Discovery and Development of a Three-Component Oxidopyrylium Cycloaddition and Its Application Towards alpha-Hydroxytropolone Synthesis

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DISCOVERY AND DEVELOPMENT OF A THREE-COMPONENT OXIDOPYRYLIUM CYCLOADDITION AND ITS APPLICATION TOWARDS α-HYDROXYTROPOLONE SYNTHESIS

by

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ABSTRACT

Discovery and Development of a Three-Component Oxidopyrylium Cycloaddition and Its Application Towards α-Hydroxytropolone Synthesis

by

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Advisor: Professor Ryan P. Murelli

Historically, natural products have provided unique research opportunities and challenges for organic synthesis, chemical biology, and medicinal chemistry due to their molecular complexity and effects on physiological systems. The total synthesis of natural products has not only produced novel reaction methods and strategies capable of efficiently generating complex structural motifs but also granted access to sufficient quantities of otherwise scarce natural product material for clinical evaluation. These synthetic efforts have facilitated the formation of a transdisciplinary partnership between chemistry, biology, and medicine that has been paramount in elucidating the chemical and pharmaceutical utility of natural products. Chapter I of this thesis will highlight several key examples of how natural products inspired synthetic methodology, small molecule drug and probe development, and the discovery of previously unknown biologically active scaffolds. A particular focus will be spent on the synthetic and biological endeavors made by our laboratory involving α-hydroxytropolones (αHTs).

αHTs are a subclass of troponoid natural products that possess promising activity against a broad range of therapeutically significant targets. In order to gain access to these molecules, our laboratory utilizes an oxidopyrylium cycloaddition/ring-opening strategy. During our synthetic investigations, we recently discovered a three-component oxidopyrylium cycloaddition that generates novel 8-oxabicyclo[3,2,1]octene products. In Chapter II, the
development and optimization of this synthetic method towards the construction of a library of new oxabicyclic species will be detailed. Initial attempts at applying the reaction towards αHT synthesis will also be discussed, as a tandem debenzylation/ring-opening procedure with benzyl-derived oxabicyclic intermediates is outlined. Further exploration of the utility of the three-component oxidopyrylium cycloaddition will be described in Chapter III and Chapter IV, as the first solid-phase and fluorous syntheses of αHTs are reported, respectively. The advantages and disadvantages of each strategy will be considered in these chapters, specifically pertaining to the efficiency of purification, incorporation/cleavage of solid-phase resins and fluorous tags, and modification of supported intermediates.
DEDICATION

In memory of my grandfather, Jerry Cuomo, for always being a pillar of strength and inspiration for our family.

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To my loving and caring parents, Debra and Frank D’Erasmo, for their never-ending support, encouragement, and guidance throughout the years.

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To my awesome brothers, Frank and Jerry D’Erasmo, for providing me with life-changing advice and information that has shaped my perspective of the world.

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To all the animals that have been a part of my life, especially my dogs, Spike and Bruiser, and my cats, Boomer, Rowzer, Scarlett, and R. J. You will always have a special place in my heart.
ACKNOWLEDGEMENTS

The identity of an individual is molded by life experience and the teachings obtained from family and friends. At this point in my life, there are several principles I hold very dear to my heart, including: 1) hard work and determination are pivotal for success, 2) treat all living creatures the way you want to be treated, and 3) always pursue the truth no matter how difficult it may be to accept. My perspective on the world has changed drastically by trying to apply these principles in my daily actions and aspirations for the future. With hard work and determination, I have come one step closer with the writing of this thesis to achieving my dream of making scientific contributions to humanity’s knowledge regarding neurodegenerative diseases. Coming from a position of respect and dignity for all life, I have learned to consider the impact of my actions and words on people, animals, and the environment. By placing the truth above all else, I have continued to develop a belief system devoid of hypocrisy and baselessness. What I have described may sound cliché or obvious to many individuals out there, but in order to be instilled with such concepts and principles, experience and mentorship are required. I would like to devote some time in showing appreciation to all those people that have taught me the importance of these principles and got me to this point in my career.

Since I was a child, my favorite topics in school were math and science. I often cracked open books describing the characteristics and anatomy of bugs, particularly spiders, and brought them to school for everyone to see. Despite being known as the bug boy by all my teachers and classmates, whenever I was asked what I wanted to be throughout grade school, I never considered a career in science. It was not until my junior and senior years at Mount Saint Michael Academy that I developed a love for chemistry. My interest in the field would not have emerged if it were not for my chemistry teacher, Mr. Manton, who always found a way to make
the topics interesting, challenging, and fun. I thank him for the experiences I had in his honors and AP classes, along with his guidance and support, which pushed me to seek a college degree in chemistry.

At Fordham University, I wanted to take as many science classes as possible to satisfy my curiosity and hunger for knowledge. However, I had no clue where a chemistry degree could take me outside of patent law, which was unappealing to me at the time. Fortunately, I met several professors who provided me with the inspiration to seek a doctorate in chemistry and sparked my interest in drug research and development. Most of all, I would like to thank Prof. John J. McMahon for giving me the opportunity to work in his laboratory as an undergraduate. Without his mentorship and encouragement throughout those years, I would have never appreciated the importance of chemistry research nor seen its potential applications outside of academia. I cannot thank him enough for the doors he has opened and the guidance he has given during my times of uncertainty. I would also like to thank Prof. Ipsita Banerjee for inspiring me to pursue a career in medicinal chemistry. With her excellent biochemistry classes, I became extremely interested in drug discovery and development, especially as it relates to neurodegenerative processes. Due to her constant advice and support, I decided to travel the path of a medicinal chemist and I am very grateful. Lastly, I would like to thank Prof. Christopher Bender for all of his assistance and instruction on many career and life matters, specifically relating to choosing a mentor. Due to the experiences and real-world perspective he shared, I made sure to carefully assess which individual I would work for during my graduate studies.

Though I decided to embark on the journey towards an advanced chemistry degree, I became fatigued with classes and lost hope with finding an appropriate environment to do scientific research. I ended up at The Graduate Center where I met the people who impacted my
life the most outside my family. To begin, I would like to thank Prof. Mark R. Biscoe, Prof. Stacey Brenner-Moyer, and Prof. Maria Contel for all their support and guidance over the years. Not only have their excellent chemistry classes sparked my interest in the field again, but they all gave me the chance to do rotations in their laboratories that helped immensely in refreshing my knowledge of common techniques and overcoming research jitters. I would also like to thank my committee members, Prof. Emilio Gallicchio, Prof. Guillermo Gerona-Navarro, and Prof. David R. Mootoo, for all their assistance, insight, and suggestions relating to research projects. Due to the challenges and questions I encountered in the meetings with them, I have learned a great deal about what it takes to formulate and convey an independent research project. Finally, I would like to thank Prof. Ryan P. Murelli for everything he has done. For five years, he has provided tremendous support and mentorship, and I am extremely grateful. I think the first meeting we ever had was at Science Day in The Graduate Center, where his excitement level was at a maximum while describing his research. When I needed to make the difficult decision of choosing a laboratory, his eagerness and ability to explain his scientific vision was what persuaded me to join his group. It has been an honor contributing to that vision, and I will cherish the memories I have in his laboratory.

Upon entering a research intensive program after being out of the laboratory for years, I was very nervous about being properly equipped with the skills to handle myself. Fortunately, I took advantage of the rotation requirements at The Graduate Center and came in contact with incredible senior students. I especially want to thank Dr. Malgorzata Frik, Dr. Josh Jones, Dr. Ashwini Ghogare, and Dr. Christine Meck for the patience, support, and guidance they provided throughout my studies. Their suggestions and insight relating to research and the graduate program in general assisted me greatly in overcoming initial reservations and anxiety. I have nothing but respect for them, and I appreciate all they have done.
Though very rewarding at times, the graduate school experience can be nightmarish. When you are stuck in the laboratory all day for most of the week, you are broken down both physically and emotionally, especially if a project is not going the right way. Luckily, I had the benefit of being surrounded by very supportive colleagues during my time in the Murelli laboratory to deal with the graduate roller coaster. At the top of the list, I want to acknowledge Danielle Hirsch who has been a fellow soldier in the trenches since the beginning of the program. She has not only been a great coworker but a true friend throughout the years. She is an extremely competent and skillful scientist, and I am certain success will follow her wherever she goes in the future. Outside all of that, she has demonstrated a kind, compassionate, and trustworthy personality that I think is very difficult to find. To me, she has been a very influential force on real-world topics, especially animal welfare and veganism. Due to our conversations on such issues, I have learned to better appreciate animal life, whether it is a dog in the house or a pig on the farm, and apply that respect more generally through my diet by becoming a vegetarian. I have also had the privilege of being introduced to the many animal friends that are a big part of her life, such as her angel Goldendoodle, Marley, majestic horse, Haley, handsome pony, Shadow, and spastic turtle, Turtle. I thank her for the times we have shared together, and I will cherish all of the experiences and memories. I would also like to thank Alex Berkowitz for being the wiseguy of the laboratory. I could not have made it through the day without his jokes about my Bronx accent. Beyond that, he has been a good friend and a positive force for the group. There have been many days that he has refreshed my memory or taught me something new on chemistry related topics. He has the potential to run his own laboratory one day, and I await the day that it happens. I would like to thank Daniel “Staniel” Schiavone for having one of the best personalities an individual can have. His uniqueness can only be experienced in person,
and I feel bad for those of you who are reading this and have not. He is an extremely hardworking and intelligent scientist, and I know he will be an inspiration for the generations to come. The same can be said about Lauren Bejcek, who I thank for introducing the essence of Chicago to the Murelli laboratory. Because of her, I would visit the city just to get a taste of Lou Malnati’s deep dish pizza and meet her distinguished dog, Sir Edward II. She has loads of potential as a chemist, and I look forward to seeing what she accomplishes. I would like to thank John Stasiak for his never-ending positivity throughout the day. I do not think I have ever seen him express rage at a person or an extremely negative outlook on a subject. His personality has been refreshing, especially in such an emotionally taxing field. His intelligence, work ethic, and positivity are bound to bring him prosperity. I would like to thank Nana Agyemang and Irina Kashis for their insight on career and life issues. During graduate school, you are often bombarded with questions concerning your future directions and goals that create doubt and hesitation. Their wisdom and realistic perspective continues to help me overcome many uncertainties or fears about the future path. Both of them are headed for success, and I appreciate the support and advice they have given to me. Lastly, I would like to thank Sarah Avidan, Errol Hunte, and Duygu Suyabatmaz for all of the experiences and memories. It was a privilege being a part of key events in Sarah’s life, such as her wedding and the birth of her child, Abraham. I will always remember the fiery and curious nature of Duygu, and the antics we would get into in the laboratory. I thoroughly enjoyed the philosophical discussions I had with Errol on topics ranging from politics to anime. All of them are extremely smart and hardworking individuals, and I know they will succeed in their future endeavors.

Even though a majority of your time in graduate school is spent in the laboratory discovering the unknown or trying to get reactions to work, I had the opportunity to explore
outside my research and meet some incredible classmates, future scientists, and professors. I had the pleasure of meeting Gan Zhang, Niccole Fuhr, Andy Lu, Niluksha Walalawela, Jiye Son, Vincent Mui, Dr. Jacob Fernández-Gallardo, Dr. Flavia Barragán, Dr. Americo Fraboni, Marek Wlodarczyk, Khadija Wilson, Dajana Alku, Yoko Bian, Dr. Stephen Chester, Dr. James Aramini, and many more. I could probably write a book outlining all of the fun times and conversations I had with these individuals. However, for the sake of brevity, I would like to thank all of them for making the graduate experience brighter and more epic.

Of course, I would not have gotten to this point in my career if it were not for the support and guidance from my family and friends. Most of all, I want to thank my parents, Debra and Frank D’Erasmo, for everything they have provided. I would not be the man I am today if it were not for the lessons and opportunities they have given me. Since I was a child, my dad has always been an inspiration and role model. He has taught me the principles of hard work, respecting others, and pursuing a dream no matter how tough the road gets. My mom has been a key source of support and mentorship throughout my life. I would not have learned the value of education if she did not push me as a child and beyond. They have sacrificed a lot to get me here, and I am eternally grateful. I would also like to thank my brothers, Jerry and Frank D’Erasmo, for their constant support and life-changing advice. They have exposed me to many new things, ranging from music to nutritional guidelines, which have shaped who I am as an individual. Many of the viewpoints I have of the world emerged from their influence, and I would not change them for anything. I would like to acknowledge my grandfather, Jerry Cuomo, who passed away during my doctorate studies. He always served as a pillar of strength for our family as a whole, and stopped at nothing to bring everyone together. His work ethic, compassion, and kindness were an inspiration to everyone, and he is sorely missed. I would like to thank the many friends who have
brightened up my life and supported me along the way. Specifically, I want to acknowledge Min Hur and Michael “Naps” Napolitano for being brothers from other mothers, and Vinny Rinaldi, Agostino Conte, and many others for all the great times we had together. Last and best of all, I want to acknowledge all the furry friends that I hold dear to my heart, such as Spike, Boomer, Bruiser, Rowzer, Scarlett, and R. J. These bundles of joy have impacted my life immeasurably, and words cannot express their importance to me.

On a final note, the next step for me is a trip to Emory University to work for Prof. Dennis Liotta. Every individual I have acknowledged has played a role in getting me to this point. To that end, I would like to thank our collaborators Prof. John Tavis, Prof. Lynda Morrison, Dr. John Beutler, Dr. Stuart Le Grice, Dr. Jay Bradner, Prof. Gerry Wright, and others for their hard work on the medicinal chemistry studies. I would also like to thank the financial support from the National Institutes of Health (SC2GM09959 and SC1GM111158) for making this graduate research possible. Finally, I would like to thank Prof. Brian Gibney for allowing me to speak in front of Prof. Liotta at The Graduate Center, which opened the door for the following job interview. I am very grateful for this opportunity, as it is another step towards achieving my dreams in the medicinal chemistry realm.
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ABBREVIATIONS AND ACRONYMS

Å angstrom
Ac acetyl
ACN acetonitrile
AcOH acetic acid
ACV acyclovir
Ala alanine
AlCl$_3$ aluminum trichloride
ANT(2") aminoglycoside-2"-O-nucleotidyltransferase
Asn asparagine
BBr$_3$ boron tribromide
Bn benzyl
BnOH benzyl alcohol
Boc t-butyloxycarbonyl
CC$_{50}$ half maximal cytotoxicity concentration
CCK cholecystokinin
CCl$_4$ carbon tetrachloride
C$_7$F$_{14}$ perfluoromethylcyclohexane
CH$_2$Cl$_2$ dichloromethane
CHCl$_3$ chloroform
CDCl$_3$ deuterated chloroform
Cy cyclohexyl
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM dichloromethane
DIAD diisopropyl azodicarboxylate
DIC N,N’-diisopropylcarbodiimide
DIPEA N,N-diisopropylethylamine
DMAD dimethyl acetylenedicarboxylate
DMAP 4-dimethylaminopyridine
DMF dimethylformamide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOS</td>
<td>diversity-oriented synthesis</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal effective concentration</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>triethylamine</td>
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<td>EtOAc</td>
<td>ethyl acetate</td>
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<tr>
<td>EtOH</td>
<td>ethanol</td>
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<td>FLLE</td>
<td>fluorous liquid-liquid extraction</td>
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<tr>
<td>Fmoc</td>
<td>fluorenylmethyloxycarbonyl</td>
</tr>
<tr>
<td>FRET</td>
<td>fluorescence resonance energy transfer</td>
</tr>
<tr>
<td>FSPE</td>
<td>fluorous solid-phase extraction</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
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<td>human cytomegalovirus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HMP</td>
<td>(4-(hydroxymethyl)phenoxy)acetic acid</td>
</tr>
<tr>
<td>HOBt</td>
<td>hydroxybenzotriazole</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
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<td>α-hydroxytropolone</td>
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<td>hertz</td>
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<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal inhibitory concentration</td>
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<td>μM</td>
<td>micromolar</td>
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<td>Full Form</td>
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<tr>
<td>Me</td>
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<td>methanol</td>
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<tr>
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<td>melting point</td>
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<td>mass spectrometry</td>
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<td>MsOH</td>
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<td>nanomolar</td>
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<td>NMC</td>
<td>NUT midline carcinoma</td>
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<td>NMP</td>
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</tr>
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<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<td>Ns</td>
<td>2-nitrophenylsulfonyl</td>
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<td>NTS</td>
<td>nucleotidyl transferase superfamily</td>
</tr>
<tr>
<td>OAT</td>
<td>ornithine δ-amino transferase</td>
</tr>
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<td>Pd/C</td>
<td>palladium on carbon</td>
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<td>(benzotriazol-1-yl oxy)tripyrrolidinophosphonium hexafluorophosphate</td>
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<tr>
<td>Rᶠ</td>
<td>retention factor</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>reverse transcriptase</td>
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<td>SAR</td>
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<td>sSPhos</td>
<td>water soluble SPhos</td>
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<td>solid-phase organic synthesis</td>
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<td>Teoc</td>
<td>(trimethylsilyl)-ethoxycarbonyl</td>
</tr>
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<td>TOF</td>
<td>time-of-flight</td>
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Chapter I

Exploring Nature’s Bounty: The Indispensable Partnership Between Chemistry, Biology, and Medicine

1.1. Introduction

Investigating nature’s molecular diversity and its effects on physiological systems continues to be a central area of advancement and cooperation for chemistry, medicine, and biology.\(^1\) Each natural product class isolated and characterized possesses unique three-dimensional construction and biological properties that introduces original research opportunities and challenges.\(^2\) These compounds typically demonstrate structural domains very similar to many human macromolecules, which provide intense pharmacological activity and selectivity.\(^2^3\) Hence, natural products are by far the most abundant source of new small molecule drugs,\(^4\) with penicillin V (1.1, antibiotic), artemisinin (1.2, antimalarial), and galantamine (1.3, Alzheimer’s treatment) being only a few examples (Figure 1.1). Additionally, such molecules have the capability to efficiently modulate biomolecular function, making them exemplary probes to systematically analyze cellular components, biochemical events, and signaling pathways.\(^2^5\)

![Figure 1.1. Some key examples of natural product drugs.](image-url)
1.2. (+)-Discodermolide: Total Synthesis Leading to Clinical Development

Historically, the total synthesis of natural products has brought about novel reaction methods and technologies, innovative strategies for the rapid creation of complex structural motifs, and a broad range of biologically active analogs derived from the targeted molecules. Such breakthroughs have facilitated significant strides in the synthesis and modification of drugs by enabling the production of sufficient quantities of scarce natural product material for clinical development. As a result of these efforts by organic chemists, pharmaceutical endeavors spanning both academia and industry emphasize the use of natural product isolation and organic synthetic techniques in the design, generation, and testing of small molecule inhibitors and chemical probes. This combination between organic synthesis and biology has unraveled fundamental information on many physiological systems and established the standard for drug discovery and development.

For example, (+)-discodermolide (1.4) is a polyketide natural product first isolated in 1990 by Gunasekera and co-workers from the Caribbean deep-sea marine sponge Discodermia dissoluta. Similar to paclitaxel (1.5, Taxol®) and epothilones (1.6), the molecule inhibits proliferation of cancer cells by stabilizing microtubules and arresting the cell cycle prior to mitosis (Figure 1.2). Additionally, (+)-discodermolide possesses a number of other unique biological characteristics, including immunosuppression both in vitro and in vivo, potent acceleration of cell aging, synergistic anticancer activity with paclitaxel, and neuroprotective effects. Due to its promising biological profile, the pharmaceutical industry was extremely interested in clinically evaluating the natural product. However, since (+)-discodermolide accounts for only 0.002 wt.% of *D. dissoluta* and all efforts to cultivate this organism failed, material management restricted the advancement of biological studies. Such a supply dilemma
made (+)-discodermolide an attractive target for total synthesis, and thus organic chemists sought to develop a scalable synthetic route to generate its complex structure.

In 1993, Schreiber and co-workers described the first total synthesis of the unnatural enantiomer (-)-discodermolide, which proved useful in establishing the absolute stereochemistry of the natural product. After this study, a number of unique approaches emerged from academia and industry detailing the synthesis of both discodermolide enantiomers. A retrosynthetic analysis of these total syntheses reveals that all of them deconstruct the natural product into three major fragments, each of which contain the contiguous methyl-hydroxyl-methyl array of stereogenic centers present in the target molecule (Figure 1.3 for select examples). Various strategies were then employed to couple the segments with the appropriate configuration and stereochemistry, including the Nozaki-Hiyama-Kishi coupling/enol alkylation approach of Schreiber, the Negishi coupling/Wittig olefination route of Smith, and the novel chelation-controlled aldol reactions of Paterson.
As the synthetic research became more extensive, focus shifted towards making the reaction sequences shorter, more convergent, and more practical in order to produce the material demand required for clinical development. Novartis Pharma AG took inspiration from these methods and described a 39-step synthesis of 60 g of (+)-discodermolide in 2004 (Scheme 1.1). Specifically, Novartis integrated the Smith common precursor 1.18 to produce the three major fragments and the Paterson aldol chemistry to connect the final segments together. The material generated proved to be sufficient in advancing (+)-discodermolide to early-stage human clinical trials. In addition, these synthetic developments facilitated the creation of a number of
research programs aimed at the design, synthesis, and evaluation of (+)-discodermolide analogs. Such efforts have uncovered the binding elements required for the natural product’s biological profile and enabled the rational design of more potent anticancer agents through in-depth structure-activity relationship (SAR) studies.

1.3. (-)-Diazonamide A: Chemical Probe Synthesis Elucidating Biological Pathways

Alongside its pivotal role in drug discovery, synthetic research geared towards the assembly and modification of biologically interesting natural products has elucidated key mechanistic information on many physiological processes through chemical probe development. For instance, (-)-diazonamide A (1.20, Figure 1.4), a compound isolated from
the colonial marine ascidian *Diazona angulata*, became an extremely popular target for organic chemists and the pharmaceutical industry due to its intriguing molecular structure and potent cytotoxicity against a variety of human cancer cell lines. Early reports indicated that the compound’s activity emerged from its microtubule-binding ability. However, other studies contradicted this hypothesis, demonstrating that (-)-diazonamide A does not compete with known tubulin-binding agents, such as maytansine (1.21) or vinblastine (1.22, Figure 1.4). Thus, the race was on for a practical total synthetic route to access the molecule and its analogs for biological evaluation.

By the late 1990s, nearly a dozen research groups dedicated efforts at efficiently synthesizing (-)-diazonamide A. These ventures encountered a roadblock when Harran and co-workers in 2001 made the surprising discovery that the originally proposed structure for the natural product had been misassigned based on their synthesis of 1.23 and 1.24 (Figure 1.5). Re-evaluation of the spectroscopic and crystallographic data acquired on (-)-diazonamides revealed that the molecule actually possesses diarylaminal motifs instead of the phenolic hemiacetals suggested from initial studies. Following these conclusions, attention was directed
towards generating the new structure, as a number of total syntheses on diazonamide A would emerge in the literature.\(^{22}\) However, the synthetic strategy that became the most relevant in the clinical progression of diazonamides as chemotherapeutic agents would originate from Harran and co-workers in 2003.\(^{24}\)

The Harran 19-step approach to diazonamide A (1% overall yield) consisted of constructing a *seco*-peptidyl precursor and installing the primary diarylaminal core through oxidative annulation of the tethered tryptophan and tyrosine side chains (\(1.26 \rightarrow 1.28\), Scheme 1.2).\(^{24}\) Also, the atropisomerism in the eastern region of the molecule was established with a photoinduced electron transfer reaction under basic conditions (\(1.29 \rightarrow 1.32\)). Using this route to assemble a biotinylated derivative, Harran, Wang, and co-workers disseminated the mitochondrial enzyme, ornithine δ-amino transferase (OAT), as the biological target for the natural product.\(^{21}\) These mechanistic studies also suggested that OAT serves an important function in mitotic cell division, bringing to light a potential target for anticancer drug development. More recently, the Harran synthetic method has been utilized and advanced in collaboration with the pharmaceutical industry to produce detailed SAR studies on diazonamides and potent antimitotic agents poised to enter clinical trials.\(^{25}\)
1.4. Vancomycin and Teicoplanin: Confronting Chemical and Biological Challenges with Synthetic Methodology

As outlined earlier, since physiologically active natural products are already equipped with structural characteristics that efficiently bind to the domains of biological macromolecules, they provide an ideal canvass for the semisynthesis of promising drug derivatives and chemical probes.\textsuperscript{1,2,18} However, direct chemical alteration of natural products can be extremely difficult due to the presence of multiple functional groups and stereogenic centers, which limit reaction efficiency and selectivity. To address the challenge of natural product reactivity and the increasing demand for SAR studies based on semisynthetic modification, sophisticated developments on the synthetic methodology front have emerged.\textsuperscript{2,26} In particular, site-selective functionalization has become an effective tool in the synthesis of natural products and their corresponding analogs.
For example, Miller and co-workers have demonstrated the site-selective bromination of the glycopeptide antibiotics, vancomycin (1.33) and teicoplanin (1.36), using peptide-based catalysts.\textsuperscript{27} In the study involving vancomycin, the research group reported that the inherent reactivity of the natural product towards halogenation can be controlled depending on the additives present (Figure 1.6).\textsuperscript{27a} On one hand, taking inspiration from the antibiotic’s natural binding mode to bacterial cell walls,\textsuperscript{28} peptide 1.34 was designed and used to accelerate the selective bromination of vancomycin at the 7f position. On the other hand, in order to reverse the site of functionalization to the 7d position, guanidine-HCl (1.35) was the additive of choice because of its capability to interact with the free carboxylate functionality and speed up bromination reactions.\textsuperscript{29}

Miller and co-workers would then apply these results to teicoplanin compound 1.36, which possesses increased biological activity and molecular diversity compared to vancomycin (Figure 1.7).\textsuperscript{27b} Not only was peptide-dependent bromination at either the 5,7-biaryl or 1,3-biaryl
ether sectors of the molecule achieved, but the group also performed Suzuki cross-coupling on the brominated derivatives using aqueous conditions (i.e. Pd(OAc)$_2$/sSPhos). This chemistry enabled the direct synthesis of eleven novel teicoplanin analogs previously unavailable through biosynthesis or total synthesis. Evaluation of the new compounds against a variety of bacterial strains revealed comparable or increased activity in relation to vancomycin and teicoplanin. Thus, the Miller site-selective bromination has the potential to grant access to a library of unique natural product derived antibiotics useful against the rising threat of glycopeptide-resistant bacteria.

1.5. γ-Hydroxybutenolides: New Chemical Entities Generated from Natural Product Synthons

The progression and cooperation of organic synthesis, structural biology, and medicinal chemistry has yielded technologies and methods to determine the primary components responsible for the biological activity of natural products (i.e. pharmacophores).$^{1,2,18}$ As a result,
considerable attention has been directed towards the development of synthetic methods capable of preparing these structural moieties. Generally, these studies produce greatly simplified analogs that mimic or exceed the function of the natural product from which they were inspired.\textsuperscript{2,18} However, depending on the synthon’s reactivity, it is possible to generate completely new chemical entities with promising pharmacological properties.

For instance, \(\gamma\)-hydroxybutenolides are heterocyclic motifs present in a variety of biologically interesting natural products (Figure 1.8).\textsuperscript{30} These structures are readily synthesized through the oxidation of furan\textsuperscript{31} and serve as synthetic precursors to elaborate lactone-containing derivatives.\textsuperscript{32} Moreover, reports on \(\gamma\)-hydroxybutenolide reactivity have demonstrated that these molecules actively engage in cascade and cycloaddition reactions\textsuperscript{32} and act as intermediates in natural product biosynthesis.\textsuperscript{33}

1.5.1. The Discovery of Novel Spirocyclic Ketal-Lactones

Considering their ease of preparation and capability to form intricate constructs through multi-bond forming processes, our laboratory further investigated \(\gamma\)-hydroxybutenolide chemistry.\textsuperscript{34} These studies, conducted by Alberto Munoz, illustrated that \(\gamma\)-methyl-\(\gamma\)-hydroxybutenolide (1.40) reacts with aromatic aldehydes in the presence of triflate-
based acids (e.g. triflic acid or trimethylsilyl triflate) to produce new spirocyclic ketal-lactones (1.44, Scheme 1.3). An inspection of the substrate scope determined that electronically poor aromatic aldehydes provide the highest yields (e.g. 1.44a-c), as more electron rich aromatic and aliphatic species require large excesses of reagent to force conversion or lead to little or no incorporation (1.44d-f). Lastly, γ-methyl-γ-hydroxybutenolide can be replaced with the γ-ethyl derivative, supplying a molecule with 4 stereogenic centers (1.44g).

Our proposed mechanism for the process involves an elimination/Prins cascade, whereby the lactone 1.41 forms in situ under acidic conditions and undergoes a reaction with 2 equiv. of aldehyde to generate the spirocyclic ketal-lactones (Scheme 1.3). Butenolide 1.41 is also known as protonanemonin, which is a toxic metabolite found in the Ranunculaceae plant family and synthon that efficiently performs Diels-Alder and dipolar cycloaddition reactions. Supported by NMR experiments and crystallographic data, the transformation demonstrates reversibility at the steps that introduce relative stereochemistry and exhibits high diastereoselectivity that is
thermodynamically driven. Additionally, partial incorporation was observed after selected spirocycles were re-subjected to reaction conditions with aromatic aldehydes, providing further evidence for the reversibility of the process (Scheme 1.4). 34

1.5.2. Biological Evaluation of Novel Spirocyclic Ketal-Lactones

With rapid access to a series of unprecedented spirocyclic diaryl butenolides that contain an ‘extended ketal-lactone’ moiety present in many well-established bioactive molecules (Figure 1.9), we directed our attention towards assessing the pharmaceutical utility of the novel constructs. In collaboration with the Bradner group, the compounds we generated were evaluated for anticancer activity through a previously reported 48-hour viability assay. 38 These experiments uncovered that the butenolides illustrate potent cytotoxicity against a T-cell lymphoma cell line (MJ) and a very aggressive epithelial cancer cell line (797 NUT midline carcinoma or NMC). Moreover, the cytotoxic behavior of the molecules appears to be limited to mammalian cells, as no noticeable growth inhibition was observed in Gram-negative bacteria assays.
Our structure-function study revealed that spirocyclic butenolides with electron-withdrawing functionalities on the phenyl appendages possessed the greatest potency (1.44a, Figure 1.10). When the electron-withdrawing groups or the aromatic rings were removed, the activity was severely reduced (1.44d, 1.44f). Diminished cytotoxicity also occurred when a methyl substituent was added to the dioxane ring (1.44g). Additionally, when the size of the aromatic appendages was extended, as shown with derivatives 1.44j and 1.44k, the inhibition was negatively impacted. Thus, the information obtained illustrates that the spirocyclic butenolide core is responsible for cytotoxicity, while the aromatic functionalities increase potency. Though electron poor appendages yield the greatest inhibition, the activity is influenced by a size restriction. Unfortunately, due to the limitations of the synthetic method outlined above, a more diverse array of electronically rich aldehydes could not be examined.

We next tested if the pseudosymmetry of spirocyclic butenolides 1.44h and 1.44i had any effect on biological activity (Figure 1.10). Despite differing merely in the position of the nitro group, the compounds possessed nearly identical potency against the NMC and MJ carcinomas and were approximately half as active as 1.44a. With regard to the binding mode of these molecules, this data suggests that one aromatic ring does not have more control than the other.
Two possibilities emerge as a result: 1) the aromatic substituents work in combination during binding or 2) one group is responsible for interacting but the pseudosymmetry of the molecules makes each enantiomeric form roughly equivalent in potency. Our current methods do not allow for the enantioenrichment of the spirocycles to prove which hypothesis is correct. Nonetheless, efforts are currently being dedicated towards studying the mode in which the aromatic appendages induce increased potency to the butenolide analogs.

Finally, we tested whether or not the electrophilic alkene on the butenolide core was important to biological activity. Since α,β-unsaturated carbonyls frequently appear in covalent
enzyme inhibitors, the possibility that the spirocyclic structures are covalent modifiers exists. Therefore, compound 1.48b was synthesized by reducing 1.44b with Pd/C under a hydrogen atmosphere (Scheme 1.5). The newly made molecule demonstrated no cytotoxicity, indicating that the spirocyclic butenolides are covalent inhibitors.

In summary, natural product scaffolds can lead to new chemical entities with promising physiological properties. Our laboratory has discovered a novel synthetic method to synthesize a previously unknown class of spirocyclic ketal-lactones. Subsequently, we reported that these molecules are potent cytotoxic agents against NMC797 and MJ carcinomas, outlining an in-depth structure-function study on their biological activity.

1.6. α-Hydroxytropolones: Natural Product ‘Privileged Scaffolds’ Inspiring Clinically Effective Drug Libraries

Many physiologically active natural products contain ‘privileged substructures’ that have been molded by evolutionary processes to bind to a variety of receptors and enzymes. Coined by the Evans group in their 1988 pharmacological study of benzodiazepines, a ‘privileged scaffold’ is applied to molecular constructs with the binding versatility and potential to provide ligands for a wide range of biological macromolecules. It is surmised that these
compounds achieve such promiscuous binding through mimicry of typical biomolecular surface elements, such β- and γ-turns in proteins. Considering their synthesis and modification are directed by physiological mechanisms and their function might involve completely different cellular pathways, a plethora of natural product classes embody this concept (Figure 1.11 for examples).

Due to their promising bioactivity, a number of research programs have dedicated efforts at synthesizing compound libraries based on natural product-derived privileged structures. The strategies reported provide quick access to novel chemical entities through the alteration of a central core framework and side-chain optimization. Additionally, the resulting privileged constructs typically exhibit favorable drug-like characteristics, allowing for the discovery and
development of new lead molecules for multiple receptors. For example, Nicolaou and co-workers have detailed the combinatorial synthesis of a 10,000-member benzopyran library using a traceless phenylselenium resin. Biological studies on the compound collection revealed a high hit rate, with some molecules inhibiting hypoxic activation of tumor growth. Overall, rational drug design based on privileged structures can be beneficial to the drug discovery process and improve the effectiveness of biologically active species.

Our laboratory focuses on another privileged class of molecules, α-hydroxytropolones (αHTs). These compounds are a subset of troponoid natural products that possess therapeutic potential against a wide variety of biological targets (Figure 1.12). Pharmacological studies on β-thujaplicinol (1.58) and manicol (1.59) have revealed that αHTs exhibit promising activity against human immunodeficiency virus (HIV), hepatitis B virus (HBV), herpes simplex virus (HSV), and aminoglycoside resistant bacteria. Structurally, the molecules are defined by a non-benzenoid aromatic ring system with a contiguous array of three oxygen atoms (1.60, Figure 1.12B). Under basic conditions, this motif adopts a dianionic form (1.61), which can further resonate to a stabilized tropylium ion with significant negative charge localized on the oxygen assembly (1.62). Their promiscuous activity is generally attributed to the three contiguous oxygen atoms, which can bind to and inhibit an assortment of dinuclear metalloenzymes (represented by 1.62). The remaining positions on the αHT core can be manipulated to increase enzymatic potency and selectivity. Thus, αHTs are appealing scaffolds for developing new drug leads against several therapeutically challenging diseases.

1.6.1. Oxidopyrylium Cycloaddition/Ring-Opening Route to αHTs

Despite the promising inhibitory profile of this natural product class, the number of synthetic methods available to access αHTs and SAR studies probing their bioactivity is lacking. Motivated by the deficiency in synthetic and medicinal chemistry developments, our
laboratory invented a strategy to generate di- and trisubstituted αHT analogs utilizing 8-oxabicyclo[3,2,1]octene intermediates (1.66, Scheme 1.6).\(^{49}\) In the two-phase approach, a 3-hydroxy-4-pyrone-based oxidopyrylium cycloaddition gives the oxabicyclic compounds, which further undergo acid-mediated ring opening to αHTs (1.68). Among the advantages of our synthetic route are the use of readily available alkynes (1.65) and the facile introduction of structural diversity to the αHT core. Moreover, triflate salt 1.64, a key component of the oxidopyrylium cycloaddition step, can be made on a large-scale from kojic acid (1.63), which is a very cheap skin-bleaching agent and a by-product of rice fermentation during sake production.\(^{50}\)
Our synthetic method also grants access to more structurally complex αHTs through modification of the various reagents and intermediates. For instance, a series of ketone-containing αHTs 1.68a-d was synthesized by initially performing oxidopyrylium cycloadditions between triflate salt 1.64a and ynone derivatives (1.70, Scheme 1.7). The ynones were generated using a previously described procedure, whereby the analogous acyl chlorides (1.69) are reacted with TMS acetylene in the presence of AlCl₃. The resulting oxabicyclic compounds (1.66a-d) were then subjected to acid-mediated ring-opening/demethylation to yield the final products.

1.6.2. Structure-Function Studies with Synthetic αHTs

With this route in hand, our group was able to synthesize a sizable library of over 60 αHTs and execute SAR studies on various pharmacological targets. In collaboration with several labs, we tested the compounds against HIV reverse transcriptase ribonuclease H (RNase H), HBV RNase H, HSV-associated enzymes, aminoglycoside-2”-O-nucleotidyltransferase (ANT(2”)), and fungal pathogens. These biological studies present in-depth inhibitory information on the collection of αHTs, including the ketone-containing derivatives outlined in Scheme 1.7 (Table 1.1). However, the current discussion will focus on the significant HSV-related discoveries made with the ketone-containing derivatives.
HSV-1 and HSV-2 are highly related and ubiquitous human pathogens that have infected over half a billion individuals worldwide.\textsuperscript{47,54,57} The herpesviruses chronically infect mucosal surfaces and abraded skin and maintain a lifelong latency, whereby periodic reactivation of viral replication results in recurrent and transmissible diseases. HSV-1 is generally associated with cold sores, a rare form of encephalitis, and corneal blindness, while HSV-2 leads to genital ulcerative disease. In order to treat acute infections or reduce viral replication, nucleoside analog drugs such as acyclovir (ACV) are employed.\textsuperscript{47,54,57,58} However, the treatments are incompletely effective, and the emergence of drug-resistant viral variants is becoming an increasing threat, especially for immunocompromised patients.\textsuperscript{47,54,57,59} Thus, new molecules are required to achieve more efficient suppression of HSV.

HSV genomic replication relies upon numerous processes typically catalyzed by enzymes in the nuleotidyltransferase superfamily (NTS).\textsuperscript{47,54} These enzymes perform many functions in nucleic acid metabolism, including DNA and RNA digestion and DNA repair, integration and recombination. The NTS contains dinuclear metalloproteins, such as Human RNase H, HBV RNase H, HIV RNase H, and HIV integrase.\textsuperscript{47,54,60} Within their active sites, the enzymes possess three or four conserved carboxylates that coordinate two divalent cations pivotal for nucleic acid cleavage (\textbf{Figure 1.13} for example). Tavis et al. demonstrated that compounds with the capability to suppress these enzymes, including β-thujaplicinol and manicol, could also inhibit wild-type and ACV-resistant HSV-1 and HSV-2 replication in cell culture.\textsuperscript{47} In collaboration with Tavis, Morrison, and co-workers, our laboratory then tested a series of αHTs against HSV to assess their viability as drug candidates.\textsuperscript{54b} The most potent molecule to emerge from the study was \textbf{1.68d}, which exhibited nanomolar (nM) inhibition in HSV replication assays and displayed a synergistic therapeutic effect with ACV (\textbf{Figure 1.14}).
Subsequently, studies were conducted in order to identify the binding target for 1.68d. Based on NTS activity and homology, the αHT analog could interact with several possible HSV enzymes. One option is the pUL15 terminase, which is an end-stage RNase H-like divalent metalloprotein responsible for mobilizing viral DNA into the capsid. Inhibition and thermal stabilization experiments conducted in collaboration with Le Grice and co-workers illustrate that 1.68d weakly binds to pUL15, indicating that the enzyme might not be the primary target of action. A second choice is the exonuclease pUL12, which plays a role in DNA recombination earlier in the replication process. Initial experiments conducted with Weller and co-workers demonstrate that 1.68d interacts with pUL12. However, more data is required in order to obtain a complete mechanistic understanding.

In summary, many natural product classes possess ‘privileged scaffolds’ that can interact with various therapeutically significant biomacromolecules. Designing compound libraries based on these privileged substructures has the potential to produce drug leads for multiple targets.
Our laboratory has dedicated efforts towards synthesizing and biologically assessing αHTs, which bind to and inhibit an assortment of dinuclear metalloenzymes.\textsuperscript{49,52-56} During our screening of a 60 αHT library against a number of viral targets, we discovered the very potent HSV inhibitor 1.68d.\textsuperscript{54} Thus far, mechanistic studies have not fully elucidated the primary mode of action for the αHT derivative. However, biological studies aimed at identifying the viral target are currently ongoing.

1.7. Conclusion

The drive to understand the structural complexity and physiological effects of natural products has led to incredible advancements across scientific disciplines. While exploring the chemistry of γ-hydroxybutenolides, a heterocyclic motif present in many biologically active molecules, our laboratory has discovered a synthetic method to access novel spirocyclic ketal lactones with potent cytotoxicity against the MJ T-cell lymphoma and NMC797 epithelial cancer
cell lines. Moreover, our group has invented a two-phase approach to generate α-hydroxytropolones, which are natural product-derived privileged substructures that possess activity against a wide range of therapeutically viable targets. This route has allowed us to construct a library of αHTs for several medicinal chemistry studies. Out of these efforts, we have reported highly potent synthetic analogs. One such example is 1.68d, a promising drug candidate with intense cellular activity against HSV. Utilizing this synthetic method, our laboratory continues to produce αHT analogs for pharmacological examination. The remainder of this thesis will highlight advancements made towards αHT synthesis. Specifically, herein will be described the discovery and development of a new three-component oxidopyrylium cycloaddition, and its application in the first solid-phase and fluorous-supported syntheses of αHTs.

1.8. Experimental and Supporting Information

General Information: All starting materials and reagents were purchased from commercially available sources and used without further purification, with exception of CH₂Cl₂, which was purified on a solvent purification system prior to reactions.¹³¹H NMR shifts are measured using the solvent residual peak as the internal standard (CHCl₃ δ 7.26), and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, m = multiplet), coupling constant (Hz), integration. ¹³C NMR shifts are measured using the solvent residual peak as the internal standard (CDCl₃ δ 77.16), and reported as chemical shifts. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Mass spectra were recorded on a spectrometer by electrospray ionization (ESI) technique and time-of-flight (TOF) mass analyzer. Microwave reactions were performed via the Biotage® Initiator (External IR Temperature Sensor). Where noted, reaction products were purified via silica gel chromatography using a Biotage® Isolera Prime, with Biotage® SNAP 10 g cartridges, in a solvent system of ethyl acetate (EtOAc) in hexane.
Synthesis of Spirocyclic Ketal-Lactones:

(5S,7R,9S)-7,9-bis(perfluorophenyl)-1,6,8-trioxaspiro[4.5]dec-3-en-2-one (1.44j). To a solution of γ-hydroxybutenolide 1.40 (40 mg, 0.35 mmol) and pentafluorobenzaldehyde (866 μL, 7.0 mmol, 20 equiv.) in CH₂Cl₂ (0.2 M, 1.75 mL) over 3Å molecular sieves (8 pellets) was added trimethylsilyltriflate (126 μL, 0.7 mmol, 2 equiv.). The reaction mixture was stirred for 3 h, after which time Et₃N (8 drops) was added. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 2% EtOAc/hexane to 15% EtOAc/hexane gradient over 32 column volumes), giving 1.44j as a pale yellow oil (95.0 mg, 56% yield). R_f = 0.21 in 10% EtOAc in hexanes. IR (thin film, KBr): 3109 (w), 2935 (w), 2855 (w), 1787 (s), 1657 (s), 1526 (s), 1514 (s), 1420 (m), 1304 (m), 1169 (s), 1139 (s), 1061 (m), 1017 (s), 976 (s), 888 (m), 788 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.29 (d, J = 5.6 Hz, 1H), 6.61 (s, 1H), 6.30 (d, J = 5.6 Hz, 1H), 5.74 (dd, J = 12.2, 2.3 Hz, 1H), 2.92 (t, J = 12.8 Hz, 1H), 1.93 (dd, J = 13.4, 2.5 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 168.8 (s), 152.0 (s), 147.0 – 146.4 (m), 144.6 – 144.0 (m), 143.9 – 142.8 (m), 141.6 – 140.2 (m), 139.5 – 138.6 (m), 137.0 – 136.2 (m), 124.7 (s), 112.1 – 111.5 (m), 110.7 – 110.2 (m), 105.1 (s), 92.0 (s), 67.6 (s), 35.2 (s).


(5S,7R,9S)-7,9-bis(1-nitronaphthalen-2-yl)-1,6,8-trioxaspiro[4.5]dec-3-en-2-one (1.44k). To a solution of γ-hydroxybutenolide 1.40 (20 mg, 0.175 mmol) and 1-nitro-2-naphthaldehyde (211.2 mg, 1.05 mmol, 6 equiv.) in CH₂Cl₂ (0.2 M, 875 μL) over 3Å molecular sieves (4 pellets) was added trimethylsilyltriflate (63 μL, 0.35 mmol, 2 equiv.). The reaction mixture was stirred for 1.5 h, after which time Et₃N (4 drops) was added. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 10% EtOAc/hexane to 33% EtOAc/hexane gradient over 30 column volumes), giving 1.44k as a brown oil (27.3 mg, 31% yield). R_f = 0.23
in 30% EtOAc in hexanes. **IR (thin film, KBr):** 3099 (w), 3066 (w), 2929 (w), 2877 (w), 1781 (s), 1531 (s), 1359 (m), 1344 (m), 1200 (m), 1161 (m), 1140 (m), 1079 (w), 913 (m), 868 (w), 822 (m), 731 (m) cm$^{-1}$. **$^1$H NMR (400 MHz, CDCl$_3$):** δ 8.05 (dd, $J = 12.0, 8.7$ Hz, 2H), 7.98 – 7.87 (m, 2H), 7.82 – 7.71 (m, 4H), 7.69 – 7.58 (m, 4H), 7.23 (d, $J = 5.6$ Hz, 1H), 6.63 (s, 1H), 6.29 (d, $J = 5.6$ Hz, 1H), 5.63 (dd, $J = 11.6, 2.2$ Hz, 1H), 2.57 – 2.45 (m, 1H), 2.20 (dd, $J = 13.6, 2.4$ Hz, 1H). **$^{13}$C NMR (100 MHz, CDCl$_3$):** δ 169.0, 151.8, 146.8, 146.1, 134.4, 133.7, 131.9, 131.0, 129.2, 129.1, 128.8, 128.4, 128.2, 128.2, 128.1, 125.2, 124.8, 124.5, 124.4, 123.5, 123.1, 122.3, 122.1, 105.1, 95.8, 72.8, 38.3. **HRMS (ESI+):** $m/z$ calc’d for C$_{27}$H$_{19}$N$_2$O$_8$: 499.1136. Found: 499.1139.

**5R,7R,9S)-7,9-bis(3-(trifluoromethyl)phenyl)-1,6,8-trioxaspiro[4.5]decan-2-one (1.48b).**

To an argon degassed solution of **1.44b** (46.9 mg, 0.105 mmol) in MeOH (0.09 M, 1.2 ml) was added palladium on carbon (11.2 mg, 0.105 mmol, 1 equiv.). The reaction mixture was equipped with a balloon of H$_2$(g), stirred for 2 h at room temperature, and placed through a pad of Celite®. The reaction mixture was then purified by column chromatography (Silica (10 g), 2% EtOAc/hexanes to 25% EtOAc/hexanes gradient over 22 column volumes), giving **1.48b** as a colorless oil (21.6 mg, 46% yield). $R_f$ = 0.31 in 20% EtOAc in hexanes. **IR (thin film, KBr):** 3075 (w), 2956 (w), 2927 (w), 2854 (w), 1790 (s), 1379 (w), 1329 (s), 1209 (s), 1166 (s), 1124 (s), 1074 (s), 1017 (w), 902 (m), 870 (m), 801 (m), 702 (m) cm$^{-1}$. **$^1$H NMR (400 MHz, CDCl$_3$):** δ 7.81 (s, 1H), 7.76 – 7.49 (m, 7H), 6.22 (s, 1H), 5.36 (t, $J = 7.2$ Hz, 1H), 2.96 – 2.83 (m, 1H), 2.63 (dd, $J = 17.0, 8.7$ Hz, 1H), 2.52 – 2.44 (m, 1H), 2.31 – 2.15 (m, 3H). **$^{13}$C NMR (100 MHz, CDCl$_3$):** δ 175.5 (s), 141.1 (s), 138.0 (s), 132.0 – 130.4 (m), 130.1 (s), 129.4 (s), 129.3 (s), 129.1 (s), 126.4 (d, $J = 3.7$ Hz), 125.5 (s), 125.3 (d, $J = 3.8$ Hz), 123.7 – 123.4 (m), 122.7 (d, $J = 4.0$ Hz), 106.3 (s), 96.1 (s), 75.2 (s), 40.9 (s), 34.6 (s), 27.7 (s). **HRMS (ESI+):** $m/z$ calc’d for C$_{21}$H$_{16}$F$_6$O$_4$Na$: 469.0845. Found: 469.0853.
Synthesis of 3-Methoxy-8-oxabicyclo[3.2.1]octenes:

6-isobutyryl-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (1.66a). Triflate salt 1.64a (258.3 mg, 0.890 mmol), N,N-diisopropylaniline (433 μL, 2.23 mmol, 2.5 equiv.), 4-methylpent-1-yn-3-one (427.6 mg, 4.45 mmol, 5 equiv.), and CDCl₃ (0.15 M, 6 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was subjected to microwave irradiation at 100 °C for 45 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 2% EtOAc/hexane to 35% EtOAc/hexane gradient over 48 column volumes), giving 1.66a as a yellow oil (148.1 mg, 70% yield). Rᵥ = 0.34 in 20% EtOAc in hexanes. IR (thin film, KBr): 3082 (w), 2974 (m), 2936 (w), 1713 (s), 1671 (s), 1610 (s), 1459 (w), 1383 (m), 1343 (m), 1291 (m), 1213 (m), 1180 (m), 1128 (s), 1048 (m), 989 (m), 873 (w) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 6.93 (d, J = 2.2 Hz, 1H), 6.06 (s, 1H), 4.98 (d, J = 2.4 Hz, 1H), 3.46 (s, 3H), 3.02 (sept, J = 6.9 Hz, 1H), 1.61 (s, 3H), 1.07 (d, J = 7.1 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 201.3, 188.8, 155.5, 144.9, 136.7, 119.8, 86.2, 85.9, 54.6, 37.9, 21.0, 19.5, 17.6. HRMS (ESI+): m/z calc’d for C₁₃H₁₇O₄⁺: 237.1121. Found: 237.1124.

6-(cyclohexanecarbonyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (1.66b). Triflate salt 1.64a (94 mg, 0.324 mmol), N,N-diisopropylaniline (75.7 μL, 0.389 mmol, 1.2 equiv.), 1-cyclohexylprop-2-yn-1-one (220.5 mg, 1.62 mmol, 5 equiv.), and CHCl₃ (0.16 M, 2 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was subjected to microwave irradiation at 100 °C for 45 min. The reaction mixture was then immediately purified by column chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: 5% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (100 mL); 20% EtOAc in hexanes (200 mL); 30% EtOAc in hexanes (100 mL)), giving 1.66b as a yellow oil.
(78.2 mg, 87% yield). R\textsubscript{f} = 0.24 in 15% EtOAc in hexanes. IR (thin film, KBr): 3063 (w), 2928 (m), 2853 (m), 1709 (s), 1667 (s), 1609 (s), 1450 (m), 1444 (m), 1337 (m), 1263 (m), 1179 (m), 1128 (s), 1046 (m), 987 (m), 866 (m), 738 (s) cm\textsuperscript{-1}.\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 6.91 (d, J = 2.5 Hz, 1H), 6.05 (s, 1H), 4.97 (d, J = 2.6 Hz, 1H), 3.45 (s, 3H), 2.72 (dd, J = 11.2, 7.2, 3.4 Hz, 1H), 1.85 – 1.61 (m, 5H), 1.59 (s, 3H), 1.47 – 1.06 (m, 5H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 200.7, 188.8, 155.5, 144.9, 136.5, 119.9, 86.2, 85.9, 54.6, 48.0, 29.9, 27.7, 25.8, 25.7, 25.1, 21.0. HRMS (ESI+): m/z calc’d for C\textsubscript{16}H\textsubscript{21}O\textsubscript{4}: 277.1434. Found: 277.1439.

6-(2-cyclohexylacetyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (1.66c).

Triflate salt 1.64a (100 mg, 0.345 mmol), N,N-diisopropylaniline (80.6 μL, 0.414 mmol, 1.2 equiv.), 1-cyclohexylbut-3-yn-2-one (258 mg, 1.72 mmol, 5 equiv.), and CH\textsubscript{2}Cl\textsubscript{2} (0.16 M, 2.2 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was subjected to microwave irradiation at 100 °C for 35 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 2% EtOAc/hexane to 35% EtOAc/hexane gradient over 46 column volumes), giving 1.66c as a yellow oil (68.1 mg, 67% yield). R\textsubscript{f} = 0.20 in 15% EtOAc in hexanes. IR (thin film, KBr): 3081 (w), 2924 (s), 2851 (s), 1713 (s), 1668 (s), 1609 (s), 1449 (m), 1342 (m), 1303 (w), 1190 (m), 1178 (m), 1127 (s), 1048 (m), 987 (m), 866 (m), 773 (w) cm\textsuperscript{-1}.\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 6.96 (d, J = 2.3 Hz, 1H), 6.07 (s, 1H), 5.01 (d, J = 2.4 Hz, 1H), 3.50 (s, 3H), 2.55 (dd, J = 15.3, 6.5 Hz, 1H), 2.44 (dd, J = 15.3, 7.3 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.67 (s, 3H), 1.72 – 1.54 (m, 5H), 1.30 – 1.02 (m, 3H), 1.00 – 0.80 (m, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 197.2, 189.0, 156.8, 145.1, 137.7, 119.8, 86.2, 85.9, 54.7, 47.9, 34.7, 33.4, 33.2, 26.2, 26.1, 26.1, 21.3. HRMS (ESI+): m/z calc’d for C\textsubscript{17}H\textsubscript{23}O\textsubscript{4}: 291.1591. Found: 291.1593.
6-((1,1'-Biphenyl)-4-carbonyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (1.66d). Triflate salt 1.64a (100 mg, 0.345 mmol), N,N-diisopropylaniline (81 μL, 0.414 mmol, 1.2 equiv.), 1-((1,1'-biphenyl)-4-yl)prop-2-yn-1-one (712 mg, 3.45 mmol, 10 equiv.), and CH₂Cl₂ (0.07 M, 5 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 10-20 mL), and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction mixture was then immediately concentrated and purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 35% EtOAc/hexane gradient over 20 column volumes), giving 1.66d as an orange solid (92.8 mg, 77% yield). MP = 156-159 °C. R_f = 0.22 in 20% EtOAc in hexanes. IR (thin film, KBr): 3063 (w), 2979 (w), 2935 (w), 2837 (w), 1711 (s), 1641 (m), 1603 (s), 1449 (w), 1323 (m), 1228 (w), 1127 (m), 1043 (w), 989 (w), 844 (m), 744 (s), 698 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.65 – 7.61 (m, 2H), 7.51 – 7.39 (m, 3H), 6.83 (d, J = 2.4 Hz, 1H), 6.30 (s, 1H), 5.20 (d, J = 2.5 Hz, 1H), 3.60 (s, 3H), 1.77 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 190.2, 188.5, 155.1, 146.5, 145.1, 139.6, 138.6, 135.5, 129.7, 129.1, 128.5, 127.4, 127.3, 120.4, 87.2, 86.8, 54.8, 20.9. HRMS (ESI+): m/z calc’d for C₂₂H₁₉O₄⁺: 347.1278. Found: 347.1280.

Synthesis of α-Hydroxytropolones:

2,7-dihydroxy-4-isobutyryl-5-methylcyclohepta-2,4,6-trien-1-one (1.68a). To a solution of bicycle 1.66a (31.8 mg, 0.127 mmol) in CH₂Cl₂ (1.5 M, 86.7 μL) was added triflic acid (45.0 μL, 0.507 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 min, after which time it was quenched with sodium acetate (98 mg, 1.20 mmol, 10 equiv.), stirred for 20 min, and concentrated under reduced pressure. The crude mixture was then dissolved in 25% HBr in acetic acid (4 mL), and heated to 90 °C for 4 h. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 10 mL), and diluted with CH₂Cl₂ (5 mL).
The organic layer was washed with phosphate buffer (pH 7, 3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated to give 1.68a as a brown oil (21.7 mg, 77% yield). IR (thin film, KBr): 3261 (br), 2971 (w), 2933 (w), 2873 (w), 1701 (m), 1538 (m), 1465 (m), 1397 (m), 1284 (m), 1282 (m), 1189 (m), 1147 (w), 1092 (w), 904 (w), 826 (w), 729 (w) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.47 (s, 1H), 7.28 (s, 1H), 3.14 (sept, J = 6.9 Hz, 1H), 2.38 (s, 1H), 1.21 (d, J = 6.9 Hz, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 210.3, 168.2, 158.8, 157.3, 141.5, 137.8, 124.8, 118.1, 40.7, 24.6, 18.2. HRMS (ESI⁺): m/z calc’d for C₁₂H₁₅O₄⁺: 223.0965. Found: 223.0965.

4-(cyclohexanecarbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trienone (1.68b). To a solution of bicycle 1.66b (35.1 mg, 0.121 mmol) in CH₂Cl₂ (95.3 μL) was added triflic acid (43.0 μL, 0.486 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 min, after which time it was quenched with sodium acetate (99 mg, 1.21 mmol, 10 equiv.), stirred for 20 min, and concentrated under reduced pressure. The crude mixture was then dissolved in 25% HBr in acetic acid (2 mL) and heated to 90 ºC for 4 h. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 10 mL), and diluted with CH₂Cl₂ (5 mL). The organic layer was washed with phosphate buffer (pH 7, 3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated to give 1.68b as a black oil (26.6 mg, 84% yield). IR (thin film, KBr): 3262 (br), 2930 (s), 2854 (s), 1698 (m), 1538 (s), 1449 (s), 1395 (m), 1281 (s), 1233 (s), 1193 (s), 1160 (w), 1089 (w), 1030 (w), 958 (w), 906 (w), 731 (w) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 7.28 (s, 1H), 2.89 – 2.76 (m, 1H), 2.37 (s, 3H), 1.98 – 1.65 (m, 5H), 1.51 – 1.16 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ 209.6, 168.2, 158.7, 157.2, 141.7, 137.8, 124.7, 118.1, 50.6, 28.6, 25.8, 25.8, 24.6. HRMS (ESI⁺): m/z calc’d for C₁₅H₁₉O₄⁺: 263.1278. Found: 263.1283.
4-(2-cyclohexylacetyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trienone (1.68c). To a solution of bicycle 1.66c (31.2 mg, 0.103 mmol) in CH$_2$Cl$_2$ (0.11 M, 900 μL) was added triflic acid (37.0 μL, 0.413 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 min, after which time it was quenched with sodium acetate (85 mg, 1.03 mmol, 10 equiv.), stirred for 20 min, and concentrated under reduced pressure. The crude mixture was then dissolved in 25% HBr in acetic acid (2 mL) and heated to 90 ºC for 4 h. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 10 mL), and diluted with CH$_2$Cl$_2$ (5 mL). The organic layer was washed with phosphate buffer (pH 7, 3 x 10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated to give 1.68c as a brown oil (23.3 mg, 82% yield). IR (thin film, KBr): 3255 (br), 2924 (s), 2852 (m), 1704 (m), 1538 (s), 1448 (m), 1397 (m), 1351 (m), 1280 (s), 1208 (s), 1156 (m), 1115 (m), 1090 (w), 906 (w), 785 (w), 733 (w) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.46 (s, 1H), 7.27 (s, 1H), 2.67 (d, $J = 6.7$ Hz, 2H), 2.40 (s, 3H), 2.06 – 1.94 (m, 1H), 1.84 – 1.61 (m, 5H), 1.38 – 0.93 (m, 5H). $^{13}$C NMR (50 MHz, CDCl$_3$): δ 206.1, 168.1, 158.8, 157.4, 142.3, 137.4, 125.0, 118.1, 50.9, 33.6, 33.4, 26.3, 26.2, 24.4. HRMS (ESI+): m/z calc’d for C$_{16}$H$_{21}$O$_4$+: 277.1434. Found: 277.1441.

4-([1,1'-biphenyl]-4-carbonyl)-2,7-dihydroxy-5-methylcyclolcohepta-2,4,6-trien-1-one (1.68d). To a solution of bicycle 1.66d (46.4 mg, 0.134 mmol) in CH$_2$Cl$_2$ (0.09 M, 1.5 mL) was added trifluoromethanesulfonic acid (47.3 μL, 0.536 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 min, after which time it was quenched with sodium acetate (110 mg, 1.34 mmol, 10 equiv.), stirred for 20 min, and concentrated under reduced pressure. The crude mixture was then dissolved in 25% HBr in acetic acid (2 mL), and heated to 90 ºC for 4 h. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 10 mL), and diluted with CH$_2$Cl$_2$ (5 mL). The organic layer was washed phosphate buffer (pH 7,
3 x 10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated to give **1.68d** as a brown oil (26.2 mg, 59% yield). **IR (thin film, KBr)**: 3262 (br), 3060 (w), 2961 (w), 1669 (s), 1601 (s), 1534 (s), 1398 (m), 1284 (s), 1232 (s), 1191 (s), 1083 (s), 1007 (m), 906 (m), 859 (m), 750 (s), 696 (m) cm$^{-1}$. **$^1$H NMR (400 MHz, CDCl$_3$)**: δ 7.88 (d, $J = 8.2$ Hz, 2H), 7.71 (d, $J = 8.2$ Hz, 2H), 7.63 (d, $J = 7.4$ Hz, 2H), 7.54 (s, 1H), 7.52 – 7.39 (m, 3H), 7.36 (s, 1H), 2.36 (s, 3H). **$^{13}$C NMR (100 MHz, CDCl$_3$)**: δ 196.8, 168.5, 158.8, 157.1, 147.3, 140.0, 139.7, 138.2, 134.4, 130.9, 129.2, 128.8, 127.8, 127.5, 124.5, 119.0, 24.7. **HRMS (ESI+)**: $m/z$ calc’d for C$_{21}$H$_{17}$O$_4^+$: 333.1121. Found: 333.1124.
Figure 1.15. $^1$H NMR spectrum of compound 1,44 in CDCl$_3$. 

**Chemical Structure**

[Chemical structure diagram]
Figure 1.16. $^13$C NMR spectrum of compound 1.44 in CDCl$_3$. 
Figure 1.17. H NMR spectrum of compound 1.44k in CDCl₃.
Figure 1.18. $^{13}$C NMR spectrum of compound 1,44k in CDCl$_3$. 
Figure 1.19. $^1$H NMR spectrum of compound 1.486 in CDCl$_3$. 

[Diagram of the NMR spectrum and chemical structure of the compound]
Figure 1.20. $^{13}$C NMR spectrum of compound 1.48b in CDCl$_3$. 
Figure 1.21. $^1$H NMR spectrum of compound 1.66a in CDCl$_3$. 
Figure 1.22. $^{13}$C NMR spectrum of compound 1.66a in CDCl$_3$. 
Figure 1.23. $^1$H NMR spectrum of compound 1.66b in CDCl$_3$. 

![NMR Spectrum Diagram]
Figure 1.24. $^1$C NMR spectrum of compound 1.66b in CDCl$_3$. 
Figure 1.25. $^1$H NMR spectrum of compound 1.66c in CDCl$_3$. 
Figure 1.26. $^{13}$C NMR spectrum of compound 1,66c in CDCl$_3$. 

[Diagram of the $^{13}$C NMR spectrum with chemical shifts and assignments labeled.]
Figure 1.27: $^1$H NMR spectrum of compound 1,66d in CDCl$_3$. 

![NMR Spectrum Image]
Figure 1.28. $^{13}$C NMR spectrum of compound 1.66d in CDCl$_3$. 
Figure 1.29. $^1$H NMR spectrum of compound 1.68a in CDCl$_3$.
Figure 1.30. $^{13}$C NMR spectrum of compound 1.68a in CDCl$_3$. 

![NMR Spectrum Image]
Figure 1.31. $^1$H NMR spectrum of compound 1.68b in CDCl$_3$. 

[Image of the NMR spectrum]
Figure 1.32. $^{13}$C NMR spectrum of compound 1.68b in CDCl$_3$. 

[Diagram of the NMR spectrum with chemical shifts labeled.]

[Structure of compound 1.68b with labels for C, COC, Me, HO, and HO.]
Figure 1.33. $^1$H NMR spectrum of compound 1.68c in CDCl$_3$. 
Figure 1.34. $^{13}$C NMR spectrum of compound 1.68c in CDCl$_3$. 

![NMR spectrum diagram]
Figure 1.35. $^1$H NMR spectrum of compound 1.68d in CDCl$_3$. 

![NMR spectrum of compound 1.68d in CDCl$_3$.](image)
Figure 1.3. $^{13}$C NMR spectrum of compound 168-d in CDCl$_3$. 

![NMR spectrum of compound 168-d in CDCl$_3$.]
Chapter II

The Discovery and Development of a Three-Component Oxidopyrylium Cycloaddition

2.1. Analyzing the Oxidopyrylium Cycloaddition/Ring-Opening Route to αHTs

2.1.1. Synthetic Method Limitations

As reviewed in the previous chapter, our laboratory has reported an oxidopyrylium cycloaddition/acid-mediated ring-opening approach to gain access to polysubstituted αHTs (Scheme 2.1). This strategy has allowed us to construct a sizable library of over 60 derivatives that have been dedicated to medicinal chemistry studies for several therapeutically significant targets. Nevertheless, the synthetic method is not without limitation in regards to SAR and chemical probe development. Specifically, the strongly acidic demethylation conditions required for conversion of 2.5 to 2.6 prevent the introduction of a wide range of pharmacologically relevant functional groups (e.g. many amides, esters, amines, etc.) and activity-based probes and linkers (e.g. diazarines and pegylated biotin) to the αHT scaffold (Figure 2.1). Demethylation generally necessitates harsh reagents and procedures that are not functional group
tolerant, including boron tribromide (BBr₃) and HBr/AcOH or LiCl/DMSO at high temperatures.⁶⁶ Thus, in order to address the restrictions on αHT design, the final step of our route must be bypassed.

2.1.2. 3-Hydroxy-4-Pyrone-Based Oxidopyrylium Cycloadditions and Their Origins

To carry out this task, we must first understand the importance of the methoxy functionality to the overall αHT synthesis. The incorporation of the methyl ether that requires deprotection at the end of Scheme 2.1 occurs during the formation of triflate salt 2.2. The methoxy group enables the following intermolecular [5 + 2] cycloaddition reaction between 2.2 and alkynes (2.3) in the presence of base to produce the oxabicyclic intermediates (2.4). Also classified as a 3-hydroxy-4-pyrone-based oxidopyrylium cycloaddition, this process mechanistically entails the generation of an oxidopyrylium ylide as the reactive species prior to bond formation.⁶⁷
Historically, various methods have been employed using kojic acid derivatives to create the essential zwitterionic intermediate in situ (Scheme 2.2). Most synthetic strategies leverage the tautomerization or rearrangement of 3-hydroxy-4-pyrones to oxidopyrylium ylides (2.12 → 2.13, Path A). However, higher temperatures are necessary to initiate the reaction, which exclude many thermally unstable alkenyl and alkynyl substrates. In addition, oxidopyrylium cycloadditions performed through group transfer are only effective for intramolecular processes due to the transience of the active ylide.

To circumvent the high temperature rearrangement, Wender and co-workers developed an alternative and milder approach whereby the ylide is created through simple activation of a methyl triflate-derived oxidopyrylium salt (2.15 → 2.16, Path B). The triflate salt or ‘pre-ylide’ is initially synthesized by executing an O-4 alkylation on 3-hydroxy-4-pyrones with methyl triflate (MeOTf). The resulting salt then engages in low temperature [5 + 2] cycloadditions when exposed to a non-nucleophilic base or a fluoride source, depending on the

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**Scheme 2.2.** Overview of 3-hydroxy-4-pyrene-based oxidopyrylium cycloadditions.
nature of the R group at O-3. With this method in hand, the Wender group not only demonstrated intramolecular reactions but reported the intermolecular construction of cycloadducts with both alkenes and alkynes (Scheme 2.3).

In our synthetic route to αHTs, we utilize a modified version of the oxidopyrylium cycloaddition developed by Wender and co-workers. A key characteristic of oxidopyrylium ylides is their capacity to dimerize upon formation (Scheme 2.4A). Believing the dimerization to be detrimental to the overall productivity of the intermolecular oxidopyrylium cycloaddition, the Wender group optimized against this process by using lower temperatures and a weaker base (i.e. N,N-dimethylaniline, Scheme 2.3). However, the work conducted in our laboratory by Dr. Christine Meck illustrated that the dimerization is reversible, as a cycloaddition between dimer 2.24a and dimethyl acetylenedicarboxylate (DMAD) occurs when heated (Scheme 2.4B). In addition, our laboratory discovered that ylide 2.23a demethylates in the presence of N,N-dimethylaniline at higher temperatures, effectively destroying the reaction (Scheme 2.4C). The demethylation was suppressed with the use of a bulkier base, N,N-diisopropylaniline,
permitting an efficient intermolecular oxidopyrylium cycloaddition with a variety of alkynes (Scheme 2.5 for select examples).

In summary, the harsh demethylation conditions required at the final stage of our αHT synthesis emerge as a result of the stipulations set by the oxidopyrylium cycloaddition. The O-4 methylation of 3-hydroxy-4-pyrone derivatives to oxidopyrylium triflate salts allows for facile and effective intra- and intermolecular [5 + 2] cycloadditions versus reaction variants that rely on
high temperature group transfers and tautomerization. Thus, we shifted our efforts towards adjusting the cycloaddition phase of Scheme 2.1 in order to remove the methoxy functionality.

2.1.3. Attempts at Synthesizing Alternative Oxidopyrylium Triflate Salts

As detailed earlier, triflate salt 2.2a is very easily generated by methylating allomaltol (2.18) with MeOTf. The process permits a gram-scale synthesis of 2.2a, which is both storable and bench-stable. In principle, 3-hydroxy-4-pyrone should react with alternative alkyl triflates to produce novel oxidopyrylium salts. Nevertheless, attempts performed by our laboratory to synthesize other triflate-derived species, including benzyl and trifluoroethyl triflate analogs, have been unsuccessful. Therefore, a different strategy is needed to bypass the formation of α-methoxyenone-containing oxabicycles.

2.2. The Three-Component Oxidopyrylium [5 + 2] Cycloaddition

2.2.1. Serendipitous Discovery and Initial Optimization with Triflate Salt/Base

Due to a serendipitous discovery made by Dr. Christine Meck, our laboratory was able to develop a procedure to overcome the limitation of exclusively synthesizing α-methoxyenone-derived oxabicyclic intermediates. Specifically, when ylide 2.23 is treated with various alcohols prior to the oxidopyrylium cycloaddition, a three-component process transpires, resulting in the generation of new oxabicyclic products (2.27, Scheme 2.6). The original observation was made while conducting slower oxidopyrylium cycloaddition reactions with
ethanol-stabilized chloroform (Table 2.1, Entry 1). Chloroform (CHCl$_3$) with ethanol (EtOH) stabilizer typically contains 1% alcohol concentration, which corresponds to 0.33 equivalents under our studied conditions. Following an oxidopyrylium cycloaddition between triflate salt 2.2a and phenylacetylene in the presence of base, approximately 15% of the overall yield is attributed to the α-ethoxyenone compound 2.27a.

Moving forward with this finding, we ventured to optimize the process towards a higher output of 2.27a. Our results revealed that an increase in EtOH concentrations led to more incorporated product, while having no influence on total bicyclic yields (Entries 2-3). Prolonging the oxidopyrylium cycloaddition did not improve 2.27a production, and resubjecting bicycle 2.4f to the reaction conditions with EtOH gave no noticeable incorporation. On the other

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Table 2.1. Preliminary optimization results for ethanol incorporation with triflate salt 2.2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>EtOH equiv.</th>
<th>Temperature (ºC)</th>
<th>Time ($^{a}$)</th>
<th>Yield (2.4f:2.27a)$^{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.33</td>
<td>-</td>
<td>-</td>
<td>62% (5.2:1)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>62% (2.7:1)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>25</td>
<td>12 h</td>
<td>65% (1:1.2)</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>25</td>
<td>1 wk</td>
<td>64% (1:3.9)</td>
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<tr>
<td>5</td>
<td>5</td>
<td>60$^{c}$</td>
<td>1 h</td>
<td>63% (1:1.4)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>60$^{c}$</td>
<td>2 h</td>
<td>63% (1:2)</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>80$^{c}$</td>
<td>4 h</td>
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<tr>
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<td>5</td>
<td>80$^{c}$</td>
<td>1 h</td>
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<td>5</td>
<td>80$^{c}$</td>
<td>4 h</td>
<td>30% (1:6.2)</td>
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<tr>
<td>10</td>
<td>5</td>
<td>60$^{c}$</td>
<td>2 h</td>
<td>56% (1:2.3)</td>
</tr>
</tbody>
</table>

[a] Reaction temperatures and times correspond to the first step. [b] Yields were calculated on the basis of combined 2.4f and 2.27a, and ratios were determined by $^1$H NMR integration. [c] Heated with microwave irradiation. [d] Conventional heating throughout reaction.
hand, when the oxidopyrylium ylide was reacted with alcohol for a period of time prior to alkyne addition, 2.27a was provided in larger quantities (Entries 4-8). However, upon exposing the ylide and alcohol to higher temperatures and longer reaction times, observed yields decreased markedly (Entries 9-10). Lastly, since a multi-hour process in a microwave reactor is impractical, the three-component cycloaddition was investigated with conventional heating. Similar yields were obtained between experiments with different heating methods, allowing for the study of a wider range incorporation times (Entries 7 vs. 11).

After deeming it viable to obtain yields around 50% for 2.27a with a three-component reaction, we attempted to generate a series of novel oxabicycles by incorporating alternative alcohols (Table 2.2). During the substrate scope, we found that each alcohol required new optimization conditions and demonstrated varying levels of efficiency. For example, the more sterically demanding alcohols, such as isopropanol and neopentanol, produced 2.27m and 2.27k in lower overall yields and demanded much longer reaction times (Entries 4-9). Alcohols with even greater steric demand (e.g. t-butanol and trimethylsilanol) displayed no observable incorporation (not shown). Benzyl and allyl alcohols provided lower yields of 2.27f and 2.27n at 60 ºC for 2 h, demanding shorter intervals and lower temperatures for optimization (Entries 10-15). Lastly, attempts at using electron rich substituents, such as p-methoxybenzyl (PMB) alcohol, failed to supply incorporated species, and instead led to the formation of allomaltol (not shown).

Overall, though reasonably effective for ethanol incorporation, the initial optimization conditions involving triflate salt 2.2a and base were not very versatile. We speculated that the reduction in efficiency for other alcohols involved decomposition pathways mediated by the conjugate acid that forms after deprotonation of 2.2a. Thus, our focus shifted toward conducting the three-component oxidopyrylium cycloaddition without the use of base.
Table 2.2. Preliminary substrate scope results with triflate salt 2.2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol (R =)</th>
<th>Temperature (ºC)</th>
<th>Time (h)</th>
<th>Yield (2.27:2.4f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et (2.27a)</td>
<td>60</td>
<td>2</td>
<td>56% (2.3:1)</td>
</tr>
<tr>
<td>2</td>
<td>Et (2.27a)</td>
<td>60</td>
<td>4</td>
<td>41% (5:1)</td>
</tr>
<tr>
<td>3</td>
<td>Et (2.27a)</td>
<td>60</td>
<td>12</td>
<td>13% 2.27a</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr (2.27m)</td>
<td>60</td>
<td>2</td>
<td>47% (1:9)</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr (2.27m)</td>
<td>60</td>
<td>4</td>
<td>39% (1:3)</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr (2.27m)</td>
<td>60</td>
<td>12</td>
<td>10% 2.27m</td>
</tr>
<tr>
<td>7</td>
<td>Np (2.27k)</td>
<td>60</td>
<td>0.5</td>
<td>53% (1:4.4)</td>
</tr>
<tr>
<td>8</td>
<td>Np (2.27k)</td>
<td>60</td>
<td>2</td>
<td>51% (1:1.6)</td>
</tr>
<tr>
<td>9</td>
<td>Np (2.27k)</td>
<td>60</td>
<td>12</td>
<td>15% (2:1)</td>
</tr>
<tr>
<td>10</td>
<td>Bn (2.27f)</td>
<td>60</td>
<td>2</td>
<td>15% (3:1)</td>
</tr>
<tr>
<td>11</td>
<td>Bn (2.27f)</td>
<td>60</td>
<td>0.5</td>
<td>41% (2:1)</td>
</tr>
<tr>
<td>12</td>
<td>Bn (2.27f)</td>
<td>25</td>
<td>12</td>
<td>63% (1:1.3)</td>
</tr>
<tr>
<td>13</td>
<td>Allyl (2.27n)</td>
<td>60</td>
<td>2</td>
<td>13% (2:1)</td>
</tr>
<tr>
<td>14</td>
<td>Allyl (2.27n)</td>
<td>60</td>
<td>0.5</td>
<td>56% (1:1.4)</td>
</tr>
<tr>
<td>15</td>
<td>Allyl (2.27n)</td>
<td>25</td>
<td>12</td>
<td>40% (1:3)</td>
</tr>
</tbody>
</table>

[a] Reaction temperatures and times are for the first step of process prior to addition of alkyne. [b] Yield calculated from combined isolated 2.4f and 2.27. [c] Average of 2 separate runs.

2.2.2. Mechanistic Hypothesis and Re-Optimization with Oxidopyrylium Dimer

Considering the preliminary results, our proposed mechanistic hypothesis for the alcohol incorporation involves a nucleophilic aromatic substitution on ylide 2.23 (Scheme 2.7). Though 2.23 rapidly dimerizes to 2.24 and cannot be detected in solution, the transformation is presumed to be reversible based on previous reports from our laboratory.\(^{49a}\) The interconversion ultimately allows the alcohol to interact with 2.23, generating new ylide species (2.26) that further undergoes cycloaddition. Alcohol exchange directly with the dimer is improbable due to the requirement for an S\(_N\)1-type reaction on a bridgehead carbon and/or the replacement of an...
\(\alpha\)-alkoxy group on an enone. Nonetheless, the incorporation mechanism could reasonably entail an unknown intermediate between the ylide and dimer. Studies are currently being performed in order obtain a better mechanistic understanding of the three-component reaction.

In order to increase the efficiency of the synthetic method, we leveraged the reversible dimerization. The purified dimer \(2.24a\) was readily prepared in high yields by adding triethylamine to triflate salt \(2.2a\), then performing an aqueous ammonium chloride wash. We surmised that eliminating residual base and stoichiometric conjugate acid emerging from deprotonation of \(2.2a\) would permit longer incorporation times and limit decomposition. This assumption was verified as experiments conducted with oxidopyrylium dimer provided greater overall yields and tolerated prolonged exposure to heating conditions in comparison to the triflate salt/base combination (Table 2.3). The optimal reaction time for this process was 12 hours, as anything beyond that led to comparable amounts of \(2.27b\). In addition, lower overall yields were observed with the 18 and 24 hour time points due to the formation of less \(2.4h\).
Table 2.3. Results comparing three-component reaction carried out with triflate salt/base vs. purified oxidopyrylium dimer.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Time (h)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>2.27b&lt;sup&gt;c&lt;/sup&gt;</th>
<th>2.4h&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>2</td>
<td>12</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>2</td>
<td>25</td>
<td>56</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>6</td>
<td>25</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>6</td>
<td>47</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>8</td>
<td>30</td>
<td>28</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>8</td>
<td>47</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>12</td>
<td>37</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>12</td>
<td>52</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>18</td>
<td>51</td>
<td>10</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>B</td>
<td>24</td>
<td>55</td>
<td>7</td>
<td>62</td>
</tr>
</tbody>
</table>

[a] Equivalents are calculated on the basis of monomeric ylide for consistency. [b] Time for first step, with conventional heating. [c] Isolated yields following silica gel chromatography. [d] Product 2.4h was isolated along with benzyl alcohol, and yields were approximated on the basis of the <sup>1</sup>H NMR integration ratio of signature peaks of 2.4h and benzyl alcohol.

With these new reaction conditions in hand, we decided to employ alternative alkynes and alcohols to the system (Table 2.4). Benzyl-containing oxabicyclic intermediates with a variety of substituents were generated in 40-65% yield (2.27b-f). Benzyl alcohols with distinct electronic properties were also used with comparable results (2.27g-h), as electronically poor benzyl derivatives required less incorporation time. Furthermore, a dimer possessing methylene
Table 2.4. Substrate scope for three-component reaction using optimized conditions with oxidopyrylum dimer \(2.24a\).

\[
\begin{align*}
\text{2.24} & \xrightarrow{i. R^4\text{OH (5 equiv.)},^a CH_2Cl_2, 60^\circ C} \text{OR}^4 \\
& \quad \text{O}^{\circ} \text{Me} \\
& \xrightarrow{ii. R^2 \equiv R^3 (20 equiv.),^a 100^\circ C, \mu \text{wave}} \text{OR}^4 \\
& \quad \text{O}^{\circ} \text{Me} \\
& \quad \text{R}^1 \\
& \quad \text{2.27} \\
& \quad \text{2.4} \\
& \quad \text{24-65% yield} \\
& \quad \text{0-24% yield}
\end{align*}
\]

- \(\text{2.27b, 52% yield}^d\) (2.4h, 24% yield)
- \(\text{2.27c, 55% yield}^d\) (2.4d, 10% yield)
- \(\text{2.27d, 65% yield}^d\) (2.4e, 16% yield)
- \(\text{2.27e, 48% yield}^d\) (2.4a, 11% yield)
- \(\text{2.27f, 40% yield}\)
- \(\text{2.27g, 43% yield}\)
- \(\text{2.27h, 46% yield}\)
- \(\text{2.27i, 54% yield}^d\) (2.4i, 20% yield)
- \(\text{2.27j, 57% yield}^d\) (2.4d, 26% yield)
- \(\text{2.27k, 43% yield}^d\) (2.4f, 7% yield)
- \(\text{2.27l, 42% yield}^d\) (2.4f, 22% yield)
- \(\text{2.27m, 32% yield}^d\) (2.4f, 26% yield)
- \(\text{2.27n, 24% yield}^d\) (2.4f, 12% yield)
- \(\text{2.27o, 44% yield}^d\)

[a] Equivalents are calculated based upon monomeric ylide. [b] Time for step 1. [c] Time for step 2. [d] Isolated yields following silica gel chromatography. [e] In cases where methyl enol ethers (2.4) appeared substantial and isolatable, they were isolated and the yields are provided in parentheses. [f] 10 equiv. of alkyne was used, 80% of which was recovered during chromatography.
methyl ether groups was implemented without any competitive transetherification (2.27i). Primary alcohols with adjacent steric (2.27j-k) or base-sensitive functionality (2.27l) were successfully incorporated. However, steric limitations apply, with secondary alcohols necessitating longer reaction times and producing lower yields (2.27m), and tertiary alcohols showing no product formation. Allyl alcohol again provided diminished yields, which may be due to competing Claisen-rearrangement-type decomposition pathways (2.27n). In a majority of cases, an excess amount of alkyne (20 equiv.) was used to maximize product output. Nonetheless, for more costly reagents, as represented by 1,4-diethynylbenzene, such liberal usage can be prohibitive. For these situations, decreased quantities of alkyne (10 equiv.) can be employed with comparable yields (2.27o), and the alkyne can be recovered and recycled (i.e. 80% recovery at a net consumption of 2 equiv.).

In summary, we successfully re-optimized the three-component oxidopyrylium cycloaddtion by utilizing the purified dimer 2.24a and removing the base from the system. This protocol granted access to a series of novel α-alkoxyenone-containing oxabicycles through the incorporation of various alcohols and alkynes, which could not be achieved with the triflate salt/base combination (Table 2.4). Many of these compounds possess acid- or base-sensitive protecting groups, such as benzyl and cyanoethyl functionalities respectively, that require much milder conditions to cleave in comparison to methyl ethers.66 Thus, our next step was to apply the newly developed synthetic method towards αHT generation.

2.2.3. Utility of Three-Component Reaction in αHT Synthesis

Considering benzyl ethers are widely used in protecting group chemistry and can be removed more easily than methyl appendages with much weaker acids,66 our studies began with bicycle 2.27f. Following a previously reported procedure for benzyl deprotection,72 we
discovered that treatment of 2.27f with methane sulfonic acid leads directly to the αHT 2.6a, despite the presence of benzyl methanesulfonate impurity (Scheme 2.8, Method A). In order to remove this contaminant, the acid source was changed to a solid-supported sulfonic acid resin, Amberlyst® 15. The obtained yields from the resin reaction were lower, but the product was much cleaner (Scheme 2.8, Method B). It must be noted that with the latter method, an aqueous wash is necessary to dissociate the αHT from the resin, most likely due to hydrogen bonding between the troponoid system and solid-bound sulfonic acids. While the overall mechanism for the deprotections is unknown, shorter reaction times lead to observable amounts of benzyloxytropolones along with 2.6a, suggesting that ring opening occurs prior to debenzylolation. Overall, these promising results demonstrated that the three-component oxidopyrylium cycloaddition can be leveraged to synthesize αHTs with much milder conditions than previously outlined.

2.3. Conclusion

Our group has discovered and developed a new three-component 3-hydroxy-4-pyrone-based oxidopyrylium cycloaddition that generates novel oxabicyclic compounds. The data
presented above illustrates the potential utility of the synthetic method towards αHT assembly, as a wider range of milder deprotection conditions can be used to bypass harsher demethylation requirements. The remainder of this thesis will describe further applications of the three-component reaction, specifically detailing the solid-phase and fluorous supported synthesis of αHTs.

2.4. Experimental and Supporting Information

**General Information:** All starting materials and reagents were purchased from commercially available sources and used without further purification, with exception of CH₂Cl₂, which was purified on a solvent purification system prior to reactions.¹ H NMR shifts are measured using the solvent residual peak as the internal standard (CHCl₃ δ 7.26), and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, m = multiplet), coupling constant (Hz), integration.¹³C NMR shifts are measured using the solvent residual peak as the internal standard (CDCl₃ δ 77.16), and reported as chemical shifts. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Mass spectra were recorded on a spectrometer by electrospray ionization (ESI) technique and time-of-flight (TOF) mass analyzer. Microwave reactions were performed via the Biotage® Initiator (External IR Temperature Sensor). Where noted, reaction products were purified via silica gel chromatography using a Biotage® Isolera Prime, with Biotage® SNAP 10 g cartridges, in a solvent system of ethyl acetate (EtOAc) in hexane.

**Synthesis of Oxidopyrylium Dimers:**

(1R,2S,6S,7R)-6,9-Dimethoxy-4,7-dimethyl-3,11-dioxatricyclo[5.3.1.1²,6]dodeca-4,8-diene-10,12-dione (2.24a). To a solution of triflate salt 2.2a (5 g, 17.2 mmol) in CH₂Cl₂ (43 ml) was added triethylamine (2.89 mL, 20.7 mmol, 1.2 equiv.). After it was stirred for 10 min at room
temperature, the reaction mixture was washed with aqueous NH₄Cl (5 x 50 mL). The organic layer was dried with Na₂SO₄, filtered, and concentrated under reduced pressure to yield 2.24a as a pale yellow solid (2.21 g, 92% yield), demonstrating ¹H NMR data consistent with previously reported data. ⁴⁹a ¹H NMR (400 MHz, CDCl₃): δ 5.89 (s, 1H), 4.74 (d, J = 2.7 Hz, 1H), 4.69 (s, 1H), 4.42 (d, J = 2.7 Hz, 1H), 3.59 (s, 3H), 3.40 (s, 3H), 1.95 (s, 3H), 1.42 (s, 3H). (1R,2S,6S,7S)-6,9-Dimethoxy-4,7-bis(methoxymethyl)-3,11-dioxatricyclo[5.3.1.2,6]dodeca-4,8-diene-10,12-dione (2.24b). To a solution of 5-hydroxy-4-methoxy-2-(methoxymethyl)-pyrylium trifluoromethanesulfonate (1.64 g, 5.12 mmol) in CH₂Cl₂ (13 ml) was added triethylamine (857 µL, 6.15 mmol, 1.2 equiv.). After it was stirred for 10 min at room temperature, the reaction mixture was washed with aqueous NH₄Cl (5 x 20 mL). The organic layer was dried with Na₂SO₄, filtered, and concentrated under reduced pressure to yield 2.24b as a brown solid (683.4 mg, 78% yield). Melting Point (MP) = 140-143 ºC. Rf = 0.25 in 50% EtOAc in hexanes. IR (thin film, KBr): 3074 (w), 2938 (m), 2839 (m), 1748 (s), 1705 (s), 1669 (m), 1621 (s), 1455 (m), 1369 (m), 1282 (m), 1194 (s), 1105 (s), 992 (m), 901 (m), 834 (m), 729 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 6.00 (s, 1H), 5.00 (s, 1H), 4.91 (d, J = 2.7 Hz, 1H), 4.54 (d, J = 2.7 Hz, 1H), 4.03 (d, J = 13.5 Hz, 1H), 3.96 (d, J = 13.6 Hz, 1H), 3.88 (d, J = 10.4 Hz, 1H), 3.67 (d, J = 11.1 Hz, 1H), 3.66 (s, 3H), 3.47 (s, 3H), 3.43 (s, 3H), 3.43 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 197.4, 185.1, 157.2, 151.2, 115.7, 95.7, 87.3, 86.6, 85.2, 82.1, 73.5, 70.6, 59.9, 58.7, 55.4, 54.4. HRMS (ESI+): m/z calc’d for C₁₆H₂₁O₈⁺: 341.1231. Found: 341.1233.

Procedure for Alcohol Incorporation/Cycloaddition Sequence:

3-Ethoxy-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27a). Representative Procedure for Synthesis of 2.27a. Triflate salt 2.2a (50 mg, 0.172 mmol), N,N-diisopropyl
aniline (41 μL, 0.208 mmol, 1.2 equiv.), and CDCl₃ (0.5 M, 344 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL) and stirred until no solid was observed. Ethanol (50 μL, 0.860 mmol, 5 equiv.) was then added, and the reaction mixture was heated to 60 ºC in silicone oil bath for 2 h. After the reaction mixture was cooled to room temperature, phenyl acetylene (378 μL, 3.44 mmol, 20 equiv.) was added and the sealed tube was heated to 100 ºC for 30 min. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 in. height of silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 5% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (150 mL)). Product fractions were concentrated to give 2.27a as a yellowish oil (17 mg, 38% yield) and 2.4f as a yellow solid (8 mg, 19% yield). The ¹H NMR for 2.4f was consistent with previously reported data. Characterization Data for 2.27a. Rᵣ = 0.21 in 15% EtOAc in hexanes. IR (thin film, KBr): 3057 (w), 2981 (m), 2936 (w), 1713 (s), 1603 (s), 1493 (m), 1446 (m), 1381 (w), 1339 (m), 1264 (m), 1130 (s), 1058 (m), 898 (m), 864 (m), 755 (s), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.41 – 7.30 (m, 3H), 7.30 – 7.25 (m, 2H), 6.27 (d, J = 2.5 Hz, 1H), 6.18 (s, 1H), 4.98 (d, J = 2.5 Hz, 1H), 3.85 – 3.67 (m, 2H), 1.66 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 190.2, 158.8, 145.2, 133.2, 128.82, 128.77, 126.1, 123.2, 119.7, 86.5, 86.0, 63.3, 22.2, 14.3. HRMS (ESI+): m/z calc’d for C₁₆H₁₇O₃⁺: 257.1172. Found: 257.1173.

tert-Butyl 3-(benzyloxy)-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (2.27b). Representative Procedure Employing Method A. Triflate salt 1 (50 mg, 0.172 mmol), N,N-diisopropyl aniline (41 μL, 0.208 mmol, 1.2 equiv.), and CH₂Cl₂ (0.5 M, 344 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL) and stirred until no solid was observed. Benzyl alcohol (89 μL, 0.860 mmol, 5 equiv.) was then added, and the
reaction mixture was heated to 60 ºC in silicone oil bath for 12 h. After the reaction mixture was cooled to room temperature, tert-butyl propiolate (472 µL, 3.44 mmol, 20 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 ºC for 15 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 30 column volumes), yielding 2.27b as a white solid (21.6 mg, 37% yield) and 2.4h as a white solid (8.3 mg, 18%).

Representative Procedure Employing Method B. Dimer 2.24a (24 mg, 0.0860 mmol), benzyl alcohol (89 µL, 0.860 mmol, 10 equiv.), and CH₂Cl₂ (0.25 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5–2 mL), and the reaction mixture was heated to 60 ºC in silicone oil bath for 12 h. tert-Butyl propiolate (472 µL, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 ºC for 15 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 25 column volumes), yielding 2.27b as a white solid (30.8 mg, 52% yield) and 2.4h as a white solid (10.8 mg, 24%).

Characterization Data for 2.27b. MP = 99-102 ºC. Rf = 0.22 in 10% EtOAc in hexanes. IR (thin film, KBr): 3065 (w), 3034 (w), 2978 (w), 2936 (w), 1706 (s), 1614 (m), 1455 (m), 1369 (m), 1327 (s), 1160 (s), 1122 (s), 1072 (s), 874 (m), 751 (m), 698 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.38–7.27 (m, 5H), 6.98 (d, J = 2.5 Hz, 1H), 6.13 (s, 1H), 4.99 (d, J = 2.5 Hz, 1H), 4.80 (d, J = 11.9 Hz, 1H), 4.73 (d, J = 11.9 Hz, 1H), 1.72 (s, 3H), 1.48 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 189.0, 162.2, 151.1, 144.0, 137.8, 135.6, 128.7, 128.3, 127.6, 121.6, 86.0, 85.5, 82.3, 69.6, 28.2, 21.5. HRMS (ESI+): m/z calc’d for C₂₀H₂₃O₅⁺: 343.1540. Found: 343.1545.

Characterization Data for 2.4h. MP = 82-85 ºC. Rf = 0.26 in 15% EtOAc in hexanes. IR (thin film, KBr): 3092 (w), 2979 (w), 2937 (w), 1708
(s), 1615 (m), 1605 (m), 1456 (w), 1369 (m), 1328 (m), 1272 (m), 1161 (m), 1128 (m), 1073 (m),
1024 (m), 873 (w), 760 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.96 (d, \(J = 2.5\) Hz, 1H), 6.06 (s, 1H), 4.97 (d, \(J = 2.5\) Hz, 1H), 3.55 (s, 3H), 1.74 (s, 3H), 1.50 (s, 9H). \(^{13}\)C NMR (50 MHz,
CDCl\(_3\)): \(\delta\) 189.2, 162.3, 151.1, 145.1, 137.6, 119.7, 85.8, 85.6, 82.4, 54.8, 28.3, 21.5. HRMS (ESI+): \(m/z\) calc’d for C\(_{14}\)H\(_{19}\)O\(_5\): 267.1227. Found: 267.1229.

Ethyl 3-(benzyloxy)-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (2.27c).

Dimer 2.24a (24 mg, 0.0860 mmol), benzyl alcohol (89 \(\mu\)L, 0.860 mmol, 10 equiv.), and CH\(_2\)Cl\(_2\)
(0.25 M, 344 \(\mu\)L) were placed in a sealed tube reactor (Biotage\(^\circledR\) microwave reaction vial,
0.5-2 mL), and the reaction mixture was heated to 60 °C in silicone oil bath for 12 h. Ethyl
propionate (349 \(\mu\)L, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture
was subjected to microwave irradiation at 100 °C for 15 min. The reaction mixture was then
immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 15%
EtOAc/hexane gradient over 33 column volumes), giving 2.27c as a yellow oil (29.6 mg, 55%)
and 2.4d as a yellow oil (4 mg, 10% yield). The \(^1\)H NMR for 2.4d was consistent with previously
reported data.\(^{49a}\) Characterization Data for 2.27c. \(R_f = 0.25\) in 15% EtOAc in hexanes. IR (thin
film, KBr): 3065 (w), 2982 (w), 2937 (w), 1711 (s), 1615 (m), 1602 (m), 1455 (m), 1370 (m),
1317 (s), 1221 (m), 1123 (s), 1073 (s), 1037 (m), 875 (m), 750 (m), 698 (m) cm\(^{-1}\). \(^1\)H NMR
(400 MHz, CDCl\(_3\)): \(\delta\) 7.37 – 7.27 (m, 5H), 7.09 (d, \(J = 2.5\) Hz, 1H), 6.16 (s, 1H), 5.03
(d, \(J = 2.5\) Hz, 1H), 4.77 (d, \(J = 11.7\) Hz, 1H), 4.72 (d, \(J = 11.7\) Hz, 1H), 4.30 – 4.17 (m, 2H),
1.75 (s, 3H), 1.31 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 188.7, 162.9, 149.6,
144.1, 138.8, 135.4, 128.7, 128.3, 127.7, 121.4, 86.2, 85.6, 69.7, 61.3, 21.4, 14.3. HRMS (ESI+): \(m/z\) calc’d for C\(_{18}\)H\(_{19}\)O\(_5\): 315.1227. Found: 315.1228.
6-Acetyl-3-(benzyloxy)-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27d). Dimer 2.24a (24 mg, 0.0860 mmol), benzyl alcohol (89 μL, 0.860 mmol, 10 equiv.), and CH₂Cl₂ (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction was heated to 60 ºC in silicone oil bath for 12 h. 3-Butyne-2-one (269 μL, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 ºC for 15 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 25% EtOAc/hexane gradient over 60 column volumes), giving 2.27d as a pale yellow solid (32 mg, 65% yield) and 2.4e as a yellow solid (5.8 mg, 16%). The ¹H NMR for 2.4e was consistent with previously reported data.⁴⁹a Characterization Data for 2.27d. MP = 84-87 ºC. Rₛ = 0.32 in 25% EtOAc in hexanes. IR (thin film, KBr): 3066 (w), 3034 (w), 2981 (w), 2936 (w), 1712 (s), 1672 (s), 1608 (s), 1455 (m), 1365 (m), 1311 (s), 1269 (m), 1121 (s), 1065 (m), 872 (s), 739 (m), 699 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.26 (m, 5H), 7.04 (d, J = 2.5 Hz, 1H), 6.18 (s, 1H), 5.06 (d, J = 2.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 2.36 (s, 3H), 1.71 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 194.3, 188.7, 156.4, 144.1, 139.1, 135.4, 128.7, 128.4, 127.8, 121.5, 86.1, 86.0, 69.7, 27.8, 21.3. HRMS (ESI⁺): m/z calc’d for C₁₇H₁₈O₄⁺: 285.1121. Found: 285.1122.

Dimethyl 3-(benzyloxy)-1-methyl-4-oxo-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate (2.27e). Dimer 2.24a (24 mg, 0.0860 mmol), benzyl alcohol (89 μL, 0.860 mmol, 10 equiv.), and CH₂Cl₂ (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 ºC in silicone oil bath for 12 h. Dimethyl acetylenedicarboxylate (422 μL, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 ºC for 10 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0%
EtOAc/hexane to 35% EtOAc/hexane gradient over 45 column volumes), giving 2.27e as a pale yellow solid (29.8 mg, 48% yield) and 2.4a as a yellow solid (5.2 mg, 11%). The \( ^1 \text{H NMR} \) for 2.4a was consistent with previously reported data.\(^{49a} \)

**Characterization Data for 2.27e.**

MP = 104-107 °C. \( R_f = 0.26 \) in 25% EtOAc in hexanes. **IR (thin film, KBr):** 3066 (w), 3034 (w), 2954 (w), 1721 (s), 1652 (w), 1605 (m), 1455 (w), 1437 (m), 1323 (m), 1287 (s), 1124 (m), 1073 (m), 1031 (m), 868 (w), 747 (m), 698 (w) cm\(^{-1} \). \( ^1 \text{H NMR (400 MHz, CDCl}_3\): δ 7.39 – 7.28 (m, 5H), 6.09 (s, 1H), 5.26 (s, 1H), 4.78 (s, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 1.64 (s, 3H). \( ^{13} \text{C NMR (100 MHz, CDCl}_3\): δ 186.8, 163.8, 161.5, 153.5, 144.3, 136.0, 135.2, 128.7, 128.4, 127.8, 119.9, 87.9, 86.8, 69.9, 52.9, 52.8, 20.9. \( \text{HRMS (ESI+):}\ m/z \text{ calc’d for C}_{19}\text{H}_{19}\text{O}_7^+: 359.1125. \) Found: 359.1130.

3-(Benzyloxy)-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27f). Dimer

2.24a (24 mg, 0.0860 mmol), benzylic alcohol (89 \( \mu \)L, 0.860 mmol, 10 equiv.), and CH\(_2\)Cl\(_2\) (0.25 M, 344 \( \mu \)L) were placed in a sealed tube reactor (Biotage\(^{®}\) microwave reaction vial, 0.5-2 mL), and the reaction was heated to 60 °C in silicone oil bath for 12 h. Phenyl acetylene (378 \( \mu \)L, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (100 mL); 5% EtOAc in hexanes (100 mL); 7% EtOAc in hexanes (200 mL); 10% EtOAc in hexanes (100 mL)). Product fractions concentrated to give 2.27f as a white solid (21.9 mg, 40% yield). MP = 112-114 °C. \( R_f = 0.24 \) in 15% EtOAc in hexanes. **IR (thin film, KBr):** 3061 (w), 3033 (w), 2979 (w), 2933 (w), 1709 (s), 1604 (s), 1491 (m), 1454 (m), 1339 (m), 1263 (m), 1125 (s), 1106 (m), 1058 (m), 866 (m), 754 (s), 697 (s) cm\(^{-1} \). \( ^1 \text{H NMR (400 MHz, CDCl}_3\): δ 7.40 – 7.27 (m, 8H), 7.18 – 7.12
(m, 2H), 6.27 (d, $J = 2.4$ Hz, 1H), 6.24 (s, 1H), 5.01 (d, $J = 2.5$ Hz, 1H), 4.92 (d, $J = 12.0$ Hz, 1H), 4.79 (d, $J = 12.0$ Hz, 1H), 1.62 (s, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$): δ 189.9, 158.9, 144.7, 135.6, 133.1, 128.8, 128.7, 128.3, 127.5, 126.0, 123.2, 121.6, 86.5, 86.1, 69.7, 22.0. HRMS (ESI+): $m/z$ calc’d for C$_{21}$H$_{19}$O$_3$: 319.1329. Found: 319.1332.

5-Methyl-3-((4-methylbenzyl)oxy)-6-(4-(trifluoromethyl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27g). Dimer 2.24a (25 mg, 0.0892 mmol), 4-methylbenzyl alcohol (105 mg, 0.860 mmol, 9.6 equiv.), and CH$_2$Cl$_2$ (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 °C in silicone oil bath for 12 h. 4-Ethynyl-α,α,α-trifluorotoluene (561 µL, 3.44 mmol, 39 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 35 min. The reaction was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 25 column volumes), giving 2.27g as a yellow solid (30.2 mg, 42% yield). MP = 115-119 °C. R$_f$ = 0.31 in 15% EtOAc in hexanes. IR (thin film, KBr): 3054 (w), 2982 (w), 2936 (w), 1712 (m), 1615 (m), 1603 (m), 1455 (w), 1326 (s), 1165 (m), 1125 (s), 1069 (s), 1016 (w), 869 (m), 835 (w), 804 (w), 740 (w) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.57 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 7.9$ Hz, 2H), 6.36 (d, $J = 2.4$ Hz, 1H), 6.18 (s, 1H), 5.02 (d, $J = 2.5$ Hz, 1H), 4.93 (d, $J = 12.1$ Hz, 1H), 4.76 (d, $J = 12.1$ Hz, 1H), 2.32 (s, 3H), 1.59 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 189.6 (s), 157.8 (s), 144.5 (s), 138.1 (s), 138.1 (s), 136.8 (d, $J = 1.2$ Hz), 132.5 (s), 130.6 (q, $J = 32.7$ Hz), 129.5 (s), 127.5 (s), 126.3 (s), 125.7 (q, $J = 3.8$ Hz), 125.6 (s), 124.0 (q, $J = 272.1$ Hz), 121.4 (s), 86.5 (s), 86.3 (s), 69.7 (s), 21.9 (s), 21.2 (s). HRMS (ESI+): $m/z$ calc’d for C$_{23}$H$_{19}$F$_3$O$_3$Na$: 423.1179. Found: 423.1182.
6-(4-Methoxyphenyl)-5-methyl-3-((4-(trifluoromethyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27h). Dimer 2.24a (25 mg, 0.0892 mmol), 4-(trifluoromethyl)benzyl alcohol (118 µL, 0.860 mmol, 9.6 equiv.), and CH₂Cl₂ (0.26 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 °C in silicone oil bath for 4 h. 4-Ethynylanisole (446 µL, 3.44 mmol, 39 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 40 min. The reaction was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 20% EtOAc/hexane gradient over 30 column volumes), giving product contaminated with aryl alcohol. The aryl alcohol was removed with vacuum distillation, giving 2.27h as a yellow oil (34.1 mg, 46% yield). Rᵢ = 0.23 in 20% EtOAc in hexanes. IR (thin film, KBr): 3055 (w), 2977 (w), 2937 (w), 1711 (s), 1607 (m), 1510 (s), 1457 (w), 1326 (s), 1253 (s), 1164 (m), 1125 (s), 1067 (s), 1020 (m), 867 (m), 828 (m), 725 (w) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.19 (s, 1H), 6.16 (d, J = 1.8 Hz, 1H), 4.99 (d, J = 2.1 Hz, 1H), 4.97 (d, J = 13.5 Hz, 1H), 4.83 (d, J = 12.7 Hz, 1H), 3.82 (s, 3H), 1.62 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 189.7 (s), 160.2 (s), 158.5 (s), 144.5 (s), 139.8 (q, J = 1.1 Hz), 130.5 (q, J = 32.5 Hz), 127.5 (s), 127.3 (s), 125.8 (q, J = 3.7 Hz), 125.4 (s), 124.1 (q, J = 272.1 Hz), 122.1 (s), 121.0 (s), 114.3 (s), 86.4 (s), 86.0 (s), 68.8 (s), 55.5 (s), 22.1 (s). HRMS (ESI⁺): m/z calc’d for C₂₃H₂₀F₃O₄⁺: 417.1308. Found: 417.1310.

Ethyl 3-(benzyloxy)-5-(methoxymethyl)-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (2.27i). Dimer 2.24b (29 mg, 0.0860 mmol), benzyl alcohol (89 µL, 0.860 mmol, 10 equiv.), and CH₂Cl₂ (0.25 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction was heated to 60 °C in silicone oil bath for
12 h. Ethyl propiolate (349 µL, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 20 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 30% EtOAc/hexane gradient over 35 column volumes), yielding 2.27i as a white solid (31.8 mg, 54% yield) and 2.4i as a yellow oil (9 mg, 20%). Characterization Data for 2.27i. MP = 80-84 °C. Rf = 0.30 in 30% EtOAc in hexanes. IR (thin film, KBr): 3065 (w), 2983 (w), 2931 (w), 1712 (s), 1617 (w), 1604 (m), 1455 (w), 1370 (w), 1320 (m), 1278 (w), 1217 (m), 1114 (m), 1097 (m), 1032 (w), 869 (w), 749 (w) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.27 (m, 5H), 7.12 (d, J = 2.4 Hz, 1H), 6.09 (s, 1H), 5.12 (d, J = 2.4 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.30 – 4.18 (m, 2H), 3.97 (d, J = 10.9 Hz, 1H), 3.93 (d, J = 11.0 Hz 1H), 3.44 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 188.4, 162.7, 147.5, 145.2, 139.0, 135.3, 128.7, 128.4, 127.8, 116.8, 88.4, 86.4, 72.2, 69.8, 61.4, 59.8, 14.3. HRMS (ESI+): m/z calc’d for C₁₉H₂₁O₆⁺: 345.1333. Found: 345.1334.

Characterization Data for 2.4i. Rf = 0.27 in 35% EtOAc in hexanes. IR (thin film, KBr): 3067 (w), 2982 (w), 2935 (w), 1712 (s), 1618 (m), 1607 (m), 1455 (w), 1319 (m), 1218 (m), 1120 (s), 1098 (s), 1033 (m), 986 (w), 868 (w), 828 (w), 769 (w) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.11 (d, J = 2.5 Hz, 1H), 6.01 (s, 1H), 5.10 (d, J = 2.5 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 4.00 (d, J = 10.9 Hz, 1H), 3.97 (d, J = 10.8 Hz, 1H), 3.57 (s, 3H), 3.45 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 188.7, 162.8, 147.7, 146.3, 138.9, 115.0, 88.4, 86.2, 72.3, 61.4, 59.9, 54.9, 14.3. HRMS (ESI+): m/z calc’d for C₁₃H₁₇O₆⁺: 269.1024. Found: 269.1024.

**Ethyl 5-methyl-3-(neopentyloxy)-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (2.27j).** Dimer 2.24a (25 mg, 0.0892 mmol), neopentyl alcohol (76 mg, 0.860 mmol, 9.6 equiv.), and CDCl₃ (0.26 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction
vial, 0.5-2 mL), and the reaction mixture was heated to 60 °C in silicone oil bath for 12 h. Ethyl propiolate (349 µL, 3.44 mmol, 39 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 20 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 25% EtOAc/hexane gradient over 25 column volumes), giving 2.27j as a yellow solid (29.8 mg, 57% yield) and 2.4d as a yellow solid (10.9 mg, 26% yield). The ¹H NMR for 2.4d was consistent with previously reported data. Characterization Data for 2.27j. MP = 69-73 °C. Rᵣ = 0.31 in 10% EtOAc in hexanes. IR (thin film, KBr): 3066 (w), 2958 (m), 2870 (w), 1712 (s), 1616 (m), 1602 (m), 1478 (w), 1367 (m), 1316 (s), 1220 (m), 1125 (s), 1074 (w), 874 (m), 752 (m), 677 (w) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.09 (d, J = 2.5 Hz, 1H), 6.02 (s, 1H), 4.99 (d, J = 2.5 Hz, 1H), 4.24 (q, J = 6.9 Hz, 2H), 3.26 (d, J = 8.9 Hz, 1H), 3.21 (d, J = 8.9 Hz, 1H), 1.75 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 0.96 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 188.7, 163.1, 149.6, 144.8, 138.9, 119.7, 86.2, 85.6, 77.2, 61.2, 31.8, 26.7, 21.5, 14.3. HRMS (ESI+): m/z calc’d for C₁₆H₂₃O₅⁺: 295.1540. Found: 295.1542.

5-Methyl-3-(neopentyloxy)-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27k). Dimer 2.24a (25 mg, 0.0892 mmol), neopentyl alcohol (76 mg, 0.860 mmol, 9.6 equiv.), and CDCl₃ (0.26 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 °C in silicone oil bath for 12 h. Phenyl acetylene (378 µL, 3.44 mmol, 39 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (100 mL); 3% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (100 mL)). Product
fractions were concentrated to give $2.27k$ as a yellow solid (22.9 mg, 43% yield) and $2.4f$ as a yellow solid (3.2 mg, 7% yield). The $^1$H NMR for $2.4f$ was consistent with previously reported data.\textsuperscript{49a} Characterization Data for $2.27k$. MP = 114-117 °C. $R_f$ = 0.33 in 10% EtOAc in hexanes.

IR (thin film, KBr): 3057 (w), 2957 (m), 2869 (w), 1714 (s), 1603 (m), 1478 (w), 1446 (w), 1365 (w), 1338 (w), 1260 (w), 1130 (m), 1059 (w), 995 (w), 865 (m), 755 (m), 697 (w) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.27 (m, 5H), 6.29 (d, $J = 2.4$ Hz, 1H), 6.14 (s, 1H), 4.97 (d, $J = 2.5$ Hz, 1H), 3.34 (d, $J = 8.8$ Hz, 1H), 3.25 (d, $J = 8.8$ Hz, 1H), 1.67 (s, 3H), 0.99 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.7, 158.7, 145.7, 133.3, 128.8, 128.7, 126.1, 123.3, 119.4, 86.5, 86.1, 77.3, 31.8, 26.7, 22.2. HRMS (ESI+): $m/z$ calc'd for C$_{19}$H$_{23}$O$_3$: 299.1642. Found: 299.1645.

3-((1-Methyl-4-oxo-7-phenyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)oxy)propanenitrile ($2.27l$). Dimer $2.24a$ (25 mg, 0.0892 mmol), 3-hydroxypropionitrile (59 µL, 0.860 mmol, 9.6 equiv.), and CDCl$_3$ (0.26 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction was heated to 60 °C in silicone oil bath for 12 h. Phenyl acetylene (378 µL, 3.44 mmol, 39 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 35 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 40% EtOAc/hexane gradient over 30 column volumes), giving $2.27l$ as an orange oil (21.1 mg, 42% yield) and $2.4f$ as a yellow solid (9.6 mg, 22%). The $^1$H NMR for $2.4f$ was consistent with previously reported data.\textsuperscript{49a} Characterization Data for $2.27l$. $R_f$ = 0.24 in 35% EtOAc in hexanes. IR (thin film, KBr): 3058 (w), 2979 (w), 2937 (w), 2253 (w), 1710 (s), 1606 (m), 1492 (w), 1446 (w), 1342 (w), 1264 (w), 1132 (s), 1057 (m), 878 (m), 864 (m), 755 (m), 698 (m) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43 – 7.33 (m, 3H), 7.30 – 7.23 (m, 2H),
6.32 (s, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.00 (d, J = 2.5 Hz, 1H), 4.05 – 3.87 (m, 2H), 2.81 (t, J = 6.8 Hz, 2H), 1.68 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.2, 158.5, 144.3, 132.9, 129.0, 128.9, 126.1, 123.2, 122.7, 116.7, 86.4, 86.0, 62.7, 22.0, 18.2. HRMS (ESI+): $m/z$ calc’d for C$_{17}$H$_{15}$NO$_3$Na$: 304.0944$. Found: 304.0948.

**3-Isopropoxy-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27m).** Dimer

2.24a (25 mg, 0.0892 mmol), isopropyl alcohol (66 $\mu$L, 0.860 mmol, 9.6 equiv.), and CDCl$_3$ (0.26 M, 344 $\mu$L) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 °C in silicone oil bath for 36 h. Phenyl acetylene (378 $\mu$L, 3.44 mmol, 39 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 5% EtOAc in hexanes (100 mL); 8% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (100 mL), 15% EtOAc in hexanes (100 mL)). Product fractions were concentrated to give **2.27m** as a yellowish oil (15.3 mg, 32% yield) and **2.4f** as a yellowish solid (11.3 mg, 26% yield). The $^1$H NMR for **2.4f** was consistent with previously reported data.$^{49a}$ Characterization Data for **2.27m**. $R_f = 0.27$ in 15% EtOAc in hexanes. IR (thin film, KBr): 3057 (w), 2979 (m), 2935 (w) 1710 (s), 1600 (s), 1596 (s), 1493 (w), 1447 (w), 1384 (w), 1375 (w), 1263 (w), 1125 (s), 1058 (w), 865 (m), 754 (m), 697 (w) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.31 (m, 3H), 7.30 – 7.25 (m, 2H), 6.28 (d, J = 2.4 Hz, 1H), 6.19 (s, 1H), 4.98 (d, J = 2.5 Hz, 1H), 4.24 (sept, J = 6.1 Hz, 1H), 1.66 (s, 3H), 1.32 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.0 Hz, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 190.7, 158.8, 143.8, 133.3, 128.9, 128.7, 126.1, 123.4, 121.1, 86.5, 86.1, 69.9, 22.2, 21.5. HRMS (ESI+): $m/z$ calc’d for C$_{17}$H$_{19}$O$_3$Na$: 271.1329$. Found: 271.1331.
3-(Allyloxy)-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27n). Dimer 2.24a (25 mg, 0.0892 mmol), allyl alcohol (58 µL, 0.860 mmol, 9.6 equiv.), and CDCl₃ (0.26 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 ºC in silicone oil bath for 12 h. Phenyl acetylene (378 µL, 3.44 mmol, 39 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 ºC for 30 min. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (100 mL); 5% EtOAc in hexanes (100 mL); 7% EtOAc in hexanes (150 mL); 10% EtOAc in hexanes (50 mL); 15% EtOAc in hexanes (100 mL)). Product fractions were concentrated to give 2.27n as yellowish oil (11.5 mg, 24% yield) and 2.4f as yellowish solid (5.2 mg, 12% yield). The ¹H NMR for 2.4f was consistent with previously reported data. Characterization Data for 2.27n. Rᵥ = 0.24 in 15% EtOAc in hexanes. IR (thin film, KBr): 3081 (w), 3057 (w), 2981 (w), 2935 (w), 1710 (s), 1603 (s), 1491 (w), 1447 (w), 1338 (w), 1264 (w), 1125 (m), 1106 (m), 1058 (m), 865 (w), 755 (s), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.41 – 7.32 (m, 3H), 7.29 – 7.25 (m, 2H), 6.28 (d, J = 2.5 Hz, 1H), 6.21 (s, 1H), 6.02-5.91 (m, 1H), 5.35 (dq, J = 17.3, 1.5 Hz, 1H), 5.27 (dq, J = 10.5, 1.3 Hz, 1H), 4.99 (d, J = 2.5 Hz, 1H), 4.34 (ddt, J = 12.6, 5.4, 1.4 Hz, 1H), 4.26 (ddt, J = 12.7, 5.6, 1.3 Hz, 1H), 1.66 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 190.0, 158.8, 144.7, 133.2, 132.1, 128.84, 128.80, 126.1, 123.3, 120.8, 118.7, 86.5, 86.1, 68.6, 22.2. HRMS (ESI+): m/z calc’d for C₁₇H₁₆O₃Na⁺: 291.0992. Found: 291.0997.

3-(Benzyloxy)-6-(4-ethylphenyl)-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2.27o). Dimer 2.24a (24 mg, 0.0860 mmol), benzyl alcohol (89 µL, 0.860 mmol, 10 equiv.), and CH₂Cl₂ (0.25 M, 344 µL) were placed in a sealed tube reactor (Biotage® microwave reaction vial,
0.5-2 mL), and the reaction mixture was heated to 60 ºC in silicone oil bath for 14 h. 1,4-Diethynylbenzene (217 mg, 1.72 mmol, 20 equiv.) and CH₂Cl₂ (344 μL) were added to the sealed tube, and the reaction mixture was stirred until no solid was observed. The reaction mixture was then subjected to microwave irradiation at 100 ºC for 35 min and immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 30 column volumes). Product fractions were concentrated to give 2.27o as an orange oil (25.7 mg, 44% yield). Due to high value of 1,4-diethynylbenzene (2.28), fractions containing it were also concentrated (174 mg, 89% recovery (195 mg would be 100% theoretical yield of un-reacted product)). R_f = 0.28 in 15% EtOAc in hexanes. IR (thin film, KBr): 3287 (m), 3035 (w), 2981 (w), 2935 (w), 2106 (w), 1709 (s), 1600 (m), 1498 (m), 1455 (m), 1339 (m), 1264 (m), 1124 (s), 1058 (m), 867 (m), 734 (m), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, J = 8.4 Hz, 2H), 7.35 – 7.27 (m, 5H), 7.08 (d, J = 8.4 Hz, 2H), 6.30 (d, J = 2.5 Hz, 1H), 6.19 (s, 1H), 5.01 (d, J = 2.5 Hz, 1H), 4.93 (d, J = 12.1 Hz, 1H), 4.78 (d, J = 12.1 Hz, 1H), 3.15 (s, 1H), 1.60 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 189.7, 158.2, 144.7, 135.6, 133.6, 132.5, 128.8, 128.3, 127.5, 126.0, 124.3, 122.5, 121.4, 86.4, 86.2, 83.2, 78.6, 69.7, 22.0. HRMS (ESI+): m/z calc’d for C₂₃H₁₈O₃Na+: 365.1148. Found: 365.1150.

**Synthesis of α-Hydroxytropolones via Acid-Mediated Debenzylation: Procedure A.** To a solution of 2.27f (25.6 mg, 0.0804 mmol) in CH₂Cl₂ (500 μL) was added methanesulfonic acid (210 μL, 3.22 mmol, 40 equiv.). The reaction mixture was stirred for 1 h, at which time it was quenched with phosphate buffer (pH 7, 15 mL), extracted with CH₂Cl₂ (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield 2.6a as a reddish brown oil (19.0 mg, >95% crude yield). The ¹H NMR for 2.6a was consistent with previously reported data.⁵⁵ ¹H NMR (400 MHz, CDCl₃): δ 7.58 (s, 1H), 7.50 (s, 1H), 7.48 – 7.35 (m, 3H),
7.25 – 7.21 (m, 2H), 2.26 (s, 3H). *Procedure B.* To a solution of 2.27f (25 mg, 0.0785 mmol) in CH₂Cl₂ (1 mL) was added Amberlyst® 15 (4.7 mmol/g, 671 mg, 3.14 mmol, 40 equiv.). The reaction mixture was stirred for 16 h, at which time the Amberlyst was washed with CH₂Cl₂ (5 x 2 mL). The Amberlyst was then stirred in phosphate buffer (pH 7, 15 mL) for 10 min, and the aqueous layer was extracted with EtOAc (5 x 10 mL). Combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield 2.6a as a light brown oil (11.6 mg, 65% yield). The ¹H NMR for 2.6a was consistent with previously reported data.⁵⁵

¹H NMR (400 MHz, CDCl₃): δ 7.58 (s, 1H), 7.50 (s, 1H), 7.48 – 7.35 (m, 3H), 7.25 – 7.21 (m, 2H), 2.26 (s, 3H).
Figure 2.2. $^1$H NMR spectrum of compound 2.2.4. in CDCl$_3$. 
Figure 2.3. $^1$H NMR spectrum of compound 2.4b in CDCl$_3$. 
Figure 2.4. $^{13}$C NMR spectrum of compound 2.24b in CDCl$_3$. 
Figure 2.5: $^1$H NMR spectrum of compound 2.27a in CDCl$_3$. 
Figure 2.6. $^{13}$C NMR spectrum of compound 2.27a in CDCl$_3$. 

(Chart showing the $^{13}$C NMR spectrum with chemical shifts and peak assignments.)
Figure 2.7. $^1$H NMR spectrum of compound 2.27b (Method A) in CDCl$_3$. 
Figure 2.8. $^1$H NMR spectrum of compound 2.27b (Method B) in CDCl$_3$. 
Figure 2.9. $^{13}$C NMR spectrum of compound 2.27b in CDCl$_3$. 
Figure 2.10. $^{1}H$ NMR spectrum of compound 2.4h in CDCl$_3$. 
Figure 2.11. $^{13}$C NMR spectrum of compound 2.4h in CDCl$_3$. 
Figure 2.12. $^1$H NMR spectrum of compound 2.27c in CDCl$_3$.
Figure 2.13. $^{13}$C NMR spectrum of compound 2.27c in CDCl$_3$. 
Figure 2.14. $^1$H NMR spectrum of compound 2.27d in CDCl$_3$. 
Figure 2.15. $^{13}$C NMR spectrum of compound 2.27d in CDCl$_3$. 

![13C NMR spectrum of compound 2.27d in CDCl$_3$.]
Figure 2.16, H NMR spectrum of compound 2.27e in CDCl₃.
Figure 2.17. $^{13}$C NMR spectrum of compound 2.27e in CDCl$_3$. 
Figure 2.18. $^1$H NMR spectrum of compound 2.27f in CDCl$_3$. 
Figure 2.19. $^{13}$C NMR spectrum of compound 2.27f in CDCl₃.

![NMR Spectrum](image-url)
Figure 2.20. H NMR spectrum of compound 2.27g in CDCl3.
Figure 2.21. $^{13}$C NMR spectrum of compound 2.27g in CDCl$_3$. 

![NMR Spectrum](image)
Figure 2.22. $^1$H NMR spectrum of compound 2.27h in CDCl$_3$. 
Figure 2.23. $^{13}$C NMR spectrum of compound 2.27h in CDCl$_3$. 

![Chemical structure of compound 2.27h with NMR spectrum graph]
Figure 2.24. $^1$H NMR spectrum of compound 2.27i in CDCl$_3$. 

![NMR spectrum of compound 2.27i in CDCl$_3$.](image)
Figure 2.25. $^{13}$C NMR spectrum of compound 2.27i in CDCl$_3$. 
Figure 2.26. $^1$H NMR spectrum of compound 2.4 in CDCl$_3$. 
Figure 2.27. $^1$H NMR spectrum of compound 2.4i in CDCl$_3$. 
Figure 2.28, $^1$H NMR spectrum of compound 2.27j in CDCl$_3$.
Figure 2.29. $^{13}$C NMR spectrum of compound 2.27j in CDCl$_3$. 
Figure 2.30. $^1$H NMR spectrum of compound 2.27k in CDCl$_3$. 
Figure 2.31. $^{13}$C NMR spectrum of compound 2.27k in CDCl$_3$. 
Figure 2.32. $^1$H NMR spectrum of compound 2.271 in CDCl$_3$. 
Figure 2.33. $^{13}$C NMR spectrum of compound 2.27 in CDCl$_3$. 
Figure 2.34. $^1$H NMR spectrum of compound 2.27m in CDCl$_3$. 
Figure 2.35. $^{13}$C NMR spectrum of compound 2.27m in CDCl$_3$. 

![C NMR spectrum of compound 2.27m in CDCl$_3$.](image)
Figure 2.36. $^1$H NMR spectrum of compound 2.27n in CDCl$_3$. 
Figure 2.37. $^{13}C$ NMR spectrum of compound 2.27 in CDCl$_3$. 

[Image of the NMR spectrum with chemical shifts and a structural formula of the compound.]
Figure 2.38: $^1$H NMR spectrum of compound 2.27 in CDCl$_3$. 
Figure 2.39. $^{13}$C NMR spectrum of compound 2.270 in CDCl$_3$. 
Figure 2.40. $^1$H NMR spectrum of recovered alkyne 2.28 in CDCl$_3$. 
Figure 2.41. $^1$H NMR spectrum of compound 2.6a (Procedure A) in CDCl$_3$. 

[Image of the NMR spectrum with chemical shifts and peaks labeled, including a structure of the compound represented with Ph (phenyl) and Me (methyl) groups.]
Figure 2.42. $^1$H NMR spectrum of compound 2.6a (Procedure B) in CDCl$_3$. 
Chapter III

A Traceless Solid-Phase Synthesis of α-Hydroxytropolones

3.1. Solid-Supported Synthesis of Small Molecule Libraries

Solid-phase organic synthesis (SPOS), in which compounds are assembled on insoluble polymer resin beads, has revolutionized synthetic organic chemistry since first introduced by Merrifield in 1963.\textsuperscript{40a,74} Solid-phase techniques possess two major advantages over traditional procedures in solution. First, resin-bound products can simply be isolated by washing away reagents or impurities from the supported material, allowing the use of excess reagents to drive reactions to completion. Secondly, the overall time scale for solid-phase synthesis is significantly reduced due to its ease of purification and amenability to automation. Though primarily associated with peptide, nucleic acid, and carbohydrate chemistry, solid supports have been utilized in the combinatorial synthesis of small molecule drugs and natural products. To gain access to these compound libraries, novel polymer resins, traceless linkers, and automated technologies were discovered and developed. These solid-phase strategies and innovations are extensively detailed in several reviews,\textsuperscript{40a,74} and hence the current discussion will highlight only a few examples.

3.1.1. Ellman’s Library Synthesis of 1,4-Benzodiazepin-2-ones

1,4-Benzodiazepin-2-ones are the class of compounds in which the term “privileged scaffold” was first applied.\textsuperscript{41} Though they demonstrate an expansive therapeutic profile that includes coronary vasodilation and viral inhibition, most of the biological activity of these molecules can be attributed to their effects on the central nervous system.\textsuperscript{75} In one of the first reports outlining the combinatorial synthesis and biological testing of small molecule libraries, Ellman and co-workers described a solid-phase approach to produce 1,4-benzodiazepin-2-one
analogs (Scheme 3.1). The compound collection was constructed by initially attaching aminobenzophenone derivatives to a solid support via a (4-(hydroxymethyl)phenoxy)acetic acid (HMP) linker (3.1 → 3.2). The resin-bound intermediate 3.2 was then reacted with Fmoc-protected amino acid fluoride to create compound 3.3. After Fmoc deprotection, ring closure on 3.3 was induced by an acid-mediated condensation reaction, giving molecule 3.4. Alkylation of anilide 3.4 was achieved in the presence of lithiated 5-phenylmethyl-2-oxazolidinone. Finally, the 1,4-benzodiazepine with four points of functionality was cleaved in acidic conditions. The Ellman group prepared a 192-member library using this synthetic route and performed biological screening on targets such as cholecystokinin (CCK) receptor A, which is a protein implicated in gastrointestinal cancer, neuroprotection, and appetite satiety. The work would stimulate further studies on the therapeutic potential of 1,4-benzodiazepines as a whole.
3.1.2. Nicolaou’s Combinatorial Synthesis of 2,2-Dimethylbenzopyrans

At the turn of the millennium, Nicolaou and co-workers reported an extremely thorough combinatorial synthesis of the privileged substructure 2,2-dimethylbenzopyrans. Natural products with the benzopyran structural motif exhibit antitumor, antimicrobial, and anti-inflammatory activity and interact with a plethora of biological targets. The synthetic strategy implemented by the Nicolaou group entails the attachment of an ortho-prenylated phenol (3.7) to a polymer support through a traceless selenium linker (Scheme 3.2). The resulting resin-bound intermediate 3.8 then undergoes a 6-endo-trig cyclization to furnish the benzopyran core (3.9), which can be derivatized using an array of chemical modifications (e.g. organometallic additions, condensations, annulations, etc.). The compound is finally cleaved via selenium oxidation, which facilitates a spontaneous syn-elimination at room temperature to produce the benzopyran product (3.10 → 3.12). Nicolaou and coworkers would go on to generate a 10,000-member library of these molecules in just eight days by combining the
traceless solid-phase route with optically encoded split-and-pool techniques. Biological evaluation of the benzopyran library revealed a high hit rate for a diverse range of targets.

3.1.3. Merck’s Solid-Phase Synthesis of 2-Arylindole Derivatives

The indole structure is a near-ubiquitous subunit of biologically active natural products and pharmaceuticals, and the scope of its physiological effects is astronomical. Considering its vast therapeutic potential, a number of research groups have described combinatorial syntheses towards indole-derived drugs. For example, Merck reported the construction of a 128,000-member 2-arylindole library in order to search for G-protein-coupled receptor (GPCR) ligands. The group’s synthetic strategy initially entailed the anchoring of arylalkyl keto acids to a sulfonamide resin (3.13 → 3.14, Scheme 3.3). The indole core was then generated through a cyclization reaction with arylhydrazines in the presence of a Lewis acid (i.e. Fischer indole synthesis). At this stage, up to 400 unique combinations for 3.15 were possible due to the
incorporation of 20 distinct derivatives of each building block. The resin-bound molecule was separated into 80 equal portions, where the sulfonamides were subsequently alkylated with Mitsunobu conditions and displaced by 80 individual amines (3.15 → 3.16). After recombining the compound pools (now with 32,000 possibilities), it was split into two equal portions, whereby 128,000 molecules were produced through the creation of one library containing amides (3.16) and the other consisting of amines (3.17). Physiological evaluation of the 2-arylindoles resulted in multiple hits for several GPCRs, and led Merck to advance the program towards the discovery of clinical candidates.80

3.2. The Solid-Phase Synthesis of αHTs

3.2.1. Leveraging Three-Component Oxidopyrylium Cycloaddition to Incorporate Solid Supports

As discussed previously, our laboratory discovered a three-component oxidopyrylium cycloaddition that generates new oxabicyclic products through alcohol incorporation into oxidopyrylium ylides (3.18 → 3.20, Scheme 3.4A).71 Furthermore, benzyl alcohol-derived oxabicyclic intermediates generated from this reaction can be directly converted to αHTs when subjected to methanesulfonic acid (3.20 → 3.21g). Given the prevalence of solid supports in organic synthesis (reviewed above), we integrated a polystyrene-bound benzyl alcohol into our αHT route by utilizing the three-component oxidopyrylium cycloaddition (Scheme 3.4B).82 This resin possesses a major advantage over more widely used derivatives, such as Wang resin, in that no additional components appear in solution upon cleavage (i.e. traceless). Therefore, the entire procedure grants access to assay-ready compounds without necessitating column chromatography.

The protocol was conducted in a sealed vessel, where polystyrene-supported benzyl alcohol was lightly stirred in a solution of triflate salt 3.24 and base at 60 °C overnight (Table
We speculate that this initial phase forms an oxidopyrylium heterodimer (3.25c and/or 3.25d) according to the known rapid dimerization processes of oxidopyrylium ylides.\textsuperscript{49a} However, more mechanistic data is required to eliminate the possibility that the cross-linked homodimer 3.25b acts as an intermediate. After completion of the overnight alcohol incorporation, an on-bead cycloaddition was facilitated by heating the reaction mixture at 100 °C in the presence of alkynes (3.24 → 3.23).\textsuperscript{82} For liquid alkynes, the solvent and solutes were removed from the system prior to alkyne addition to increase the efficiency of the reaction (Table 3.1, Procedure A). On the other hand, solid alkynes were directly added to the mixture without expelling the solvent and solutes to allow for dissolution of the reagent (Procedure B). The optimal cycloaddition reaction times were dictated by alkyne reactivity, as insufficient time points gave increased amounts of allomaltol (3.26). Procedures with electronically poor alkynes were generally complete within 2 hours, while more sluggish aromatic alkynes demanded ~5
Table 3.1. Solid-phase synthesis of αHTs using oxidopyrylium triflate salt 3.24, along with the corresponding conditions, byproducts, and yields.

![Chemical structure of 3.24 leading to 3.25](image1)

**Procedure**: i-Pr_{2}NPh (1.8 equiv.), CH_{2}Cl_{2}, 60 °C, 14 h

**Time** (h): 1.5

**Yield** (%): 8% (3.21a: 9:1:0)

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<th>Procedure</th>
<th>Time (h)</th>
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</table>

[a] CH_{2}Cl_{2} and solutes not removed prior to addition of alkyne. [b] Time for step 2. [c] Reaction ran at twice the scale of prior run. [d] DMAD = Dimethyl acetylenedicarboxylate.
hours of heating for maximum output. Lastly, besides allomaltol and trace baseline contaminants, furan byproducts (3.27) emerging from acid-mediated ring-opening/cleavage were the only other impurities observed. As expected from previous reports, furan 3.27j was the major product when dimethyl acetylenedicarboxylate (DMAD) was used for the process.49b

From 33 mg of polystyrene-supported benzyl alcohol and 50 mg of triflate salt 3.24, between 1-5 mg of various αHTs were obtained, corresponding to approximately 5-10% yield based on resin loading (Table 3.1).82 Though large quantities of alkyne (400-500 mg) were required for the cycloaddition reaction, the overall process is highly time efficient and bypasses the need for chromatographic purification. As many as 8 αHTs were generated in parallel over a single 24 hour period during our studies, with enough material being collected to determine product formation and purity level by 1H NMR and perform several bioassays. Thus, despite the low overall yields, the protocol may serve as an important tool in the rapid library synthesis of αHTs for biological screening purposes.

3.2.2. Utilizing Solid-Phase αHT Synthesis as a Screening Tool for Biological Studies

Considering that αHTs are capable of binding to and inhibiting a variety of dinuclear metalloenzymes,44 we directed our focus towards applying the solid-phase platform as a screening tool for discovering potent inhibitors. A very promising target for αHTs is HIV ribonuclease H (RNase H), against which the natural products β-thujaplicinol and manicol have illustrated IC50 values of 200 nM and 600 nM, respectively.45a,45c HIV RNase H is an enzyme located on the C-terminal domain of HIV reverse transcriptase (RT).83 The RNase H active site works in conjunction with the DNA polymerase of HIV RT to facilitate viral genomic replication. Though a majority of treatments on the market inhibit the polymerase activity, the RNase H domain remains clinically unexploited. However, due to the emergence of resistant
viral variants, significant efforts are underway to identify viable drug candidates for HIV RNase H. Our newly developed solid-supported synthesis has potential utility towards the increased throughput of αHT-derived leads for this enzyme. Thus, we experimentally evaluated the assay-ready nature of the solid-supported library against HIV RNase H.

In collaboration with Le Grice and co-workers, we began by measuring αHT inhibition with a fluorescence resonance energy transfer (FRET) endpoint to monitor the RNase H activity of HIV-1 RT (Figure 3.1). A majority of the compounds possessed a consistent inhibitory potency, with typical IC₅₀ values between 200 nM and 1 μM. When compared to the solution phase counterparts, the solid-supported molecules were all within 2-3 fold difference, and also within a standard deviation. Next, we analyzed the capability of the αHTs to stabilize HIV
RNase H against thermal denaturation with the use of differential scanning fluorimetry (Thermofluor, Figure 3.2). Regardless of the corresponding impurities, all compounds increased the melting point of the enzyme by 2-3 °C. In addition, those species that stabilized the enzyme the least did so in both solution and solid-phase cases. Lastly, the protective effects of the molecules were investigated in HIV-associated cellular assays. Only three derivatives (i.e. 3.21a, 3.21e, 3.21f) demonstrated protective activity, as the trend was consistent for both types of synthesis. Overall, these biological studies revealed that enzymatic and cell-based assays are not severely impacted by the minor impurities observed with samples prepared from solid-supported chemistry. Hence, the synthetic method produces αHTs with assay-ready purity and possesses potential utility in future screening endeavors.
3.2.3. Limitations of Solid-Supported αHT Synthesis

The proof-of-principle synthetic and biological experiments outlined above illustrate that the solid-supported platform is extremely time efficient and generates compounds with assay-ready purity. Nevertheless, improvements to the system are necessary for it to be completely viable as a combinatorial technique for αHT synthesis. First, though yields for the process are practical for biological screening, they are substantially low overall (i.e. ~5-20% yield for 9 substrates). These results are at least partially related to the heterogeneous nature of the reaction, which would make complete alcohol exchange during the three-component oxidopyrylium cycloaddition more difficult. For instance, prior optimization efforts for the solution phase process demonstrated considerable increases in productivity when the purified dimer 3.25a served as the ylide source.71 No such yield increases were observed when this strategy was employed for the solid-supported synthesis (Scheme 3.5).82

On the other hand, some advantages did emerge when 3.25a was used in place of the triflate salt/base combination. Through the elimination of the base, we easily recovered the starting material by simply removing the supernatant liquid and evaporating the solvent. Additionally, we could monitor the efficiency of incorporation by measuring the amount of dimer re-isolated. For example, in Reaction A of Scheme 3.5, 16 out of 24 mg of 3.25a were retrieved. Assuming that the remaining 8 mg of material is attached to the solid-support as heterodimer, approximately half of that compound would be available for subsequent phases of the synthetic sequence. In light of this data, the dimer concentration was increased to 4 equiv. (8 equiv. based on monomeric ylide), and the incorporation step was stirred at room temperature for 9 days (Scheme 3.5, Reaction B). We recovered 87% of 3.25a (104 out of 120 mg), and improved our yields to 20% based on resin loading, providing some direction for future attempts at optimization.
Another major issue with the solid-phase platform is the inability to modify resin-bound intermediates. Efforts at conducting chemical transformations on supported oxabicyclic compounds, including Suzuki coupling or trifluoroacetic acid (TFA) deprotection, resulted in unintended cleavage and no end product. These observations indicate that the polystyrene-bound oxabicycle is generally unstable. We hypothesize that the decomposition is due to the electron donating properties of the benzyl alcohol resin, which would potentially drive the intermediate towards detrimental side-reactions or early deprotection. A possible solution to such a dilemma is the use of different resins and/or linkers to stabilize the attachment of the oxabicycle. These studies are currently underway to improve the solid-supported αHT synthesis towards a completely functional combinatorial technique.

3.3. Conclusion

Our laboratory has leveraged a newly discovered three-component oxidopyrylium cycloaddtion in the first reported solid-phase synthesis of αHTs. The method is extremely time efficient and produces molecules with assay-ready purity, making it a useful tool for therapeutic development. However, due to the low overall yields and an inability to modify on-bead, the system still requires improvements to meet its full potential. Though endeavors are presently
ongoing to address the issues with the solid-supported platform, the next chapter will detail an approach that bypasses these limitations. Specifically, the discussion will describe the incorporation of fluorous phase chemistry into our αHT route.

3.4. Experimental and Supporting Information

General Information: All starting materials and reagents were purchased from commercially available sources and used without further purification, with exception of CH₂Cl₂, which was purified on a solvent purification system prior to reactions. \(^1\)H NMR shifts are measured using the solvent residual peak as the internal standard (CHCl₃ δ 7.26), and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, m = multiplet), coupling constant (Hz), integration. \(^13\)C NMR shifts are measured using the solvent residual peak as the internal standard (CDCl₃ δ 77.16), and reported as chemical shifts. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Mass spectra were recorded on a spectrometer by electrospray ionization (ESI) technique and time-of-flight (TOF) mass analyzer. Microwave reactions were performed via the Biotage® Initiator (External IR Temperature Sensor). Where noted, reaction products were purified via silica gel chromatography using a Biotage® Isolera Prime, with Biotage® SNAP 10 g cartridges, in a solvent system of ethyl acetate (EtOAc) in hexane.

Solution Phase Synthesis of 3-Methoxy-8-oxabicyclo[3.2.1]octenes:

Methyl 3-methoxy-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (3.28f).

Triflate salt 3.24 (100 mg, 0.345 mmol), N,N-diisopropylaniline (81 μL, 0.414 mmol, 1.2 equiv.), and CH₂Cl₂ (0.46 M, 750 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL) and stirred until no solid was observed. Methyl propiolate (307 μL, 3.45 mmol, 10 equiv.) was added to the sealed tube, and the reaction mixture was
subjected to microwave irradiation at 100 ºC for 20 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 35% EtOAc/hexane gradient over 22 column volumes), giving 3.28f as a yellow oil (54.8 mg, 71% yield). R_f = 0.29 in 25% EtOAc in hexanes. IR (thin film, KBr): 3095 (w), 2954 (w), 2840 (w), 1712 (s), 1616 (m), 1604 (m), 1438 (w), 1323 (m), 1223 (m), 1127 (m), 1075 (m), 1035 (w), 873 (w), 859 (w), 752 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.06 (d, \(J = 2.5\) Hz, 1H), 6.05 (s, 1H), 4.98 (d, \(J = 2.5\) Hz, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 1.73 (s, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 188.89, 163.49, 149.57, 145.27, 139.15, 119.53, 86.16, 85.75, 54.92, 52.32, 21.57. HRMS (ESI+): \(m/z\) calc’d for C\(_{11}\)H\(_{13}\)O\(_5\): 225.0757. Found: 225.0757.

Solution Phase Synthesis of \(\alpha\)-Hydroxytropolones:

**Methyl 4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-trienecarboxylate (3.21f).**

To a solution of bicycle 3.28f (54.8 mg, 0.244 mmol) in CH\(_2\)Cl\(_2\) (0.16 M, 1.5 mL) was added trifluoromethanesulfonic acid (86.3 μL, 0.978 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 min, at which time it was quenched with phosphate buffer (pH 7, 10 mL), extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude mixture was then dissolved in 33% HBr in acetic acid (2 mL), and heated to reflux for 1.5 h. The reaction was cooled to room temperature, quenched with pH 7 phosphate buffer (10 mL), and extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated to give 3.21f as a brown solid (30.0 mg, 58% yield). MP = 137-141 ºC. IR (thin film, KBr): 3239 (br), 2963 (w), 1731 (s), 1544 (s), 1435 (m), 1400 (m), 1288 (s), 1214 (s), 1141 (m), 1100 (m), 1067 (w), 948 (w), 904 (w), 764 (w), 635 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.73 (s, 1H), 7.48 (s, 1H), 3.93 (s, 3H), 2.56 (s, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 169.30, 168.82, 159.40, 156.96, 141.27, 132.64, 124.60, 120.92, 53.22, 25.97. HRMS (ESI+): \(m/z\) calc’d for C\(_{10}\)H\(_{11}\)O\(_5\): 211.0601. Found: 211.0602.
Solid-Phase Synthesis of α-Hydroxytropolones Using Oxidopyrylium Triflate Salt:

**General Procedure for Liquid Alkynes (Procedure A).** Polystyrene supported benzyl alcohol (3.5 mmol/g loading capacity, 1 equiv.) was placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL) and allowed to swell for 30 min in CH₂Cl₂. Triflate salt 3.24 (1.5 equiv.) and N,N-diisopropylaniline (1.8 equiv.) were added to the sealed tube, and the reaction mixture was gently stirred at 60 ºC for 14 h. The beads were drained of CH₂Cl₂, submerged in alkyne, and heated to 100 ºC for various time points. After the reaction mixture was cooled to room temperature, the beads were rinsed with CH₂Cl₂ (6 x 1 mL) and then resuspended in CH₂Cl₂. Trifluoromethanesulfonic acid (4 equiv.) was added to the sealed tube, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH₂Cl₂ (2 mL) and quenched with pH 7 phosphate buffer (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL), and combined organics were dried over Na₂SO₄, filtered, and concentrated to give αHT 3.21.

**General Procedure for Solid Alkynes (Procedure B).** Polystyrene supported benzyl alcohol (3.5 mmol/g loading capacity, 1 equiv.) was placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL) and allowed to swell for 30 min in CH₂Cl₂. Triflate salt 3.24 (1.5 equiv.) and N,N-diisopropylaniline (1.8 equiv.) were added to the sealed tube, and the reaction mixture was gently stirred at 60 ºC for 14 h. Alkyne was added to the sealed tube, and the reaction mixture was heated to 100 ºC for various time points. After the reaction mixture was cooled to
room temperature, the beads were rinsed with CH$_2$Cl$_2$ (6 x 1 mL) and then resuspended in CH$_2$Cl$_2$. Trifluoromethanesulfonic acid (4 equiv.) was added to the sealed tube, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH$_2$Cl$_2$ (2 mL) and quenched with pH 7 phosphate buffer (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL), and combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated to give αHT 3.21.
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| **Table 3.2** Detailed conditions and results for solid-phase αHT synthesis using oxidoypyrimidine herald 3.2.4
Solid-Phase Synthesis of α-Hydroxytropolones Using Oxidopyrylium Dimer:

Procedure A. Polystyrene supported benzyl alcohol (3.5 mmol/g, 33 mg, 0.114 mmol, 1 equiv.) was placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL) and allowed to swell for 30 min in CH₂Cl₂. Oxidopyrylium dimer 3.25a (24 mg, 0.086 mmol, 0.74 equiv.) was added to the sealed tube, and the reaction mixture was gently stirred at 60 ºC for 14 h. The beads were rinsed with CH₂Cl₂ (6 x 1 mL), and the supernatant liquid was collected (16 mg of 3.25a, 66% recovery). Ethyl propiolate (500 μL) was added to the sealed tube, and the reaction mixture was heated to 100 ºC for 1.5 h. After the reaction mixture was cooled to room temperature, the beads were rinsed with CH₂Cl₂ (6 x 1 mL) and then resuspended in CH₂Cl₂ (500 μL). Trifluoromethanesulfonic acid (41 μL, 0.464 mmol, 4 equiv.) was added to the sealed tube, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH₂Cl₂ (2 mL) and quenched with pH 7 phosphate buffer (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL), and combined organics were dried over Na₂SO₄, filtered, and concentrated to give 3.21e (1.5 mg, 6% yield).

Procedure B. Polystyrene supported benzyl alcohol (3.5 mmol/g, 33 mg, 0.114 mmol, 1 equiv.) was placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL) and allowed to swell for 30 min in CH₂Cl₂. Oxidopyrylium dimer 3.25a (120 mg, 0.428 mmol, 3.8 equiv.) was added to the sealed tube, and the reaction mixture was gently stirred at 60 ºC for 14 h. The beads were rinsed with CH₂Cl₂ (6 x 1 mL), and the supernatant liquid was collected (104 mg of 3.25a, 66% recovery). Ethyl propiolate (500 μL) was added to the sealed tube, and the reaction mixture was heated to 100 ºC for 1.5 h. After the reaction mixture was cooled to room temperature, the beads were rinsed with CH₂Cl₂ (6 x 1 mL) and then resuspended in CH₂Cl₂ (500 μL). Trifluoromethanesulfonic acid (41 μL, 0.464 mmol, 4 equiv.) was added to the sealed tube, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH₂Cl₂ (2 mL) and quenched with pH 7 phosphate buffer (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL), and combined organics were dried over Na₂SO₄, filtered, and concentrated to give 3.21e (1.5 mg, 6% yield).
87% recovery). Ethyl propiolate (500 μL) was added to the sealed tube, and the reaction mixture was heated to 100 °C for 1.5 h. After the reaction mixture was cooled to room temperature, the beads were rinsed with CH₂Cl₂ (6 x 1 mL) and then resuspended in CH₂Cl₂ (500 μL). Trifluoromethanesulfonic acid (41 μL, 0.464 mmol, 4 equiv.) was added to the sealed tube, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH₂Cl₂ (2 mL) and quenched with pH 7 phosphate buffer (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL), and combined organics were dried over Na₂SO₄, filtered, and concentrated to give 3.21e (5 mg, 20% yield).
Figure 3.3. $^1$H NMR spectrum of compound 3.28f in CDCl$_3$. 

- 0.97 ppm
- 1.00 ppm
- 0.98 ppm
- 3.11 ppm
- 3.16 ppm
- 3.21 ppm
- 1.73 ppm
- 7.07 ppm
- 7.06 ppm
- 6.05 ppm
- 4.98 ppm
- 4.97 ppm
- 3.76 ppm
- 3.52 ppm
Figure 3.4. $^{13}$C NMR spectrum of compound 3.28f in CDCl$_3$. 
Figure 3.5. $^1$H NMR spectrum of compound 3.21f in CDCl$_3$. 
Figure 3.6: $^{13}$C NMR spectrum of compound 3.21 in CDCl$_3$. 

[Diagram showing the $^{13}$C NMR spectrum with peaks labeled.]
Figure 3.7. $^1$H NMR spectrum of compound 3.21a (Entry 1) in CDCl$_3$. 
Figure 3.8. $^1$H NMR spectrum of compound 3.21a (Entry 2) in CDCl$_3$. 
Figure 3.9, $^1$H NMR spectrum of compound 3.21a (Entry 3) in CDCl$_3$. 

[Image of the NMR spectrum with a chemical structure of the compound 3.21a]
Figure 3.10. $^1$H NMR spectrum of compound 3.21a (Solution Phase) in CDCl$_3$. 
Figure 3.11. $^1$H NMR spectrum of compound 3.21b (Entry 4) in CDCl$_3$. 
Figure 3.12. $^1$H NMR spectrum of compound 3.21b (Solution Phase) in CDCl$_3$. 

![NMR spectrum diagram](image-url)
Figure 3.13. $^1$H NMR spectrum of compound 3.21c (Entry 5) in CDCl$_3$. 
Figure 3.14. $^1$H NMR spectrum of compound 3.21c (Entry 6) in CDCl$_3$. 

PhOC

HO

Me

HO

HO
Figure 3.15. $^1$H NMR spectrum of compound 3.21e (Solution Phase) in CDCl$_3$.
Figure 3.16: $^1H$ NMR spectrum of compound 3.21d (Entry 7) in CDCl$_3$. 

![Chemical structure and NMR spectrum](image-url)
Figure 3.17. 
\( ^1H \) NMR spectrum of compound 3.21d (Solution Phase) in CDCl₃.
Figure 3.18. $^1$H NMR spectrum of compound 3.21e (Entry 8) in CDCl$_3$. 
Figure 3.19. $^1$H NMR spectrum of compound 3.21e (Entry 9) in CDCl$_3$. 

[Diagram showing a spectrum with chemical shifts labeled 1.00, 0.96, 7.71, 7.49, 2.72, 3.17, 3.43, 2.56, 1.43, 1.41, 1.39, 4.43, 4.41, 4.39, 4.37.]
Figure 3.21. $^1$H NMR spectrum of compound 3.21e (Solution Phase) in CDCl$_3$. 
Figure 3.22. 1H NMR spectrum of compound 3.21f (Entry 11) in CDCl₃.
Figure 3.23. $^{1}H$ NMR spectrum of compound 3.21f (Entry 12) in CDCl$_3$. 

[Diagram of the spectrum with peaks labeled at specific ppm values and a chemical structure representing compound 3.21f.]
Figure 3.24. $^1$H NMR spectrum of compound 3.21f (Solution Phase) in CDCl$_3$. 
Figure 3.25. $^1$H NMR spectrum of compound 3.21g (Entry 13) in CDCl$_3$. 

[Diagram of a molecule with peaks at specific chemical shifts]
Figure 3.26. $^1$H NMR spectrum of compound 3.21g (Entry 14) in CDCl$_3$. 
Figure 3.27. $^1$H NMR spectrum of compound 3.21g (Entry 15) in CDCl$_3$. 
Figure 3.28. $^1$H NMR spectrum of compound 3.218 (Solution Phase) in CDCl$_3$. 
Figure 3.29. $^1$H NMR spectrum of compound 3.21h (Entry 16) in CDCl$_3$. 

[Image of the H NMR spectrum]
Figure 3.30 $^1$H NMR spectrum of compound 3.21h (Entry 17) in CDCl$_3$. 

![NMR Spectrum](image-url)
Figure 3.31. $^1$H NMR spectrum of compound 3.21h (Solution Phase) in CDCl$_3$. [Image of the NMR spectrum]
Figure 3.32. $^1$H NMR spectrum of compound 3.21i (Entry 18 in CDCl$_3$).
Figure 3.33. $^1$H NMR spectrum of compound 3.21i (Entry 19) in CDCl$_3$. 
Figure 3.34. $^1$H NMR spectrum of compound 3.21i (Solution Phase) in CDCl$_3$. 

![NMR spectrum of compound 3.21i](image-url)
Figure 3.35. $^1$H NMR spectrum of compound 3.27j (Entry 20) in CDCl$_3$. 

[Image of the NMR spectrum with peaks labeled 7.74, 3.86, 3.83, 2.51, and 2.94.]
Figure 3.36: $^1$H NMR spectrum of recovered dimer 3.25a (Procedure A) in CDCl$_3$. 

![NMR Spectrum Image]
Figure 3.37. $^1$H NMR spectrum of compound 3.21e (Procedure A) in CDCl$_3$. 
Figure 3.38. $^1$H NMR spectrum of recovered dimer 3.25a (Procedure B) in CDCl$_3$. 

![NMR Spectrum Image]
Figure 3.39. $^1$H NMR spectrum of compound 3.21e (Procedure B) in CDCl$_3$. 

[Image of the NMR spectrum with peaks labeled and a structure of the compound.]
Chapter IV

A Fluorous Phase Approach to α-Hydroxytropolone Synthesis

4.1. An Introduction to Fluorous Phase Chemistry

Synthesis is universally restricted by the efficiency of the reactions being performed and the ability to purify resultant mixtures. Though organic chemists have traditionally focused on the effectiveness of transformations in solution, a number of techniques have recently emerged that simplify purification. The most prevalent method entails the integration of solid supports into a synthetic sequence (reviewed in Chapter III).\textsuperscript{40a,74} A second, lesser known approach started in the 1990s utilizes the unique interactions between perfluorinated molecules and other reaction media (i.e. fluorous phase chemistry).\textsuperscript{88} Specifically, the higher the fluorine content a compound possesses, whether it be solvent or reactant, the more insoluble the species becomes in aqueous and organic environments (>60% typically produces complete partition).\textsuperscript{89} However, unlike in water, the miscibility of fluorous molecules in organic solvents depends on temperature, as heated systems become increasingly monophasic. This distinct solubility profile was pivotal to the early success of fluorous chemistry and has granted access to a plethora of novel linkers, catalysts, scavengers, and purification technologies.\textsuperscript{88}

4.1.1. The Major Advantages of Fluorous Phase Synthesis

Fluorous synthesis successfully incorporates solution phase reaction conditions with a phase-tag separation that relies on perfluoroalkyl chains instead of resins to facilitate purification.\textsuperscript{88,90} The fluorous tags are chemically stable and typically have minor influence on the reactivity of a molecule to which they are attached. In contrast to solid-phase synthesis, fluorous reactions can be monitored by conventional analytical techniques (e.g. TLC, NMR, IR, etc.) and can adapt literature procedures without severe alteration. Additionally, although
Fluorous molecules can be isolated through traditional methods, including chromatography, distillation, and recrystallization, exclusive purification procedures exist that rely on selective fluorine-fluorine interactions between the tagged compound and the surrounding media (Figure 4.1). 89,91

The first approach takes advantage of the inherent immiscibility between fluorous solvents and other fluids to isolate individual reaction components, otherwise known as fluorous liquid-liquid extraction (FLLE, Figure 4.1A). 89 Separations are generally achieved with organic/fluorous biphasic systems or organic/aqueous/fluorous triphasic extractions when water-soluble reagents are used. Nevertheless, this process is geared toward heavier fluorous molecules (>60% fluorine content) since they demonstrate an optimal partition coefficient between organic and fluorous phases. Also, FLLE often requires expensive and environmentally destructive fluorous solvents, such as perfluoroalkanes, which could make it prohibitive for large-scale endeavors.
The second purification method is a fluorous solid-phase extraction (FSPE, Figure 4.1B). As the name implies, the procedure involves the use of a fluorinated solid-phase component, specifically in the form of fluorocarbon bonded silica gel (–SiMe(CH2)2C8F17, FluoroFlash®). This stationary phase retains organic species to a much lower degree than ordinary reverse-phase silica. Hence, organic compounds will rapidly pass through the column with an appropriate eluent. On the other hand, the fluorous silica is extremely retentive to fluorous molecules and can even partition compounds based on fluorine content. For instance, Curran employed FSPE to separate a series of molecules containing fluorous tags that ranged from C3F7 to C10F21. However, the approach does not necessitate fluorous solvents to elute reaction mixtures, as common organic and aqueous solvent media will suffice. In particular, nonfluorous compounds are eluted with fluorophobic solutions, such as 60% acetonitrile (ACN) in H2O or 80% methanol (MeOH) in H2O, while MeOH or acetone will pass fluorinated species through the column. Additionally, the fluorous silica can be recycled dozens of times, making FSPE a more economically and environmentally friendly purification strategy than FLLE.

Overall, fluorous chemistry incorporates standard solution phase reaction conditions and analytical techniques with simplified and highly selective purification procedures. Due to these properties, fluorous supports have successfully been exploited in combinatorial library synthesis and synthetic methods development. These efforts have been thoroughly detailed in several reviews, and thus the current discussion will highlight only a few examples to illustrate the power of the fluorous phase platform.

4.1.2. Curran’s and Zhang’s Fluorous Combinatorial Synthesis of Mappicine Analogs

Nothapodytine B (4.1, Figure 4.2) is a natural product isolated from Nothapodytes foetida that displays potent cytotoxicity in human KB lines and antiviral activity against
HSV-1, HSV-2, and human cytomegalovirus (HCMV). The molecule is an oxidized analog of the *Mappa foetida* alkaloid mappicine (4.2) and a decarboxylated derivative of camptothecin (4.3), an effective DNA topoisomerase I inhibitor. In the early 2000s, the Curran and Zhang groups reported the fluorous mixture synthesis of a 560-member mappicine analog library (Scheme 4.1). The team employed a fluorous tagging system, where seven pyridinyl alcohols were paired with a series of silyl fluorous tags possessing different chain lengths (4.4 → 4.5).
The tagged molecules were then mixed together and subjected to consecutive iodination/demethylation reactions to generate tagged pyridones \(4.6\).\(^{96}\) After splitting the resulting mixture into eight portions, N-alkylation with eight distinct propargyl bromides was conducted in parallel \(\textbf{4.6} \rightarrow \textbf{4.7}\). The following eight pools were then separated into 10 portions for parallel radical tandem cyclization with 10 isonitriles to produce 80 mixtures of fluorous tagged mappicine analogs \(\textbf{4.7} \rightarrow \textbf{4.8}\). Subsequently, fluorous HPLC was used to isolate the individual components from each pool on the basis of the fluorine content the tags provide. A total of 560 pure mappicine derivatives \(\textbf{4.9}\) were obtained after silyl deprotection.

Curran’s and Zhang’s combinatorial synthesis of mappicine analogs demonstrates that fluorous phase techniques can be leveraged to separate individual, pure products after a reaction process involving a mixture of organic molecules. Generally, solution phase reactions performed on organic mixtures are highly efficient and demonstrate favorable reaction kinetics. Nevertheless, the overall procedures can be exceedingly difficult to achieve due to time-consuming challenges that emerge with the analysis, identification, and separation of each mixture component. The group’s fluorous supported route bypassed these dilemmas and granted access to a pure library of compounds that was adequately evaluated in biological systems.\(^{98}\) Moreover, the strategy accommodated key reaction steps that could not be optimized on a solid-phase platform.\(^\text{96}\)

4.1.3. Zhang’s Fluorous Synthetic Method Towards Novel Fused Heterocyclic Ring Systems

Zhang and co-workers utilized a fluorous phase approach to generate three novel triaza tricyclic and tetracyclic ring systems.\(^{99}\) The reaction method began with the synthesis of proline derivative \(\textbf{4.13}\) from a one-pot, three-component \([3 + 2]\) cycloaddition between a fluorous amino ester \(\textbf{4.10}\), an N-alkylmaleimide \(\textbf{4.11}\), and a benzaldehyde \(\textbf{4.12}\). Scheme 4.2. This process
was conducted under conventional or microwave heating and provided highly stereoselective bicyclic products after FSPE. The proline analogs obtained were then used for diversity-oriented synthesis (DOS) to produce hydantoin-, piperazinedione-, and benzodiazepine-fused ring systems 4.15, 4.17, and 4.19 respectively (Scheme 4.3). The heterocyclic structures possessed four stereocenters on the central pyrrolidine scaffold and up to four points of diversity (R\textsuperscript{1}-R\textsuperscript{4}). In addition, each compound contained privileged moieties which exhibit a wide range of pharmaceutical utility.\textsuperscript{40a,100}

Synthetically speaking, the hydantoin-fused molecules 4.15 were generated by first reacting intermediates 4.13 with phenylisocyanate in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) to provide 4.14.\textsuperscript{99} Next, compounds 4.14 were subjected to base-promoted detagging and cyclization under microwave irradiation to give the final products. Moving forward, the synthesis of the piperazinedione tricyclic species 4.17 was accomplished by acylation of 4.13 with chloroacetylchloride, followed by substitution with amines to create 4.16. The linker cleavage/cyclization reactions on 4.16 were then promoted with 1,8-diazabicyclo[4.3.0]non-5-ene (DBU) using microwave irradiation. Finally, the benzodiazepine scaffolds 4.19 were produced with a three-step sequence involving the acylation/reduction of pyrrolidine 4.13 to intermediate 4.18, followed by cyclative linker
cleavage in DBU to give the final derivatives. All of the intermediate reactions were purified by FSPE, while the final steps for each analog class required FSPE and HPLC for maximum purity. The Zhang group would further apply the chemistry developed for 4.15 and 4.19 in the fluorous mixture synthesis of heterocyclic combinatorial libraries.\textsuperscript{101}

4.2. The Fluorous Phase Synthesis of αHTs

As previously reviewed, we recently discovered a three-component oxidopyrylium cycladdition that generates new oxabicyclic compounds through alcohol incorporation (Scheme 4.4A).\textsuperscript{71} Additionally, benzyl alcohol-derived oxabicyclic intermediates produced from this
reaction can be directly converted to αHTs when subjected to methanesulfonic acid (Scheme 4.4B). Considering this information, we developed a solid-phase synthesis of αHTs utilizing polystyrene-supported benzyl alcohol (Scheme 4.4C).\(^{82}\) The method is extremely time efficient (i.e. a batch of 8 molecules produced over a 24 hour period) and provides compounds with assay-ready purity. However, improvements to the system are necessary to reach its full potential as a combinatorial technique for αHT synthesis. First, though yields for the process are practical for biological screening, they are substantially low overall (i.e. 5-20% yield for 9 substrates). Secondly, the platform does not permit the modification of resin-bound intermediates, as conditions for both Suzuki coupling and trifluoroacetic acid (TFA) deprotection cause unintended cleavage (results not reported).

In order to address the issues corresponding with solid-phase synthesis, we turned our attention to a fluorous phase approach. As outlined above, fluorous chemistry allows the successful integration of solution phase reaction conditions and provides the ability to monitor reactions through conventional analytical methods that cannot be performed on resin-bound
molecules. Moreover, in relation to traditional organic synthesis, fluorous tagged compounds can be purified easily and efficiently by exclusive techniques based on fluorine-fluorine interactions (i.e. FLLE and FSPE). The following describes our attempts at synthesizing αHTs by employing fluorous supported synthesis.

4.2.1. Fluorous Tag Incorporation and Cleavage

The integration of fluorous phase chemistry into our synthetic route poses three challenges: 1) verify that fluorous tagged alcohols could successfully be incorporated into oxabicyclic products, 2) assess how well the tagged compounds work with fluorous separation techniques, and 3) demonstrate the capability to remove the tagged segment and form the final product. Our studies began with the preparation of the fluorous tagged benzyl alcohol derivative 4.27, which can be generated in high yields through a previously reported approach. Generally, the three-component oxidopyrylium cycloaddition is conducted under sealed conditions with a surplus of alcohol (5 equivalents in relation to monomeric ylide) to drive the incorporation. Considering the large molecular weight of 4.27, slight modifications to our originally optimized procedure were required (Scheme 4.5A). For instance, the quantity of alcohol was reduced (i.e. stoichiometric with monomeric ylide) to avoid excessive use of starting material. Also, the incorporation time was increased to accommodate the lower alcohol concentration. We were able to synthesize the fluorous tagged oxabicyclic compound 4.28a with a 34% yield using these adjustments, which is consistent for aryl-containing products obtained through the previously described method.

However, when larger scale experiments were performed under these sealed conditions, reaction times were significantly increased, yielding little to no incorporation after 6 days.
we speculated that the lack of conversion was due to the increased generation of MeOH that accompanies the scaled up procedure. Since MeOH is more prevalent and trapped within the reactor, the equilibrium of the alcohol incorporation is driven significantly from the fluorous tagged ylide back to 4.21. In order to remove the MeOH byproduct from the reaction, the solvent system was changed to a 2:1 mixture of carbon tetrachloride (CCl₄) and perfluoromethylcyclohexane (C₇F₁₄) and the vessel was exposed to a light stream of argon (Scheme 4.5B). This solvent combination was chosen not only for its ability to dissolve the quantities of fluorous tagged alcohol necessitated by the reaction but for its higher boiling point (76 °C for both solvents) that supersedes MeOH (64.7 °C). The boiling temperature, along with the argon flow, allows for the evaporation of MeOH without drying out the reaction. Thus, the equilibrium of the alcohol incorporation is shifted towards the product and the reaction time is...
decreased. With these scale-up alterations, compound 4.28a was generated in a 38% yield in approximately 2 days, demonstrating a similar yield to its smaller scale counterpart.

Moving forward, we wanted to test if the newly obtained oxabicyclic product could be purified by fluororous phase separation techniques. Since the fluorine content of 4.28a (<50%) is not acceptable for FLLE, we chose FSPE as our starting point. Compound 4.28a was purposely contaminated with the non-fluorinated derivative 4.29a and loaded onto a 4 gram column of standard tridecafluoro functionalized silica gel (SiliaBond® Tridecafluoro, Figure 4.3). Following a typical FSPE procedure, 4.29a was extracted with 80% MeOH in water and 4.28a was retrieved with acetone. Overall, 94% of 4.28a and 93% of 4.29a were recovered, proving that FSPE can be used to purify the fluororous tagged oxabicycles.

After demonstrating that it is possible to incorporate fluororous tagged alcohols into our oxabicyclic products and purify them with fluororous extraction, we directed our attention towards
the ring-opening/debenzylation phase of 4.28a to αHT 4.24a. In our previous report, the benzyl-derived oxabicycle 4.23a underwent both ring-opening and debenzylation when exposed to liquid- and solid-phase methanesulfonic acid. Upon subjecting 4.28a to these conditions, we only observed the ring-opening product, as fluorous tagged tropolone 4.30a was isolated in quantitative yields (Scheme 4.6). The fluorous segment was removed upon returning to our original demethylation procedure (i.e. HBr in acetic acid), and a crude mixture of αHT 4.24a and fluorous tagged impurities was obtained. Considering the high fluorine content of the benzylated byproducts (>50%), both FSPE and FLLE were successfully used to purify the final product. With regard to the latter purification method, a 50% solution of methoxyperfluorobutane (HFE-7100) in C7F14 proved very effective in separating unwanted contaminants from the αHT (refer to Supp. Info.). Compound 4.24a was obtained in 85% yield after FSPE and 95% yield after FLLE.

**4.2.2. The Chemical Modification of Floruous Tagged Oxabicyclic and Tropolone Intermediates**

We found the result described above very promising since it indicates that the electron deficient nature of the fluorous tag introduces stability to our intermediates in harsh media. The added stabilization would allow us to perform modification at multiple stages of our synthetic route, unlike in the case of solid-phase synthesis. To test this hypothesis, we synthesized a pair of

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**Scheme 4.6.** Ring-opening/debenzylation of 4.28a to corresponding αHT 4.24a.

[a] Rf = 4-C8F17Ph.
fluorous tagged oxabicycles (4.28j and 4.28k) with functional handles to attempt a series of experiments involving metal catalyzed cross coupling and amide coupling.

Initially, various palladium catalyzed Suzuki reactions, including systems with Pd(OAc)$_2$/JPhos or Pd(PPh)$_4$, were performed on compound 4.28j with benzyl and naphthyl boronic acids to complete conversion. The resulting oxabicycles were subjected to ring-opening/debenzylation conditions, and the corresponding αHTs were synthesized and confirmed through NMR analysis (results not shown). Unfortunately, pure final compounds could not be obtained with these procedures due to the presence of phosphine derived byproducts. Such impurities are not very soluble in the nonfluorous mobile phase of FSPE (80% MeOH in water or 70% ACN in water), and hence contaminate the fluorous eluent (acetone or MeOH) to the detriment of subsequent reaction purity.

In order to bypass this issue, we moved towards Suzuki conditions that utilize water soluble SPhos as the activating ligand (Scheme 4.7).$^{27b}$ The phosphine byproducts were significantly removed from the intermediate but large amounts of solvent were still necessary during FSPE to achieve adequate purity (refer to Supp. Info.). However, the resulting bisphenyl oxabicyclic intermediate was successfully converted to pure αHT 4.24j after ring-opening/debenzylation. Studies on making purification for metal-catalyzed cross-coupling reactions on our fluorous tagged oxabicyclic products more efficient are currently ongoing.
Nevertheless, this data demonstrates that modification through a fluorous phase approach is more tolerated than our previously reported solid-phase synthesis.

Moving forward to amide coupling reactions, compound 4.28k was used as a starting point to generate fluorous tagged intermediates with carboxylic acid functionalities (Scheme 4.8). Through a simple reaction sequence involving an acid-mediated deprotection, followed by a ring-opening, 4.28k was converted to oxabicycle 4.28l and tropolone 4.30l near quantitatively.
Each of these carboxylic acid derivatives was reacted with piperidine in the presence of PyBOP and N,N-diisopropylethylamine (DIPEA) to either produce compound **4.28m** in 59% yield or **4.30m** in 84% yield after FSPE and hexane wash (Scheme 4.9). The corresponding αHT was then obtained by two different paths: 1) ring-opening/debenzylation of oxabicycle **4.28m** and 2) debenzylation of tropolone **4.30m**. Both steps were purified by FLLE to separate the fluorous tagged impurities from the final product **4.24m**, demonstrating a divergent synthetic pathway to access an amide-derived αHT with fluorous phase chemistry.

Taking into account that a secondary amine was used during our initial amide modification experiments, we tested if primary amines could also undergo a divergent approach to αHTs (Scheme 4.10). When oxabicycle **4.28l** was subjected to PyBOP coupling conditions with 1-naphthylmethylamine, major decomposition was observed and the anticipated amide

![Scheme 4.10. Overview of divergent amide coupling on fluorous tagged intermediates using primary amine. [a] Rf = 4-C$_6$F$_{17}$Bn.](image)
could not be obtained after FSPE. On the other hand, tropolone 4.30 was successfully converted to the corresponding amide-derivative 4.30n using the PyBOP procedure outlined above and taken further to αHT 4.24n in high yields for both steps. Thus, even though the oxabicycle route is limited to more sterically hindered secondary amines, the tropolone pathway can be used to achieve the coupling of both types of amines.

4.3. Conclusion

In summary, we have demonstrated the first fluorous phase synthesis of αHTs utilizing three-component oxidopyrylium cycloaddition chemistry. In a prior report, we have shown that this reaction could be leveraged towards incorporation of solid-phase resins. Though the method was time efficient and yielded assay-ready compounds, our solid-supported synthesis resulted in low yields and an inability to modify intermediates while attached to the resin. By incorporating fluorous tags instead of solid supports, we have significantly improved reaction output and generated intermediates that can undergo modification through metal catalyzed cross coupling and amide coupling. Studies are currently ongoing to fully optimize this platform in order to make it a combinatorial technique for αHTs.

4.4. Experimental and Supporting Information

**General Information:** All starting materials and reagents were purchased from commercially available sources and used without further purification, with the exception of CH₂Cl₂, which was purified on a solvent purification system prior to reactions.¹³¹H,¹⁹F, and¹³C NMR shifts were measured using the solvent residual peak as the internal standard and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quartet, m = multiplet), coupling constant (Hz), integration. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Mass
spectra were recorded on a spectrometer by the electrospray ionization (ESI) technique with a time-of-flight (TOF) mass analyzer. Microwave reactions were performed via the Biotage® Initiator (external IR temperature sensor). Where noted, reaction products were purified via silica gel chromatography using a Biotage® Isolera Prime, with Biotage® SNAP Ultra 10 g or 25 g cartridges, in a solvent system of ethyl acetate (EtOAc) in hexane. Fluorous solid-phase extraction (FSPE) was performed using columns packed with SiliaBond® Tridecafluoro silica gel.

**Synthesis of Fluorous Tagged 3-Benzylxylo-8-Oxabicyclo[3.2.1]octenes:**

5-Methyl-3-((4-(perfluorooctyl)benzyl)oxy)-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (4.28a). *Method A.* Dimer 4.26 (24 mg, 0.0856 mmol), benzyl alcohol 4.27 (91 mg, 0.172 mmol, 2 equiv.), and CH₂Cl₂ (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 ºC in silicon bath oil for 36 h. Phenyl acetylene (378 μL, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 ºC for 1 h. The reaction was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 20% EtOAc/hexane gradient over 23 column volumes), giving 4.28a as a yellow oil (43 mg, 34% yield). *Method B.* Dimer 4.26 (200 mg, 0.714 mmol) and benzyl alcohol 4.27 (751 mg, 1.43 mmol, 2 equiv.) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 10-20 mL) and the vessel was purged with argon (3x). Carbon tetrachloride (2.75 mL) and perfluoromethylcyclohexane (1.38 mL) were added to the sealed reactor, and the reaction mixture was heated to 60 ºC in silicon bath oil for 48 h under argon. Phenyl acetylene (3.14 mL, 28.6 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 ºC for 2.5 h. The reaction mixture was evaporated and purified by
column chromatography (silica (25 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 17 column volumes), giving 4.28a as a yellow oil (401.9 mg, 38% yield). *FSPE Protocol A.* A Biotage® SNAP Ultra 10 g cartridge was filled with SiliBond® Tridecafluoro silica gel (4 g) and preconditioned with 50% MeOH in H₂O. Compound 4.28a (46.4 mg, 0.063 mmol) was contaminated with 4.29a (13.5 mg, 0.056 mmol), and the mixture was loaded onto the cartridge in CHCl₃. The nonfluorous material was provided by elution with 80% MeOH in H₂O (40 mL), while the fluorous component was obtained by elution with acetone (40 mL). The resulting fractions were then concentrated, giving 4.28a as a yellow oil (43.4 mg, 94% recovery) and 4.29a as a white solid (12.6 mg, 93% recovery). The cartridge was washed with MeOH (40 mL) and acetone (40 mL) prior to reuse, and it was recycled up to 30 times. The 1H NMR for 4.29a was consistent with previously reported data.⁴⁹a **Characterization of 4.28a.** Rᵣ = 0.27 in 15% EtOAc in hexanes. **IR (thin film, KBr):** 3060 (w), 2981 (w), 2935 (w), 1712 (s), 1606 (s), 1492 (m), 1427 (m), 1296 (s), 1211 (s), 1150 (s), 1059 (m), 868 (m), 754 (s), 697 (s), 657 (s) cm⁻¹. **¹H NMR (400 MHz, CDCl₃):** δ 7.58 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.20 – 7.15 (m, 2H), 6.29 (d, J = 2.4 Hz, 1H), 6.24 (s, 1H), 5.02 (d, J = 2.5 Hz, 1H), 4.97 (d, J = 12.7 Hz, 1H), 4.85 (d, J = 12.7 Hz, 1H), 1.64 (s, 3H). **¹⁹F NMR (376 MHz, CDCl₃):** δ -80.8 (t, J = 9.9 Hz, 3F), -110.7 (t, J = 14.5 Hz, 2F), -121.1 – -121.4 (m, 2F), -121.7 – -122.1 (m, 6F), -122.56 – -122.89 (m, 2F), -126.0 – -126.2 (m, 2F). **¹³C NMR (100 MHz, CDCl₃):** δ 189.7 (s), 158.8 (s), 144.6 (s), 140.0 (s), 133.0 (s), 128.9 (s), 128.9 (t, J = 24.4 Hz), 128.8 (s), 127.4 (s), 127.4 (t, J = 6.4 Hz), 126.0 (s), 123.2 (s), 122.0 (s), 86.5 (s), 86.1 (s), 68.8 (s), 22.0 (s). **HRMS (ESI+):** m/z calc’d for C₂₉H₁₇F₁₇O₃Na⁺: 759.0798. Found: 759.0802.
**6-(3-Bromophenyl)-5-methyl-3-((4-(perfluoroctyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (4.28j).** Dimer 4.26 (200 mg, 0.714 mmol) and benzyl alcohol 4.27 (751 mg, 1.43 mmol, 2 equiv.) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 10-20 mL), and the vessel was purged with argon (3x). Carbon tetrachloride (2.75 mL) and perfluoromethylcyclohexane (1.38 mL) were added to the sealed reactor, and the reaction mixture was heated to 60 °C in silicon bath oil for 36 h under argon. 1-Bromo-3-ethynylbenzene (1.72 mL, 14.3 mmol, 20 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 3 h. The reaction mixture was evaporated and purified by column chromatography (silica (25 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 27 column volumes), giving 4.28j as a yellow oil (366.7 mg, 32% yield). Due to the high cost of 1-bromo-3-ethynylbenzene, fractions containing it were also concentrated (2.029 g, 87% recovery (2.321 g would be 100% theoretical yield of unreacted product)).

R<sub>f</sub> = 0.29 in 15% EtOAc in hexanes. **IR (thin film, KBr):** 3064 (w), 2982 (w), 2936 (w), 1713 (s), 1605 (s), 1588 (m), 1558 (m), 1473 (m), 1338 (m), 1295 (s), 1210 (s), 1151 (s), 1059 (m), 869 (s), 773 (s), 657 (s) cm<sup>-1</sup>. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.58 (d, J = 8.3 Hz, 2H), 7.52 – 7.44 (m, 3H), 7.38 – 7.35 (m, 1H), 7.24 – 7.18 (m, 1H), 7.09 – 7.05 (m, 1H), 6.34 (d, J = 2.4 Hz, 1H), 6.23 (s, 1H), 5.02 (d, J = 2.5 Hz, 1H), 4.96 (d, J = 12.6 Hz, 1H), 4.85 (d, J = 12.6 Hz, 1H), 1.63 (s, 3H). **<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -80.8 (t, J = 9.5 Hz, 3F), -110.7 (t, J = 14.5 Hz, 2F), -121.2 (bs, 2F), -121.6 – -122.1 (m, 6F), -122.6 – -122.9 (m, 2F), -126.0 – -126.3 (m, 2F). **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 189.3 (s), 157.5 (s), 144.7 (s), 139.9 (s), 135.1 (s), 131.8 (s), 130.3 (s), 129.1 (s), 129.0 (t, J = 24.3 Hz), 127.4 (s), 127.4 (t, J = 6.5 Hz), 124.8 (s), 124.5 (s), 123.0 (s), 121.5 (s), 86.4 (s), 86.1 (s), 68.8 (s), 22.0 (s).

**HRMS (ESI+):** m/z calc’d for C<sub>29</sub>H<sub>16</sub>BrF<sub>17</sub>O<sub>3</sub>Na<sup>+</sup>: 836.9904. Found: 836.9907.
**tert-Butyl 5-methyl-2-oxo-3-((4-(perfluorooctyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (4.28k).** Dimer 4.26 (200 mg, 0.714 mmol) and benzyl alcohol 4.27 (751 mg, 1.43 mmol, 2 equiv.) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 10-20 mL), and the vessel was purged with argon (3x). Carbon tetrachloride (2.75 mL) and perfluoromethylcyclohexane (1.38 mL) were added to the sealed reactor, and the reaction mixture was heated to 60 °C in silicon bath oil for 48 h under argon. tert-Butyl propiolate (1.96 mL, 14.3 mmol, 20 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction mixture was evaporated and purified by column chromatography (silica (25 g), 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 24 column volumes), giving 4.28k as a white solid (550.5 mg, 51% yield). MP = 109-112 °C. Rf = 0.21 in 10% EtOAc in hexanes. IR (thin film, KBr): 3059 (w), 2982 (w), 2938 (w), 1703 (s), 1645 (m), 1370 (m), 1329 (m), 1300 (m), 1197 (s), 1146 (s), 1076 (m), 944 (m), 863 (m), 659 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 2.5 Hz, 1H), 6.15 (s, 1H), 5.01 (d, J = 2.5 Hz, 1H), 4.86 (d, J = 12.5 Hz, 1H), 4.79 (d, J = 12.5 Hz, 1H), 1.72 (s, 3H), 1.48 (s, 9H). ¹⁹F NMR (376 MHz, CDCl₃): δ -80.7 (t, J = 9.9 Hz, 3F), -110.7 (t, J = 14.5 Hz, 2F), -121.1 – -121.3 (m, 2F), -121.7 – -122.0 (m, 6F), -122.5 – -122.8 (m, 2F), -126.0 – -126.2 (m, 2F). ¹³C NMR (100 MHz, CDCl₃): δ 188.7 (s), 162.2 (s), 151.1 (s), 143.8 (s), 139.9 (s), 137.6 (s), 128.9 (t, J = 24.4 Hz), 127.5 (s), 127.4 (t, J = 6.4 Hz), 121.9 (s), 86.0 (s), 85.6 (s), 82.4 (s), 68.6 (s), 28.2 (s), 21.4 (s). HRMS (ESI+): m/z calc’d for C₂₈H₁₇F₁₇O₅Na⁺: 783.1010. Found: 783.1011.

**5-Methyl-2-oxo-3-((4-(perfluorooctyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylic acid (4.28l).** Oxabicycle 4.28k (435.8 mg, 0.573 mmol) and 50% trifluoroacetic acid in CH₂Cl₂ (2.2 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial,
2-5 mL), and the reaction mixture was subjected to microwave radiation at 70 ºC for 2 min. The organic layer was concentrated under reduced pressure and then subjected to azeotropic removal with CH₂Cl₂ (5 x 2 mL), resulting in a yellowish solid. The solid was washed with hexane (5 x 4 mL) and dried under vacuum to give 4.28l as an off-white solid (396.7 mg, >95% yield). MP = 144-146 ºC. Rf = 0.25 in 10% MeOH in CH₂Cl₂. IR (thin film, KBr): 3070 (w), 2989 (w), 2867 (br), 1708 (m), 1676 (s), 1616 (m), 1605 (m), 1422 (w), 1335 (m), 1199 (s), 1147 (s), 1091 (m), 942 (m), 879 (m), 659 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 2.5 Hz, 1H), 6.17 (s, 1H), 5.10 (d, J = 2.5 Hz, 1H), 4.84 (d, J = 12.3 Hz, 1H), 4.79 (d, J = 12.3 Hz, 1H), 1.77 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃): δ -80.9 (t, J = 9.9 Hz, 3F), -110.8 (t, J = 14.4 Hz, 2F), -121.3 (bs, 2F), -121.8 – -122.1 (m, 6F), -122.8 (bs, 2F), -126.0 – -126.7 (m, 2F). ¹³C NMR (100 MHz, CDCl₃): δ 188.1 (s), 167.9 (s), 148.9 (s), 143.9 (s), 142.3 (s), 139.6 (s), 129.1 (t, J = 24.3 Hz), 127.6 (s), 127.4 (t, J = 6.4 Hz), 121.5 (s), 86.3 (s), 85.5 (s), 68.8 (s), 21.3 (s). HRMS (ESI+): m/z calc’d for C₂₄H₁₃F₁₇O₅Na⁺: 727.0384. Found: 727.0387.

5-Methyl-3-((4-(perfluorooctyl)benzyl)oxy)-6-(piperidine-1-carbonyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (4.28m). A solution of oxabicycle 4.28l (60 mg, 0.0852 mmol), PyBOP (48.8 mg, 0.0937 mmol, 1.1 equiv.), and DIPEA (32.6 μL, 0.187 mmol, 2.2 equiv.) in CH₂Cl₂ (0.04 M, 2 mL) was stirred at room temperature for 20 min in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). Piperidine (9.3 μL, 0.0937 mmol, 1.1 equiv.) was then added to the sealed vessel, and the reaction mixture was subjected to microwave radiation at 85 ºC for 5 min. The mixture was concentrated under reduced pressure and purified by FSPE as described in Protocol A. The acetone layer was evaporated, producing a yellow solid. The solid was washed with hexane (5 x 2 mL) to give 4.28m as a white solid (38.7 mg, 59% yield).
MP = 173-175 °C. Rf = 0.29 in 40% EtOAc in hexanes. IR (thin film, KBr): 3070 (w), 2942 (m), 2862 (m), 1711 (s), 1609 (s), 1445 (s), 1287 (s), 1212 (s), 1151 (s), 1089 (m), 1026 (m), 989 (m), 913 (w), 874 (m), 735 (m), 652 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 6.35 (s, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.11 (d, J = 2.4 Hz, 1H), 4.85 (d, J = 12.2 Hz, 1H), 4.80 (d, J = 12.2 Hz, 1H), 3.67 – 3.45 (m, 4H), 1.76 – 1.66 (m, 2H), 1.65 – 1.49 (m, 7H). ¹³C NMR (100 MHz, CDCl₃): δ 188.3 (s), 163.6 (s), 150.7 (s), 143.9 (s), 140.1 (s), 128.8 (t, J = 24.5 Hz), 127.8 (s), 127.3 (t, J = 6.5 Hz), 123.6 (s), 87.4 (s), 87.1 (s), 68.7 (s), 47.9 (s), 42.9 (s), 27.0 (s), 25.8 (s), 24.7 (s), 20.7 (s). HRMS (ESI+): m/z calc’d for C₂₉H₂₁F₁₇NO₄⁺: 772.1350. Found: 772.1352.

Synthesis of Fluorous Tagged Benzylxy Tropolones:

2-Hydroxy-5-methyl-7-((4-(perfluorooctyl)benzyl)oxy)-4-phenylcyclohepta-2,4,6-trien-1-one (4.30a). To a solution of 4.28a (135.2 mg, 0.184 mmol) in CH₂Cl₂ (0.16 M, 1.15 mL) was added methanesulfonic acid (477 μL, 7.36 mmol, 40 equiv). The reaction mixture was stirred at room temperature for 1 h, at which time it was quenched with phosphate buffer (pH 7, 0.1 M, 5 mL) and extracted with CHCl₃ (3 x 5 mL). The organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield a golden brown solid. This solid was washed with hexane (5 x 2 mL) and dried under vacuum to give 4.30a as a light brown solid (131.6 mg, >95% yield). MP = Decomposes at 155 °C. IR (thin film, KBr): 3220 (br), 3029 (w), 2917 (w), 2858 (w), 1575 (m), 1564 (m), 1473 (m), 1384 (w), 1332 (m), 1199 (s), 1148 (s), 1116 (s), 912 (m), 765 (m), 703 (m), 656 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.67 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.46 – 7.35 (m, 4H), 7.31 (s, 1H),
7.24 – 7.20 (m, 2H), 5.39 (s, 2H), 2.18 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -80.8 (t, $J = 9.9$ Hz, 3F), -110.6 (t, $J = 14.3$ Hz, 2F), -121.2 (bs, 2F), -121.6 – -122.1 (m, 6F), -122.7 (bs, 2F), -126.0 – -126.2 (m, 2F). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 169.5 (s), 160.3 (s), 156.6 (s), 145.2 (s), 143.5 (s), 140.7 (s), 135.0 (s), 128.9 (t, $J = 24.3$ Hz), 128.7 (s), 128.2 (s), 127.9 (s), 127.6 (s), 127.6 (s), 127.5 (t, $J = 6.5$ Hz), 122.3 (s), 71.0 (s), 26.5 (s). HRMS (ESI+): $m/z$ calc’d for C$_{29}$H$_{18}$F$_{17}$O$_3$: 737.0979. Found: 737.0982.

6-Hydroxy-2-methyl-5-oxo-4-((4-(perfluorooctyl)benzyl)oxy)cyclohepta-1,3,6-triene-1-carboxylic acid (4.30l). To a solution of 4.281 (116.1 mg, 0.165 mmol) in CH$_2$Cl$_2$ (0.1 M, 1.42 mL) was added trifluoromethanesulfonic acid (58.2 μL, 0.659 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 30 min, at which time it was quenched with phosphate buffer (pH 7, 1 M, 5 mL). The CH$_2$Cl$_2$ was drained and the remaining residue was extracted with EtOAc (3 x 5 mL). All organics were collected, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give a yellow solid. The solid was washed with 50% CH$_2$Cl$_2$ in hexanes (6 x 2 mL) and dried under vacuum to give 4.30l as a light yellow solid (107.3 mg, 92% yield). MP = 163-166 °C. IR (thin film, KBr): 3442 (br), 1699 (m), 1570 (m), 1482 (w), 1382 (w), 1372 (w), 1299 (m), 1230 (s), 1201 (s), 1149 (s), 1111 (m), 1051 (w), 946 (w), 850 (w), 663 (m) cm$^{-1}$. $^1$H NMR (400 MHz, Acetone): $\delta$ 7.85 (d, $J = 8.2$ Hz, 2H), 7.77 (d, $J = 8.3$ Hz, 2H), 7.57 (s, 1H), 7.49 (s, 1H), 5.50 (s, 2H), 2.56 (s, 3H). $^{19}$F NMR (376 MHz, Acetone): $\delta$ -81.6 (t, $J = 10.1$ Hz, 3F), -110.7 (t, $J = 14.5$ Hz, 2F), -121.6 – -121.9 (m, 2F), -122.2 – -122.6 (m, 6F), -123.2 (bs, 2F), -126.6 – -126.9 (m, 2F). $^{13}$C NMR (100 MHz, Acetone): $\delta$ 171.8 (s), 170.2 (s), 160.2 (s), 159.2 (s), 142.5 (s), 137.1 (s), 133.8 (s), 128.9 (s), 128.6 (t, $J = 24.3$ Hz), 127.9 (t, $J = 6.5$ Hz), 125.9 (s), 117.0 (s), 71.0 (s), 25.4 (s). HRMS (ESI+): $m/z$ calc’d for C$_{24}$H$_{14}$F$_7$O$_5$+: 705.0564. Found: 705.0570.
2-Hydroxy-5-methyl-7-((4-(perfluorooctyl)benzyl)oxy)-4-(piperidine-1-carbonyl)-cyclohepta-2,4,6-trien-1-one (4.30m). A solution of tropolone 4.30l (50 mg, 0.071 mmol), PyBOP (40.6 mg, 0.0781 mmol, 1.1 equiv.), and DIPEA (27.2 μL, 0.156 mmol, 2.2 equiv.) in EtOAc (0.04 M, 1.67 mL) was stirred at room temperature for 20 min in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). Piperidine (7.7 μL, 0.0781 mmol, 1.1 equiv.) was then added to the sealed vessel, and the reaction mixture was subjected to microwave radiation at 85 ºC for 5 min. The reaction mixture was concentrated under reduced pressure and purified by FSPE as described in Protocol A. The acetone layer was evaporated, producing a yellow solid. The solid was washed with hexane (5 x 2 mL) and dried under vacuum to give 4.30m as a light yellow solid (45.8 mg, 84% yield). MP = 183-186 ºC. IR (thin film, KBr): 3175 (br), 2942 (w), 2929 (w), 2861 (w), 1621 (m), 1568 (m), 1462 (m), 1450 (m), 1324 (m), 1202 (s), 1151 (s), 1135 (s), 1110 (s), 810 (m), 735 (m), 661 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.93 (bs, 1H), 7.63 (s, 4H), 7.17 (s, 1H), 7.16 (s, 1H), 5.36 (d, J = 12.8 Hz, 1H), 5.32 (d, J = 12.8 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.69 – 3.61 (m, 1H), 3.27 – 3.13 (m, 2H), 2.34 (s, 3H), 1.76 – 1.62 (m, 4H), 1.60 – 1.43 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃): δ -80.7 (t, J = 9.9 Hz, 3F), -110.7 (t, J = 14.4 Hz, 2F), -121.1 – -121.3 (m, 2F), -121.7 – -122.0 (m, 6F), -122.5 – -122.8 (m, 2F), -125.9 – -126.3 (m, 2F). ¹³C NMR (100 MHz, CDCl₃): δ 170.4 (s), 168.6 (s), 161.2 (s), 157.2 (s), 140.2 (s), 138.6 (s), 132.8 (s), 129.1 (t, J = 24.3 Hz), 127.6 (s), 127.5 (t, J = 6.5 Hz), 126.6 (s), 116.2 (s), 71.0 (s), 47.9 (s), 42.6 (s), 26.6 (s), 25.7 (s), 24.5 (s), 24.2 (s). HRMS (ESI+): m/z calc’d for C₂₉H₂₁F₁₇NO₄⁺: 772.1350. Found: 772.1351.

6-Hydroxy-2-methyl-N-(naphthalen-1-ylmethyl)-5-oxo-4-((4-(perfluorooctyl)benzyl)oxy)cyclohepta-1,3,6-triene-1-carboxamide (4.30n). A solution of tropolone 4.30l (51.7 mg, 0.0734 mmol), PyBOP (42 mg, 0.0807 mmol, 1.1 equiv.), and DIPEA (28.1 μL, 0.161 mmol,
2.2 equiv.) in EtOAc (0.04 M, 1.67 mL) was stirred at room temperature for 20 min in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). 1-Naphthylmethylamine (11.8 μL, 0.0807 mmol, 1.1 equiv.) was then added to the sealed vessel, and the reaction mixture was subjected to microwave radiation at 85 ºC for 5 min. The reaction mixture was concentrated under reduced pressure and purified by FSPE as described in Protocol A. The acetone layer was evaporated, producing a yellow solid. The solid was washed with hexane (5 x 2 mL) and ACN (5 x 2 mL) and dried under vacuum to give 4.30n as a light yellow solid (53.8 mg, 87% yield).

\[\text{MP} = 175-177 \, ^\circ\text{C} \].

IR (thin film, KBr): 3239 (br), 3048 (w), 2923 (w), 1666 (m), 1541 (m), 1471 (m), 1398 (w), 1373 (w), 1325 (m), 1212 (s), 1199 (s), 1146 (s), 1112 (m), 945 (w), 788 (m), 658 (m) cm\(^{-1}\). \(^1\text{H NMR (400 MHz, CDCl}_3\)): \(\delta 8.10\) (d, \(J = 8.1\) Hz, 1H), 7.87 (d, \(J = 8.0\) Hz, 1H), 7.81 (d, \(J = 8.1\) Hz, 1H), 7.65 – 7.47 (m, 7H), 7.46 – 7.40 (m, 1H), 7.22 (s, 1H), 7.00 (s, 1H), 6.40 (bs, 1H), 5.15 (s, 2H), 5.01 (s, 2H), 2.34 (s, 3H). 

\(^{19}\text{F NMR (659 MHz, CDCl}_3\)): \(\delta -80.7\) (t, \(J = 9.4\) Hz, 3F), -110.7 (t, \(J = 13.7\) Hz, 2F), -121.2 (bs, 2F), -121.6 – -122.1 (m, 6F), -122.7 (bs, 2F), -126.1 (bs, 2F). \(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \(\delta 170.2\) (s), 169.1 (s), 160.6 (s), 157.4 (s), 139.9 (s), 138.5 (s), 134.5 (s), 134.1 (s), 132.9 (s), 131.5 (s), 129.3 (s), 129.1 (t, \(J = 26.6\) Hz), 129.1 (s), 127.5 (t, \(J = 6.4\) Hz), 127.5 (s), 127.4 (s), 127.0 (s), 126.4 (s), 126.1 (s), 125.6 (s), 123.5 (s), 116.9 (s), 70.8 (s), 42.3 (s), 24.7 (s). \(\text{HRMS (ESI+)}\): \(m/z\) calc’d for C\(_{35}\)H\(_{23}\)F\(_{17}\)NO\(_4^+\): 844.1350. Found: 844.1353.

**Synthesis of α-Hydroxytropolones:**

**2,7-Dihydroxy-4-methyl-5-phenylcyclohepta-2,4,6-trien-1-one (4.24a). FSPE Purification.**

Tropolone 4.30a (50 mg, 0.068 mmol) and 33% HBr in acetic acid (197 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 ºC in silicon bath oil for 1 h. The reaction mixture was cooled to room
temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with CHCl$_3$ (3 x 5 mL). The organic layer was evaporated under reduced pressure and purified by FSPE as described in Protocol A. The 80% MeOH in H$_2$O layer was concentrated to yield 4.24a as a white solid (13.2 mg, 85% yield). The $^1$H NMR for 4.24a was consistent with previously reported data.$^{55}$ FLE Purification, Protocol A. Tropolone 4.30a (50.5 mg, 0.0686 mmol) and 33% HBr in acetic acid (199 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 ºC in silicon bath oil for 1 h. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with CHCl$_3$ (3 x 5 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give a crude oil. The residue was taken up in ACN (2 mL) and washed with 50% HFE-7100 in perfluoromethylcyclohexane (5 x 2 mL). The ACN layer was concentrated to yield 4.24a as a brown oil (15.5 mg, >95% yield). The $^1$H NMR for 4.24a was consistent with previously reported data.$^{55}$

4-((1,1'-Biphenyl)-3-yl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (4.24j). FSPE Protocol B. Compound 4.28j (36.1 mg, 0.0443 mmol), phenyl boronic acid (54 mg, 0.443 mmol, 10 equiv.), water soluble SPhos (23 mg, 0.0443 mmol, 1 equiv.), K$_2$CO$_3$ (61.2 mg, 0.443 mmol, 10 equiv.), Pd(OAc)$_2$ (5 mg, 0.0222 mmol, 0.5 equiv.) and 33% ACN in H$_2$O (0.01 M, 4.5 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 50 ºC in silicon bath oil for 5 h. The reaction mixture was cooled to room temperature and immediately loaded to a Biotage® SNAP Ultra 10 g cartridge that was filled with SiliBond® Tridecafluoro silica gel (4 g) and preconditioned with 30% ACN in H$_2$O. Any remaining residue in the reactor was loaded onto the column with CHCl$_3$, and the nonfluorous material was provided by elution with ACN in H$_2$O (0% ACN/H$_2$O to 70%
ACN/H₂O gradient over 12 column volumes) and MeOH in H₂O (80% MeOH/H₂O over 3 column volumes). The fluorous component was obtained by elution with MeOH (100% MeOH over 5 column volumes) and the resulting fractions were then concentrated, giving **4.28o** as a yellow oil (26.4 mg, 73% crude yield).

To a solution of oxabicycle **4.28o** (26.4 mg, 0.0325 mmol) in CH₂Cl₂ (0.1 M, 325 μL) was added trifluoromethanesulfonic acid (11.5 μL, 0.13 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 minutes, after which time it was quenched with phosphate buffer (pH 7, 0.1 M, 5 mL) and extracted with CHCl₃ (3 x 5 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was then dissolved in 33% HBr in acetic acid (100 μL) and heated to 120 °C for 1 h in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with CHCl₃ (3 x 5 mL). The organic layer was then dried over Na₂SO₄, filtered, and concentrated to give a crude oil. The residue was purified by FLLE according to Protocol A, giving **4.24j** as a brown oil (8.9 mg, 90% yield over two steps). **IR (thin film, KBr):** 3248 (br), 3059 (w), 3033 (w), 2928 (w), 2854 (w), 1525 (s), 1477 (m), 1450 (m), 1386 (s), 1277 (s), 1231 (s), 1131 (m), 1093 (m), 908 (m), 758 (s), 698 (m) cm⁻¹. **¹H NMR (400 MHz, CDCl₃):** δ 7.65 – 7.59 (m, 4H), 7.55 (s, 1H), 7.54 – 7.42 (m, 4H), 7.40 – 7.34 (m, 1H), 7.24 – 7.20 (m, 1H), 2.31 (s, 3H). **¹³C NMR (100 MHz, CDCl₃):** δ 167.3, 157.9, 156.6, 144.2, 143.8, 141.8, 140.6, 139.2, 129.2, 129.0, 127.8, 127.3, 127.3, 127.2, 126.6, 124.5, 124.3, 26.6. **HRMS (ESI+):** m/z calc’d for C₂₀H₁₇O₃⁺: 305.1172. Found: 305.1176.

**2,7-Dihydroxy-4-methyl-5-(piperidine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (4.24m).**

**Method A.** To a solution of oxabicycle **4.28m** (39.4 mg, 0.0511 mmol) in CH₂Cl₂ (0.1 M, 511 μL) was added trifluoromethanesulfonic acid (18 μL, 0.204 mmol, 4 equiv.). The reaction
mixture was allowed to stir for 30 minutes, after which time it was quenched with phosphate buffer (pH 7, 0.1 M, 5 mL) and extracted with CHCl₃ (3 x 5 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure producing a brown residue. The crude mixture was then dissolved in 33% HBr in acetic acid (150 μL), and heated to 120 °C for 1 h in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with CHCl₃ (3 x 5 mL). The organic layer was then dried over Na₂SO₄, filtered, and concentrated to give a crude oil. The residue was purified by FLLE according to Protocol A, giving 4.24m as a brown oil (10.4 mg, 77% yield over two steps). Method B. Tropolone 4.30m (40 mg, 0.0518 mmol) and 33% HBr in acetic acid (150 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 °C in silicon bath oil for 1 h. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with CHCl₃ (3 x 5 mL). The organic layer was then dried over Na₂SO₄, filtered, and evaporated under reduced pressure to give a crude oil. The residue was purified by FLLE according to Protocol A, giving 4.24m as a brown oil (12.5 mg, 92% yield). Characterization of 4.24m. IR (thin film, KBr): 3246 (br), 2940 (s), 2859 (m), 1627 (s), 1541 (s), 1446 (s), 1389 (s), 1353 (s), 1265 (s), 1232 (s), 1136 (s) 1075 (m), 1026 (m), 912 (s), 811 (m), 730 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.47 (s, 1H), 7.27 (s, 1H), 3.86 – 3.77 (m, 1H), 3.70 – 3.62 (m, 1H), 3.25 – 3.13 (m, 2H), 2.41 (s, 3H), 1.77 – 1.44 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 168.7, 168.2, 158.3, 157.8, 137.5, 137.0, 124.3, 118.6, 47.9, 42.7, 26.5, 25.7, 24.5, 24.1. HRMS (ESI+): m/z calc’d for C₁₄H₁₈NO₄⁺: 264.1230. Found: 264.1230.
4,6-Dihydroxy-2-methyl-N-(naphthalen-1-ylmethyl)-5-oxocyclohepta-1,3,6-triene-1-carboxamide (4.24n). Tropolone 4.30n (53 mg, 0.0628 mmol) and 33% HBr in acetic acid (185 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 ºC in silicon bath oil for 1 h. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with CHCl₃ (3 x 5 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated under reduced pressure to give a crude oil. The residue was purified by FLLE according to Protocol A, giving 4.24n as a brown oil (18.8 mg, 89% yield). IR (thin film, KBr): 3263 (br), 3060 (m), 2928 (m), 1697 (s), 1640 (s), 1536 (s), 1512 (s), 1441 (m), 1397 (s), 1248 (s), 1144 (m) 1091 (m), 1055 (m), 903 (w), 780 (m), 726 (w) cm⁻¹. ¹H NMR (400 MHz, Acetone): δ 8.28 (d, J = 8.3 Hz, 1H), 8.02 (bs, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.64 – 7.46 (m, 4H), 7.42 (s, 1H), 7.34 (s, 1H), 5.07 (d, J = 5.7 Hz, 2H), 2.42 (s, 3H). ¹³C NMR (100 MHz, Acetone): δ 169.9, 169.1, 159.7, 158.3, 138.3, 138.0, 135.2, 134.9, 132.5, 129.6, 129.1, 127.6, 127.2, 126.8, 126.3, 124.7, 124.3, 119.9, 42.1, 24.3. HRMS (ESI+): m/z calc’d for C₂₀H₁₈NO₄⁺: 336.1230. Found: 336.1233.
Figure 4.4. $^1$H NMR spectrum of compound 4.28a (Method A) in CDCl$_3$. 
Figure 4.5. $^1$H NMR spectrum of compound 4.28a (Method B) in CDCl$_3$. 

![NMR Spectrum of Compound 4.28a](image)
Figure 4.6. $^{19}$F NMR spectrum of compound 4.28a in CDCl$_3$. 
Figure 4.7. $^{13}C$ NMR spectrum of compound 4.28a in CDCl$_3$. 

[Diagram showing the NMR spectrum]
Figure 4.8. $^1$H NMR spectrum of compounds 4.28a and 4.29a (prior to FSPE) in CDCl$_3$. 
Figure 4.9. $^1\text{H}$ NMR spectrum of compound 4.29a (after FSPE) in CDCl$_3$.
Figure 4.10. 1H NMR spectrum of compound 4.28a (after FSPE) in CDCl₃.
Figure 4.11: H NMR spectrum of compound 4.28 in CDCl₃.
Figure 4.12. $^{19}F$ NMR spectrum of compound 4.28j in CDCl$_3$. 

[Diagram of the $^{19}F$ NMR spectrum with peaks labeled and compound structure shown below]
Figure 4.13. $^{13}$C NMR spectrum of compound 4.28j in CDCl$_3$. 

![NMR Spectrum of Compound 4.28j](image-url)
Figure 4.14. $^1$H NMR spectrum of recovered alkyne 4.31 in CDCl$_3$. 
Figure 4.15. $^1$H NMR spectrum of compound 4.280 in CDCl$_3$. 
Figure 4.16. $^1$H NMR spectrum of compound 4.28k in CDCl$_3$. 

![NMR spectrum of compound 4.28k](image)
Figure 4.17. $^{19}$F NMR spectrum of compound 4.28k in CDCl$_3$. 

\[
\text{Compound 4.28k in CDCl}_3
\]

-110.63, -110.67, -110.71, -121.17, -121.20, -121.23, -121.79, -121.89, -122.66, -122.67, -122.69, -126.05, -126.67, -126.10
Figure 4.18. $^{13}$C NMR spectrum of compound 4.28k in CDCl$_3$. 
Figure 4.19. $^1$H NMR spectrum of compound 4.281 in CDCl$_3$. 
Figure 4.20. $^{19}$F-NMR spectrum of compound 4.281 in CDCl$_3$. 

[Image of the NMR spectrum with chemical shifts and structural formula]
Figure 4.21. $^{13}$C NMR spectrum of compound 4.281 in CDCl$_3$. 
Figure 4.22. $^1$H NMR spectrum of compound 4.28m in CDCl$_3$. 
Figure 4.23. $^{19}$F NMR spectrum of compound 4.28m in CDCl$_3$. 
Figure 4.24. $^{13}$C NMR spectrum of compound 4.28 in CDCl$_3$. 

The spectrum shows the chemical shifts of various carbon atoms in the compound, with peaks indicating the presence of different functional groups. The inset provides a close-up view of the region around 127 ppm, highlighting specific carbon signals. The structure of compound 4.28 is also shown, with labels for key atoms and functional groups.
Figure 4.25. $^1$H NMR spectrum of compound 4.30a in CDCl$_3$. 

![NMR spectrum of compound 4.30a in CDCl$_3$.]
Figure 4.26. $^{19}$F NMR spectrum of compound 4.30a in CDCl$_3$. 
Figure 4.27  $^{13}$C NMR spectrum of compound 4.30a in CDCl$_3$. 

![NMR spectrum image]
Figure 4.28. $^1$H NMR spectrum of compound 4.30l in acetone-d$_6$. 

[Diagram of the NMR spectrum with peaks labeled at 2.13, 2.09, 1.02, 2.02, 2.56, 2.99, 5.50, 7.49, 7.57, 7.76, 7.78, 7.84, 7.86.]
Figure 4.29. $^{19}$F NMR spectrum of compound 4.30 in acetone-d$_6$. 
Figure 4.30. $^{13}$C NMR spectrum of compound 4.30l in acetone-$d_6$. 
Figure 4.31. $^1$H NMR spectrum of compound 4.30m in CDCl$_3$.
Figure 4.32. $^1$H NMR spectrum of compound 4.30m in CDCl$_3$. 
Figure 4.33. $^{13}$C NMR spectrum of compound 4.30m in CDCl$_3$. 
Figure 4.34. $^1$H NMR spectrum of compound 4.30n in CDCl$_3$. 
Figure 4.3. $^{19}$F-NMR spectrum of compound 4.3.0 in CDCl$_3$. 
Figure 4.36. $^{13}$C NMR spectrum of compound 4.30n in CDCl$_3$. 
Figure 4.37. H NMR spectrum of compound 4.24a (after SPE) in CDCl₃.
Figure 4.38. $^1$H NMR spectrum of compound 4.24a (after FLLE) in CDCl$_3$. 

![NMR Spectrum](image)
Figure 4.39. $^1$H NMR spectrum of compound 4.24j in CDCl$_3$. 
Figure 4.40. $^{13}$C NMR spectrum of compound 4.24j in CDCl$_3$.
Figure 4.41. $^1$H NMR spectrum of compound 4.24m (Method A) in CDCl$_3$. 

![NMR Spectrum Diagram]
Figure 4.42. $^1$H NMR spectrum of compound 4.24m (Method B) in CDCl$_3$. 
Figure 4.43. $^{13}$C NMR spectrum of compound 4.24m in CDCl$_3$. 
Figure 4.44. $^1$H NMR spectrum of compound 4.24n in acetone-$d_6$. 
Figure 4.4. $^1$H NMR spectrum of compound 4.24n in acetone-$d_6$. 
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