| 3 | 212.1 s | |
| 4 | 45.5 s | |
| 4a | 176.0 s | |
| 4b | 158.4 s | |
| 5 | 104.0 s | |
| 6 | 162.5 s | |
| 7 | 108.7 s | |

| 8 | 152.2 s | |
|-------------|---------|----------------------|
| 8a | 104.9 s | |
| 9 | 45.9 d | 4.74 (s) |
| 9a | 113.0 s | |
| 10 | 23.8 q | 1.43 (s) |
| 11 | 25.8 q | 1.24 (s) |
| 12 | 24.5 q | 1.47 (s) |
| 13 | 23.8 q | 1.36 (s) |
| 1' | 204.6 s | |
| 2' | 51.9 t | 2.99 (dd, 15.0, 6.9) |
| | | 2.89 (d, 15.0, 6.9) |
| 3' | 25.6 d | 2.23 (m, 6.9) |
| 4' | 22.8 q | 1.03 (d, 6.9) |
| 5' | 22.7 q | 1.01 (d, 6.9) |
| 1″ | 128.8 s | |
| 2″ | 34.9 d | 2.37 (hept, 6.9) |
| 3″ | 15.8 q | 1.11 (d, 6.9) |
| 4″ | 15.8 q | 1.09 (d, 6.9) |
| 1‴ | 197.5 s | |
| 2‴ | 56.3 s | |
| 3‴ | 212.5 s | |
| 4 ‴ | 47.6 s | |
| 5‴ | 167.7 s | |
| 6 ‴ | 113.9 s | |
| 7‴ | 25.3 d | 4.28 (t, 5.4, 5.4) |
| 8‴ | 45.4 t | 1.40 |
| 9‴ | 25.1 d | 1.40 |
| 10 ‴ | 23.2 q | 0.83 (d, 6.6) |
| 11‴ | 23.6 q | 0.75 (d, 6.6) |
| 12‴ | 22.0 q | 1.36 (s) |
| 13‴ | 24.7 q | 1.42 (s) |
| 14 ‴ | 25.3 q | 1.67 (s) |
| 15‴ | 23.2 q | 1.74 (s) |
| 6-OH | | 13.62 (s) |

¹H NMR resonance were further analyzed and showed a downfield phenolic proton 6-OH, which was suggested to be due to a strong intramolecular hydrogen bond, consequently the isovaleryl group was assigned to the carbon *ortho* to it at C-5. An additional ring between C-8

and C-5^{*'''*} via an oxygen bridge was assigned to fulfill the double bond equivalence defined by the molecular formula assigned to **1.6** (**Table 1.4**).

The structure elucidation for tomentosone B **1.7** started by analyzing the mass spectrometry data.³ High-resolution mass spectrometry data displayed a molecular ion peak at m/z 688.3610 corresponding to the molecular formula of $C_{41}H_{52}O_9$. Other spectroscopic data (UV, IR, MS, ¹H NMR and ¹³C NMR) were very similar to those of **1.6**. The methyl proton signals H-3-14^{*'''*}/H-3-15^{*'''*} and nonequivalent methylene protons H-2-2', in the ¹H NMR spectrum were the only differences observed. HMBC data were also similar for **1.6** and **1.7** suggesting that **1.7** was a diastereomer of **1.6** (**Table 1.5**).





| C # | ¹³ C NMR (mult, ppm) | ¹ H NMR (mult, ppm, J Hz) |
|-----|---------------------------------|--------------------------------------|
| 1 | 192.1 s | |
| 2 | 55.7 s | |
| 3 | 212.0 s | |
| 4 | 45.4 s | |
| 4a | 176.9 s | |
| 4b | 158.7 s | |
| 5 | 103.9 s | |
| 6 | 162.8 s | |
| 7 | 107.9 s | |
| 8 | 152.1 s | |
| 8a | 103.8 s | |
| 9 | 46.3 d | 4.81 (s) |
| 9a | 113.2 s | |
| 10 | 24.8 q | 1.36 (s) |

| 11 | 24.1 q | 1.24 (s) |
|-------------|---------|----------------------|
| 12 | 24.2 q | 1.49 (s) |
| 13 | 24.0 q | 1.41 (s) |
| 1′ | 204.7 s | |
| 2' | 52.0 t | 3.12 (dd, 14.7, 6.6) |
| | | 2.73 (dd, 14.7, 6.6) |
| 3' | 26.0 d | 2.18 (m, 6.6) |
| 4′ | 22.5 q | 0.99 (d, 6.6) |
| 5' | 22.9 q | 1.03 (d, 6.6) |
| 1″ | 128.9 s | |
| 2″ | 34.9 d | 2.35 (hept, 6.9) |
| 3″ | 15.7 q | 1.11 (d, 6.9) |
| 4″ | 15.8 q | 1.08 (d, 6.9) |
| | | |
| 1‴ | 198.3 s | |
| 2‴ | 198.3 s | |
| 3‴ | 55.3 s | |
| 4 ‴ | 212.6 s | |
| 5‴ | 47.9 s | |
| 6‴ | 165.9 s | |
| 7‴ | 113.6 s | |
| 8‴ | 25.4 d | 4.32 (dd, 5.7, 4.2) |
| 9‴ | 45.3 t | 1.51(m) |
| 10‴ | 25.1 d | 1.40 |
| 11‴ | 23.3 q | 0.85 (d, 6.3) |
| 12‴ | 23.4 q | 0.69 (d, 6.3) |
| 13‴ | 24.3 q | 1.37 (s) |
| 14 ‴ | 198.3 s | |
| 15‴ | 55.3 s | |
| 6-OH | 212.6 s | |

To identify the relative stereochemistry at the three stereogenic centers present in **1.6** and **1.7**, ROESY experiments were performed. Correlations between H-9 and H-2" were observed for both **1.6** and **1.7** suggesting that the *bis*-furan junction was of *cis* configuration which was similar to what had previously been observed for rhodomyrtosone A **1.5**. Consequently, **1.6** and **1.7** were assigned to be epimeric at C-7". ROESY data showed a correlation from H-9 to methyl proton

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in C-15" and C-13" indicating that both methyl groups were located on the top face of the β -triketone. The proton of C-13" showed a correlation with H-7" indicating that the the isopropyl group was located on the opposite face of H-9 or the β -face of the molecule in **1.6**. This assignment was confirmed by additional ROESY correlations. Therefore tomentosone A **1.6** relative stereochemistry was assigned as 1" S*, 9R*, 7"S* and tomentosone B **1.7** was assigned as 1" S*, 9R*, 7"R*.

1.2 Biosynthesis of Select Tetramethyldihydroxanthenes

We were interested in developing a biomimetic synthesis for this class of natural products, so we turned our attention to the two proposed biosynthetic pathways discussed in the literature.

1.2.1 1,4 Conjugate Addition

Scheme 1. 1. Bloor's Isolation Studies and Biosynthetic Proposal.



In 1992, Bloor isolated phloroglucinol-derived natural products from the *Kunzea ericoides* plant.¹¹ Leptospermone **1.21**, robustaol **1.22**, **1.23** and two adducts **1.3** and **1.24** were co-isolated. Bloor proposed that both adducts **1.3** and **1.23** may result from an enzymatic condensation of robustaol and leptospermone (**Scheme 1.1**). In their work during the isolation of the bullataketals, Perry and coworkers also proposed an aldol reaction/reduction sequence between acylated

phloroglucinol **1.25** and compound **1.26** parent to leptospermone **1.21** to account for this condensation.¹² Perry and coworkers proposed that acyl phloroglucinol **1.28** may be derived from isobutyryl-CoA **1.26** by a polyketide synthase (PKS) leading to **1.27** followed by addition of three malonyl-CoA units **1.27** similarly to the biosynthesis proposed by Eisenreich and coworkers for hyperforin. Then methylation of **1.28** with S-adenosyl methionine (SAM) may lead to the formation of **1.29**. They proposed an aldol reaction/reduction sequence to explain the formation of **1.30**, a parent compound of **1.3** and **1.24**, which upon cyclization and dehydration may lead to myrtucommulone B **1.9** and other tetramethyldihydroxanthenes (**Scheme 1.2**).

Scheme 1. 2. Perry's Proposed Biosynthesis of the Tetramethyldihydroxanthenes.



Bloor has shown that the cyclization, dehydration sequence was prompted to occur under acidic conditions. This biosynthetic pathway is relevant for rhodomyrtone A **1.1** and rhodomyrtosone B **1.2** as they have been co-isolated with lepstopermone **1.21** and intermediate **1.3**.

Crow and coworkers proposed a different pathway for the biosynthesis of this class of natural products, which did not involve condensation with lepstospermone **1.21**. During their synthetic studies toward the G inhibitors **1.34-36**, they found that the G inhibitors could stem from a

monoalkylidene derivative **1.33**, which could result from the Knoevenagel condensation of syncarpic acid **1.31** and isobutyraldehyde **1.32**.¹³





In their work, they showed that the monalkylidene **1.31** was prompt to react with dioxygen without any enzymatic catalysis to form the G inhibitors endoperoxides **1.34-36** (Scheme 1.3).

Scheme 1. 4. Crow's Studies of Monoalkylidene 1.33.



They were also able to show that the monoalkylidene **1.33** can readily undergo, 1,4 conjugate addition with another unit of syncarpic acid **1.31** or a pyrrolidine **1.40** to form dimer **1.39** (Scheme 1.3) or adduct **1.41** (Scheme 1.4).

In his review about the bioactive phloroglucinols derived from the *eucalyptus* genus, Ghisalberti proposed the same reaction sequence for the biosynthesis of the G inhibitors.¹⁴ Interestingly rhodomyrtone A and rhodomyrtosone were co-isolated with both dimer **1.39** and syncarpic acid **1.31**. One could argue that instead of being produced by an aldol reaction/reduction sequence, **1.3** may actually result from a three step sequence which first involves the reduction and dehydration of lepstospermone **1.21** to form a monoalkylidene **1.42** followed by a 1,4 conjugate addition with **1.43** to from **1.3**. Following this 1,4 conjugate addition, **1.3** may undergo a cyclization/dehydration sequence to form **1.1** or **1.2** (Scheme 1.5).

Scheme 1.5. Proposed Biosynthesis for Rhodomrytone A 1.1 and Rhodomyrtosone B 1.2.



The biosynthesis of the rhodomyrtosone A **1.5**, which has also been co-isolated with **1.39**, **1.21**, **1.31**, **1.1** and **1.2** involved the same intermediates. Mahabusarakam and coworkers proposed

that the ketal core of rhodomyrtosone A **1.5** may be derived from an oxidation of the isobutyl chain of intermediate **1.3** to form **1.44**, followed by ketal formation.²

It is interesting to note that the condensation of leptsospermone **1.21** with acylphloroglucinol **1.43** and then oxidation and ketal formation was proposed in this order. Again according to the work of Ghisalberti, Crow, and coworkers, as for the biosynthesis of **1.1** and **1.2** we can question this sequential order. Another possible order for reactions may involve the formation of monalkylidene **1.42** followed by a rapid oxidation to form endoperoxide **1.45**. This endoperoxide intermediate may undergo a dehydration and 1,4 addition with acyl-phloroglucinol **1.43** to form intermediate **1.46** which upon ketal formation may lead to **1.5** (Scheme 1.6).

Scheme 1. 6. Proposed Biosyntheses for Rhodomyrtosone A 1.5.



Biosyntheses of tomentosones **1.6** and **1.7** may follow a similar pathway. After formation of **1.1**, a second condensation with leptospermone **1.21** may occur to form **1.47**. Next,cyclization and dehydration could occur leading to dimer **1.4** which was co-isolated with **1.1** and **1.5** or upon oxidation, **1.48** may form allowing for ketal formation to occur to yield tomentosones A **1.6** and B **1.7**.



Scheme 1.7. Proposed Biosyntheses for Tomentosones A 1.6 and B 1.7.

As mentioned previously, the oxidation occurred before the condensation event and that the tomentosones A **1.6** and B **1.7** may be the results of the 1,4 addition of **1.1** with the endoperoxide **1.45** followed by ketal formation (**Scheme 1.7**). Both the aldol condensation followed by a reduction and 1,4-conjugate addition biosynthetic pathways were supported by the studies and observations of co-isolated compounds as well as the studies reported by of Crow, Bloor, Perry, and Ghisalberti. The 1,4-conjugate addition pathway constituted an appealing biomimetic synthetic strategy as it involved known reaction processes and a limited number of easily accessible intermediates.

1.2.1 Quinone Methide Pathways

Another biosynthetic pathway invoking [4+2] cycloaddition has also been proposed for compounds related to the fully cyclized tetramethyldihydroxanthene family members including rhodomyrtone A **1.1** and rhodomyrtosone B **1.2**. In his review, Ghisalberti studied the biogenetic origins of several polyhydroxylated xanthenes derived from monoterpenes or formylated, and acylated phloroglucinols. In these studies, it was proposed that euglobals **1.54** and **1.55** could stem from the reaction of phloroglucinol derivative **1.50** and the monoterpene α -phellandrene **1.53**.¹⁴ Phloroglucinol derivative **1.50** may undergo a reduction to **1.51** followed by elimination of the hydroxyl group to form *ortho*-quinone methide **1.52**. Next, [4+2] cycloaddition may occur between **1.52** and the more substituted alkene functionality of α -phellandrene **1.53** to yield euglobals **1.54** and **1.55**. The two diastereomers resulted from the *cis* or *trans* conformation of the *ortho*-quinone methide **1.52** alkene chain (**Scheme 1.8**).

This biosynthetic proposal was supported by Singh and coworkers in their synthetic work to access S-euglobals¹⁵ and robustadials.¹⁶



Scheme 1.8. Ghisalberti Biosynthesis Proposal for Euglobals 1.54 and 1.55.

In their studies, they accessed robustadials and S-euglobals using a three component reaction involving phloroglucinol derivatives **1.56-58**, aldehydes **1.59-60**, 2-carene **1.61**, myrtenol **1.62**, and β -pinene **1.63**. They proposed a mechanism involved a Knoevenagel-like condensation of phloroglucinols **1.56-58** with aldehydes **1.59-60** to form *ortho*-quinone methide intermediates (non-isolated) followed by a [4+2] cycloaddition to obtain S-euglobals **1.64-71**, and robustadials A **1.72** and B **1.73** all in 65-70 % (Scheme 1.9).

This proposal for the formation of this ring structure seemed relevant for rhodomyrtone A **1.1** and rhodomyrtosone B **1.2** which may be derived from the [4+2] cycloaddition of the syncarpic acid **1.31** enol functionality with an isovaleryl-phloroglucinol **1.43** and isovaleraldehyde **1.60**-derived *ortho*-quinone methide **1.74** or **1.76** to form intermediate **1.75** and **1.77**. Upon dehydration, these may form **1.1** and **1.2** (Scheme 1.10).

Scheme 1.9. Singh Biomimetic Synthesis of Robustadials and S-Euglobals.



Scheme 1. 10. Proposed Biosyntheses for 1.1 and 1.2 Involving an *ortho*-Quinone Methide Intermediate.



1.3 Previous Synthetic Work

Several groups have contributed to the advancement of the tetramethyldihydroxanthene synthesis field. The syntheses of myrtucommulones A, C, F and analogues, rhodomyrtone A and several endoperoxide- containing compounds are described in the section below.

1.3.2 Myrtucommulones

Jauch and coworkers published their syntheses of myrtucummulones A, C, F and analogues in 2010.¹⁷ Their synthetic strategy was biomimetic and involved two successive 1,4-addition conjugate additions with acylphloroglucinol **1.28** and monoalkylidene **1.36**. This process was enabled by addition of two equivalents of sodium hydride. The transformation provided compound **1.10** in quantitative yield (**Scheme 1.11**).

Scheme 1. 11. Jauch's Synthesis of Myrtucommulones A 1.10 and F 1.14.



The characterization of **1.10** proved to be difficult and therefore an acid-mediated cyclization was undertaken which provided a mixture of racemic **1.78** and *meso* **1.78**. The cyclization of the *para*-phenol of **1.10** was never observed under these conditions. The double 1,4-conjugate addition of acylated phloroglucinol **1.79** with two units of **1.36** provided myrtucommulone F **1.14** in quantitative yield (Scheme 1.11). The methodology was also applied to the synthesis of myrtucommulone C **1.13**. Base-mediated 1,4 conjugate addition was conducted with **1.28** and **1.36** which was followed by an acid-mediated *ortho*-cyclization to provide **1.9**, which was resubmitted to base-mediated 1,4-conjugate addition conditions to provide compound **1.13** in quantitative yield (Scheme 1.12). Analogues **1.80**, **1.81** and **1.82** were also obtained using the same base-mediated 1,4-conjugate addition although with lower yields observed for **1.82** (Scheme 1.12).

Scheme 1. 12. Jauch's Synthesis of Myrtucommulone C 1.13 and Analogues.



Although this synthetic methodology offered access to several analogues of myrtucommulone A, it remains limited and may be difficult to apply to acyl phloroglucinols bearing enolizable ketones.

Shortly after, the Jauch group proposed an enantioselective synthesis of myrtucommulone A **1.10**. Using a stoichiometric amount of the base (S,S)-**1.84**, they performed an enantioselective 1,4 addition of **1.36** with **1.28**, this first addition was followed by a second 1,4 conjugate of intermediate **1.83** with a second unit of **1.36** using the chiral base (R,R)-**1.84** to obtain (+)-myrtucommulone A **1.10** in 70 % ee (Scheme 1.13).¹⁸





Although this work represents an interesting first step toward the enantioselective synthesis of this class of natural products, it remains limited. The catalyst **1.84** has to be used in excess (3 equiv) in order to obtain both good yield and selectivity. Furthermore, the basicity of this catalytic system may be problematic for the family members possessing longer enolizable acyl

chain on the aromatic ring as it may generate two competing nucleophiles in the system. Therefore, the study of an alternative catalytic system, allowing for sub-stoichiometric loading and tolerating a broad range of acyl groups, remained of interest.

1.3.3 Rhodomyrtone A

The exact same strategy was used in 2013 by *Maier* and coworkers during their studies toward the synthesis of rhodomyrtone A **1.1** and rhodomyrtosone B **1.2**. ¹⁹ Using monoalkylidene **1.42** and isovaleryl-phloroglucinol **1.43** in the presence of sodium hydride they were able to obtain compound **1.3** in 43 % yield.

Scheme 1. 14. Maier's Synthesis of Rhodomyrtone A 1.1.



The enolizable nature of the isovaleryl carbonyl group may contribute to the low yield obtained. With **1.3** in hand they undertook a *p*-TsOH catalyzed cyclization that only yielded the *ortho*-cyclization thus, providing rhodomyrtosone B **1.2** in 69 % yield. By using an excess of *p*-TsOH they enabled a deacylation process to occur providing **1.85** in 60 % yield. Their attempt to perform an acylation of the rhodomyrtone core **1.85** was met with limited success and provided rhodomyrtone A **1.1** in a 6:1 ratio with rhodomyrtosone B **1.2** and 40 % isolated yield. Traces of diacylated compound **1.86** were also observed in this process. Rhodomyrtone A **1.1** was obtained in a three-step sequence and 10 % overall yield from **1.42** and **1.43** (Scheme **1.14**).

Although this work showcases a biomimetic synthesis of rhodomyrtone A **1.1**, the noncatalytic and low yielding processes used are non-desirable for large scale processes. Later in thesis we will describe our efforts towards the development of catalytic processes and initial studies towards enantioselective reaction development.

1.3.4 Endoperoxide-Containing Compounds

Crow and coworkers are responsible for the early work in the synthesis of G-inhibitors. They were able to synthesize three G inhibitors using a biomimetic sequence (see 1.2.1). Andre-Barres and coworkers developed their methodology based on Crow's early discoveries in order to investigate G-inhibitors and analogues with anti-malarial activity. Using syncarpic acid **1.31** and aldehydes **1.87** in the presence of piperidine **1.88**, they obtained Mannich bases **1.89** in quantitative yield. Elimination of the piperidine **1.88** in the presence of hydrochloric acid induced the formation of monoalkylidenes **1.90**. Monoalkylidenes **1.90** are believed to equilibrate with dienol intermediates **1.90a** allowing for oxygen uptake during a [4+2] cycloaddition event in benzene at room temperature. Endoperoxides **1.36** and **1.91a,b** and **1.92a,b** were formed in 60-80 % yield.



Scheme 1. 15. Andre-Barres'Synthesis of G-inhibitors and Analogues.

Interestingly, when monoalkylidene **1.90** was exposed to irradiation at 300 nm, the rate of formation for endoperoxides **1.92a** and **1.92b** was doubled. Photo-excitation may be increasing the rate of formation of dienol intermediate formation (Scheme 1.15).²⁰ G-inhibitor G₃ **1.36** was found to be one of the more promising compounds for anti-malarial properties. Alkylated analogues **1.93-1.94** were prepared using methyl iodide, ethyl iodide, and propyl iodide in the presence of potassium carbonate in dimethylformamide with good to moderate yields. Benzylated analogue **1.95** was obtained in 33 % yield by using benzyl bromide. In the case of endoperoxides **1.92a** and **b**, harsher conditions were required for the methylation. Analogue **1.96** was obtained in 72 % yield using butyl-lithium and methyl triflate in THF. Only the major *trans* diastereomer of analogue **1.96** was readily deprotected to the corresponding alcohol, which was activated using lutidine and chloromethylsulfonyl chloride. This activated alcohol was then substituted with several secondary amines to form analogues **1.97-1.100** in moderate to good yields (Scheme **1.15**). Unfortunately, methylated inhibitor G₃ **1.36** remained the best lead compound for anti-malarial activities.

In an effort to find other potentially anti-malarial analogues, Andre-Barres and coworkers synthesized α -spiro endoperoxides.²¹ Using syncarpic acid **1.31**, piperidine **1.88** and diverse β -*di*-substituted aldehydes **1.101-1.104** in ethanol, they were able to obtain Mannich bases **1.105-1.108**, which were reacted with oxygen to produce endoperoxides (not shown) in 13 %, 85 %, 87 % and 21 % respectively. Methylation of these endoperoxide intermediates provided methylated α -spiro endoperoxides **1.109-1.112** in 47 %, 79 %, 59 % and 73 % respectively (**Scheme 1.16**).



Scheme 1. 16. Synthesis of α-spiro Endoperoxide Analogues.

Compounds 1.109-1.112 were tested against malaria inducing parasites and no increase in activity was observed, methylated G_3 1.36 remained the most active lead compound.

These synthetic efforts provide invaluable insights about the formation and reactivity of endoperoxides. Accessing endoperoxides requires oxygen-mediated photo-oxidation involving dienol intermediates. Aldehyde partners can be broadly varied allowing for rapid access to analogues, and endoperoxides tolerate harsh basic conditions, which were used for alkylations.

1.4 Conclusion

The structural, isolation, and biosynthetic data reported by the aforementioned groups provided us with insights to design efficient biomimetic syntheses for this class of natural products which will be described in detail in the following chapters. In Chapter 2, we describe our studies toward the synthesis of rhodomyrtone A **1.1** and rhodomyrtosone B **1.2** and our efforts toward the development of an enantioselective 1,4 conjugate additions. In Chapter 3, we give an overview of endoperoxides chemistry and describe our synthetic work toward rhodomyrtosone A **1.5** and tomentosones A **1.6** and B **1.7**. Finally, in Chapter 3 we described our work toward the bullataketals A and B and previous related literature examples.

Chapter 2

Syntheses of Rhodomyrtone A, Rhodomyrtosone B, and Analogues

2.1 Rhodomyrtone A: Introduction

Rhodomyrtone A 2.1 and its isomer rhodomyrtosone B 2.2 are derived from the plant *Rhodomyrtus Tomentosa* found in Thailand (Figure 2.1).^{1,2} Rhodomyrtone A 2.1 and rhodomyrtosone B 2.2 present an interesting synthetic challenge due to the highly oxygenated triketone moiety and the ether linkage to an acylated phloroglucinol, which is present in both isomers. In rhodomyrtone A 2.1 this linkage is *para* to the acyl group, while in rhodomyrtosone B 2.2 it is *ortho* to the acyl group. Designing a process leading to the selective formation of either 2.1 or 2.2 is of high interest and has not been previously achieved. Additionally, rhodomyrtone A 2.1 posesses excellent biological activities which are making it a very relevant synthetic target. The synthesis of 2.1 and 2.2 and related studies are described in this chapter.

Figure 2.1. Rhodomyrtone A 2.1 and Rhodomyrtosone B 2.2.



2.1 rhodomyrtone A



2.1.1 Antibacterial Properties

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been prevalent in hospitals and at risk communities. *Staphylococcus* infections constitute a serious public health concern as infectious bacteria are constantly developing new resistance to commonly used

antibiotic classes rendering their treatments more and more challenging. Even more alarmingly, resistance is emerging for novel antibiotics such as linezolid, quinupristindalfopristin, daptomycin, telavancin, and ceftobiprole, compounds currently used or still under studies in advanced clinical trials.²² Therefore, the need for identifying and synthesizing new antibacterial agents is growing. Meeting this need will allow us to enrich the dangerously dwindling antibiotic inventory. In addition to possessing a synthetically challenging structure, rhodomyrtone A 2.1 was found to be a very potent antibiotic against gram positive bacteria including Staphylococcus Aureus, methicillin-resistant Staphylococcus Aureus (MRSA), and several Streptococcus strains (MIC = 0.39-0.78 μ g/mL).²³ Moreover, it was shown that treating bacterial cell lines with rhodomyrtone A 2.1 limited the emergence of resistance. Treatment of *Staphylococcus Aureus* and methicillinresistant Staphylococcus Aureus strains with incremental concentrations of rhodomyrtone followed by growth on rhodomyrtone-free medium led the MIC and MBC values of the compound to revert to the initial MIC and MBC values, which were observed during the first exposure to the compound. This result is very promising, as many other agents have shown to develop resistance in similar studies.²⁴ Upon exposure to rhodomyrtone A 2.1, both the replication rate and membrane biosynthesis could be inhibited eventually leading to cell death. Initial biological studies have thus far implicated that rhodomyrtone A 2.1 may interfere with the WalK/WalR (YycG/YycF) two-component system, which is involved in membrane biosynthesis.²⁵ Although the development of resistance in vivo remains unpredictable and can only be determined after clinical studies, rhodomytone A 2.1 seems to be a very strong candidate for development as an antibiotic agent.

2.1.2 Proposed Retrosynthesic Analysis

In our retrosynthetic analysis, we envisioned that **2.1** and **2.2** could be generated from acyclic precursor **2.3** using selective dehydrative cyclizations (Figure 2. 2). Intermediate **2.3** may arise from conjugate addition of acyl phloroglucinol **2.4** 26 to monoalkylidene **2.5**.

Figure 2. 2. Retrosynthetic Analysis.



Route achievement would offer a highly efficient synthesis of this class of natural products and targeted analogues.

2.2 Attempted Synthetic Routes

In the published synthesis of the related myrtucummulone A (for details see Chapter 1),²⁵ basic conditions were used to achieve conjugate addition. Therefore, our initial studies involving reaction of intermediates **2.4** and **2.5** focused on implementing phase transfer catalysis using bases as stoichiometric reagents.

2.2.1 Phase Transfer Catalysis: Background

The field of phase-transfer catalysis was developed by Starks in the early 1970s where he

introduced the term.²⁷ This term was meant to describe the role played by *tetra*-alkylammonium or phosphonium salts in reactions involving two substances located in two immiscible phases. The rates of such reactions in the presence of phase-transfer catalyst were shown to be tremendously increased, likely due to an increased solubility of the two reaction partners that can then react at the interface of the two immiscible solvents. Along with Starks, Makosza and Brändström contributed to the advancement of the field in the mid to late 1960s.²⁸ Since its early development, the field has seen tremendous progresses leading to the development of new catalysts, an increasing scope of substrates, as well the development of asymmetric variants for many reaction classes.²⁹ In particular, phase–transfer catalysis has been employed with a wide array of substrates undergoing 1,4 conjugate addition. Initial studies from the Tocke group³⁰ and Shishido group ³¹ focused on using methyl vinyl ketone and methyl acrylate as simple electrophiles. A particularly interesting example from the Shishido group was featured in the synthesis of (+)-triptoquinone A where methyl vinyl ketone **2.6** was reacted with intermediate **2.7** in the presence of catalyst **2.8** and [18]-crown-6 to provide the fully cyclized compound **2.9**, which eventually led to (+)-triptoquinone **2.11** (Scheme 2.1).

Scheme 2. 1. Shishido's Synthesis of (+)-Triptoquinone A.



Other electrophiles, such as chalcones, were also studied extensively by Loupa,³² Maruoka (complex tetra-substituted phase transfer catalyst, Scheme 2. 2),³³ and Corey (cinchona-alkaloid derived phase transfer catalyst, (Scheme 2. 3).³⁴

Scheme 2. 2. Maruoka's Catalytic System for 1,4-Conjugate Addition of Malonates with Chalcones.



Scheme 2. 3. Corey's Catalytic System for the Michael Addition of Aromatic Ketone with Chalcones.



More interestingly, our lab developed a very efficient dearomatization alkylation sequence mediated by a dimeric phase transfer catalyst to access hyperibone-K. This work is particularly relevant for our proposed synthesis because it also involves a phloroglucinol derived nucleohile. I In her work Dr. Qi subjected the diprenylated acylphloroglucinol **2.22** and **2.23** to basic conditions in the presence of cinchonidine derived dimeric catalyst **2.24**. She was able to obtain compound **2.25** in a 70 % yield and 90 % ee. Intermediate **2.25** was further reacted to afford hyperibone K (Scheme 2. 4).³⁵

Mechanistic studies have been shone some light on the operative mechanism in this process that likely involved successive dearomatizations of diprenylated acyl phloroglucinol **2.22**, which reacted as an enolate equivalent during the alkylation event (Scheme 2. 4).





Encouraged by these results obtained in our lab, we decided to initiate preliminary studies involving the use of phase transfer catalyst for the 1,4 conjugate addition we envisioned in our retrosynthetic analysis.

2.2.2 Phase Transfer Catalysis: Initial Studies

Our studies began by evaluating achiral phase transfer catalysts for 1,4 conjugate addition of **2.5** with **2.4** (Scheme 2. 5). Phloroglucinols have shown the propensity to readily dearomatize under basic conditions thus becoming more nucleophilic and able to facilitate C-C bond formation.^{35, 36} The phase-transfer catalyst benzyl *tri*-methyl ammonium bromide was used in the presence of potassium hydroxide in toluene at low temperature.

Scheme 2. 5. Phase Transfer-Mediated 1,4-Conjugate Addition and Cyclization Sequence.



Due the to extreme complexity of the reaction mixture resulting from the conjugate addition reaction, we conducted the subsequent cyclization reaction on the crude mixture. Submitting the crude mixture to acidic conditions involving excess trifluoroacetic acid in dichloromethane at room temperature provided 34 % of rhodomyrtosone B **2.2** over two steps (Scheme 2. 5). Using basic conditions with sodium hydroxide in methanol, less than 20 % of rhodomyrtone A **2.1** was obtained, but this reaction was not easily reproduced. The conjugate addition catalyzed under basic conditions may be low yielding due to the presence of an enolizable ketone in the substrate, which may compete with the deprotonation of the phenol leading to undesired byproducts and

decomposition. This reaction sequence was very difficult to reproduce and low yielding. To overcome this issue, we turned our attention to Lewis-acid catalyzed 1,4 conjugate addition involving related substrates.

2.3 Development of a Nickel-Mediated 1,4 Conjugate Addition

2.3.1 Literature precedent

Lewis-acids catalysis of 1,4 conjugate and Michael additions is well described in the literature. Specifically, rare-earth triflates have been extensively studied as reported in an excellent review by the Kobayashi group.³⁷ Additionally, transition metal and lanthanides have also been used.³⁸

2.3.1.a Electrophile Activation

The Fillion group investigated 1,4 conjugate addition of allyl metal **2.29** with Meldrum's acid derived monoalkylidene **2.28** using scandium triflate as the catalyst to obtain **2.30** in good yield (Scheme 2. 6).³⁹ In related studies, the investigators were able to utilize a phenol derived nucleophiles **2.31**, which underwent 1,4 conjugate addition followed by cyclization to efficiently access coumarin derivatives **2.33-2.36** (Scheme 2.7).⁴⁰

Scheme 2. 6. Allylation of Meldrum Acid Derived Alkylidenes.



Scheme 2. 7. Fillion's Coumarin Synthesis.



Perchlorate salts have also been used to mediate related 1,4 conjugate additions. For example, magnesium (II) perchlorate and nickel perchlorate Lewis-acid have been described and employed to develop an enantioselective conjugate addition as reported in the excellent mini-review by Melchiore and coworkers.⁴¹

Kanemasa and coworkers developed a nickel(II) perchlorate salt catalyst in the development of the addition of dimedone **2.37** with a crotonyl oxazolidinone **2.38** to obtain enol lactone **2.39** (Scheme 2. 8).⁴² Optimal yields were obtained by using the nickel perchlorate hexahydrate complex in the presence of catalytic TMP to enable the formation of the reactive enolate species.

Scheme 2.8. Kanemasa's Synthesis of Enol Lactones.



Both Kanemasa and Melchiore reported that the perchlorate metal salts had a very strong chelating power allowing for efficient activation of both the electrophile and nucleophile in the reaction (*eg.* **2.40** see Scheme 2. 8).

2.3.1.a Nucleophile Activation

In their work Moreno-Mañas and coworkers were able to efficiently alkylate cyclic β -keto ester **2.41** by using salicylaldehyde copper complex **2.43** as a catalyst. Several electrophiles **2.42** were tolerated in this reaction and **2.44-2.47** were obtained in excellent to moderate yields (Scheme 2. 9). Extensive mechanistic were undertaken by the investigators who proposed that the copper complex may activate the nucleophile by generating the reactive complex enolate **2.48**, which then promptly underwent reaction with the electrophile (Scheme 2. 9).⁴³





In their studies, Christoffers and coworkers were able to react several cyclic β -keto esters **2.49** with methyl vinyl ketone **2.50** to obtain alkylated products **2.52-2.54** in moderate yields and moderate ee's (Scheme 2. 10).⁴⁴ They used chiral Nickel diamine complex **2.51** to mediate this reaction. They proposed that the nucleophile may be activate and may form the nickel enolate

complex **2.55**, which after coordinating to the methyl vinyl ketone **2.50** may undergo alkylation (Scheme 2. 10).

Inspired by these interesting studies, we selected a diverse range of Lewis-acids including rare earth-triflates, transition metals, and perchlorate salts in order to evaluate their reactivity in the conjugate addition of acylated phloroglucinol **2.5** with monoalkylidene **2.4**.

Scheme 2. 10. Christoffers's Studies.



(R)-2.52 37 %, 91 % ee (R)-2.53 89 %, 21 % ee (R)-2.54 79 %, 41 % ee

2.3.2 Initial Catalyst Screen

A screen was conducted using stoichiometric amounts of Lewis-acids. Both polar aprotic solvents such as dichloromethane and carbocation stabilizing, polar protic solvent like *hexa*-fluoro-isopropanol (HFIP) were investigated.

Control experiments without catalyst gave 2.3 in 18 % in dichloromethane and 2.3 in 14 % yield in HFIP (Table 2.1, entry1). Several Lewis-acids with chloride as the counterion were also investigated (Table 2.1, entries 2-6). These Lewis acids yielded complex mixtures of products and very low yields of 2.3. Bivalent Lewis-acids with triflate as the counter-ion provided limited amounts of 2.3 and very complex reaction mixtures as well (Table 2.1, entries 7-8). Finally, rare-

earth triflates were screened (**Table 2.1**, entries 9-12). Among these rare-earth triflates, ytterbium triflate afforded **2.3** in the highest yield of 45 %. Using dichloromethane provided less complex reaction mixtures and was selected for further reaction screening under sub-stoichiometric conditions.

Table 2. 1. Stoichiometric Screen of Lewis-acids.


2.3.3 Sub-Stoichiometric Catalyst Screen

Dichloromethane was subsequently selected as the solvent for a sub-stoichiometric catalyst screen of select Lewis-acids. Some Lewis-acids were not successful in the stoichiometric screen, which may have been due to chelation of the final product with the Lewis-acid and subsequent low recovery of the desired product. Therefore, the low yielding Lewis-acids that provided cleaner reactions were screened again under sub-stoichiometric conditions with the intent to minimize chelation. A control experiment without catalyst provided a 9 % of adduct 2.3 and a significant amount of endoperoxide byproduct 2.36 (Table 2.2 entry 1). This byproduct may be derived from [4+2] cycloaddition between the dienol tautomer of 2.4 and triplet oxygen (Table 2.2, entry 1). ^{13b, 20, 45} This reaction process will be discussed in detail in Chapter 4.

| Ta | ble | 2. | 2. I | Eval | luation | of | Lewis | -Acid | s und | er S | Sub | - S 1 | toic | hior | netric | C | Condi | tions |
|----|-----|----|------|------|---------|----|-------|-------|-------|------|-----|--------------|------|------|--------|---|-------|-------|
|----|-----|----|------|------|---------|----|-------|-------|-------|------|-----|--------------|------|------|--------|---|-------|-------|

| + 0 H0 | OH O CH_2Cl_2 CH_2Cl_2 OH rt to 40°C, 12 h O 2.5 | онно 2.3 | + + 2.36 |
|-----------|--|-------------|----------------|
| Entry | Lewis-acid | 2.3:2.56° | $2.3^{b}(\%)$ |
| 1 | No Catalyst | 1:2.7 | 9 |
| 2 | YbCl ₃ | 1.15 : 1 | 38 |
| 3 | FeCl ₃ | 1.3 : 1 | 36 |
| 4 | Yb(OTf) ₃ | 1:3.3 | 16 |
| 5 | Gd(OTf) ₃ | 1:2.4 | 29 |
| 6 | Lu(OTf) ₃ | 1:1.7 | 17 |

| 7 | $\operatorname{Cu}(\operatorname{ClO}_4)_2$ | 1:4.3 | 6 |
|------------------------|---|-------|----|
| 8 | Mg(ClO ₄) ₂ | N/A | 0 |
| 9 | Zn(ClO ₄) ₂ | N/A | 0 |
| 10 | $Ni(ClO_4)_2 \bullet 6H_2O$ | 4.6:1 | 74 |
| 11 | Ni(ClO ₄) _{2•} 6H ₂ O (7 mol%) CH ₂ Cl ₂ :AcOH (5:1) | 2.8:1 | 80 |
| 12 ^{<i>d</i>} | Ni(ClO ₄) ₂ •6H ₂ O (7 mol%) CH ₂ Cl ₂ :AcOH (5:1) | 1:0 | 90 |

^{*a*}Reactions conducted with monoalkylidene **2.4** (10 mg, 0.04 mmol, 1 equiv) and acylphloroglucinol **2.5** (5 mg, 0.04 mmol, 1 equiv) in 1 mL of CH_2Cl_2 with Lewis acid catalyst (0.004 mmol, 0.1 equiv). ^{*b*}Yields reported after isolation by silica gel column chromatography. ^{*c*} Compound **2.56** is the only byproduct observed after complete consumption of starting materials.^{*d*} Solvents thoroughly degassed using the freeze-pump-thaw method.

In the presence of YbCl₃ or FeCl₃, a moderate amount of **2.3** was isolated albeit in low selectivity (**Table 2.2**, entries 2 and 3). Rare-earth triflates were also investigated; however, these reactions resulted in low yields and low selectivity (**Table 2.2**, entries 4-6).⁴⁶ We also investigated metal perchlorate catalysts, which had previously been used for 1,4 conjugate addition.⁴⁷ Cu(ClO₄)₂, Mg(ClO₄)₂, and Zn(ClO₄)₂ did not result in significant amounts of adduct **2.3** (**Table 2.2**, entries 7-9). Ni(ClO₄)₂ proved to be a more effective catalyst, affording a 2.8:1 ratio of **2.3:2.56** in 74 % isolated yield (**Table 2.2**, entry 10). Using a solvent mixture of CH₂Cl₂ and acetic acid⁴⁸ in a 5:1 ratio led to an increase yield and selectivity (**Table 2.2**, entry 11). Likewise, thorough degassing of solvent eliminated endoperoxide byproduct formation (**Table 2.2**, entry 12) and provided **2.3** in 90 % yield. A control screen using the same catalysts with

degassed dichloromethane was conducted and the results are shown in **Table 2.3**. Although, using degassed dichloromethane alleviated the formation of byproduct **2.56**, yields remained low (**Table 2.3**, entries 2, 6-8) except when nickel perchlorate hexahydrate was used for this transformation.

Additionally, it was found that Pd(II) catalyst was not efficient for this reaction (**Table 2.3**, entry 10) and that the reaction solvent alone was enabling the reaction to occur in 30 % yield (**Table 2.3**, entry 11). Based on these results, nickel perchlorate hexahydrate was identified as the best catalyst for this reaction.

Table 2. 3. Control Screen.

| о + 0 но 2.4 | $\begin{array}{c c} OH & O \\ H & O \\ H & H \\ OH \\ OH \\ \end{array}$ $\begin{array}{c} L. A.(0.1 equiv) \\ CH_2Cl_2 \\ H \\ OH \\ Tt to 40^{\circ}C, 12 h \\ O \\ \end{array}$ | онно 2.3 |
|-----------------------|--|---------------|
| Entry | Lewis-acid | $2.3^{b}(\%)$ |
| | | |
| 1 | CH ₂ Cl ₂ :AcOH (10:1) | 30 |
| 2 | YbCl ₃ | 43 |
| 3 | FeCl ₃ | 20 |
| 4 | Yb(OTf) ₃ | 0 |
| 5 | Gd(OTf) ₃ | 0 |
| 6 | Lu(OTf) ₃ | 5 |
| 7 | $Cu(ClO_{4_{2}})$ | 30 |

| 8 | Mg(ClO ₄) ₂ | 16 |
|----|---------------------------------------|----|
| 9 | $Zn(ClO_4)_2$ | 30 |
| 10 | PdCl ₂ (PhCN) ₂ | 19 |
| 11 | $Ni(ClO_4)_2 \bullet 6H_2O$ | 74 |

Reactions conducted with monoalkylidene **2.4** (10 mg, 0.04 mmol, 1 equiv) and acylphloroglucinol **2.5** (5 mg, 0.04 mmol, 1 equiv) in 1 mL of CH_2Cl_2 with Lewis acid catalyst (0.004 mmol, 0.1 equiv). ^{*b*}Yields reported after isolation by silica gel column chromatography.

2.3.4 Reaction Scope

The scope of the conjugate addition using alternative acyl-phloroglucinol substrates was investigated (Scheme 2. 11).

Scheme 2. 11. Reaction Scope.



Compounds 2.57⁴⁹ and 2.58²⁷ were prepared and submitted to the conjugate addition reaction conditions. We found that addition of acetic acid in the conjugate additions with substrates 2.57, and 2.58 was detrimental. Using dichloromethane as solvent, we found that a formyl group 2.57

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or a second acyl group **2.58** was well tolerated and provided the 1,4 adduct **2.59** and **2.60** in 70 % and 84 % yield respectively.

2.3.5 Further Analysis of 1,4 Adduct 2.3 and Preliminary Mechanistic Studies

2.3.5. a NMR studies

The structure of adduct **2.3** was determined unambiguously by X-ray crystallography (Figure 2. 3). The X-ray structure shows hydrogen bonds between the enol/phenols and carbonyl moieties.

Figure 2. 3. X-ray Crystal Structure of 2.3.



In solution, **2.3** was found to exist as a mixture of two atropisomers in a 2.4:1 ratio at room temperature by ¹H NMR in CDCl₃. The tight hydrogen bond network existing within the structure may hinder free rotation along the C_9-C_{8a} axis generating two rotational conformers in equilibrium at room temperature. Variable temperature NMR studies were performed to determine the coalescence temperature.

Variable temperature NMR studies were performed with the same sample of **2.3** in CDCl₃ and the temperature was varied from 10 °C to 60 °C. The coalescence temperature was found to be 60 °C. The initial Δv was determined to be 142.58 Hz at 10 °C. With Δv = 142.58 Hz and T °C

= 60 °C using the Rich Shoemaker method⁵⁰ (Figure 2. 4), the rotational energy was determined to be 15 kcal/mol.

Figure 2.4. Equation Used for Rotational Energy Calculation.

 $\Delta G \ddagger aT \left[9.972 + log\left(\frac{Tc}{\Delta v}\right)\right]$ where a = 4.575 x 10⁻³ kcal/mol where a = 1.914 x 10⁻³ kJ/mol at coalescence temperature $kc = \pi \Delta v / \sqrt{2}$

The ratio observed at room temperature corresponds to a difference of 0.6 kcal.mol⁻¹ in energy for the two atropisomers. Spectra showing coalescence can be found in **Chapter 2**, Section 2.8. Unfortunately, NMR studies did not allow us to assign which isomer was the major one.

2.3.5. b Computational Studies

Computational studies³⁴ were performed in order to determine which one of the **2.3** rotamers was energetically favored at room temperature. Using a conformer search using Spartan 2012 MMFF, the two ground state conformers were identified for both rotamers. DFT minimization using B3LYP/3G* were perfomerd on each of the rotamers. **2.3** B was found to be favored by 2.89 kcal.mol⁻¹ suggesting that it may be the major rotamer at room temperature.

However, it should be noted that the computational studies were undertaken in vacuum and this hypothesis may not be accurate in solvents (**Figure 2.5**).



Figure 2. 5. Computational Studies for 2.3 Rotamers.

2.3.5.c Mechanistic Studies

We undertook mechanistic studies by studying the 1,4 conjugate addition of **2.4** with **2.5** catalyzed by nickel perchlorate in a dichloromethane and acetic acid mixture (Scheme 2. 12). Two sets of experiments were conducted.

First, two equivalents of isovaleryl phloroglucinol **2.5** were mixed in dichloromethane with nickel perchlorate hexahydrate. The reaction was followed by direct mass injection. Samples were obtained every hours for three hours and studied by direct mass injection. After one hour, three main peaks appeared in the mass spectrum accounting for [2.5+H], $[Ni(ClO_4)_2+3H_20+H]$ and [Ni+2(2.5)+H]. Additionally, a final sample was submitted for more detailed analysis by direct injection and a peak accounting for $[Ni+ 2ClO_4+ 2(2.5)]$ was observed. Similar masses were observed after two and three hours. These results suggested that a complex of nickel 2.61 (see Scheme 2.12) and two equivalents of 2.5 may initially formed in the reaction and may be a

reactive intermediate in the catalytic process. This observation is in agreement with the observation made by Moreno-Mañas and Christoffers with salicylaldehyde Ni(II) catalysts.^{43,44}

To verify this hypothesis, one equivalent of monoalkylidene **2.4** was then added to the reaction. After three hours, a sample was taken and direct mass injection data were obtained. The mass accounting for [Ni+ ClO_4 +**2.4**+**2.5**+5H₂O] was observed suggesting that a ligand exchange may occur during the course of the reaction and may allow **2.4** and **2.5** to come in close proximity around the nickel center which possesses six coordination sites. The reaction mixture was then heated and stirred at 40 °C overnight and provided 37 % of the expected product **2.3** providing further evidence that both complexes may be involved in catalytic process.

In order to understand this process better another experiment was performed. A reaction was run using the optimized reaction conditions and was followed by direct mass injection every hour for six hours. The main peaks observed during this process accounted for [Ni+2(2.5)+H] and $[Ni+2ClO_4+2(2.5)+2H_2O]$. Then the formation of peaks accounting for [Ni+2.4+2.5] and $[Ni+2.4+2.5+2AcOH+2H_2O+Na^+]$ and a peak accounting for the product [2.3+H] were observed.

These results supported our initial hypothesis and led us to propose a mechanism where initially, two equivalents of **2.5** may coordinate to the nickel center to form active complex **2.61**. A ligand exchange may follow and two perchlorate counter ions may be released in the reaction mixture. Both [Ni+2(2.5)+H] and $[Ni+2ClO_4+2(2.5)+2H_2O]$ were observed and it was unclear if the lower mass [Ni + 2(2.5)+H] observed was due to ionization during the direct mass injection or if it was due to lignad exchange. Despite analyzing the reaction at different time points, evidence supporting a ligand exchange were not convincing enough to rule out the ionization hypothesis. After formation of **2.61**, we proposed that **2.4** may come in close proximity to the nickel center and take advantage of empty coordination sites to coordinate to the nickel center and form **2.63** and eventually bind to nickel by displacing a unit of **2.5** and form **2.64**. With **2.4** and **2.5** in close

proximity, 1,4-conjugate may occur to provide product **2.3**. After release of **2.3** in the reaction medium, the nickel(II) catalyst may re-enter the catalytic cycle.

Scheme 2. 12. Proposed Mechanism for the nickel-mediated 1,4-conjugate addition.



2.4 Dehydrative Cyclization Studies

With information about the rotameric character of **2.3**, conditions to achieve selective dehydrative cyclization were investigated.

2.4.1 Acid-mediated Dehydrative Cyclization

Under acidic conditions, we observed formation of rhodomyrtosone B **2.2** exclusively *via* dehydrative cyclization (Table 2.4).

| Entry | Solvent | Reagent | Yield (%) | Temperature (°C) |
|-------|------------|----------------|---------------|------------------|
| 1 | Benzene | <i>p</i> -TsOH | Decomposition | 80 |
| 2 | CH_2Cl_2 | TFA excess | 30 | 80 |
| 3 | MeOH | TFA (1 equiv) | 20 | 80 |
| 4 | HFIP | TFA (1 equiv) | 60 | 80 |
| 5 | HFIP | TFA (3 equiv) | 60 | 80 |

Table 2. 4. Cyclization of Adduct 2.3 under Acidic Conditions.

After optimization, it was found that using the carbocation-stabilizing protic solvent hexafluoroisopropanol (HFIP)⁵¹ with one equivalent of trifluoroacetic acid (80 °C, 6 h) afforded rhodomyrtosone B **2.2** in 60 % yield (Scheme 2. 13).

Scheme 2. 13. Synthesis of Rhodomyrtosone B 2.2.



Despite our best efforts, we were unable to develop conditions leading to selective dehydrative cyclization providing rhodomyrtone A **2.1** in a high yielding and reproducible fashion from **2.3** using either basic or acidic conditions (**Table 2.5**).

| | о он но | OH O OH Conditions | |
|-------|---------|----------------------------------|---------------|
| | 2.3 | 2.1 | |
| Entry | Solvent | Reagent | Results |
| | | | |
| 1 | MeOH | NaOH (1 equiv) | No Conversion |
| 2 | _ | NaOH (3 equiv) | Decomposition |
| 3 | _ | $ZnCl_2(1 \text{ equiv}), \mu w$ | 20 % |
| 4 | HFIP | DIEA | Decomposition |
| 5 | _ | NaOH (0.5 equiv) | No Conversion |
| 6 | _ | NaOH (1 equiv) | 30 % |
| 7 | _ | NaOH (2 equiv) | Decomposition |
| 8 | _ | LiOH (1 equiv) | No Conversion |
| 9 | _ | LiOH (1 equiv) | No Conversion |
| 10 | _ | $ZnCl_2(1 equiv)$ | Decomposition |
| 11 | _ | $La(O-iPr)_3(0.3 \text{ equiv})$ | No Conversion |
| 12 | _ | Li(HFIP) (1 equiv) | No Conversion |
| 13 | _ | $Zn(HFIP)_2(1 \text{ equiv})$ | No Conversion |
| 14 | _ | Ba(HFIP) ₂ (1 equiv) | No Conversion |
| 15 | _ | Ca(HFIP) ₂ (1 equiv) | No Conversion |
| 16 | _ | Na(HFIP) (1 equiv) | No Conversion |
| 17 | MeCN | NaH (1 equiv) | Decomposition |

 Table 2. 5. Attempted Reactions for the Synthesis of Rhodomyrtone A 2.1.

| 18 | - | Li(HFIP) (1 equiv) | No Conversion |
|----|-----|---------------------------------|---------------|
| 19 | - | $Zn(HFIP)_2(1 \text{ equiv})$ | 10 % |
| 20 | _ | $Ba(HFIP)_2(1 equiv)$ | 10 % |
| 21 | _ | Ca(HFIP) ₂ (1 equiv) | No Conversion |
| 22 | _ | Na(HFIP) (1 equiv) | No Conversion |
| 23 | THF | NaH (1 equiv) | Decomposition |
| 24 | _ | NaH (3 equiv) | Decomposition |
| 25 | _ | $La(O-iPr)_3(0.3 equiv)$ | No Conversion |
| | | | |

Basic conditions in polar protic or polar non-protic solvents (Table 2.5 entries 1, 2, 4-9, 17, 23-24) provided decomposition or no conversion except when using sodium hydroxide in hexafluoroisoporpanol, leading to a 30 % yield of rhodomyrtone A 2.1 (Table 2.5 entry 6). However this result was not reproducible. Similarly, using zinc chloride as a Lewis-acid in the microwave provided 20 % of rhodomyrtone A 2.1. Unfortunately, these results could not be reproduced after numerous attempts. Lewis-acids with basic counter-ions were also screened (Table 2.5 entries 11 and 25) without success. HFIP salts (e.g. Li(HFIP), Na(HFIP), Ba(HFIP)2, Ca(HFIP)2, Zn(HFIP)2) were also studied, which were prepared using reported procedures.52 The use of fluorinated alkoxides as mild base has been previously reported.53 HFIP has a pKa of 9. The pKa of para-phenols with regards to the acyl substituent in acylated phloroglucinol compounds such as 2.65 and 2.66 are of 8. For ortho-phenols with regards to the acyl substituent in acylated phloroglucinol compounds such as 2.65 and 2.66 the pKa are of 10-11 (**Figure 2.6**)³⁵

Figure 2. 6. pKa's of Acylated Phloroglucinols.



We envisioned that the HFIP salts may enable a selective deprotonation of the *para*-phenol as their pKa's are likely situated between the *para* and *ortho* phenols pKa values. Thus, it may lead to the selective cyclization of the *para*-phenol. Additionally, the metal counter-ion may offer another regioselectivity handle as it may chelate to the acyl ketone and the *ortho*-phenol preventing the cyclization of the *ortho*-phenol. Using HFIP salts may therefore produce rhodomyrtone A **2.1** selectively.

We tested our hypothesis by using one equivalent of HFIP salts in HFIP or acetonitrile for the dehydrative cyclization (**Table 2.5**. entries 12-16 and 18-22). Unfortunately, our efforts were met with limited success. The competitive deprotonation between the *para*-phenol and the enol hydroxide on the triketone moiety may explain the very low yields observed in this process.

In order to understand the absence of selectivity for the cyclization process, additional computational studies and a mechanistic proposal were investigated.

2.4.2 Proposed Mechanism and Selectivity Rationale

Our proposed mechanism for the selective dehydrative cyclization leading to rhodomyrtosone B 2.2 is shown in Scheme 2.14. Protonation of vinylogous acid 2.3 leads to oxonium intermediate 2.67 which may exist in equilibrium with its atropisomer 2.68. Cyclization of 2.68 to hemiacetal 2.69 followed by dehydration affords rhodomyrtosone B 2.2. Hemiacetal 2.69 is likely a relevant intermediate in the proposed mechanism as this structural motif exists in closely related structures including myrtucommulone D 2.70 (Scheme 2.14).^{3,8,54}





We believe that the hydrogen bond formed between the *ortho*-phenol (C_8) and the $C_{1^{\circ}}$ ketone contributes to render the *ortho*-phenol more nucleophilic by increasing the electron density of the phenolic oxygen.⁵⁵

Additionally, computational studies involving a conformational search and energy minimization of intermediates 2.67/2.68 showed that 2.68 was the ground state protonated atropisomer, which should favor 1,2 addition/cyclization to afford 2.69 producing rhodomyrtosone B 2.2.³³ Intermediate 2.67 leading to 2.1 was found to be less stable by 5.8 kcal.mol⁻¹, rendering this corresponding 1,2 addition less likely to occur (Figure 2.7).

Figure 2.7. Computational Studies of Protonated Compounds 2.67 and 2.68.



Compound **2.67** rel. energy: $+ 5.8 \text{ kcal/mol}^{-1}$ Compound **2.68** rel.energy= 0 kcal.mol⁻¹

2.5 Synthesis of Rhodomyrtone A

In order to overcome the regioselectivity problem, several strategies were envisioned: the conversion of rhodomyrtosone B **2.2** to rhodomyrtone A **2.1** using a base-mediated retro-1,4 conjugate addition; the selective deacylation of a diacylated cyclized intermediate; and the use of a formyl derivative to fine tune the regioselectivity in the dehydrative cyclization.

2.5.1 Conversion of Rhodomyrtosone B to Rhodomyrtone A

In Kozlowski and coworkers' synthetic work toward (*R*)-nigerone 2.72, intermediate 2.71 was subjected to a catalytic amount of sodium hydroxide in order to promote a retro-conjugate addition affording (*R*)-nigerone 2.72 in good yields (Scheme 2.15).⁵⁶ This process was successfully achieved because the final product was more thermodynamically stable by 1.2 kcal.mol⁻¹. Thiophenol has also been used previously to trigger retro-addition/addition processes.⁵⁷

Scheme 2. 15. Kozlowski's studies toward (*R*)-nigerone.



Computational studies were performed to determine if such a process would be thermodynamically favored in the case of rhodomyrtone A **2.1** and rhodomyrtosone B **2.2**. A conformer search followed by a DFT minimization for each natural product was conducted. It

showed that rhodomyrtone A **2.1** was found to be more stable than rhodomyrtosone B **2.2** by 14 kcal.mol⁻¹ which encouraged us to pursue our hypothesis (Figure 2. 8).

Figure 2. 8. Minimized Structure for Rhodomyrtone A 2.1 and Rhodomyrtosone B 2.2.



Our studies began with using stoichiometric amount of sodium hydroxide and thiophenol in MeOH in order to trigger a retro-1,4 conjugate addition. Unfortunately, these processes did not yield rhodomyrtone A **2.1** and raising the reaction temperature decomposed the starting material. Using catalytic amount of sodium hydroxide was also unsuccessful, leading to no conversion and recovery of the starting material rhodomytosone B **2.2** (Scheme **2.16**). We elected to pursue an alternative strategy.

Scheme 2. 16. Studies toward the Conversion of Rhodomyrtosone B to Rhodomyrtone A.



2.5.2 Dehydrative Cyclization and Deacylation

During the previously described 1,4 conjugate studies and scope development we were able to obtain compounds **2.58** (see 2.3.4) in 84 % yield. Dehydrative cyclization for compound **2.58** was achieved using *para*-toluene sulfonic acid in benzene in the presence of a Dean-Stark apparatus and yielded 70 % of fully dehydrated compound **2.73** (Scheme 2.17).

Scheme 2. 17. Dehydrative Cyclization of 2.41.







| Entry | Acid or Lewis Acid | Yield of 2.74 | Yield of 2.1 |
|-------|--|---------------|--------------|
| 1 | CF_3SO_2H/H_2O (3 equiv) | 80 % | - |
| 2 | CF ₃ SO ₂ H/H ₂ O (1 equiv) | 80 % | _ |
| 3 | CF ₃ SO ₂ H 20mol% | N.R. | - |
| 4 | $NHTf_2$ (1 equiv) | 60 % | _ |
| 5 | NHTf ₂ 20 mol% | N.R. | _ |
| | | | |

Deacylation studies were undertaken using strong acids to generate rhodomyrtone A 2.1. Surprisingly, in all cases double deacylation was observed, and the core 2.74 was obtained (Table **2.6**). Attempts to lower the reaction temperature led to no reactions. Due to no observed selective deacylation, an alternative strategy involving electronic modifications of compound **2.3** was next explored.

2.5.3 Studies of Formyl derivative 2.57

The formyl derivative **2.57** was obtained in 74 % yield during studies of the scope for the 1,4 conjugate addition (see section 2.3.4).

2.5.3.a Selectivity Rationale

With intermediate **2.57** in hand, we investigated the development of a regioselective dehydrative cyclization. Introducing a formyl group was intended to modify both the hydrogen bond network within the structure and change the electronics of the aromatic moiety thus potentially allowing the desired *para* selective dehydrative cyclization to occur. An X-ray of **2.57** was obtained and also showed showcase tight hydrogen bond network within the structure (**Scheme 2.18**). We screened acidic conditions and found that treatment of **2.40** with excess trifluoroacetic acid provided a 1:1 mixture of the two regioisomers **2.75** and **2.76** in 75 % yield (**Scheme 2.18**).

The hydrogen bond formed between the *para* phenol and the formyl group may shift the electron density to the oxygen non bonding orbital and thus render the *para* phenol more nucleophilic.³⁶ This may explain the formation of both dehydrative cyclization products **2.75** and **2.76** in this process.



Scheme 2. 18. Dehydrative Cyclization of Formyl Derivative 2.57.

2.5.3.b Decarbonylation

Decarbonylation of aromatic compounds have been previously studied and in some example phenols and other functional groups are tolerated. In their studies Maiti and coworkers were able to develop and efficient methodology using palladium diacetate as the catalyst. Their initial conditions required high temperature, and they later came up with a methodology using the same catalyst and microwaves to shorten the reaction time. Rapid access to substrates **2.77-2.81** was obtained by using this methodology (**Scheme 2.19**).⁵⁸

Tsuji and coworkers focused on developing a methodology using $[Ir(cod)Cl]_2$ as a catalyst, which allowed access to substrates **2.83-2.84**. These conditions also required vigorous heating in dioxane (**Scheme 2.20**). Additionally, Wilkinson's catalyst has been successfully used for aromatic decarbonylation in the Kozlowski group's synthesis of (*S*)-bisoranjidiol **2.87**, although no phenol groups were present in that case.⁵⁹



Scheme 2. 19. Maiti's Studies for Aromatic Aldehydes Decarbonylation.

Compound **2.85** was submitted to a reduction, oxidation, and decarbonylation sequence to yield **2.86** in 63% and lead eventually to (*S*)-bisoranjidiol **2.85** (Scheme 2.21).

Scheme 2. 20. Tsuji's Methodology for Decarbonylation of Aromatic Aldehydes.



Several catalysts were studied for the decarbonylation of 2.75 and 2.76. The mixture of 2.75 and 2.76 was easily separated using a C^{18} column and preparative HPLC. Initial studies using 2.75 with Pd(OAc)₂ as the catalyst and potassium carbonate as the base provided a 30% yield of rhodomyrtone A 2.1 (Table 2.7 entry 1).



Scheme 2. 21. Kozlowski Synthesis of (S)-Bisoranjidiol.

Using the same catalyst under microwave conditions led mostly to absence of conversion (**Table 2.7** entry 2).

Table 2.7. Studies toward the Decarbonylation of 2.50 and 2.51.



| Entry | Reactant | Catalyst | Solvent | Product | Yield |
|-------|--------------|---|--|---------|-------|
| 1 | 2.75 | Pd(OAc) ₂ 10 mol % K ₂ CO ₃ 2.5 equiv | EtOAc, 80 °C | 2.1 | 39 % |
| 2 | 2.75 | Pd(OAc) ₂ 10 mol % K ₂ CO ₃ 2.5 equiv | EtOAc, μw,100 °C | 2.1 | 0 % |
| 3 | 2.75 or 2.76 | RhCl(PPh ₃) ₃ 10 mol % | CH ₂ Cl ₂ 90 °C | 2.2 | 0 % |
| 4 | 2.76 | $[Ir(cod)Cl]_2$ 25 mol % PPh ₃ 50 mol % | Dioxane 110 °C | 2.2 | 60 % |
| 5 | 2.76 | [Ir(cod)C1] ₂ 25 mol % PPh ₃ 50 mol % | Dioxane 110 °C | 2.2 | 30 % |

Using Wilkinson's catalyst and conditions similar to those used by Kozlowski did not provide any decarbonylated product using either **2.75** or **2.76** (Table 2.7 entry 3). Finally, using $[Ir(cod)Cl]_2$ with triphenylphosphine as the ligand provided 60% of 2.2 starting from 2.76 and 30 % of 2.1 starting form 2.75.

In order to avoid preparative HPLC separation, further optimization studies using $[Ir(cod)Cl]_2$ were undertaken on the mixture of **2.75** and **2.76**. The mixture of **2.75** and **2.76** was treated with a catalytic amount of $[Ir(cod)Cl]_2^{60}$ in the presence of JohnPhos ligand and did not provide to any desired mixture of **2.1** and **2.2**.

Although we were not able to design an efficient and reliable way to produce rhodomyrtone A **2.1**, this project allowed us to understand the effect of different substituents on the acylated phloroglucinol partner onto the 1,4 conjugate addition and the regioselectivity of the dehydrative cyclization event. Hydrogen bonds play a crucial role to control the selectivity of the dehydrative cyclization and our attempt to control the regioselectivity of the cyclization reaction by introducing activating hydrogen bond generating group was encountered with success and verified our hypothesis.

2.6 Future Plan: Toward an Enantioselective Synthesis

Rhodomyrtone A **2.1** and rhodomyrtosone B **2.2** have been isolated as a racemic compound and biological studies have been performed with a racemic mixture of the compound. Therefore, developing an enantioselective synthesis became of interest and may allow for a better assessment of biological activities, toxicities and pharmacokinetic properties associated with each enantiomers of rhodomyrtone A **2.1** and rhodomyrtosone B **2.2** for potential drug development endeavors.

2.6.1 Nickel-based Enantioselective 1,4 Conjugate Addition: Background

Several catalytic systems using nickel (II) have been used for the development of enantioselective 1,4 conjugate additions with a wide range of substrates. These systems can be sorted in four different classes: amino-alcohol ligands and nickel (II), biphosphine ligands and nickel (II), PyBox ligands and nickel (II), and binuclear nickel catalysts. Select examples of these different catalytic systems are described below.

2.6.1.a. Amino-alcohol and diamine ligands, and Nickel (II)

In the early 2000's several groups were investigating 1,4 conjugate addition of organozinc reagents to a range of enones with control of the enantioselectivity.⁶¹ Among them, the Nayak group introduced a β -amino alcohol as a ligand to control the enantioselectivity of the addition of diethylzinc to chalcones. By using Ni(acac)₂ with β -amino alcohol **2.89** in acetonitrile, they were able to submit a large scope of chalcones **2.88** to the reaction conditions and obtained adducts **2.90-2.95** (Scheme 2.22).⁶²





Scheme 2. 23. Evans' Catalytic System.



Evans and coworkers furthered the field by introducing a readily prepared nickel based catalyst containing two chiral diamine ligands for the conjugate addition of 1,3 dicarbonyl compounds to conjugated nitroalkenes. By using substituted cyclohexanediamine ligands and NiBr₂, they were able to prepare bench stable catalyst **2.98**, which was used for the conjugate addition of malonates with β -ketosester **2.96** to obtain adducts **2.99-2.105** in high yield and enantioselectivity. The stereoinduction was proposed to stem from dipole reduction and minimization of the interaction ligand-substrate (**Scheme 2.23**). ⁶³

2.6.1.b. Biphosphine ligands, and Nickel (II)

Corey group and Evans group, both developed biphosphine ligand and nickel (II) catalytic systems to enable the development of enantioselective 1,4 conjugate additions. In their work, the Corey group used a H₈-BINAP ligand **2.108** to control the conjugate addition of alkynes **2.107** to cyclohexanone derivatives **2.106**. They were able to obtain adducts **2.109-2.112** with high yield and high selectivity and to extend the methodology to 7 members ring α , β -enone **2.113** (Scheme **2.24**).⁶⁴

Scheme 2. 24. Corey's Catalytic System.



The Evans group used a similar catalytic system to develop enantioselective Michael additions involving β -ketoesters **2.114** and unsaturated N-acylthiazolidinethiones **2.113** to obtain adducts **2.116-2.120** very efficiently (Scheme 2.25).⁶⁵

Scheme 2. 25. Evans' Catalytic System-Biphosphine Ligand.



The biphosphine ligand nickel systems allowed the use of more diverse nucleophiles for the 1.4conjugate addition.

2.6.1.c. PyBox ligands and Nickel (II)

In an effort to broaden the scope for enantioselective 1,4 conjugate addition the Kanemasa group has brought an important contribution by introducing PyBox nickel(II) catalytic systems. In their initial work, they were able to effectively catalyze the addition of malonitrile **2.120** with **2.121** using **2.122** as a catalyst to obtain adducts **2.123-2.125** with high yield and selectivity. In these reactions, they proposed addition of the deprotonated malonitrile to the nickel-chelated electrophile. These conditions proved superior when bulkier substituents were present in the Y-position of the enone **2.121**, whereas they were less effective with highly electron rich substituents. Stereocenters were assigned to be of (*S*) configuration, implying that the attack of the malonitrile was coming from the *Re* face of the electrophile (**Scheme 2.26a**). ⁶⁶

Kanemasa and coworkers were able to utilize these conditions with dimedone **2.126** and **2.127** to synthesize enol lactones **2.128-2.131** with high yield and selectivity using **2.132** and nickel perchlorate hexahydrate complex as the catalyst. Acetic anhydride was used as an additive in these reactions to prevent double addition and formation of dimers (**Scheme 2.26b**).⁶⁷

2.6.1.d. Binuclear Nickel Complex

Some of the latest advancements in the field of enantioselective 1,4 conjugate additions were developed in the late 2000's by the Shibasaki and Matsunaga groups and involved dinuclear metallic complexes, which are containing two nickel metal centers. In their methodology, they studied the addition of unsaturated Y-butyrolactams **2.132** with nitroalkenes **2.133**. The nickel dinuclear complex **2.134** was the most effective and other metallic complexes or hetero-metallic complexes, which contained two metals centers including, only one nickel

center were found inefficient in this process. Shibasaki and coworkers were able to obtained several adducts **2.135-2.138** in high yield and selectivity (**Scheme 2.27**).

Scheme 2. 26. Kanemasa's Catalytic Systems.





2.135 98 %, 30:1 dr, 97 % ee 2.136 98 %, 30:1 dr, 98 % ee 2.137 97 %, 30:1 dr, 99 % ee



The mechanism for this process was proposed to involve the bifunctional character of the dinuclear catalyst, which possesses Lewis-acid and Brønsted-base functionalities.⁶⁸ The addition of nucleophiles into nitroalkenes was later expanded to include α -ketoanilide

2.6.2 Preliminary Studies

nucleophiles.

To begin our studies we selected several catalytic systems that had been successfully used previously. Our investigational work started with a screen of catalytic systems for the conjugate addition of **2.4** and **2.5** (**Table 2.8**). The ligands **2.139** and **2.140** were obtained from our laboratory library and were obtained following reported procedures.⁶⁹ The binuclear nickel complex **2.141** was also prepared according to reported procedures (**Figure 2.9**).⁷⁰





The reaction utilizing ligand **2.139** with nickel perchlorate provided 52 % of **2.3** (**Table 2.8**, Entry 1). The enantiomeric excess could not be measured on the 1,4 adduct **2.3** due to its atropisomeric character. Therefore, cyclizations under acidic conditions to obtain **2.2** were attempted. The cyclization of intermediate **2.3** obtained from the **entry 1** reaction using hexafluoroisopropanol and trifluoroacetic acid provided 22 % of the desired **2.2**. We attempted to measure the enantiomeric excess after cyclizations without success. The reaction utilizing ligand **2.140** with nickel perchlorate provided 17 % of **2.3** (**Table 2.8**, Entry 2), further cyclization was not successful due to the very limited amount of material obtained. Similarly, The reaction utilizing the catalytic system **2.141** provided 15 % of **2.3** (**Table 2.8**, Entry 3), further cyclization was not successful due to the very limited amount of material obtained.

For further development, other PyBox ligands, the Kanemasa group DBPhox/Ni catalytic system and other binuclear complexes with nickel or copper may be screened.

 Table 2. 8. Catalytic Systems Screen for the Development of an Enantioselective Nickel

 Mediated 1,4 Conjugate Addition.



| Entry ^{a,d} | Catalytic System | 1,4 Conjugate Addition Yield | Cyclization (HFIP, TFA) Yield ^b | ee |
|----------------------|---|---------------------------------------|--|----|
| 1 | Ni(ClO ₄) ₂ .6H ₂ O + 2.139 | 52 % | 22 % | - |
| 2 | Ni(ClO ₄) ₂ .6H ₂ O + 2.140 | 17 % | - | - |
| 3 | 2.141 | 15 % | - | - |

^{*a*} Reactions conducted with monoalkylidene **2.4** (5 mg, 0.02 mmol, 1 equiv) and acylphloroglucinol **2.5** (2.5 mg, 0.02mmol, 1 equiv) in 0.5 mL of CH_2Cl_2 with Lewis acid catalyst (1.45 mg, 0.004 mmol, 0.2 equiv). ^{*b*} Yields reported after isolation by silica gel column chromatography.^{*d*} Solvents thoroughly degassed using the freeze-pump-thaw method.

2.7 Biological Data

During the course of our studies we became interested in evaluating the biological activities of the diverse analogues, which had been synthesized. A sample of natural rhodomyrtone A was provided by the group of Prof. Voravuthikunchai from the Prince of Songkla University. The enantiomeric composition of this sample was evaluated by chiral HPLC using a ChiralCel-OD column and the natural sample was found to be a racemic mixture (**Figure 2.10**).

The solubilities of natural rhodomyrtone A 2.1, rhodomyrtosone B 2.2 and analogues 2.3, 2.57 and 2.73 were also evaluated. Rhodomyrtone A 2.1 has been reported to be only partially soluble in water and ongoing studies are evaluating liposome encapsulation in order to increase solubility of 2.1 and subsequently its potency against bacterial strains.⁷¹ It was found that 2.1, 2.2, 2.3 were soluble at the require concentration of 3.2 mg.mL⁻¹ for further biological testing. Analogues 2.57 and 2.73 were found to be not soluble enough, which may explain their lack of potency (Figure 2.11).

Figure 2. 10. Chiral HPLC Analysis of 2.1 Natural Sample.



Figure 2. 11. Evaluated Analogues for Solubility.



| | | E. coli | S. Aureus | C aurous | E. faecalis | S. | |
|-------|------|---------|-----------|-----------|-------------|------------|--|
| Entry | | ATCC | USA300 | S. aureus | ATCC | pneumoniae | |
| | | 25922 | (MRSA) | | 29212 | ATCC 49619 | |
| 1 | 2.1 | >32 | 8 | 4 | 16 | >32 | |
| 2 | 2.2 | >32 | 16 | 16 | 32 | 8 | |
| 3 | 2.3 | NS | NS | NS | NS | NS | |
| 4 | 2.57 | NS | NS | NS | NS | NS | |
| 5 | 2.73 | NS | NS | NS | NS | NS | |

Table 2. 9. Analogues Biological Activities Against Select Bacterial Strains (MIC, µg.mL⁻¹).

Data showed that a non-dehydrated compound such as **2.3** were not active against *S. aureus* strains (**Table 2.9**, entry 3). Therefore a fully cyclized structure may be correlated to biological activity for this class of natural product. Rhodomyrtone A **2.1** was the most active compound with a lowest MIC value of 4 μ g.mL⁻¹ corresponding to concentration of 9 nM. This may indicate that the biological target of **2.1** possesses a very specific conformation. Supporting this hypothesis, the regioisomer rhodomyrtosone B **2.2** was shown to be less active in most case with a lowest MIC concentration of 18 nM (**Table 2.9**, entry 2).

2.8 Conclusion

During the course of our studies, we were able to develop and efficient nickel-mediated 1,4 conjugate addition of acylated-phloroglucinols with monoalkylidene **2.4**. We synthesized rhodomyrtosone B **2.2** and evaluated several analogues for biological activities. Additionally, we were able to evaluate and understand the effect of different substituents on the acylated-

phloroglucinols onto the dehydrative cyclization selectivity. This allowed us to highlight the importance of hydrogen bonds for selectivity control in this process.

2.9 Experimental Section

2.9.1 General Information

¹H NMR spectra were recorded at either at 400 MHz or 500 MHz (as noted) at ambient temperature with CDCl₃ as the solvent unless otherwise stated. ¹³C NMR spectra were recorded either at 100.0 MHz or 125.0 MHz (as noted) at ambient temperature with CDCl₃ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (¹H, δ 7.27; ${}^{13}C$, δ 77.0). Data for ¹H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. All ¹³C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF mass spectrometer. Melting points were recorded on a Mel-temp (Laboratory Devices). Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Preparative TLC was conducted with glass backed 1000 µm silica gel 60-F plates (Silicycle, Inc.). Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Preparative HPLC was performed using the Gilson[™] PLC 2020 and a SunFire[™] preparative C18 column (OBD[™] 5 µm, 19x50 mm). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. All reactions were carried out in flame-dried glassware under an argon atmosphere unless

otherwise noted. The Arthur[™] Suite Reaction Planner (Symyx Technologies, Inc.) was used for experimental procedure planning.

2.9.2 Reagents and solvents

HPLC grade tetrahydrofuran, methylene chloride, diethyl ether and hexanes were purchased from Fisher and VWR and were purified and dried by passing through a PURE SOLV[®] solvent purification system (Innovative Technology, Inc.). Methanol was purchased from Fisher and used after distillation following a procedure previously described by Lund and Bjerrum.⁷²

All other chemicals and reagents were used as received from Sigma-Aldrich, except for syncarpic acid, prepared from a reported procedure,⁷³ compound **6** was prepared from syncarpic acid **S1** by using intermediate **S2** (see below), and acylated phloroglucinol compound **2.5** and formylated compound **2.57** and **2.58** were prepared using literature described procedures.^{74, 50}

2.9.3 Characterization Data

Additional characterization data for syncarpic acid 2.S1:

R_f: 0.33 (hexanes/EtOAc=1:1 plus 5% MeOH) UV-KMnO₄

Mp: 185-189 °C (water)

IR (thin film): 3922.02, 3849.90, 3669.18, 2980.8, 2940.55, 2718.36, 2661.31, 2599.83, 1709.24, 1609.93, 1535.85, 1478.29, 1377.61, 1343.15, 1303.09, 1247.81, 1232.00, 1180.43, 1042.27 cm⁻¹ **¹H NMR (CDCl₃, 500 MHz):** δ 3.626 (s, 2H), 1.338 (s, 12H)

¹³C NMR (CDCl₃, 100 MHz): δ 208.4, 177.3, 175.1, 147.0, 131.7, 129.2 (two carbons overlapping), 128.8, 126.2 (ovrlp), 123.4, 71.5, 51.2, 44.7, 41.3, 39.8, 32.8, 25.4, 20.7, 20.0

HRMS--ESI (m/z): $[M+Na]^+$ calculated for $C_{10}H_{14}NaO_3$, 183.1021; found, 183.1016

Experimental Procedure for the synthesis of acylated phloroglucinol 2.5:74



Into a large flask was added 1,3,5-benzenetriol **2.S2** (5 g, 40 mmol, 1 equiv) and aluminum trichloride (9.95 g, 74.6 mmol, 1.8 equiv) in methylene chloride (25 mL) at room temperature. Then, nitromethane (4.04 mL, 74.6 mmol, 1.8 equiv) was added dropwise at 0°C. The reaction was heated to 30°C and from 35°C to 40°C over 5 min. Gas was released during this step. Isovaleryl chloride, (5 g, 40 mmol, 1 equiv) was added dropwise carefully at 40°C using an addition funnel under an inert atmosphere with an exit needle to avoid over pressurization and the reaction was heated to reflux for one hour. The reaction mixture thickened and yellow brown flakes were observable on the surface of the liquid. The reaction mixture was cooled to 0°C and iced cold water was very slowly poured in the oversized flask. Solvents in the resulting mixture were distilled under atmospheric pressure (solvent evaporation can also be done using a Rotovap for small scale-under 1-2 g) until the water was the only solvent remaining in the reaction flask. The resulting precipitate was recrystallized from water and filtered through a fritted funnel to afford 4.8 g (60 %) of **2.5** as yellow crystalline solid.

 $\mathbf{R}_{\mathbf{f}}$: 0.58 hexanes: ethyl acetate: MeOH (1:1:0.1)

Mp: >250°C (water, nitromethane)

IR (thin film): 3092.63, 3059.51, 3027.47, 3008.10, 2996.09, 2957.73, 2944.06, 2912.77, 2893.45, 2850.40 cm⁻¹
¹**H NMR (CDCl₃, 500 MHz):** δ 0.97 (d, J= 5 Hz, 6H), 1.56 (s, 12H), 2.26 (m, J= 10Hz, 1H), 2.92 (d, J=5 Hz, 2H), 5.36 (broad s, 1H), 5.86 (s, 2H)

¹³C NMR (MeOD, 125.67 MHz): δ 23.31, 26.85, 53.83, 95.88, 105.73

HRMS--ESI (m/z): $[M+Na]^+$ calculated for $C_{11}H_{14}O_4$, 211.0970; found, 211.0979

Experimental procedure for the synthesis of adduct 2. S3:



To a flask was added syncarpic acid **2.S1**, (500 mg, 3 mmol, 1 equiv) and anhydrous diethyl ether (45 mL). The resulting solution was cooled to 0°C and pyrrolidine (275 μ L, 3.29 mmol, 1.2 equiv) was added dropwise followed by the addition of isovaleraldehyde (370 μ L, 3.43 mmol, 1.25 equiv). The solution became slightly cloudy. The reaction was stirred at 0 °C until a white precipitate was formed (about 30 min). The white solid was filtered and washed with cold ether and dried *in vacuo* to yield **2.S3** as a white powder (800 mg, 90 %).

R_f: 0.44 hexanes:EtOAc:MeOH (1:1:0.1)

Mp: 165-168 °C (diethyl ether)

IR (thin film): 2974.01, 1698.89, 1583.04, 1470.19, 1455.19, 1410.05, 1366.04, 1296.99, 1215.98 cm⁻¹

¹**H NMR (CDCl₃, 500 MHz):** δ 0.83 (s, 3H), 0.90 (s, 3H), 1.30 (s, 12H), 1.37 (t, J=9.9 Hz), 1.46 (s, 1H), 1.96 (s, 2H+1H), 2.01 (t, J= 9.9 Hz), 2.13 (s, 1H), 2.82 (t, J= 5 Hz), 2.98 (s, 1H), 3.30 (s, 1H), 3.54 (s, 1H), 4.43 (d, J= 9.9 Hz)

¹³C NMR (CDCl₃, 125.67 MHz): δ 216.91, 98.68, 77.48, 77.23, 76.98, 69.45, 54.08, 48.92, 32.06, 25.27, 24.51, 22.58, 20.43, 17.52 ppm

HRMS--ESI (m/z): [M+H]⁺ calculated for C19H31NO3, 322.2382; found, 322.2384

Experimental procedure for the formation of monoalkylidene compound 2.4:



To a flask was added adduct **2.S3** (200 mg, 0.62 mmol) then methylene chloride was added (15 mL, 0.04 M). A 1M solution of hydrochloric acid in water was prepared and saturated with ammonium chloride. This solution (15 mL, 0.04 M) was added to the reaction mixture. The mixture was vigorously stirred at room temperature for 1h. The organic layer was washed with saturated brine (3 times) and gathered organic fractions were dried over anhydrous sodium sulfate. Solvents were concentrated *in vacuo* to yield compound **2.4** (116 mg, 75 %) as a pale yellow oil.

 $\mathbf{R}_{\mathbf{f}}$: 0.6 hexanes: EtOAc (3:1)

IR (thin film): 2965.63, 1695.43, 1606.38, 1465.51, 1383.58,1296.07, 1215.98. 1132.50, 1039.52 cm⁻¹

¹**H NMR (CDCl₃, 500 MHz):** δ 7.52 (t, *J* = 7.6 Hz, 1H), 2.61 (t, *J* = 7.3 Hz, 2H), 1.89 (ddt, *J* = 13.5, 10.8, 6.8 Hz, 1H), 1.46 – 1.42 (m, 3H), 1.40 – 1.36 (m, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.00 (dd, *J* = 14.8, 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (CDCl₃, 125.67 MHz): δ 208.79, 199.50, 196.40, 159.10, 133.10, 58.55, 57.93, 38.86, 35.62, 28.68, 22.55, 22.26, 21.96.

HRMS--ESI (m/z): [M+H]⁺ calculated for C₁₅H₂₂O₃, 251.1647; found, 251.1647





The dichloromethane and acetic acid used in this reaction were previously degassed using the freeze-pump-thaw method (x3). To acyl phloroglucinol **2.5** (25 mg, 0.12 mmol, 1.5 equiv) was added Ni(ClO₄)₂.6H₂O (2.9 mg, 0.0080 mmol, 0.1 equiv) and methylene chloride (2 mL) at room temperature under argon followed by addition of 4Å MS (20mg). Next, a solution of monoalkylidene **2.4** (20 mg, 0.08 mmol. 1 equiv) in dichloromethane (1 mL) was added to the reaction mixture followed by acetic acid (0.5 mL). The global concentration of **2.4** was 0.04 M. The reaction was stirred at room temperature for 5 h and heated to 40 °C for 12 h. The reaction was quenched with water and a solution of 1M KHSO₄ at 0 °C until reaching a pH \approx 2. The reaction mixture was extracted with CH₂Cl₂ and washed with saturated brine. Organic fractions were gathered and dried over anhydrous sodium sulfate. Solvents were evaporated *in vacuo* yielding an yellow oil. Column chromatography purification on silica gel with a gradient of CH₂Cl₂: MeOH (90:1 to 20:1) provided compound **2.3** in 80% yield and only traces of the endoperoxide byproduct **2.36**.

Characterization data for 2.3

 $\mathbf{R}_{\mathbf{f}}$: 0.45 CH₂Cl₂:MeOH

Mp: 51-54 °C (hexanes, MeOH)

IR (thin film): 2958.19, 2872.19, 1716.58, 1622.77, 1594.68, 1467.34, 1383.88, 1367.29, 1300.61, 1215.23, 1118.62, 754.18 cm⁻¹

¹**H NMR** (**CDCl**₃, **500 MHz**): δ 0.83 (quad, J= 5 Hz, 6H), 0.97 (d, J= 5 Hz, 6H), 1.23 (s, 3H), 1.31 (d, J= 5 Hz, 3H), 1.36 (d, J=5 Hz, 3H), 1.42 (broad m, 1H), 1.47 (s, 3H), 1.75 (m, J= 10 Hz, 1H), 2.06 (m, J= 10 Hz, 1H), 2.25 (m, J=10Hz, 1H), 2.95 (d, J= 5Hz, 2H), 4.34 (t, J= 10 Hz, 1H), 5.86 (s, 2/3H) and 5.92 (s, 1/3H), 10.28 (s, 2/3H) and 10.55 (s, 1/3H); 11.15 (s, 1/3H) and 11.57 (s, 2/3H)

¹³C NMR (CDCl₃, 125.67 MHz): δ 22.56, 22.76, 23.07, 24.51, 25.50, 26.37, 27.10, 28.19, 29.59, 29.92, 38.44, 48.87, 52.43, 55.32, 98.25, 109.50, 114.94, 158.60, 176.83, 203.38, 206.41, 212.51 HRMS--ESI (m/z): [M+Na]⁺ calculated for C₂₆H₃₆O₇, 461.2539; found, 461.2534

Characterization data for 2.36

Diastereomer 1:

 $\mathbf{R}_{\mathbf{f}}$: 0.67 hexanes: EtOAc (2:1)

Mp: 115-120 °C (CH₂Cl₂, MeOH)

IR (thin film): 3408.97, 2975.64, 1726.15, 1690.59, 1633.86, 1469.19, 1377.38, 1286.22, 1216.22, 1159.82.11, 1100.16 cm⁻¹

¹**H NMR (500 MHz, Chloroform-***d***)** δ 7.29 (d, *J* = 1.6 Hz, 1H), 4.74 (dd, *J* = 5.9, 1.6 Hz, 1H), 3.51 (s, 1H), 2.03 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.38 (d, *J* = 8.1 Hz, 7H), 1.31 (s, 3H), 1.06 (dd, *J* = 6.8, 1.4 Hz, 7H), 1.03 (s, 3H).

¹³C NMR (126 MHz, cdcl₃) δ 210.48, 197.69, 137.86, 134.34, 97.92, 83.48, 54.90, 51.68, 30.50, 26.61, 24.06, 20.67, 18.18, 17.89, 15.12.

HRMS--ESI (**m**/**z**): $[M+H]^+$ calculated for $C_{15}H_{22}O_5$, 283.1545; found, 265.1440 $[M+H-H_2O]^+$ Diastereomer 2:

 $\mathbf{R}_{\mathbf{f}}$: 0.38 hexanes: acetone (2:1)

IR (thin film): 3000.50, 2933.43, 2872.53, 1693.60, 1638.03, 1470.98, 1375.00, 1262.55, 1187.51, 1131.25, 1100.01 cm⁻¹

¹**H NMR (500 MHz, Chloroform-***d***):** δ 7.43 (d, *J* = 4.1 Hz, 1H), 4.13 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.62 (s, 1H), 2.19 – 2.09 (m, 1H), 1.43 (s, 3H), 1.39 (d, *J* = 5.4 Hz, 6H), 1.33 (d, *J* = 3.4 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 6H)

¹³C NMR (126 MHz, cdcl₃): δ 207.08, 197.87, 149.01, 137.88, 97.62, 84.95, 32.22, 31.08, 30.12, 26.78, 24.21, 21.12, 20.04, 19.19, 15.35.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{15}H_{22}O_5$, 283.1545; found, 283.1547 $[M+H]^+$

Experimental procedure to form rhodomyrtosone B 2.2 from compound 2.3:



To a solution of 1,4 adduct **2.3** (20 mg, 0. 04 mmol, 1 equiv) in hexafluoroisopropanol (0.2 mL) was added trifluoroacetic acid (0.05 mL) at room temperature. The reaction was stirred at 60°C for 12h. Then, the reaction was dissolved in water and saturated brine and the mixture was extracted with ethyl acetate (three times). Gathered organic fractions were dried over anhydrous sodium sulfate and solvents were evaporated *in vacuo* to yield a yellow solid. Purification using column chromatography on silica gel with an hexane:acetone gradient (12:1 to 4:1), provided 8 mg of rhodomyrtosone B **2.2** (60% yield).

 $\mathbf{R}_{\mathbf{f}}$: 0.4 hexanes : acetone (3:1)

Mp: 58-62 °C (hexanes, acetone)

IR (thin film): 3359.86, 2959.21, 2925.37, 2869.81, 1719.44, 1656.43, 1625.75, 1597.94, 1504.38, 1469.46, 1431.80, 1388.20, 1368.12, 1255.28, 1161.24, 1121.96, 1041.55, 1015.89 cm⁻¹

¹**H NMR (CDCl₃, 500 MHz):** δ 13.46 (s, OH), 6.26 (s, OH), 4.30 (t, *J* = 6.1 Hz, 1H), 3.24 – 2.89 (m, 2H), 2.36 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.64 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.39 – 1.31 (m, 4H), 1.02 (dd, *J* = 14.3, 6.6 Hz, 6H), 0.87 (dd, *J* = 8.5, 6.4 Hz, 6H).

¹³C NMR (CDCl₃, 125.67 MHz): δ 211.72, 203.88, 198.28, 167.21, 164.24, 159.53, 153.06, 114.53, 105.92, 105.57, 100.19, 56.10, 53.41, 47.22, 46.88, 25.35, 25.02, 24.75, 24.72, 24.46, 24.43, 24.22, 23.39, 23.08, 22.88, 22.62.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{26}H_{34}O_6$ 443.2434; found, 443.2427

Table 2. 10. NMR Data Comparison for Natural Rhodomyrtosone B and Synthetic Dialactic and the second seco

Rhodomyrtosone B.



| | C ppm (mult) | | H ppm (m, J Hz) | | |
|----|--------------|-----------------------------------|-----------------|---------------|--|
| C# | Natural 2.2 | Synthetic 2.2 | Natural 2.2 | Synthetic 2.2 | |
| 1 | 197.6 s | 198.28 | | | |
| 2 | 56.1 s | 56.1 | | | |
| 3 | 211.7 s | 211.72 | | | |
| 4 | 47.2 s | 47.22 | | | |
| 4a | 166.9 s | 167.21 | | | |
| 4b | 153.3 s | 153.06 | | | |
| 5 | 105.9 s | 105.57 | | | |
| 6 | 159.0 s | 164.24 ^{<i>a</i>} | | | |
| 7 | 100.3 d | 100.19 | 6.23 (s) | 6.26 (s) | |
| 8 | 159.0 s | 159.53 | | | |
| 8a | 105.9 s | 105.92 | | | |
| 9 | 25.1 d | 25.02 | 4.25 (t, 6.0) | 4.3 (t, 6.06) | |
| 9a | 114.5 s | 114.53 | | | |
| 10 | 24.3 q | 24.22 | 1.39 (s) | 1.39 (s) | |

| 11 | 24.4 q | 24.43 | 1.42 (s) | 1.43 (s) |
|----|---------|--------|---|------------------------|
| 12 | 24.8 q | 24.72 | 1.63 (s) | 1.64 (s) |
| 13 | 25.4 q | 25.35 | 1.47 (s) | 1.47 (s) |
| 1' | 204.0 s | 203.88 | | |
| 2' | 53.6 t | 53.41 | 3.18 (dd, 17.0, 6.5), 2.96 (dd, 17.0, 6.5) | 3.07 (m) |
| 3' | 24.5 d | 24.46 | 2.37 (m, 6.5) | 2.36 (dd, 6.57, 13.23) |
| 4' | 22.9 q | 22.88 | 1.04 (d, 6.5) | 1.02 (dd, 6.64, 14.29) |
| 5' | 22.6 q | 22.62 | 1.01 (d, 6.5) | 1.02 (dd, 6.64, 14.29) |
| 1" | 46.9 t | 46.88 | 1.38 (obscure) | 1.37 (m) |
| 2" | 24.9 d | 24.75 | 1.38 (obscure) | 1.37 (m) |
| 3" | 23.4 q | 23.39 | 0.89 (d, 6.5) | 0.87 (dd, 6.37, 8.47) |
| 4" | 23.1 q | 23.08 | 0.87 (d, 6.5) | 0.87 (dd, 6.37, 8.47) |
| 6- | | | 13 /3 (s) | 13.46 (s) |
| OH | | | 13.43 (8) | 13.40 (8) |
| 8- | | | 6.40 (br s) | |
| OH | | | | |

Figure 2. 12. HMBC Data for Rhodomyrtosone B 2.2.



General procedure for synthesis of 2.59 and 2.60:



The dichloromethane used in this reaction was previously degassed using the freeze-pump-thaw method three times. To phloroglucinol derivatives **2.57** or **2.58** (1.5 equiv) was added Ni(ClO₄)₂.6H₂O (0.1 equiv) and CH₂Cl₂ at room temperature under argon and 4Å MS (10 w/w Ni(ClO₄)₂.6H₂O). Next, a solution of monoalkylidene **2.4** (20 mg, 0.08 mmol. 1 equiv) in CH₂Cl₂ was added to the reaction mixture. The global concentration of **2.4** was 0.04 M. The reaction was stirred at room temperature for 1h and heated to 40 °C for 12 h. The reaction was quenched with water and a solution of 1M KHSO₄ at room temperature until reaching a pH \approx 2-3. The reaction mixture was extracted with dichloromethane and washed with saturated brine. Organic fractions were gathered and dried over anhydrous sodium sulfate. Solvents were evaporated *in vacuo*.

Characterization data for 2.59

Column chromatography purification on silica gel with a gradient of hexanes: acetone (15:1 to

6:1) provided compound **2.59** (70 %) as a pink solid

 $\mathbf{R}_{\mathbf{f}}$: 0.40 hexanes: acetone (3:1)

Mp: 156-160 °C (hexanes, acetone)

IR (thin film): 2957.24, 2609.21, 1721.14, 1629.31, 1428.14, 1278.11, 1189.78, 1049.16, 914.23 cm⁻¹

¹H NMR (CDCl₃, 500 MHz): δ 4.34 (t, J = 7.6 Hz, 1H), 3.02 (dd, J = 6.7, 1.8 Hz, 2H), 2.27 (dq, J = 13.4, 6.7 Hz, 1H), 2.12 - 2.01 (m, 1H), 1.79 (dt, J = 14.1, 7.3 Hz, 1H), 1.50 (d, J = 3.1 Hz, 4H), 1.41 (s, 3H), 1.39 (d, J = 4.3 Hz, 2H), 1.36 (d, J = 3.2 Hz, 6H), 1.27 - 1.23 (m, 1H), 1.01 (dd, J = 6.7, 1.5 Hz, 7H), 0.91 - 0.81 (m, 7H).

¹³C NMR (CDCl₃, 100 MHz): δ 207.35, 203.95, 193.91, 177.29, 167.11, 114.53, 52.21, 48.82, 38.24, 27.64, 27.19, 27.01, 26.34, 25.29, 24.36, 22.94, 22.63, 22.53, 22.47.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{27}H_{36}O_8$; 489.2488 found, 489.2493

Characterization data for 2.60

Column chromatography purification on silica gel with a gradient of Hexane: Acetone (15:1 to 6:1) provided the 1,4 adduct as a yellow solid in 84% yield.

 $\mathbf{R}_{\mathbf{f}}$: 0.85 (hexanes:acetone, 3:1)

Mp: 55-60 °C (hexanes, acetone)

IR (thin film): 2959.31, 2871.52, 1720.96, 1619.79, 1586.75, 1468.58, 1428.35, 1383.92, 1367.30, 1197.89, 1049.16

¹**H NMR (CDCl₃, 500 MHz):** δ 12.88 (s, 1H), 12.00 (s, 0.5H), 11.25 (s, 0.5H), 10.40 (s, 1H), 4.44 – 4.28 (m, 1H), 3.13 (ddd, *J* = 16.1, 14.1, 6.6 Hz, 1H), 3.06 – 2.98 (m, 3H), 2.34 – 2.19 (m, 2H), 2.12 – 1.98 (m, 2H), 1.78 (dt, *J* = 13.8, 7.3 Hz, 1H), 1.50 (d, *J* = 3.7 Hz, 3H), 1.41 (s, 3H), 1.39 (d, *J* = 3.8 Hz, 3H), 1.38 – 1.35 (m, 6H), 1.00 (ddd, *J* = 6.9, 4.4, 2.7 Hz, 12H), 0.90 – 0.80 (m, 6H).

¹³C NMR (CDCl₃, 100 MHz): 8 211.93, 207.88, 203.92, 171.06, 168.14, 167.21, 114.65, 107.50, 105.71, 103.78, 55.05, 53.37, 52.42, 48.87, 38.32, 27.90, 27.11, 26.34, 25.46, 25.25, 24.40, 22.98, 22.67, 22.50.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{31}H_{44}O_8$; 545.3114 found, 545.3105

Experimental procedure for the cyclization of 2.58 leading to 2.73:



To a flask containing a solution of 2.58 (100 mg, 0.18 mmol) in toluene 10 mL was added *p*-TsOH (17 mg, 0.9 mmol, 0.5 equiv). The flask was equipped with a Dean-Stark apparatus and a reflux condenser. The reaction was heated to reflux for 12 h. The reaction was allowed to cool to room temperature and was quenched with a saturated sodium bicarbonate aqueous solution and

brine. The reaction mixture was extracted with ethyl acetate and the organic fractions were gathered and dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield a yellow solid. Column chromatography purification over silica gel using a gradient of hexanes:acetone (10:1 to 5:1) provided **2.73** in 70 % (66 mg) as a pink solid.

 $\mathbf{R}_{\mathbf{f}}$: 0.6 (hexanes: acetone 3:1)

Mp: >250 °C (toluene, hexanes, acetone)

IR (thin film): 2957.95, 2946.29, 2932.27, 2871.61, 2857.80, 1721.37, 1663.59, 1615.02, 1498.24, 1384.01, 1299.52, 1193.51, 1158.69, 1121.93, 1048.47 cm⁻¹

¹**H NMR (CDCl₃, 500 MHz):** δ 4.31 (t, *J* = 6.0 Hz, 1H), 3.18 (dd, *J* = 17.2, 7.5 Hz, 1H), 3.08 (dd, *J* = 15.9, 6.6 Hz, 1H), 3.03 – 2.94 (m, 2H), 2.42 – 2.34 (m, 1H), 2.28 (hept, *J* = 6.7 Hz, 2H), 1.63 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.38 (s, 4H), 1.03 (dd, *J* = 18.1, 6.7 Hz, 6H), 0.99 (dd, *J* = 6.6, 0.8 Hz, 6H), 0.89 (dd, *J* = 8.2, 6.3 Hz, 6H).

¹³C NMR (CDCl₃, 100 MHz): δ 211.52, 207.51, 204.45, 197.31, 168.97, 168.79, 165.96, 156.77, 115.37, 107.37, 106.51, 103.59, 53.49, 47.18, 46.89, 25.40, 25.34, 25.03, 24.91, 24.71, 24.57, 24.37, 24.14, 23.37, 23.37, 23.22, 23.05, 22.96, 22.89, 22.75.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{31}H_{42}O_7$; 527.3009 found, 527.3002

Experimental procedure for the formation of 2.74:



To sealed tube glassware was added 2.73 (10 mg, 0.018 mmol) and 1,2-dichloroethane (1 mL) followed by triflic acid (1.58 μ L, 0.018 mmol, 1 equiv) and water (1.56 μ L). The tube was sealed and heated to reflux for 1 h. The reaction was allowed to cool to room temperature and them quenched by adding brine. The reaction mixture was extracted with dichloromethane and the

organic fraction were gathered and dried over anhydrous sodium sulfate. Solvents were evaporated *in vacuo* to yield a pale yellow oil. Column chromatography purification over silica gel using a hexanes: acetone gradient (8:1 to 1:1) provided **2.74** in 80 % (5 mg) as a transparent gummy oil.

 $\mathbf{R}_{\mathbf{f}}$: 0.2 Hexane: Ethyl Acetate (3:1)

IR (thin film): 3341.11, 3324.23, 2980.19, 2949.07, 2920.42, 2857.80, 1628.82, 1599.33 1517.81, 1466.80, 1391.22, 1281.22 cm⁻¹

¹**H NMR (CDCl₃, 500 MHz):** δ 0.81 (d, J= 5 Hz, 3H), 0.84 (d, J= 5 Hz, 3H), 1.23 (s, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 1.39 (s, 3H) 4.17 (t, J= 7.5 Hz, 1H) 4.76 (s, 1H), 4.93 (s, 1H), 6.14 (d, J= 5Hz, 1H), 6.20 (s, 1H)

¹³C NMR (MeOD, 125.67 MHz): δ 23.88, 24.43, 24.88, 25.15, 25.33, 26.29, 30.82, 47.19, 48.58, 56.97, 95.49, 100.31, 106.20, 115.07, 153.93, 157.28, 170.04, 199.74, 199.75, 213.95, 213.96
HRMS--ESI (m/z): [M+Na]⁺ calculated for C₂₁H₂₆O₅, 359.1858; found, 359.1859

Experimental procedure for the cyclization of 2.57:



To compound **2.57** in a solution of 1,2 dichloroethane (44 mg, 0.09 mmol in 9 mL of solvent, 0.01 M) under inert atmosphere and at room temperature was added 25% v/v of trifluoroacetic acid. The reaction was warmed to 80 °C for 12 h. The reaction solvents were evaporated *in vacuo* and the remaining oil was purified by column chromatography on a silica gel column to provide

30 mg (70 %) of a 1:1 mixture of compound 2.75 and 2.76. For characterization, 2.75 and 2.76 were separated using preparative HPLC to provide 2.75 (14 mg, 33 %) and 15 (13.5 mg, 32 %) of 2.76.

Characterization Data for 2.75:

R_f: 0.645 (hexanes : acetone 2:1)

IR (thin film): 2959.21, 2933.32, 1720.48, 1660.32, 1631.93, 1455.01, 1423.83, 1383.85, 1366.93, 1294.69, 1163.79, 1129.83, 1001.61 cm⁻¹

¹**H NMR (CDCl₃, 500 MHz):** δ 10.18 (s, 1H), 4.29 – 4.21 (m, 1H), 3.10 – 2.96 (m, 1H), 2.34 – 2.22 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.95 – 0.73 (m, 3H)

¹³C NMR (CDCl₃, 100 MHz): δ 211.29, 207.05, 197.40, 190.35, 167.61, 165.76, 156.77, 115.14, 53.20, 47.39, 46.19, 25.39, 25.11, 25.04, 24.85, 24.82, 23.99, 23.40, 23.26, 22.93, 22.85.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{27}H_{34}O_7$; 471.2383 found, 471.2374

Characterization Data for 2.76:

 $\mathbf{R_{f}:} 0.7 \text{ (hexanes : acetone 2:1)}$

IR (thin film): 2959.28, 1721.59, 1661.33, 1627.14, 1451.38, 1382.79, 1308.03, 1216.87, 1192.68, 1152.62, 1121.14, 1048.27 cm⁻¹

¹**H NMR (CDCl₃, 500 MHz):** δ 13.26 (s, 1H), 10.31 (s, 1H), 4.29 (dd, *J* = 6.5, 5.8 Hz, 1H), 3.22 – 2.90 (m, 2H), 2.43 – 2.31 (m, 1H), 1.03 (dd, *J* = 15.6, 6.7 Hz, 6H), 0.90 (dd, *J* = 6.4, 4.1 Hz, 7H)

¹³C NMR (CDCl₃, 100 MHz): δ 211.29, 204.32, 197.26, 193.38, 168.74, 166.70, 165.91, 158.12, 115.21, 107.22, 106.14, 104.01, 56.50, 53.58, 47.18, 47.00, 25.41, 25.29, 24.86, 24.49, 24.45, 24.15, 24.01, 23.41, 23.02, 22.74.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{27}H_{34}O_7$; 471.2383 found, 471.2373

2.9.4 Enantioselective System Screen

2.8.4.a General Information

The ligands and catalyst for the following experiments were prepared according to reported procedures.^{49, 50} Characterization data for those ligands and catalyst are available in the literature.





The dichloromethane used in these reaction were previously degassed using the freeze-pump-thaw method (x3). ^{*a*} Reactions conducted with monoalkylidene **2.4** (5 mg, 0.02 mmol, 1 equiv) and acylphloroglucinol **2.5** (2.5 mg, 0.02mmol, 1 equiv) in 0.5 mL of CH_2Cl_2 with Lewis acid catalyst (0.004 mmol, 0.2 equiv). ^{*b*}Yields reported after isolation by silica gel column chromatography.^{*d*}Solvents thoroughly degassed using the freeze-pump-thaw method.

For Table 2.8, Entries 1 and 2: To Ni(ClO₄)₂.6H₂O (1.45 mg, 0.004 mmol, 0.2 equiv) in methylene chloride (0.5 mL) was added 2.139/2.140 (1.47(2.139) mg/ 2.08(2.140) mg 0.004 mmol, 0.2 equiv). After stirring for 10 min, acyl phloroglucinol 2.5 (2.5 mg, 0.02mmol, 1 equiv) was added at room temperature under argon followed by addition of 4Å MS (5 mg). Next, a solution of monoalkylidene 2.4 (5 mg, 0.02 mmol, 1 equiv) in methylene chloride (0.5 mL) was added to the reaction mixture. The reaction was stirred at room temperature for 1h and heated to 40 °C for 12 h. The reaction was quenched with water and a solution of 1M KHSO₄ at 0 °C until reaching a pH \approx 2. The reaction mixture was extracted with CH₂Cl₂ and washed with saturated brine. Organic fractions were gathered and dried over anhydrous sodium sulfate. Solvents were evaporated *in vacuo*

yielding a yellow oil. Column chromatography purification on silica gel with a gradient of CH_2Cl_2 : MeOH (90:1 to 20:1) provided compound **2.3** in 52 % yield when using ligand **2.139** and in 197% when using ligand **2.140**.

For Table 2.8, Entry 3: To acyl phloroglucinol 2.5 (2.5 mg, 0.02mmol, 1 equiv in methylene chloride (0.5 mL) was added 2.141 (3.55 mg 0.004 mmol, 0.2 equiv) and 4Å MS (5 mg) at room temperature under argon. Next, a solution of monoalkylidene 2.4 (5 mg, 0.02 mmol, 1 equiv) in methylene chloride (0.5 mL) was added to the reaction mixture. The procedure from Table 2.8, Entries 1 and 2 was then followed. Column chromatography purification on silica gel with agradient of CH_2Cl_2 : MeOH (90:1 to 20:1) provided compound 2.3 in 15 % yield. Cyclization reactions were performed using the same procedure as described for compound 2.2. The reactions yielded 22% of 2.2 with 1.239 and led to no decomposition for 1.240 and 1.241.

2.9.5 Chiral HPLC Data for Natural 2.1



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Reported by User: System Report Method: CHIRAL LC Report Method ID: 1255 Page: 1 of 2 Project Name: Anais Gervais1 Date Printed: 4/29/2010 7:07:35 PM US/Eastern

Solubility Test Protocol

- 1) A reference UPLC spectra of target compounds was obtained.
- 2) Appropriate volumes of 20 mM stocks were diluted to obtain 50 uL of 3.2 mg/mL stocks.
- 3) 10uL of 3.2 mg/mL stock were pipeted into 1 mL deionized water glass vial.
- 4) Visible precipitate apparition was observed.
- 5) Aqueous from glass vial were transferred to a plate for centrifuge.
- 6) Water samples were centrifuged.
- 7) Supernatant was pipeted off into eppendorf.
- 8) Eppendorf were dried down on Genevac.
- 9) Dried supernatants were resuspended in 100 uL DMSO.
- 10) DMSO solutions were transfered to conical UPLC vial.
- 11) UPLC in (conical vial) were acquired and were analyzed and compared to original sample to check for presence of compound.

Determination of minimum inhibitory concentration (MIC)

Assay plate prep protocol for MIC experiments

1) Compound samples: to be prepared as 3.2 mg/mL stock solutions in DMSO; 250 μ L per sample.

2) Compound stock plates: sterile 96-well round-bottom polypropylene plates, 0.5 mL (Nunc 267334)

2x dilution series in anhydrous DMSO, 10 points (columns 1-10) in duplicate

100 μ L/well sample or DMSO in column 1, 50 μ L/well DMSO in columns 2-12.

50 μ L transfers from column 1 into successive columns containing 50 μ L DMSO, to column 10.Final concentration range will be 3.2 mg/mL to 0.00625 mg/mL. Columns 11 and 12 contain DMSO only. Rows C and F contain DMSO only.

Final result is 50 μ L per well. Compound stock plates will be sealed for storage at -20 °C with desiccant (Costar 6570 aluminum seals, non-sterile).

 Assay stock plate: sterile 96-well round-bottom polypropylene deep well plates, 2.0 mL (Axygen 47749-930; VWR catalog #P-DW-20-C-S)

Prepare by 100x dilution of DMSO stocks into appropriate growth medium (1% DMSO final); mix. (e.g., 16 μ L into 1.6 mL cation-adjusted Mueller-Hinton, followed by mixing).

4) Assay plates: Corning 3799 (sterile polystyrene, individually wrapped with lid)

Dispense 100 μ L per well from assay stock plate using Bravo (in hood).

Lids to be replaced immediately (no stacking of unlidded plates), no plate seals.

Place lidded plates in Ziploc bags, freeze/store at -80 °C (long term) or -20 °C (short term).

Transfer to Core A for MIC testing.













2.56





















2.11 X-ray Crystallographic Data for Compound 2.3 and Compound 2.39

2.9.1 X-ray Crystallographic Data for Compound 2.3

Figure 2. 13. ORTEP X-Ray for Compound 2.3.



Crystals of compound **2.3** suitable for x-ray analysis were obtained by slow evaporation from a solution in hexanes with a couple drops of diethyl ether for solubility purposes. (Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 978312). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

| Table 2.11 | . Crystal | Data for | Compound | 12.3. |
|------------|-----------|----------|----------|-------|
|------------|-----------|----------|----------|-------|

| $C_{26}H_{36}O_7$ | $V = 2460.74 (11) \text{ Å}^3$ |
|-------------------|--------------------------------|
| $M_r = 460.55$ | Z = 4 |

| Μ | Ionoclinic, $P2_1/c$ | Cu $K\alpha$ radiation, $I = 1.54178$ Å | |
|---|--------------------------|---|--|
| | a = 10.9488 (3) Å | $\mu = 0.73 \text{ mm}^{-1}$ | |
| | <i>b</i> = 11.2504 (3) Å | T = 100 K | |
| | c = 20.0504 (5) Å | $0.11 \times 0.05 \times 0.03 \text{ mm}$ | |
| | β= 94.903 (2)° | | |

Table 2.12 Data Collection Parameters for Compound 2.3.

| Bruker Proteum-R diffractometer | 9339 independent reflections |
|--|-----------------------------------|
| Absorption correction: multi-scan SADABS (Sheldrick, 1997) | 6243 reflections with $I > 2s(I)$ |
| $T_{\min} = 0.773, T_{\max} = 0.864$ | $R_{\rm int} = 0.052$ |
| 9339 measured reflections | |

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

 Table 2. 13. Refinement Data for 2.3.

| $R[F^2 > 2s(F^2)] = 0.065$ | 136 restraints |
|----------------------------|---|
| $wR(F^2) = 0.209$ | H-atom parameters constrained |
| <i>S</i> = 1.06 | $D\rangle_{\rm max} = 0.44 \ e \ \text{\AA}^{-3}$ |
| 9339 reflections | $D_{\min} = -0.32 \text{ e} \text{ Å}^{-3}$ |
| 398 parameters | |

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2 , conventional R-factors R are based on F, with F set to zero for

negative F^2 . The threshold expression of $F^2 > 2 \operatorname{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Table 2. 14. Fractional Atomic Coordinates and Isotropic or Equivalent IsotropicDisplacement Parameters ($Å^2$).

| | x | у | Z. | $U_{\rm iso}*/U_{\rm eq}$ |
|------|------------------|--------------|-----------------|---------------------------|
| 01 | -0.22465 (18) | 0.7186 (2) | 0.56403 (9) | 0.1130 (8) |
| O2 | 0.48108 (13) | 1.04885 (13) | 0.43100 (7) | 0.0654 (4) |
| O3 | 0.29875 (13) | 1.15970 (11) | 0.25116 (7) | 0.0552 (4) |
| Н3 | 0.2503 | 1.1740 | 0.2173 | 0.083* |
| O4 | 0.01721 (14) | 0.84770 (14) | 0.25940 (7) | 0.0630 (4) |
| H4 | -0.0130 | 0.8012 | 0.2864 | 0.094* |
| O5 | 0.33160 (12) | 0.89024 (12) | 0.43663 (7) | 0.0558 (3) |
| H5 | 0.3967 | 0.9289 | 0.4453 | 0.084* |
| O6 | 0.17386 (13) | 0.82016 (13) | 0.52131 (7) | 0.0597 (4) |
| H6 | 0.2192 | 0.8322 | 0.4903 | 0.090* |
| 07 | -0.11577 (13) | 0.72908 (12) | 0.34317 (7) | 0.0587 (4) |
| C1 | -0.1517 (2) | 0.74213 (19) | 0.52386 (11) | 0.0637 (6) |
| C2 | -0.0227 (2) | 0.77330 (17) | 0.54965 (10) | 0.0562 (5) |
| C3 | 0.06408 (18) | 0.78369 (15) | 0.49556 (10) | 0.0498 (5) |
| C4 | 0.03846 (18) | 0.75459 (14) | 0.42988 (9) | 0.0470 (4) |
| C11A | 0.1489 (5) | 0.7450 (5) | 0.3874 (3) | 0.0405 (12) |
| H11A | 0.2216 | 0.7328 | 0.4204 | 0.049* |
| C12A | 0.1450 (3) | 0.6332 (2) | 0.34159 (15) | 0.0504 (8) |

| H12A | 0.1305 | 0.5622 | 0.3690 | 0.060* |
|------|--------------|--------------|-----------------|-------------|
| H12B | 0.0749 | 0.6407 | 0.3072 | 0.060* |
| C13A | 0.2622 (4) | 0.6142 (5) | 0.3065 (2) | 0.0503 (10) |
| H13A | 0.2686 | 0.6829 | 0.2753 | 0.060* |
| C14A | 0.3768 (4) | 0.6153 (5) | 0.3533 (2) | 0.0902 (16) |
| H14A | 0.3950 | 0.6969 | 0.3681 | 0.135* |
| H14B | 0.4453 | 0.5842 | 0.3301 | 0.135* |
| H14C | 0.3649 | 0.5654 | 0.3923 | 0.135* |
| C15A | 0.2504 (3) | 0.5027 (3) | 0.26301 (19) | 0.0686 (10) |
| H15A | 0.2380 | 0.4333 | 0.2913 | 0.103* |
| H15B | 0.3254 | 0.4919 | 0.2403 | 0.103* |
| H15C | 0.1802 | 0.5111 | 0.2296 | 0.103* |
| C16 | 0.17694 (17) | 0.85893 (15) | 0.34956 (9) | 0.0456 (4) |
| C17 | 0.27683 (16) | 0.92545 (15) | 0.37608 (9) | 0.0458 (4) |
| C18 | 0.32439 (17) | 1.02671 (15) | 0.34432 (9) | 0.0460 (4) |
| C22 | 0.4341 (2) | 1.08423 (19) | 0.37550 (10) | 0.0597 (5) |
| C23A | 0.4748 (4) | 1.2016 (4) | 0.34409 (18) | 0.0489 (10) |
| H23A | 0.4928 | 1.1865 | 0.2973 | 0.059* |
| H23B | 0.4066 | 1.2595 | 0.3432 | 0.059* |
| C24A | 0.5865 (4) | 1.2547 (3) | 0.38194 (19) | 0.0601 (12) |
| H24A | 0.6478 | 1.1902 | 0.3928 | 0.072* |
| C25A | 0.5562 (9) | 1.3140 (8) | 0.4467 (4) | 0.0631 (19) |
| H25A | 0.4914 | 1.3731 | 0.4369 | 0.095* |
| H25B | 0.6296 | 1.3532 | 0.4677 | 0.095* |
| H25C | 0.5280 | 1.2538 | 0.4773 | 0.095* |
| C26A | 0.6430 (5) | 1.3473 (4) | 0.3376 (3) | 0.0776 (15) |
| H26A | 0.6656 | 1.3091 | 0.2965 | 0.116* |
| H26B | 0.7163 | 1.3815 | 0.3618 | 0.116* |
| H26C | 0.5833 | 1.4105 | 0.3262 | 0.116* |

| C6 | -0.19282 (19) | 0.73947 (16) | 0.44964 (10) | 0.0543 (5) |
|------|------------------|--------------|-----------------|------------|
| C10 | -0.2691 (3) | 0.8511 (2) | 0.43350 (15) | 0.0892 (9) |
| H10A | -0.3384 | 0.8530 | 0.4614 | 0.134* |
| H10B | -0.2999 | 0.8502 | 0.3862 | 0.134* |
| H10C | -0.2179 | 0.9217 | 0.4426 | 0.134* |
| C9 | -0.2698 (2) | 0.6278 (2) | 0.43530 (13) | 0.0790 (7) |
| H9A | -0.2178 | 0.5573 | 0.4424 | 0.119* |
| H9B | -0.3056 | 0.6295 | 0.3888 | 0.119* |
| Н9С | -0.3356 | 0.6250 | 0.4655 | 0.119* |
| C5 | -0.08718 (19) | 0.73932 (15) | 0.40452 (10) | 0.0509 (5) |
| C19 | 0.25960 (18) | 1.06197 (15) | 0.28317 (9) | 0.0471 (4) |
| C20 | 0.15812 (18) | 1.00107 (16) | 0.25719 (9) | 0.0484 (4) |
| H20 | 0.1154 | 1.0271 | 0.2166 | 0.058* |
| C21 | 0.11676 (17) | 0.90090 (16) | 0.28987 (9) | 0.0482 (4) |
| C8 | -0.0251 (3) | 0.8900 (2) | 0.58873 (14) | 0.0875 (8) |
| H8A | 0.0579 | 0.9092 | 0.6079 | 0.131* |
| H8B | -0.0794 | 0.8815 | 0.6249 | 0.131* |
| H8C | -0.0554 | 0.9540 | 0.5585 | 0.131* |
| C7 | 0.0269 (3) | 0.6717 (3) | 0.59697 (14) | 0.0957 (9) |
| H7A | 0.0296 | 0.5975 | 0.5715 | 0.144* |
| H7B | -0.0273 | 0.6617 | 0.6330 | 0.144* |
| H7C | 0.1096 | 0.6919 | 0.6162 | 0.144* |
| C11B | 0.1201 (12) | 0.7385 (12) | 0.3707 (7) | 0.048 (4) |
| H11B | 0.0677 | 0.7066 | 0.3315 | 0.057* |
| C12B | 0.2207 (9) | 0.6462 (6) | 0.3908 (5) | 0.078 (3) |
| H12C | 0.1821 | 0.5720 | 0.4051 | 0.093* |
| H12D | 0.2744 | 0.6769 | 0.4292 | 0.093* |
| C13B | 0.3001 (15) | 0.6184 (14) | 0.3315 (8) | 0.094 (5) |
| H13B | 0.3438 | 0.6932 | 0.3208 | 0.113* |
|------|-------------|-------------|-------------|-------------|
| C14B | 0.2264 (12) | 0.5783 (13) | 0.2682 (8) | 0.114 (4) |
| H14D | 0.1747 | 0.5107 | 0.2784 | 0.170* |
| H14E | 0.2822 | 0.5544 | 0.2350 | 0.170* |
| H14F | 0.1746 | 0.6439 | 0.2503 | 0.170* |
| C15B | 0.3887 (16) | 0.5367 (12) | 0.3572 (10) | 0.150 (6) |
| H15D | 0.4592 | 0.5797 | 0.3788 | 0.224* |
| H15E | 0.4152 | 0.4878 | 0.3207 | 0.224* |
| H15F | 0.3534 | 0.4856 | 0.3902 | 0.224* |
| C23B | 0.5277 (6) | 1.1576 (5) | 0.3422 (3) | 0.0531 (15) |
| H23C | 0.6114 | 1.1374 | 0.3614 | 0.064* |
| H23D | 0.5222 | 1.1406 | 0.2936 | 0.064* |
| C24B | 0.5019 (5) | 1.2878 (5) | 0.3538 (2) | 0.0523 (16) |
| H24B | 0.4118 | 1.3013 | 0.3444 | 0.063* |
| C25B | 0.5684 (7) | 1.3606 (5) | 0.3037 (4) | 0.0697 (19) |
| H25D | 0.6553 | 1.3385 | 0.3070 | 0.105* |
| H25E | 0.5608 | 1.4454 | 0.3137 | 0.105* |
| H25F | 0.5319 | 1.3447 | 0.2582 | 0.105* |
| C26B | 0.5391 (15) | 1.3261 (14) | 0.4264 (5) | 0.071 (4) |
| H26D | 0.6270 | 1.3118 | 0.4369 | 0.107* |
| H26E | 0.4925 | 1.2798 | 0.4569 | 0.107* |
| H26F | 0.5216 | 1.4108 | 0.4315 | 0.107* |

2.11.1 X-ray crystallographic data for compound 2.57

Figure 2. 14. ORTEP X-Ray for Compound 2.57.



Crystals of compound **2.39** suitable for x-ray analysis were obtained by slow evaporation from a solution in hexanes with a couple drops of acetone for solubility purposes. (Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 978313). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

| C ₂₇ H ₃₆ O ₈ | γ = 71.976 (1)° |
|--|---|
| $M_r = 488.56$ | V = 1236.90 (7) Å ³ |
| Triclinic, <i>P</i> ⁻¹ | <i>Z</i> = 2 |
| a = 9.1154 (3) Å | Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å |
| <i>b</i> = 11.3915 (3) Å | $\mu = 0.79 \text{ mm}^{-1}$ |
| c = 12.7117 (4) Å | T = 100 K |
| $\alpha = 82.220 (1)^{\circ}$ | $0.16 \times 0.12 \times 0.06 \text{ mm}$ |
| $\beta = 81.963 \ (1)^{\circ}$ | |

Table 2. 15. Crystal Data for Compound 2.57.

Table 2. 16. Data Collection Parameters for Compound 2.57.

| Bruker Proteum-R diffractometer | 4310 independent reflections |
|------------------------------------|--|
| Absorption correction: multi-scan | 4204 reflections with $I > 2\sigma(I)$ |

| SADABS (Sheldrick, 1997) | |
|--|-----------------------|
| $T_{\rm min} = 0.709, T_{\rm max} = 0.753$ | $R_{\rm int} = 0.033$ |
| 27208 measured reflections | |

Table 2. 17. Refinement Data for 2.57.

| $R[F^2 > 2\sigma(F^2)] = 0.036$ | 54 restraints |
|---------------------------------|--|
| $wR(F^2) = 0.093$ | H atoms treated by a mixture of independent and constrained refinement |
| <i>S</i> = 1.05 | Δ _{max} = 0.25 e Å ⁻³ |
| 4310 reflections | Δ _{min} = -0.23 e Å ⁻³ |
| 378 parameters | |

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2 , conventional R-factors R are based on F, with F set to zero for negative F^2 . The threshold expression of $F^2 > 2 \operatorname{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Table 2. 18. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2) .

| | x | у | z | $U_{\rm iso}$ */ $U_{\rm eq}$ |
|------|---------------|--------------|---------------|-------------------------------|
| O2 | 0.11073 (11) | 0.42702 (8) | 0.14848 (8) | 0.0248 (2) |
| H2 | 0.214 (2) | 0.3991 (16) | 0.1324 (14) | 0.037* |
| O3 | 0.41309 (10) | 0.34609 (8) | 0.07961 (8) | 0.0228 (2) |
| Н3 | 0.4637 (19) | 0.3778 (15) | 0.0184 (12) | 0.034* |
| O4 | 0.57526 (11) | 0.37837 (8) | -0.08239 (8) | 0.0289 (2) |
| 05 | 0.81127 (10) | -0.00096 (8) | -0.04844 (7) | 0.0227 (2) |
| H5 | 0.8398 (19) | -0.0866 (17) | -0.0246 (14) | 0.034* |
| O6 | 0.44154 (10) | -0.06046 (8) | 0.23395 (7) | 0.0196 (2) |
| H6 | 0.347 (2) | -0.0271 (15) | 0.2646 (13) | 0.029* |
| 07 | 0.81972 (11) | -0.21286 (8) | 0.04560 (8) | 0.0270 (2) |
| 08 | 0.15571 (10) | 0.02601 (8) | 0.31521 (7) | 0.0217 (2) |
| C24 | -0.12073 (15) | 0.37742 (12) | 0.20094 (11) | 0.0244 (3) |
| C27 | 0.05328 (14) | 0.33875 (11) | 0.20106 (10) | 0.0195 (3) |
| C18 | 0.14270 (14) | 0.23053 (11) | 0.24866 (9) | 0.0178 (3) |
| C13 | 0.31454 (14) | 0.21207 (12) | 0.25706 (10) | 0.0207 (3) |
| H13 | 0.3223 | 0.2986 | 0.2473 | 0.025* |
| H13A | 0.3283 | 0.1346 | 0.3070 | 0.025* |
| C11 | 0.42991 (13) | 0.14918 (11) | 0.16772 (10) | 0.0171 (3) |
| C12 | 0.48466 (14) | 0.22382 (11) | 0.08441 (10) | 0.0179 (3) |
| C6 | 0.61038 (14) | 0.17800 (11) | 0.00514 (10) | 0.0183 (3) |
| C5 | 0.65211 (14) | 0.26594 (11) | -0.07989 (11) | 0.0213 (3) |
| C4 | 0.78560 (15) | 0.22901 (12) | -0.16456 (11) | 0.0227 (3) |
| H4A | 0.7866 | 0.1497 | -0.1887 | 0.027* |
| H4B | 0.8835 | 0.2143 | -0.1326 | 0.027* |
| C2 | 0.78151 (16) | 0.32469 (12) | -0.26205 (11) | 0.0265 (3) |
| H2A | 0.7586 | 0.4086 | -0.2369 | 0.032* |
| C1 | 0.93950 (17) | 0.29345 (14) | -0.32708 (12) | 0.0339 (3) |

| H1A | 0.9637 | 0.2108 | -0.3514 | 0.051* |
|------|---------------|---------------|---------------|------------|
| H1B | 1.0187 | 0.2944 | -0.2827 | 0.051* |
| H1C | 0.9378 | 0.3550 | -0.3891 | 0.051* |
| C23A | -0.19549 (19) | 0.28992 (16) | 0.27575 (18) | 0.0249 (5) |
| C3 | 0.65557 (18) | 0.32686 (14) | -0.33029 (12) | 0.0343 (3) |
| НЗА | 0.6543 | 0.3890 | -0.3918 | 0.052* |
| H3B | 0.5545 | 0.3480 | -0.2875 | 0.052* |
| H3C | 0.6770 | 0.2450 | -0.3554 | 0.052* |
| C7 | 0.68488 (14) | 0.04875 (11) | 0.01605 (10) | 0.0177 (3) |
| C8 | 0.62609 (14) | -0.02999 (11) | 0.09446 (10) | 0.0175 (3) |
| C10 | 0.49495 (13) | 0.02135 (11) | 0.16672 (9) | 0.0167 (3) |
| С9 | 0.70122 (14) | -0.16161 (12) | 0.10271 (10) | 0.0209 (3) |
| H9 | 0.6574 | -0.2124 | 0.1551 | 0.025* |
| C14A | 0.36865 (15) | 0.16256 (13) | 0.36757 (11) | 0.0186 (3) |
| H14A | 0.4770 | 0.1638 | 0.3661 | 0.022* |
| H14B | 0.3687 | 0.0749 | 0.3821 | 0.022* |
| C15A | 0.27134 (18) | 0.23362 (15) | 0.45996 (12) | 0.0202 (4) |
| H15A | 0.1655 | 0.2229 | 0.4672 | 0.024* |
| C16A | 0.2541 (2) | 0.37158 (14) | 0.44172 (13) | 0.0336 (4) |
| H16A | 0.3570 | 0.3839 | 0.4263 | 0.050* |
| H16B | 0.2006 | 0.4113 | 0.5059 | 0.050* |
| H16C | 0.1937 | 0.4086 | 0.3812 | 0.050* |
| C17A | 0.34453 (18) | 0.17699 (15) | 0.56293 (14) | 0.0269 (4) |
| H17A | 0.3519 | 0.0886 | 0.5744 | 0.040* |
| H17B | 0.2802 | 0.2193 | 0.6231 | 0.040* |
| H17C | 0.4485 | 0.1867 | 0.5576 | 0.040* |
| C19 | 0.07409 (14) | 0.13325 (11) | 0.28956 (9) | 0.0187 (3) |
| C20 | -0.10106 (14) | 0.15580 (12) | 0.30389 (10) | 0.0207 (3) |
| C14B | 0.3462 (12) | 0.2815 (9) | 0.3310 (7) | 0.015 (2) |
| H14C | 0.3135 | 0.3694 | 0.3012 | 0.017* |
| H14D | 0.4604 | 0.2570 | 0.3302 | 0.017* |
| C16B | 0.2997 (19) | 0.3825 (11) | 0.5024 (11) | 0.0336 (4) |
| H16D | 0.4048 | 0.3893 | 0.4824 | 0.050* |

| H16E | 0.2832 | 0.3648 | 0.5801 | 0.050* |
|------|---------------|--------------|--------------|------------|
| H16F | 0.2239 | 0.4608 | 0.4798 | 0.050* |
| C17B | 0.3624 (16) | 0.1531 (12) | 0.5079 (12) | 0.0269 (4) |
| H17D | 0.3545 | 0.0852 | 0.4714 | 0.040* |
| H17E | 0.3131 | 0.1479 | 0.5813 | 0.040* |
| H17F | 0.4719 | 0.1467 | 0.5089 | 0.040* |
| C15B | 0.2800 (18) | 0.2783 (13) | 0.4483 (10) | 0.0202 (4) |
| H15B | 0.1669 | 0.2866 | 0.4526 | 0.024* |
| C22 | -0.14133 (16) | 0.07371 (14) | 0.23218 (12) | 0.0302 (3) |
| H22A | -0.2538 | 0.0881 | 0.2400 | 0.045* |
| H22B | -0.0895 | -0.0138 | 0.2534 | 0.045* |
| H22C | -0.1062 | 0.0946 | 0.1575 | 0.045* |
| C21 | -0.14981 (16) | 0.11733 (16) | 0.42083 (11) | 0.0338 (3) |
| H21A | -0.1226 | 0.1676 | 0.4674 | 0.051* |
| H21B | -0.0958 | 0.0295 | 0.4387 | 0.051* |
| H21C | -0.2621 | 0.1304 | 0.4310 | 0.051* |
| C26A | -0.1631 (2) | 0.3754 (2) | 0.08744 (15) | 0.0348 (4) |
| H26A | -0.1197 | 0.4322 | 0.0371 | 0.052* |
| H26B | -0.2762 | 0.4015 | 0.0878 | 0.052* |
| H26C | -0.1201 | 0.2911 | 0.0657 | 0.052* |
| C25A | -0.1906 (2) | 0.50968 (17) | 0.2345 (2) | 0.0410 (6) |
| H25A | -0.1614 | 0.5126 | 0.3052 | 0.062* |
| H25B | -0.3038 | 0.5334 | 0.2370 | 0.062* |
| H25C | -0.1510 | 0.5674 | 0.1826 | 0.062* |
| O1A | -0.33129 (13) | 0.32462 (13) | 0.30732 (17) | 0.0457 (7) |
| O1B | -0.3160 (16) | 0.2947 (16) | 0.225 (2) | 0.059 (9) |
| C23B | -0.184 (2) | 0.2761 (17) | 0.245 (2) | 0.0249 (5) |
| C26B | -0.155 (2) | 0.4303 (18) | 0.0864 (12) | 0.0348 (4) |
| H26D | -0.1278 | 0.5079 | 0.0690 | 0.052* |
| H26E | -0.2660 | 0.4466 | 0.0803 | 0.052* |
| H26F | -0.0943 | 0.3703 | 0.0366 | 0.052* |
| C25B | -0.179 (3) | 0.4854 (17) | 0.2754 (17) | 0.0410 (6) |
| H25D | -0.1468 | 0.4541 | 0.3469 | 0.062* |

| H25E | -0.2922 | 0.5175 | 0.2798 | 0.062* |
|------|---------|--------|--------|--------|
| H25F | -0.1337 | 0.5522 | 0.2459 | 0.062* |

2.12 Mass Spectrospcopy Data: Mechanistic Studies

A. Data were acquired by direct injection after every hour. The reaction followed is shown in **Figure 2.16**.

Figure 2. 15. Mechanistic Studies: Reaction.



B. Compound 2.5 (25.2 mg, 0.024 mmol, 2 equiv) was placed in a flask containing dichloromethane. Then, Ni(ClO₄)₂.6H₂O (21.9 mg, 0.012 mmol, 1 equiv) was added. The reaction was stirred at room temperature and followed every hour for three hours and direct injection data were obtained. Then, 2.4 (15mg, 0.012 mmol, 1 equiv) was added to the reaction. The reaction was stirred at room temperature for an additional three hours and a sample was obtained for direct injection. Then, the reaction was heated at 40 °C for 12h. The workup and purification used, were described in the procedure for the formation of 2.3 (see above). Compound 2.3 was obtained in 37 % yield.







2 h







300 400 500 *** End of Report ***

5 h after monoalkylidene addition



Chapter 3

Synthesis of Rhodomyrtosone A and Studies toward the Tomentosones A, B and Bullataketals A, B.

3.1 Introduction

Rhodomyrtosone A **3.1** and tomentosones A **3.2** and B **3.3** were isolated from the *Rhodomyrtus* genus and present an intriguing *bis*-furan acylphlroglucinol core.^{2,3} Recently, the natural product watsonianone B **3.4** containing the same *bis*-furan core has been isolated from a parent genus growing in Australia (*Corymbia watsonia*).⁷⁵ The tomentosones and watsonianone were found to possess anti-malarial properties (*vide infra*) (**Figure 3.1**).^{2,3,2}





3.1.1 Biological Activities

Malaria is an entirely preventable mosquito borne disease, which has caused significant suffering and mortality over the course of human history than perhaps any other disease. In 2013, malaria transmission occurred in more than 90 countries and over three billion people were at risk

to be exposed to the disease with more than one billion people at high risk to be exposed. About 207 million cases of malaria inducing more than half a million death were observed worldwide in 2012. Children aged five and under represent 70 % of the death toll, which occurred in majority in sub-Saharian Africa.⁷⁶

The search for antimalarial remedies had been ongoing for centuries and reached inflection points with the isolation and identification of quinine **3.5** in 1820 and much later the isolation and identification of artemisinin **3.6** in the mid-1970s (**Figure 3.2**).³ Today, the standard of care to treat malaria generally consists of artemisinin-combination-therapy (ACT). Artemisinin is obtained from semi-synthetic processes relying heavily on the availability of raw plant material and the production process remains costly. Several chemical syntheses of artemisinin have been reported. The first synthesis, starting from (-)-isopulegol, was reported by Hofheinz and coworkers in 1983.⁷⁷ It was followed by several synthesis of (+)-artemisinin **3.6**.⁷⁸

Figure 3. 2. Antimalarial Artemisinin and Quinine.



Although these synthetic efforts tried to reduce the artemisinin high production cost, current hopes reside in artemisinin production using bioengineered microorganisms, developed mainly by the San Fransisco Bay area company Amyris. Additionally, resistance to ACT treatment has started to emerge in Cambodia and Vietnam and has begun to spread more widely to Africa reinforcing the need for the discovery and development of new therapeutic agents. Therefore, investigating the chemical space to identify and synthesize novel anti-malarial therapeutics is both a moral imperative and of great interest to the scientific community.

Both tomentosones A **3.2** and B **3.3** possesses anti-malarial properties. The compounds were tested against chloroquine-sensitive (3D7) and chloroquinine-resistant (Dd2) strains of the malaria parasite *Plasmodium falciparum* and showed parasite growth inhibition IC₅₀ values of $1.49 \pm 0.45 \mu$ M and 1.0μ M, respectively, for tomentosone A **3.2**. Tomentosone B **3.3** was significantly less active against both strains, reaching only 75% and 45% inhibition at the highest dose (40 μ M) tested, respectively.¹ This may be an indication that the relative stereochemistry between the *bis*-furan isopropyl chain and the isovaleryl subtituent is important for antiplasmodial activity. Both compounds were also tested for cytotoxicity toward human embryonic kidney cells (HEK) and no toxicity was observed for either compounds up to 40 μ M making tomentosone A an interesting candidate for future development.

Watsonianone B **3.4** was found to inhibit the growth of chloroquine sensitive (3D7) and resistant (Dd2) strains of the malarial parasite, *Plasmodium falciparum*. Human cell cytotoxicity was assessed using the mammalian cell line HEK-293. Watsonianone B was more active than tomentosone A and B against both the (Dd2) and (3D7) strains displaying IC₅₀ values of 0.44 and 0.29 μ M, respectively.

It is interesting to note that watsonianone B **3.4** is more active than tomentosone A **3.2**. The compounds differ only by the addition of a second alkyl syncarpic acid in **3.2** and the replacement of the benzyl group in **3.4** with an isopropyl group in **3.2**. Therefore, the second syncarpic acid group may reduce activity or alternatively replacement of the isopropyl with a benzyl group may enhance antimalarial activity. The tomentosones and watsonianone represent the first reported β -triketone inhibitors of *P. falciparum*.

3.1.2 Proposed Retrosynthetic Analysis

Both their challenging *bis*-furan structure and their enthralling biological activities lead us to consider rhodomyrtosone A **3.1** and the tomentosones A **3.2** and B **3.3** as possible synthetic targets.

We envisioned a synthetic pathway for rhodomyrtosone A **3.1**, which was inspired by their biosynthesis (**Scheme 4.1**).⁷⁹ Rhodomyrtosone A **3.1** may be obtained from addition of acyl-phloroglucinol **3.7** with endoperoxide **3.8** and *bis*-furan formation (**Scheme 4.1**). Endoperoxide **3.8** could arise from [4+2] cycloaddition of oxygen and the dienol **3.10** which may be obtained *via* photo-enolization of monoalkylidene **3.11**.





Several challenges and questions arose from this proposed synthesis. The formation of the *bis*-furan core will constitute one of the main challenges of this synthesis. The *bis*-furan formation may be an acid-mediated event for which two limiting mechanisms can be proposed (Scheme 3.2).

Both pathways may start with the formation of vinyloxocarbenium intermediate **3.13** upon protonation of **3.8** to form intermediate **3.12** and dehydration to form **3.13**. Intermediate **3.13** could undergo a Kornblum DeLaMare⁸⁰ like rearrangement to form diketone intermediate **3.14**, which would then react with acyl-phloroglucinol **3.7** *via* 1,4 conjugate addition and subsequently form hemiketal intermediate **3.15**. Acid-mediated ketal formation would provide rhodomyrtosone A **3.1**. In pathway B, 1,4 conjugate addition with the reactive vinyloxocarbenium **3.13** and acyl-phloroglucinol **3.7** may occur first to form intermediate **3.16**. Upon rearrangement, **3.16** may lead to the keto intermediate **3.17**, which may promptly undergo ketalization under acid-mediated conditions to provide rhodomyrtosone A **3.1**.

The development of an efficient and high yielding process to prepare endoperoxide **3.8** is also of high interest in this synthetic proposal. We turned our attention to the pioneering work of Snider and coworkers in order to better understand the challenge at hand. In their synthesis of racemic chondrillin and plakorin, both biologically active compounds isolated from marine organisms, Snider and coworkers extensively studied the formation of endoperoxides. Upon photoirradiation of **3.18**, they obtained a 1.7:1 mixture of diastereomers **3.23** in 72 % yield and 1.7:1 diastereomeric ratio (**Scheme 3.3**). They proposed a facile photoisomerization of ketone **3.18** to its *E* isomer **3.19** in order to allow the photo-enolization to occur and produce reactive dienol **3.20**. Dienol **3.20** can exist as a mixture of two diastereomers. Then, photohydroperoxidation may occur.



Scheme 3. 2. Limiting Mechanisms for the Formation of Rhodomyrtosone A.

Although very minor, the formation of *trans*-enone **3.21** was observed by NMR in this process suggesting that *cis*-enone **3.22** may be produced directly and may also result for another rapid

photo-isomerization process. Upon cyclization, cis-enone **3.22** may yield **3.23**. Although this process was proposed to be stepwise and to involve intermediates **3.21** and **3.22**, a concerted process cannot be ruled out.

Scheme 3. 3. Snider's Mechanistic Observation.



During their studies, Snider and coworkers ruled out the possibility that singlet oxygen may be involved. Additionally, they proposed that the role of the sensitizer Rose Bengal Lactore (RBL) may be to promote the formation of the dienol intermediate and excite this dienol to an excited state to allow it to react with triplet oxygen or serve as an initiator for a radical process.

In the context of our proposed retrosynthesis, efficient formation of endoperoxide is of crucial importance. Photo-irradiation of monoalkylidene **3.11** may provide dienol **3.10** which may undergo a concerted [4+2] cycloaddition with triplet oxygen. In this case a possible photo-isomerization from the E, Z dienol to the E, E dienol therefore may occur providing a mixture of diastereomeric endoperoxides **3.8A** and **3.8B**. Alternatively, dienol **3.10** may undergo photo-mediated hydroperoxidation to produce enone **3.24** and/or its isomer **3.25**. Enone **3.25** would provide a mixture of diastereomeric endoperoxides **3.8A** and **3.8B** upon cyclization.



Scheme 3. 4. Mechanistic Considerations for the Formation of Monoalkylidenes 3.8.

These mechanistic considerations will need to be addressed in our work. This prompted us to gain a better understanding of the methodologies available to prepare endoperoxides as well as to gather more information regarding their reactivities and uses.

3.2 Literature Background on Endoperoxides

Several groups have been investigating methods to prepare efficiently endoperoxides and all have studied their reactivity and used them as intermediates en route to the syntheses of more advanced compounds. As previously mentioned, endoperoxides have been of interest in the development of new anti-malarial compounds. Although there is no consensus regarding the mechanism through which artemisinin derivatives kill the parasites, several research groups have proposed that artemisinin exerts its antimalarial action by perturbing redox homeostasis in malaria parasites.⁸¹ Redox homeostasis is induced when the malaria causing parasites consume red blood cells, which contain hemoglobin, a process that generates oxidative stress. A theory is that the iron of the heme directly reduces the peroxide bond in artemisinin, which damages the parasite and lead to its death. Accordingly, some of the reactivity studies presented herein involve iron reduction of endoperoxides.

3.2.1 Endoperoxides: Preparation, Reactivity and Mechanism

In 1979, Adam and coworkers synthesized α -pyrone endoperoxides and studied their thermal decomposition.⁸² α -Pyrone endoperoxides were prepared from α -pyrone **3.26** which upon exposure to light (589 nm) and oxygen at 0 °C provided formal [4+2] adduct **3.27** in over 90 % yield. They proposed a radical mechanism for this event involving singlet oxygen. Then, thermal decomposition of **3.27** extruded carbon dioxide to provide two compounds, diketone **3.28** and endoperoxide **3.29**. Adam and coworkers hypothesized that diketone **3.28** may be an intermediate in the formation of **3.29** by a 6π electrocyclization or may be the result of further decomposition of **4.29** by an electrocyclic ring opening. Their studies lead them to conclude the second was more likely (**Scheme 3.5**). During their work they noticed a chemiluminescence phenomena, which prompted them to use fluorescers to enhance the phenomenon. When running the decomposition reaction of **3.27** in chloroform in a sealed tube under vacuum and in the presence of the fluorescer rubrene, the chemiluminescence rate was increased and consequently the rate for the decomposition of **3.27** (**Scheme 3.5**).

Scheme 3. 5. Adam's Pioneering Work.



In 1982, Holfheinz and coworkers achieved the first synthesis of artemisin **3.6** (also named qinghaosu) from (-)-isopulegol **3.30**. By using a photo-oxygenation reaction with **3.31**, methylene blue as singlet sensitizer, oxygen at -78 °C, they were able to obtain racemic artemisisin **3.6** after acidic workup with formic acid in 30 % yield over two steps (**Scheme 3.6**).⁴



Scheme 3. 6. Hofheinz Synthesis of Artemisinin.

In 1989, Yoshida and coworkers prepared several endoperoxides using electrochemistry to generate the required radicals to form **3.35-3.38** in 11 % to 79 % yields (**Scheme 3.7**).⁸³ They were able to confirm that a radical mechanism may likely be involved by repeating their experiment using AIBN as a radical initiator and successfully obtained **3.35-3.38** in 12 % to 90% yield. Calculations demonstrated that the chair–chair conformation and a *cis*-junction was favored for the bicyclic endoperoxides.

Scheme 3.7. Yoshida's Synthesis of Endoperoxides.



This result was confirmed experimentally and the proposed radical mechanism is outlined in **Scheme 3.8**. Further mechanistic studies confirmed that molecular oxygen was required to

observe any reaction and that the oxidation of cyclopentadione **3.34** was likely the first step of the reaction sequence. They setup to study the reactivity of endoperoxides **3.35** and found that upon exposure to acidic conditions endoperoxides **3.35** was forming diketone **3.41**.

Scheme 3. 8. Yoshida's Mechanistic Proposal for the formation of 3.35-3.38.



They confirmed the formation of a tertiary carbocation at the bicyclic junction in intermediate **3.39** by repeating the experiment in methanol and obtaining the methanol-substituted endoperoxides **3.40** (Scheme 3.9, a). Iron-mediated reduction of endoperoxide **3.35** was also evaluated (Scheme 3.9, b).

They rationalized the occurrence of Fe(II)-promoted reactions by proposing a mechanism involving an equilibrium between the cyclic peroxide **3.35** and the keto-hydroperoxide **3.24**. In the open form the hydroperoxide moiety may be reduced by ferrous sulfate to give the alkoxyl radical **3.43**, which provided **3.44** in 43 % yield. The fact that the methylated version of cyclic peroxide **3.40** did not react in a similar fashion may be explained by its inability to equilibrate with an acyclic form. This fact was consistent with their hypothesis. If the α -position of the alkoxyl radical is substituted with an hydrogen, C-H bond cleavage takes place to give the triketone. Ferric ion may be reduced to ferrous ion under the conditions, and thus the reaction was

found to be catalytic with respect to the ferrous sulfate.



Scheme 3. 9. Yoshida's Reactivity Studies.

In their work to access endoperoxypropellanes, Asahi and coworkers used manganese triacetate and acetic acid as the solvent, under air exposure.⁸⁴ They applied these conditions to triketones **3.46** and alkene **3.45** to obtain endoperoxy propellanes **3.47-3.50** (Scheme 3.10, a). When applied to **3.52**, the reaction was not complete and provided **3.53** in 94 % yield. Activating **3.53** with a Lewis acid was attempted and provided the desired endoperoxypropellane **3.55**. By selecting EtAlCl₂ the reaction was driven to completion and afforded 97 % of desired **3.55** (Scheme 3.10, b).

Both limiting mechanisms may be operating in this process. Intermediate **3.53** may be activated by the Lewis acid EtAlCl₂, which may ionize the hydroxyl group and allow peroxycarbenium **3.56** to form (**Scheme 3.11**). Reactive intermediate **3.56** may be attacked by an enolate in an intramolecular fashion to form endoperoxypropellane **3.55** (**Scheme 3.11 a**). Alternatively, EtAlCl₂ may activate the ketone and render it more electrophilic allowing for the hydroxyl group to add promptly. Water elimination would provide the desired endoxypropellane **3.55** (**Scheme 3.11 b**). In their publication, Asahi and coworkers proposed the second mechanism

as the operative one although they did not discuss the first one.



Scheme 3. 10. Asahi's Synthesis of Endoperoxypropellanes.

Scheme 3. 11. Proposed Mechanism for the Formation of Endoxypropellane 3.55.



In their work toward the synthesis of antimalarial G regulators, Andre-Barres and coworkers proposed triplet oxygen-mediated formation of related endoperoxides (**Scheme 3.12**).

Scheme 3. 12. Andre-Barres' Mechanistic Work.



In their studies, they demonstrated that endoperoxide formation was not inhibited in the presence of DABCO, a well-known triplet quencher, confirming their hypothesis. They proposed that the formation of endoperoxide may involve dienol **3.61** which needs to be formed to allow oxygen to add. The formation of dienol **3.61** was not inhibited by acid addition and therefore this ruled out the hypothesis of a required base-mediated formation. Therefore, Andre-Barres and coworkers proposed a radical mechanism for the formation of dienol **3.61** which would be followed by reaction with triplet oxygen. EPR spin studies demonstrated the presence of two different radicals intermediate in the reaction process.⁸⁵ Although EPR-spin studies were not able to identify the structure of the radical formed in the reaction, one radical was identified as tertiary, leading to the two possible reaction intermediates **3.62** and **3.63** (Scheme **3.12**).

The investigators undertook reduction studies using iron sulfate and obtained different results with non-alkylated endoperoxide **3.64**, methylated endoperoxide **3.65** or fluoro-endoperoxide **3.66** (Scheme 3.13).⁸⁶ Reduction of **3.64** with a stoichiometric amount of Fe (II) lead to the recovery of syncarpic acid-derivative **3.73** as the major product. Reduction of **43.65** yielded **3.77**, **3.78** and, **3.73** each in 24 % yield, whereas **3.66** iron-mediated reduction afforded **3.76**. A

mechanism implying the homolytic cleavage of the peroxo-bond in **3.64-3.66** and the formation of radical intermediate **3.67** in equilibrium with **3.68** was proposed. After formation of **3.67**; opening of the triketone may occur yielding **3.69**. Then, three divergent pathways may lead to the different products observed. First, in pathway A and C, a 5-*exo* trig may occur yielding five member ring radical intermediate **3.70**, which may form cyclopropane radical **3.71**. Then the two pathways A and C diverge. In pathway A, upon opening of **3.71**, **3.72** may be obtained (**Scheme 3.13, pathway A**). In pathway C, the presence of the electron-withdrawing fluoro-substituent, may be operative and cyclopropane intermediate may open forming a more stable radical **3.74** eventually leading to **3.75**, which upon lactonization and fluorohydric acid elimination may yield **3.76** (**Scheme 3.13, pathway C**). For compound **3.65** pathway A may exist along with pathway B, which may involve a dismutation and lactonization event yielding **3.77** and **3.78** (**Scheme 3.13, pathway B**).

Johnson and coworkers obtained Meldrum-acid-derived endoperoxides using a copper (I)mediated hydroperoxidation of derivatives **3.79** (Scheme **3.14**, **a**). Methyl, alkene and alkynes substituents were well tolerated in this reaction, providing hydroxyperoxides **3.80-3.82** in high yields.⁸⁷ Then, a gold-mediated endoperoxidation with **3.83** afforded **3.84** in 83 % yield (Scheme **3.14**, **b**). Compound **3.84** was subsequently reduced in a two-step sequence. Using palladium on carbon and hydrogen, they obtained compound **3.85**, which was further reduced under ionic hydrogenation conditions yielding tetrahydrofuran **3.86** in 90 % yield. Interestingly, when reversing the order of these two steps, endoperoxide intermediate **3.87** was obtained and rearranged to form lactone **3.88** during the second reduction.



Scheme 3. 13. Andre-Barres' Reduction Studies.



Scheme 3. 14. Johnson's Hydroperoxidation of Meldrum Acid Derivatives.

All this examples have in common the necessary use of molecular oxygen to form endoperoxides as well as the necessary radical initiation of the reaction process either by using light or oxidant. Several mechanistic pathways have been proposed for the reduction and the opening of the endoperoxides, it seems that a diketone or a peroxycarbenium intermediates may be relevant in the process.

3.2.2 Bis-Furan Formation

Using endoperoxides to access *bis*-furan core structures has never been reported to the best of our knowledge, and therefore, our approach will constitute a novel way to access the *bis*-furan core of rhodomyrtosone A. Additionally, relatively few compounds possess a similarly substituted *bis*-furan core and very few synthetic examples for the synthesis of similar *bis*-furan structure were described in the literature.

During their synthetic studies toward the racemic lysidicin A **3.93**, Watanabe and coworkers prepared the required γ -diketone precursor **3.91** in 83 % yield by performing an ozonolysis of intermediate **3.90**, which was obtained from **3.89** in 10 steps.⁸⁸ After ozonolysis, deprotection of the acetyl protecting group was achieved, followed by acid-mediated ketal formation using *p*-TsOH in 81 % yield over two steps, providing lysidicin A precursor **3.92** in 81 % yield after benzyl protection (**Scheme 3.15**). Lysidicin A **3.93** was obtained after 3 additional steps involving acylation and deprotection.

In this work, the γ -diketone precursor **3.91** was obtained from ozonolysis and not from an endoperoxide intermediate. Nevertheless, these studies illustrate the relevance of such 1,4 diketone intermediate in a synthetic sequence.

Finally, Yin and coworkers were able to prepare several substituted *bis*-furan compounds.⁸⁹ Starting from easily accessible substituted furan intermediates **3.94**, they used a palladium (II)/TMEDA-mediated Claisen rearrangement/dearomatization/aromatization sequence to obtain compounds **3.95-3.99** in good yields (**Scheme 3.16**).



Scheme 3. 15. Watanabe's synthesis of racemic lysidicin A.

Scheme 3. 16. Yin's Dihydro-furo-furans and Polysubstituted Furans Synthesis.



All the previous examples have provided useful insights about the reactivity of endopereoxides and the likely mechanism occurring when opening them, as well as some information about the type of intermediate formed upon opening. These literature precedents for ketal formation provide some insight regarding reaction conditions that could ultimately be used for *bis*-furan formation.

3.2.3 Vinyloxocarbeniums: Literature Precendents

The relevance of a peroxycarbenium intermediate in our retrosynthetic analysis prompted us to examine our previous investigators studies regarding vinyloxocarbenium intermediates preparation and reactivity. In their excellent review, Harmata and coworkers gave an overview on ways to generate vinyl oxocarbeniums or oxocarbeniums as well as their uses in cycloaddition reactions.⁹⁰ These methodologies include Lewis acid mediated, Brønsted acid mediated or thermal generations.

3.2.3.a. Vinyl oxocarbeniums in [4+2] cycloadditions.

In 1994, Sammakia and coworkers revisited the ionic Diels-Alder methodology initially developed by Gassman⁹¹ and coworkers in the late 1980s. Sammakia and coworkers developed a diastereoselective variant, which instead of using Brønsted acid to generate the ionized partners, utilized a mixture of titanium tetrachloride and titanium isopropoxide as activating Lewis acids.⁹² They were able to react chiral acetal **3.100** with isoprene using excess titanium (IV) in dichloromethane at low temperature. The Diels-Alder adduct **3.103-3.104** were obtained in 54 % to 85 % yield and moderate diastereomeric ratio. The diastereoselectivity was proposed to stem from the minimization of $A_{1,3}$ steric interactions between the two methyl groups in the transition state **3.101** as well as the favored eclipsed interaction between the oxygen chelated to the Lewis acid and the C-H bond α to the oxonium ion (**Scheme 3.17**).



Scheme 3. 17. Sammakia's Lewis Acid Mediated Vinyloxocarbenium Synthesis.

In 1995, Sammakia and coworkers were able to generate vinyl oxocarbenium intermediates and use them in Diels Alder reaction with simple dienes **3.106-3.108**. They used catalytic fluoroboric acid as Brønsted acid to generate the vinyl oxocarbenium intermediate in toluene and synthesized **3.109-3.111** in moderate to good yields and excellent diastereoselectivities, which may likely be linked to the size of the substituent in the α ' position (Scheme 3.18).⁹³

Scheme 3. 18. Sammakia's Brønsted Acid Mediated Vinyl Oxocarbeniums Preparation.



3.109 d.r. 98:1 72 % 3.110 d.r. 1.4:1 72 % 3.111 d.r. 3.5:1 62 %

Interestingly, more recent examples demonstrated that the use of Brønsted acid to generate vinyl oxocarbeniums is a powerful method allowing for asymmetric reaction development.

Nagorny and coworkers were able to successfully use BINOL-derived chiral phosphoric acid with a triflimide **3.114** to catalyze the [4+2] cycloaddition of α , β -unsaturated acetals **3.112** with

simple dienes **3.113** to obtain substituted cyclohexenes **3.115-3.118** in moderate yield, diastereoselectivity, and enantioselectivity (**Scheme 3.19**).⁹⁴

Scheme 3. 19. Nagorny's Enantiocontrolled Bronsted Acid-Mediated Vinyloxocarbenium Preparation.



3.2.3.b. Vinyl oxocarbeniums in [3+2] cycloadditions.

Although rare, [3+2] cycloadditions involving vinyl oxocarbenium intermediate have been described in the literature. Lee and coworkers and Nakamura and coworkers were among the first to develop [3+2] cycloaddition with vinyloxocarbenium.⁹⁵

More interestingly, in 2004 and 2006, Wilson and coworkers synthesized the xyloketals A **3.119** and xyloketals B **3.120**, C **3.121** analogues using a vinyloxocarbenium carbenium intermediate and phloroglucinol as the nucleophile (Figure 3.3).

Figure 3. 3. Xyloketals A, B, and C.



ketal moiety although with a different bond connectivity than in the bullataketals could be assembled by the addition of phloroglucinol **3.9** with vinyl oxocarbenium intermediate **3.124**, which was generated *in situ* from hydroxylated precursor **3.123**. They were able to obtain xyloketal A **3.119** in 79 % yield, and in a 5:2 diastereomeric ratio by using a stoichiometric amount of boron trifluoride etherate in diethyl ether at -78 °C.⁹⁷ They proposed that the diastereoselectivity may stem from the steric effects induced by the methyl substituent at C-4 with regard to the ether oxygen in **3.123** (Scheme 3.20 a). They were able to use their synthetic strategy to prepare xyloketals B and C analogues **3.127-3.129** (Scheme 3.20 b).⁹⁸

To achieve the syntheses of **3.127-3.129**, the investigators introduced an ester group on the phloroglucinol to obtain **3.126** and were able to block selectively one of the nucleophilic sites and only generate two additions. By reacting **3.125** with **3.126**, they were able to obtain a mixture of linear and an angular pentacyclic fused bicyclic ketals **3.127-3.129** in a 58 % combined yield and a 5:5:1 selectivity. The products were obtained as a mixture of diastereoisomers due to a lack of selectivity control with this methodology.



Scheme 3. 20. Synthesis of Xyloketal A and B and C Analogues.

Removal of the ester group using a decarboxylative saponification using sodium hydroxide in a methanol and water mixture under reflux conditions provided xyloketals B and C analogues. These synthetic examples provided encouraging insights for our proposed synthetic approach. Indeed, they demonstrated the feasibility of a formal [3+2] using vinyl oxocarbeniums as active intermediates.

3.3 Synthetic Studies: Rhodomyrtosone A, Plan Toward The Tomentosones

3.3.1 Flow-Mediated Synthesis of Endoperoxides: Literature Precedent

We first attempted to prepare our initial endoperoxides as efficiently as possible under photochemical conditions. Synthetic photochemistry carried out in classic batch reactors has, for over half a century, proved to be a powerful but underutilized technique in organic synthesis. Recent developments in flow photochemistry have the potential to allow this technique to be applied in a more mainstream setting.⁹⁹

Bond formation using ultra-violet light irradiation in synthetic organic chemistry has a long history dating back to the mid-19th century. The most common apparatus, which had been used for the past 50 years, was the immersion-well photo-reactor in conjunction with mercury-vapor-discharge lamps. Although pioneering work has been achieved in this field, many chemists shied away from photochemistry due to several pitfalls associated with the batch method. The equipment was often not suitable and it may have been difficult to identify the right lamp for the proper irradiation. Additionally, safety concerns such as over-heating mercury lamps and potentially damaging UV radiation have rendered the technique less desirable.

Finally, and perhaps the biggest issue with the medium, was the difficulty to scale up, at least at the laboratory scale, limiting synthetic efforts. Therefore, this method has been underutilized and many interesting bond connections were not achieved photochemically.

Flow chemistry has begun to emerge about 15 years ago and has been pioneered by the Ley group and others.¹⁰⁰ This technology has started to make a major impact in the way many organic chemists perform synthesis. Complex organic molecules can be constructed continuously in well-designed multi-reactor systems linked in sequence and under precise software control allowing to perform nearly all-common reaction which were usually run in batch.
Flow chemistry has made photochemistry more attractive as it has solved many of the issues associated with the technique. Under flow conditions, only a very small amount of the total reaction solution is exposed intense UV irradiation from the light source at a given time, thus leading to very efficient, uniform irradiation of the whole reaction solution over time. Both the under and over irradiation problems, often encountered when performing batch reaction, can be addressed by precisely controlling the UV exposure using different flow-rates and reactor volumes. Scaling-up is now allowed efficiently. Flow devices usually operate continuously and therefore are scale independent, a single reactor can in principle be used to process a few milligrams of substrate up to nearly a kilogram per day. Both high concentration and very low concentration are enabled due to shorter path length. Finally, most of the safety concerns are alleviated. With this method, the bulk of the solution is kept remote from the lamp and only a minimal amount of flammable solvent is near a potential ignition source at any one time.

Scheme 3. 21. Seeberger's Flow-Mediated Synthesis of Artemisin 4.6.



The synthesis of artemisisin was achieved by Seeberger and coworkers, using flow photochemistry (**Scheme 3.21**).¹⁰¹ Photo-oxidation of dihydroartemisinic acid **3.131** to tertiary allylic hydroperoxide **3.136** was achieved using a 20 mL volume device consisted of fluorinated

ethylene propylene (FEP) tubing wrapped around a Schlenk photochemical reactor containing a 450W medium-pressure mercury lamp that was cooled to 25 °C. A solution of 3.131 in dichloromethane (2.5 mL.min⁻¹) was added by a Vapourtec R2C+ pump and oxygen gas (5 mL.min⁻¹) was delivered by a mass-flow controller connected to a gas cylinder. The solution of 3.131 and the oxygen gas were mixed using an ethylene tetrafluoroethylene (ETFE) T-mixer. Tetraphenylporphyrin (TPP) was used as a sensitizer. Under these conditions, 1.5 mmol of 3.136 was produced per minute, in 91% conversion and 75% yield. Then, the Hock cleavage was investigated independently and TFA was found to be the best Brønsted acid to mediate this reaction.¹⁰² Optimal results were obtained when a 42 mL reactor was used with the solution of 3.131 in dichloromethane added at a flow rate of 2.5 mL.min⁻¹, oxygen at 5.0 mL.min⁻¹, and TFA in dichloromethane at 0.5 mL.min⁻¹. The first portion of the reactor (32 mL) was maintained at room temperature while the last portion (10 mL) was heated to 60 °C to push the reaction to completion. Hock cleavage took place in a PTFE reactor (26 mL volume total, with 16 mL maintained at room temperature and 10 mL heated at 60°C). A residence time of approximately 2.5 min was required for the Hock cleavage, oxidation with triplet oxygen, and further condensation. After a total residence time of 4.5 min, a product stream comprising mainly artemisinin was obtained in a 39 % from 3.6 after purification. This gave us confidence that endoperoxides could be obtained using this method.

3.3.2 Flow-Mediated Synthesis of Endoperoxide 3.8

3.3.2.a Initial Set-Up

Our studies were initiated with the preparation of monoalkylidene **3.11** described in **Chapter 2**, followed by the evaluation of different solvent systems in batch, using a Rayonet apparatus for

irradiation. We obtained a 20% yield of a **3.8** using dichloromethane and methanol as a solvent system, which was saturated with oxygen (**Table 3.1, entry 1**).

Adding a triplet sensitizer, either in stoichiometric or catalytic amount, did not improve the reaction yield (**Table 3.1, entries 2-4**). Switching to triplet sensitizing solvent also yielded 20 % of **3.8** (**Table 3.1, entry 5**). We then hypothesized that a base could facilitate the formation of the require dienol intermediate **3.10**. Adding a catalytic amount of DBU decreased the yield by half producing only 10 % of the desired endoperoxide.

Inclusion of either triplet sensitizers or bases was found to be inefficient. Accordingly, we decided to utilize dichloromethane and methanol to develop photo-flow conditions (**Table 3.1**, entries 6 and 7).

Table 3. 1. Optimization Studies for the Synthesis of Endoperoxide 4.8.



| Entry | Solvent | Additives (equiv) | Process | Yield (3.8) |
|-------|--|---------------------------|---------|---------------|
| 1 | CH ₂ Cl ₂ :MeOH (1:1) | none | Rayonet | 20 % |
| 2 | CH ₂ Cl ₂ | Rose Bengal (1 equiv) | Rayonet | Decomposition |
| 3 | CH ₂ Cl ₂ | Rose Bengal (2.5 mol%) | Rayonet | 20 % |
| 4 | CH_2Cl_2 | Benzophenone | Rayonet | Decomposition |
| 5 | Acetone | none | Rayonet | 20 % |

| 6 | CH_2Cl_2 | DBU (0.1 equiv) | Rayonet | 10 % |
|---|--|---|--|---------------|
| 7 | CH_2Cl_2 | DBU (0.1 equiv) Rose Bengal (2.5 mol%) | Rayonet | Decomposition |
| 8 | CH ₂ Cl ₂ :MeOH (1:1) | none | Flow (rate= 0.6 mL/min; RT = 5.1 min) | 40 % |
| 9 | MeOH | none | Flow (rate=0.5mL/min; RT= 6.2 min) | 54 % |

We used Idex Health Science PFA (perfluoroalkoxyalkane) tubing (ID 0.062 in, OD 0.125 in, 500 psi max pressure). This material offered the advantage to be highly transluscent and to have higher tolerance for high temperature and a broader chemical compatibility. The reactor was 1.614 meter in length and the total volume was 3.1 mL. The lamp provided UV light at 350 nm. Using a flow rate of 0.6 mL.min⁻¹ provided 40 % of the diastereomeric mixture (**Table 3.1, entry 8**). Switching the solvent to methanol and slowing down the flow rate provided 50 % of the diastereomeric mixture (**Table 3.1, entry 9**). The flow-chemistry set-up is shown in **Figure 3.4**.

These results demonstrated that flow photochemistry is superior to regular batch photochemistry for this process probably reducing the decomposition of products. Additionally, we believe that the dienol **3.10** formation is photo-mediated whereas the [4+2] reaction may not be and may involve triplet oxygen (see Chapter 3, 3.1.2). This was reported for similar substrates, by Andre-Barres and coworkers.¹¹



Figure 3. 4. Flow Set-Up for The Synthesis of Endoperoxides 3.8.

3.3.2.b Disatereomeric Outcome: Discussion and Rationale

In this process, both diastereomers of **3.8** are formed in a ratio close to 1:1. This prompted us to undertake model studies. Both the *cis*-dienol **3.10B** and the *trans*-dienol **3.10A** can form during the photo-enolization process. After performing DFT calculations, the *trans*-dienol **3.10A** was found to be slightly lower in energy by 1.77 kcal.mol⁻¹ at ground-state (Figure 3.5). Since formation of both dienols involves photo-irradiation, this process may likely implicate excited state intermediates and therefore the ground-states energy difference may not influence the reaction outcome. The [4+2] cycloaddition with oxygen may then occur and produce *trans*-endoperoxide **3.8A** and *cis*-endoperoxide **3.8B**. DFT calculations have found that *trans*-endoperoxide **3.8A** and *cis*-endoperoxide **3.8B** were only separated by 0.19 kcal.mol⁻¹ and we experimentally observed a 1:1 ratio for this process. Therefore, the formation of the dienol may likely influence the diastereomeric outcome of this process.

Exposing dienols to triplet oxygen was the limiting factor in this flow set-up. The reactions were run with balloons of oxygen constantly bubbling in the starting material flask and the receiving flask. Because it was difficult to control the amount of oxygen incorporated in the solvent the reliability of this process was low.

Figure 3. 5. DFT Models for 3.10 and 3.8.



3.10A (*trans*) rel. E: 0 kcal.mol⁻¹ **3.10B** (*cis*) rel. E: 1.77 kcal.mol⁻¹



3.8A (*trans*) rel. E: 0 kcal.mol⁻¹ **3.8B** (*cis*) rel. E: 0.19 kcal.mol⁻¹

Additionally, we observed the formation of several non-isolable byproducts with higher molecular masses and some decomposition during the course of the reaction. Decreasing the concentration of the starting material solution helped reducing the occurrence of high molecular mass byproducts. Decomposition was still an issue and may have been due to the presence of irradiated oxygen in the photo-enolization process. Utilizing only one balloon of oxygen in the receiving flask did not yield any products probably because the amount of oxygen in contact with the dienols was not sufficient.

3.3.2.c Improved Flow Set-up: Preliminary Studies

To improve the yield for the endoperoxides formation and obtain a cleaner reaction profile, we decided to revisit the flow set-up. We attached a chamber containing a PFA gas porous tubing loop to the photo-box exit. This chamber could be sealed and put under a constant pressure of oxygen. The oxygen pressure could be controlled with a back-pressure regulator (**Figure 3.6**). Our hypothesis was that by suppressing the oxygen from the starting material solution and therefore in the photo-enolization process the reaction profile would be significantly cleaner. Additionally, applying a sufficient pressure of oxygen in the chamber could efficiently promote the [4+2] cycloaddition.



Figure 3. 6. Oxygen Pressured Flow Set-up.

Our initial experiment was done with an oxygen pressure of 4 PSI and a flow rate of 0.7 ml.min⁻¹. It provided only 10 % of a 1:1 mixture of **3.8A** and **3.8B**. The mixture of **3.8A** and **3.8B** was the only product observed in this reaction and unreacted monoalkylidene **3.11** constituted the rest of the mass balance(**Scheme 3.23a**). When the flow rate was decreased to 0.46 mL.min⁻¹ the yield was doubled and the reaction profile remained clean (**Scheme 3.23b**).

We believed that in this case the low conversion observed was due to the limited formation of dienol **3.10** from **3.11**. This may be explained by several phenomena. The flow rate may be too rapid to allow for a complete conversion of **3.11** to **3.10** and therefore some non-reacted **3.11** remained in the reaction.



Scheme 3. 22. Initial Experiment with the Oxygen Pressured Flow Set-Up.

Additionally, several questions regarding the lifetime of the dienol were brought to our attention. In their work, Weedon and coworkers, found that after being formed from **3.134**, dienol **3.135** was involved in a reketonization process *via* a 1,5 hydride shift. This process was found to be very rapid and the half-lifes of the studied dienols were ranging from 20-100 μ s (**Scheme 3.23**).¹⁰³

Scheme 3. 23. Weedon's Dienol Lifetime Studies.



Therefore, we believed that in our studies dienol **3.10** may be involved in a similar process and when dioxygen was added at the end of the photoenolization only a small amount of reactive dienol **3.10** was available to react. This may explain the lower yields observed in the second flow set-up experiments. The cleaner reaction profile may be explained by the fact without irradiation the dienol **3.10** can only engage in a reketonization process and reform **3.11**. Additionally, the reketonization may be faster than the cycloaddition with oxygen impairing the conversion of **3.10** to **3.8** even more. In the first set-up the presence of oxygen in the irradiation process may help trap the dienol promptly which may explain the higher yields observed but it may also caused byproducts formation which may explain the messy reaction profile.

Future development may involve the determination of a slower optimal flow rate to obtain a higher yielding process as well as the determination of a more efficient way to incorporate oxygen in the reaction.

3.3.3 Rhodomyrtosone A

With a reliable way to produce endoperoxide **3.8**, we next investigated the synthesis of rhodomyrtosone A **3.1**, in order to develop methodology for *bis*-furan-containing natural product syntheses. Endoperoxide **3.8** and acyl-phloroglucinol **3.7** were submitted to acidic conditions (excess AcOH) and heat and provided the *bis*-furan containing rhodomyrtosone A **3.1** in 60 % yield (**Scheme 3.24**).

Scheme 3. 24. Synthesis of Rhodomyrtosone A 3.1.



This methodology could be utilized to access watsonianone B and more complex members of the family.

3.3.4 Mechanistic Studies

In our proposed retrosynthetic analysis, we discussed two mechanisms for the formation of the *bis*-furan during the synthesis of rhodomyrtosone A **3.1** (Scheme 3.2). We decided to perform a mechanistic experiment by following a reaction by ¹H NMR in order to track reactive

intermediates formation under acidic conditions. We submitted a solution of endoperoxide **3.8** (one isolated diastereomer) in CDCl₃ to 30 mol % of triflimide (**Figure 3.7**). After five minutes, the hydroxyl proton had disappeared letting us suspect that protonation of the hydroxyl group may have occured. After one hour, a peak at 9.64 ppm started to form. After five hours a ratio of 1.4:1 was observed between the peak at 9.64 ppm and the protons at 4.73 ppm (H-8) and at 7.29 ppm (H-7). This suggested that about 40 % of the endoperoxide had converted to a non-isolable reactive intermediate.

We propose that the reactive intermediate formed may be tetraketone **3.14** or active peroxycarbenium intermediate **3.13**.¹⁰⁴ We calculated a model of **3.14** and estimated the ¹H NMR and ¹³C NMR spectra of **3.14** by using an EDF2, DFT equilibrium geometry conformer model (**Figure 3.8**). A peak at 8 ppm was found to account for the vinylic proton H_a . Additionally, similar compounds were successfully isolated by other researchers and are reported to have vinylic protons in the 8 to 9 ppm range. ¹⁰⁵ The experimental data and the calculated and reported data differed by more than 1 ppm. Although our experiments showed the formation of reactive intermediates, the data gathered were not sufficient to clearly identify the type of intermediate formed.

Figure 3. 7. ¹H NMR Studies: Evidence for the Formation of Diketone 3.14.





Figure 3.8. Model of Tetraketone 3.14.



To shed some light on this mechanism and try to identify which intermediates were involved in this process we engaged in an independent synthesis of tetraketone intermediate **3.14** (Scheme **3.25**). 3-Methyl-2-butanone **3.136** was oxidized to aldehyde **3.137** using selenium dioxide in low yield following a reported procedure.¹⁰⁶ Condensation with syncarpic acid **3.138** and pyrrolidine provided adduct **3.139**. Several acidic conditions were attempeted to eliminate the pyrrolidine and obtain **3.14**. Biphasic conditions involving ammonium chloride dissolved in hydrochloric acid and dichloromethane let to no reaction. Using trifluoroacetic acid was also unsuccessful as it yielded to decomposition and formation of unidentifiable byproducts. Finally, a substoichiometric amount of triflimide was attempted without success.

Scheme 3. 25. Independent Synthetic Work toward Tetraketone 3.14.



Although mechanistic evidence strongly support the formation of an active intermediate during the formation of rhodomyrtosone A **3.1**, the nature of this intermediate remains unclear. Both peroxycarbenium intermediate **3.13** and diketone **3.14** are possible relevant intermediates in the process, determination of the order of events for the 1,4 addition of **3.8** with acylphloroglucinol **3.7** will require further studies. Either the 1,4 addition may occur with the peroxycarbenium intermediate **3.13** and a rearrangement may occur and form a diketone intermediate or the diketone **3.14** may form first and then the 1,4 addition may occur (**see Scheme 3.2**).

3.3.5 Plan for the Syntheses of Tomentosones A and B

During the course of our studies, we developed a reliable way to prepare endoperoxides, produce *bis*-furan core with the synthesis of rhodomyrtosone A **3.1** and in **Chapter 2** we

presented our nickel-mediated 1,4 conjugate addition. With these synthetic tools in hand we are proposing two synthetic routes to access the tomentosones **3.2-3.3**.

In our first proposed route, endoperoxide **3.8** may be reacted with racemic rhodomyrtone A **3.140** under acid-mediated conditions to produce a diastereomeric mixture of tomentosone A **3.2** and B **3.3** (Scheme 3.26).

Scheme 3. 26. Synthesis of Tomentosones A and B from Rhodomyrtone A.



Alternatively, we could use our nickel-mediated 1,4 conjugate addition methodology with rhodomyrtosone A **3.1** and monoalkylidene **3.11** to obtain a 1,4 adduct intermediate **3.141**. Dehydrative cyclization of **3.141** under acid conditions may provide a mixture or regioisomers **3.2**, **3.3** and **3.142** resulting respectively from the *para*-phenol and *ortho*-phenol cyclization. We believe that the additional hydrogen bond between the *para*-phenol and the monoalkylidene ketone may render the *para* phenol sufficiently nucleophilic⁵² to compete with the *ortho* cyclization (**Scheme 3.27**).



Scheme 3. 27. Synthesis of Tomentosones A and B from Rhodomyrtosone A.

3.4 Studies Toward the Bullataketals

Bullataketals A **3.143** and B **3.144** were isolated from the leaves of the plant *Lophomyrtus bullata* in New Zealand.¹² Named "ramarama" by the Maori people, it was extensively used as a folk medicine to dress cuts and bruises. The dichloromethane extracts demonstrated cytotoxic and more importantly antibiotic activities, which confirmed the traditional ethno-pharmacopeia and later were attributed to bullataketals A **3.143** and B **3.144** (Figure 3.9).

Figure 3.9. Bullataketals A and B.



Both **3.143** and **3.144** possess a β -triketone moiety (syncarpic acid) attached by an alkyl linkage to a phloroglucinol derived bicyclic ketal. They were isolated as racemates. Importantly, this unique bicyclic ketal structure has been observed in only three other natural products named castavinols **3.145-3.147** (Figure 3.10). The castavinols were isolated from Bordeaux red wines and also possess the unique [3.2.1]-bicyclic ketal moiety.¹⁰⁷





An estimated 287,963 people are currently living with leukemia in the United States. About 48,000 new cases were diagnosed in 2013 leading to an estimated 24,000 deaths. Although the survival rate for leukemia nearly doubled in the last 30 years, there is still an outstanding need for efficient treatments. Bullataketals A **3.143** and B **3.144** demonstrated activity against P388 mouse leukemia cell line with IC₅₀ of 1 μ g.ml⁻¹. They also showed antibiotic activity against *Bacillus*

subtilis with an IC₅₀ of 30 μ g per disk. These biological activities render these targets very attractive from a medicinal point of view and for further SAR studies.

No syntheses have been achieved to date for the bullataketals **3.143-3.144**, which added to their unique and challenging structure and their interesting biological activities, makes them compelling synthetic targets and warrants investigation.

The proposed structure for bullataketals A **3.143** and B **3.144** was ultimately confirmed by X-ray crystallography. Interestingly, the bullataketals A **3.143** and B **3.144** co-crystallized in a single unit cell, a phenomenon also oberserved for the kunzeanones A and B.¹⁰⁸ Bullataketals A **5.1** and B **5.2** were found to be epimeric at C-7'.

3.4.1 Biosynthesis

We were interested in developing a biomimetic synthesis for the bullataketals A **3.143** and B **3.144** based on the proposed biosynthetic pathways discussed in the literature.

In their work during the isolation of the bullataketals A **3.143** and B **3.144**, Perry and coworkers proposed an aldol reaction/reduction sequence between acylated phloroglucinol **3.152** and compound **3.153** to account for the formation of intermediate **3.154**.¹ The authors also proposed that the central acyl phloroglucinol fragment **3.152** may be derived from isobutyryl-CoA **3.149** by a polyketide synthase (PKS) leading to **3.151** and then adding three malonyl-CoA units **3.150**. Then a poly-methylation of **3.152** with S-adenosyl methionine (SAM) may lead to the formation of **3.153**. A first Aldol reaction/reduction sequence involving the fragments **3.152** and **3.153** may provide **3.154**, which will undergo a second Aldol reaction/reduction sequence with intermediate **3.158** to yield **3.159**. Intermediate **3.158** may stem from a biosynthetic Claisen condensation of benzoyl-CoA **3.155** and **3.151** followed by a dehydrative cyclization to form bullatenone **3.158**. Bullatenone **3.158** was co-isolated with the bullataketals and therefore may

likely be a relevant intermediate in their biosynthesis. Intermediate **3.159** may undergo an acid catalyzed cyclization to afford bullataketals A **3.143** and B **3.144** (Scheme 3.28).

Scheme 3. 28. Perry's Bullataketals A and B Proposed Biosynthesis.



3.143 and 3.144 bullataketals A and B

In their isolation of the castavinols **3.145-3.147**, Vercauteren and coworkers proposed that the pyrylium intermediate **3.160**, derived from the malvidin family, may react with a diacetyl unit

3.161 to form oxonium **3.162** (Scheme 3.29). Upon addition of the non-conjugated alkene into the ketone, the bicyclic ketal **3.163** may form while generating a tertiary oxonium. An enzymatic reduction may provide the desired castavinols bicyclic ketal **3.164**.

Both biosynthetic proposals offer some insight on possible reaction intermediates, which could be envisioned for the synthesis of the bullataketals **3.143-3.144**. Bullatenone **3.158** may be an intermediate in the synthesis, which also may require the formation of an activated oxonium species for the formation of a bicylic ketal core.

Scheme 3. 29. Vercauteren's Proposed Castavinols Biosynthesis.



3.4.2 Retrosynthetic Analysis

Compelled by the aforementioned proposed biosynthesis, we were interested in proposing a biomimetic synthesis for the bullataketals A **3.143** and B **3.144**. We envisioned that the bullataketals A **3.143** and B **3.144** may be obtained from the 1,4 conjugate addition of intermediate **3.164** with monoalkylidene **3.60**, which would be derived from syncarpic acid **3.138** (**Scheme 3.30**). Intermediate **3.164** may be obtained from a formal [3+2] cycloaddition involving the addition of acyl phloroglucinol **3.166** with a reactive vinyloxocarbenium intermediate **3.165**,

which itself may be obtained rapidly from bullatenone **3.158** through reductive dehydration. Bullatenone **3.158** may be obtained from benzoyl chloride **3.167** and alkyne **3.168** by a Sonogashira coupling/cycloisomerization sequence. Acyl phloroglucinol **3.166** may be obtained from a selective acylation of phloroglucinol **3.9** (Scheme 3.30).

Scheme 3. 30. Retrosynthetic Analysis for Bullataketals A 5.1 and B 5.2.



3.4.3 Previous Work: Bullatenone Synthesis

Bullatenone **3.158** was isolated in 1954 by Taylor and coworkers¹⁰⁹ form the shrub *Myrtacea bullata*. It was synthesized and its structure unambiguously assigned in 1958 by Wilkinson and coworkers.³ In their synthesis, Wilkinson and coworkers began with acetylenic diol **3.169**, which was oxidized to ynone **3.170** using a Jones oxidation. The ynone **3.170** was then reacted with an

ethanolic diethylamine solution followed by acid treatment to provide bullatenone **3.158** in 60 % yield (**Scheme 3.31**).

Scheme 3. 31. First Synthesis of Bullatenone 5.19.



The ynone intermediate **3.170** seemed to be a relevant intermediate in the synthesis of bullatenone and therefore we were interested in finding a more expeditious way to obtain **3.170**, which will not require harsh conditions or high pressure of carbon dioxide as reported by Inoue and coworkers.¹¹⁰

Attracted by the idea of utilizing a mild Sonogashira reaction for the preparation or **3.170** we were pleased to find that Maleczka and coworkers developed a methodology to enable Sonogashira coupling of alkyne **3.171** with aromatic acyl chloride **3.172** to obtain ynones **3.170**, **3.173-3.174** (Scheme 3.32).¹¹¹ Using polymethylhydrosiloxane (PMHS) as an additive with cesium fluoride, copper chloride and NMP as solvent, they obtained ynones **3.170**, **3.173-3.174** in 47 %, 68 % and 73 % yields respectively (Scheme 3.32).

Scheme 3. 32. Maleczka's Ynone Synthesis.



Similarly, Müller and coworkers developed mild Sonogashira conditions during their synthetic work towards iodopyrroles. Using aromatic acyl chloride 3.175 and alkyne 3.176 in the presence of catalytic PdCl₂(Ph₃P)₂ and copper iodide they were able to prepare ynones **3.177**, which were readily reacted sodium iodide under acidic conditions to produce 4-iodopyrroles 3.178 in moderate to high yields (Scheme 3.33).¹¹²

Scheme 3. 33. Müller Iodopyrroles Synthesis.



3.178 11 examples, 61% to 74 %

3.4.4 Synthesis of Vinyloxocarbenium Precursor

Our synthesis of bullataketals 3.143 and 3.144 began with the preparation of the vinyloxocarbenium precursor 3.179. Synthesis of 3.179 began with Sonogashira cross-coupling of benzoyl chloride 3.180 with the commercially available alkyne 3.181, which afforded ynone 3.170 in 60 % yield (Scheme 3.34).¹¹³ Diethylamine-mediated cycloisomerization of 3.170 provided bullatenone 3.158 in 40 % yield.⁴ This synthesis was one step shorter than Wilkinson's and coworkers. DIBAL-H-mediated 1,2 reduction of 3.158 in a THF: Toluene (1:1) solvent mixture provided alcohol 3.179 quantitatively (Scheme 3.34).



Scheme 3. 34. Synthesis of a vinyloxocarbenium precursor 3.179.

3.4.5 Formation of Core 3.164

Our hypothesis was that bullataketal core **3.164** could be accessed by reacting bullatenol **3.179** and acyl phloroglucinol **3.167** under acidic conditions, which would allow for the active vinyloxocarbenium **3.165** species to form (**Scheme 3.35 a**).

During this reaction, both the *ortho* and *para* -phenol of acyl-phloroglucinol **3.167** may react as the nucleophile in the cyclization event occurring in the second step to provide **3.164** and **3.164'**. This regio-selectivity question is similar to the one raised during our studies toward rhodomyrtone A and rhodomyrtosone B (see **Chapter 2**). A similar rationale could be utilized to explain the outcome of this process. DFT minimization studies of **3.164** and **3.164'** models showed that **3.164** was thermodynamically favored by 8 kcal.mol⁻¹ (**Figure 3.12**), Additionally **3.164** was also found more stable than the adduct **3.165'** resulting from the 1,4 addition of acylphloroglucinol **3.167** with vinyloxocarbenium **3.165**. Finally, the *ortho*-phenol of acylphloroglucinol **3.167** may be rendered more nucleophilic due to the proximity of the acyl ketone, which may form an activating hydrogen bond with the *ortho* phenol.



Scheme 3. 35. Formation of the Bullataketals Core.

Therefore, in this process the *ortho* cyclization may be kinetically and thermodynamically favored and **3.164** was expected to be formed may **3.164** exclusively. We were pleased to obtain **3.164** exclusively in 18 % yield by using catalytic triflimide in chloroform (**Scheme 35.b**). We proposed that a vinyloxocarbenium carbenium intermediate may be involve in this process although mechanistic studies would be necessary to confirm the involvement of such intermediate. NOESY data allowed us to assign **3.164** to be the desired core, these data are reported in the supporting information section.





3.4.6 Future Plan: End Game

With a methodology available to access the core of the bullataketal core **3.164**, we proposed to access the bullataketal A **3.143** and B **3.144** by using the methodology we developed for the synthesis of rhodomyrtosone A **3.1**. The last step would involve our previously described nickel-mediated 1,4 conjugate addition. Reacting monoalkylidene **3.60** with the core **3.164** may afford bullataketals A **3.143** and B **3.144** as a mixture of diastereomers (**Scheme 3.36**).

Scheme 3. 36. Nickel-Mediated 1,4 Conjugate Addition for the Bullataketals End Game.



We believe that an enantioselective synthesis of the bullataketals could be easily accessible. Using chiral Bronsted acids, including BINOL-based *N*-triflyl thiophosphoramide 3.180^{114} or BINOL-phosphoric acid catalysts¹¹⁵ may afford a chiral ion pair during the formation of vinyloxocarbenium 3.165 this may provide enantio-enriched 3.164. Additionally, using chiral ligands such as PyBox ligands for the nickel-mediated 1,4 conjugate addition may allow to

control the enantioselectivity of the last step to afford bullataketal A or B selectively (Scheme 3.37).

Scheme 3. 37. Proposed Enantioselective Synthesis of Bullataketals.



3.5 Conclusion

In this chapter, we described the synthesis of rhodomyrtosone A **3.1** *via* a flow photochemical process and the synthesis of the bullataketals core **3.164**. For both syntheses, the implication of a peroxycarbenium or a vinyloxocarbenium during the acid-mediated formation of the *bis*-furan or bicyclic ketal core was proposed. Acid-mediated formation of rhodomyrtosone **3.1** and **3.164** was undertaken and ¹H NMR mechanistic studies provided preliminary evidences for the formation of active carbenium species. Application of these newly developed reaction methodologies to the synthesis of more complex targets and to the enantioselective synthesis of the bullataketals was proposed.

3.6 Experimental Section

3.6.1 General Information

¹H NMR spectra were recorded at either at 400 MHz or 500 MHz (as noted) at ambient temperature with CDCl₃ as the solvent unless otherwise stated. ¹³C NMR spectra were recorded either at 100.0 MHz or 125.0 MHz (as noted) at ambient temperature with CDCl₃ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (¹H, δ 7.27; ¹³C, δ 77.0). Data for ¹H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. All ¹³C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF mass spectrometer. Melting points were recorded on a Mel-temp (Laboratory Devices). Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Preparative TLC was conducted with glass backed 1000 µm silica gel 60-F plates (Silicycle, Inc.). Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Preparative HPLC was performed using the Gilson[™] PLC 2020 and a SunFire[™] preparative C18 column (OBD[™] 5 µm, 19x50 mm). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. All reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise noted. The ArthurTM Suite Reaction Planner (Symyx Technologies, Inc.) was used for experimental procedure planning.

HPLC grade tetrahydrofuran, methylene chloride, diethyl ether and hexanes were purchased from Fisher and VWR and were purified and dried by passing through a PURE SOLV[®] solvent

purification system (Innovative Technology, Inc.). Methanol was purchased from Fisher and used after distillation following a procedure previously described by Lund and Bjerrum.⁷²

3.6.2 Characterization Data

All chemicals and reagents were used as received from Sigma-Aldrich. Acyl-phloroglucinols **3.7** and **3.167** were prepared following a previously described procedure.⁷⁴ Ynone **3.170** was prepared following a reported procedure by Muller and coworkers³⁸ and bullatenone **3.158** was prepared following a reported procedure by Wilkinson and coworkers.³ The procedure to prepare monoalkylidene **3.11** was described in **Chapter 2, section 2.9.3.** Compound **3.137** was obtained using a reported procedure and characterization have also been reported.^{106, 116}

Experimental Procedure for the formation of endoperoxides 3.8A and B:

Rayonet procedure:



A 0.01M solution of monoalkylidene **3.11** (40 mg, 0.16 mmol) was prepared in 16 mL of methanol in a flamed dried pyrex tube under argon at room temperature. A balloon of oxygen was bubbled through the solution until it was completely empty. This operation was repeated twice. The pyrex tube with a balloon of oxygen still bubbling through was placed in a ice-filled beaker in order to avoid over-heating during the irradiation process and to maintain a temperature close to 23 °C during the overall process. The beaker was placed in the Rayonet apparatus for 6 h and the balloon of oxygen was replaced as needed to maintain an oxygen flow during that time. After 6 h, the reaction was stopped and the solvents were evaporated *in vacuo*. Purification using

column chromatography over silica gel and a gradient of hexanes:acetone (20:1 to 10:1) provided 9 mg , 20 % yield of **3.8** as a 1:1 mixture.

Flow procedure:



A 0.01M solution of monoalkylidene **3.11** (80 mg, 0.32 mmol) was prepared in 32 mL of methanol in a flamed dried flask under argon at room temperature. A balloon of oxygen was bubbled through the solution until it was completely empty. This operation was repeated twice. The reaction flask with a balloon of oxygen still bubbling through was placed hooked to the flow set-up. We used Idex Health Science PFA (perfluoroalkoxyalkane) tubing (ID 0.062 in, OD 0.125 in, 500 psi max pressure). This material offered the advantage to be highly transluscent and to have higher tolerance for high temperature and a broader chemical compatibility. The reactor was 1.614 meter in length and the total volume was 3.1 mL. The lamp provided UV light at 350 nm. A chiller maintain set to -10 °C and a fan were used to maintain the overall temperature at 23 °C. The optimal flow rate used was 0.5 mL.min⁻¹. After the entire solution was replaced by a waste container. The irradiation was stopped. The flow set-up was flushed clean with benzene. The solution contained in the receiving flask was collected and the solvent was evaporated *in vacuo*. Purification using column chromatography over silica gel and a gradient of hexanes:acetone (20:1 to 10:1) provided 45 mg of **3.8** as a 1:1 mixture.

Characterization data for both diastereomers can be found in Chapter 2, Section 2.9.3.





A solution of endoperoxides **3.8** (1:1 mixture) (6 mg, 0.021 mmol) in acetic acid 1mL was placed in a sealed tube and heated a 100 °C for 12 h. Then the reaction mixture was dissolved with water and quenched with a saturated sodium bicarbonate solution. The pH was kept slightly acidic. The reaction mixture was extracted with ethyl acetate (3 times) and the organic fractions were gathered and dried over anhydrous sodium sulfate. The solvents were evaporated *in vacuo* to yield a dark yellow oil. Purification by column chromatography over silica gel provided 6 mg (60 %) of **3.1** as a pale yellow gum.

 $\mathbf{R}_{\mathbf{f}}$: 0.7 hexanes: EtOAc 1:1

IR (thin film): 2960.88, 2930.37, 2873.99, 1720.40, 1649.79, 122.93, 1469.93, 1420.62, 1384.14, 1305.44, 1215.98, 1171.78, 1052.58, 921.63 cm⁻¹

¹**H NMR (500 MHz, Chloroform-***d*): δ 13.27 (s, 1H), 9.79 (s, 1H), 6.11 (s, 1H), 4.49 (s, 1H), 2.96 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.76 (dd, *J* = 14.7, 7.2 Hz, 1H), 2.40 (d, *J* = 6.8 Hz, 1H), 1.52 (s, 3H), 1.42 (d, *J* = 5.3 Hz, 6H), 1.34 (s, 3H), 1.10 (dd, *J* = 11.8, 6.8 Hz, 6H), 1.00 (dd, *J* = 10.8, 6.7 Hz, 6H).

¹³C NMR (126 MHz, cdcl₃): δ 211.28, 203.82, 198.45, 179.82, 166.83, 159.90, 159.76, 129.50, 113.32, 104.34, 101.84, 99.70, 55.26, 51.69, 45.76, 45.10, 35.50, 26.06, 24.50, 24.26, 23.28, 22.91, 22.87, 15.87, 15.81

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{26}H_{32}O_7$; 457.2226 found, 457.2218

Table 3. 2. NMR Data Comparison for Synthetic Rhodomyrtosone A and Natural

Rhodomyrtosone A.



| | ¹³ C NMR(ppm) | | ¹ H NMR (ppm, | mult, J Hz) |
|----|--------------------------|---------------|--|---|
| C# | | ~ | | |
| | Natural 3.1 | Synthetic 3.1 | Natural 3.1 | Synthetic 3.1 |
| 1 | 198.3 s | 198.45 | | |
| 2 | 55.1 s | 55.26 | | |
| 3 | 211.1 s | 211.28 | | |
| 4 | 45.6 s | 45.76 | | |
| 4a | 179.7 s | 179.82 | | |
| 4b | 159.8 s | 159.9 | | |
| 5 | 101.7 s | 101.84 | | |
| 6 | 166.7 s | 166.83 | | |
| 7 | 99.6 d | 99.7 | 6.11 (s) | 6.11 (s) |
| 8 | 159.6 s | 159.76 | | |
| 8a | 104.2 s | 104.34 | | |
| 9 | 45.0 d | 45.1 | 4.50 (s) | 4.49 (s) |
| 9a | 113.2 s | 113.32 | | |
| 10 | 24.4 q | 24.5 | 1.52 (s) | 1.52 (s) |
| 11 | 24.1 q | 24.26 | 1.42 (s) | 1.42 (d, 5.3) |
| 12 | 23.1 q | 23.28 | 1.34 (s) | 1.34 (s) |
| 13 | 25.9 q | 26.06 | 1.41 (s) | 1.42 (d, 5.3) |
| 1' | 203.7 s | 203.82 | | |
| 2' | 51.5 t | 51.69 | 2.96 (dd, 14.7, 6.6), 2.76 (dd, 14.7, 6.6) | 2.96 (dd, 14.7, 6.6), 2.76 (dd, 14.7, 7.2) |
| 3' | 25.8 d | 25.94 | 2.17 (m, 6.6) | 2.17 (m, 6.6) |
| 4′ | 22.8 q | 22.91 | 1.01 (d, 6.6) | 1.00 (dd, 10.8, 6.7) |
| 5' | 22.7 q | 22.87 | 0.99 (d, 6.6) | 1.00 (dd, 10.8, 6.7) |
| 1″ | 129.4 s | 129.5 | | |
| 2″ | 35.4 d | 35.5 | 2.40 (hept, 6.9) | 2.40 (hept, |

| | | | | 6.8) |
|------|--------|-------|---------------|-------------------------|
| 3″ | 15.7 q | 15.87 | 1.11 (d, 6.9) | 1.11 (dd, 11.8, 6.8) |
| 4″ | 15.6 q | 15.81 | 1.09 (d, 6.9) | 1.09 (dd, 11.8, 6.8) |
| 6-OH | | | 13.27 (s) | 13.27 (s) |
| 8-OH | | | 9.78 (s) | 9.79 (s) |

Experimental Procedure for the mechanistic studies with endoperoxides 3.8:



Pure diastereomer 1 (see chapter 2) (6 mg, 0.021 mmol, 1 equiv) was dissolved in 0.5 mL of $CDCl_3$ and placed in an NMR tube. A triflimide solution (15.3 mg in 1 mL of CDCl3) was prepared. At t= 0 min, 0.1 mL of the triflimide solution (1.53 mg, 0.006 mmol, 0.3 equiv) was added to the NMR tube. ¹H NMR spectra were acquired at 5 min, 15 min, 1 h, 2.2 h, 3 h and 5 h.

Experimental Procedure for the formation of bullatenol 3.179:



Bullatenone **3.158** (50 mg, 0.26 mmol, 1 equiv) was placed in a flask under argon at 0 °C. A 1:1 solution of THF:toluene was prepared and 2 mL were added to the reaction flask. DIBAL-H (1M in hexanes, 364 μ L, 0.364 mmol, 1.4 equiv) was added at -78 °C to the reaction mixture. The mixture turned bright orange. The reaction mixture was allowed to warm up to room temperature and was stirred until TLC analysis showed complete consumption of the starting material (about 30 min). Then, it was quenched with a Rochelle salt solution. The reaction mixture was

thoroughly washed with brine and extracted with ethyl acetate. Gathered organic fractions were dried over anhydrous sodium sulfate and solvents were evaporated *in vacuo* to yield 50 mg (quant. yield) of a bright yellow-orange oil.

 $\mathbf{R}_{\mathbf{f}}$: 0.41 hexanes: EtOAc (2:1)

IR (thin film): 2960.53, 1620.14, 1434.97, 1368.56, 1299.85, 1214.95, 1085.65 cm⁻¹

¹**H NMR (500 MHz, Chloroform-***d***):** δ 7.63 – 7.59 (m, 1H), 7.36 – 7.33 (m, 1H), 5.46 (d, *J* = 2.9 Hz, 0H), 4.47 (d, *J* = 2.9 Hz, 0H), 1.49 (s, 2H), 1.36 (d, *J* = 0.5 Hz, 2H).

¹³C NMR (126 MHz, cdcl₃): δ 159.12, 129.39, 128.42, 97.22, 87.72, 80.95, 26.39, 20.88.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{12}H_{14}O_2$; 191.11072 found 173.0966 $[M-H_2O+H]+$

Experimental Procedure for the formation of bullataketals core 3.164:



A bullatenol **3.179** (9 mg, 0.047 mmol, 1 equiv) solution in chloroform 1 mL was placed in flask under argon. Triflimide (3.4 mg, 0.0141 mmol, 0.3 equiv) was added to the flask. The reaction mixture was stirred at room temperature for 30 min and turned orange-pink. Then, acylphloroglucinol **3.167** (11 mg, 0.056 mmol, 1.2 equiv) was added to the reaction flask. The reaction mixture was stirred at room temperature for 12 h and when no further conversion was observed it was dissolved in water and quenched with a saturated solution of sodium bicarbonate. The reaction mixture was extracted with ethyl acetate and gathered organic fractions were dried over anhydrous sodium sulfate. Solvents were evaporated *in vacuo* and provided a dark orange oil. Column chromatography purification over silica gel using and hexanes:ethyl acetate gradient provided 3 mg (18 % yield) of **3.164** as a pale yellow oil. $\mathbf{R}_{\mathbf{f}}$: 0.55 hexanes: acetone (2:1)

IR (thin film): 2977.67, 2926.66, 2873.24, 1614.78, 1448.88, 1368.66, 1260.32, 1198.02, 1138.21, 1095.69, 1063.66 cm⁻¹

¹H NMR (500 MHz, Chloroform-*d*): δ 13.35 (s, 1H), 8.57 (s, 1H), 8.09 – 7.88 (m, 2H), 7.69 – 7.55 (m, 1H), 7.49 (dd, *J* = 8.3, 7.4 Hz, 2H), 5.96 (s, 1H), 3.71 (p, *J* = 6.7 Hz, 1H), 3.54 – 3.41 (m, 2H), 3.33 (dd, *J* = 19.1, 10.2 Hz, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.16 (d, *J* =6.7 Hz, 6H).
¹³C NMR (126 MHz, cdcl₃): δ 208.84, 202.93, 166.33, 161.53, 160.17, 136.05, 134.59, 129.01, 128.98, 128.59, 108.23, 97.45, 90.83, 41.66, 41.47, 38.49, 30.13, 28.51, 23.65, 19.52, 18.75.
HRMS--ESI (m/z): [M+H]⁺ calculated for C₂₂H₂₄O₅; 369.11702 found 369.1701.

Figure 3. 12. NOESY Data for 3.164.



Experimental Procedure for the formation of bullataketals core 3.139:



To a solution of syncarpic acid **3.138** (30 mg, 0.164 mmol, 1 equiv) in 2 mL diethyl ether at 0 C was added pyrrolidine (16 L, 0.197 mmol, 1.2 equiv) followed by a solution glyoxal **3.137** (20 mg, 0.164 mmol, 1 equiv) in 0.4 mL of diethyl ether. A white precipitate was formed after 15 min and it was filtered on fritted funnel to provide 10 mg (20 % yield) of **3.139** as a white gum. **R**_f: 0.4 hexanes:acetone (1:1) **IR** (thin film): 3390.41, 2975.72, 2939.52, 1702.62, 1587.49, 1518.99, 1457.33, 1400.88, 1178.87, 1030.16 cm⁻¹

¹**H NMR (400 MHz, Chloroform-***d***):** δ 5.44 (d, *J* = 0.8 Hz, 1H), 3.16 – 3.01 (m, 2H), 2.80 (dt, *J* = 13.7, 7.0 Hz, 1H), 2.06 (s, 4H), 1.96 – 1.83 (m, 2H), 1.43 – 1.21 (m, 12H), 1.05 (ddd, *J* = 37.8, 6.9, 0.8 Hz, 6H).

¹³C NMR (101 MHz, cdcl₃): δ 216.56, 207.59.192.74, 97.56, 70.94, 53.18, 45.51, 45.41, 36.23, 25.14, 24.76, 19.92, 19.83, 18.07.

HRMS--ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{29}NO_4$; 336.2175 found 369.2176.

3.7 Select Spectra






Ph 10











LIST OF JOURNAL ABBREVIATIONS

| Acc. Chem. Res. | Account of Chemical Research |
|---------------------------------------|--|
| Adv. Phys. Org. Chem. | Advances in Physical Organic Chemistry |
| Adv. Pharmacol. | Advances in Pharmacology |
| Adv. Synth. Catal. | Advanced Synthesis & Catalysis |
| Angew. Chem., Int. Ed. | Angewandte Chemie International Edition |
| Antimicrob. Agents and Chemother. | Antimicrobial Agents and Chemotherapy |
| Arkivoc | Archive for Organic Chemistry |
| Aust. J. Chem. | Australian Journal of Chemistry |
| Bioorg. Med. Chem. | Bioorganic & Medicinal Chemistry |
| Bioorg. Med. Chem. Lett. | Bioorganic & Medicinal Chemistry Letters |
| Bull. Chem. Soc. Jpn. | Bulletin of the Chemical Society of Japan |
| Can. J. Chem. | Canadian Journal of Chemistry |
| Chem. Ber. | Chemische Berichte |
| Chem. Comm. | Chemical Communications |
| Chem. Eng. Comm. | Chemical Engineering Communications |
| Chem. Eur. J. | Chemistry - A European Journal |
| Chem. Lett. | Chemistry Letters |
| Chem. Pharm. Bull. | Chemical and Pharmaceutical Bulletin |
| Chem. Rev. | Chemical Reviews |
| Chem. Sci. | Chemical Science |
| Eur. J. Clin. Microbiol. Infect. Dis. | European Journal of Clinical Biology: Infectious |
| | Diseases |

| Eur. J. Org. Chem. | European Journal of Organic Chemistry |
|--------------------------------|--|
| Evidence-Based Comp. Alt. Med. | Evidence Based Complementary and Alternative |
| | Medicine |
| Free Radical Research | Free Radical Research |
| Health Sci. | Health Sciences |
| J. Am. Chem. Soc. | Journal of the American Chemical Society |
| J. Chemother. | Journal of Chemotherapy |
| J. Chem. Soc. | Journal of the Chemical Society |
| J. Chem. Soc., Chem. Commun. | Journal of the Chemical Society, Chemical |
| | Communications |
| J. Chem. Soc., Perkin Trans. 1 | Journal of the Chemical Society, Perkin |
| | Transactions 1 |
| J. Chem. Soc., Perkin Trans. 2 | Journal of the Chemical Society, Perkin |
| | Transactions 2 |
| J. Inorg. Biochem. | Journal of Inorganic Biochemistry |
| J. Med. Microbiol. | Journal of Medicinal Microbiology |
| J. Microbiol. | Journal of Microbiology |
| J. Nat. Prod. | Journal of Natural Products |
| J. Org. Chem. | Journal of Organic Chemistry |
| J. Pharmaco. Exp. Ther. | Journal of Pharmacology and Experimental |
| | Therapeutics |
| Liebigs. Ann. Chem. | Liebigs Annalen der Chemie |
| Med. Chem. Comm. | Medicinal Chemistry Communications |
| Naturwissenschaffen | Naturwissenschaffen |

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| OelKohle | OelKohle | |
|------------------------|--|--|
| Org. Biomol. Chem. | Organic & Biomolecular Chemistry | |
| Org. Lett. | Organic Letters | |
| Org. Process Res. Dev. | Organic Process Research & Development | |
| Organometallics | Organometallics | |
| Parasite | Parasite | |
| Phytochemistry | Phytochemistry | |
| Planta Med. | Planta Medica | |
| PloS ONE | Public Library of Science ONE | |
| Polyhedron | Polyhedron | |
| Synthesis | Synthesis | |
| Synth. Commun. | Synthetic Communications | |
| Science | Science | |
| Tetrahedron | Tetrahedron | |
| Tetrahedron: Assym. | Tetrahedron: Assymetry | |
| Tetrahedron Lett. | Tetrahedron Letters | |

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Education

| Ph.D. Chemistry | 2014 |
|--|------------------|
| Boston University, Department of Chemistry | |
| Outstanding Teaching Fellow, Boston University, Department of Chemistry | 2009-2011 |
| M.Sc. Chemistry and Chemical Engineering | 2007-09 |
| National Graduate School of Chemistry- Montpellier University, France | |
| B.Sc. Chemistry and Chemical Engineering | 2004-07 |
| National Graduate School of Chemistry- Montpellier University, France | |
| Research Experience | |
| Boston University, Department of Chemistry, Boston, MA | 2008-2014 |
| Pre-doctoral Academic Research Assistant | |
| Advisor: Prof. John A. Porco Jr. | |
| • Developed a new methodology to access a family of very potent antibiotics | |
| • Collaborated with biology groups for the biological evaluation of these antibi | otics |
| • Designed a new process to access precursors to a potent antimalarial compour | nd |
| • Identified a new synthetic route toward the production of potent antimalarial n | natural products |
| • Assigned group jobs to each group member in order to maintain a well-su laboratory | applied and safe |
| TopChem Pharmaceuticals Ltd., Dublin, Ireland | Summer 2008 |
| Research Assistant Intern | |
| TopChem Pharmaceuticals Ltd. is a GMP supplier of APIs and support | services to the |
| pharmaceuticals sector worldwide. | |
| • Developed a large-scale crystallization process for the purification of an anti- | fungal drug |
| • Synthesized a drug used as a monotherapy in early Parkinson's disease | |
| • Synthesized a library of APIs | |
| Presented findings regularly at informal group meetings | |
| University of Montpellier, School of Pharmacy, UMR CNRS 5618 | |
| Montpellier, France | October 2006 |

Research Assistant Intern

The UMR CNRS 5618 studies focus on the development of catalytic materials and catalytic processes in organic chemistry that can be used by the health care sector.

- Conducted preliminary studies for the development of silica-based mesoporous materials with small molecules trapping.
- Developed a Sol-Gel method synthesis for silica based materials preparation

Leadership and Outreach

Boston University Science and Engineering Business Group (BUSEBG)2013-2014Founder and President2013-2014

- Provided information and resources to the BU community about business related careers for MD, PhD students and post-doctoral fellows
- Created a weekly case practice session and a case data bank
- Assembled and led a committee for event organization
- Created and maintained a group website providing: Information about career in business development, technology transfer, IP law, consulting and case practice material

Boston University, Office of Technology Development (OTD), Boston, MA2011-2013New Ventures Associate while completing pre-doctoral studies2011-2013

The OTD mission is to encourage, educate, and enable the BU community to realize the commercial potential of their ideas.

- Assessed technology and developed business plans for four projects, three of which have found leadership for their development as Start-Up companies
- Analyzed the competitive landscape for four projects with patents and clinical trial assessments, leading to the identification of potential exits (License or Stand-Alone)
- Interviewed key opinion leaders to determine clinical needs and developed strategies to reach key scientific inflexion point
- Served as the point-person between the scientific teams and the new venture team and facilitated communication of high-level scientific information by preparing more than 10 presentations for potentials investors
- Helped identify a turnaround strategy taking into account equity and intellectual property assets to find appropriate leadership for a new company

Boston University, Boston University Women In Chemistry (BUWIC)2009-2010Secretary and Outreach & Social Chair2009-2010

- Coordinated more than 10 events and took care of the logistics for seminars and panels
- Developed and managed community outreach programs with two high schools:
- Provided tutoring opportunities to high school students and exposure to practical lab chemistry
- Organized a one-day chemistry event to allow high school students:

- To have hands-on experience in a college laboratory setting
- To visit research labs and interact with graduate students

Boston University, Department of Chemistry

Teaching Assistant

- Instructed and mentored 48 students for five semesters
- Designed and instructed sophomore organic chemistry discussion and laboratory sessions to illustrate and clarify lecture material

Other

Languages: French (Native Fluency), Spanish (Professional Proficiency) Societies: American Chemical Society (ACS), Boston University Women in Chemistry (BUWIC), Association for Women In Sciences (AWIS)

Publications and Presentations

Presentations and Posters:

Total Synthesis and Biological Evaluation of Rhodomyrtone A and Related Natural Products, <u>Anais Gervais</u> and John A. Porco, Jr. 245th ACS National Meeting & Exposition, New Orleans, LA, United States, (2013), ORGN-394

Total Synthesis of Rhodomyrtone A and Analogues: Toward a Regioselective Synthesis <u>Anais</u> <u>Gervais</u> and John A. Porco, Jr. Boston Symposium On Organic and Bioorganic Chemistry (2013)

Total Synthesis and Biological Evaluation of Rhodomyrtone A and Related Natural Products, Anais Gervais and John A. Porco, Jr. Novartis Drug Discovery Event (2013)

Total Synthesis and Biological Evaluation of Rhodomyrtone A and Related Natural Products, Anais Gervais and John A. Porco, Jr. CMLD symposium (2012)

Synthesis of Myrtucommulones and Related Natural Products, Anais Gervais and John A. Porco, Jr. CMLD symposium (2009)

References

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