Total Synthesis of Hyperforin

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Accessibility
Total Synthesis of Hyperforin

A dissertation presented

by

Brian Andrew Sparling

to

The Department of Chemistry and Chemical Biology

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University
Cambridge, Massachusetts
August, 2013
Total Synthesis of Hyperforin

Abstract

Hyperforin (1) is the component of the medicinal herb St. John’s Wort (*Hypericum perforatum*) responsible for its antidepressant activity. It works by blocking the reuptake of a variety of neurotransmitters through a unique mechanism of action and may be a critical lead for the treatment of depression and possibly other human diseases. However, the therapeutic potential of hyperforin is severely handicapped by its poor water solubility, facile oxidative degradation, and potent activation of pregnane X receptor, leading to increased expression of many genes involved in xenobiotic metabolism. Access to a wide variety of hyperforin analogs is critical for mitigating these shortcomings while maintaining therapeutic activity. While limited semisynthetic manipulation of isolated hyperforin is feasible, total synthesis is the only possible means of obtaining diverse hyperforin analogs.

The goal of the work presented in this thesis was to devise a new enantioselective, versatile approach to hyperforin that would not only incorporate elements of modularity but also exploit latent symmetry within the natural product that would enable facile analog synthesis. Early strategies that we explored included the carbocyclic cyclization of a polyketide and the electrocyclic cascade reaction involving an acylketene. These strategies were inherently flawed, and we subsequently pursued an alternative approach involving a diastereoselective epoxide-opening cascade cyclization.

This approach led to the enantioselective total synthesis of hyperforin. The synthesis is 18 steps in its longest linear sequence and can be deconstructed as the stepwise fusion of six easily obtainable chemicals. The key step in this sequence involved a group-selective, Lewis acid-mediated epoxide-opening cyclization of 381, in which the strategically placed epoxide functionality relayed stereochemical information to the C1, C5, and C8 carbon centers of hyperforin, allowing 2 quaternary stereocenters and
the bicyclic core of hyperforin to be established in a single transformation in forming 382. Using this 18-step sequence, we were able to synthesize over 40 mg of the natural product in a single batch.

Further, a small library of analogs has been synthesized using the framework of the hyperforin synthesis. These efforts have resulted in the first total synthesis of the natural product secohyperforin and the first enantioselective synthesis of (–)-nemorosone.
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Acknowledgments

First and foremost, I thank my advisor, Prof. Matthew Shair. Matt has been a great mentor, teacher, and motivator, and I am truly grateful for the opportunity to work in his lab and to learn from him. One thing I truly appreciate and will try to emulate in my future career is Matt’s drive and determination to pursue projects that have profound applications beyond the realm of synthetic organic chemistry. I am truly honored to have helped establish one such research program, and I look forward to seeing further breakthroughs in the hyperforin project after I leave.

Additionally, I thank my graduate advising committee and thesis committee members, Profs. Eric Jacobsen and Andrew Myers. During our annual meetings, they offered me valuable advice not only on my research project but also on chemistry in general. Their implorations for me to not only think about the “how?” but also the much more fundamental “why?” have had a lasting impact on how I approach and evaluate chemical research.

Before starting my graduate studies at Harvard, I was also fortunate to study under Prof. Timothy Jamison at the Massachusetts Institute of Technology. Tim was willing to let an eager, inexperienced freshman start working in his lab, and I would certainly not be who I am today without him doing so. In particular, the freedom and responsibility he gave to me in the last few years in his lab were crucial towards preparing me for graduate research. In addition, Dr. Graham Simpson was my first mentor, and many of my fundamental practical chemistry skills were a direct result of his endless patience.

In the Shair lab, I have had the opportunity to work alongside many talented and amazing colleagues that are too numerous to all be named in this space. Dave Moebius has been my partner in crime for the hyperforin project, and it has been a real joy getting to know him and work with him. I wish him and his family the best as they head west. I also thank my bay mate Ben Milgram for countless hours of entertainment and brainstorming sessions that I hope will continue at our next place of employment. Shota Kikuchi and Brian Liau are pillars of wisdom and have given me valuable advice throughout the
course of my research. Bill Morris was my mentor when I first started my graduate studies, and I thank him for helping me start on a strong foot.

Outside of the lab, I cannot thank my family enough for their support and love throughout my life. My parents have sacrificed so much so that I could have the best education, and I would not be where I am today without their unconditional love. My grandparents have always been an inspiration to me, and I thank all my all my in-laws, cousins, uncles, aunts, and extended family for their love and encouragement.

I do not know what I would do without my loving wife and best friend Jamie, who has stood by my side through thick and thin these last five years. She has been my anchor and my strength, being my neverending source of encouragement and love. Even during my worst days in the lab, I would come home, see that beautiful smile, and be at ease. I love you so much, and I cannot wait for little Abigail Mae to be here!

Finally, I praise the Lord, my God, for giving me the strength, perseverance, and diligence to accomplish all that is in this dissertation. None of this work would be possible without Him, and I thank God for all that I have been able to do. I thank the community of believers, especially at Park Street Church, for their prayers and fellowship during my time in graduate school. I have truly been blessed, and I hope continue to glorify Him as I move on to the next stage in my life.

I can do all things through Christ who strengthens me.

Philippians 4:13
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List of Abbreviations

A alanine
A2780 human ovarian carcinoma cell line
A2780_{CP} cisplatin-resistant A2780 cell line
A2780_{Dox} doxorubicin-resistant A2780 cell line
A375 human malignant melanoma cell line
A431 human squamous carcinoma cell line
A549 human lung carcinoma cell line
A. Actinomyces
ABCG1 ATP-binding cassette sub family G member 1
ABCG2 ATP-binding cassette sub family G member 2
ABTS 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
Ac acetyl
Ac_2O acetic anhydride
ACF aberrant crypt foci
AChE acetylcholinesterase
ACP acyl carrier protein
AGEs advanced glycation end-products
AGs human gastric adenocarcinoma cell line
AIBN 2,2’-azobis(2-methylpropionitrile)
AIDS acquired immunodeficiency syndrome
Akt protein kinase B
Aliquat 336 tri-n-octylmethylammonium chloride
aq. aqueous
Ar aryl
AR42J rat pancreas cell line
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<th>Description</th>
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<tr>
<td>ARIP</td>
<td>Wistar rat pancreatic tumor cell line</td>
</tr>
<tr>
<td>AT-2.1</td>
<td>rat prostatic cancer cell line</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve, integration of concentration-time curve</td>
</tr>
<tr>
<td>Aβ</td>
<td>β-amyloid</td>
</tr>
<tr>
<td>B16-LU8</td>
<td>murine melanoma cell line</td>
</tr>
<tr>
<td>B.</td>
<td><em>Bacillus</em></td>
</tr>
<tr>
<td>BAE</td>
<td>bovine aortic endothelial cell line</td>
</tr>
<tr>
<td>Bax</td>
<td>Bcl-2-associated X protein</td>
</tr>
<tr>
<td>BChE</td>
<td>butyrylcholinesterase</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>B-cell lymphoma 2</td>
</tr>
<tr>
<td>Bcl-xL</td>
<td>B-cell lymphoma-extra large</td>
</tr>
<tr>
<td>BCRP</td>
<td>breast cancer resistance protein</td>
</tr>
<tr>
<td>BDX2</td>
<td>rat fibrosarcoma cell line</td>
</tr>
<tr>
<td>BEt₃</td>
<td>triethylborane</td>
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<tr>
<td>BF₃·Et₂O</td>
<td>boron trifluoride ethyl etherate</td>
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<td>BHT</td>
<td>2,6-di-tert-butyl-4-methylphenol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BnEt₃NCl</td>
<td>benzyltriethylammonium chloride</td>
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<tr>
<td>Boc</td>
<td><em>tert</em>-butoxy carbonyl</td>
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<td>BPS</td>
<td>benzophenone synthase</td>
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<td>BPX</td>
<td>2-butanone peroxide</td>
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<tr>
<td>BrBMe₂</td>
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</tr>
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</tr>
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</tr>
<tr>
<td>BT-549</td>
<td>human breast ductal carcinoma cell line</td>
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<tr>
<td>Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>Bu₄N[Fe(CO)₃(NO)]</td>
<td>tetrabutylammonium tricarbonylnitrosylferrate</td>
</tr>
<tr>
<td>BUS</td>
<td>isobutyrophenone synthase</td>
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<tr>
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<tr>
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<tr>
<td>Caco-2</td>
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<tr>
<td>cAMP</td>
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<tr>
<td>cat.</td>
<td>catalyst</td>
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<tr>
<td>CB</td>
<td>cytochalasin B</td>
</tr>
<tr>
<td>CBP</td>
<td>CREB-binding protein</td>
</tr>
<tr>
<td>CC₅₀</td>
<td>half maximal cytotoxic concentration</td>
</tr>
<tr>
<td>CCD-18Co</td>
<td>human colon fibroblast cell line</td>
</tr>
<tr>
<td>CCD-841 CoN</td>
<td>human colon fibroblast cell line</td>
</tr>
<tr>
<td>CD</td>
<td>circular dichroism</td>
</tr>
<tr>
<td>CD-1</td>
<td>mouse breed originating from Dr. de Coulon at the Centre Anticancereux Romand, Lausanne, Switzerland</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
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<tr>
<td>CD4</td>
<td>cluster of differentiation 4 glycoprotein</td>
</tr>
<tr>
<td>cDNA</td>
<td>complementary DNA</td>
</tr>
<tr>
<td>CDP</td>
<td>cytidyl diphosphate</td>
</tr>
<tr>
<td>CEM-SS</td>
<td>human lymphoblastoid cell line susceptible to HIV infection</td>
</tr>
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<td>CEMx174-SEAP</td>
<td>human lymphoblastoid cell line containing SEAP reporter gene</td>
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<tr>
<td>c-Hex</td>
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<td>CIC(S)OPh</td>
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<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>cLogP</td>
<td>calculated partition coefficient</td>
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<td>cm</td>
<td>centimeter</td>
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<tr>
<td>$C_{max}$</td>
<td>maximum plasma concentration of a drug after administration</td>
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<tr>
<td>CMP</td>
<td>cytidyl monophosphate</td>
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<td>Co-115</td>
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<tr>
<td>CoA</td>
<td>coenzyme A</td>
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<tr>
<td>Colo-320-DM</td>
<td>human colon carcinoma cell line</td>
</tr>
<tr>
<td>compound 48/80</td>
<td>a polymer of $N$-methyl-para-methoxyphenethylamine and formaldehyde</td>
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<tr>
<td>COX-1</td>
<td>cyclooxygenase-1</td>
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<tr>
<td>COX-2</td>
<td>cyclooxygenase-2</td>
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<tr>
<td>CpG</td>
<td>consecutive cytosine and guanine nucleotides</td>
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<tr>
<td>cPLA2</td>
<td>cytosolic phospholipase A$_2$</td>
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<td>CREB</td>
<td>cAMP response element-binding protein</td>
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<td>CRL-1623</td>
<td>human tongue squamous cell carcinoma cell line</td>
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<td>CRL-1624</td>
<td>human squamous cell carcinoma cell line</td>
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<tr>
<td>CRMM-1</td>
<td>human conjunctival melanoma cell line</td>
</tr>
<tr>
<td>CRMM-2</td>
<td>human conjunctival melanoma cell line</td>
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CrO$_3$·DMP  chromium(VI) oxide-3,5-dimethylpyrazole
CSA  10-camphorsulfonic acid
CTP  cytidyl triphosphate
CXCR3  chemokine receptor 3
Cy  cyclohexyl
CYP1A1  cytochrome P450, family 1, subfamily A, polypeptide 1
CYP1A2  cytochrome P450, family 1, subfamily A, polypeptide 2
CYP2C9  cytochrome P450, family 2, subfamily C, polypeptide 9
CYP2C19  cytochrome P450, family 2, subfamily C, polypeptide 19
CYP2D6  cytochrome P450, family 2, subfamily D, polypeptide 6
CYP3A  cytochrome P450, family 3, subfamily A
CYP3A4  cytochrome P450, family 3, subfamily A, polypeptide 4
CYP4F2  cytochrome P450, family 4, subfamily F, polypeptide 2
CYP24A1  mitochondrial 1,25-dihydroxyvitamin D$_3$ 24-hydroxylase
CYP27B1  25-hydroxyvitamin D$_3$ 1-α-hydroxylase
Cy  cyclohexyl
Cys  cysteine
d  days
d  dextrorotatory
DAOY  human desmoplastic cerebellar medulloblastoma cell line
dba  dibenzylideneacetone
DCE  1,2-dichloroethane
DDQ  2,3-dichloro-5,6-dicyano-para-benzoquinone
DFT  density functional theory
DIBAL  di-iso-butylaluminum hydride
DMAP  4-(dimethylamino)pyridine
DME 1,2-dimethoxyethane
DMF $N,N$-dimethylformamide
DMP Dess–Martin periodinane
DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO dimethyl sulfoxide
DNA deoxyribonucleic acid
DOHH-2 human non-Hodgkin's B-cell lymphoma cell line
L-dopa L-3,4-dihydroxyphenylalanine
dppf 1,1'-bis(diphenylphosphino)ferrocene
DPPH 2,2-diphenyl-1-picrylhydrazyl
dr diastereomeric ratio
DTBMP 2,6-di-$\text{-t}$ert-butyl-4-methylpyridine
DU145 human prostate cancer cell line
DU145MDR multidrug-resistant DU145 cell line
E. Enterococcus or Escherichia
e.g. exempli gratia
EC$_{50}$ half maximal effective concentration
ECD electronic circular dichroism
ee enantiomeric excess
EJ human endometrioid adenocarcinoma cell line from uterine corpus
ent enantiomer
epi epimer
equiv stoichiometric equivalents
ERK extracellular signal-regulated kinase
Et ethyl
Et$_2$AlCl diethylaluminum chloride
<table>
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<th>Full Form</th>
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<td>Et₂AlI</td>
<td>diethylaluminum iodide</td>
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<td>Et₂O</td>
<td>diethyl ether</td>
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<tr>
<td>EtAlCl₂</td>
<td>ethylaluminum dichloride</td>
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<td>EtOH</td>
<td>ethanol</td>
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<td>EtSH</td>
<td>ethanethiol</td>
</tr>
<tr>
<td>f</td>
<td>female</td>
</tr>
<tr>
<td>FDA</td>
<td>Federal Drug Administration</td>
</tr>
<tr>
<td>fMLP</td>
<td>N-formylmethionine leucyl-phenylalanine</td>
</tr>
<tr>
<td>FMO5</td>
<td>flavin containing monooxygenase 5</td>
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<tr>
<td>FRAP</td>
<td>ferric reducing ability of plasma</td>
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<td>g</td>
<td>gram</td>
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<tr>
<td>G protein</td>
<td>guanine nucleotide-binding protein</td>
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<tr>
<td>GADD153</td>
<td>growth arrest and DNA damage-inducible gene 153</td>
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<tr>
<td>GI₅₀</td>
<td>half maximal cell growth inhibition concentration</td>
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<tr>
<td>h</td>
<td>hours</td>
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<tr>
<td>H.</td>
<td>Hypericum</td>
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<tr>
<td>H₂DCFDA</td>
<td>6-carboxy-2',7'-dichlorodihydrofluorescein diacetate</td>
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<tr>
<td>H₃</td>
<td>histone 3</td>
</tr>
<tr>
<td>H₄</td>
<td>histone 4</td>
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<td>HaCaT</td>
<td>human keratinocyte cell line</td>
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<tr>
<td>HAT</td>
<td>histone acetyltransferase</td>
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<tr>
<td>HC(OMe)₃</td>
<td>trimethyl orthoformate</td>
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<td>HCT-116</td>
<td>human colorectal carcinoma cell line</td>
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<tr>
<td>HCT-116MDR</td>
<td>multidrug-resistant HCT-116 cell line</td>
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<tr>
<td>HCT-8</td>
<td>human ileocecal colorectal adenocarcinoma cell line</td>
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<tr>
<td>HCT-8Ral</td>
<td>raltitrexed-resistant HCT-8 cell line</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>HCT-8&lt;sub&gt;SN-38&lt;/sub&gt;</td>
<td>7-ethyl-10-hydroxycamptothecin-resistant HCT-8 cell line</td>
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<td>HD-MY-Z</td>
<td>human Hodgkin's lymphoma cell line</td>
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<tr>
<td>HDAC</td>
<td>histone deacetylase</td>
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<td>HDMEC</td>
<td>human dermal microvascular endothelial cell line</td>
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<td>HEK293</td>
<td>human embryonic kidney cell line</td>
</tr>
<tr>
<td>HEK293T</td>
<td>human embryonic kidney cell line containing the SV40 large T-antigen</td>
</tr>
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<td>HeLa</td>
<td>human cervical carcinoma cell line</td>
</tr>
<tr>
<td>HeLa-C3</td>
<td>cisplatin-resistant human cervical carcinoma cell line</td>
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<tr>
<td>Hep3B</td>
<td>human hepatocellular carcinoma cell line</td>
</tr>
<tr>
<td>HEp-2</td>
<td>human larynx carcinoma cell line</td>
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<tr>
<td>HepG2</td>
<td>human hepatocellular carcinoma cell line</td>
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<tr>
<td>HFIP</td>
<td>1,1,1,3,3,3-hexafluoro-2-propanol</td>
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<tr>
<td>Hg(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>mercury(II) acetate</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HL-60</td>
<td>human promyelocytic leukemia cell cell line</td>
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<tr>
<td>HL-60&lt;sub&gt;Dox&lt;/sub&gt;</td>
<td>multidrug-resistant HL-60 cell line</td>
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<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<td>HN-5</td>
<td>human tongue carcinoma cell line</td>
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<tr>
<td>HNCy&lt;sub&gt;2&lt;/sub&gt;</td>
<td>dicyclohexylamine</td>
</tr>
<tr>
<td>HOAc</td>
<td>acetic acid</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
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<td>HT1080</td>
<td>human fibrosarcoma cell line</td>
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<td>HT144</td>
<td>human malignant melanoma cell line</td>
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<td>HT-29</td>
<td>human colorectal adenocarcinoma cell line</td>
</tr>
<tr>
<td>HT-29&lt;sub&gt;FU&lt;/sub&gt;</td>
<td>5-fluorouracil-resistant HT-29 cell line</td>
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<td>HT-29&lt;sub&gt;SN-38&lt;/sub&gt;</td>
<td>7-ethyl-10-hydroxycamptothecin-resistant HT-29 cell line</td>
</tr>
</tbody>
</table>
### Chemical Compounds

- **i-Pr**: isopropyl
- **i-PrBr**: 2-bromopropane
- **i-PrC(O)Cl**: isobutyryl chloride
- **i-PrC(O)CN**: isobutyryl cyanide
- **i-PrCHO**: isobutyraldehyde
- **i-PrMgCl**: isopropylmagnesium chloride
- **i-Pr₂NEt**: N,N-diisopropylethylamine, Hünig’s base

### Biological Terms

- **HUVEC**: human umbilical vein endothelial cell line
- **i.e.**: id est
- **IBX**: 2-iodoxybenzoic acid
- **IC₅₀**: half maximal inhibitory concentration
- **ICAM-1**: intercellular adhesion molecule-1
- **IFN-γ**: interferon-γ
- **IL-8**: interleukin-8
- **imid**: imidazole
- **iNOS**: inducible nitric oxide synthase
- **ITGAM**: integrin alpha M
- **IUPAC**: International Union of Pure and Applied Chemistry
- **JNK**: activator protein 1 N-terminal kinase
- **Jurkat**: human leukemic T cell leukemia cell line
- **Jurkat E6-1**: human leukemic T cell leukemia cell line
- **K**: lysine
- **Kᵢ**: dissociation constant
- **K562**: human myelogenous leukemia cell line
- **K562ADR**: adriamycin-resistant K562 cell line
- **KB**: HeLa contaminated nasopharyngeal carcinoma cell line
KB<sub>vin</sub>  Vincristine-resistant KB cell line
KE-37  human acute lymphoblastic T cell leukemia cell line
KELLY  human neuroblastoma cell line
kg  kilogram
KG-1  human acute myelogenous leukemia cell line
KHMDS  potassium hexamethyldisilazide
KOt-Bu  potassium tert-butoxide
L  levorotatory
L-(+)-DET  (+)-diethyl L-tartrate
L.  Listeria or Leishmania
L6  rat skeletal muscle cells
LA  Lewis acid (generic)
LAH  lithium aluminum hydride
LAMA-84  human chronic myeloid leukemia cell line
LAN-1  human neuroblastoma cell line
LAN-1<sub>5-FU</sub>  5-fluorouracil-resistant LAN-1 cell line
LAN-1<sub>ADR</sub>  adriamycin-resistant LAN-1 cell line
LAN-1<sub>CP</sub>  cisplatin-resistant LAN-1 cell line
LAN-1<sub>ETO</sub>  etoposide-resistant LAN-1 cell line
LD<sub>50</sub>  median lethal dose
LDA  lithium di-iso-propylamide
LDL  low-density lipoprotein
Leu  leucine
LHMDS  lithium hexamethyldisilazide
Li(2-Th)CuCN  lithium (2-thienyl)cyanocopper(I)
LiNEt<sub>2</sub>  lithium diethylamide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>LiTMP</td>
<td>lithium 2,2,6,6-tetramethylpiperide</td>
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<td>LN-229</td>
<td>human glioblastoma cell line</td>
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<td>LNCaP</td>
<td>androgen-sensitive human prostate adenocarcinoma cell line</td>
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<td>LNCaPETO</td>
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<td>LOE 908</td>
<td>3,4-dihydro-6,7-dimethoxy-α-phenyl-N,N-bis[2-(2,3,4-trimethoxyphenyl)ethyl]-1-isoquinolineacetamide hydrochloride</td>
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<td>LPS</td>
<td>lipopolysaccharides</td>
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<td>LS180</td>
<td>human intestinal colon adenocarcinoma cell line</td>
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<td>LXR</td>
<td>liver X receptor</td>
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<td>M</td>
<td>male or molar</td>
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<td>M51</td>
<td>human stomach carcinoma cell line</td>
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<td>M51&lt;sub&gt;CP&lt;/sub&gt;</td>
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<td>monoamine oxidase</td>
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<td>MAPK</td>
<td>mitogen-activated protein kinase</td>
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<tr>
<td>MAPKAPK-2</td>
<td>mitogen-activated protein kinase activated protein kinase 2</td>
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<td>MAT-Lu</td>
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<td>MBTE</td>
<td>methyl tert-butyl ether</td>
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<td>MC&lt;sub&gt;100&lt;/sub&gt;</td>
<td>maximal cytotoxic concentration</td>
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<td>doxorubicin-resistant MCF-7 cell line</td>
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<tr>
<td>MDCK</td>
<td>Madin–Darby canine kidney epithelial cells</td>
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<tr>
<td>Me</td>
<td>methyl</td>
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<tr>
<td>Me₂S</td>
<td>dimethylsulfide</td>
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<td>Me₂SO₄</td>
<td>dimethyl sulfate</td>
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<td>Me₃Al</td>
<td>trimethylaluminum</td>
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<td>acetonitrile</td>
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<td>MeCu(TMP)CNLi₂</td>
<td>dilithium (cyano-κC)methyl(2,2,6,6-tetramethyl-1-piperidiny)l copper</td>
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<td>MEF</td>
<td>mouse embryonic fibroblasts</td>
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<td>MeI</td>
<td>iodomethane</td>
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<td>MeOH</td>
<td>methanol</td>
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<td>Mes</td>
<td>2,4,6-trimethylphenyl</td>
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<td>MeSO₂NH₂</td>
<td>methanesulfonamide</td>
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<td>MFC</td>
<td>minimum fungicidal concentration</td>
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<td>MH1C1</td>
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<td>MIA PaCa-2</td>
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<td>MIHA</td>
<td>human liver cell line</td>
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<td>minutes</td>
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<td>mg</td>
<td>milligram</td>
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<td>MIC</td>
<td>minimum inhibitory concentration</td>
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<td>mL</td>
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<td>MMP-9</td>
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<td>Mn(OAc)₃</td>
<td>manganese(III) acetate</td>
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<td>methoxymethyl</td>
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<td>mPGES-1</td>
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<td>MRC-5</td>
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<td>mRNA</td>
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<td>molecular sieves</td>
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<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
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<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
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<td>sodium ethoxide</td>
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<td>NaOMe</td>
<td>sodium methoxide</td>
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<td>NB69</td>
<td>human stage III neuroblastoma cell line</td>
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<td>NBT-II</td>
<td>Wistar rat bladder carcinoma cell line</td>
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<td>NEt₃</td>
<td>triethylamine</td>
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<td>Neuro-2a</td>
<td>human neuroblastoma cell line</td>
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</table>
NF-κB  nuclear factor kappa-light-chain-enhancer of activated B cells
ng  nanogram
NHA  human astrocyte cell line
NHS  N-hydroxysuccinimide
NIH  National Institutes of Health
NIH-3T3  murine embryonic fibroblast cell line
nM  nanomolar
nm  nanometer
NMDA  N-methyl-D-aspartate
NMO  4-methylmorpholine N-oxide
NQO2  nicotinamide adenine dinucleotide dehydrogenase, quinone 1
Noxa  phorbol-12-myristate-13-acetate-induced protein 1
NTUB1  human bladder carcinoma cell line
OAc  acetate
OP  phosphate
OPP  pyrophosphate or diphosphate
ORAC  oxygen radical absorbance capacity
Tf  trifluoromethanesulfonyl
Tf₂O  trifluoromethanesulfonic anhydride
OVCAR 03  human ovarian carcinoma cell line
OZ  opsonized zymosan
p  para
P388  murine leukemia cell line
p53  tumor protein 53
P.  Plasmodium
P-gp  P-glycoprotein 1
\( p\text{-}TsOH \) \hspace{1cm} \textit{para}-toluenesulfonic acid

\( \text{P}(\text{OME})_3 \) \hspace{1cm} \text{trimethyl phosphite}

\( \text{PANC-1} \) \hspace{1cm} \text{human pancreatic epithelioid carcinoma cell line}

\( \text{Pb}(\text{OAc})_4 \) \hspace{1cm} \text{lead(IV) acetate}

\( \text{PBCEC} \) \hspace{1cm} \text{porcine brain capillary endothelial cell line}

\( \text{PBu}_3 \) \hspace{1cm} \text{tributylphosphine}

\( \text{PC-3} \) \hspace{1cm} \text{human prostate cancer cell line}

\( \text{PC-3ETO} \) \hspace{1cm} \text{etoposide-resistant PC-3 cell line}

\( \text{PC12} \) \hspace{1cm} \text{rat adrenal medulla pheochromocytoma cell line}

\( \text{PCAF} \) \hspace{1cm} \text{p300/CBP-associated factor}

\( \text{Pd}_3(\text{dba})_3 \) \hspace{1cm} \text{tris(dibenzylideneacetone)dipalladium(0)}

\( \text{Pd(OAc)}_2 \) \hspace{1cm} \text{palladium(II) acetate}

\( \text{Pd(OH)}_2/C \) \hspace{1cm} \text{Pearlman’s catalyst}

\( \text{PDC} \) \hspace{1cm} \text{pyridinium dichromate}

\( \text{PdCl}_2(\text{PPh}_3)_2 \) \hspace{1cm} \text{bis(triphenylphosphine)palladium(II) dichloride}

\( \text{PDGFR} \) \hspace{1cm} \text{platelet-derived growth factor receptor}

\( \text{pentOAc} \) \hspace{1cm} \text{amyl acetate}

\( \text{Ph} \) \hspace{1cm} \text{phenyl}

\( \text{PhCl} \) \hspace{1cm} \text{chlorobenzene}

\( \text{Phe} \) \hspace{1cm} \text{phenylalanine}

\( \text{PhI} \) \hspace{1cm} \text{iodobenzene}

\( \text{PhI(OAc)}_2 \) \hspace{1cm} \text{(diacetoxyiodo)benzene}

\( \text{PhI(TFA)}_2 \) \hspace{1cm} \text{[bis(trifluoroacetoxy)iodo]benzene}

\( \text{PhIO} \) \hspace{1cm} \text{iodosobenzene}

\( \text{PhIO}_2 \) \hspace{1cm} \text{iodylbenzene}

\( \text{PhMe} \) \hspace{1cm} \text{toluene}
RNA  ribonucleic acid
ROS  reactive oxygen species
rt  room temperature
s  seconds
S.  *Staphylococcus*
s-Bu  sec-butyl
s-BuLi  sec-butyllithium
Saos-2  human primary osteosarcoma cell line
sat.  saturated
SB1  human melanoma cell line
SB3  human melanoma cell line
SCoA  coenzyme A
Sc(OTf)₃  scandium(III) trifluoromethanesulfonate
SEAP  secreted alkaline phosphatase
SF-268  human highly anaplastic astrocytoma cell line
SGC-7901  human gastric adenocarcinoma cell line
SIRT1  sirtuin 1
SIRT2  sirtuin 2
SIV  simian immunodeficiency virus
SJW  St. John’s wort (*Hypericum perforatum*)
SK-N-AS  human neuroblastoma cell line
SK-N-BE  human neuroblastoma cell line
SK-OV-3  human ovarian adenocarcinoma cell line
SKF-96365  1-[2-(4-methoxyphenyl)-2-[3-(4-methoxyphenyl)propoxy]ethyl]imidazole,  1-[β-(3-(4-methoxyphenyl)propoxy)-4-methoxyphenethyl]-1H-imidazole hydrochloride
SKW-3 human T cell leukemia cell line
SMMC-7721 human hepatocellular carcinoma cell line

\( sn \) stereospecifically numbered, as in positions of glycerol derivatives

Sn(OTf)\(_2\) tin(II) trifluoromethanesulfonate

SOCE store-operated \( Ca^{2+} \) entry

SR12813 tetraethyl 2-(3,5-di-\( tert \)-butyl-4-hydroxyphenyl)ethenyl-1,1-bisphosphonate

St. Saint

STAT-1 signal transducer and activator of transcription-1

STAT-3 signal transducer and activator of transcription-3

\( Strept. \) \( Streptomyces \)

SV40 simian vacuolating virus 40

SW480 human colon adenocarcinoma cell line

\( t_1/2 \) elimination half-life

T24 human bladder carcinoma cell line

T84 human colon carcinoma cell line

\( T. \) \( Trypanosoma \)

\( t \)-AmOK potassium \( tert \)-pentoxide

T-box a group of transcription factors involved in limb and heart development

\( t \)-Bu \( tert \)-butyl

\( t \)-BuLi \( tert \)-butyllithium

\( t \)-BuOH \( tert \)-butanol

\( t \)-BuOK potassium \( tert \)-butoxide

TBAF tetrabutylammonium fluoride

TBAI tetrabutylammonium iodide

TBARS thiobarbituric acid reactive species

TBHP \( tert \)-butyl hydroperoxide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBSCI</td>
<td>tert-butyldimethylsilyl chloride</td>
</tr>
<tr>
<td>TBSOTf</td>
<td>tert-butyldimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal cytotoxicity</td>
</tr>
<tr>
<td>TEAC</td>
<td>Trolox equivalent antioxidant capacity</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidine 1-oxyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TESCl</td>
<td>chlorotriethylsilane</td>
</tr>
<tr>
<td>TESOTf</td>
<td>triethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>Th</td>
<td>thienyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Thr</td>
<td>threonine</td>
</tr>
<tr>
<td>Ti(Oi-Pr)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>titanium(IV) isopropoxide</td>
</tr>
<tr>
<td>TIPSOTf</td>
<td>triisopropylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>time to achieve C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N',N',N''-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMP</td>
<td>2,2,6,6-tetramethylpiperidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSCl</td>
<td>chlorotrimethylsilane</td>
</tr>
<tr>
<td>TMSI</td>
<td>iodontrimethylsilane</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TMSN&lt;sub&gt;3&lt;/sub&gt;</td>
<td>trimethylsilyl azide</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-α</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-&lt;i&gt;n&lt;/i&gt;-propylammonium perruthenate</td>
</tr>
</tbody>
</table>
TPEN: \(N,N',N''\)-tetrakis(2-pyridylmethyl)ethylenediamine

TPP: thiamine pyrophosphate

TRAIL: TNF-related apoptosis-inducing ligand

TRAMP-C1: murine prostate adenocarcinoma cell line

TrkB: neurotrophic tyrosine kinase receptor, type 2

Trolox: 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid

TRPC: canonical transient potential protein channel

TRPC3: canonical transient potential protein channel, member 3

TRPC6: canonical transient potential protein channel, member 6

TRPC7: canonical transient potential protein channel, member 7

Ts: \(\text{para}\)-toluenesulfonyl

U: uniform isotopic labeling

U251: human neuronal glioblastoma cell line

U266: human B cell malignant myeloma cell line

U87: human primary glioblastoma cell line

U937: human histiocytic leukemia cell line

UACC-62: human malignant melanoma cell line

VEGF: vascular endothelial growth factor

VERO: kidney epithelial cell line originating from an African green monkey

VPS: phlorisovalerophenone synthase

W: tryptophan

w/v: weight over volume

WRL-68: human liver carcinoma cell line

wt%: percentage by weight

XO: xanthine oxidase
| **Z-DEVD-FMK** | N-benzoyl-aspartic acid(0-Me)-glutamate(0-Me)-valine-aspartic acid(0-Me)-fluoromethylketone |
| **Z-VAD-FMK** | N-benzoyl-valine-alanine-aspartic acid-(0-Me) fluoromethyl ketone |
| **Zn(OTf)₂** | zinc trifluoromethanesulfonate |
| **1F6** | human melanoma cell line |
| **3T3-L1** | murine preadipocyte cell line |
| **3T3.T4.CCR5** | CD4+ human fibroblast cell line |
| **5-LO** | 5-lipoxgenase |
| **5-HT₂** | serotonin receptor, subfamily 2 |
| **5637** | human stage II bladder carcinoma cell line |
| **786-0** | human renal cell adenocarcinoma cell line |
| **µg** | microgram |
| **µL** | microliter |
| **µM** | micromolar |
| **µm** | micrometer |
| **µmol** | micromole |
| **µwave** | microwave irradiation |
| (DHQD)₂PHAL | hydroquinidine 1,4-phthalazinediyl diether |
| (PhSe)₂ | diphenyl diselenide |
| (Sia)₂BH | bis(1,2-dimethylpropyl)borane |
| (S)-tol-BINAP | (S)-(−)-2,2′-para-tolyl-phosphino)-1,1′-binaphthyl |
| (TMS)₃SiH | tris(trimethylsilyl)silane |
| [O] | oxidation |
Chapter 1

Polycyclic Polyrenylated Acylphloroglucinols: An Overview
Overview

In 1971, a group of Soviet scientists studying the antibacterial properties of St. John’s wort (*Hypericum perforatum*, SJW) reported the discovery of a natural product hyperforin (1, Figure 1.1) from the medicinal herb’s alcoholic extract.¹ Using extensive chemical degradation methods, the flat structure of hyperforin was deduced four years later.² Concurrent to these studies was the isolation and X-ray crystallography-guided elucidation of isoxanthochymol (2) from the Indian gamboge (*Garcinia xanthochymus*).³ Hyperforin and isoxanthochymol are the founding and prototypical members of a sprawling natural product family known as the polycyclic polyrenylated acylphloroglucinols (PPAPs),⁴ of which there are 260 members to date.

![Figure 1.1. Structures of hyperforin (1) and isoxanthochymol (2).](image_url)

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A PPAP natural product may be defined as a bicyclo[3.3.1]nonane (or a larger bridged polycyclic containing a bicyclo[3.3.1]nonane element) bearing a C9 ketone (Figure 1.2).\textsuperscript{5,6} Aside from the C9 position, oxidation is also found at the C2 and C4 positions, and in approximately 80% of PPAPs, these two oxidation sites are conjugated through C3 to form a $\beta$-hydroxyenone or $\beta$-alkoxyenone functionality array. The periphery of this carbocyclic core is decorated with multiple isoprenoid groups at the C1, C3, C5, C7, and C8 positions. In the great majority of instances, these substituents are derived from the following parent isoprenoids: prenyl in 75% of substituents; lavandulyl in 10% of substituents; and geranyl in 7.5% of substituents. These isoprenoid substituents undergo secondary cyclization to form additional oxacyclic and carbocyclic rings in many PPAPs. Nearly all of these natural products contain a quaternary center at the C8 position, and in 81% of PPAPs, this position is substituted with two methyl groups.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{PPAP-skeleton.png}
\caption{Generic PPAP skeleton and typical substituents.}
\end{figure}

\textsuperscript{5} The general method of PPAP numbering used throughout is in accordance with IUPAC guidelines for bicyclic compounds. For more information, see: Moss, G. P. Pure Appl. Chem. \textbf{1999}, \textit{71}, 513-529.

The placement of an acyl group around the bicyclic ring system is used to classify PPAPs into three different subgroups: (1) “Type A” PPAPs contain a C1 acyl substituent; (2) “Type B” PPAPs contain a C3 acyl substituent; and (3) “Type C” PPAPs contain a C5 acyl substituent. Approximately 52% of PPAPs are Type A, and 46% are Type B. There are only three known Type C PPAPs, and an additional three PPAPs lack acyl substitution all together. When an acyl group is present, it is either an isobutyryl (15%), 2-methylbutyryl (6%), isovaleryl (1.5%), benzoyl (36.5%), or an oxidized benzoyl (41%) group. A comprehensive listing of all published PPAPs with references to chemotaxonomical, geographical, and spectroscopic data is found in Appendix A.

**Stereochemistry**

The absolute configurations of only a few PPAP natural products have been ascertained. Since the most electron-rich atom found in all PPAPs is oxygen, anomalous scattering is not normally large enough to permit the refinement of the Flack parameter\(^7\) and thus absolute configuration during X-ray diffraction analysis. To circumvent this issue, the crystal structures of PPAPs that have been appended with various brominated groups have been resolved, which now contain atoms with sufficient electron density to allow determination of the Flack parameter. The absolute configurations of hyperforin,\(^8\) isogarcinol,\(^9\) isoxanthochymol,\(^10\) and xanthochymol\(^10,11\) have been solved using this methodology. Recent advancements using Bijvoet pair analysis and subsequent determination of the Hooft parameter allows for the determination of absolute structure at low temperatures without requiring the presence of heavy atoms.\(^12\) The absolute configuration of 7-epi-clusianone has been solved in this manner.\(^13\)

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The absolute configurations of several PPAPs have been determined through comparison of spectroscopic data and direct semisynthetic conversion. Isoxanthochymol and isogarcinol have identical spectroscopic properties except for optical rotations of opposite sign. Through the observation of similar Cotton effects in the circular dichroism (CD) spectra of isogarcinol, the absolute configuration of isogarcinol 13-\(O\)-methyl ether\(^{14}\) and 13,14-didehydroxyisogarcinol\(^{15}\) were determined. The absolute configuration of guttiferone E (and thus its enantiomer, garcinol) was determined through acid- and heat-mediated conversion to isoxanthochymol (2).\(^{16}\) Ozonolysis of sinaicone produced the previously characterized (2R,4R)-2,4-dimethylhexanoic acid.\(^{17}\) Through comparison of CD spectra with computed electronic circular dichroism (ECD) spectra calculated using density functional theory (DFT), the absolute configurations of 7-\(\text{epi}\) -guttiferone J,\(^{18}\) oxy-guttiferone K,\(^{19}\) guttiferone M,\(^{19}\) 32-hydroxy-\(\text{ent}\) -guttiferone M\(^{18}\) have been determined.

In addition, several PPAPs have been isolated in both enantiomeric forms. Specifically, these enantiomeric pairs are: chamuangone (cowanone) and guttiferone Q; cycloxanthochymol and \(\text{ent}\)-cycloxanthochymol; garcinialiptone A and \(\text{ent}\)-garcinialiptone A; garcinielliptone I and hyperibone A; garcinol and guttiferone E; guttiferone G (guttiferone I2) and oblongifolin C; guttiferone O2 and oblongifolin F; hyperibone G and propolone D; isogarcinol and isoxanthochymol; and samponione G and \(\text{ent}\)-sampsonione G.


\(^{17}\) Řezanka, T.; Sigler, K. *Phytochemistry* 2007, 68, 1272-1276.


\(^{19}\) Masullo, M.; Bassarello, C.; Bifulco, G.; Piacente, S. *Tetrahedron* 2010, 66, 139-145.
Distribution

PPAPs have been isolated from 128 different plant species spanning 18 different genii in 6 different families. The great majority (257 out of 260) of PPAPs have been isolated from plants from the Clusiaceae (Guttiferae) and Hypericeae families, members of the Malpighiales order.\textsuperscript{20,21} The genii Clusia, Garcinia, and Hypericum are particularly prolific, having PPAPs isolated from 132 different subordinate species.\textsuperscript{22} Many PPAPs have been observed in multiple species; hyperforin alone has been detected in 38 distinct species.\textsuperscript{23} Only five PPAPs have been isolated outside of the Clusiaceae and Hypericeae families (Figure 1.3): dorstenpictanone (3) from Dorstenia picta (Moraceae);\textsuperscript{24} spiranthenones A-B (4,5) from Spiranthera odoratissima (Rutaceae);\textsuperscript{25} xanthochymol (6) from Endodesmia calophyloides (Calophyllaceae);\textsuperscript{26} and hyperforin (1) has been isolated from Apocynum venetum (Apocynaceae)\textsuperscript{27} and from Scutellaria baicalensis (Lamiaceae).\textsuperscript{28}

\textsuperscript{20} Hypericeae has traditionally been regarded as a separate family, but recent phylogenic analysis based on the chloroplast gene \textit{rbcL} has shown that it can be classified as a tribe (i.e., Hypericoideae) of the Clusiaceae family. For more information, see: Gustafsson, M. H. G.; Bittrich, V.; Stevens, P. F. \textit{Int. J. Plant Sci.} \textbf{2002}, \textit{163}, 1045-1054.

\textsuperscript{21} Wurdack, K. J.; Davis, C. C. \textit{Am. J. Bot.} \textbf{2009}, \textit{96}, 1551-1570.


While most species of the Clusiaceae family are found in tropical regions, Hypericeae species are found in temperate climes. Given the fact that most PPAPs exhibit some degree of antibacterial properties, it is unsurprising that these compounds are isolated from the flowers and fruit rinds of these species, protecting vulnerable and sexually important organs from bacterial parasites. Hyperforin may exist in concentrations up to 11% in the flowering parts of *Hypericum perforatum*, and its concentration generally decreases as the flowers develop and mature. Moreover, PPAPs are also found in the latex of many Clusiaceae species, protecting against the development of infections in injuries to these plants. Garcinol (7) and isogarcinol (8) were initially isolated in “surprisingly in large quantities” from the latex of *Garcinia cambogia*; garcinol comprised 37% of total mass of this material (Figure 1.4).

Species of both the Clusiaceae and Hypericeae families are also noted for their high degree of evolutionary plasticity, and this may be a direct result of adaptation to different methods of pollination. Further, while most flowers in general use nectar and pollen as pollinator rewards, a unique adaptation and defining feature of flowering plants from the Clusiaceae family is the additional use of resins as rewards. Certain honeybees will use these resins to create a material known as propolis, which is used to patch holes in their hives as well as to embalm the carcasses of intruders. Propolis is used widely in a variety of folk medicines, and its application traces back to the ancient Egyptians who used this substance in cadaver mummification. The contents of propolis vary according to geography and climate, and PPAPs are the dominant chemicals found in the propolis of New World bee colonies from as far north as the Caribbean islands to as far south as central Brazil. It is interesting to note that while the majority of the 25 distinct PPAPs that have been isolated from these propola have also been found in nearby flora, the plant source of 7 propolis PPAPs have not been identified.

**Biosynthesis**

Very little evidence beyond conjecture is known specifically about PPAP biosynthesis. The only PPAP that has undergone any biosynthetic experimental scrutiny is hyperforin (1); however, several generalizations about PPAP biosynthesis can be extrapolated from these studies. In general, the biosynthesis of PPAPs can be broken down into three distinct phases: (1) polyketide synthesis of an 

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acylphloroglucinol precursor; (2) alkylation of this core with isoprenoid side chains and subsequent
cyclization to form the characteristic bicyclo[3.3.1]nonane core of PPAPs; and (3) secondary cyclizations,
oxidations, and rearrangements.

The first step in PPAP biosynthesis involves the stepwise, decarboxylative condensation of an
alkoyl-SCoA or an aroyl-SCoA group (9) with three molecules of malonyl-CoA (10, Scheme 1.1). This
enzyme-bound linear tetraketide (11) then undergoes an intramolecular Claisen cyclization to form an
acylphloroglucinol (12). The enzymes that catalyze these reactions are members of the type III
polyketide synthase (PKS) superfamily. While type I and II PKSs contain acyl carrier proteins (ACPs)
that shuttle the growing polyketide across modular functional domains (e.g., ketoreductase and
dehydratase), type III PKSs lack ACPs and contain a single active site in which the growing polyketide
chain is anchored.33

![Scheme 1.1. The first steps in PPAP biosynthesis.](image)

All known type III PKSs are homodimers and contain a highly conserved cysteine-histidine-
asparagine catalytic triad within the active site of each monomer.34 The cysteine acts as the polyketide
attachment site, and the histidine and asparagine residues play critical roles in the decarboxylation of
malonyl-CoA during chain extension. Additionally, two generally conserved phenylalanine residues near
the entrance of the active site facilitate some degree of substrate specificity; however, PKSs in general
poorly differentiate starter units in vitro and rely upon compartmentalization within plant tissue and cells

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33 For reviews of type III PKS, see: (a) Flores-Sanchez, I. J.; Verpoorte, R. Plant Physiol. Biochem. 2009, 47, 167-

to engender a high degree of substrate selectivity.\textsuperscript{33a} For PPAPs such as hyperforin (1) containing an isopropyl ketone moiety, isobutyrophenone synthase (BUS) is used to synthesize phlorisobutyrophenone (13, Figure 1.5). PPAPs containing phenyl and isobutyl ketones utilize benzophenone synthase (BPS) and phlorisovalerophenone synthase (VPS) to synthesize 2,4,6-trihydroxybenzophenone (14) and phlorisovalerophenone (15), respectively. Only two PKS systems utilized in PPAP biosynthesis have been characterized: the hyperforin and adhyperforin BUS from \textit{Hypericum calycinum}\textsuperscript{35} and the hyperandrone A BPS from \textit{Hypericum androsaemum}.\textsuperscript{36} In addition, the gene responsible the PKS involved in hyperforin and adhyperforin biosynthesis in \textit{Hypericum perforatum}, named \textit{HpPKSI}, has also been characterized.\textsuperscript{37}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/figure1.5.png}
\caption{Specific examples of intervening acylphloroglucinols in PPAP biosynthesis.}
\end{figure}

For the biosynthesis of PPAPs, exactly three molecules of malonyl-CoA are condensed with a starter acyl-CoA subunit. For type III PKSs, termination of polyketide chain length is determined by active site volume. For example, if a Thr135Leu point mutation is introduced in the active site of the \textit{Hypericum androsaemum} BPS, the subsequent decrease in active site volume causes this enzyme to become a phenylpyrone sythase without a decrease in catalytic efficiency, in which only two molecules of


malonyl-CoA are incorporated. This triketide then undergoes lactonization to form 6-phenyl-4-hydoxy-2-pyrone (16, Scheme 1.2a) instead of 2,4,6-trihydroxybenzophenone (14, Scheme 1.2b).

Scheme 1.2. (a) Phenylpyrone synthase activity of Thr135Leu H. androsaemum BPS and (b) benzophenone synthase activity of wild-type H. androsaemum BPS.

The next step in PPAP biosynthesis involves polyisoprenylation of the acylphloroglucinol nucleus. All isoprenoids are derived from the two C5 precursors: isopentenyl diphosphate (17) and dimethylallyl diphosphate (18). Until the early 1990s, it was thought that these precursors were produced from a single pathway involving a melavonate (19) intermediate (Scheme 1.3).39 This pathway involves the condensation of three molecules of acetyl-CoA (20) to 3-hydroxy-3-methylglutaryl-CoA (21), and upon reduction to melavonate (19), pyrophosphorylation to 22, and decarboxylative elimination, 17 is synthesized, which can then be isomerized to 18. Indeed, this is the pathway by which eukaryotes synthesize sterols and other important metabolites.

Scheme 1.3. Melavonate pathway of terpene biosynthesis.


However, in the early 1990s, inconsistencies regarding $^{13}$C-labelled intermediates led to the independent discoveries of a non-melavonate means of isoprenoid biosynthesis in plants and bacteria by the research groups of Rohmer and Arigoni. The absence of this pathway in humans has garnered significant attention as a means to develop novel anti-infective pharmaceutical agents. This deoxyxylulose phosphate pathway commences with the thiamine pyrophosphate (TPP) mediated decarboxylative coupling of pyruvate ($23$) to d-glyceraldehyde-3-phosphate ($24$) to form 1-deoxy-d-xylulose-3-phosphate ($25$, Scheme 1.4). A subsequent rearrangement with concomitant reduction affords 2C-methyl-d-erythritol 4-phosphate ($26$). Sequential cytidyl phosphorylation and phosphorylation yields 4-diphosphocytidyl 2C-methyl-d-erythritol 2-phosphate ($27$). Cytidyl monophosphate (CMP) is then released to form 2C-methyl-d-erythritol-2,4-cyclodiphosphate ($28$). Single-electron transfer from an iron-sulfur cluster cofactor mediates the reductive rearrangement of $28$ to E-1-hydroxy-2-methyl-2-butenyl diphosphate ($29$) through an unknown mechanism of action. Finally, another iron-sulfur cluster-facilitated single-electron transfer process affords either $17$ or $18$, depending on the specific enzyme.

Scheme 1.4. Deoxyxylulose phosphate pathway of terpene biosynthesis.


Higher plants utilize both the melavonate and deoxyxylulose pathways to synthesize terpenoids, and this is a reason for the relatively belated discovery of the latter. In general, the melavonate route is used in the cytoplasm and mitochondria, and it is responsible for the synthesis of sesquiterpenoids and ubiquinones. Other metabolites, such as hemiterpenes, monoterpenes, diterpenes, and carotenoids, are formed via the deoxyxylulose pathway localized in the plastids.\textsuperscript{43} Given the fact that most substituents on PPAPs are hemiterpenoid or monoterpenoid in origin, it is unsurprising that they are synthesized using the deoxyxylulose phosphate pathway. Due to the presence of a skeletal rearrangement in this pathway (i.e., 25 to 26), the introduction of isotopically-labeled feedstocks may be used to differentiate between these pathways. A feeding study of \textit{Hypericum perforatum} sprouts performed in the dark utilizing both [1-\textsuperscript{13}C]glucose and [U-\textsuperscript{13}C\textsubscript{6}]glucose provided evidence for the involvement of the deoxyxylulose pathway in hyperforin biosynthesis.\textsuperscript{44}

Further, this study demonstrated that hyperforin is synthesized from the alkylation of phlorisobutyrophenone (13) with 3 molecules of dimethylallyl diphosphate (18) and 1 molecule of geranyl diphosphate (30). Although the details concerning the specific order of alkylation remain scant, a reasonable biosynthetic sequence can be deduced for hyperforin (Scheme 1.5). Originally proposed by Bystrov and coworkers in 1975,\textsuperscript{2} conversion of 13 to deoxycohumulone (31) followed by dearomative alkylation with 30 produces cyclohexadienone 32. Prenylation of the proximal olefin present in the geranyl side chain of 32 with 18 with either concerted or stepwise cyclization affords hyperforin (1).

\textsuperscript{43} For more information on the biosynthesis of phytochemical terpenoids, see ref. 42b. In some cases, both pathways may be operational in the biosynthesis of a single natural product. For an example, see: Nabeta, K.; Ishikawa, T.; Kawae, T.; Okuyama, H. \textit{J. Chem. Soc., Chem. Commun.} \textbf{1995}, 681-682.

Scheme 1.5. Proposed biosynthesis of hyperforin (1) from phlorisobutyrophenone (13).

The intermediates of this hyperforin biosynthesis bear resemblance to other families of natural products. Polyprenylated acylphloroglucinols such as 31, also known as deoxycohumulone, were first isolated in hops in 1961.\textsuperscript{45} Hops are the female seed cones of \textit{Humulus lupulus} (Cannabaceae) and have been extensively studied by the brewing industry due to the importance of hops in beer flavor and aroma.\textsuperscript{46} Deoxycohumulone (31) is a direct precursor of both colupulone (33),\textsuperscript{47} a typical hop \(\beta\)-acid, and cohumulone (34),\textsuperscript{48} a typical hop \(\alpha\)-acid (Scheme 1.6).\textsuperscript{49} In the brewing of beer, hops are boiled with malt and wort in water. Under these conditions, isomerization of cohumulone takes place to give bitter hop iso-\(\alpha\)-acids, an important flavoring agent in beer. While hop \(\beta\)-acids like colupulone are thought to


mostly decompose during the wort boiling process, recent studies have shown that they also isomerize to bitter-tasting compounds that may further add to the complex composition of beer flavor.\textsuperscript{50}

![Scheme 1.6. Deoxycohumulone (31) as a biosynthetic precursor to both colupulone (33) and cohumulone (34).](image)

The enzymes responsible for the isoprenylation en route to natural products such as PPAPs and hop acids are collectively known as prenyltransferases.\textsuperscript{51} In plants, prenyltransferase activity is mainly located in the plastids, and the alkylating terpenoid is derived from the deoxyxylulose pathway. All known prenyltransferases require a divalent metal cation. The prenyltransferase responsible for the conversion of phlorisobutyrophenone (13) to prenyl phlorisobutyrophenone (35, also known as “compound co-X”), which is the first prenylation step in the biosyntheses of hop bitter acids and hyperforin, has been characterized in both \textit{Humulus lupulus} and \textit{Hypericum calycinum} (Scheme 1.7). The enzyme utilized in \textit{Humulus lupulus} has an unusually wide substrate scope, and there are conflicting reports as to whether this enzyme is membrane-bound or not.\textsuperscript{52} All other plant prenyltransferases are membrane-bound.\textsuperscript{51} The analogous prenyltransferase utilized in hyperforin biosynthesis in \textit{Hypericum}


*Calycinum* has also been characterized as being non-membrane-bound.\(^{53}\) To date, the prenyltransferases involved in the formation of deoxycohumulone or the dearomative prenylation of deoxycohumulone have not been characterized.

\[
\text{Scheme 1.7. The first prenylation step in hyperforin and hop bitter acid biosynthesis.}
\]

After dearomative poly-isoprenylation of a polyketide acyphloroglucinol, a cascade cyclization takes place to form the characteristic bicyclo[3.3.1]nonane core of PPAP natural products. Hop \(\beta\)-acids, such as colupulone (33) are alkylated\(^{54}\) to produce a tertiary carbocationic intermediate, which then is trapped through nucleophilic addition of the cyclohexadienone ring (e.g., see Scheme 1.5). Several modes of nucleophilic addition are available to trap this carbocationic intermediate, as illustrated for grandone (36)\(^{55}\) in Scheme 1.8. Following prenyl transfer and subsequent formation of the carbocation 37, simple E1-type deprotonation may lead to the formation of weddellianone A (38, Scheme 1.8a), a lavandulyl-substituted hop \(\beta\)-acid that has been isolated from *Clusia weddelliana* (Clusiaceae).\(^{56}\) In addition, two different nucleophilic carbon centers in the cyclohexadienone ring of 37 may trap this carbocation, either at C1 or at C3, and this divergence leads to either a Type A or Type B PPAP, respectively. If the carbocation is trapped at C1, the Type A PPAP nemorosone\(^{55b}\) is generated (39, 39).


\(^{54}\) Note that two possible diastereomers may be generated at C7 from this alkylation event. Only one diastereomer is depicted throughout Scheme 1.8.


Scheme 1.8. Cyclization modes of grandone (36) after prenylation via intermediate 37: (a) deprotonation, (b) C1 cyclization, (c) C3 cyclization, and (d) etherification.
Scheme 1.8b), and if cyclization occurs at C3, the Type B PPAP 7-epi-clusianone\(^{57}\) is produced (40, Scheme 1.8c). An oxygen atom, such as the ketone oxygen attached to C9, may also intercept this carbocation as depicted in Scheme 1.8d to generate benzopyran-type products like 41. However, only a single analogous natural product that may involve such a cyclization has been isolated to date (bronianone, 42, Figure 1.6).\(^{58,59}\)

![Figure 1.6. Structure of bronianone (42).](image)

Unlike Types A and B PPAPs, the relatively rare Type C PPAPs cannot be made via intermediates such as grandone (36) but rather an isomeric compound represented as 43 (Figure 1.7a). Only three Type C PPAPs have been isolated to date (Figure 1.7b), garcinielliptone K (44), L (45), and M (46), from *Garcinia subelliptica*.\(^{60}\)

---


\(^{59}\) The originally proposed structure of xanthochymol (6) was similar to 41 and 42 prior to revision. See ref. 3.

Following formation of the bicyclo[3.3.1]nonane ring, a variety of oxidations, cyclizations, and isomerizations may occur, further diversifying the family of PPAP natural products. Many of these transformations are potentially facilitated by epoxidation of an isoprenoid side chain. Examples of secondary cyclization are found in Scheme 1.9 involving plukenetione D/E (7-epi-nemorosone, 47) and its epoxidation product 48. 5-exo epoxide opening of the epoxide found in 48 by the oxygen attached to C4 leads to a PPAP containing a dihydrofuran ring, sampsonione O (49). A 6-endo cyclization (followed by elimination of the resulting alcohol) is also possible, illustrated by the natural products plukenetione F (50) and G (51). Carbocyclization involving the prenyl substituent at C7 is also possible, as evidenced by the formation of plukenetione B (52) from 48, exemplifying the formation of a tetracyclic PPAP bearing a homoadamantyl subunit.

While some PPAPs containing secondary cyclization may arise through enzymatic processes, some other PPAPs may simply be artifacts of the isolation process. For example, simple treatment of xanthochymol (6) with acid or heat forms isoxanthochymol (2, Scheme 1.10). More in-depth analysis is necessary in order to further elucidate the later stages of PPAP biosynthesis.

**Scheme 1.9.** Formation of PPAPs through an epoxide intermediate of plukenetione D/E (47).

**Scheme 1.10.** Acid- or heat-mediated conversion of xanthochymol (6) to isoxanthochymol (2).
Bioactivity

Widespread interest in the biological activity of PPAPs stems from the prevalence of these compounds in medicinally-relevant herbs used in a variety of traditional and ethnopharmaceutical treatments. Rather than utilizing an organization based upon natural product, this section is organized into distinct disease areas in order to facilitate greater understanding of the relationship between PPAP structure and bioactivity. The structures of PPAPs discussed herein may be found in Appendix A.

Anti-infective Activity

The anti-infective properties of PPAPs were one of the first types of bioactivity to be recognized. As mentioned previously, it has been theorized that plants biosynthesize PPAPs as a defense against infection. A variety of PPAPs are effective antibacterial agents particularly amongst gram-positive bacteria (Table 1.1); however, some are active against gram-negative bacteria as well (Table 1.2). While many of these bacteria are normally harmless and are intestinal commensals or found on normal skin flora (e.g., B. subtilis, E. faecalis, S. aureus, S. epidermidis), they may lead to often fatal infections in immunocompromised individuals, particularly in nosocomial environments. Particularly effective, broad-spectrum PPAPs include hyperforin, garcinol, and guttiferone A.
Table 1.1. Evaluation of PPAPs against gram-positive bacteria.

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Active PPAPs (MIC in µg/mL)</th>
<th>Inactive PPAPs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomyces naeslundii</td>
<td>hyperbione A (1.65-3.3)</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>garcinol (1.5), guttiferone A, hyperatomarin (1.56), hyperpapuanone (8), isoxanthochymol (9.8), papuaforin A (64), papuaforin C (64), papuaforin D (130), papuaforin E (64)</td>
<td>7-epi-clusianone, guttiferone G</td>
<td>64, 64, 66, 62, 68, 69</td>
</tr>
<tr>
<td>Bacillus coagulans</td>
<td>garcinol (2.0)</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>Bacillus megaterium</td>
<td>guttiferone G (0.61)</td>
<td>isoxanthochymol</td>
<td>67</td>
</tr>
<tr>
<td>Bacillus mesentericus</td>
<td>hyperforin (2)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bacillus mycoides</td>
<td>hyperforin (0.2)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bacillus stearothermophilus</td>
<td>isoxanthochymol (4.88)</td>
<td>guttiferone G</td>
<td>67</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
<td>chamuangone (31), enervosanone (0.013), garcinol (0.05), hyperatomarin (3.1), hyperforin (0.2)</td>
<td>methyl clusianone, furohyperforin, furohyperforin A, guttiferone G, isoxanthochymol, pyrohyperforin</td>
<td>65, 66, 67, 70, 71, 72, 73, 74</td>
</tr>
<tr>
<td>Coryophanon latum</td>
<td>hyperforin (1)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Clavibacter michiganensis</td>
<td>hyperforin (1)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Corynebacterium diphtheriae</td>
<td>hyperforin (1)</td>
<td></td>
<td>75</td>
</tr>
</tbody>
</table>

70 Lokvam, J.; Braddock, J. F.; Reichardt, P. B.; Clausen, T. P. Phytochemistry 2000, 55, 29-34.
73 Taher, M.; Idris, M. S.; Ahmad, F.; Arbaïn, D. Iran. J. Pharm. Th. 2007, 6, 93-98.
### Table 1.1 (continued), Evaluation of PPAPs against gram-positive bacteria.

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Active PPAPs (MIC in µg/mL)</th>
<th>Inactive PPAPs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>guttiferone G (0.61), isogarcinol (32), xanthochymol (0.78)</td>
<td>hyperforin, isoanthonchymol</td>
<td>67,75, 76,77</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td>chamuanonge (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>garcinol (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Micrococcus luteus</em></td>
<td>furohyperforin, furohyperforin A, hyperatomarin (1.6), hyperpapuanone (16), papuaforin C (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium B5</em></td>
<td>hyperforin (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Rhodococcus equi</em></td>
<td>methyl clusianone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Sarcina lutea</em></td>
<td>hyperforin (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-sensitive)</td>
<td>chamuanonge (2.31), 7-epi-clusianone (0.6-1.2), cycloxyanthenchomal (25), enervosanone (0.013), furohyperorin A (50), garcinol (0.05-63), guttiferone A (2.4-4.5), guttiferone E, hyperatomarin (1.56), hyperforin (1.0), hyperbione A (0.73-1.4), hyperbione B, hyperbione D, isoanthonchymol (25), makandechnamone, nemorosone (8.1), scrobiculatone A (130), scrobiculatone B (130), xanthochymol (3.1)</td>
<td>furohyperforin, guttiferone G, hyperbione C, isogarcinol, hyperibone A, hyperibone B, hyperibone D, isoxanthochymol, propolone A, pyrohyperforin</td>
<td>65, 66, 67, 68, 71, 72, 73, 74, 75, 76, 77, 78, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89</td>
</tr>
</tbody>
</table>

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**Table 1.1 (continued). Evaluation of PPAPs against gram-positive bacteria.**

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Active PPAPs (MIC in µg/mL)</th>
<th>Inactive PPAPs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-resistant)</td>
<td>chamuangone (0.5),(^a) 7-epi-clusianone (3.7), cycloxanthochymol (25), garcinol (6.3-16),(^a) hyperforin (1.0), hyperibone A,(^d) hyperibone B,(^d) hyperibone D,(^d) isoxanthochymol, (25), peroxysampsone A (62) xanthochymol (25)(^d)</td>
<td>hyperibone C, isogarcinol, peroxysampsone B, phakenetione C 62,75,81, 89,90,91, 92</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>hyperpapuanone (8), papuaforin E (32), propolone A (100)</td>
<td>guttiferone A, papuaforin A, papuaforin C, papuaforin D 64,69,82</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>hyperforin (1.0)</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td><em>Streptococcus gordonii</em></td>
<td>hyperibone A (1.7-3.3)</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td><em>Streptococcus mutans</em></td>
<td>7-epi-clusianone (1.3-2.5),(^a) hyperibone A (3.3-6.6)</td>
<td></td>
<td>63,93,94, 95,96</td>
</tr>
<tr>
<td><em>Streptococcus oralis</em></td>
<td>hyperibone A (1.7-3.3)</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>garcinol (125)</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>hyperforin (1.0)</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td><em>Streptococcus sobrinus</em></td>
<td>hyperibone A (1.7-3.3)</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td>chamuangone (16), garcinol (130)</td>
<td></td>
<td>74,80</td>
</tr>
<tr>
<td><em>Streptomyces aurantiogriseus</em></td>
<td>propolone A (100)</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td><em>Streptomyces chartreensis</em></td>
<td>propolone A (50)</td>
<td></td>
<td>82</td>
</tr>
</tbody>
</table>

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Table 1.1 (continued). Evaluation of PPAPs against gram-positive bacteria.

<table>
<thead>
<tr>
<th>Bacterium</th>
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<th>Inactive PPAPs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptomyces griseus</em></td>
<td>hyperforin (100)</td>
<td></td>
<td>97</td>
</tr>
<tr>
<td><em>Strept. phaeochromogenes</em></td>
<td>propolone A (100)</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td><em>Strept. violochromogenes</em></td>
<td>propolone A (50)</td>
<td></td>
<td>82</td>
</tr>
</tbody>
</table>

\(a\) See text.

\(b\) More active or similar activity as positive control (e.g., vancomycin, chloramphenicol, chlorhexidine).

\(c\) Reported to have activity in a diffusion assay.

\(d\) Reported to have low to moderate activity in an antibiogram assay.

Many PPAPs have been evaluated against bacteria involved in areas beyond nosocomial infections. *B. mesentericus* and *B. stearothermophilus* are responsible for food spoilage (particularly bread),\(^98\) and hyperforin\(^1\) and isoxanthochymol\(^67\) show significant activity against these species, respectively. Potato “ring rot” is a particular devastating infection caused by *Clavibacter michiganensis*,\(^99\) and hyperforin is effective against this bacterium.\(^1\) *B. cereus* is a leading cause of foodborne illness, including “fried rice syndrome.”\(^100\) A variety of PPAPs show activity against this bacterium, including garcinol\(^66,73\) and hyperatomarin.\(^65\) Garcinol is effective against *L. monocytogenes*, a cause of listeriosis.\(^66\)

Given that honeybees will utilize *Clusia* plant species resins in propolis, it is unsurprising that both chamone I and nemorosone were active against *Paenibacillus alvei* and *Paenibacillus larvae*, two honeybee pathogens.\(^56\) Both of these PPAPs have been identified in Caribbean propola.

A variety of PPAPs have also been evaluated against bacteria involved in tooth decay. Typically, bacterial synthesis of extracellular glucans allows for biofilm formation, followed by acidification, plaque


development, and the formation of dental caries.\textsuperscript{101} Hyperibone A is fairly effective against a range of bacteria involved in this process, including \textit{A. naeslundii}, \textit{S. gordonii}, \textit{S. mutans}, \textit{S. oralis}, and \textit{S. sobrinus}. Aside from hyperibone A, 7-\textit{epi}-clusianone also displayed activity against \textit{S. mutans} dental caries.\textsuperscript{94} Analyses of \textit{S. mutans in vitro} have shown that this PPAP inhibits glucosyltransferases B and C, which are involved in glucan synthesis.\textsuperscript{93} In addition, it inhibited F-ATPase activity, preventing acidification without affecting bacterial viability. Using a rodent model of dental caries, treatment with 7-\textit{epi}-clusianone alone or in combination with fluoride produced significant cariostatic effects by reducing the amount of extracellular glucans and disrupting biofilm development without any observed side effects in the treated rats.\textsuperscript{95} These cariostatic effects were attributed to glucosyltransferase inhibition as well as acidification prevention.\textsuperscript{96}

The mechanism of antibacterial activity of PPAPs remains largely unknown. Lipophilicity may play an important role in determining antibacterial activity. PPAPs containing a free \(\beta\)-hydroxyenone functionality at the C2–C4 bridge are more active than similar PPAPs that contain \(\beta\)-alkoxyenone at this site; for instance, garcinol and xanthochymol are more potent antibiotics than isogarcinol and isoxanthochymol, respectively. A series of guttiferone A (\textbf{53}) derivatives have been synthesized with functionalization at the phenolic oxygen atoms (Figure 1.8).\textsuperscript{69} The analogs with \(c\text{Log}P\) (octanol/water) lower than guttiferone A (i.e., \textbf{54}, \textbf{55}, and \textbf{56}) had more potent antibacterial activity than the parent compound across a range of bacteria and were more active than chloramphenicol, used as a positive control. Analogs with higher lipophilicity (i.e., \textbf{57}, \textbf{58}, and \textbf{59}) were less active.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{guttiferone_a_analogs.png}
\caption{Guttiferone A and semisynthetic analogs.}
\end{figure}

Also, it appears that bacterial resistance to PPAPs is orthogonal to that of known antibiotics, which has important implications considering the widespread use of SJW extract to treat depression.\textsuperscript{92} Hyperforin has also been shown to act as an immunomodulatory agent towards bacterial phagocytosis in an \textit{in vitro} model.\textsuperscript{102} At concentrations as low as 1 µg/mL, hyperforin activated human polymorphonuclear neutrophils towards either opsonized or non-opsonized \textit{E. coli}.

<table>
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<tbody>
<tr>
<td>\textit{Citrobacter freundii}</td>
<td>guttiferone G (1.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>isoxanthochymol</td>
<td>67</td>
</tr>
<tr>
<td>\textit{Enterobacter aerogenes}</td>
<td>guttiferone G (1.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>guttiferone G, isoxanthochymol</td>
<td>67</td>
</tr>
<tr>
<td>\textit{Enterobacter cloacae}</td>
<td>guttiferone G (1.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>isoxanthochymol</td>
<td>67</td>
</tr>
<tr>
<td>\textit{Escherichia coli}</td>
<td>cycloxanthochymol (25), enervosanone (0.013), garcinol (25-500), guttiferone E&lt;sup&gt;b&lt;/sup&gt;, hyperforin (1), isogarcinol (25), isoxanthochymol (25)</td>
<td>chamuangone, methyl clusianone, 7-epi-clusianone, hyperforin, furohyperforin A, guttiferone A, guttiferone E, guttiferone G, nemorosone, pyrohyperforin, xanthochymol</td>
<td>1,67,69,71,72, 73,74,75,79, 80,81,83,86, 88,102</td>
</tr>
<tr>
<td>\textit{Helicobacter pylori}</td>
<td>chamuangone (16), garcinol</td>
<td>g</td>
<td>74,103</td>
</tr>
<tr>
<td>\textit{Klebsiella pneumoniae}</td>
<td>isogarcinol (16), xanthochymol (1.6)</td>
<td>garcinol, guttiferone G, isoxanthochymol</td>
<td>67,76,77</td>
</tr>
<tr>
<td>\textit{Morganella morganii}</td>
<td>guttiferone G, isoxanthochymol</td>
<td>g</td>
<td>67</td>
</tr>
<tr>
<td>\textit{Proteus mirabilis}</td>
<td>guttiferone G (1.2)</td>
<td>guttiferone G, isoxanthochymol</td>
<td>1,67</td>
</tr>
<tr>
<td>\textit{Proteus vulgaris}</td>
<td>guttiferone G (1.2)</td>
<td>hyperforin, isoxanthochymol</td>
<td>1,67,69,72, 73,75,77,80, 97</td>
</tr>
<tr>
<td>\textit{Pseudomonas aeruginosa}</td>
<td>enervosanone (0.013), garcinol (0.05-250), isogarcinol (16)</td>
<td>guttiferone A, guttiferone G, hyperforin, isoxanthochymol</td>
<td>1,67,69,72, 73,75,77,80, 97</td>
</tr>
<tr>
<td>\textit{Salmonella enterica}</td>
<td>isogarcinol (5)</td>
<td>guttiferone G, isoxanthochymol</td>
<td>67,77</td>
</tr>
<tr>
<td>\textit{Salmonella typhimurium}</td>
<td>guttiferone A (39)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>guttiferone G, isoxanthochymol</td>
<td>67,69</td>
</tr>
<tr>
<td>\textit{Serratia marcescens}</td>
<td>guttiferone G (1.2)</td>
<td>guttiferone G, isoxanthochymol</td>
<td>67,69</td>
</tr>
<tr>
<td>\textit{Shigella flexneri}</td>
<td>garcinol (31), isogarcinol (16)</td>
<td>guttiferone G, isoxanthochymol</td>
<td>67,77,80</td>
</tr>
<tr>
<td>\textit{Shigella sonnei}</td>
<td>garcinol (63)</td>
<td>chamaruangone</td>
<td>74</td>
</tr>
<tr>
<td>\textit{Yersinia enterocolitica}</td>
<td>garcinol</td>
<td>g</td>
<td>66</td>
</tr>
</tbody>
</table>

\textsuperscript{a} More active or similar activity as positive control (e.g., chloramphenicol, gentamycin).

\textsuperscript{b} Reported to have activity in a diffusion assay.

\textsuperscript{c} See text.

\textsuperscript{102} Brondz, I.; Brondz, A. \textit{J. Biophys. Chem.} 2012, 3, 304-310.

The antiviral activity of several PPAPs has also been evaluated with limited success. Garcinol was completely ineffective against viral infection of VERO cells with an adenovirus, coxsackievirus, herpes simplex virus type 1, measles, poliomyelitis virus type 1, and the Semliki forest virus.\(^8\) Garcinol was however active at preventing long-terminal repeat promoter activity of porcine endogenous retrovirus, which increases the likelihood of pig-to-human viral transplantation.\(^{104}\) Considering that this activity could be replicated using CpG methyltransferase, the antiretroviral activity of garcinol in this case may stem from its ability to act as an epigenetic modulator.

A variety of PPAPs have been evaluated for activity against lentiviruses, particularly human immunodeficiency virus (HIV) strains. HIV infection leads to a progressive failure of the immune system, otherwise known as acquired immunodeficiency syndrome (AIDS), which leaves infected individual susceptible to often fatal opportunistic infections and cancer.\(^{105}\) Similar to PPAP antibacterial activity, a free C2–C4 \(\beta\)-hydroxyenone moiety generally leads to greater activity against HIV pathophysiology. Clusianone decreased HIV infection of 3T3.T4.CCR5 and Jurkat E6-1 cells in a dose-dependent manner compared to control, while its \(O\)-methyl ether was inactive at all concentrations tested.\(^{106}\) Interestingly, \textit{ent}-clusianone was similarly active against both cell lines (its \(O\)-methyl ether was also inactive). Guttiferones A-E were found to have EC\(_{50}\) values in the range of 1-10 \(\mu\)g/mL against the cytopathic effects of CEM-SS cells infected HIV, although viral replication was not inhibited.\(^{16}\) Isoxanthochymol, on the other hand, was in inactive in this assay. It should be noted that these compounds were also found to be noncytotoxic to the CEM-SS cells used in this study. Laxifloranone was also found to be active in this CEM-SS HIV assay (EC\(_{50}\) = 0.62 \(\mu\)g/mL); however, if the free carboxylic acid was blocked, all cytopathic effects were lost.\(^{107}\) In another assay involving C8166 cells,

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aristophenone, clusianone, 7-epi-clusianone, nemorosone, and propolone A potently prevented HIV infection.\textsuperscript{108} Clusianone was the most effective PPAP screened, with an EC\textsubscript{50} of 20 nM, but showed a TC\textsubscript{50} value of 0.1 \mu M in uninfected C8166 cells. The most selective PPAP test was propolone A, with an EC\textsubscript{50} of 0.32 \mu M and a TC\textsubscript{50} value of 5.0 \mu M. Using an MT-4 cell line, guttiferone E, guttiferone O2, and isoxanthochymol did not inhibit HIV replication at subtoxic concentrations.\textsuperscript{109}

Further, it appears that PPAP anti-HIV activity may occur through several mechanisms of action. Plukenetione A and plukenetione D/E were both evaluated using CEMx174-SEAP cells as well as HEK293T cells infected with a simian immunodeficiency virus vector.\textsuperscript{110} While both compounds were found to be cytotoxic in the cell lines employed (ca. 4 \mu M), both were potent below 2 \mu M against lentiviral infection. The activity of plukenetione A was primarily due to its inhibition of reverse transcriptase (IC\textsubscript{50} = 1.75 \mu M), and the activity of plukenetione D/E was due to its interruption of the Akt/PKB signaling cascade. Guttiferone F and 30-epi-isogarcinol were both active in an \textit{in vitro} HIV protease assay, demonstrating that at least some PPAPs might target this enzyme.\textsuperscript{111}

The action of several PPAPs against the highly infectious, epidemic-causing influenza and hepatitis B viruses has also been reported. The hepatitis B virus causes liver inflammation and while a vaccine is available in developed countries, a significant portion of the world population remains vulnerable to infection.\textsuperscript{112} Hypersampsones A-F demonstrated activity against hepatitis B e antigen secretion by infected MS-G2 cells at 10 \mu g/mL, but viral particle replication was not inhibited.\textsuperscript{113}


Influenza, otherwise known as the flu, is a highly infectious disease and particularly dangerous owing to the ability of new strains to cross species barriers, incorporating genes from other mammals and birds.\textsuperscript{114} Guttiferone E, guttiferone O2, and isoxanthochymol have been evaluated against influenza A-infected MDCK cells.\textsuperscript{109} All three PPAPs showed minimum cytotoxic concentrations of 4 µg/mL against these infected cells. However, they were inactive at preventing replication of influenza A subtypes H1N1 and H3N2 and influenza B.

Since several retroviruses use proteases during their reproductive cycle, protease inhibitors may be used in antiretroviral therapies. The serine and cysteine protease inhibition ability of several PPAPs have been evaluated (Table 1.3). While both 7-epi-clusianone and garciniaphenone modestly inhibited protease activity, guttiferone A moderately inhibited all four proteases screened.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
PPAP & Papain & Trypsin & Cathepsin B & Cathepsin G & References \\
\hline
7-epi-clusianone & 19.5 & 20.1 & 73.7-74.1 & 37.4-37.9 & 115,116 \\
\hline
garciniaphenone & 130.8 & 103.5 & 102.0-103.5 & 97.6-98.8 & 115,116 \\
\hline
guttiferone A & 1.9 & 9.4 & 2.1 & 2.7 & 115 \\
\hline
\end{tabular}
\caption{Antiproteolytic activity of several PPAPs.}
\end{table}

The antiparasitic properties of a variety of PPAPs have also been evaluated. Malaria is a highly infectious disease spread by female \textit{Anopheles} mosquitoes and is often caused by the protozoan \textit{Plasmodium falciparum}. There were an estimated 219 million cases of malaria reported in 2010, mostly in sub-Saharan Africa, resulting in 1.2 million deaths.\textsuperscript{117} A variety of PPAPs and semisynthetic analogs of


hyperforin (Figure 1.9) have been evaluated against *P. falciparum* (Table 1.4) and chloroquine-resistant *P. falciparum* (Table 1.5).

**Table 1.4. Evaluation of PPAPs against *Plasmodium falciparum*.

<table>
<thead>
<tr>
<th>PPAP</th>
<th>IC₅₀ (µM)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>adhyperforin HNCy₂</td>
<td>1.4</td>
<td>118</td>
</tr>
<tr>
<td>farifores A</td>
<td>1.7</td>
<td>118</td>
</tr>
<tr>
<td>gutiferone A</td>
<td>0.5-3.0</td>
<td>88,119</td>
</tr>
<tr>
<td>hyperforin HNCy₂</td>
<td>1.5</td>
<td>118</td>
</tr>
<tr>
<td>hyperforin, lithium salt</td>
<td>2.1</td>
<td>118</td>
</tr>
<tr>
<td>isoxanthochymol</td>
<td>2.2-4.5</td>
<td>120,121</td>
</tr>
<tr>
<td>nemorosone</td>
<td>0.4</td>
<td>88</td>
</tr>
<tr>
<td>oxyhyperforin</td>
<td>2.6</td>
<td>118</td>
</tr>
<tr>
<td>pyrohyperforin</td>
<td>8.6</td>
<td>118</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PPAP</th>
<th>IC₅₀ (µM)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>spiranthenone B</td>
<td>32.1</td>
<td>25</td>
</tr>
<tr>
<td>spiranthenone A</td>
<td>8.2</td>
<td>25</td>
</tr>
<tr>
<td>spiranthenone HNCy₂</td>
<td>8.6</td>
<td>118</td>
</tr>
<tr>
<td>spiranthenone, lithium salt</td>
<td>2.7</td>
<td>118</td>
</tr>
</tbody>
</table>


Table 1.5. Evaluation of PPAPs against chloroquine-resistant *P. falciparum*.

<table>
<thead>
<tr>
<th>PPAP</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>coccinone A</td>
<td>4.3</td>
<td>9</td>
</tr>
<tr>
<td>coccinone B</td>
<td>5.5</td>
<td>9</td>
</tr>
<tr>
<td>guttiferone A</td>
<td>3.17</td>
<td>88,122</td>
</tr>
<tr>
<td>7-epi-coccinone B</td>
<td>9.3</td>
<td>124</td>
</tr>
<tr>
<td>coccinone C</td>
<td>9.0</td>
<td>9</td>
</tr>
<tr>
<td>14-deoxy-7-epi-isogarcinol</td>
<td>2.5</td>
<td>124</td>
</tr>
<tr>
<td>coccinone D</td>
<td>7.0</td>
<td>9</td>
</tr>
<tr>
<td>symphonone A</td>
<td>2.8</td>
<td>124</td>
</tr>
<tr>
<td>coccinone E</td>
<td>4.9</td>
<td>9</td>
</tr>
<tr>
<td>symphonone B</td>
<td>3.3</td>
<td>124</td>
</tr>
<tr>
<td>coccinone F</td>
<td>17.0</td>
<td>9</td>
</tr>
<tr>
<td>symphonone C</td>
<td>2.6</td>
<td>124</td>
</tr>
<tr>
<td>phomone G</td>
<td>19.2</td>
<td>9</td>
</tr>
<tr>
<td>symphonone D</td>
<td>2.1</td>
<td>124</td>
</tr>
<tr>
<td>isogarcinol</td>
<td>3.5</td>
<td>9,123</td>
</tr>
<tr>
<td>symphonone E</td>
<td>2.7</td>
<td>124</td>
</tr>
<tr>
<td>7-epi-garcinol</td>
<td>2.1</td>
<td>124</td>
</tr>
<tr>
<td>symphonone F</td>
<td>3.2</td>
<td>124</td>
</tr>
<tr>
<td>garcinol</td>
<td>12.6</td>
<td>9</td>
</tr>
<tr>
<td>symphonone G</td>
<td>2.1</td>
<td>124</td>
</tr>
<tr>
<td>14-deoxygarcinol</td>
<td>37.2</td>
<td>9,124</td>
</tr>
<tr>
<td>symphonone H</td>
<td>3.0</td>
<td>124</td>
</tr>
<tr>
<td>7-deoxygarcinol</td>
<td>37.2</td>
<td>9</td>
</tr>
<tr>
<td>symphonone I</td>
<td>6.7</td>
<td>124</td>
</tr>
</tbody>
</table>

Nemorosone and oxidized hyperforin analog 64 were most active against chloroquine-sensitive *P. falciparum*, and cycloxanthochymol and symphonones D and G were the most active against chloroquine-resistant *P. falciparum*. Nemorosone was found to be as active as chloroquine against *P. falciparum*.88 Amongst the hyperforin derivatives, a limited degree of structural modification of the bicyclo[3.3.1]nonane core does not lead to significant changes in potency; analogs with C4 oxygen atom functionalization, with a quaternary center at C3, or hydrogenation of the pendant olefins had similar activity to that of hyperforin.118 The only inactive derivatives screened were 61 and 63. A semisynthetic analog of guttiferone A, 67, was found to be more active than the parent PPAP (Figure 1.10).119 Also noteworthy is the potency trend within the coccinone and symphonone families of PPAPs. Those that contain a free C2–C4 β-hydroxyenone (i.e., coccinones F-H) were significantly less potent than the other members, which bear a tetrahydropyran ring containing the C4 oxygen atom.


Unfortunately, many PPAPs that exhibited antimalarial properties were found to be fairly cytotoxic. Adhyperforin, guttiferone A, hyperforin, isoxanthochymol, octahydrohyperforin (66), and 67 had cytotoxicity concentrations comparable to their antimalarial activity, but furohyperforin, and oxyhyperforin, and 62 were marginally less cytotoxic. The only PPAPs screened for cytotoxicity that were significantly more potent than cytotoxic were spiranthenones A and B.

In addition, several PPAPs have been evaluated for possible treatment of leishmaniasis. This disease is caused by a variety of different protozoa belonging to the genus Leishmania, and is transmitted through the bite of sand flies from the subfamily Phlebotominae.125 During sand fly feeding, Leishmania promastigotes enter the body. Upon macrophage phagocytosis, amastigotes are produced and proliferate. Leishmaniasis can take several forms, the most common of which involves skin sores, which appear weeks to months after initial exposure. If the parasite migrates to vital organs, visceral leishmaniasis may occur, which is the second largest fatal parasitic disease in the world, after malaria. Despite its prevalence, especially in developing countries, very few treatment options are available. A summary of PPAPs evaluated for leishmanicidal activity is found in Table 1.6.

Table 1.6. Evaluation of PPAPs against various *Leishmania* species.

<table>
<thead>
<tr>
<th><em>Leishmania</em> species</th>
<th>Life-cycle phase</th>
<th>Evaluated PPAPs (IC$_{50}$ in µM)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. amazonensis</em></td>
<td>amastigotes</td>
<td>7-epi-Clusianone (3.2),$^a$ Garcia phenone (inactive), guttiferone A (4.9)</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>promastigotes</td>
<td>guttiferone A (15.6-30.1), nemorosone (11.2)</td>
<td>88,126,127</td>
</tr>
<tr>
<td><em>L. donovani</em></td>
<td>amastigotes</td>
<td>garcinol (0.82), guttiferone A (0.16),$^a$ guttiferone F (0.20),$^a$ isogarcinol (0.33)$^a$</td>
<td>128</td>
</tr>
<tr>
<td><em>L. infantum</em></td>
<td>promastigotes</td>
<td>guttiferone A (13.5), iso xanthochymol (2.0), nemorosone (32.9)</td>
<td>88,121</td>
</tr>
</tbody>
</table>

$^a$ More active or similarly active as a positive control (e.g., amphotericin B or miltefosine).

In general, leishmanicidal activity is inversely related to hydrophobicity. 7-epi-Clusianone was one of the most active PPAPs screened, against both the amastigote and promastigote forms of the New World protozoan *L. amazonensis*, and it was found to be more potent than amphotericin B in both cases.$^{126}$ Interestingly, garciniph enone was active against the promastigote form of this *Leishmania* species but inactive against the amastigote form. While iso xanthochymol was fairly potent against *L. infantum* amastigotes, it was found to be fairly cytotoxic towards MRC-5 cells.$^{121}$ Guttiferones A and F and isogarcinol were the most effective leishmanicidal PPAPs screened against the Old World pathogen *L. donovani*.$^{128}$ At 8.0 µM concentration, both guttiferone A and F inhibited parasite growth by 98%. Since guttiferone A was shown to be relatively noncytotoxic (CC$_{50}$ = 17.8 µM in murine peritoneal macrophages),$^{126}$ it may be a lead structure in the development of a treatment for Old World leishmaniasis.

A variety of PPAPs has also been evaluated against trypanosomiasis, another parasitic protozoan disease. There are two major forms of trypanosomiasis: (1) African trypanosomiasis, otherwise known as

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sleeping sickness, and (2) Chagas disease. As the name suggests, African trypanosomiasis is most prevalent in sub-Saharan Africa, and it is caused by the protozoa of *Trypanosoma brucei*, transmitted by the tsetse fly. Chagas disease is the most common form of trypanosomiasis in Latin America, in which *Trypanosoma cruzi* is transmitted by a variety of bloodsucking bugs, such as *Rhodnius prolixus* and *Triatoma brasiliensis*.

A summary of the effects of several PPAPs on the viability of trypanosomiasis protozoa is found in Table 1.7. Guttiferone A, isoxanthochymol, and nemorosone were found to be moderately active against both *T. brucei* and *T. cruzi*. As mentioned earlier, isoxanthochymol is cytotoxic against MRC-5 cells at a concentration similar to its concentration for effective trypanocidal outcomes. Guttiferone A and 67 suffer from similar problems. One study established that guttiferone A had MC\textsubscript{100} values against *T. cruzi* epimastigotes and trypanomastigotes of 99.5 µM and 82.9 µM, respectively, and these values were well above the 10.7 µM IC\textsubscript{50} value of the PPAP against murine peritoneal macrophages. 7-epi-Clusianone was also evaluated against *T. cruzi*; however, it was found to be ineffective *in vivo* in infected mice. Interestingly, nemorosone was also found to be non-cytotoxic against the predominant insect vector of Chagas disease, *Rhodnius prolixus*, but it displayed dose-dependent anti-molting effects.

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Table 1.7. Evaluation of PPAPs against *Trypanosoma brucei* and *T. cruzi*.

<table>
<thead>
<tr>
<th>PPAP</th>
<th>IC₅₀ (µM)</th>
<th><em>T. brucei</em></th>
<th><em>T. cruzi</em></th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>guttiferone A</td>
<td>3.0-13.5</td>
<td>11.8</td>
<td>88,119</td>
<td></td>
</tr>
<tr>
<td>isoxanthochymol</td>
<td>1.9</td>
<td>2.7</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>nemorosone</td>
<td>17.5</td>
<td>12.5</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>spiranthenone A</td>
<td>n.d.</td>
<td>inactive</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>spiranthenone B</td>
<td>n.d.</td>
<td>211.3</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>2.1</td>
<td>n.d</td>
<td>119</td>
<td></td>
</tr>
</tbody>
</table>

7-epi-Clusianone has also been evaluated for its molluscicidal effects upon *Biomphalaria glabrata*, a Brazilian freshwater snail and known carrier of *Schistosoma mansoni*, one of several parasitic worms responsible for schistosomiasis. However, this PPAP was found to be inactive in the snail toxicity assay.

The antifungal properties of various PPAPs have also been explored, which is summarized in Table 1.8. In general, the PPAPs evaluated were much less effective against fungi than against bacteria, viruses, and parasites, and generalizations about structure-activity relationships cannot be made. Guttiferone A was found to be most active across a wide range of fungi, including several *Candida* species responsible for infections in immunocompromised individuals, the cryptococcosis-causing *Cryptococcus neoformans*, and two *Trichophyton* species involved in tinea-type skin infections. Two semisynthetic guttiferone A derivatives, 54 and 57, were generally more active than the parent PPAP, and other semisynthetic analogs, namely 55, 56, 58, and 59, were less active. Unlike antibacterial activity, cLogP values did not correlate with fungicidal activity. Isogarcinol and pyrohyperforin were found to be active against *Candida albicans*, the most common pathogen involved in yeast infections of the genitals and oral cavity. Xanthochymol was found to be active in a dose-dependent manner against *Phomopsis viticola*, a leading cause of grapevine dead arm (grape canker). Treatment with xanthochymol in the 1-10 µg/mL range caused motility inhibition and lysis of *Phomopsis viticola* zoospores. Only a few other PPAPs have been evaluated against phytopathogenic fungi (i.e., *Aspergillus flavus*, *Aspergillus niger*,...
Cladosporium cucumerinum, and Fusarium avenaceum), and while garcinol has some phytopathogenic fungicidal activity, it would be interesting to see if other PPAPs exhibit activity against these fungi.

### Table 1.8. Evaluation of PPAPs against various fungi.

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Active PPAPs (MIC in µg/mL)</th>
<th>Inactive PPAPs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus flavus</td>
<td>garcinol (100)</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Aspergillus niger</td>
<td>garcinol (100)</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>guttiferone A (40), isogarcinol (64), pyrohyperforin (25)</td>
<td>7-epi-clusianone, furohyperforin, garcinol, guttiferone A, guttiferone E, guttiferone G, hyperforin, isoaxanthochymol, nemorosone, xanthochymol</td>
<td>67,69, 71, 75, 76, 77, 80, 86, 88</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>guttiferone A (5.0)</td>
<td>guttiferone G, isoaxanthochymol</td>
<td>67,69</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>isogarcinol (64)</td>
<td></td>
<td>67,69, 77</td>
</tr>
<tr>
<td>Candida lusitaniae</td>
<td></td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>guttiferone A (20.0)</td>
<td></td>
<td>69</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>guttiferone A (20.0)</td>
<td>garcinol</td>
<td>69,80</td>
</tr>
<tr>
<td>Cladosporium cucumerinum</td>
<td>hyperevolutin A, hyperevolutin B</td>
<td></td>
<td>133</td>
</tr>
<tr>
<td>Cladosporium sphaerospermum</td>
<td>7-epi-clusianone</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>guttiferone A (5.0), isogarcinol (64)</td>
<td></td>
<td>69,77,80</td>
</tr>
<tr>
<td>Fusarium avenaceum</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Microsporum gypseum</td>
<td>guttiferone A (100)</td>
<td>hyperforin</td>
<td>69</td>
</tr>
<tr>
<td>Microsporum canis</td>
<td>garcinol (100)</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Mucor plumbeus</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Penicillium chrysogenum</td>
<td>hyperforin</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Phomopsis viticola</td>
<td>xanthochymol</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Trichophyton ajelloi</td>
<td>isogarcinol (64)</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>Trichophyton interdigitale</td>
<td>garcinol (100), guttiferone A (20.0)</td>
<td></td>
<td>69,76,80</td>
</tr>
<tr>
<td>Trichophyton rubrum</td>
<td>guttiferone A (11.8), isogarcinol (32)</td>
<td></td>
<td>77,88</td>
</tr>
</tbody>
</table>

* Value reported is IC₅₀ (in µg/mL).

*b See text.

### Antioxidant and Anti-inflammatory Activity

The antioxidant properties of PPAPs have also been explored in a variety of contexts, both in vitro and in vivo. A summary of PPAP performance in various in vitro antioxidant assays is found in Table 1.9. Unsurprisingly, PPAPs that bear a 3,4-dihydroxybenzoyl group at the C3 position were found to be the most active at scavenging radical or reactive oxygen species in these assays. If one of the

phenolic hydroxyl groups is alkylated, as in the 13-\(O\)-methyl ethers of garcinol and isogarcinol, antioxidant potential is lost.\textsuperscript{14} The presence of a C2–C4 \(\beta\)-hydroxyenone was also important but not essential given the strong antioxidant properties of PPAPs such as guttiferone K2, isogarcinol, and isoxanthochymol. A comparison of nemorosone and its \(O\)-methyl ether illustrates the significance of C2–C4 \(\beta\)-hydroxyenone functionality.\textsuperscript{146}

<table>
<thead>
<tr>
<th>PPAP</th>
<th>Antioxidant activity\textsuperscript{a,b}</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>acuminophenone A</td>
<td>DPPH (1.8), ABTS (3.4), TEAC (7.8)</td>
<td>134</td>
</tr>
<tr>
<td>aristophenone</td>
<td>DPPH (125)</td>
<td>135</td>
</tr>
<tr>
<td>clusianone</td>
<td>DPPH (inactive)</td>
<td>14</td>
</tr>
<tr>
<td>(\beta)-epi-clusianone</td>
<td>DPPH (inactive), ABTS (inactive)</td>
<td>14, 136, 137</td>
</tr>
<tr>
<td>garcinnelliptone A</td>
<td>DPPH (inactive), ABTS (inactive), XO (inactive)</td>
<td>138</td>
</tr>
<tr>
<td>garcinnelliptone C</td>
<td>XO (59.9)</td>
<td>139</td>
</tr>
<tr>
<td>garcinnelliptone F</td>
<td>ABTS (inactive), XO (inactive)</td>
<td>138</td>
</tr>
<tr>
<td>garcinnelliptone P</td>
<td>XO (48.1)</td>
<td>140</td>
</tr>
<tr>
<td>garcinnelliptone S</td>
<td>DPPH (inactive), ABTS (inactive), XO (inactive)</td>
<td>138</td>
</tr>
<tr>
<td>garcinol</td>
<td>DPPH (10.2), ABTS (3.4), TEAC (7.8)</td>
<td>139</td>
</tr>
<tr>
<td>garcinol 13-(O)-methyl ether</td>
<td>DPPH (inactive)</td>
<td>14</td>
</tr>
<tr>
<td>garsubellin A</td>
<td>DPPH (inactive), ABTS (inactive), XO (inactive)</td>
<td>138</td>
</tr>
</tbody>
</table>


Table 1.9 (continued), *In vitro* PPAP antioxidant activity.

<table>
<thead>
<tr>
<th>PPAP</th>
<th>Antioxidant activity&lt;sup&gt;b&lt;/sup&gt;</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
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<sup>a</sup> Assay abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); XO, xanthine oxidase; TEAC, Trolox equivalent antioxidant capacity.

<sup>b</sup> Values reported in parentheses refer to IC<sub>50</sub> (in µM) for DPPH, ABTS, and XO assays, and Trolox equivalents for TEAC assay.

Other than the results presented in Table 1.9, several other PPAPs have been evaluated for antioxidant properties *in vitro*. Using an HPLC-DPPH assay system, hyperforin and adhyperforin were both identified as very active antioxidant components of alcoholic *Hypericum perforatum* extracts.<sup>147</sup> Similar results were obtained using partially purified HPLC fractions containing hyperforin, adhyperforin, hyperfirin, and adhyperfirin across a variety of tests, including the DPPH assay, FRAP, superoxide anion

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test, NO radical inhibition assay, and the lipid peroxidation assay. A mixture of scrobiculatones A and B was found to be active in the DPPH assay. Guttiferone K and semsinone A were both active in the DPPH, ORAC, and anti-AGEs inhibition assays.

The reactions of garcinol with various radical systems were studied in order to further understand how this PPAP behaves as an antioxidant. Exposure of an acetone solution of garcinol (7) to DPPH in the dark afforded two oxidative cyclization products, 68 and 69 (Scheme 1.11a). Coincidentally, these two compounds were later isolated from Garinia nuijiangensis and named nuijiangfolin A and B. A possible mechanistic manifold for this transformation is shown in Scheme 1.11b. A resonance-stabilized enoxy radical 70 formed via hydrogen atom abstraction may cyclize onto the electron-rich aromatic ring to form 71, which after tautomerization provides 68 and 69. The formation of these two oxidation products from garcinol provides evidence that the antioxidant properties of certain PPAPs may be derived from the 3,4-dihydroxybenzoyl and the C2–C4 β-hydroxyenone functional groups. Similar results were observed when a heated acetone solution of garcinol (7) was exposed to AIBN, affording hydroperoxide 72 and isogarcinol (8) as well as 68 and 69 (Scheme 1.11c). The formation of 72 likely involves radical 6-endo-trig cyclization of the enoxy radical 70 onto the C1 prenyl group, followed by trapping with molecular oxygen. The formation of isogarcinol may not involve radical intermediates, given that its heat-mediated formation from garcinol has been previously reported.

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Scheme 1.11. (a) The reaction of garcinol (7) with DPPH and (b) a possible mechanism, and (c) the reaction of garcinol (7) with AIBN.

Several PPAPs have been evaluated in cell-based assays for antioxidant activity. A St. John’s wort extract with standardized hyperforin content showed inverse dose-dependent superoxide inhibition in a XO-human placental vein assay. In other words, the most concentrated sample had a pro-oxidant effect, while the most dilute sample had the largest free radical inhibitory effect in this model, showing nearly an 80% decrease compared to control. The radical scavenging ability of hyperforin was further explored in another study involving skin exposed to solar simulated radiation. Hyperforin was found to be more effective than Trolox (and without displaying phototoxicity) in a H2DCFDA irradiation assay involving HaCaT cells, with an EC50 value of 0.7 μM. A cream containing 1.5% hyperforin was then


formulated and determined to have a radical scavenging ability of $200 \cdot 10^{14}$ radicals/mg, corresponding to a radical protection factor of 39 (comparable to a good sunscreen). After demonstrating that the cream reduced radical formation on irradiated porcine ear skin \textit{ex vivo}, it was applied to 20 volunteers in a randomized, double-blind, vehicle-controlled clinical study. The cream was well tolerated and successfully reduced ultraviolet B-induced erythema. A later study also showed that a hyperforin-rich skin cream provided protection from radical formation in a 9-person study. These results contrast an earlier study, which found that hyperforin was a significant phototoxic component of St. John’s wort extracts in an assay involving photosensitized peroxidation of linoleic acid.

Several studies of the antioxidant properties of garcinol have been reported. Aside from being almost three times more active by weight than vitamin E in the DPPH assay, it also displayed moderate activity against linoleic acid peroxidation and suppressed protein glycation in an \textit{in vitro} bovine serum albumin/fructose system. Its free radical scavenging ability was also validated in Fenton reaction and H$_2$O$_2$/NaOH/DMSO systems, and \textit{in vivo} by preventing indomethacin-induced acute gastric ulceration in rats through oral administration. Garcinol was also shown to protect DNA and neurons from radical-induced damage. With an IC$_{50}$ value of 0.32 µM, garcinol prevented pUC-19 supercoiled DNA from strand breakage under Fenton reaction conditions.

While reactive oxygen species (ROS) are produced normally through metabolism or via immune system oxidative burst, if they accumulate too quickly, cell membrane damage may occur with the concomitant formation of mutagenic or carcinogenic lipid peroxides. Table 1.10 summarizes the activity of a variety of PPAPs against ROS formation in polymorphonuclear leukocytes (PMNs), rat

\begin{footnotes}
\end{footnotes}
neutrophils, and human neutrophils stimulated with N-formylmethionine leucyl-phenylalanine (fMLP) alone or in combination with cytochalasin B (CB), opsonized zymosan (OZ), or phorbol 12-myristate 13-acetate (PMA). The garcimultiflorone family and 13,14-didehydroxyisogarcinol were found to be potent inhibitors of ROS generated from PMNs stimulated with fMLP/CB.\textsuperscript{15} 7-epi-Clusianone also displayed dose-dependent decrease in ROS in PMNs stimulated with either fMLP or PMA.\textsuperscript{137} Most other PPAPs were either inactive or displayed marginal antioxidant activity, with the only exception being hyperforin, having an IC\textsubscript{50} value of 1.8 \(\mu\text{M}\) against fMLP-stimulated PMNs.\textsuperscript{166} Later studies on hyperforin revealed that its ROS inhibition activity was lost when the PMNs were treated with PMA.\textsuperscript{167} This, combined with the observation that hyperforin decreased Ca\textsuperscript{2+} levels in resting PMNs and caused a decreased Ca\textsuperscript{2+} response to fMLP, led the authors to conclude that hyperforin targeted components of G protein signaling cascades involved in both Ca\textsuperscript{2+} homeostasis and inflammatory response. The antioxidant properties garcinielliptone FC have also been investigated.\textsuperscript{162} Treatment of male mice with 2 mg/kg garcinielliptone FC caused a statistically significant increase in the activity of superoxide dismutase but not catalase.

**Table 1.10. Evaluation of PPAPs against ROS generation.**

<table>
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<tr>
<th>PPAP</th>
<th>Cell line</th>
<th>Stimulation</th>
<th>IC50 ((\mu\text{M}))</th>
<th>References</th>
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<th>PPAP</th>
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Several PPAPs have been evaluated against markers of inflammatory response aside from superoxide burst, such as the release of histamine, elastase, lysozyme, and β-glucuronidase as well as nitrite accumulation (Table 1.11). Given the short half-life of nitric oxide, nitrite accumulation may be used to gauge its release during inflammatory response. The garcimultiflorone family of PPAPs displayed fairly potent activity against elastase release in PMNs.\textsuperscript{15} However, to a large degree, the garcinielliptones showed little or no effect on these inflammatory response markers.


activated protein kinase 2 (MAPKAPK-2), a serine/threonine kinase involved in inflammation-response

<table>
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<tr>
<th>PPAP</th>
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<th>Measured outcome</th>
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The effects of PPAPs on a variety of other markers of inflammation have been explored. Sundaicumones A and B were found to be weak activators of glucocorticoid receptor, which inhibits pro-inflammatory transcription factors. ¹⁶⁸ Guttiferones O and P inhibited mitogen-activated protein kinase activated protein kinase 2 (MAPKAPK-2), a serine/threonine kinase involved in inflammation-response.

transcriptional regulation, both with an IC₅₀ value of 22.0 µM.¹⁶⁹ Hyperforin has also been evaluated in several anti-inflammatory assays. In human primary hepatocytes and intestinal epithelia, hyperforin induced interleukin-8 (IL-8) and intercellular adhesion molecule-1 (ICAM-1) expression.¹⁷⁰ These effects were found to be dependent on extracellular signal-regulated kinase (ERK) 1 and 2 but independent of pregnane X receptor (PXR) and nuclear factor kappa B (NF-κB). The dicyclohexylammonium salt of hyperforin also prevented fMLP-induced PMN chemotaxis and tissue infiltration in a dose-dependent manner (IC₅₀ = 1 µM).¹⁷¹ The authors found that this was caused by decreased expression of the adhesion molecule integrin alpha M (ITGAM) and inhibition of matrix metalloproteinase-9 (MMP-9) activation. Subsequent studies found that hyperforin downregulated other markers in activated T cells (e.g., IFN-γ, T-box, CXCR3) and was successfully evaluated in a murine model of experimental allergic encephalomyelitis, an autoimmune disease of the central nervous system.¹⁷²

Hyperforin, garcinol, garcinielliptone FC, and guttiferone K were all found to potently inhibit lipid oxidation using the thiobarbituric acid reactive species (TBARS) assay. Hyperforin prevented low-density lipoprotein (LDL) oxidation in Cu²⁺- and nonmetal-mediated oxidation at concentrations as low as 2.5 µM.¹⁷³ Garcinol prevented LDL oxidation mediated by both Fe²⁺ (IC₅₀ = 0.42 µM) and AAPH (IC₅₀ = 1.2 µM).¹⁷⁴ This was more potent than vitamin E in both assays. Garcinielliptone FC completely inhibited lipid peroxidation in the TBARS assay at 8.3 µM, and had an IC₅₀ below 2 µM.¹⁷⁵ Garcinol and

guttiferone K were found to protect human blood platelets from oxidative damage due to peroxynitrite, but these PPAPs did not prevent protein nitration.\textsuperscript{176}

Several PPAPs have been evaluated for their ability to inhibit general pro-inflammatory response. Garcinol displayed a neuroprotective effect in rat astrocytes exposed to LPS.\textsuperscript{141} Under normal circumstances, LPS exposure causes an inflammatory response including iNOS and COX-2 induction, which correlates with neurodegenerative processes. It is believed that garcinol not only behaves as an antioxidant but also inhibits this inflammatory response. In rats with carrageenan-induced paw edema and peritonitis, 7-epi-clusianone reduced inflammation in a dose-dependent manner, with oral doses of 5, 10, and 15 mg/kg.\textsuperscript{177} Topical treatment of the dicyclohexylammonium salt of hyperforin as well as adhyperforin were similarly effective at the reduction of murine croton oil-induced ear edema as indomethacin, with EC\textsubscript{50} values of 0.25 and 0.30 μmol/cm\textsuperscript{2}.\textsuperscript{178} In an 8-person clinical trial, the anti-inflammatory effects of hyperforin were found to at least be partly due to the ability of this PPAP to reduce the epidermal cells’ ability to recruit alloreactive T cells.\textsuperscript{179} These effects were similar to solar-simulated radiation, a known immunosuppressive agent. Hyperforin treatment was also well tolerated and was cosmetically acceptable. When epidermal cells were treated with hyperforin \textit{in vitro}, a dose-dependent reduction of T cell and PMN proliferation was observed. As a result, hyperforin therapy may be a possible treatment option for chronic atopic dermatitis or other skin conditions involving overreactive inflammatory response.

Phagocyte activation of iNOS (inducible nitric oxide synthase) causes the release of nitric oxide; however, excessive NO production may lead to neurodegenerative disease. Garcinielliptone FC was


found to be a potent scavenger of NO in a sodium nitroprusside decomposition assay. Hyperforin inhibited LPS-induced NO release in the 0.25-0.75 µM range in murine microglia by decreasing iNOS expression. These effects correlated with suppression of the activated states of NF-κB and eAMP response element-binding protein (CREB). Prior results had suggested hypericin, and not hyperforin, was the component of St. John’s wort extracts responsible for inhibition of NF-κB. In rat aorta at concentrations below 10 µM, 7-epi-clusianone induced vasodilation via NO release. Interestingly, at concentrations above 10 µM, vasoconstriction was observed and was dependent on eicosanoid production.

In addition, several PPAPs have been found to directly inhibit or modulate key proteins involved in the biosynthesis of pro-inflammatory eicosanoids. 5-Lipoxygenase (5-LO) catalyzes the oxidation of arachidonic acid to arachidonic acid 5-hydroperoxide, an intermediate in the biosynthesis of leukotrienes. Arachidonic acid can also be oxidized by cyclooxygenases 1 and 2 (COX-1 and COX-2) to prostaglandin H₂, the progenitor to prostanoids, prostacyclin, and thromboxanes. While several classes of drugs have been developed to broadly inhibit the action of these enzymes, the discovery and development of specific inhibitors of each of these pro-inflammatory enzymes is still actively pursued.

Several PPAPs are reported to be sub-micromolar inhibitors of proteins involved in eicosanoid biosynthesis. Early studies with hyperforin established that it is an uncompetitive inhibitor of both 5-LO

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and COX-1. Hyperforin inhibited purified 5-LO with an IC$_{50}$ value of 90 nM and had an IC$_{50}$ in the range of 1-2 µM in Ca$^{2+}$ ionophore-stimulated (PMNs), which was comparable to the known 5-LO inhibitor zileuton. COX-1 activity was also inhibited in stimulated platelet cells, with IC$_{50}$ values ranging from 0.3 to 3 µM depending on the method of stimulation. No COX-2 inhibition activity was observed. When RAW264.7 mouse macrophages and LPS-stimulated human blood samples were exposed to hyperforin, prostaglandin E$_2$ biosynthesis was inhibited. Aside from 5-LO and COX-1, hyperforin acts as an inhibitor of membrane-associated prostaglandin E synthetase-1 (mPGES-1) with an IC$_{50}$ value of 1 µM. Further, hyperforin may have a unique pharmacological profile compared to other known 5-LO inhibitors. When carrageenan-treated rats were treated with hyperforin (4 mg/kg, intraperitoneal), suppression of leukotriene B$_4$ was observed; however, when 5-LO point mutations were introduced (W13A-W75A-W102A) or phosphatidylcholine was present, the inhibitory activity of hyperforin was abolished. Other 5-LO inhibitors of different structural classes, ZM230487 and BWA4C, continued to inhibit leukotriene B$_4$ production in the presence of the modifications.

Given the distinctive nature of hyperforin 5-LO inhibition and moderate potency, a series of semisynthetic hyperforin analogs were evaluated against 5-LO in PMNs. Overall, oxidation of hyperforin produced more active 5-LO inhibitors, and alkylation or acylation produced less active 5-LO inhibitors (Table 1.12, Figure 1.11). The most active analog found in the study was oxyhyperforin, which had an IC$_{50}$ value of 40 nM. Interestingly, analogs featuring a C9 carbinol were similarly active to those

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containing a C9 ketone functionality. Aside from hyperforin and its derivatives, garcinol also displayed inhibitory activity against various enzymes involved in eicosanoids. Garcinol was found to be most active against 5-LO (IC$_{50}$ = 0.1 μM), mPGES-1 (IC$_{50}$ = 0.3 μM), and COX-1 (IC$_{50}$ = 12 μM) but showed no activity against COX-2.192

Table 1.12. 5-LO inhibition activity of semisynthetic hyperforin analogs.191

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Figure 1.11. Semisynthetic hyperforin analogs.

Aside from being an inhibitor of several enzymes involved in eicosanoid biosynthesis, garcinol also acts as an anti-inflammatory agent by blocking pro-inflammatory protein expression. In a study using LPS-activated RAW264.7 cells, it was found that garcinol (at 1 μM concentration) inhibited the phosphorylation of cytosolic phospholipase A$_2$ (cPLA$_2$).193 This phosphorylation activates cPLA$_2$, which hydrolyzes phospholipids at the sn-2 position, releasing arachidonic acid. On the other hand, hyperforin

was found to induce phosphorylation of cPLA2 with its activity more pronounced in cells with depleted intracellular Ca$^{2+}$. The authors proposed that hyperforin inserts itself into lipid membranes and enables cPLA2 to access phospholipids and thus release arachidonic acid. Along with cPLA2 inhibition, garcinol reduced iNOS expression and NO release in RAW264.7 cells at 1 µM concentration, presumably through inhibition of signal transducer and activator of transcription-1 (STAT-1) or NF-κB, master transcriptional regulators. Isogarcinol and semisynthetic garcinol derivatives 68 and 69 had similar effects to garcinol across these assays but were not as active. Akin to garcinol, hyperforin has been shown to downregulate both STAT-1 and NF-κB in rat and human pancreatic islets in the 0.5-5 µM range, preventing the cytokine-induced apoptosis of insulin-secreting β-cells, a cause of type 1 diabetes.

7-epi-Clusianone and guttiferone A have also been evaluated for anti-inflammatory and antioxidant properties in other contexts. 7-epi-Clusianone inhibited carbachol- and histamine-induced guinea pig ileum spasms in a dose-dependent manner, with EC$_{50}$ values in the 2-4 µM range. It also prevented allergen-induced contraction of guinea pig trachea at 10 µM, and these effects were replicated in an in vivo mouse model at 25-100 mg/kg oral dosing. The effects of 7-epi-clusianone were blocked by the addition of nitric oxide synthase inhibitors as well as cation channel blockers. Guttiferone A dose-dependently reduced the number of ulcerative lesions in a mouse model and was found to be as effective as omeprazole. This indicates that guttiferone A may impart gastroprotective effects.

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Chemotherapeutic Activity

Many PPAPs have been evaluated for their antiproliferative activity against a variety of cancer cell lines. Overall, many PPAPs possess the ability to kill or modify cancer cells to a moderate extent, and a variety of underlying mechanisms have been explored. In many instances, apoptosis activation leads to cell death. A summary of the antiproliferative activity of PPAPs as well as several semisynthetic PPAP derivatives (Figure 1.12) against a variety of cancer cell lines is found in Table 1.13.

<table>
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<tr>
<th>PPAP</th>
<th>Cancer cell type</th>
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<th>IC_{50} (µM)</th>
<th>References</th>
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Table 1.13 (continued). Evaluation of PPAPs against cancer cell proliferation.

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Table 1.13 (continued). Evaluation of PPAPs against cancer cell proliferation.

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Table 1.13 (continued). Evaluation of PPAPs against cancer cell proliferation.

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Table 1.13 (continued). Evaluation of PPAPs against cancer cell proliferation.

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a Antiproliferative activity was observed, but no IC_{50} value was reported.

b IC_{50} value after 48 h of incubation with the compound.

c IC_{50} value after 72 h of incubation with the compound.

Figure 1.12. Semisynthetic PPAP analogs tetrahydrohyperforin (76) and octahydroxanthochymol (77).

Overall, the presence of a relatively acidic hydroxyl group (either an enolic or phenolic –OH) is imperative for antiproliferative activity. A common feature of inactive PPAPs found in Table 1.13 is the presence of a tetrahydrofuran ring encompassing the C4 (or C2) enolic oxygen atom, such as garciniielliptone I, guttiferone R, hyperibone B, and propolone D. These PPAPs lack any phenolic hydroxyl functionality, as well. Interestingly, while hyperforin O-acetate maintains moderate activity across a variety of cell lines, octahydrohyperforin O-acetate is inactive.\(^{231}\) A decrease in the activity of nemorosone as its O-methyl ether also demonstrates the importance of this free acidic hydroxyl group to antiproliferative activity.\(^{146}\) In addition to the PPAPs listed in Table 1.13, the tin complex of 7-epi-
clusianone [SnClPh₃(7-epi-clusianone)], has been evaluated against HN-5 cells, however with inconclusive results.²⁵⁰

In some instances, the underlying mechanisms by which PPAPs affect cancer cells have been explored. Several studies have provided evidence that hyperforin influences cancer survival and proliferation through a variety of pathways.²⁵¹ An early study by Schempp and coworkers with MT-450 cells established that hyperforin induces apoptosis through caspase activation.²²⁸ The addition of the nonspecific caspase inhibitor Z-VAD-FMK prevented hyperforin-induced apoptosis. Aside from caspase activation, hyperforin also caused a loss of the mitochondrial transmembrane potential. Given that this latter effect occurred in the presence of Z-VAD-FMK and that hyperforin treatment induced cytochrome c release from isolated mitochondria, the authors concluded that hyperforin’s ability to increase mitochondrial membrane permeability caused caspase activation and ultimately cell death through apoptosis. Similar results were found in a later study using K562 cells treated with hyperforin·HNCy₂.²³³

In leukemia cells, hyperforin upregulates the pro-apoptotic regulator Noxa in addition to caspase mediated pathways. In cells taken from CLL patients, Noxa upregulation was observed upon treatment with hyperforin, leading to apoptosis.²⁵² siRNA-mediated Noxa silencing partially reduced the effects of hyperforin in these cells. Studies involving various AML cell lines also demonstrated Noxa-induced apoptosis.²⁵³ In U937 cells, Noxa upregulation was accompanied with downregulation of anti-apoptotic Bcl-2, an increase in mitochondrial permeability, and inhibition of the kinase activity of the survival factor PKB.


In addition to acting as a pro-apoptotic, hyperforin also acts as an anti-angiogenic agent and an inhibitor of cancer metastasis. In an *in vitro* assay involving BAE cells, treatment with 1-10 μM hyperforin strongly inhibited proliferation.\(^{254}\) Zymographic analysis revealed that hyperforin significantly inhibited urokinase and MMP-2 production. Similar results were observed in a later study involving a panel of murine and human cancer cell lines,\(^{232}\) as well as HDMECs and *in vivo* with rats injected with MT-450 cells.\(^{255}\) In cultured B-CLL cells taken from patients, hyperforin inhibited the secretion of MMP-9, with IC\(_{50}\) values below 10 μM, and inhibited the formation of microtubules of human bone marrow endothelial cells cultured on Matrigel.\(^{256}\) Along with decreased secretion of urokinase, MMP-2, and MMP-9, hyperforin:HNCy\(_2\) inhibited elastase noncompetitively (IC\(_{50}\) = 3 μM). In mouse models involving both B16-LU8 and C-26, sub-cytotoxic administration of hyperforin: HNCy\(_2\) significantly reduced tumor metastasis and infiltration. Capillary-like structure development of HUVECs was also inhibited, and hyperforin treatment prevented the proliferation of the highly angiogenic Kaposi’s sarcoma cell line.\(^{257}\) In the latter instance, significant reduction of vascularization and tumor size was observed compared to control. In contrast to these results, sub-micromolar concentrations of hyperforin actually *increased* VEGF expression in DAOY cells.\(^{258}\) No effect was observed in U87 cells, which overexpresses VEGF.

Due to the instability of pure hyperforin, several semisynthetic analogs have been prepared and their antiproliferative properties have been studied. While alkylation of the C4 enolic oxygen atom imparts stability, this may worsen the already marginal water solubility of hyperforin. To address these issues, the semisynthetic derivative aristoforin (78) was synthesized in two steps from hyperforin.


Not only was aristoforin more stable and more water-soluble than hyperforin, it also possessed very similar antiproliferative and pro-apoptotic properties as the parent natural product in MT-450 tumor assays. A loss of activity was observed with octahydroaristoforin, the hydrogenolysis product of aristoforin. Both hyperforin and aristoforin were similarly active at suppressing tumor-induced lymphangiogenesis in vivo at concentrations below 10 µM. Above 10 µM, both compounds induced apoptosis in lymphatic endothelial cells through increased mitochondrial membrane permeability and induction of caspase 9.

A variety of oxidized and reduced hyperforin derivatives have also been evaluated, and some of the results are shown in Table 1.13. Both octahydrohyperforin (66) tetrahydrohyperforin (76) were found to be similarly effective towards MDA-MB-231 cells. Tetrahydrohyperforin displayed antiangiogenic properties comparable to hyperforin·HNCy₂ in a BAE cell growth assay and the Matrigel tubule-like structure formation assay. Several other semisynthetic derivatives, including furohyperforin, oxyhyperforin, 79, 80, and 81 (Figure 1.13), were also evaluated but were ineffective at inhibiting angiogenesis. This illustrates the importance of the enolic C4 oxygen atom for anti-angiogenic activity.

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As mentioned previously, a significant loss of antiproliferative activity was observed with hyperforin O-acetate and octahydrohyperforin O-acetate across a variety of cancer cell lines.\textsuperscript{231}

![Figure 1.13. Semisynthetic hyperforin derivatives lacking C4 functionality.](image)

Garcinol is another PPAP that has undergone rather extensive mechanistic studies, and it has been found to promote apoptosis and inhibit cancer proliferation, angiogenesis, and metastasis in a variety of ways.\textsuperscript{261} Similar to hyperforin, garcinol activates apoptosis in certain cancer cell lines by increasing mitochondrial membrane permeability. This loss of membrane potential was observed in three different leukemia cell lines and led to activation of caspase 3.\textsuperscript{262} In this study, similar activity was observed with isogarcinol but not xanthochymol. The addition of the caspase 3 inhibitor Z-DEVD-FMK prevented garcinol-induced apoptotic DNA fragmentation.\textsuperscript{214} Later studies involving pancreatic\textsuperscript{211} and breast\textsuperscript{215} cancer cell lines found that garcinol suppressed NF-κB. In HT-29 cells, 10 μM garcinol induced apoptosis and prevented migration by inhibiting the phosphorylation of FAK as well as preventing the activation of the MAPK and PI3K/Akt signaling pathways.\textsuperscript{263} Downregulation of STAT-3 was observed

\textsuperscript{261} For a review of the chemotherapeutic properties of garcinol, see: Saadat, N.; Gupta, S. V. \textit{J. Oncol.} \textbf{2012}, 647206.


in a variety of cancer cell lines and in an MDA-MD-231 mouse xenograft model. In another study involving the MDA-MD-231 and the BT-549 breast carcinoma cell lines, garcinol treatment reversed the epithelial-to-mesenchymal transition and increased phosphorylation of β-catenin. These results were also validated in a xenograft mouse model. Breast cancer proliferation may also be inhibited through the ability of garcinol to downregulate the expression of cyclin D3, which is highly upregulated in cancer cells compared to nearby normal tissue. Treatment with 1 μM garcinol in a nicotine-induced MDA-MD-231 cell line prevented cancer proliferation. Garcinol has also been shown to be particularly cytotoxic to cells expressing PDGFRs, kinases implicated in several forms of cancer including medulloblastoma. Inhibition of PDGFRs in several cell lines by garcinol led to apoptosis; however, PDGFR-negative MEF cells were not affected by garcinol treatment.

In addition to increased mitochondrial membrane permeability, garcinol may also promote apoptosis through the accumulation of ROS within cancer cells. In garcinol-treated (50 μM) p53-negative Hep3B cells, this ROS accumulation was observed along with increased expression of endoplasmic reticulum stress modulator GADD153 and loss of mitochondrial membrane potential, leading to cell death. Interestingly, an independent study found that while high concentrations of garcinol caused apoptosis in HT-29 and HCT-116 cells, low concentrations (<1 μM) actually promoted cancer cell proliferation. This latter effect may be mediated by ROS; in the presence of superoxide dismutase and catalase and with concentrations of garcinol 0.5-1 μM, cell growth was inhibited.


Administration of garcinol has been shown to prevent carcinogenesis in several animal models. Dietary feeding of garcinol (0.01-0.05% of diet) caused a significant reduction of the formation of azoxymethane-induced colonic aberrant crypt foci (ACF) in rats compared to control.269 Rats were given a garcinol-laden diet 1 week prior to the induction of ACF and during the next four weeks. Up to 40% reduction of ACF frequency was observed (with the 0.05% dietary garcinol cohort). Dietary feeding of garcinol (0.01-0.05%) also prevented 4-nitroquinoline 1-oxide-induced rat tongue carcinogenesis.270 Rats were given garcinol either for 10 weeks during carcinogen administration or for 22 weeks following exposure, and in both instances, the frequency of tongue lesions were significantly reduced. Topical treatment of garcinol also prevented 7,12-dimethylbenz[a]anthracene-induced hamster cheek pouch carcinogenesis.271 Both short- and long-term application of garcinol prevented inflammation, lesion formation, and tumor size. In these three studies reported, a possible explanation for the suppression of carcinogenesis by garcinol may be due to its ability to decrease the expression of enzymes involved in inflammation response, such as iNOS, COX-2, and 5-LO.

Nemorosone also displays anti-cancer properties and may operate in a similar manner to hyperforin and garcinol. Nemorosone, in concentrations of 50-500 nM, has been shown to increase membrane permeability in mitochondria isolated from rat livers.272 The authors hypothesized that nemorosone acted as a proton shuttle across the mitochondrial membrane, thus dissipating membrane potential. Indeed, nemorosone was found to be cytotoxic to HepG2 cells in 1-25 μM concentrations. In various breast cancer cell lines, nemorosone was selectively cytotoxic to cells expressing estrogen receptor 1, and when an estrogen receptor antagonist was used in conjunction with nemorosone, these


effects were enhanced." Significant decreases in Akt and ERK activity were observed and may be the cause of apoptosis in this cell line. Aside from facilitating apoptosis in pancreatic cells via mitochondrial membrane potential dissipation and caspase activation, transcription profiling revealed that nemorosone altered the expression of many proteins involved in unfolded protein response. This cellular stress response mechanism may be one avenue by which nemorosone facilitates apoptosis in cancer cells.

The mechanisms by which several other PPAPs inhibit cancer cell proliferation have been explored. Unsurprisingly, guttiferone A also increases mitochondrial membrane permeability and caused apoptosis of the pancreatic cancer cell line HepG2. Plukenetione A promoted apoptosis in a variety of cancer cell lines, and this may be due to its ability to repress the expression of topoisomerase I and DNA polymerase. In its ability to facilitate LNCaP prostate carcinoma cell apoptosis, 7-epi-nemorosone may inhibit MAPK, similar to garcinol. The ability of guttiferone K to promote apoptosis may also be due to MAPK inhibition. The addition of a JNK (a type of MAPK) inhibitor partially rescued HT-29 cells from guttiferone K-induced apoptosis. Oblongifolin C promoted apoptosis in HeLa cells via caspase and Bax activation. In the presence of a pan-caspase inhibitor or the anti-apoptotic protein Bcl-xL, apoptosis was prevented. Caspase activation has also been noted in hyperatomarin-induced cancer cell apoptosis. Cathepsin inhibition has been implicated as a major factor in the antiproliferative properties of 7-epi-clusianone and garcinaphenone.

Further, several other PPAPs have been evaluated specifically for antimutagenic and antimitotic activity. Nemorosone displayed modest inhibitory activity in the Ames mutagenicity assay involving various Salmonella typhimurium strains, especially against mitomycin C- and aflatoxin B1-induced

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mutagenesis.\textsuperscript{276} Garcinielliptone FC facilitated DNA damage and cleavage in the presence of Cu\textsuperscript{2+}, possibly involving the formation of ROS.\textsuperscript{277} While garcinol, guttiferone B, and oblongifolins A-D were found to be ineffective at microtubule disassembly inhibition, they inhibited tubulin assembly, with IC\textsubscript{50} values ranging from 50-100 \textmu M.\textsuperscript{278} Guttiferones G and J\textsuperscript{222} as well as a mixture of cycloxanthochymol and isoxanthochymol\textsuperscript{249} showed no effect on tubulin assembly.

Several studies have addressed whether certain PPAPs can be used in concert with other therapeutic agents to treat cancer. When hyperforin was combined with hypericin or procyanidin B2, synergistic cytotoxic effects were observed in K562 and U937 cells upon treatment.\textsuperscript{229} Thus, the authors of the study purport that the crude St. John’s wort extract may be a viable therapeutic option for various leukemias. In another study, an enhancement of activity was observed in hypericin-mediated photodynamic therapy of HT-29 cells when hyperforin or aristoforin was present.\textsuperscript{279} In leukemia cells, hyperforin has been shown to impair the activity of P-gp and BCRP, ATP-binding cassette transporters responsible for the development of multidrug resistance in several cancer cell lines.\textsuperscript{280} Hyperforin’s ability to inhibit drug efflux from cancer cells may find use in chemotherapies in which drug resistance develops.

Other than hyperforin, garcinol may be useful as a co-therapeutic in cancer treatment. By inhibiting DNA repair via non-homologous end joining, garcinol has been shown to radiosensitize cancer cells.\textsuperscript{281} Garcinol may prevent this DNA damage repair by acting as a histone acetyltransferase inhibitor.

\begin{itemize}
\end{itemize}
Garcinol’s ability to change gene expression has also been applied to the sensitization of pancreatic cancer cells to the chemotherapeutic gemcitabine.²⁸² A synergistic effect was noted when garcinol and gemcitabine were co-applied to pancreatic cancer cells. Synergistic antiproliferative and apoptotic effects were also noted between garcinol and curcumin in the pancreatic cancer cell lines BXP-3 and PANC-1.²⁸³ Potency of a combination of the two agents was 2- to 10-fold greater than the individual potency of each agent.

Activity against Neurological Disorders

Diseases and disorders of the central nervous system have also been targeted with PPAP-based therapeutics. The most studied PPAP in this area is hyperforin, a component of the medicinal herb St. John’s wort, and much work has been done to elucidate its effects on clinical depression.²⁸⁴ For over 2,000 years, St. John’s wort has been used to treat a variety of ailments, and several ancient Greek and Roman historians and doctors have recorded the medicinal use of an herb called hyperikon that matches the description of Hypericum perforatum.²⁸⁵ Indeed, hyperikon is derived from the Latin words hyper (meaning “over”) and eikon (meaning “apparition”), which in the pre-modern medicine era may refer to depression. A traditional English proverb below effectively summarizes the use of St. John’s wort prior to the advent of modern medicine:

St. John's wort doth charm all the witches away,
If gathered at midnight on the saint's holy day,
And devils and witches have no power to harm


²⁸⁵ For several excerpts of hyperikon use in antiquity, see: (a) Aulus Cornelius Celsus Da Medica 5.20.6 and 5.23.3. (b) Dioscorides Materia Medica 3.173. (c) Pliny the Elder Naturalis Historiae XXVI.53.
Those that do gather the plant for a charm
Rub the lintels and post with that red juicy flower
No thunder nor tempest will then have the power
To hurt or to hinder your houses; and bind
Round your neck a charm of a similar kind.\textsuperscript{286}

To this day, SJW extract remains a popular therapeutic for depression in European countries; during the period between April 2007 and March 2008, over 9.5 million units of SJW were sold, mostly in Germany, Russia, and Poland.\textsuperscript{287} In Germany, standardized SJW extracts are one of the most prescribed antidepressants, with sales comparable to synthetic antidepressants. In the United States, sales of SJW peaked in the late 1990’s, reaching upwards of an estimated $310 million.\textsuperscript{288} However, the discovery of side effects (to be discussed in the next section) has led to a decrease in SJW sales, with 2007 numbers an estimated $8.1 million, making it the tenth most popular herbal dietary supplement sold in the country that year.\textsuperscript{289} Dozens of clinical trials involving SJW treatment of depression have appeared in the literature enlisting over 5,000 patients. A Cochrane Collaboration meta-analysis of 29 double-blind, randomized trials involving 5,489 patients found that SJW was indeed effective for treatment of major depression with efficacy comparable to standard antidepressants.\textsuperscript{290} Importantly, fewer adverse side effects were encountered with SJW extract use than with other antidepressants.

Given the long history of use, efficacy, and safety of SJW extract, identification of the active component has received considerable attention. Chemicals found in the extract fall into three distinct categories: phloroglucinols, flavonoids, and naphthodianthrones.\textsuperscript{291} An early study purported that the


\textsuperscript{288} Golden, F. *TIME* 2001, 157 (Apr. 30), 60-61.

\textsuperscript{289} Cavaliere, C.; Rea, P.; Blumenthal, M. *HerbalGram* 2008, 78, 60-63.


\textsuperscript{291} Nahrstedt, A.; Butterweck, V. *Pharmacopsychiatry* 1997, 30 (Suppl.), 129-134.
active antidepressant component of herb was hypericin (82, Figure 1.14), a naphthodianthrone polyketide that had monoamine oxidase (MAO) inhibition activity, with IC₅₀ values of 68 nM and 420 nM for type A and B MAOs, respectively.²⁹² However, there are several reasons to doubt that hypericin, by itself, is the active principle of SJW. Attempts to replicate these original findings have been unsuccessful, using either pure hypericin or crude SJW extracts.²⁹³ In fact, the flavonoid-containing fraction of the extract was the only component to show mild MAO inhibition ability at all. Also, it appears that hypericin does not cross the blood-brain barrier. When rats were orally administered with either SJW extract (1600 mg/kg) or pure hypericin (5 mg/kg), no hypericin was detected in the brain above the detection threshold (16 pmol/g).²⁹⁴

Upon further analysis of the compounds found in SJW extract, multiple sources found that hyperforin was indeed the primary component responsible for its antidepressant activity.²⁹⁵ While it had been known since the 1970’s that hyperforin is a significant constituent of the herb,¹ comprising 2-4% of

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the dry weight of its aerial parts, it had been largely disregarded due to its chemical instability. In fact, the inconsistencies of SJW clinical trials may be due to hyperforin instability; prior to the realization of the significance of hyperforin, the PPAP was found in variable amounts in SJW medical preparations.

Upon exposure to light and air, hyperforin rapidly converts to furohyperforin, among other oxidation products. Furohyperforin is observed when air is bubbled through a methanolic solution of hyperforin for 6.5 h. Upon standing neat exposed to air at 40 °C, or dissolved in nonpolar solvents (e.g., hexane, benzene, petroleum ether), furohyperforin, 33-deoxy-33-hydroperoxy-furohyperforin, oxyhyperforin, oxepahyperforin, furohyperforin isomers 1 and 2, and a variety of monocyclic cyclohexanones were observed. Similar degradation products are found when hyperforin is photochemically irradiated in acetonitrile or exposed to peroxide oxidants. Despite its apparent instability upon exposure to light, oxidants, and nonpolar solvents, hyperforin may be stabilized in polar protic solvents. In general, the half-life of hyperforin increases with increasing solvent polarity. After 30 days at 20 °C in the dark, over 70% of hyperforin remains in ethanol, methanol, or methanol/water suspensions. Storage below −20 °C under nitrogen also prevents degradation of hyperforin; after 8 months, only marginal decomposition of hyperforin occurred. Overall, despite the fact that hyperforin


may readily decompose upon exposure to light and air, relatively straightforward precautions can be taken in order to preserve hyperforin either as a pure substance or as found in SJW extracts.

The discovery that hyperforin was the principle antidepressant component of SJW came in 1998 with a seminal paper by Müller and coworkers.\(^3\) Using two murine models for depression, the behavioral despair test and the learned helplessness test, it was found that the antidepressant potency of SJW extracts correlated with hyperforin content. More importantly, isolated hyperforin inhibited the uptake of tritiated neurotransmitters into isolated murine synaptosomes in a dose-dependent manner. IC\(_{50}\) values for these \textit{in vitro} experiments ranged from 0.011-3.35 \(\mu\text{M}\) and have been confirmed in later studies (Table 1.14).\(^4\) Unlike synthetic antidepressants, which selectively block the selective reuptake of individual neurotransmitters, hyperforin appeared to block the reuptake of a variety of neurotransmitters, possibly signifying a novel mechanistic paradigm for the treatment of depression.

### Table 1.14. Inhibition of synaptosomal \(^{3}\text{H}\)neurotransmitter uptake by hyperforin.

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>IC(_{50}) ((\mu\text{M}))</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{3}\text{H})serotonin</td>
<td>0.12-3.35</td>
<td>304,306,307,308,309,310</td>
</tr>
<tr>
<td>(^{3}\text{H})noradrenaline</td>
<td>0.033-0.080</td>
<td>304,308</td>
</tr>
<tr>
<td>(^{3}\text{H})dopamine</td>
<td>0.011-0.102</td>
<td>304,308</td>
</tr>
<tr>
<td>(^{3}\text{H})(\gamma)-aminobutyric acid</td>
<td>0.184</td>
<td>304,311</td>
</tr>
<tr>
<td>(^{3}\text{H})-glutamate</td>
<td>0.143-0.829</td>
<td>304,311</td>
</tr>
</tbody>
</table>


\(^{10}\) Wonnemann, M.; Singer, A.; Müller, W. E. \textit{Neuropsychopharmacology 2000, 23}, 188-197.
Subsequent to the realization that hyperforin may be responsible for the antidepressant activity of SJW, ensuing preclinical and clinical studies provided more evidence to verify this hypothesis. In the behavioral despair and elevated plus-maze murine models of depression, treatment with pure hyperforin led to more favorable outcomes compared to the ethanolic and supercritical CO₂ SJW extracts, which contained 4.5% and 38.8% hyperforin, respectively.³¹² Hyperforin was significantly effective in the elevated plus-maze test at concentrations as low as 1 mg/kg, and 3-day 20 mg/kg treatment with pure hyperforin in the force swim test caused a 40% reduction of immobilization time compared to vehicle. Using the same ethanolic and CO₂ SJW extracts as above, positive outcomes in a variety of other murine models of depression were shown to correlate with hyperforin content, including rat resperine syndrome, muricidal rat behavior, 5-hydroxytryptophan-induced mouse head twitches, l-dopa-induced mouse behavior, apomorphine-induced rat stereotypy, and post-swim mouse grooming response.³¹³ In rats that were chronically exposed to unavoidable stress, escape deficit developed along with an anhedonia-type behavior towards palatable food. When these conditioned rats were exposed to SJW extracts or pure hyperforin, this escape deficit behavior diminished and the rats displayed favorable appetitive behavior.³¹⁴ In addition, pure hyperforin was significantly more potent than the SJW extracts used. Hyperforin administration also displayed positive outcome in the murine passive avoidance test.³¹⁵

A variety of clinical trials has also shown that hyperforin is a critical antidepressant component of SJW extracts. In a randomized, 147 out-patient, 42-day, double-blind multicenter study of persons suffering from mild to moderate depression,³¹⁶ the treatment group receiving an extract containing a

³¹⁶ In this particular study, depression severity was determined using the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV), and the HAMD (Hamilton Rating Scale for Depression) 17-item questionnaire was used to assess change in depression severity throughout the study.
standardized 5% amount of hyperforin exhibited significantly larger positive endpoint when compared to treatment groups receiving either placebo or an extract with 0.5% hyperforin. Patients were given three 300 mg tablets per day. In particular, more severely depressed patients responded particularly well to the 5% treatment. In a Phase I trial, 18 healthy volunteers were given one 900 mg tablet a day for 8 days, containing placebo or SJW extract (0.5% or 5% hyperforin), and monitored via quantitative topographic electroencephalography. Significant pharmacodynamic effects were seen with both non-placebo treatment groups, peaking 4-8 hours after administration, and the treatment group receiving the higher dose of hyperforin saw more pronounced changes in electrical activity. In a 12-man study involving a SJW extract standardized to hypericin, no significant endpoint was achieved, providing further evidence that hyperforin, and not hypericin, is the active component of SJW.

One important note concerning outpatient clinical trials involving SJW is that results may be exacerbated by the readily available nature of its extracts, leading to patient noncompliance and confounding results. The highly publicized Hypericum Depression Trial Study, which found no difference between SJW and placebo for major depression, was replicated three years later with the addition of monitoring plasma hyperforin levels. In this study, involving a total of 340 outpatients, one out of every six taking placebo had significant plasma hyperforin, and one-sixth of patients taking the SJW extract had no detectable hyperforin in their blood.

Interest in the underlying antidepressant mechanism of hyperforin and its biomolecular targets has led to numerous studies. Aside from inhibiting the uptake of neurotransmitters by synaptosomes as previously discussed, intraperitoneal injection of hyperforin (10 mg/kg) also was found to increase the


extracellular concentration of a variety of neurotransmitters in the rat locus coeruleus. Presumably, hyperforin caused the release of synaptic vesicles containing these neurotransmitters into the synaptic cleft and prevented reuptake. This hypothesis was confirmed in a later study in which neurons in rat brain slices were preloaded with radiolabeled serotonin and dopamine. Hyperforin dose-dependently caused release of these amines. Similar results were obtained with human blood platelets preloaded with $[^{14}C]$serotonin; treatment with 300 nM hyperforin caused store depletion of this monoamine.

The above results do not support the idea that hyperforin works through direct interaction with reuptake enzymes. Michaelis–Menten kinetic analysis reveals that hyperforin blocks serotonin uptake via noncompetitive inhibition in mouse brain synaptosomes. Indeed, rat brain cortical synaptosomes pretreated with hyperforin did not prevent binding of tritiated citalopram, a selective serotonin reuptake inhibitor. Further, hyperforin failed to inhibit monoamine binding across a wide variety of neurotransmitter transporters and receptors in in vitro binding assays. Hyperforin, while inhibiting the uptake of radiolabeled monoamines in rat forebrain homogenates, did not affect binding of $[^{3}H]$dihydrotetrazenazine, a known selective vesicular monoamine transporter ligand. Interestingly, SJW extracts do seem to competitively inhibit monoamine receptors in guinea pig hippocampal slices; however, when purified hyperforin was subjected to this ex vivo assay, no inhibition was observed.

Instead of directly binding to neurotransmitter transports and receptors, numerous studies indicate that hyperforin increases intracellular ion levels, and this mediates not only monoamine uptake inhibition

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but also vesicular monoamine release. A wide variety of neurotransmitter transports rely on co-transport of sodium cations, and the presence of a sodium ion gradient across the cellular membrane facilitates this process.\textsuperscript{328} By diminishing this ion gradient, hyperforin indirectly inhibits monoamine reuptake. Accordingly, treatment of human platelets with 50 µM hyperforin caused an increase in intracellular [Na\textsuperscript{+}] over basal levels.\textsuperscript{306} A similar effect was observed when a known cation transporter monensin was used; however, hyperforin did not elevate [Na\textsuperscript{+}], to extracellular levels, as in the case of monensin, indicating a different transport mechanism. The addition of benzamil, an amiloride derivative and potent Na\textsuperscript{+} ion channel inhibitor, further differentiated hyperforin- and monensin-based pathways.\textsuperscript{311} Benzamil attenuated hyperforin-based uptake inhibition but had no effect on monensin’s activity. In addition, Ca\textsuperscript{2+} entry or electrical current may facilitate the release of neurotransmitters. In rat cortical synaptosomes, the release of glutamate induced by hyperforin was preceded by an increase of intracellular [Ca\textsuperscript{2+}], indicating that hyperforin-mediated ion influx appears to be nonselective.\textsuperscript{329} Dose-dependent Ca\textsuperscript{2+} influx was also observed when 0.6-18.6 µM hyperforin was added to hamster vas deferens smooth muscle.\textsuperscript{330} pH gradient was also dissipated across the membranes of synaptic vesicles isolated from rat striatum and hypothalamus by inhibiting the action of vacuolar H\textsuperscript{+}-ATPase with an IC\textsubscript{50} value of 0.19 µM.\textsuperscript{331} This facilitated the release of radiolabeled serotonin from preloaded vesicles. In addition, ion influx induces an electrical current across the cell membrane. Using patch clamp techniques, hyperforin caused a dose- and time-dependent inward current in isolated hippocampal pyramidal neurons and cerebellar rat Purkinje


\textsuperscript{330} Kock, E.; Chatterjee, S. S. Pharmacopsychiatry 2001, 34 (Suppl. 1), 70-73.

\textsuperscript{331} Roz, N.; Rehavi, M. Life Sci. 2003, 73, 461-470.
neurons through ion influx.\textsuperscript{332} Low concentrations of hyperforin (100-800 nM) also modulated the activity of P-type calcium channels in Purkinje neurons in a voltage-dependent manner.\textsuperscript{333}

To summarize the evidence presented above, the ability of hyperforin to inhibit the reuptake and promote the release of neurotransmitters from neurons may be reliant on nonselective inward ion influx. Taken together, these data suggest that hyperforin may activate an ion channel expressed on neuronal membranes, and elucidation of this ion channel protein may represent a new target for developing antidepressants.\textsuperscript{334} Indeed, tetrodotoxin, a potent sodium channel blocker, inhibited hyperforin-mediated monoamine release from mouse cortical neurons.\textsuperscript{335} Similar inhibition was observed in human platelets and PC12 cells with both SKF-96365 and LOE 908, two inhibitors of nonselective cation channels.\textsuperscript{336} The addition of La\textsuperscript{3+} and Gd\textsuperscript{3+} ions also inhibited the activity of hyperforin in these cells, and these cations are known blockers of the canonical transient receptor potential protein (TRPC) channel family.

TRPC channels are members of the transient receptor potential protein superfamily that can be broadly described as cell-surface ion channels involved in many aspects of sensation and response to physical or chemical stimulation.\textsuperscript{337} TRPC channels were the first members of this family discovered, and all contain six transmembrane domains. They assemble into either homo- or hetero-tetramers, and cation selectivity is determined by the size of the pore loop. Several proteins may be anchored onto the cytoplasmic end of the S6 domain, providing control elements to regulate the activity of the cation


\textsuperscript{334} Müller, W. E.; Singer, A.; Wonnemann, M. \textit{Pharmacopsychiatry} \textbf{2001}, \textit{34} (Suppl. 1), 98-102.

\textsuperscript{335} Marsh, W. L.; Davies, J. A. \textit{Life Sci.} \textbf{2002}, \textit{71}, 2645-2655.


channel. There are seven known TRPC proteins, and they may be activated by diacylglycerol, phospholipase C, or tyrosine kinases.\textsuperscript{338}

Further analysis determined that hyperforin selectively activates TRPC6.\textsuperscript{339} Hyperforin (10 µM) induced nonselective ion entry into PC12 cells expressing TRPC6. Furthermore, the entry of Ca\textsuperscript{2+} ions when TRPC6 was activated by hyperforin (0.1-0.3 µM) caused neurite outgrowth in these cells, similar to the effects of adding nerve growth factor. Cation influx was suppressed in PC12 cells by expressing a dominant negative mutant of TRPC6. This is noteworthy given that the cell expression of related TRPC proteins remained unaffected, such as TRPC3 and TRPC7, which share approximately 75% sequence homology to TRPC6.\textsuperscript{340} Given the similarity of TRPC6 to other members of the TRPC family, it seems unlikely that hyperforin interacts directly with TRPC6. When PC12 cells were pre-incubated with various tyrosine kinase and phospholipase C inhibitors, the effects of hyperforin were mitigated, possibly indicating that hyperforin interacts with a protein involved in TRPC6 activation.\textsuperscript{341}

Regardless of the nature of hyperforin’s interaction with TRPC6, its ability to act as a TRPC6 molecular probe has furthered understanding of this protein in particular and of ion homeostasis in general. When internal stores of Ca\textsuperscript{2+} are depleted from a cell, various ion channels are activated via the store-operated Ca\textsuperscript{2+} entry (SOCE) pathway.\textsuperscript{342} In murine brain cortical embryonic neurons from which internal Ca\textsuperscript{2+} stores were depleted using thapsigargin, SOCE became activated.\textsuperscript{343} Addition of the TRPC3-selective inhibitor Pyr3 potently prevented Ca\textsuperscript{2+} entry; however, the addition of hyperforin facilitated Ca\textsuperscript{2+}


\textsuperscript{343} Gibon, J.; Tu, P.; Bouron, A. \textit{Cell Calcium} \textbf{2010}, \textit{47}, 538-543.
entry presumably through TRPC6 activation. This indicates that while TRPC3 participates in SOCE, TRPC6 does not. Additionally, the activity of hyperforin was attenuated through the Zn\(^{2+}\) chelator TPEN, but SOCE-mediated Ca\(^{2+}\) entry remained unaffected. Further studies established that hyperforin also promoted the release of Ca\(^{2+}\) and Zn\(^{2+}\) stores from isolated brain mitochondria. The ability of hyperforin to increase the permeability of mitochondrial membrane has been documented. Beyond increasing mitochondrial membrane permeability, chronic hyperforin treatment (1 \(\mu\)M treatment for 3 days) has been shown to increase the gene expression of metallothioneins and thus Zn\(^{2+}\) storage capacity in cortical neurons. Metallothioneins are cysteine-rich proteins and bind to Zn\(^{2+}\) among other cationic species. Chronic intraperitoneal injection of rats with hyperforin (4 mg/kg/day) has similar effects, increasing the Zn\(^{2+}\) storage capabilities of their brain tissue. Increased intracellular Zn\(^{2+}\) stores were also achieved by expressing TRPC6 in HEK293 cells, but not with TRPC3 expression. These data suggest that TRPC6 is capable of acting as a Zn\(^{2+}\)-conducting channel.

Prior studies have suggested that TRPC proteins in general and TRPC6 in particular play crucial roles in neuronal differentiation, plasticity, and outgrowth. This may be one avenue by which hyperforin acts as an antidepressant and alters nerve tissue in the brain. Oral dosing (15 mg/kg) of the sodium salt of hyperforin in rats caused changes in the morphology of their brain membranes. Another study established that hyperforin treatment of neural stem/progenitor cells promoted the maturation of

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344 It should be noted that other hyperforin-activated ion channels mimicking TRPC6 may be present in neurons. For more information, see: Tu, P.; Kunert-Keil, C.; Lucke, S.; Brinkmeier, H.; Bouron, A. J. Neurochem. 2009, 108, 126-138.


346 See the discussion in the Chemotherapeutic Activity section on page 64.


oligodendrocytes without affecting the proliferation of the progenitor cells.\textsuperscript{351} Oligodendrocyte dysfunction may play a role in the pathogenesis of major depressive disorder.\textsuperscript{352} Hyperforin, via TRPC6 activation, caused changes in dendritic spine morphology in pyramidal neurons in rat hippocampal slices.\textsuperscript{353} These effects were blocked by the addition of La\textsuperscript{3+}, indicating the importance of TRPC6 channels on hyperforin-induced morphological effects. Hyperforin has also been shown to generate neuroprotective effects in neurons through the activation of CREB in a tissue-specific manner. Rats treated with daily hyperforin injections (4 mg/kg) for 4 weeks had increased cortical expression of TRPC6 and TrkB, a brain-derived neurotrophic factor receptor.\textsuperscript{354} Immediately following a middle cerebral artery occlusion in the brains of rats, direct injection of hyperforin into the brain reduced total cell death and increased TRPC6 and CREB activity.\textsuperscript{355} One day after the ischemic stroke, the rats treated with hyperforin also displayed higher neurologic scores than the control group. Interestingly, expression of TrkB in the hippocampus remained unaffected. Similar effects were observed in a rat model of status epilepticus, a prolonged seizure event that results in significant brain tissue damage.\textsuperscript{356} In such an event, TRPC6 expression decreases in affected tissue, ultimately leading to neuronal cell death;\textsuperscript{357} however, prior hyperforin treatment prevented this downregulation and subsequently prevents neurodegeneration. Conversely, hyperforin has also engendered neuroprotective effects by the \textit{downregulation} of TRPC6 and CREB expression in certain situations. As discussed earlier, hyperforin decreased activated CREB levels


in mouse microglia by decreasing iNOS expression. In PC12 cells that had been previously activated with NGF, hyperforin actually downregulated TRPC6 expression. Decreased expression of TRPC6 in this instance may have promoted neuroprotection by regulating the rate of neurite outgrowth.

Due to its expression throughout the human body, TRPC6 may be a unique target for the treatment of a variety of diseases. Many inflammatory skin conditions are characterized by over-proliferating skin cells, and TRPC6 has been associated with Ca\(^{2+}\)-induced keratinocyte differentiation. Additionally, skin creams formulated with SJW extracts have shown efficacy in several half-side clinical trials involving inflammatory skin diseases, including pressure ulcers, psoriasis, and atopic dermatitis. When HaCaT cells were treated with hyperforin (1 µM), an influx of Ca\(^{2+}\) was observed and differentiation was triggered, and these effects were mimicked through the addition of a high concentration of extracellular Ca\(^{2+}\). When TRPC6 was knocked down, both hyperforin- and Ca\(^{2+}\)-induced differentiation was not observed. TRPC6 is also abnormally expressed in several breast cancer cell lines (e.g., MCF-7, MCF 10A, MDA-MB-231), and the antiproliferative effect of hyperforin on these cell lines may be in part due to its interaction with TRPC6 or its effects on TRPC6 expression.

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361 Lomagno, P.; Lomagno, R. C. Fitoterapia 1979, 50, 201-205.


vascular smooth muscle, TRPC6 plays an important role in regulating vascular tone.\textsuperscript{366} Hyperforin caused dose- and time-dependent smooth muscle constriction in aortic segments taken from mice. In aortic segments taken from TRPC6-knockout mice, no such constriction was observed. In the lung, TRPC6 expression is associated with the induction of platelet-activating factor-induced vascular leakage leading to lung edema.\textsuperscript{367} Treatment of mouse lungs with hyperforin caused effects similar to platelet-activating factor, including increased intracellular $[\text{Ca}^{2+}]$ and weight gain due to fluid entry. TRPC6 malfunction has also been implicated in certain instances of focal segmented glomerulosclerosis, a significant cause of renal disease.\textsuperscript{368}

In addition to TRPC6 and neuronal monoamine receptors, several other potential biomolecular targets of hyperforin have been explored. Both hyperforin and its dicyclohexylamine salt were found to be potent inhibitors of substance P-induced interleukin-6 release in human astrocytoma cells with an IC$_{50}$ value of 1.6 $\mu$M.\textsuperscript{369} Hypersecretion of interleukin-6 and other cytokines may be involved with the pathophysiology of depression. $\beta$-Adrenergic receptors may also be involved in depression since downregulation of these proteins correlate with the antidepressant effects of other medicines.\textsuperscript{370} When rats were treated with methanolic and CO$_2$ SJW extracts, a significant decrease in $\beta$-adrenergic receptor levels was observed in the frontal cortex region of the brain.\textsuperscript{371} In rat C6 glioblastoma cells, treatment with hyperforin led to a decrease in $\beta_2$-adrenergic receptor expression, indicating that hyperforin was one of

\begin{thebibliography}{99}
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the primary components of the extracts responsible for this activity. Hyperforin treatment was later shown to also decrease β₁-adrenergic receptor in this cell line.

While hyperforin is considered the chief antidepressant component of SJW extracts, it is not exclusively responsible for the herb’s antidepressant activity; other chemicals isolated from the extract have shown efficacy in various in vitro and in vivo models. Hypericin and pseudohypericin as well as the biflavonoid amentoflavone and various xanthones inhibited monoamine receptor binding. Interestingly, SJW extracts devoid of hyperforin displayed antidepressant-like outcomes in a variety of murine behavioral models, including the elevated plus maze, tail suspension test, and the forced swim test. In other behavioral models, positive outcomes were observed even when no detectable amount of hyperforin was present in the brain. Flavonoids, such as rutin and quercetin, were found to be active in these behavioral models. Amentoflavone was the most active component of the extract at stopping stress-induced hyperthermia in mice. Quercetin also displayed potent, selective inhibition of

monoamine oxidase A, with an IC₅₀ value of 10 nM. Modulation of the hypothalamic-pituitary-adrenal axis may be a therapeutic option in the treatment of depression, and while hyperforin did not alter gene expression in brain areas involved with axis control in rats, various flavonoids and pseudohypericin present in SJW extracts modulated axis function. Overall, while hyperforin is the consensus active principle of SJW, various other components display activity across a range of biochemical systems implicated in depression.

Aside from hyperforin, very few PPAPs have been evaluated for antidepressant activity. Adhyperforin is also isolated from SJW, usually in concentrations one-seventh that of hyperforin. Unsurprisingly, this PPAP also potently inhibits neurotransmitter uptake in the synaptosome uptake assay with IC₅₀ values lower than hyperforin to some extent (Table 1.15). Hyperfoliatin (hyperbone J) has also been evaluated in synaptosomal reuptake assays but was several orders of magnitude less active than hyperforin and adhyperforin (Table 1.15). Like hyperforin, adhyperforin and hyperfoliatin do not bind directly to monoamine receptors. In addition, hyperfoliatin reduced the immobility time of the forced swim test in rats. Hyperatomarin has also been evaluated for uptake inhibition, but was found to be only weakly active against serotonin reuptake (IC₅₀ = 16.8 µM), and was actually one of the least potent

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components of *Hypericum annulatum* evaluated in this study. Furohyperforin was reported to have one-tenth the activity of hyperforin against synaptosomal serotonin uptake.

Table 1.15. Inhibition of synaptosomal [3H]neurotransmitter uptake by adhyperforin.

<table>
<thead>
<tr>
<th>PPAP</th>
<th>[3H]serotonin</th>
<th>[3H]noradrenaline</th>
<th>[3H]dopamine</th>
<th>[3H]-glutamate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>adhyperforin</td>
<td>0.027-0.32</td>
<td>0.014-0.67</td>
<td>0.003</td>
<td>2.40</td>
<td>308,391</td>
</tr>
<tr>
<td>hyperfolatin</td>
<td>3.5</td>
<td>1.8</td>
<td>1.2</td>
<td>n.d</td>
<td>388</td>
</tr>
</tbody>
</table>

*All data reported are IC₅₀ values (in µM).*

Several semisynthetic hyperforin analogs have been evaluated for antidepressant activity. Crude SJW extracts containing hyperforin and adhyperforin conjugates still retained significant activity in the forced swim test, even though they did not contain detectable hyperforin or adhyperforin. In studies involving more resolved hyperforin analogs, hyperforin esters generally show favorable antidepressant activity whereas oxidation products display decreased activity. Across four different animal models of depression (i.e., forced swim test, learned helplessness test, elevated plus maze, and light-dark test), hyperforin O-acetate at 3-5 mg/kg dosing showed efficacy. Hyperforin O-3,4,5-trimethoxybenzoate (61) also shortened immobility time during the forced swim test when injected at 3.1-6.3 mg/kg concentrations. At these concentrations, plasma levels of this analog were 30-50 µM and brain levels were found to be 0.3 µM. While both of these analogs were active in animal models of depression, neither possessed the ability to inhibit *in vitro* synaptosomal neurotransmitter uptake. A variety of

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other hyperforin analogs were found to be inactive in this uptake assay, including hyperforin \(O\)-methyl ether (60), hyperforin \(O\)-2,4-dinitrobenzoate, 63, 64, oxyhyperforin, pyrohyperforin, and 83 (Figure 1.15). It should be noted that various diacylphloroglucinol derivatives have been developed as TRPC6-selective inhibitors, but these compounds bear little resemblance to hyperforin.

![Figure 1.15. A semisynthetic hyperforin analog evaluated for antidepressant activity.](image)

Several PPAPs have been evaluated for their activity against neurological disorders beyond clinical depression.396 Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are possible targets for the treatment of various neurological diseases, such as Alzheimer’s disease, glaucoma, and myasthenia gravis.397 Various PPAPs exhibit fairly potent inhibition activity against both of these enzymes in an \textit{in vitro} assay (Table 1.16). At a concentration of 10 \(\mu\)M, garsubellin A increased choline acetyltransferase activity by 154\% in P10 rat septal neurons.398 Mice injected with 1-10 mg/kg hyperforin caused an increase of acetocholine release, and at the highest concentration tested, a significant decrease in locomotor activity was observed.399 The former results could be explained by the ability of hyperforin

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to activate ion channels in neurons, and the latter result may indicate that very high, chronic doses of hyperforin may lead to Parkinson’s disease. A subsequent study found that hyperforin-induced acetylcholine release in the rat hippocampus is indeed Ca\(^{2+}\)-dependent.\(^{400}\)

### Table 1.16. AChE and BChE inhibition activity of several PPAPs.

<table>
<thead>
<tr>
<th>PPAP</th>
<th>AChE IC(_{50}) (µM)</th>
<th>BChE IC(_{50}) (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>garcinol</td>
<td>0.66</td>
<td>7.39</td>
</tr>
<tr>
<td>guttiferone A</td>
<td>0.88</td>
<td>2.77</td>
</tr>
<tr>
<td>guttiferone F</td>
<td>0.95</td>
<td>3.50</td>
</tr>
<tr>
<td>isogarcinol</td>
<td>1.13</td>
<td>8.30</td>
</tr>
</tbody>
</table>

Hyperforin and its reduced derivative tetrahydrohyperforin (76) have been evaluated for their ability to affect β-amyloid (Aβ) biochemistry, a poorly understood but important component of the pathophysiology of Alzheimer’s disease.\(^{401}\) In rat PC12 cells, hyperforin treatment accelerated the proteolysis of amyloid precursor protein.\(^{402}\) The activity of hyperforin was distinct from other, known activators of amyloid precursor protein proteolytic secretion. Hyperforin also significantly decreased the formation of amyloid deposits in rats injected with amyloid fibrils.\(^{403}\) The rats also displayed more favorable outcomes in the circular water maze test compared to control and decreased Aβ-related neurotoxicity in hippocampal neurons. Similar \textit{in vivo} effects were observed for tetrahydrohyperforin (76).\(^{404}\) In amyloid precursor protein-transgenic mice, tetrahydrohyperforin caused a reduction in Aβ


plaque formation, possibly due to the release of AChE from the precursor fibril assemblies or the prevention of AChE association with amyloid plaques. Later studies established that this semisynthetic hyperforin derivative dose-dependently prevented cognitive deficit and memory impairment in this transgenic mouse model as well as a decrease in neurotoxicity and an increase in hippocampal neurogenesis. Part of this activity could be explained by the inhibition of the proteolytic processing of amyloid precursor protein to Aβ peptide. In addition to affecting Aβ generation and plaque formation, the ability of hyperforin to upregulate P-gp and thus increase clearance of Aβ peptide from the brain may also be effective in preventing the onset of Alzheimer’s disease.

Deficit of prepulse inhibition is a common phenomenon in patients suffering from a variety of neurological disorders including Alzheimer’s disease and schizophrenia. Since inhibition of monoamine receptors may be involved in disruption of prepulse inhibition, it is unsurprising that hyperforin caused a significant decrease in rat startle amplitude in the acoustic startle response test. Given its effects on prepulse inhibition, hyperforin may exacerbate the symptoms of several mental disorders.

Both garcinol and hyperforin have been evaluated for their effects on the acquisition of new memories. Treatment of mice and rats with the sodium salt of hyperforin (1.25 mg/kg/day) for 7 days caused significant increases in learned responses in the conditioned avoidance test. After 9 days of treatment, hyperforin significantly increased the number of avoided shocks in a conditioned avoidance test.

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following the last dose of hyperforin, the learned response was retained in the animals. Hyperforin also showed improvement after a single dose in the passive avoidance test and reversed scopolamine-induced amnesia. In another study, direct injection of garcinol into the rat lateral amygdala immediately following fear conditioning reduced the consolidation of the Pavlovian fear memory.\textsuperscript{411} Similarly, garcinol also prevented the reconsolidation of a fear memory following fear memory retrieval. This property of garcinol may be useful for the treatment of post-traumatic stress disorder.

Hyperforin has also been evaluated for the treatment of other neurological conditions. When rats were injected with hyperforin (10 mg/kg) once a day for 7 days, they showed significantly less aggression across four behavioral models: foot shock-induced aggression, isolation-induced aggression, resident-intruder aggression, and the water competition test.\textsuperscript{412} In a study in which rats were given access to alcohol, injection of SJW extracts containing hyperforin caused a reduction of ethanol consumption that was proportional to the amount of hyperforin in the extracts.\textsuperscript{413} Similar dose-dependent results were found using a breed of mice that preferred alcohol.\textsuperscript{414} These effects may be due hyperforin-based \textit{N}-methyl-\textit{D}-aspartate-induced (NMDA) antagonism. NMDA receptors overactivity has been noted in alcohol withdrawal, often causing agitation and seizures in some cases.\textsuperscript{415} Hyperforin (at a 10 \textmu M concentration) inhibited NMDA-induced Ca\textsuperscript{2+} influx in isolated rat cortical neurons and blocked the NMDA receptor-induced release of phospholipid-based choline in rat hippocampal slices.\textsuperscript{416} These effects may contribute to apparent reduction alcohol consumption observed with hyperforin treatment.

\begin{thebibliography}{99}
\end{thebibliography}
In addition to hyperforin, garcinol and guttiferone have displayed neuroprotective effects. Garcinol has been shown to promote the development of neurons.\textsuperscript{417} Cortical progenitor cells taken from embryonic rats developed into neurospheres upon treatment of garcinol, and this may be facilitated by Ca\textsuperscript{2+} entry through the extracellular signal-regulated kinase pathway, which also promoted neuronal survival. The neuroprotective effects of guttiferone A are most likely derived from its ability to scavenge free radicals. Incubation of PC12 cells with guttiferone A garnered protection from Fe\textsuperscript{3+} auto-oxidation\textsuperscript{418} as well as from various reactive oxygen species.\textsuperscript{142}

Given its ability to inhibit neurotransmitter reuptake by neurons, hyperforin has also been evaluated for its effects on neuroendocrine response. Injection of 9.3 mg/kg hyperforin into rats increased plasma corticosterone, and lowered haloperidol-induced plasma prolactin levels.\textsuperscript{419} Since ketanserin but not WAY-100635 inhibited hyperforin-induced plasma corticosterone effects, 5-HT\textsubscript{2} receptors may be involved in this response. A small-scale, single-blind study involving 12 healthy volunteers found that a hyperforin-enriched SJW extract (at 600, 900, and 1200 mg/kg daily oral dosing over 4 days) stimulated adenocorticotropic hormone, while cortisol and prolactin levels remained unaffected.\textsuperscript{420} Several patients experienced an increase in growth hormone release, but this effect was not statistically significant compared to placebo.

The analgesic properties of several PPAPs have also been evaluated. Through analyzing the components of SJW extracts individually, it was discovered that both hypercin and hyperforin displayed antinociceptive properties in murine models of neuropathic pain.\textsuperscript{421} Hyperforin was particularly effective


\textsuperscript{419} Franklin, M.; Chi, J. D.; Mannel, M.; Cowen, P. \textit{J. Psychopharmacol.} \textbf{2000}, \textit{14}, 360-363.


at the prevention of thermally induced pain. This pain inhibition was abolished by the addition of naloxone, indicating hyperforin’s effects are most likely opioid-dependent. The analgesic effects of 7-epi-clusianone were not limited to thermally induced pain in mouse models, imparting antinociceptive effects in tests including acetic acid-induced writhing, hot plate exposure, the formalin subplantar injection. In the acetic acid-induced writhing model, guttiferone A dose-dependently reduced abdominal constrictions with an EC$_{50}$ value of 4.5 mg/kg.

Other Bioactivity

As the popularity of SJW extracts grew in the late 1990’s, several instances of alarming side effects were reported. By the end of 1999, more than 8 reported cases suggested that SJW extracts may cause increased hepatic metabolism of prescribed medication. In particular, women consuming SJW extracts experienced a significant decrease in co-medicated theophylline, cyclosporin, warfarin, and ethinylestradiol. A subsequent study conducted by the NIH in 16 healthy volunteers found that SJW extract caused a decrease in indivanir, and two German heart transplant patients suffered acute transplant rejection due to SJW extract-accelerated cyclosporine metabolism. These alarming

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observations led the FDA to issue a public healthy advisory\(^{428}\) and the British Medicines Control Agency to issue a reminder to doctors.\(^{429}\)

It was soon discovered independently by two different groups that hyperforin is the component of SJW that potently activates pregnane X receptor (PXR, steroid X receptor).\(^{430}\) PXR is a transcription factor that serves as a key regulator of many enzymes involved in xenobiotic metabolism, such as cytochrome P450s and P-gp. It contains a DNA-binding domain and a ligand-binding domain, the latter of which is substantially flexible and allows for the binding of structurally diverse compounds (i.e., xenobiotics). For instance, the compound SR12813 binds to PXR in three distinct orientations.\(^{431}\) With an EC\(_{50}\) value of 23 nM, hyperforin is the most potent PXR activator discovered.\(^{430b}\) Using tritiated SR12813 in a competition binding assay, it was also discovered that hyperforin binds directly to PXR. A resolved crystal structure of hyperforin bound to PXR provided unambiguous proof of direct interaction (Figure 1.16a).\(^{432}\) Compared to an earlier crystal structure of the ligand-binding domain of PXR in its apo form, hyperforin caused a 250 Å\(^3\) increase in binding site volume. In addition, most of the contacts hyperforin makes to PXR are through hydrophobic interactions of its prenyl side-chains (Figure 1.16b).


Further, hyperforin-induced PXR activation directly results in the upregulation of genes involved in xenobiotic metabolism and drug efflux. Treatment of primary human hepatocytes with hyperforin induced increased *CYP3A4* expression.\textsuperscript{430b} *CYP2C9* induction was also noted in the hyperforin treatment of HepG2 cells.\textsuperscript{433} The increased expression of these cytochrome P450s is significant since CYP3A4 and CYP2C9 are responsible for the metabolism of approximately 50% and 20% of all known drugs, respectively.\textsuperscript{434} While *CYP3A4* and *CYP2C8* expression did increase upon hyperforin exposure in primary human hepatocytes,\textsuperscript{435} *CYP24A1* and *CYP27B1* levels remained unchanged.\textsuperscript{436} In another study, *CYP1A1*, *CYP1A2*, and gene for the monooxygenase FMO5 were upregulated in HepG2 cells, while *CYP4F2* and *NQO2* were downregulated.\textsuperscript{437} Hyperforin also caused tissue-specific activation of the ATP-binding cassette transporters, which play important roles in controlling the passage of drugs and xenobiotics.


across intracellular and extracellular membranes. Using porcine brain capillary endothelial cells (PBCECs) as a model for the blood-brain barrier in humans, hyperforin treatment caused significant increases in mRNA levels for P-gp\textsuperscript{438} and both ABCG1 and 2.\textsuperscript{439} P-gp expression also significantly increased in LS180\textsuperscript{440} and T84\textsuperscript{441} cells, demonstrating that hyperforin may accelerate the excretion of drugs. Interestingly, while hyperforin caused upregulation of CYP3A4 in Caco-2 cells, P-gp expression actually decreased.\textsuperscript{442} Aside from regulating xenobiotic metabolism, PXR may also play a role in other areas of human health. Hyperforin-induced PXR activation may prevent liver steatosis, given that hyperforin treatment of HepG2 cells overexpressing PXR exacerbated steatogenic effects in these cells.\textsuperscript{443} PXR may be important in bone homeostasis and thus prevent osteoporosis; treatment of primary osteocytes with vitamin K\textsubscript{2} or hyperforin activated PXR and led to an increase in bone marker expression.\textsuperscript{444} However, chronic activation of PXR may lead to osteomalacia via increased CYP24A1 expression, leading to vitamin D deficiency.\textsuperscript{445}

It is also important to note that activation of PXR is species-specific. As mentioned previously, porcine PXR is hyperforin-sensitive.\textsuperscript{438} It is unclear whether mouse PXR is a hyperforin target. One study found that hyperforin did not induce cytochrome P450 expression in Swiss Webster mice,\textsuperscript{446} but another study found that hyperforin-HNCy\textsubscript{2} increased CYP3A-mediated hepatic erythromycin-N-
demethylase activity in CD-1 mice. The cynomolgus monkey (i.e., crab-eating macaque) response to hyperforin is very similar to that of humans, making this species an effective animal model for predicting downstream metabolic enzyme induction via PXR activation. Unlike mouse PXR, rat PXR is unambiguously unaffected by hyperforin exposure. In order to study which residues in rat PXR confer hyperforin insensitivity, a variety of rat-human PXR cDNA chimeras were prepared. Rat PXR hyperforin sensitivity was conferred by converting Phe305 to leucine, and human PXR was rendered hyperforin insensitive via mutagenesis of Leu308 to phenylalanine.

Further evidence for hyperforin activation of xenobiotic metabolism was provided through a variety of drug-specific, small-scale clinical trials involving SJW extracts containing variable amounts of the PPAP. In a study involving 10 renal transplant patients, only those that took SJW extracts with significant hyperforin experienced a cyclosporine drug interaction. Similar herb-drug interactions were encountered in studies involving healthy volunteers taking digoxin, theophylline, alprazolam, caffeine, tolbutamide, midazolam, ethinylestradiol, and 3-ketodesogestrel. SJW extracts with little to no hyperforin content failed to increase cytochrome P450 expression in several studies.

Apart from hyperforin, the binding affinity of other PPAPs to PXR has not been explored. The only other PPAP reported to interact with a nuclear receptor is guttiferone G. Guttiferone G preferentially binds to the liver X receptor \( \alpha \) isoform (LXR-\( \alpha \)) with an IC\(_{50} \) value of 3.4 \( \mu \)M, having little to no interaction with LXR-\( \beta \) (IC\(_{50} > 15 \) \( \mu \)M). Since LXRs play important roles in cholesterol homeostasis, guttiferone G may be a lead structure in the development of cholesterol regulation therapy.

Aside from increasing their expression levels via PXR activation, hyperforin appears to inhibit several proteins involved in xenobiotic metabolism. An early study found that hyperforin noncompetitively inhibited CYP2D6 with a \( K_i \) of 1.5 \( \mu \)M and competitively inhibited CYP3A4 (\( K_i = 0.48 \) \( \mu \)M) and CYP2C9 (\( K_i = 1.8 \) \( \mu \)M) in \textit{in vitro} binding assays. Hyperforin also potently inhibited cDNA-expressed CYP1A2, CYP2C9, and CYP2C19 with IC\(_{50} \) values of 3.9, 0.01, and 0.02 \( \mu \)M, respectively. CYP1A1 was also inhibited by hyperforin (\( K_i = 1.1 \) \( \mu \)M, IC\(_{50} = 1.2 \) \( \mu \)M), and this was demonstrated by the prevention of the carcinogen formation from CYP1A1-mediated benzo[\( a \)]pyrene-7,8-dihydrodiol epoxidation. While hyperforin inhibited CYP3A4 with an IC\(_{50} \) value of 0.63 \( \mu \)M, three of its naturally occurring analogs were found to be more potent inhibitors of the cytochrome P450 isoform (IC\(_{50} \) values in parentheses): furoadhyperforin (0.072 \( \mu \)M), furohyperforin isomer 1 (0.079 \( \mu \)M), furohyperforin isomer 2 (0.23 \( \mu \)M). Furohyperforin was also found to inhibit CYP3A4 with an IC\(_{50} \) value of 1.3 \( \mu \)M. P-gp activity was also moderately inhibited by hyperforin (IC\(_{50} = 30 \) \( \mu \)M), ascertained by monitoring the active

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efflux of daunorubicin from NIH-3T3 cells expressing P-gp.\textsuperscript{463} P-gp and ABCG2 inhibition was also observed in leukemia cell lines.\textsuperscript{464} Using PBCECs and freshly isolated porcine brain capillaries as models for the blood-brain barrier, hyperforin was found to directly inhibit P-gp activity.\textsuperscript{465} Hyperforin also partially inhibited paclitaxel efflux from xenopus oocytes expressing the liver-specific organic anion transporting polypeptide isoform 1B3.\textsuperscript{466}

Several preclinical and small-scale clinical trials were performed to determine hyperforin’s pharmacokinetic profile in various orally available forms.\textsuperscript{467} This is particularly intriguing considering that hyperforin on one hand activates PXR and on the other inhibits various cytochrome P450s. In rats given a SJW extract containing 5% hyperforin (300 mg/kg) orally, hyperforin plasma levels reached a maximum of 370 ng/mL (approximately 690 nM) after a single dose.\textsuperscript{468} After dosing either an extract containing 4.5% or with pure hyperforin-HNCy\textsubscript{2} once a day for 12 days in mice, plasma concentrations of hyperforin were significantly lower than after a single dose.\textsuperscript{447} These data are unsurprising given the fact that hyperforin may increase xenobiotic metabolism through activation of PXR in mice. When a 5% hyperforin extract was co-medicated with the CYP3A4 inhibitor ritonavir (20 mg/kg) in mice, a significant increase in hyperforin bioavailability was observed.\textsuperscript{467} Co-medication with the P-gp inhibitor valsodar did not have any effect on hyperforin AUC. Another study established that hyperforin does indeed cross the blood-brain barrier in mice.\textsuperscript{469,470} While treatment with the purified sodium salt of


\textsuperscript{467} For an overview of hyperforin pharmacokinetics, see: Caccia, S. \textit{Curr. Drug Metab.} 2005, 6, 531-543.

\textsuperscript{468} Biber, A.; Fischer, H.; Römer, A.; Chatterjee, S. S. \textit{Pharmacopsychiatry} 1998, 31 (Suppl.), 36-43.

hyperforin (15 mg/kg) produced a 28.8 ng/g brain concentration, treatment with 300 mg/kg SJW extract containing 5% hyperforin only gave a 15.8 ng/g concentration. Hyperforin rat brain concentrations were increased through co-medication with borneol or through electroacupuncture, two techniques that have shown some positive results in increasing blood-brain barrier permeability.471

Hyperforin pharmacokinetics have been determined in humans through various small-scale studies, and the results of several single- and multiple-dose studies involving various SJW ethanolic extract preparations are shown in Table 1.17. A large degree of pharmacokinetic parameter variation is observed, and this is in part due to the variable nature of the extracts and inherent metabolite ratios as well as inter-individual differences in response to treatment. In general, $C_{\text{max}}$ is rapidly attained within 3-4 hours and follows a linear relationship to the amount of hyperforin administered in single-dose studies. Overall, hyperforin plasma concentrations peaked in the range of 0.16-0.81 M. Single-dose $AUC$ also follows a linear relationship up to about 40 mg hyperforin, and at higher concentrations, lower than expected bioavailability is observed. Elimination half-life remained fairly consistent across dosing regimens.

470 For an overview of murine brain hyperforin pharmacokinetics, see: Caccia, S.; Gobbi, M. Curr. Drug Metab. 2009, 10, 1055-1065.

471 Yu, B.; Ruan, M.; Sun, Y.; Cui, X.; Yu, Y.; Wang, L.; Fang, T. Neural Regen. Res. 2011, 6, 1876-1882.
<table>
<thead>
<tr>
<th>Extract dose (mg x day)</th>
<th>Participants</th>
<th>Hyperforin per dose (mg)</th>
<th>t(_{\text{max}}) (h)</th>
<th>C(_{\text{max}}) (ng/mL)</th>
<th>AUC (ng/mL·h)</th>
<th>t(_{1/2}) (h)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 x 1</td>
<td>18 M</td>
<td>13.5</td>
<td>4.4 (1.5)</td>
<td>84 (28)</td>
<td>1009 (203)</td>
<td>19.6 (6.3)</td>
<td>472</td>
</tr>
<tr>
<td>600 x 14</td>
<td>18 M</td>
<td>13.5</td>
<td>4.3 (1.0)</td>
<td>97 (30)</td>
<td>826 (176)</td>
<td>4.3 (1.0)</td>
<td>472</td>
</tr>
<tr>
<td>300 x 1</td>
<td>6 M</td>
<td>14.8</td>
<td>3.6 (0.6)</td>
<td>153 (21)</td>
<td>1336 (145)</td>
<td>9.5 (1.1)</td>
<td>468</td>
</tr>
<tr>
<td>300 x 1</td>
<td>6 M, 6 F</td>
<td>15</td>
<td>3.1 (0.8)</td>
<td>84 (36)</td>
<td>586 (240)</td>
<td>n.d.</td>
<td>473</td>
</tr>
<tr>
<td>300 x 1</td>
<td>6 M, 6 F</td>
<td>15</td>
<td>2.5 (0.8)</td>
<td>168 (58)</td>
<td>1483 (697)</td>
<td>n.d.</td>
<td>473</td>
</tr>
<tr>
<td>900 x 1</td>
<td>18 M</td>
<td>17.2</td>
<td>4.5 (1.2)</td>
<td>122 (46)</td>
<td>1550 (371)</td>
<td>17.5 (4.5)</td>
<td>474</td>
</tr>
<tr>
<td>900 x 1</td>
<td>18 M</td>
<td>17.2</td>
<td>3.9 (1.3)</td>
<td>87 (37)</td>
<td>1769 (255)</td>
<td>n.d.</td>
<td>474</td>
</tr>
<tr>
<td>600 x 1</td>
<td>6 M</td>
<td>28.6</td>
<td>3.5 (0.3)</td>
<td>302 (47)</td>
<td>2215 (279)</td>
<td>8.5 (0.7)</td>
<td>468</td>
</tr>
<tr>
<td>900 x 1</td>
<td>7 M, 2 F</td>
<td>42.8</td>
<td>2.9 (0.3)</td>
<td>300 (23)</td>
<td>3352 (329)</td>
<td>7.2 (0.3)</td>
<td>468</td>
</tr>
<tr>
<td>900 x 8</td>
<td>7 M, 2 F</td>
<td>42.8</td>
<td>3.1 (0.4)</td>
<td>246 (22)</td>
<td>2336 (303)</td>
<td>11.2 (1.0)</td>
<td>468</td>
</tr>
<tr>
<td>900 x 1</td>
<td>3 M, 9 F(^d)</td>
<td>55.1</td>
<td>4.0 (n.d.)</td>
<td>1500 (200)</td>
<td>13600 (2400)</td>
<td>16.6 (1.9)</td>
<td>475</td>
</tr>
<tr>
<td>900 x 14</td>
<td>3 M, 9 F(^d)</td>
<td>55.1</td>
<td>3.0 (n.d.)</td>
<td>1300 (200)</td>
<td>10900 (2200)</td>
<td>14.7 (2.2)</td>
<td>475</td>
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<tr>
<td>1200 x 1</td>
<td>6 M</td>
<td>59.2</td>
<td>2.8 (0.3)</td>
<td>437 (101)</td>
<td>3378 (670)</td>
<td>9.7 (0.8)</td>
<td>468</td>
</tr>
</tbody>
</table>

\(^a\) Pharmacokinetic data are reported as means (± standard error).

\(^b\) Listed are the number of male (M) and female (F) participants. Unless noted, all participants were healthy volunteers.

\(^c\) A softgel capsule formulation was used.

\(^d\) Patients in these studies were diagnosed with clinical depression prior to treatment. See text below.

\(^e\) The SJW extract was co-medicatied with the antidepressant amitriptyline (75 mg twice daily).

While most of the data presented in Table 1.17 is derived from studies involving healthy volunteers, one study utilized patients suffering from clinical depression, with initial scores ranging from 10-34 in the Hamilton Rating Scale for Depression.\(^{475}\) Intriguingly, hyperforin exposure was significantly higher for these patients than in healthy patients consuming similar amounts of hyperforin. Formulation of the SJW extract also appears to have an effect on oral bioavailability; a softgel capsule formulation led to significant increases in C\(_{\text{max}}\) and AUC when directly compared to a traditional two-piece hard gelatin capsule.\(^{473}\)


Multiple-dose hyperforin pharmacokinetics were also investigated.\textsuperscript{468,472,474} In all three instances, significantly lower $AUC$ at the end of the treatment regimen was observed and can be explained by hyperforin’s ability to activate PXR and thus upregulate xenobiotic metabolism. Similar results were observed upon co-medication of amitriptyline with hyperforin; aside from decreased amitriptyline plasma concentrations, the concentrations of all hydroxylated metabolites of amitriptyline decreased significantly, indicating increased drug efflux.\textsuperscript{475} A study involving five mothers taking SJW extract daily (containing 22.4 mg hyperforin) demonstrated that hyperforin is present in breast milk, but at low levels.\textsuperscript{476} In two breastfed infants, the plasma concentration of hyperforin was present, albeit at the lowest limit of detection (0.1 ng/mL).

The only other PPAP to have undergone pharmacological studies is xanthochymol.\textsuperscript{76} Doses of 1.0-10.0 mg/kg given to anesthetized cats did not lead to cardiovascular side effects. In mice, the LD$\textsubscript{50}$ of xanthochymol was determined to be 1000 mg/kg, and no detrimental nervous system effects were observed at one-fifth the LD$\textsubscript{50}$.

The packaging and unpackaging of eukaryotic DNA around histones largely determines the extent to which genes are expressed. Modifications of these histone proteins, such as through acetylation, alter chromatin structure and regulates transcription.\textsuperscript{477} The enzymes responsible for histone acetylation and deacetylation are called histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively, and alteration of HAT and HDAC activity has been implicated in a variety of diseases, such as cancer and neuodegeneration.\textsuperscript{478} Given the ability of a variety of PPAPs to penetrate cell membranes and perturb a variety of biochemical processes, their ability to modulate HAT/HDAC activity has been


actively investigated. Early studies found that hyperforin altered protein expression in hamster smooth muscle cells and that garcinol altered gene expression in rat livers, implying that these PPAPs may be interacting with epigenetic modulators.

Indeed, garcinol was later found to dose-dependently inhibit two HATs, p300 (IC$_{50} = 7$ μM) and PCAF (IC$_{50} = 5$ μM) both in in vitro assay studies as well as in vivo studies involving HeLa cells. Over a hundred genes were affected in HeLa cells treated with garcinol, and apoptosis was observed. Kinetic analysis revealed that garcinol acted as a competitive inhibitor for both enzymes. However, garcinol also exhibited considerable cytotoxicity. In order to find a HAT inhibition-specific molecular probe, nearly 50 semisynthetic garcinol derivatives were screened for p300 inhibition activity. Isogarcinol inhibited p300 activity but was also cytotoxic. Three derivatives of garcinol, 84, 85, and 86, were identified as non-cytotoxic, p300-specific inhibitors with IC$_{50}$ values in the range of 5-7 μM (Figure 1.17). T cells treated with 84 were not only viable but also experienced histone acetylation inhibition after HIV infection, thus preventing viral replication. Subsequent mechanistic studies found that the inhibition of p300 HAT activity by 84 is dissimilar to that of garcinol and isogarcinol. Using in silico docking methods, garcinol and isogarcinol were found to bind p300 in two distinct sites, including the ATP-binding pocket, but 84 bound to a single, allosteric site. These data were supported by experimental isothermal calorimetric data.

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The ability of garcinol to alter gene expression has been applied across several settings relevant to human health. When garcinol was co-administered with the apoptosis-inducing cytokine TRAIL, several cancer cell lines resistant to TRAIL became sensitive.\textsuperscript{485} Garcinol increased expression of death receptors 4 and 5, receptors of TRAIL, and also decreased the expression of various proteins involved in cell survival. In addition, the epigenetic changes mediated by garcinol and \textsuperscript{84} in inhibiting MCF-7 cell proliferation were elucidated.\textsuperscript{486} Increased levels of H4K16 acetylation and H4K20 trimethylation accompanied significant reduction in H3K18 acetylation. A major but limited source of hematopoietic stem cells is human cord blood, and when human cord blood cells were treated with either garcinol or isogarcinol in the presence of thrombopoietin, a significant increase in cell proliferation was observed.\textsuperscript{487} This stem cell expansion may be due to the ability of these PPAPs to inhibit HAT activity. In 3T3-L1 preadipocytes, garcinol treatment prevented adipogenesis and lowered expression levels of proteins associated with this differentiation process, including leptin, resistin, and fatty acid synthase.\textsuperscript{488} This epigenetically-induced anti-adipogenic effect of garcinol may be one avenue for the treatment and prevention of obesity.


\textsuperscript{488} Hsu, C.-L.; Lin, Y.-J.; Ho, C.-T.; Yen, G.-C. \textit{Food Funct.} \textbf{2012}, \textit{3}, 49-57.
Aside from garcinol and its derivatives, a variety of other PPAPs have been evaluated for HAT and HDAC activity. While garcinielliptone, hyperibone B, propolones A-D, and propolone D peroxide had no significant interaction with p300, guttiferones A and E as well as clusianone inhibited p300 HAT activity with IC\textsubscript{50} values in the 5-10 µM range.\textsuperscript{489} Interestingly, nemorosone was a potent activator of p300 HAT activity. Surface plasmon resonance established that guttiferones A and E, clusianone, and nemorosone all interact directly with p300. Aside from modulating HAT activity, oblongifolin C, hyperforin, and the semisynthetic hyperforin derivative aristoforin (78) inhibited HDAC activity of sirtuins SIRT1 and SIRT2 (Table 1.18).\textsuperscript{490} Both oblongifolin C and aristoforin were less cytotoxic toward HUVECs than hyperforin.

<table>
<thead>
<tr>
<th>PPAP</th>
<th>SIRT1 IC\textsubscript{50} (µM)</th>
<th>SIRT2 IC\textsubscript{50} (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oblongifolin C</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>hyperforin</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>aristoforin (78)</td>
<td>7</td>
<td>21</td>
</tr>
</tbody>
</table>

Hyperforin has been evaluated for the ability to modulate contractility. Overactive bladder contractions causes a loss of urine control and leads to incontinence. At concentrations as low as 10 µM, hyperforin inhibited electric field stimulated contractions in isolated rat bladder strips.\textsuperscript{491} Naloxone but not neurotransmitter receptor inhibitors and ion channel blockers abrogated the ability of hyperforin to inhibit contractions. This suggests the involvement of opioid receptors. In contrast, at low concentration (10 nM), hyperforin caused a slight increase in carbachol-induced contractions.\textsuperscript{492} Orally dosed hyperforin delayed acethocholine-induced gastric emptying with an EC\textsubscript{50} value of about 1 µM in a rat


\textsuperscript{491} Capasso, R.; Borrelli, F.; Capasso, F.; Mascolo, N.; Izzo, A. A. Urology 2004, 64, 168-172.

\textsuperscript{492} Valeri, A.; Capasso, R.; Valoti, M.; Pessina, F. J. Pharm. Pharmacol. 2012, 64, 1770-1776.
model, which may lead to drug-drug interactions since gastric motility plays an important role in drug uptake. Overactive contractions of the vas deferens smooth muscle may lead to premature ejaculation. An early study found that hyperforin, in concentrations as low as 0.6 µM, inhibited neurotransmitter-induced contractions of hamster vas deferens smooth muscle tissue. Similar inhibition was observed in phenylephrine-induced contractions of both isolated rat and human vas deferens tissue. A hyperforin-enriched supercritical CO\textsubscript{2} SJW extract was shown to prevent chemically-induced ejaculation acceleration in anesthetized rats, the first instance of hyperforin showing efficacy against premature ejaculation in an animal model.

**Synthesis Strategies**

Owing to their fascinating biological activity and unique structural features, PPAPs have been popular targets over the past fifteen years, and many strategies have been developed for their synthesis. Several salient features of PPAP structure apropos to bond construction are summarized in Scheme 1.13. All PPAPs contain a heavily substituted bicyclo[3.3.1]nonane core in which one component carbocycle is highly oxygenated and the other carbocycle contains stereochemically-rich functionalization. In particular, a synthetically challenging C7–C8–C1 stereoarray includes contiguous quaternary centers. All studies toward PPAP total synthesis may be broken down into two general strategic camps: (1) a “bottom-up” approach and (2) a “top-down” approach. Bottom-up tactics rely on the synthesis of a functionalized cyclohexanone followed by attachment of a 1,3-propanedial synthon. Likewise, top-down strategies typically involve the construction of a functionalized phloroglucinol (or cyclohexane-1,3-dione) which

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then undergoes dearomative annulation\textsuperscript{497} or stepwise alkylation-cyclization with a 3-carbon electrophile. An overview of the PPAP synthesis literature is provided below, following this general framework.

Several 1,3-dielectrophiles have been utilized in “bottom-up” annulation approaches (Figure 1.18). Malonyl dichloride (87) is especially useful for the synthesis of PPAPs considering that annulation would directly afford the correct oxidation state of the C2–C4 bridge. Malonyl dichloride was first used to synthesize bicyclo[3.3.1]nonanes by Effenberger in 1984; however, a fourfold excess of 1-methoxy-1-cyclohexene was required in this initial report.\textsuperscript{498} Stoltz demonstrated that silyl enol ethers may be utilized in addition to alkyl enol ethers and that an excess of malonyl dichloride may be used instead of the enol ether component in this Effenberger annulation.\textsuperscript{499} Nicolaou has utilized methacrylaldehyde (88) in acid-mediated annulation reactions to create a series of bicyclic medium-sized rings, including bicyclo[3.3.1]nonanes.\textsuperscript{500} Kraus has explored several strategies toward the construction of PPAP model systems, using the electrophiles vinylsulfone 89\textsuperscript{501} and methyl acrylate 90.\textsuperscript{502} Simpkins also attempted to utilize diaryl malonate 91 but to no avail.\textsuperscript{503}

\textsuperscript{497} For a review that features dearomative annulation and cyclization approaches to PPAPs, see: Roche, S. P.; Porco, J. A., Jr. Angew. Chem. Int. Ed. 2011, 50, 4068-4093.


A total synthesis of (±)-clusianone (rac-92) by Simpkins utilizing an Effenberger annulation strategy is shown in Scheme 1.14. Starting with 2-methoxycyclohexenone 93, α-prenylation followed by methyl lithium addition afforded enone 94. Conjugate addition of methyl cuprate and subsequent methyl enol ether formation afforded 95. Exposure of enol ether 95 to malonyl dichloride and subsequent treatment of the product with trimethyl orthoformate afforded vinylogous ester 96 in 24% yield over 2 steps. LDA-mediated bridgehead lithiation and alkylation with prenyl bromide gave 97, and subsequent benzylation afforded rac-clusianone O-methyl ether 98. Lithium hydroxide-facilitated demethylation revealed rac-clusianone. By replacing LDA with a chiral bis-lithium amide in the bridgehead lithiation reaction of 96, a kinetic resolution allowed 96 to be recovered with 98% ee and facilitated the synthesis of ent-clusianone (ent-92). Effenberger annulations are also utilized in Delpech and Marazano’s synthesis of rac-92, and Coltart has synthesized ent-92 using a chiral auxiliary to

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504 Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. Org. Lett. 2006, 8, 5283-5285.

505 Prior to 1999, the only synthesis studies directed toward a PPAP are found in a graduate thesis from the Univeristy of Arizona: Heidt, J. C. Thesis, University of Arizona, Tucson, Arizona, United States of America, 1988. A compound similar to 95 was the most advanced intermediate synthesized in an approach to hyperforin.


establish absolute stereocontrol. Mehta has utilized an Effenberger annulation in studies directed toward prolifenones A and B.

A prominent feature of Simpkin’s total synthesis of clusianone is the bridgehead lithiation and subsequent alkylation of intermediate 96. The reaction involves the formation of a somewhat unusual pyramidalized carbanionic species from a bridgehead methine whose trajectory limits hyperconjugative delocalization into the neighboring carbonyl π* molecular orbitals. In the context of PPAP total synthesis, the scope and limitations of bridgehead functionalization has been studied in detail. In Scheme 1.14, the bridgehead alkylation occurs at the C5 position of 96. Bridgehead substitutions at the C1 position, which is proximal to the C8 quaternary center, are understandably more challenging due to its steric environment, and only a limited number of electrophiles have been utilized to functionalize this

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Simpkins's total synthesis of racemic nemorosone \( (rac-39) \) illustrates the difficulties of direct C1 bridgehead substitution (Scheme 1.15).\(^{503,510}\) Starting from enone \( 99,\)\(^{499} \) \( \alpha \)-prenylation followed by conjugate methyl addition accessed cyclohexanone \( 100.\)\(^{503} \) Sequential silylation, Effenberger annulation with malonyl dichloride \( (87) \), and methylation revealed \( 101 \), which was silylated at the C3 position to yield \( 102.\)

A more direct route to nemorosone would involve C3 prenylation; however, such an intermediate would not undergo bridgehead lithiation owing to an acidic bisallylic methylene subunit.\(^{503} \) A variety of conditions for the bridgehead functionalization of \( 102 \), including the use of several carbogenic electrophiles, did not provide any desired products. This illustrates the difficulty of performing bridgehead substitution chemistry at the C1 position relative to the C5 position when compared to the efficient conversion of \( 96 \) to \( 97 \) in Scheme 1.14. In the end, metalation of \( 102 \) with LDA followed by

trapping with iodine provided bridgehead iodide 103. Having installed a functional handle at C1, metalation with butyllithium, trapping with benzyol chloride, and desilylation provided phenyl ketone 104. Finally, installation of the C3 prenyl group was facilitated by sequential deprotonation, transmetalation with Lipshutz’s cuprate, 511 and prenyl bromide alkylation, and demethylation with lithium chloride provided (±)-nemorosone (rac-39).

Aside from using 1,3-dielectrophiles, several groups have explored the use of an intramolecular aldol reaction to construct the PPAP bicyclo[3.3.1]nonane core. Shibasaki has utilized this reaction in his total synthesis of ent-hyperforin (ent-1), the first enantioselective total synthesis of a PPAP (Scheme 1.16). 512 Starting with diene 105 (available in 7 steps from propargyl bromide) 513 and oxazolidinone 106, a catalytic, enantioselective Diels–Alder reaction involving FeBr3 and pybox ligand 107 (Figure 1.19) afforded siloxycyclohexene 108. This is a particularly effective transformation for the construction of the cyclohexanone carbocycle of PPAPs, since both the C7 and C8 stereocenters of hyperforin are established in a single step. Removal of the oxazolidinone ring and silyl groups of 108 revealed cyclohexanone 109, and a subsequent series of reactions including a Barbier reaction produced 110 containing the carbon framework of the isopropyl ketone of hyperforin. α-Prenylation gave 111 as a single epimer at the C5 position. After C5 epimerization and functional group manipulations, O-allylation afforded 112, and heating a toluene solution of 112 quantitatively yielded 113 in a high diastereomeric ratio at the newly formed quaternary C1 stereocenter. The high degree of diastereocontrol in this transformation may be rationalized by assuming the C5 prenyl group of 112 directs the carbon-carbon bond formation to the opposite face of the cyclohexene ring. Hydroboration of the olefin present in 113 followed by DMP-mediated oxidation provided aldehyde 114. Exposure of this aldehyde to sodium ethoxide in ethanol


Scheme 1.16. Total synthesis of ent-hyperforin by Shibasaki (ref. 512).a

114

a Conditions: (a) 107, FeBr3, Ag2SbF6, 5 Å MS, CH2Cl2, –70 ºC, 93%, 98% ee; (b) EtSLi, THF, 96%; (c) LAH, THF, 99%; (d) MOMCl, TBAL, i-Pr2NEt, CH2Cl2, 94%; (e) TBAF, HOAc, THF; (f) HF/pyr, pyr, THF, 91% (2 steps); (g) TMSCI, NEt3, CH2Cl2; (h) TIPSOTf, i-Pr2NEt, CH2Cl2; (i) K2CO3, MeOH; (j) TPAP, NMO, 4 Å MS, MeCN, CH2Cl2; (k) i-PrBr, Li, THF; (l) TBAF, HOAc, THF, 58% (6 steps); (m) TMSCI, imid, DMF, 94%; (n) LDA, HMPA, pre nyl bromide, THF, 89%; (o) LDA, THF, NH4Cl, H2O, 88%; (p) HF/pyr, pyr, THF; (q) DMP, CH2Cl2, 96% (2 steps); (r) NaHMDS, allyl bromide, HMPA, THF, >99%; (s) PhMe, N,N-diethylaniline, 170 ºC, >99%; 12:1 dr; (t) (Sia)2BH, THF, H2O2, MeOH, 95%; (u) TFAA, DTBMP, CH2Cl2, –40 ºC, H2O, 65%; (v) DMP, CH2Cl2, 96% (2 steps); (w) NaBH4, MeOH, 91% (2 steps); (x) CSA, MeOH, 93% (3 steps); (y) (COCl)2, DMSO, CH2Cl2, NEt3, 95%; (z) vinyl magnesium bromide, THF, 92%; (aa) Ac2O, DMP, i-Pr2NEt, CH2Cl2, 98%; (bb) Pd(PPh3)4, HCO2NH4, PhMe, 95%; (cc) 117, 2-methyl-2-butenone, CH2Cl2, >99%; (dd) TMSCI, NEt3, DMAP, CH2Cl2, 84%; (ee) Pd(OAc)2, DMSO, O2, >99%; (ff) NaBH4, MeOH, 95%; (gg) CS2, NaH, THF, MeI, >99%; (hh) PhMe, 150 ºC; (ii) EtSLi, THF, MeI, NEt3, 98% (2 steps); (jj) NaBO3·4H2O, HOAc, 95%; (kk) TFAA, DTBMP, CH2Cl2, –40 ºC; H2O2, 65%; (ll) H2O2, HFIP, 87%; (mm) DMP, CH2Cl2, 86%; (nn) Amberlyst-15DRY, PhMe, 55%; (oo) LiH, allyl alcohol, 67%; (pp) [Pd2(dba)3]·CHCl3, (S)-tol-BINAP, THF; Ac2O, pyr, 50%; (qq) 117, 2-methyl-2-butenone, CH2Cl2, 34%; (rr) K2CO3, MeOH, 94%.
facilitated the key aldol cyclization reaction,\textsuperscript{514} and subsequent DMP-mediated oxidation afforded 115, which contains the bicyclo[3.3.1]nonane core of hyperforin with all key stereocenters established.

![Figure 1.19. A Pybox ligand and an olefin metathesis catalyst, both utilized in the total synthesis of ent-hyperforin.](image)

At this point in the synthesis, the only remaining tasks were the installation of the C3 and C7 prenyl groups as well as the 1,3-diketone oxidation state about the C2–C4 bridge. First, the C7 prenyl group was installed via sequential MOM group removal, oxidation, and vinylmagnesium bromide addition of 115 to afford allylic alcohol 116 as a mixture of epimers. Deoxygenation was then accomplished via stepwise acetylation and Pd-catalyzed allylic reduction, and a resulting olefin cross metathesis with 2-methyl-2-butene utilizing Hoveyda–Grubbs second-generation catalyst (117, Figure 1.19) afforded 118. It is noteworthy that the C8 homoprenyl olefin was previously protected as a tertiary methyl ether; if a homoprenyl group was present during this cross metathesis, the authors observed ring-closing metathesis. After considerable experimentation, installation of the C2–C4 1,3-diketone oxidation was accomplished through a vinylogous Pummerer rearrangement. First, a Saegusa oxidation of 118 followed by 1,2-reduction and xanthate formation led to 119. Thermal [1,3]-rearrangement of the xanthate functionality, thiolysis, S-methylation, and S-oxidation yielded the rearrangement precursor 120. Exposure of 120 to trifluoroacetic anhydride and 2,6-di-tert-butyl-4-methylpyridine followed by hydrolysis afforded a product, 121, bearing oxygenation at both the C2 and C4 positions. S-Oxidation, DMP-mediated oxidation, elimination of the homoprenyl protecting group, and addition-elimination

afforded allylic ether 122. Finally, intramolecular Pd-catalyzed allyl transfer, acetylation, cross metathesis, and deacetylation revealed *ent*-hyperforin (*ent*-1).

Other groups have utilized an intramolecular aldol strategy in their studies toward PPAP natural products. Grossman’s approach involved a Pb(OAc)$_4$-mediated $\alpha$-alkynylation of $\beta$-ketoester 123 with stannane 124, and subsequent hydrosilylation of an insipient Co$_2$(CO)$_6$ complex to reveal enal 125, which upon exposure to aqueous acid afforded allylic alcohol 126 (Scheme 1.17a).$^{515}$ Mehta has reported the DIBAL reduction of tetrahydrochromene 127 to bicyclo[3.3.1]nonane 128, which may proceed through an intermediate hemiacetal 129 that undergoes formal [1,3] rearrangement via aldehyde 130 (Scheme 1.17b).$^{516}$ Very similar reductive rearrangements have been reported by Shibasaki$^{517}$ and Delpech.$^{518}$ In studies toward hyperforin, Chen has reported the synthesis of aldehyde 131 via sequential Pd-catalyzed hydrostannylation of alkyne 132 followed by oxidative cleavage (Scheme 1.17c).$^{519}$ Exposure of this aldehyde to NaOEt in EtOH afforded bicyclo[3.3.1]nonane 133.

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Scheme 1.17. Intramolecular aldol approaches to PPAPs by (a) Grossman, (b) Mehta, and (c) Chen.\textsuperscript{a}

\textsuperscript{a} Conditions: (a) 124, \text{Pb(OAc)}\textsubscript{4}, THF, \textdegree30 to rt, 48%; (b) \text{HCO}_2\text{H}, 71%; (c) \text{Co}_2(\text{CO})_8, \text{CH}_2\text{Cl}_2, 0 \textdegree\text{C}, 87%; (d) \text{Et}_3\text{SiH}, bis(trimethylsilyl)acetylene, DCE, 65 \textdegree\text{C}, 94%; (e) \text{HCl, H}_2\text{O}, 72%; (f) \text{DIBAL, CH}_2\text{Cl}_2, 0 \textdegree\text{C}, 52%; (g) \text{PdCl}_2(\text{PPh}_3)_2, \text{Bu}_3\text{SnH}, \text{THF}; \text{OsO}_4, \text{NMO, H}_2\text{O}; (h) \text{Pb(OAc)}\textsubscript{4}, \text{CH}_2\text{Cl}_2, 79\% (2 \text{ steps}); (i) \text{NaOEt, EtOH, 0 \textdegree\text{C to rt}; (j) DMP, NaHCO}_3, \text{CH}_2\text{Cl}_2, 70\% (2 \text{ steps}).

In addition to the aldol strategies outlined previously, Plietker has utilized an intramolecular Dieckmann cyclization approach for the synthesis of (±)-7-\textit{epi}-clusianone (\textit{rac}-40, Scheme 1.18).\textsuperscript{520}

Starting with acetylacetone (134), stepwise prenylation and deacylative aldol methylation provided enone 135. Treatment of this enone with dimethyl acetylenedicarboxylate (136) afforded cyclohexenone 137 as a result of a tandem Michael addition-Knoevenagel condensation. Sequential regioselective methyllithium 1,2-addition, \textalpha\text{-prenylation, and conjugate methylation afforded cyclohexanone 138. In order to facilitate the key Dieckmann cyclization step, stereoselective prenylation at the C1 position of 138 was required in order to position the methyl ketone and methyl ester upon the same face of the

cyclohexanone ring. After some experimentation, a Fe-catalyzed allylation using methyl prenyl carbonate (139) afforded cyclization precursor 140. Treatment with KO-t-Bu followed by BzCN directly afforded (±)-7-epi-clusianone (rac-40). Further, Plietker was able to synthesize racemic hyperpapuanone, hyperibone L, and oblongifolin A, highlighting the utility of this methodology to obtain Type B PPAPs bearing an exo C7 substituent.

Scheme 1.18. Total synthesis of (±)-7-epi-clusianone by Plietker (ref. 520).§

Other “bottom-up” approaches involve the use of transition metals or cycloaddition chemistry to facilitate the formation of the bicyclo[3.3.1]nonane core of PPAPs. Garsubellin A was the first PPAP to be synthesized, and Shibasaki utilized ring-closing metathesis to establish the C2–C4 bridge. Kraus has utilized a Mn(OAc)₂-mediated oxidative free-radical cyclization to facilitate to formation of the PPAP

§ Conditions: (a) NaH, EtOH, 0 °C; prenyl bromide, 0 °C to rt; CH₂O, K₂CO₃, H₂O, 60%; (b) MeMgCl, 136, THF, MeOH, 60 °C, 89%; (c) NaH, THF, 0 °C; MeLi, 0 °C; (d) NaH, 18-crown-6, THF, 0 °C; prenyl bromide, 0 °C to rt, 61% (2 steps); (e) MeMgBr, CuI, TMSCl, LiCl, THF, –78 °C, 96%; (f) t-AmOK, 1,3-dimesitylimidazolin-2-ylidene hexafluorophosphat, MTBE, 60 °C; Bu₄N[Fe(CO)₃(NO)], rt to 60 °C; 138, LiH, THF, 0 °C to rt; (139, 100 °C, 86%; (g) t-BuOK, THF, 0 °C; BzCN, 0 to 45 °C, 78%.


core in several model systems. Mehta has also synthesized a model bicyclo[3.3.1]nonane using a Pd-catalyzed Kende cyclization. In an approach to hyperevolutin A, Young utilized an allene-nitrile oxide [3+2] cycloaddition reaction (Scheme 1.19). Treatment of 141 with PhNCO facilitated the cycloaddition to form isoxazoline 142, presumably through intermediate nitrile oxide 143. Only a single C4 epimer of 142 was isolated, indicating that only one diastereomer of 143 underwent cyclization. Reduction of 142 using Raney Ni quantitatively afforded enamine 144 through cleavage of the isoxazoline ring.

Scheme 1.19. Young's [3+2] allene-nitrile oxide cycloaddition approach to hyperevolutin A (ref. 526).a

*a Conditions: (a) PhNCO, NEt3, 40%; (b) Raney Ni, H2, MeOH, >99%.

Contrasting “bottom-up” strategies, “top-down” approaches to PPAP synthesis typically involve dearomatization of an oxidized benzene ring through the attachment of the C6–C8 bridge. Many of these strategies are inspired by the proposed biosynthesis of PPAPs, involving the dearomative alkylation of an acylphloroglucinol (e.g., Scheme 1.5). As previously discussed, a challenge of many “bottom-up” strategies is the oxidation of the C2–C4 subunit; in “top-down” strategies, establishing this oxidation very

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early in the synthesis circumvents this problem. Likewise, a difficulty of latter approaches is the installation of stereochemical elements at a late stage.

Many of these principles were incorporated in the total synthesis of (±)-garsubellin A (rac-145) by Danishefsky (Scheme 1.20). 527 Starting with phloroglucinol triether 146, 528 regioselective ortho lithiation-prenylation, dihydroxylation, acetonide formation, and desilylation afforded phloroglucinol diether 147. The reaction of this electron-rich phenol and allyl methyl carbonate under Pd- and Ti-cocatalysis provided divinylogous carbonate 148 via a dearomatative allylation reaction. 529 A possible mechanism for this transformation involves Lewis acid-activation of the phenolic hydroxyl group followed by direct para C-allylation. Treatment of 148 with perchloric acid facilitated the formation of alcohol 149 as a single diastereomer, bearing the tetrahydrofuran ring of garsubellin A. Cross metathesis with 2-methyl-2-butene facilitated by Grubbs second-generation catalyst (150) afforded 151. Exposure of 151 to iodine not only provided the desired bicyclo[3.3.1]nonane core through a i odocarboxyclization reaction but also promoted iodination at the C1 position, which after treatment with iodine and CAN provided triiodide 152. Aside from a tandem desired magnesium-iodine exchange with subsequent allylation at the C3 position of 152, a transannular Wurtz cyclopropanation yielded 153. Iodide 1,5-addition to the activated cyclopropane in 153 was accomplished by treatment with TMSI, affording 154. The synthesis of C7 prenylation product 155 was accomplished in two steps: (1) a AIBN-mediated Keck radical allylation 530 with allyltributylstannane and (2) cross-metathesis with 2-methyl-2-butene. At this juncture, only C1 acylation was necessary to complete the total synthesis; however, direct bridgehead lithiation-acylation of 155 was not feasible. Accordingly, bridgehead iodination was accomplished using LDA and iodine to afford iodide 156. Magnesium-iodide exchange, trapping with isobutyraldehyde, DMP-mediated oxidation, and desilylation subsequently afforded (±)-garsubellin A (rac-145). In

addition, these strategies were later utilized in racemic total syntheses of both nemorosone and clusianone.\textsuperscript{531}

Scheme 1.20. Total synthesis of (+)-garsubellin A by Danishefsky (ref. 527).\textsuperscript{a}

\textsuperscript{a} Conditions: (a) BuLi, Et\textsubscript{2}O, 0 °C; prenyl bromide; (b) K\textsubscript{2}OsO\textsubscript{4}, 2H\textsubscript{2}O, K\textsubscript{2}CO\textsubscript{3}, K\textsubscript{3}[Fe(CN)\textsubscript{6}], MeSO\textsubscript{2}NH\textsubscript{2}, t-BuOH, H\textsubscript{2}O; (c) p-TsOH, 2,2-dimethoxypropane, acetone; (d) TBAF, THF, 70% (4 steps); (e) allyl-O\textsubscript{CO}Me, Pd(OAc)\textsubscript{2}, Ti(O\textsubscript{i}-Pr)\textsubscript{4}, allyl methyl carbonate, PhH, 80 °C, 62%; (f) HClO\textsubscript{4}, H\textsubscript{2}O, dioxane, 60 °C, 71%; (g) 150, 2-methyl-2-butene, CH\textsubscript{2}Cl\textsubscript{2}, 40 °C, 68%; (h) I\textsubscript{2}, KI, KHCO\textsubscript{3}, THF, H\textsubscript{2}O, 85%; (i) I\textsubscript{2}, CAN, MeCN, 50 °C, 77%; (j) i-PrMgCl, THF, −78 °C; Li\textsubscript{2}CuCl\textsubscript{4}, allyl bromide, –78 to 0 °C, 67%; (k) TMSI, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C; HCl, H\textsubscript{2}O, 0 °C, 98%; (l) AIBN, allyltributylstannane, PhH, 80 °C, 82%; (m) 150, 2-methyl-2-butene, CH\textsubscript{2}Cl\textsubscript{2}, 40 °C, 73%; (n) LDA, TMSCl, −78 °C; I\textsubscript{2}, −78 to 0 °C, 25-36%; (o) i-PrMgCl, THF, −78 °C; i-PrCHO, −78 to 0 °C, 72%; (p) DMP, CH\textsubscript{2}Cl\textsubscript{2}; (q) Et\textsubscript{3}N(HF)\textsubscript{3}, THF, 88% (2 steps).

Other groups have utilized activated-olefin carboxylic acid as key steps in their studies toward PPAP natural products. Jacobsen employed a Claisen rearrangement of enol ether 157, catalyzed by guanidinium catalyst 158, to yield 159, in one step garnering the highly congested C1–C8 bond of hyperforin flanked by two stereogenic quaternary centers (Scheme 1.21a).\textsuperscript{532} Enol ether hydrolysis


followed by treatment with iodine yielded bicyclic diiodide 160. In studies toward garsubellin A, Nicolaou performed a Lewis acid-mediated selenocarbocyclization upon 161 using \(N\)-(phenylseleno)phthalamide (162), yielding bicyclo[3.3.1]nonane 163 (Scheme 1.21b). Couladourous reported a dearomatic \(C\)-alkylation of deoxycohumulone (31) with allyl chloride 164 to yield cyclohexadienone 165 (Scheme 1.21c). Following monoacetylation to give 166, exposure to MsCl afforded \(S_N1\)-type alkylation product 167. However, a substantial amount of \(O\)-alkylation product 168 was produced in addition to the desired \(C\)-alkylation product. \(SnCl_4\)-mediated carbocyclization of a prenylated phloroglucinol derivative has also been reported by Marazano; however, this reaction formed a variety of products.


Scheme 1.21. Carbocyclization approaches to PPAPs by (a) Jacobsen, (b) Nicolaou, and (c) Couladouros.\(^a\)

\(^a\) Conditions: (a) 158, hexane, 30 °C, 81%, 7:1 dr, 81% ee; (b) HCl, THF, 90%; (c) I\(_2\), KI, NHCO\(_3\), THF, H\(_2\)O, 65%; (d) 162, SnCl\(_4\), CH\(_2\)Cl\(_2\), –23 °C, 95%. (e) 164, KOH, Aliquat 336, PhCl, H\(_2\)O, 81%; (f) Ac\(_2\)O, pyr, acetone, 89%; (g) MsCl, NEt\(_3\), THF, –40 °C, 89% (total yield).

Other unique dearomatization strategies have been explored. Njardarson has pursued an oxidative dearomatization-double radical cyclization strategy for the synthesis of Type B PPAPs (Scheme 1.22a).\(^{536}\) Hypervalent iodine-mediated oxidative dearomatization of 169 afforded cyclohexadienone 170, and exposure of this compound to BEt\(_3\) gave bicyclo[3.3.1]nonane 171, the result of two 5-exo-trig cyclizations. Simpkins has utilized an unusual rearrangement of the flavonoid catechin (172) to catechinic acid (173), a reaction previously reported by Sears in 1974 (Scheme 1.22b).\(^{537}\)

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Nakada has explored an alternative approach to PPAPs involving a Birch reduction-cyclopropanation-cyclopropane opening sequence, exemplified by the racemic total synthesis of hyperforin (Scheme 1.23). Starting with methyl 2,6-dimethoxybenzoate (174), Birch reduction with concomitant allylation followed by reduction and silylation produced cyclohexadiene 175. The allyl moiety in 175 was converted to a methyl ketone using a three step protocol involving dihydroxylation and oxidative cleavage followed by methyl addition mediated with AlMe3 with an ensuing Oppenauer oxidation, affording 176. Subsequent trifluoracetylation of this compound followed by diazo transfer yielded α-diazoketone 177. Exposure of 177 to [Cu(OTf)]2 in the presence of achiral bisoxazoline ligand 178 facilitated an intramolecular cyclopropanation reaction, forming 179. Unfortunately, the use of chiral ligands did not lead to high levels of absolute stereocontrol. Stepwise α-alkylation of ketone 179 with allyl iodide and iodomethane followed by acid-mediated cyclopropane opening led to isolation of 180, a bicyclo[3.3.1]nonane core containing the key C1 and C8 vicinal stereogenic quaternary centers of hyperforin. Formal silanolysis of the allyl group of 180, formation of an enol triflate at the C7 position,

\[ \text{Scheme 1.22. Other dearomative carbocyclization approaches by (a) Njardarson and (b) Simpkins.}^a \]

\[ ^a \text{Conditions: (a) PhI(OAc)}_2, \text{MeOH, 75%}; (b) BEt}_3, (\text{TMS})_3\text{SiH, air, PhMe, 73%}; (c) \text{NaOH, H}_2\text{O, reflux, 91%}. \]
and subsequent Pd-mediated carbonylation led to ester 181. Crabtree’s catalyst facilitated stereoselective hydrogenation of the C6–C7 olefin, and subsequent functional group manipulations afforded acetate 182. Allylic oxidation mediated by TBHP and Pearlman’s catalyst afforded $\beta$-methoxyenone 183. Monodesilylation and Wittig homologation produced 184, and a subsequent aldehyde Wittig homologation yielded enol ether 185. Hydrolysis of this enol ether, another Wittig homologation, and C5 bridgehead allylation gave 186. Deprotonation at C3, followed by transmetalation with Lipshutz’s cuprate,$^{511}$ and alkylation with allyl bromide yielded 187. Conversion of the C1 hydroxymethylene of 187 to an isopropyl ketone afforded 188, and subsequent global cross metathesis and C2 methyl ether cleavage revealed (±)-hyperforin (rac-1). A similar strategy was utilized in the total synthesis of (±)-nemorosone by Nakada.$^{540}$
Scheme 1.23. Racemic total synthesis of (±)-hyperforin by Nakada (ref. 539).a

a Conditions: (a) Na, NH₃, t-BuOH, Et₂O, –78 ºC; allyl bromide; (b) LAH, Et₂O, 0 ºC; (c) TIPSOTf, NEt₃, CH₂Cl₂, 0 ºC, 74% (3 steps); (f) Me₂Al, PhMe, 0 ºC; 3-nitrobenzaldehyde, PhMe, 0 ºC to rt, 85%; (g) LHMDS, THF, –78 ºC; CF₃CO₂CH₂CF₃; 4-nitrobenzenesulfonyl azide, NEt₃, 0 to 40 ºC, 85%; (h) [Cu(OTf)]₂, PhMe, 178 ºC, PhMe; (i) KHMDS, HMPA, PhMe, THF, –78 ºC; allyl iodide, –78 to 0 ºC; (j) KHMDS, allyl–I; HCl, H₂O, THF, 88% (3 steps); (k) (Sia)₂BH, THF, –20 ºC; NaOH, H₂O₂, H₂O, 78%; (l) TBSCl, NEt₃, DMAP, CH₂Cl₂, 99%; (m) Comins’ reagent, KHMDS, PhMe, THF, 78 ºC, 90%; (n) CO, Pd(OAc)₂, dppf, MeOH, DMF, 50 ºC, 93%; (o) H₂, Crabtree’s catalyst, DCE, reflux, 97%; (p) DIBAL, CH₂Cl₂, –78 ºC; (q) Ac₂O, DMAP, NEt₃, CH₂Cl₂; (r) DMP, NaHCO₃, CH₂Cl₂, 89% (3 steps); (s) TBHP, Pd(OH)₂/C, K₂CO₃, CH₂Cl₂, 69%; (t) CSA, MeOH, CH₂Cl₂; (u) DMP, NaHCO₃, CH₂Cl₂; (v) PPh₃CH₃Br, t-BuOK, THF, 0 ºC, 74% (3 steps); (w) K₂CO₃, MeOH; (x) DMP, CH₂Cl₂, 93% (2 steps); (y) PPh₃ClCH₂OCH₃, KHMDS, THF, 0 ºC, 79%; (z) p-TsOH, acetone, H₂O, 40 ºC; (aa) PPh₃CH₃Br, t-BuOK, THF, 0 ºC, 79% (2 steps); (bb) LiTMP, HMPA, THF, –78 ºC; allyl bromide, 84%; (cc) LiTMP, THF, –78 ºC; Li(2-Th)CuCN; allyl bromide, 90%; (dd) TBAF, THF; (ee) DMP, CH₂Cl₂, 84% (2 steps); (ff) i-PrMgCl, CeCl₃·2LiCl, THF, –78 ºC; (gg) DMP, NaHCO₃, CH₂Cl₂, 71% (2 steps); (hh) 150, isobutene, 120 ºC, 93%; (ii) LiCl, DMSO, 120 ºC, 62%.

While these dearomative alkylation approaches to PPAP natural products are useful and have successfully led to the synthesis of several PPAPs, a more direct strategy would involve annulation of a C6–C8 carbon bridge directly onto an aromatic nucleus. However this strategy is not without its
challenges, especially concerning the control of absolute and C7–C8 relative stereochemistry. Both Takagi and Porco have explored such dearomative annulation strategies, utilizing electrophiles such as acrylates $^{189,541}$ $^{190,542}$ $^{191,543}$ as well as enals $^{192,544}$ $^{193,545}$ and vinylsulfone $^{194,544}$ (Figure 1.20).

![Figure 1.20. Various electrophiles utilized in “top-down” annulation strategies.](image)

The total synthesis of $\text{ent}$-hyperibone K ($\text{ent-195}$) by Porco exemplifies the dearomative annulation strategy for PPAP construction (Scheme 1.24).$^{545}$ Bis-Prenylation of 2,4,6-trihydroxybenzophenone (14)$^{546}$ using basic, aqueous conditions provided the natural acylphloroglucinol clusiaphenone B (196).$^{547}$ Upon exposure of 196 to enal 193 in the presence of Cinchona alkaloid-derived phase-transfer catalyst 197, adamantane 198 was produced enantioselectively. This is a remarkable reaction, considering that two quaternary stereocenters are formed along with the characteristic PPAP bicyclo[3.3.1]nonane core. Initially, this annulation was performed using enal 192, but shorter reaction times and higher enantioselectivity was garnered using 193. A mechanistic model for this transformation

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546 14 is available in 2 steps from 1,3,5-trimethoxybenzene: Mondal, M.; Puranik, V. G.; Argade, N. P. J. Org. Chem. 2007, 72, 2068-2076.

involves the formation of a tight ion pair between 196 and 197 in which only one face of 196 is available to engage in binding interactions with the enal electrophile. The remaining C–C bond required for the synthesis of hyperibone K from intermediate 198 was installed via deprotonation with LDA, revealing an aldehyde from a retro-aldol reaction, and trapping with 2-methyl-1-propenylmagnesium bromide, forming alcohol 199. Exposure of this alcohol to Sc(OTf)₃ yielded the enantiomer of hyperibone K (ent-195). This represents one of the only two total syntheses of adamantyl PPAPs reported to date. Using this synthesis strategy, Porco has successfully prepared (±)-clusianone, (±)-plukenenione A, and (±)-plukenenione D/E (7-epi-nemorosone).

Scheme 1.24. Total synthesis of ent-hyperibone K by Porco (ref. 545).

Aside from the approaches outlined above that were developed specifically for PPAP synthesis, more general strategies toward the construction of bicyclo[3.3.1]nonanes have been developed. Several


tactics include intramolecular conjugate addition reactions to both enones and ynones. Intermolecular cascade annulations involving unsaturated carbonyl systems have also been explored. Rhenium-, gold-, and copper-mediated additions of cyclohexanones and their enol ether derivatives have yielded bicyclo[3.3.1]nonane systems. Barriault has reported the use of a Prins-pinacol reaction to fashion a variety of bicyclic ring scaffolds. An $S_N2$-type cyclization involving primary tosylate displacement has been explored.

Apart from cyclization strategies, Tadano has developed a zinc-mediated Barbier-type allylation reaction utilizing sugar-based aldehydes to construct stereogenic quaternary carbon centers that resemble the C8 center of PPAPs that bear differential substitution at that position (e.g., hyperforin).

Chapter 2

Strategies Toward Hyperforin Synthesis
Synthesis Overview

As elaborated above, hyperforin displays a broad spectrum of biological activity. Moreover, hyperforin is believed to be the component of St. John’s wort that is responsible for its antidepressant activity. This is particularly noteworthy given hyperforin’s unique mechanism of action and absence of deleterious side effects that often accompany the use of other clinical antidepressants. However, hyperforin’s therapeutic potential is handicapped by several factors: (1) its poor water-solubility; (2) its fragility, readily decomposing in the presence of light and air; and (3) its potent activation of PXR, causing increases in gene expression levels of many proteins involved in xenobiotic metabolism.

In order to mitigate these shortcomings while maintaining potential salutary benefits, access to a broad spectrum of hyperforin analogs is necessary. While semisynthetic manipulation of hyperforin has led to a limited number of such derivatives, total synthesis is the only means by which diverse hyperforin analogs may be obtained. Even though several synthesis endeavors have led to the total synthesis of both racemic and ent-hyperforin, the considerable length of these routes renders analog synthesis impractical. Therefore, our goal was to devise a short, enantioselective approach to hyperforin that would be amenable to the synthesis of a variety of hyperforin mimetics and enable the first full structure-activity relationship study of hyperforin.

Further, we rationalized that latent symmetry elements in hyperforin may be exploited to expedite total synthesis. Imbedded within the hyperforin bicyclo[3.3.1]nonane core is a 1,3,5-cyclohexanetrione subunit (highlighted in blue in Scheme 2.1a). Retrosynthetic cleavage of the C5–C6 bond in hyperforin (1) via intramolecular S_n2-type displacement-cyclization would reveal monocyclic intermediate 200.

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561 See discussion on page 75.


563 See discussion on page 108.
Given the substitution pattern around this cyclohexanetrione ring, the C1 quaternary center of 200 is prostereogenic owing to a plane of symmetry intersecting the C1 and C4 atoms. C1 stereochemistry is introduced during the subsequent alkylation event, in which two possible nucleophilic carbon atoms (i.e., C3 and C5) may engage the electrophilic C6. We rationalized that the C7 prenyl substituent stereochemistry would bias the formation of a C5–C6 bond over C3–C6 bond formation (Scheme 2.1b). The former situation would lead to transition state 201, bearing a pseudoequatorial C7 prenyl substituent, whereas the latter bond-forming event would lead to transition state 202 containing a pseudoaxial C7 prenyl moiety whose orientation begets two syn-pentane-like interactions with the C1–C9 and C3–C4 bonds.

Scheme 2.1. (a) Retrosynthetic analysis of hyperforin and (b) transition-state analysis of key cyclization event.

Polyketide Cyclization Approach

Prior to evaluating the plausibility of using this cyclization to construct hyperforin, synthesis of monocyclic precursor 200 was required. In order to evaluate the feasibility of synthesizing 200, a model system in which the C8 stereogenic center of hyperforin was replaced with a tert-butyl group (203) was
established (Scheme 2.2). We hypothesized that 203 would be accessed via dienylketene 204 via either a Dieckmann cyclization or a 6\pi electrocyclization. Conjugated dienylketenes are known to undergo cyclization under fairly mild conditions,\[^{564}\] even to form nonaromatic carbocyclic products.\[^{565}\] This dienylketene would be accessed via tetraketide 205, the product of the coupling reaction between acylketene 206 with \(\beta\)-ketocarbonyl species 207. This route was particularly appealing owing to the lack of oxidation-state changes and protecting group manipulations.

![Scheme 2.2. Retrosynthesis of model system 203 via tetraketide 205.](image)

Initially, we explored the feasibility of constructing several tetraketide-type species similar to 205 (Figure 2.1). Moreover, we chose to explore the coupling chemistry of the previously characterized and prepared \(\text{tert-butyloxycarbonylketene}\)[566] (208) before exploring the synthesis of the potentially unstable \(\alpha\)-ketoketene 206. Due to both the stabilizing effect of the conjugated ester and the steric nature of the \(\text{tert-}\)

\[^{564}\] For reviews, see: (a) Harris, T. M.; Harris, C. M. Tetrahedron 1977, 33, 2159-2185. (b) Harris, T. M.; Harris, C. M. Pure Appl. Chem. 1986, 58, 283-294.


butyl substituent, \textbf{208} can be isolated and distilled in the absence of solvent. Several candidate dienylketene precursors were explored. An \(\alpha\)-oxoketene may be generated from the thermolysis of a dioxinone,\textsuperscript{567} such as \textbf{209}. \(\alpha\)-Oxoketenes may also be generated from the elimination of alcohols and thiols from \(\beta\)-ketoesters and \(\beta\)-ketothioesters, respectively, which also led us to pursue \textbf{210} and \textbf{211}.\textsuperscript{568}

![Figure 2.1](image)

\textbf{Figure 2.1.} Carbethoxyketene \textbf{208} and several potential dienylketene precursors.

We first explored the synthesis of dioxinone \textbf{209} (Scheme 2.3). Magnesium-iodine exchange of iododioxinone \textbf{212}\textsuperscript{569} followed by CuBr-mediated transmetalation and trapping with prenyl bromide afforded intermediate \textbf{213}. Deprotonation using LDA and trapping with a second equivalent of prenyl bromide afforded \textbf{214}. However, numerous attempts of the coupling of anions derived from \textbf{209} as well as its silyl dienyl ether only led to recovery of \textbf{214} and hydrolysis of ketene \textbf{208}. We concluded that the nucleophilic derivatives of \textbf{209} were not reactive enough to engage ketene \textbf{208}.


Scheme 2.3. Attempted Synthesis of dioxinone 209

\[ \text{Conditions: (a) } i\text{-PrMgCl, CuBr; prenyl–Br, –30 ºC; CuBr, LiCl, –30 ºC; prenyl bromide, –30 ºC, 84%; (b) LDA, DMPU, THF, 0 ºC; 214, 0 ºC; prenyl bromide, –40 ºC to rt, 46%.} \]

While we failed to observe reactivity using monoanions derived from 214, we hypothesized that more nucleophilic, Weiler-type dianions generated from \( \beta \)-ketocarbonyl-type systems would react with ketene 208. Indeed, both tetraketides 210 and 211 were synthesized (Scheme 2.4). Prenylation of the dianion generated from acetoacetate 215 yielded 216. The reaction of the dianion generated from this acetoacetate with ketene 208 afforded adduct 210 as a complex mixture of diastereomers and tautomers. Likewise, the synthesis of 211 proceeded in similar fashion. Stepwise prenylation of \textit{tert}-butyl acetothioacetate 217 led to the isolation of 218. The use of DME as solvent in these alkylations was crucial in preventing the formation of byproducts. Coupling with ketene 208 was achieved, affording key tetraketide 211.


\[ \text{(a) Booth, P. M.; Fox, C. M. J.; Ley, S. V. \textit{Tetrahedron Lett.} 1983, 24, 5143-5146. (b) Booth, P. M.; Fox, C. M. J.; Ley, S. V. \textit{J. Chem. Soc., Perkin Trans. 1} 1987, 121-129.} \]
Scheme 2.4. Synthesis of tetraketides 210 and 211.\(^a\)

\(^a\) Conditions: (a) K\(_2\)CO\(_3\), prenyl bromide, DMF, acetone, reflux, 64%; (b) NaH, THF, 0 ºC; BuLi, 0 ºC; 208, 0 ºC to rt, 55%; (c) NaH, DME, 0 ºC; BuLi, –30 ºC; prenyl bromide, –30 ºC to rt, 61%; (d) NaH, DME, 0 ºC; prenyl bromide, 0 ºC to rt, 75%; (e) NaH, DME, 0 ºC; BuLi, –30 ºC; 208, –30 ºC to rt, 39%.

Unfortunately, all attempts at the generation of dienylketene 219 from either 210 or 211 en route to carbocycle 203 were unsuccessful (Scheme 2.5). Treatment of these tetraketides with acid or base in order to directly generate a ketene intermediate led to decomposition. While it was possible to obtain the extremely unstable carboxylic acid 220, any attempts to activate this intermediate (e.g., formation of an acid chloride) led to facile decarboxylation.

Scheme 2.5. Attempted ketene generation from tetraketides 210 and 211.

Concurrent to these studies, we also assessed the feasibility of synthesizing and coupling ketoketene 206 (Scheme 2.6). First, \(i\)-PrMgCl addition to carbethoxyketene 208 gave \(\beta\)-ketoester 221.
Stepwise saponification, acid chloride formation, and treatment with NEt₃ afforded ketoketene 206 as a volatile liquid that was stable in the absence of solvent. Upon coupling of β-ketothioester 218 with 206, we were surprised to isolate α-pyrene 222. Upon careful analysis of the reaction conditions, it was discovered that the direct product of the coupling reaction was linear polyketide 223, which upon acidic workup afforded pyrone 222. Performing a basic aqueous workup gave decreased amounts of this product. Similar acid-mediated heterocyclizations of triketothioacids have been reported. While the formation of pyrone 222 was undesirable, Harris has reported the conversion of 6-acyl-4-hydroxy-2-pyrone 222, to acylphloroglucinols through the use of non-nucleophilic bases, such as LDA or LiH, possibly proceeding through a dienylketene intermediate similar to 204.

We hypothesized that the conversion of 6-acyl-4-hydroxy-2-pyrone 222 to key intermediate 203 would proceed through deprotonation of the internal, doubly conjugated methine to reveal extended enolate 224 (Scheme 2.7a). Upon bond rotation and carbon-carbon bond formation, cyclohexanetrione 203 would be accessed, an overall internal O-to-C acyl migration process. Despite screening a variety of


a Conditions: (a) t-PrMgCl, THF, 0 °C to rt, >99%; (b) NaOH, MeOH, H₂O; (c) PCl₅, Et₂O, reflux, 73% (2 steps); (d) NEt₃, PhH, 51%; (e) NaH.


non-nucleophilic bases, we were not able to achieve this transformation (Scheme 2.7b). In most cases, 222 was recovered. Deuterium quench experiments indicated that the isopropyl methine and the pyrone hydroxyl group were the only two positions on 222 being appreciably deprotonated. Use of derivatives of 222 in which the pyrone hydroxyl group was blocked (i.e., 225 and 226) also did not facilitate desired carbocycle formation. We concluded that not only was deprotonation extremely difficult at the desired site, but the conversion of pyrone 222, which bears some aromatic character, to the non-aromatic cyclohexanetrione 203 is a thermodynamically unfavorable process.

Scheme 2.7. (a) Proposed and (b) unsuccessful synthesis of carbocycle 203 from pyrone 222.

Electrocyclic Cascade Approach

Due to the propensity of a linear polyketide to undergo O-cyclization to form a pyrone, we explored an alternative synthesis strategy that would mitigate heterocycle formation. We surmised that an electrocyclic cascade reaction involving two equivalents of an alkynyl ether (227) and a disubstituted ketene (228) may be used to construct 229, which is a diether of carbocycle 203 (Scheme 2.8a). In this reaction, a [2+2] cycloaddition of one equivalent of the alkynyl ether 227 with ketene 228 would produce cyclobutenone 230 (Scheme 2.8b). Subsequent thermolysis would reveal vinylketene 231 via retro-4π
electrocyclization, which upon exposure to a second equivalent of alkynyl ether 227 would undergo a second [2+2] cycloaddition to form homologated cyclobutene 232. After another retro-4π electrocyclization to reveal a dienylketene 233, a final 6π electrocyclization would yield 229. Analogous electrocyclic cascade reactions have been used to synthesize heavily substituted aryl rings, and in several instances even non-aromatic cyclohexadienones.

Scheme 2.8. (a) Proposed electrocyclic cascade and (b) mechanism for the synthesis of cyclohexadienone 229.


We first analyzed the reactivity of ketenes 206 and 208 with the known ethyl alkynyl ether 234, synthesized from the prenylation of ethoxyacetylene (Scheme 2.9).\textsuperscript{579} At temperatures below 100 ºC, no reaction occurred; however, above this threshold, oligimerization of 234 was observed. At such temperatures, a retro-ene reaction may occur with 234,\textsuperscript{580} producing the very reactive monosubstituted ketene 235.

\begin{equation}
\text{Scheme 2.9. Attempted cycloaddition of alkynyl ether 234 with ketenes 206 and 208.}
\end{equation}

In order to possibly circumvent this issue, we hypothesized that tert-butylcyanoketene\textsuperscript{581} (236) may react with alkynyl ether 234 at reduced temperatures due to the reduced steric environment surrounding the reactive ketene functionality (Scheme 2.10).\textsuperscript{582} Unlike acylketenes 206 and 208, cyanoketene 236 cannot be isolated neat; it is generated through the thermolysis of diazidobenzoquinone 237 in toluene solution.\textsuperscript{583,584} After generating a solution of 236, addition of alkynyl ether 234 afforded not only the [2+2] cycloaddition product, cyclobutenone 238, but also azabicyclo[4.2.0]octantrienone

\begin{equation}
\end{equation}

\begin{equation}
\text{580 Liang, L.; Ramaseshan, M.; MaGee, D. I. Tetrahedron 1993, 49, 2159-2168.}
\end{equation}

\begin{equation}
\text{581 For examples of reactions involving 236, see: Al-Husaini, A. H.; Moore, H. W. J. Org. Chem. 1985, 50, 2595-2597.}
\end{equation}

\begin{equation}
\text{582 For a review of cyanoketene chemistry, see: Moore, H. W.; Gheorghiu, M. D. Chem. Soc. Rev. 1981, 10, 289-328.}
\end{equation}

\begin{equation}
\text{583 Weyler, W., Jr.; Duncan, W. G.; Liewen, M. B.; Moore, H. W. Org. Synth. 1976, 55, 32-38.}
\end{equation}

\begin{equation}
\text{584 We attempted to synthesize 236 from a 2-cyanoacetyl chloride (analogous to the synthesis of ketene 206); however, an allene was cleanly afforded, presumably through NEt_3-promoted hetero-[2+2] cycloaddition of two equivalents of the ketene followed by decarboxylation of the resulting β-lactone.}
\end{equation}
A possible mechanism for the formation of 239 involves the [4+2] cycloaddition of 236 with 234 to form 240, which may be depicted as a dipole or a diradical. Coupling of this intermediate with a second equivalent of alkynyl ether 234 would afford 239 via 241. An electrocyclic cascade that may involve an intermediate similar to 240 has been reported. Further, heating a solution of 238 and 234 did not yield 239, demonstrating that 238 is not an intermediate in the synthesis of 239. Subsequent optimization of this reaction for the synthesis of cyclobutenone 238 allowed us to access functional amounts of this intermediate for later electrocyclic cascade cyclization studies.

Scheme 2.10. (a) Thermolytic formation of 238 and 239, and (b) a possible mechanism for the formation of 239.

We then explored the use of cyclobutenone 238 as an intermediate toward desired cyclohexadienone 229. As indicated above, extended heating of 238 with alkynyl ether 234 did not yield further coupling products. Attempted coupling of the more reactive lithium alkynoate 242, generated from successive lithium-bromine exchanges from α,α-dibromoester 243, only gave low yields of α-pyrone 244 and linear ethyl ester 245, formed through the interception and opening of the cyclobutenone


586 See the experimental section of this chapter for details.

by residual ethoxide from the formation of alkynoate 242 (Scheme 2.11). Akin to the polyketide route results, pyrone formation prevails in the absence of oxygen blocking groups. The ethanolysis product 245 along with its double-bond isomer was also generated by heating 238 with ethanol.

Scheme 2.11. The reaction of in situ derived lithium alkynoate 242 with cyclobutenone 238.\textsuperscript{a}

\textsuperscript{a} Conditions: (a) \textit{t}-BuLi, THF, –78 °C to rt; 238, 8\% \textit{244}, 12\% \textit{245}.

Owing to pyrone formation from the use of alkynoate 242 and the propensity of ethyl alkynyl ether 234 to undergo retro-ene cyclization, we then investigated the use of methyl alkynyl ether 246, an alkynyl ether incapable of retro-ene rearrangement. It was synthesized from the base-mediated coupling of dichloroacetylene (generated \textit{in situ} from trichloroethylene, 247), methanol, and prenyl bromide (Scheme 2.12a).\textsuperscript{588} However, when an excess of 246 was heated to 140 °C with cyclobutenone 238, the only product isolated was phloroglucinol diether 248. A plausible mechanism for the formation of this aromatic product is shown in Scheme 2.12b. Coupling of 238 with 246 to afford the desired cyclohexadienone 249 may have occurred via the proposed electrocyclic cascade reaction—\([2+2]\) cycloaddition of ring-opened vinylketene 250 with alkynyl ether 246, ensuing retro-\(4\pi\) electrocyclization of cyclobutenone 251 to dienylketene 252, and subsequent \(6\pi\) electrocyclization to give 249—but under the reaction conditions, rapid loss of the \textit{tert}-butyl group from 249 may have afforded 248. This dissociation may operate via a concerted retro-ene cyclization process or an ionic retro-\(S_N1\)-type reaction.

Miller and others have observed the elimination of sterically demanding alkyl groups from similar “blocked aromatic” cyclohexadienone systems.\(^{589}\)

\[\text{Scheme 2.12. (a) Synthesis and (b) possible mechanism for the formation of 248 from the coupling of 246 and 238.}\]

\(^a\) Conditions: (a) MeOH, KH; 247; prenyl–Br; 248; 53%; (b) xylenes, 140 °C, 25%.

We then explored potential methods of mitigating this terminal tert-butyl elimination step to isolate the desired cyclohexadienone 249 (Table 2.1). As mentioned above, Miller has observed similar tert-butyl eliminations from cyclohexadienones, and these processes were mediated by either heat or acid.\(^{589a-c}\) We repeated the reaction of alkynyl ether 246 with cyclobutenone 238 in the presence of amine base to determine if trace amounts of acid were promoting this elimination. However, in the presence of 246

$N,N$-diethylaniline (entry 1), not only was a greater proportion of 248 obtained but we also isolated ester 253 (Figure 2.2), the result of opening of cyclobutenone 238 by phenol 248. Use of the more basic Hünig’s base also gave both products with complete mass recovery (entry 2). We did not observe any conversion with the use of microwave irradiation (entry 3). Photolysis (entries 4-6) of a mixture of 238 and 246 in the presence of benzophenone as a triplet sensitizer only gave 254, the [2+2] cycloaddition product of benzophenone and 246. 590 Changing the reaction solvent from xylenes to heptane, with the goal of destabilizing tert-butyl cation formation, did not prevent the formation of 248 (entry 7).


Table 2.1. Attempted formation of 249 from 246 and 238.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhNEt (0.10 equiv), xylenes, 140 °C</td>
<td>248 (20%), 253 (20%)</td>
</tr>
<tr>
<td>2</td>
<td>i-PrNEt (0.20 equiv), xylenes, 140 °C</td>
<td>248 (22%), 253 (78%)</td>
</tr>
<tr>
<td>3</td>
<td>PhMe, µwave, 140 °C, 4 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>hv, PhH, rt, 1 d</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>hv, acetone, rt, 1 d</td>
<td>decomposition of 246</td>
</tr>
<tr>
<td>6</td>
<td>benzophenone, hv, PhH, rt, 22 h</td>
<td>254 (28%)</td>
</tr>
<tr>
<td>7</td>
<td>heptane, 140 °C, 12 h</td>
<td>248, decomposition</td>
</tr>
<tr>
<td>8</td>
<td>BHT (0.20 equiv), 140 °C, PhMe, 12 h</td>
<td>255 (6%)</td>
</tr>
<tr>
<td>9</td>
<td>BHT (0.20 equiv), i-PrNEt (0.20 equiv), PhMe, 140 °C, 12 h</td>
<td>248 (13%), 255 (5%), 257 (42%)</td>
</tr>
</tbody>
</table>
We also repeated the experimental protocol with the addition of BHT to investigate whether radical intermediates were involved (Table 2.1, entry 8); however, the only product isolated was transposed phloroglucinol diether 255. This product may form via Diels–Alder [4+2] type cycloaddition between ring-opened vinyl ketene 250 to form cyclohexadienone 256 initially, which undergoes tert-butyl elimination (Scheme 2.13). The isolation of 255 indicates that a retro-ene cyclization mechanism for this tert-butyl elimination is unlikely.\textsuperscript{591} Unsurprisingly, the combination of BHT and Hüning’s base additives gave a mixture of products, including 248, 255, and the ester adduct 257 (entry 9).

\textsuperscript{591} A retro-ene cyclization mechanism cannot be ruled out altogether, since a [1,3]-transposition of the tert-butyl group may occur, placing the substituent at the \( \alpha \)-position of the ketone. Similar alkyl shifts have been observed by Miller. For more information, see ref. 589.
Given the inability to isolate cyclohexadienone 249 from cyclobutenone 238, we investigated the chemistry of methyl alkynyl ether 246 with other ketenes (Scheme 2.14). Heating a solution of 246 and ketoketene 206 afforded γ-pyrone 258. A similar product, 259, was isolated in the reaction of 246 with carbethoxyketene 208 along with cyclobutenone 260. This cyclobutenone may have formed via initial [2+2] cycloaddition of 246 and 208 followed by [1,3]-acyl shift. We also explored the reactivity of ketenethioate 261,592 which was synthesized593 from Meldrum’s acid derivative 262594 via acid chloride 263. Heating a solution of this ketene with 246 produced α-pyrone 264.

Scheme 2.14. Reactivity of alkynyl ether 246 with various ketenes.\(^a\)

\(^a\) Conditions: (a) xylenes, 140 ºC, 4%; (b) PhMe, 110 ºC, 25% total yield (inseparable mixture of 259 and 260); (c) i-Pr\(_2\)NEt, TMSCI, MeCN, 0 ºC; EtSH, 43 ºC; HCl, H\(_2\)O; (d) PCl\(_5\), Et\(_2\)O, reflux, 77% (2 steps); (e) NEt\(_3\), PhH, 39%; (f) PhMe, 110 ºC, 38%.

592 This is the first known (alkanethiol)acylketene to be made and is the first acylketene bearing a non-first row element acyl substituent.


Overall, these results indicated that under the conditions necessary to promote the desired
electroyclic cascade reaction, tert-butyl elimination to afford an aromatic product was unavoidable.
Changes to the nature of the alkynyl ether, ketene coupling partner, solvent, and source of heat did not
hinder this deleterious division of the desired product. Another approach we pursued involved the use of
an ynamine coupling partner instead of an alkynyl ether. We hypothesized that a more nucleophilic
ynamine may allow the electrocyclic cascade reaction to proceed at a lower temperature and possibly
allow for the isolation of our desired product. Indeed, stirring a solution of diethyl ynamine and
cyclobutenone at 40 ºC afforded a mixture of vinylcyclobutenone and allenyl amide (Scheme 2.15a). Both products may originate from 1,2-addition of the ynamine to the cyclobutenone
carbonyl to form intermediate ketene-immonium ion, which after retro-4π electrocyclization may
reveal enolate (Scheme 2.15b). C-Alkylation of the immonium ion by the enolate would afford directly, and O-alkylation would provide allenyl amide via retro-4π electrocyclization of oxetene.


We then attempted to convert vinylcyclobutene 266 to cyclohexadiene 271. Given the similarity of 266 to intermediate 232 in Scheme 2.8b, we rationalized that a retro-4π electrocyclization followed by a 6π electrocyclization would afford 271. However, under a variety of conditions, we were not able to isolate this desired product (Table 2.2). While heating a benzene solution of 266 at 60 ºC did not result in any reaction (entry 1), heating at or above 90 ºC (entries 2-3) afforded aniline 272 as the sole product (Figure 2.3). The formation of 272 from 266 is analogous to the formation of 255 from the reaction of 246 and 238, in which tert-butyl elimination rapidly occurred in the reaction medium. Further heating, and the addition of BHT and Hünig’s base did not inhibit the formation of 272 (entries 4-6). The only product from photolysis of 266 was double-bond isomer 273 (entries 7-8).
Table 2.2. Attempted formation of 271 from 266.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhH, 60 °C, 19 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>PhH, 90 °C, 14 h</td>
<td>272 is only product by NMR</td>
</tr>
<tr>
<td>3</td>
<td>PhH, 140 °C, 15 min</td>
<td>272 (48%), 266 (27% recovery)</td>
</tr>
<tr>
<td>4</td>
<td>BHT, PhH, 90 °C, 14 h</td>
<td>272 is only product by NMR</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr₂NEt, PhH, 90 °C, 14 h</td>
<td>272 is only product by NMR</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr₂NEt, BHT, PhH, 90 °C, 14 h</td>
<td>272 is only product by NMR</td>
</tr>
<tr>
<td>7</td>
<td>hv, PhH, 4 h</td>
<td>273 (26%), 266 (32% recovery)</td>
</tr>
<tr>
<td>8</td>
<td>hv, PhH, 12 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

Figure 2.3. Products obtained from the reactions of 266.

Given the propensity for tert-butyl elimination from putative cyclohexadienone intermediates, we also briefly investigated the use of tert-butyl(chloro)ketene (274) as a coupling partner in this electrocyclic cascade strategy (Scheme 2.16). Replacement of the acyl or cyano group on the ketene with a chlorine atom may prevent undesirable elimination of the bulky alkyl group from a potential cyclohexadienone product. Treating a solution of acyl chloride 275 with base provided in situ generation of 274, which was trapped with alkynyl ether 246 to form cyclobutenone 276. However, further heating of this cyclobutenone with alkynyl ether 246 did not afford a desired coupling product; rather, rearranged cyclobutenone 277 was isolated, possibly the product of a [1,3]-chloride shift.

Scheme 2.16. Formation and reactivity of cyclobutenone $276$.\textsuperscript{a}

\textsuperscript{a} Conditions: (a) NEt$_3$, PhH, rt to reflux, 27%; (b) PhMe, 110 °C, 49% (16% recovered $276$).

In summary, a variety of approaches to mitigate tert-butyl elimination were explored. Varying the reaction parameters, including ketene coupling partners, heteroatom-functionalized alkynyl coupling partners, use of photolytic conditions, and use of reaction additives, failed to inhibit this process. With the inability to isolate a stable cyclohexadienone bearing a quaternary center functionalized with a tert-butyl substituent, we concluded that this electrocyclic cascade approach was inherently flawed, and we therefore sought to explore an alternative strategy for the construction of the bicyclo[3.3.1]nonane core of hyperforin.
Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried glassware under a positive pressure of argon unless otherwise noted. Flash column chromatography was performed as described by Still et al.599 employing silica gel 60 (40-63 µm, Whatman). Both preparatory and analytical thin-layer chromatography (TLC) were performed using 0.25 mm silica gel 60 F254 plates.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran, diethyl ether, dichloromethane, toluene, benzene, hexane, acetonitrile, and N,N-dimethylformamide were degassed with argon and passed through a solvent purification system (designed by J. C. Meyer of Glass Contour) utilizing alumina columns as described by Grubbs et al.600 unless otherwise noted. Triethylamine, diisopropylamine, pyridine, and chlorotrimethylsilane were distilled over calcium hydride. Hexamethylphosphoramide was distilled over calcium hydride under reduced pressure. Prenyl bromide was distilled under reduced pressure. Lithium chloride was stored in a vacuum oven for at least 24 h before use. Potassium hydride was washed five times with pentane and dried under reduced pressure directly prior to use. The molarities of butyllithium and tert-butyllithium solutions were determined by titration with 1,10-phenanthroline as an indicator (average of three determinations). THF solutions of lithium diisopropylamide were prepared by addition of a hexane solution of butyllithium (1 equiv) to a THF solution of the appropriate amine (1.1 equiv) cooled to –78 ºC and stirring the solution for 30 min at 0 ºC.

Instrumentation. 1H NMR spectra were recorded with Varian INOVA-600 and Varian INOVA-500 spectrometers, are reported in parts per million (δ), and are calibrated using residual non-deuterated solvent as an internal reference: CDCl₃, δ 7.26 (CHCl₃). Data for 1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, integration). Multiplicities are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; septet = septet; m = multiplet; br = broad, or

combinations thereof. $^{13}$C NMR spectra were recorded with a Varian INOVA-500 spectrometer, are reported in parts per million ($\delta$), and are referenced from the central peak of the carbon resonance of the solvent: CDCl$_3$, $\delta$ 77.23. Infrared (IR) data were recorded on a Varian 1000 FT-IR using NaCl plates or on a Bruker Alpha FT-IR spectrometer outfitted with an Eco-ATR sampling module. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectroscopy on an Agilent 6210 TOF LC/MS or a Bruker q-TOF Maxis Impact mass spectrometer. Gas chromatography mass spectra (GCMS) were performed on a Shimadzu GC-2014 equipped with an AOC-20i auto-injector. Microwave irradiation was accomplished using a CEM Discover microwave reactor. Photoirradiation was accomplished using a water-cooled, 5-inch 450-watt Hanovia UV immersion lamp. No filter was used unless specifically indicated.

Note: For clarity, intermediates that have are not explicitly mentioned in this chapter are numbered sequentially in the experimental section beginning with 278.
2,2,6-Trimethyl-5-(3-methylbut-2-en-1-yl)-4H-1,3-dioxin-4-one (213):

A THF (350 mL) solution of 212\textsuperscript{569} (18.5 g, 69.0 mmol, 1 equiv) in a 3-neck, 1-L round-bottom flask was cooled to –30 ºC and treated dropwise with a THF solution of isopropylmagnesium chloride (2.0 M, 38 mL, 76 mmol, 1.1 equiv) via equal-pressure dropping funnel. After stirring at –30 ºC for 20 min, copper(I) bromide (990. mg, 6.90 mmol, 0.1 equiv) and lithium chloride (585 mg, 13.8 mmol, 0.2 equiv) were added, and prenyl bromide (12 mL, 100 mmol, 1.5 equiv) was added after 5 min. After stirring at –30 ºC for 2 h, the reaction was quenched with brine and extracted thrice with Et\textsubscript{2}O. The organic extracts were combined, washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo} to a green oil. Flash column chromatography (500 mL SiO\textsubscript{2}, 95:5 → 9:1 hexane:EtOAc) afforded 12.14 g (57.74 mmol, 84\% yield) of 213 as a pale yellow oil.

\textbf{1H NMR} (600 MHz; CDCl\textsubscript{3}) \( \delta \): 5.05 (t, \( J = 6.8 \) Hz, 1H), 2.94 (d, \( J = 6.8 \) Hz, 2H), 1.96 (s, 3H), 1.68 (m, 6H), 1.63 (s, 6H).

\textbf{13C NMR} (125 MHz; CDCl\textsubscript{3}) \( \delta \): 163.5, 162.4, 132.5, 121.8, 105.14, 104.94, 25.8, 25.3, 24.1, 18.0, 17.6.

\textbf{FTIR} (thin film) \( \nu_{\max} \): 2994, 2916, 2859, 1716, 1643, 1389, 1347, 1268, 1235, 1204, 1148, 1054, 973, 919, 835, 781, 732 cm\textsuperscript{-1}.

\textbf{HRMS–ESI} (m / z): [M+Na]\textsuperscript{+} calculated for C\textsubscript{12}H\textsubscript{18}O\textsubscript{3}, 233.1144; found, 233.1148.

\textbf{TLC} \( R_f = 0.43 \) (8:2 hexane:EtOAc).
2,2-Dimethyl-5-(3-methylbut-2-en-1-yl)-6-(4-methylpent-3-en-1-yl)-4H-1,3-dioxin-4-one (214):

1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (10.4 mL, 86.3 mmol, 1.5 equiv) was added to a freshly prepared THF solution of lithium diisopropylamide (0.69 M, 82.9 mL, 57.5 mmol, 1 equiv) in a 200-mL recovery flask cooled to 0 °C. After stirring for 20 min, 213 (12.10 g, 57.5 mmol, 1 equiv) was added, and the solution was stirred at 0 °C for 20 min. After cooling to –40 °C, prenyl bromide (8.6 mL, 75 mmol, 1.3 equiv) was added, and the reaction was allowed to slowly warm overnight. After stirring for 20 h at rt, the reaction was quenched by the addition of ice-cold 1 N HCl and extracted thrice with Et₂O. The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to a brown oil. Flash column chromatography (500 mL SiO₂, 9:1 hexane:EtOAc) afforded 7.30 g (26.2 mmol, 46% yield) of 214 as a pale yellow oil.

**¹H NMR (600 MHz; CDCl₃)**: δ: 5.07 (t, J = 6.9 Hz, 1H), 5.04 (t, J = 6.1 Hz, 1H), 2.95 (d, J = 6.9 Hz, 2H), 2.29-2.27 (m, 2H), 2.21 (m, 2H), 1.68 (s, 6H), 1.67 (s, 3H), 1.63 (s, 6H), 1.60 (s, 3H).

**¹³C NMR (125 MHz; CDCl₃)**: δ: 166.2, 162.7, 133.4, 132.2, 122.5, 122.3, 105.1, 104.9, 31.2, 25.88, 25.85, 25.3, 23.9, 18.04, 17.90.

**FTIR** (thin film) v_max: 2967, 2915, 2859, 1720, 1637, 1444, 1371, 1268, 1204, 1130, 1047, 979, 845 cm⁻¹.

**HRMS–ESI** (m / z): [M+Na]⁺ calculated for C₁₇H₂₆O₃, 301.1784; found, 301.1774.

**TLC** R_f = 0.33 (9:1 hexane:EtOAc).
**tert-Butyl 7-methyl-2-(3-methylbut-2-en-1-yl)-3-oxooct-6-enoate (216):**

An acetone (500 mL) and DMF (30 mL) slurry of 215 (20. g, 88 mmol, 1 equiv), prenyl bromide (11.2 mL, 97.2 mmol, 1.1 equiv), and potassium carbonate (24.4 g, 177 mmol, 2 equiv) in a 3-neck 1-L round-bottom flask outfitted with a reflux condenser was heated to reflux. After refluxing for 21 h, the reaction was cooled to rt and concentrated *in vacuo*. Short-path distillation (6 mmHg, 110-117 °C) afforded 16.71 g (56.8 mmol, 64%) of 216 as a colorless oil.

**$^1$H NMR** (600 MHz; CDCl$_3$) δ: 5.04 (t, $J = 7.2$ Hz, 1H), 5.00 (t, $J = 7.4$ Hz, 1H), 3.33 (m, 1H), 2.55 (m, 1H), 2.50-2.43 (m, 3H), 2.26-2.21 (m, 2H), 1.66 (s, 6H), 1.61 (s, 3H), 1.60 (s, 3H), 1.43 (s, 9H).

**$^{13}$C NMR** (125 MHz; CDCl$_3$) δ: 205.4, 169.0, 134.4, 132.9, 122.9, 120.4, 81.8, 60.3, 42.3, 28.1, 27.1, 25.95, 25.87, 22.4, 18.00, 17.84.

**FTIR** (thin film) $\nu_{\text{max}}$: 2971, 2916, 2859, 1735, 1712, 1450, 1368, 1249, 1144, 845 cm$^{-1}$.

**HRMS–ESI** (m / z): [M+H]$^+$ calculated for C$_{18}$H$_{30}$O$_3$, 295.2259; found, 295.2268.

**TLC** R$_f$ = 0.39 (9:1 hexane:EtOAc).
**1-**tert-Butyl 7-ethyl 6-(**tert**-butyl)-2,4-bis(3-methylbut-2-en-1-yl)-3,5-dioxoheptanedioate (210):**

216 (346 mg, 1.18 mmol, 1 equiv) was added to a THF (3 mL) slurry of sodium hydride (60% suspension in mineral oil, 46 mg, 1.23 mmol, 1.05 equiv) cooled to 0 ºC in a 10-mL recovery flask. After stirring for 10 min, a hexane solution of butyllithium (2.73 M, 0.65 mL, 1.76 mmol, 1.5 equiv) was added, and the yellow-orange slurry was stirred at 0 ºC. After 10 min, 208 (200 mg, 1.18 mmol, 1 equiv) was added, and the solution was allowed to warm to rt. After 90 min, the reaction was quenched at rt with 2 N HCl, diluted with H₂O, and extracted thrice with Et₂O. The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (100 mL SiO₂, 95:5 → 9:1 hexane:EtOAc) afforded 299 mg (0.643 mmol, 55%) of 210 as a yellow oil.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.86-5.83 (m, ~0.5H), 5.08-4.92 (m, 2H), 4.25-4.09 (m, 2H), 4.00-3.90 (m, ~1H), 3.57-3.44 (m, ~1H), 3.23-3.17 (m, ~1H), 3.11-3.07 (m, ~0.5H), 2.59-2.38 (m, 3H), 1.74-1.56 (m, 12H), 1.46-1.41 (m, 9H), 1.30-1.24 (m, 3H), 1.12-1.04 (m, 9H) (mixture of tautomers and diastereomers).

**¹³C NMR** (125 MHz; CDCl₃) δ: 201.0, 200.1, 199.63, 199.50, 199.02, 198.82, 191.53, 191.51, 187.32, 187.22, 169.4, 169.0, 168.36, 168.34, 168.20, 168.15, 167.96, 167.89, 134.74, 134.60, 134.56, 134.53, 134.40, 134.21, 120.6, 120.41, 120.38, 120.24, 120.19, 120.14, 100.70, 100.69, 82.4, 82.1, 81.7, 67.6, 67.2, 67.0, 66.8, 66.5, 65.7, 63.83, 63.79, 61.5, 61.29, 61.22, 60.9, 60.07, 60.05, 59.5, 56.56, 56.54, 35.2, 35.02, 34.99, 34.82, 34.69, 34.51, 28.35, 28.31, 28.28, 28.25, 28.15, 28.06, 28.01, 27.97, 27.34, 27.23, 27.19, 26.8, 25.87, 25.84, 25.78, 17.92, 17.88, 14.28, 14.25, 14.23 (mixture of tautomers and diastereomers).

**FTIR** (thin film) v̅ max: 2969, 2933, 2873, 1730, 1598, 1448, 1368, 1246, 1143, 1043, 1025, 845 cm⁻¹.
HRMS–ESI (m / z): [M+H]\(^+\) calculated for C\(_{27}\)H\(_{41}\)O\(_6\), 465.3207; found, 465.3211.

TLC \(R_f = 0.61\) (8:2 hexane:EtOAc).
**S-tert-Butyl 7-methyl-3-oxooct-6-enethioate (278):**

A DME (16 mL) solution of 217 (5.52 mL, 31.5 mmol, 1 equiv) was added dropwise to a DME (125 mL) slurry of sodium hydride (60% suspension in mineral oil, 1.38 g, 34.6 mmol, 1.1 equiv) cooled to 0 °C in a 500-mL round-bottom flask. After stirring for 5 min, the slurry was cooled to −30 °C, and a hexane solution of butyllithium (2.60 M, 13.3 mL, 34.6 mmol, 1.1 equiv) was added slowly. After stirring the bright orange slurry at −30 °C for 10 min, prenyl bromide (4.0 mL, 34.6 mmol, 1.1 equiv) was added, and the yellow slurry was allowed to slowly warm to rt. After stirring 90 min, the reaction was quenched with sat. aq. NH₄Cl and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to a yellow oil. Short-path distillation (6 mmHg, 100-105 °C) afforded 4.66 g (19.2 mmol, 61% yield) of 278 as a pale yellow oil.

**1H NMR** (500 MHz; CDCl₃) δ: 5.32 (s, 1H, *minor tautomer*), 5.09-5.03 (m, 1H, *both tautomers*), 3.55 (s, 2H, *major tautomer*), 2.55 (t, *J* = 7.4 Hz, 2H, *both tautomers*), 2.28-2.22 (m, 3H, *both tautomers*), 2.15-2.12 (m, 1H, *both tautomers*), 1.69 (s, 3H, *minor tautomer*), 1.67 (s, 3H, *major tautomer*), 1.61 (s, 3H, *both tautomers*), 1.51 (s, 9H, *minor tautomer*), 1.47 (s, 9H, *major tautomer*).

**13C NMR** (125 MHz; CDCl₃) δ: 202.3, 196.4, 192.8, 176.1, 133.2, 122.65, 122.51, 99.8, 58.7, 49.2, 48.3, 43.3, 35.3, 30.4, 29.8, 25.9, 25.1, 22.4, 17.91, 17.88 (*mixture of tautomers*).

**FTIR** (thin film) ν<sub>max</sub>: 2965, 2924, 2862, 1723, 1674, 1614, 1455, 1364, 1178, 1160, 1080, 978, 863 cm⁻¹.


**TLC** R<sub>f</sub> = 0.43 (9:1 hexane:EtOAc).
**S-tert-Butyl 7-methyl-2-(3-methylbut-2-en-1-yl)-3-oxooct-6-enethioate (218):**

278 (5.76 g, 23.8 mmol, 1 equiv) was added to a DME (100 mL) slurry of sodium hydride (60% suspension in mineral oil, 950 mg, 30.9 mmol, 1.3 equiv) cooled to 0 °C in a 200-mL recovery flask. After stirring for 5 min, prenyl bromide (3.6 mL, 31 mmol, 1.3 equiv) was added to the yellow solution, and the reaction was allowed to slowly warm to rt overnight. After 12 h, the reaction was quenched with the addition of H2O and by pouring the resulting mixture onto ice-cold 1 N NaOH. The mixture was then extracted thrice with CHCl3. The organic extracts were combined, washed with H2O and brine, dried over MgSO4, filtered, and concentrated *in vacuo*. The resulting colorless oil was retaken in 98:2 hexane:EtOAc and passed through a short plug of SiO2, rinsing with 98:2 hexane:EtOAc. Concentration of the filtrate *in vacuo* afforded 7.39 g (23.8 mmol, >99% yield) of 218 as a colorless oil.

**1H NMR** (600 MHz; CDCl3) δ: 5.03 (t, *J* = 7.2 Hz, 1H), 4.98 (t, *J* = 7.3 Hz, 1H), 3.58 (t, *J* = 7.5 Hz, 1H), 2.60-2.46 (m, 4H), 2.24 (q, *J* = 7.2 Hz, 2H), 1.66 (s, 6H), 1.61 (s, 6H), 1.45 (s, 9H).

**13C NMR** (125 MHz; CDCl3) δ: 204.1, 195.9, 134.8, 133.0, 122.8, 119.9, 68.4, 58.7, 49.0, 42.2, 29.8, 28.0, 25.93, 25.87, 22.5, 17.99, 17.85.

**FTIR** (thin film) ν<sub>max</sub>: 2965, 2922, 2859, 1723, 1672, 1454, 1364, 1162, 984, 926, 825 cm<sup>-1</sup>.

**HRMS–ESI** (m / z): [M+Na]<sup>+</sup> calculated for C<sub>18</sub>H<sub>30</sub>O<sub>2</sub>S, 333.1858; found, 333.1859.

**TLC** R<sub>d</sub> = 0.65 (9:1 hexane:EtOAc).
**Ethyl 2-(tert-buty1)-6-((tert-butylthio)carbonyl)-9-methyl-4-(3-methylbut-2-en-1-yl)-3,5-dioxodec-8-enoate (211):**

A DME (1.1 mL) solution of 218 (663 mg, 2.14 mmol, 1 equiv) was added dropwise to a DME (8.5 mL) slurry of sodium hydride (60% suspension in mineral oil, 94 mg, 2.35 mmol, 1.1 equiv) cooled to 0 ºC in a 25-mL recovery flask. After stirring the pink solution at 0 ºC for 5 min, it was cooled to –30 ºC, and a hexane solution of butyllithium (2.60 M, 0.90 mL, 2.4 mmol, 1.1 equiv) was added dropwise. The resulting yellow-orange solution was stirred for 10 min at –30 ºC, and 208 (400 mg, 2.35 mmol, 1.1 equiv) was added dropwise. The resulting yellow-orange solution was allowed to slowly warm to rt overnight. After 16 h, the solution was quenched by pouring it onto sat. aq. NH₄Cl, and the resulting mixture was extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to an orange oil. Flash column chromatography (100 mL SiO₂, 98:2 → 8:2 hexane:EtOAc) afforded 398 mg (0.828 mmol, 39% yield) of 211 as a yellow oil.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.29 (m, ~0.5H), 5.08-4.81 (m, 2H), 4.22-3.88 (m, 2H), 3.72-3.31 (m, 3H), 2.51-2.23 (m, ~3.5H), 1.65-1.33 (m, 12H), 1.23-1.11 (m, 3H), 1.05-0.93 (m, 9H) (*mixture of tautomers and diastereomers*).

**¹³C NMR** (125 MHz; CDCl₃) δ: 199.30, 199.27, 199.25, 199.05, 198.8, 198.37, 198.22, 198.02, 197.3, 195.02, 194.94, 194.61, 194.55, 168.21, 168.09, 168.03, 167.6, 134.84, 134.80, 134.74, 134.70, 134.50, 134.35, 122.3, 120.30, 120.19, 120.08, 119.96, 119.84, 119.73, 119.73, 119.68, 118.3, 101.6, 77.2, 68.34, 68.21, 68.13, 67.7, 67.34, 67.29, 67.21, 67.16, 67.01, 66.92, 66.80, 66.77, 66.74, 66.61, 66.55, 65.6, 61.48, 61.31, 61.21, 61.16, 61.08, 60.96, 60.84, 60.75, 60.71, 60.4, 59.0, 56.75, 56.67, 53.5, 51.8, 49.27, 49.24, 49.04, 48.97, 36.4, 35.4, 35.1, 34.74, 34.69, 34.56, 34.53, 34.39, 34.26, 33.7, 30.06, 30.04, 29.75, 29.69, 29.66, 29.62, 29.3, 28.82, 28.64, 28.52, 28.34, 28.14, 28.10, 28.06, 28.03, 28.00, 27.65, 27.55, 27.47,

**FTIR** (thin film) $\nu_{\text{max}}$: 2963, 2914, 2872, 1725, 1671, 1455, 1365, 1302, 1221, 1144, 1043, 935 cm$^{-1}$.

**HRMS–ESI** (m / z): [M+Na]$^+$ calculated for C$_{27}$H$_{44}$O$_5$S, 503.2802; found, 503.2807.

**TLC** $R_f = 0.51$ (8:2 hexane:EtOAc).
**Ethyl 2-(*tern*-butyl)-4-methyl-3-oxopentanoate (221):**

A THF (265 mL) solution of 208 \( (18.0 \text{ g, 106 mmol, 1 equiv}) \) in a 1-L recovery flask was cooled to 0 °C, and a THF solution of isopropylmagnesium chloride (2.0 M, 58 mL, 120 mmol, 1.1 equiv) was added slowly over 10 min. After the addition was complete, the reaction was allowed to slowly warm to rt. After stirring for 3 h, the reaction was quenched via dropwise addition of H\(_2\)O followed by sat. aq. NH\(_4\)Cl and extracted thrice with EtOAc. The organic extracts were combined, washed with sat. aq. NaHCO\(_3\) and brine, dried over MgSO\(_4\), and filtered through a short plug of SiO\(_2\), rinsing with EtOAc. The filtrate was concentrated \( \text{in vacuo} \) to afford 23 g (110 mmol, >99% yield) of 221 as a colorless oil.

\[ \text{1H NMR (600 MHz; CDCl}_3\text{)} \delta: 4.15 (q, J = 7.1 \text{ Hz, 2H}), 3.52 (s, 1H), 2.69 (t, J = 6.8 \text{ Hz, 1H}), 1.24 (t, J = 7.1 \text{ Hz, 3H}), 1.09 (d, J = 6.8 \text{ Hz, 3H}), 1.08 (s, 9H), 1.04 (d, J = 6.8 \text{ Hz, 3H}). \]

\[ \text{13C NMR (125 MHz; CDCl}_3\text{)} \delta: 209.1, 168.9, 65.8, 61.0, 42.6, 34.7, 28.4, 18.35, 18.18, 14.4. \]

\[ \text{FTIR (thin film) } \nu_{\text{max}}: 2964, 2909, 2874, 1736, 1714, 1466, 1366, 1206, 1142, 1021 \text{ cm}^{-1}. \]

\[ \text{HRMS–ESI (m / z): [M+H]}^+ \text{ calculated for C}_{12}\text{H}_{22}\text{O}_3, 215.1651; \text{ found, 215.1642.} \]

\[ \text{TLC } R_f = 0.42 (9:1 \text{ hexane:EtOAc}). \]
2-(tert-Butyl)-4-methylpent-1-ene-1,3-dione (206):

A MeOH (465 mL) solution of 221 (10.0 g, 46.7 mmol, 1 equiv) in a 1-L round-bottom flask was treated with an aqueous solution of sodium hydroxide (50% by weight, 93 mL). The exothermic yellow solution was placed in a rt water bath and stirred for 12 h. The reaction was then concentrated partially in vacuo, cooled to 0 °C, and slowly acidified with concentrated HCl. After warming the mixture to rt, it was extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to a pale yellow oil. The oil was taken up in Et₂O (210 mL) in a 3-neck 500-mL round-bottom flask outfitted with a reflux condenser. Phosphorus(V) chloride (17.6 g, 84.6 mmol, 2 equiv) was added, and the mixture was heated to reflux. After stirring for 4 h at reflux, the reaction was cooled to rt and transferred via cannula to a Schlenk filter funnel and filtered under positive N₂ pressure. The yellow filtrate was distilled directly (6 mmHg, 62-64 °C) to afford 7.03 g (34.3 mmol, 73% yield over 2 steps) of 279 as a colorless oil. A PhH (48 mL) solution of 279 (6.91 g, 33.8 mmol, 1 equiv) in a 100-mL recovery flask was treated with triethylamine (9.4 mL, 68 mmol, 2 equiv), and the resulting yellow slurry was stored in the dark for 7 h. The slurry was then passed through a Schlenk filter funnel under positive N₂ pressure. The filtrate was distilled directly (6 mmHg, 30-32 °C) to afford 2.89 g (17.2 mmol, 51% yield) of 206 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 2.54 (septet, J = 6.7 Hz, 1H), 1.24 (s, 9H), 1.11 (d, J = 6.7 Hz, 5H).

¹³C NMR (125 MHz; CDCl₃) δ: 200.1, 197.1, 59.7, 41.5, 31.7, 29.5, 19.6.

FTIR (thin film) νmax: 2966, 2908, 2874, 2097, 1668, 1459, 1384, 1365, 1248, 1193, 1157, 940 cm⁻¹.
4-Hydroxy-3,5-bis(3-methylbut-2-en-1-yl)-6-(2,2,5-trimethyl-4-oxohexan-3-yl)-2H-pyran-2-one

(222):

A DME (0.6 mL) solution of 218 (336 mg, 1.08 mmol, 1 equiv) was added to a DME (5 mL) slurry of sodium hydride (60% suspension in mineral oil, 48 mg, 1.18 mmol, 1.1 equiv) cooled to 0 ºC in a 25-mL round-bottom flask. After stirring the resulting pink solution at 0 ºC for 5 min, it was cooled to –30 ºC and a hexane solution of butyllithium (1.8 M, 0.65 mL, 1.2 mmol, 1.1 equiv) was added dropwise. After stirring for 10 min at –30 ºC, 206 (200. mg, 1.18 mmol, 1.1 equiv) was added and the reaction was allowed to slowly warm to rt. After stirring for 3.5 h, the reaction was quenched with sat. aq. NH₄Cl and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash column chromatography (75 mL SiO₂, 95:5 → 9:1 → 1:1 hexane:EtOAc) afforded 218 mg (0.56 mmol, 52% yield) of 222 as a white flocculent solid.

¹H NMR (600 MHz; CDCl₃) δ: 7.95 (br s, 1H), 5.22 (t, J = 7.3 Hz, 1H), 5.02 (t, J = 6.0 Hz, 1H), 3.57 (s, 1H), 3.21 (d, J = 7.3 Hz, 2H), 3.17 (dd, J = 16.0, 5.6 Hz, 1H), 3.11 (dd, J = 16.0, 7.3 Hz, 1H), 2.68 (septet, J = 6.8 Hz, 1H), 1.72 (s, 3H), 1.70 (s, 6H), 1.66 (s, 3H), 1.04 (s, 9H), 0.91 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 209.8, 164.9, 164.5, 156.0, 136.6, 133.3, 121.0, 120.4, 114.6, 103.0, 61.1, 39.9, 35.6, 28.9, 25.92, 25.72, 24.0, 23.3, 19.6, 18.10, 18.08, 18.01.

FTIR (thin film) ν_max: 3252 (br), 2967, 2874, 1727, 1666, 1559, 1449, 1217 cm⁻¹.


TLC R_d = 0.41 (7:3 hexane:EtOAc).
A THF (3 mL) solution of 222 (168 mg, 0.432 mmol, 1 equiv) in a 20-mL scintillation vial was treated with an Et₂O solution of trimethylsilyldiazomethane (2.0 M, 0.43 mL, 0.87 mmol, 2 equiv). After stirring the yellow solution at rt for 23 h, it was quenched with sat. aq. NH₄Cl and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (20 mL SiO₂, 95:5 → 8:2 hexane:EtOAc) afforded 162.3 mg (0.4032 mmol, 93% yield) of 225 as a pale yellow oil.

**1H NMR** (600 MHz; CDCl₃) δ 5.15 (t, J = 7.1 Hz, 1H), 5.10 (t, J = 6.8 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 1H), 3.51-3.47 (m, 1H), 3.10-3.06 (m, 2H), 3.02 (dd, J = 14.4, 7.1 Hz, 1H), 2.61 (t, J = 6.8 Hz, 1H), 1.78 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.09 (s, 9H), 1.04 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H).

**13C NMR** (125 MHz; CDCl₃) δ: 210.2, 179.5, 162.5, 154.5, 132.3, 132.1, 126.3, 121.9, 121.6, 104.0, 60.2, 56.1, 41.7, 36.4, 29.0, 25.95, 25.79, 24.2, 21.2, 18.8, 18.28, 18.18, 18.0.

**FTIR** (thin film) νₘₐₓ: 2962, 2913, 2872, 1723, 1652, 1618, 1592, 1462, 1401, 1324, 1266, 1178, 1124, 1021, 974 cm⁻¹.

**HRMS–ESI** (m / z): [M+H]⁺ calculated for C₂₅H₃₈O₄, 403.2846; found, 403.2843.

**TLC** Rₐ = 0.55 (8:2 hexane:EtOAc).
3,5-bis(3-Methylbut-2-en-1-yl)-2-oxo-6-(2,2,5-trimethyl-4-oxohexan-3-yl)-2H-pyran-4-yl benzoate (226):  

A pyr (1 mL) solution of 222 (59.8 mg, 0.15 mmol, 1 equiv) in a 5-mL pear-shaped flask was treated with benzoyl chloride (16 µL, 0.17 mmol, 1.1 equiv). After stirring the reaction for 9 h, it was poured onto sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a brown oil. Flash column chromatography (15 mL SiO₂, 95:5 hexane:EtOAc) afforded 36.9 mg (74.9 µmol, 50% yield) of 226 as a pale yellow oil.  

**¹H NMR** (600 MHz; CDCl₃) δ: 8.13-8.10 (m, 2H), 7.69-7.65 (m, 1H), 7.53 (t, J = 7.8, 3.8 Hz, 2H), 5.09 (t, J = 7.0 Hz, 1H), 4.96 (t, J = 5.0 Hz, 1H), 3.66 (s, 1H), 3.20-2.96 (m, 4H), 2.76 (t, J = 6.8 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.42 (s, 3H), 1.12 (s, 9H), 1.02 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H).  

**¹³C NMR** (125 MHz; CDCl₃) δ: 209.5, 163.12, 163.04, 159.2, 134.5, 133.80, 133.70, 130.5, 128.9, 128.1, 120.9, 119.4, 118.2, 116.0, 61.2, 40.3, 36.0, 32.9, 29.0, 25.81, 25.65, 25.2, 24.6, 19.7, 18.16, 18.02, 17.94.  

**FTIR** (thin film) νmax: 2967, 2931, 2872, 1743, 1723, 1565, 1452, 1375, 1258, 1229, 1176, 1059, 1022, 706 cm⁻¹.  

**HRMS–ESI** (m / z): [M+H]+ calculated for C₃₁H₄₀O₅, 493.2949; found, 493.2957.  

**TLC** Rₜ = 0.66 (1:1 hexane:EtOAc).
A PhMe (7 mL) solution of 237 (82 mg, 0.27 mmol, 1 equiv) in a 2-neck 25-mL round-bottom flask outfitted with a reflux condenser was refluxed for 90 min, whereupon the initially orange solution turned yellow. After cooling to rt, 234 (150 mg, 1.09 mmol, 4 equiv) was added, producing an orange solution. After stirring for 8 h at rt, it was heated at 60 ºC for 12 h, and then at 120 ºC for 3 h. The bright orange red solution was cooled to rt and concentrated in vacuo to an orange red oil. Flash column chromatography (100 mL SiO₂, 95:5 → 9:1 hexane:EtOAc) afforded 46 mg (0.18 mmol, 33% yield) of 238 as an orange oil and 10 mg (0.025 mmol, 5% yield) of 239 as an orange oil.

1-(tert-Butyl)-2-ethoxy-3-(3-methylbut-2-en-1-yl)-4-oxocyclobut-2-enecarbonitrile (238):

\[ ^1\text{H NMR (600 MHz; CDCl}_3\text{)} \delta: 5.08 (t, J = 7.0 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.85-2.83 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H), 1.09 (s, 9H). \]

\[ ^{13}\text{C NMR (125 MHz; CDCl}_3\text{)} \delta: 179.6, 172.9, 134.4, 124.6, 119.3, 117.2, 70.0, 68.3, 34.6, 26.4, 25.7, 22.0, 18.0, 15.2. \]

FTIR (thin film) \( \nu_{\text{max}} \): 2972, 2229, 1768, 1654, 1619, 1599, 1381, 1334 cm\(^{-1}\).

HRMS–ESI (m/z): [M+Na\(^+\)] calculated for C\(_{16}\)H\(_{23}\)NO\(_2\), 284.1621; found, 284.1611.

TLC \( R_f = 0.39 \) (8:2 hexane:EtOAc).

6-(tert-Butyl)-3,7-dioxy-4,8-bis(3-methylbut-2-en-1-yl)-2-azabicyclo[4.2.0]octa-1,3,7-trien-5-one (239):

\[ ^1\text{H NMR (500 MHz; CDCl}_3\text{)} \delta: 5.23 (t, J = 7.1 Hz, 1H), 5.18 (t, J = 7.5 Hz, 1H), 4.53 (dq, J = 10.0, 7.1 Hz, 1H), 4.46 (dq, J = 10.5, 7.1 Hz, 1H), 4.37 (m, 2H), 3.12 (dd, J = 14.0, 7.5 Hz, 1H), 3.03 (dd, J = 16.2, 7.1 Hz, 1H), 2.94 (dd, J = 16.2, 7.0 Hz, 1H), 2.84 (dd, J = 14.0, 7.5 Hz, 1H), 1.71 (s, 6H), 1.66 (s, 3H), 1.64 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 0.99 (s, 9H). \]
\[^{13}\text{C} \text{ NMR}\] (125 MHz; CDCl\textsubscript{3}) \(\delta\): 191.9, 180.8, 168.2, 162.7, 133.7, 130.6, 124.8, 123.3, 119.7, 110.6, 69.8, 63.4, 36.8, 29.9, 28.5, 25.98, 25.82, 22.9, 22.5, 18.04, 18.02, 15.53, 15.50.

\[\text{FTIR (thin film)} \nu_{\text{max}}: 2968, 2942, 1631, 1572, 1370, 1332, 1263 \text{ cm}^{-1}.\]

\[\text{HRMS–ESI (m/z)}: [M+H]^+ \text{ calculated for C}_{25}\text{H}_{37}\text{NO}_3, 400.2846; \text{ found}, \ 400.2860.\]

\[\text{TLC } R_f = 0.30 \text{ (8:2 hexane:EtOAc).}\]

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**Optimized procedure for the synthesis of 238:**

An orange PhMe (180 mL) solution of 237\textsuperscript{582} (5.47 g, 18.1 mmol, 2.5 equiv) in a 3-neck 500-mL round-bottom flask outfitted with a reflux condenser was heated to 102.5 ± 2.5 ºC for 90 min. After cooling the reaction to rt, a PhMe (36 mL) solution of 234\textsuperscript{579} (1.00 g, 7.24 mmol, 1 equiv) was added. The resulting deep red solution was heated to 102.5 ± 2.5 ºC for 90 min, cooled to rt, and concentrated \textit{in vacuo} to a dark red oil. Flash column chromatography (500 mL SiO\textsubscript{2}, 95:5 \(\rightarrow\) 9:1 \(\rightarrow\) 8:2 hexane:EtOAc) afforded 1.70 g (6.50 mmol, 90% yield) of 238 as an orange oil.
**Ethyl 2,2-dibromo-5-methylhex-4-enoate (243):**

A THF (5.5 mL) solution of 280\(^{601}\) (3.01 g, 19.3 mmol, 1 equiv) was added dropwise to a freshly prepared THF solution of lithium diisopropylamide (0.30 M, 66 mL, 20. mmol, 1.05 equiv) cooled to –78 ºC in a 200-mL recovery flask. After stirring for 25 min at –78 ºC, 1,2-dibromo-1,1,2,2-tetrafluoroethane (3.5 mL, 29 mmol, 1.5 equiv) was added. The resulting black-brown solution was stirred at –78 ºC for 30 min and subsequently quenched by pouring onto sat. aq. NaHCO₃. The mixture was extracted thrice with hexane. The organic extracts were combined, washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated in vacuo to a yellow oil. Short-path distillation (6 mmHg, 56-58 ºC) afforded 2.25 g (9.57 mmol) of a mono-brominated intermediate. A THF (2.8 mL) solution of this intermediate (2.22 g, 9.44 mmol, 1 equiv) was added dropwise to a freshly prepared THF solution of lithium diisopropylamide (0.30 M, 34 mL, 9.9 mmol, 1.05 equiv) cooled to –78 ºC in a 100-mL recovery flask. After stirring for 25 min at –78 ºC, 1,2-dibromo-1,1,2,2-tetrafluoroethane (1.7 mL, 14.2 mmol, 1.5 equiv) was added. The pale yellow solution was stirred at –78 ºC for 30 min and subsequently quenched by pouring onto sat. aq. NaHCO₃. The mixture was extracted thrice with hexane. The organic extracts were combined, washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated in vacuo to a yellow oil. Short-path distillation (6 mmHg, 80-85 ºC) afforded 1.74 g (5.54 mmol, 29% yield over 2 steps) of 243 as a colorless oil.

\(^{1}H\ NMR\) (600 MHz; CDCl₃) \(\delta\): 5.24 (t, \(J = 7.0\) Hz, 1H), 4.32 (q, \(J = 7.1\) Hz, 2H), 3.31 (d, \(J = 7.0\) Hz, 2H), 1.75 (s, 3H), 1.68 (s, 3H), 1.35 (t, \(J = 7.1\) Hz, 3H).

\(^{13}C\ NMR\) (125 MHz; CDCl₃) \(\delta\): 166.4, 137.9, 118.7, 64.0, 60.5, 46.0, 26.2, 18.9, 14.0.

FTIR (thin film) \(\nu_{\text{max}}\): 2980, 2932, 2914, 1733, 1445, 1298, 1222, 1177, 1029, 1014, 859, 793, 628 cm\(^{-1}\).

HRMS–ESI (m / z): [M+Na]\(^{+}\) calculated for C₉H₁₄Br₂O₂, 336.9226; found, 336.9233.

TLC $R_f = 0.53$ (9:1 hexane:EtOAc).
A THF (1 mL) solution of 243 (96 mg, 0.31 mmol, 1 equiv) in a 10-mL recovery flask was cooled to –78 °C and treated with a pentane solution of tert-butyllithium (1.70 M, 0.72 mL, 12 mmol, 4 equiv) dropwise over 7 min. The yellow solution was stirred at –78 ºC for 90 min, and then slowly warmed from 0 ºC to rt. After 4 hours, 238 (80.0 mg, 0.306 mmol, 1 equiv) was added at rt. After stirring at rt for 14 h, the reaction was quenched by pouring onto sat. aq. NH₄Cl and extracted thrice with Et₂O. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a viscous orange-red oil. Flash column chromatography (100 mL SiO₂, 95:5 → 9:1 → 8:2 → 1:1 hexane:EtOAc) afforded 9 mg (0.02 mmol, 8% yield) of 244 as a pale yellow oil and 10. mg (0.038 mmol, 12% yield) of 245 as a pale yellow oil.

2-(4-Ethoxy-3,5-bis(3-methylbut-2-en-1-yl)-2-oxo-2H-pyran-6-yl)-3,3-dimethylbutanenitrile (244):

**1H NMR** (600 MHz; CDCl₃) δ: 5.17 (t, J = 6.7 Hz, 1H), 4.98 (t, J = 6.5 Hz, 1H), 3.96 (dd, J = 7.0, 1.9 Hz, 1H), 3.94 (dd, J = 7.0, 1.9 Hz, 1H), 3.63 (s, 1H), 3.17 (d, J = 6.7 Hz, 2H), 3.13 (dd, J = 16.3, 6.5 Hz, 1H), 2.98 (dd, J = 16.3, 6.5 Hz, 1H), 1.73 (s, 9H), 1.70 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H), 1.17 (s, 9H).

**13C NMR** (125 MHz; CDCl₃) δ: 165.9, 163.8, 150.9, 134.0, 133.6, 121.1, 120.5, 117.2, 116.9, 116.4, 70.7, 43.5, 36.3, 28.3, 25.91, 25.77, 24.6, 24.0, 18.27, 18.21, 15.8.

**FTIR** (thin film) νmax: 2969, 2931, 2242, 1720, 1639, 1562, 1445, 1375, 1204, 1063, 1022 cm⁻¹.

**HRMS–ESI** (m / z): [M+H]⁺ calculated for C₂₃H₃₃NO₃, 372.2533; found, 372.2524.

**TLC** Rf = 0.24 (8:2 hexane:EtOAc).

Z-Ethyl 4-cyano-3-ethoxy-5,5-dimethyl-2-(3-methylbut-2-en-1-yl)hex-3-enoate (245):

**1H NMR** (600 MHz; CDCl₃) δ: 5.09 (t, J = 7.5 Hz, 1H), 4.23 (dq, J = 10.8, 7.1 Hz, 1H), 4.18 (dq, J = 10.8, 7.1 Hz, 1H), 4.03-3.92 (m, 2H), 3.76 (dq, J = 8.9, 7.0 Hz, 1H), 2.71 (dt, J = 14.3, 6.7 Hz, 1H), 2.44
(dt, \( J = 14.3,\) 8.9 Hz, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.31 (t, \( J = 7.0\) Hz, 3H), 1.28 (t, \( J = 7.1\) Hz, 3H), 1.23 (s, 9H).

\(^{13}\)C NMR (125 MHz; CDCl\(_3\)) \( \delta \): 171.2, 165.8, 134.9, 120.10, 119.99, 108.6, 65.8, 61.7, 49.6, 33.1, 29.9, 27.6, 25.9, 18.0, 15.4, 14.3.

FTIR (thin film) \( \nu_{\text{max}} \): 2967, 2929, 2872, 2202, 1734, 1600, 1445, 1365, 1296, 1207, 1148, 1030 cm\(^{-1}\).

HRMS–ESI (m / z): [M+H]\(^+\) calculated for C\(_{18}\)H\(_{29}\)NO\(_3\), 308.2220; found, 308.2218.

TLC \( R_f = 0.36 \) (8:2 hexane:EtOAc).
1-Methoxy-5-methylhex-4-en-1-yne (246):

A THF (120 mL) solution of methanol (2.5 mL, 61 mmol, 1 equiv) was added via cannula over 15 min to a THF (120 mL) slurry of freshly washed potassium hydride (4.91 g, 122 mmol, 2 equiv) in a 500-mL round-bottom flask. After stirring at rt for 105 min, the reaction was cooled to –60 ºC, and a THF (70 mL) solution of trichloroethylene (5.5 mL, 61 mmol, 1 equiv) was added, and the cooling bath was removed. After stirring for 75 min, the reaction was cooled to –78 ºC, and a hexane solution of butyllithium (2.73 M, 54 mL, 150 mmol, 2.4 equiv) was added. After slowly warming the reaction to –10 ºC over 105 min, the reaction was cooled to –78 ºC, and a HMPA (14 mL) solution of prenyl bromide (7.1 mL, 61 mmol, 1 equiv) was added via cannula. The cooling bath was then removed, and the reaction was stirred at rt for 4 h and was subsequently quenched with a small amount of sat. aq. NaHCO₃, diluted with H₂O, and extracted thrice with pentane. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a dark brown oil. Short-path distillation (6 mmHg, 54-70 ºC) afforded 4.04 g (32.5 mmol, 53% yield) of 246 as a pale yellow oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.16 (t, J = 6.9 Hz, 1H), 3.81 (s, 3H), 2.80 (d, J = 6.9 Hz, 2H), 1.70 (s, 3H), 1.61 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 132.9, 121.0, 90.7, 65.5, 35.5, 25.7, 17.8, 16.3.

FTIR (thin film) ν max: 2965, 2927, 2857, 2281, 1449, 1376, 1241, 1172, 961, 841 cm⁻¹.

GCMS (m / z): [M]+ 124 (11%), 109 (90%), 69 (25%), 28 (100%).

TLC Rf = 0.32 (99:1 hexane:EtOAc).
2-Ethoxy-6-hydroxy-4-methoxy-3,5-bis(3-methylbut-2-en-1-yl)benzonitrile (248):

A xylenes (3 mL) solution of 238 (34.3 mg, 0.131 mmol, 1 equiv) and 246 (80. mg, 0.64 mmol, 5 equiv) was heated to 140 ºC in a 10-mL sealed tube. After stirring at 140 ºC for 22 h, the reaction was cooled to rt and concentrated in vacuo to an orange oil. Flash column chromatography (100 mL SiO₂, 95:5 → 9:1 → 8:2 hexane:EtOAc) followed by preparatory thin-layer chromatography (2 × 99:1 hexane:EtOAc) afforded 11 mg (0.033 mmol, 25% yield) of 248 as a white residue.

H NMR (600 MHz; CDCl₃) δ: 6.08 (br s, 1H), 5.21 (t, J = 7.0 Hz, 1H), 5.10 (t, J = 6.7 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.71 (s, 3H), 3.38 (d, J = 7.0 Hz, 2H), 3.27 (d, J = 6.7 Hz, 2H), 1.83 (s, 3H), 1.77 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H).

C NMR (125 MHz; CDCl₃) δ: 161.9, 159.5, 157.4, 136.7, 132.0, 123.2, 122.0, 121.2, 116.7, 114.9, 92.0, 71.2, 62.0, 26.03, 25.90, 23.61, 23.49, 18.19, 18.13, 15.9.

Key 1D nOe correlations.

FTIR (thin film) νₘₐₓ: 3363 (br), 2978, 2930, 2226, 1597, 1579, 1445, 1385, 1097 cm⁻¹.

HRMS–ESI (m / z): [M+H]⁺ calculated for C₂₀H₂₇NO₃, 330.2064; found, 330.2055.

TLC Rᵣ = 0.75 (95:5 hexane:EtOAc).
**E-2-Cyano-3-ethoxy-5-methoxy-4,6-bis(3-methylbut-2-en-1-yl)phenyl 4-cyano-3-ethoxy-5,5-dimethyl-2-(3-methylbut-2-en-1-yl)hex-3-enoate (253):**

A xylenes (1 mL) solution of 238 (12 mg, 0.046 mmol), 246 (28.5 mg, 0.230 mmol, 5 equiv), and Hünig’s base (~1 mg, 0.01 mmol, 0.2 equiv) was sparged with N₂ for 5 min in a 10-mL sealed tube and subsequently heated to 140 °C. After stirring for 8.5 h at 140 °C, the reaction was cooled to rt and concentrated *in vacuo*. Flash column chromatography (25 mL SiO₂, 98:2 → 9:1 hexane:EtOAc) afforded 3.4 mg (0.010 mmol, 22% yield) of 248 as a white residue and 10.5 mg (0.018 mmol, 78% yield) of 253 as a colorless residue.

**1H NMR** (600 MHz; CDCl₃) δ: 5.14 (t, J = 7.3 Hz, 1H), 5.10 (t, J = 6.4 Hz, 1H), 5.02 (t, J = 5.8 Hz, 1H), 4.27 (dd, J = 9.0, 6.0 Hz, 1H), 4.21-4.16 (m, 3H), 4.08-4.05 (m, 1H), 3.73 (s, 3H), 3.33 (d, J = 6.4 Hz, 2H), 3.26 (d, J = 5.8 Hz, 2H), 2.62 (m, 1H), 2.66 (m, 1H), 1.76 (s, 3H), 1.74 (s, 3H), 1.72 (s, 3H), 1.71-1.69 (s, 9H), 1.44 (t, J = 7.0 Hz, 3H), 1.36 (t, J = 6.9 Hz, 3H), 1.26 (s, 9H).

**13C NMR** (125 MHz; CDCl₃) δ: 169.0, 164.2, 162.4, 160.0, 150.1, 135.6, 133.5, 132.6, 128.4, 125.5, 122.4, 121.5, 119.7, 119.5, 114.3, 109.8, 79.4, 71.5, 67.1, 62.1, 49.8, 33.4, 29.9, 27.7, 25.95, 25.86, 25.80, 24.1, 23.8, 18.28, 18.17, 18.11, 15.9, 15.3.
Key 1D nOe correlation.

**FTIR** (thin film) $\nu_{\text{max}}$: 2961, 2923, 2854, 2229, 2203, 1769, 1599, 1440, 1385, 1099 cm$^{-1}$.

**HRMS–ESI (m / z)**: [M+Na]$^+$ calculated for C$_{36}$H$_{50}$N$_2$O$_5$, 613.3612; found, 613.3611.

**TLC** $R_f = 0.48$ (8:2 hexane:EtOAc).
4-(3-Methoxyprop-2-yn-1-yl)-3,3-dimethyl-2,2-diphenyloxetane (254):

A PhH (3 mL) solution of 238 (40. mg, 0.15 mmol, 1 equiv), 246 (95 mg, 0.77 mmol, 5 equiv), and benzophenone (9 mg, 0.05 mmol, 0.3 equiv) in a 10-mL borosilicate test tube placed in a continuous flow H₂O bath was irradiated with quartz-filtered light for 22 h. The reaction was then concentrated in vacuo to an orange-yellow oil. Flash column chromatography (30 mL SiO₂, 95:5 hexane:EtOAc) afforded 4.3 mg (0.014 mmol, 28% yield) of 254 as a white flocculent solid.

¹H NMR (600 MHz; CDCl₃) δ: 7.58 (dd, J = 8.5, 1.2 Hz, 2H), 7.43 (dd, J = 8.4, 1.2 Hz, 2H), 7.33-7.27 (m, 4H), 7.20-7.15 (m, 2H), 4.44 (dd, J = 9.2, 5.6 Hz, 1H), 3.79 (s, 3H), 2.51 (dd, J = 16.1, 5.6 Hz, 1H), 2.40 (dd, J = 16.1, 9.2 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 145.1, 144.2, 128.2, 127.9, 126.69, 126.54, 125.8, 125.2, 92.2, 91.3, 84.2, 65.5, 46.0, 31.9, 26.6, 20.9, 20.5.

FTIR (thin film) νmax: 3058, 3025, 2972, 2943, 2275, 1449, 1239, 995, 959, 709 cm⁻¹.


TLC Rf = 0.51 (8:2 hexane:EtOAc).
2-Ethoxy-4-hydroxy-6-methoxy-3,5-bis(3-methylbut-2-en-1-yl)benzonitrile (255):

A PhMe (3 mL) solution of 238 (40. mg, 0.15 mmol, 1 equiv), 246 (95 mg, 0.77 mmol, 5 equiv), and 2,6-di-tert-butyl-4-methylphenol (7 mg, 0.03 mmol, 0.2 equiv) was heated to 140 ºC in a 10-mL sealed tube. After stirring at 140 ºC for 12 h, the reaction was cooled to rt and concentrated in vacuo to an orange oil. Flash column chromatography (30 mL SiO₂, 95:5 hexane:EtOAc) followed by preparatory thin-layer chromatography (1 × 98.2 CH₂Cl₂:Et₂O) afforded 3 mg (9 µmol, 6% yield) of 255 as a colorless residue.

**¹H NMR (600 MHz; CDCl₃)**: δ: 6.11 (s, 1H), 5.17-5.14 (m, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.94-3.92 (m, 3H), 3.37-3.33 (m, 4H), 1.80 (s, 6H), 1.75 (s, 3H), 1.74 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H).

**¹³C NMR (125 MHz; CDCl₃)**: δ: 160.2, 159.3, 135.5, 135.1, 121.47, 121.42, 117.73, 117.59, 115.5, 93.4, 71.5, 62.5, 26.0, 23.20, 23.03, 18.18, 18.15, 15.9.

**FTIR (thin film)** νmax: 3396 (br), 2979, 2928, 2225, 1586, 1438, 1389, 1178, 1097 cm⁻¹.

**HRMS–ESI (m/z)**: [M+Na]⁺ calculated for C₂₀H₂₇NO₃, 352.1883; found, 352.1888.

**TLC** Rₜ = 0.68 (95:5 CH₂Cl₂:Et₂O).
**E-4-cyano-3-ethoxy-5-methoxy-2,6-bis(3-methylbut-2-en-1-yl)phenyl 4-cyano-3-ethoxy-5,5-dimethyl-2-(3-methylbut-2-en-1-yl)hex-3-enoate (257):**

A PhMe (3 mL) solution of 238 (40. mg, 0.15 mmol, 1 equiv), 246 (95 mg, 0.77 mmol, 5 equiv), 2,6-di-tert-butyl-4-methylphenol (7 mg, 0.03 mmol, 0.2 equiv), and Hünig’s base (5 µL, 0.03 mmol, 0.2 equiv) was heated to 140 ºC in a 10-mL sealed tube. After stirring for 10.5 h, the reaction was cooled to rt and concentrated in vacuo to a brown-red oil. Flash column chromatography (25 mL SiO2, 95:5 hexane:EtOAc) afforded 6.3 mg (0.019 mmol, 13% yield) of 248 as a colorless residue, 2.5 mg (7.6 µmol, 5% yield) of 255 as a colorless residue, and 19.1 mg (0.032 mmol, 42% yield) of 257 as a colorless residue.

**1H NMR (600 MHz; CDCl₃) δ:** 5.24 (t, J = 6.4 Hz, 1H), 5.11 (t, J = 6.7 Hz, 1H), 5.05 (s, 1H), 5.00 (t, J = 6.5 Hz, 1H), 4.27-4.22 (m, 1H), 4.22-4.17 (m, 2H), 4.15-4.11 (m, 1H), 3.74 (s, 3H), 3.33 (d, J = 6.6 Hz, 2H), 3.30-3.19 (m, 4H), 1.76 (s, 3H), 1.71 (s, 6H), 1.68 (s, 3H), 1.67 (s, 6H), 1.44 (t, J = 5.7 Hz, 3H), 1.42 (t, J = 5.8 Hz, 3H), 1.14 (s, 9H).

**13C NMR (125 MHz; CDCl₃) δ:** 166.5, 162.3, 160.1, 150.4, 133.8, 132.9, 132.5, 128.1, 125.2, 122.5, 121.77, 121.63, 118.9, 114.0, 98.4, 72.0, 71.5, 62.1, 43.7, 36.3, 29.9, 28.2, 26.9, 25.88, 25.86, 25.84, 25.80, 24.04, 23.86, 18.26, 18.22, 18.19, 15.95, 15.81.

**FTIR (thin film) v_max:** 2967, 2930, 2857, 2228, 1729, 1597, 1439, 1387, 1160, 1084, 1041, 1024, 988 cm⁻¹.

**HRMS–ESI (m / z): [M+Na]⁺ calculated for C₃₆H₅₀N₂O₅, 613.3623; found, 613.3612.**

**TLC R_f = 0.50 (8:2 hexane:EtOAc).**
3-(tert-Butyl)-2-isopropyl-6-methoxy-5-(3-methylbut-2-en-1-yl)-4H-pyran-4-one (258):

A xylenes (4.8 mL) solution of 206 (41 mg, 0.24 mmol, 1 equiv) and 246 (150 mg, 1.2 mmol, 5 equiv) was heated to 140 ºC in a 50-mL sealed tube. After stirring at 140 ºC for 7 h, the reaction was cooled to rt and concentrated in vacuo. Flash column chromatography (30 mL SiO₂, 95:5 → 9:1 → 8:2 hexane:EtOAc) followed by preparatory thin-layer chromatography (2 × 9:1 hexane:EtOAc) afforded 2.5 mg (8.5 µmol, 4% yield) of 258 as a colorless residue.

¹H NMR (600 MHz; CDCl₃) δ: 5.19 (t, J = 6.7 Hz, 1H), 3.93 (s, 3H), 3.67 (septet, J = 6.7 Hz, 1H), 3.02 (d, J = 6.7 Hz, 2H), 1.72 (s, 3H), 1.67 (s, 3H), 1.44 (s, 9H), 1.25 (d, J = 6.8 Hz, 6H).

¹³C NMR (125 MHz; CDCl₃) δ: 181.5, 162.7, 161.0, 131.9, 128.3, 122.4, 103.8, 55.2, 35.1, 31.7, 30.9, 26.0, 21.12, 21.06, 18.0.

FTIR (thin film) ν max: 2067, 2921, 1664, 1611, 1462, 1381, 1314, 1262, 1141 cm⁻¹.


TLC Rₜ = 0.26 (8:2 hexane:EtOAc).
A PhMe (5.8 mL) solution of 208 (50 mg, 0.29 mmol, 1 equiv) and 246 (182 mg, 1.47 mmol, 5 equiv) in a 10-mL sealed tube was heated to 110 ºC. After stirring for 19.5 h at 110 ºC, the reaction was cooled to rt and concentrated in vacuo to a yellow oil. Flash column chromatography (30 mL SiO2, 95:5 hexane:EtOAc) afforded 22.0 mg of an inseparable mixture of 259 and 260 (1.3:1 ratio by 1H NMR spectroscopy; 0.069 mmol, 25% total yield) as a colorless oil.

**FTIR** (thin film) ν<sub>max</sub>: 2967, 2954, 2930, 2916, 1719, 1679, 1624, 1608, 1381, 1350, 1263, 1239 cm<sup>-1</sup>.

**HRMS–ESI** (m / z): [M+Na]<sup>+</sup> calculated for C<sub>17</sub>H<sub>26</sub>O<sub>4</sub>, 317.1723; found, 317.1714.

**TLC** R<sub>f</sub> = 0.43 (8:2 hexane:EtOAc).

3-(tert-Butyl)-2-ethoxy-6-methoxy-5-(3-methylbut-2-en-1-yl)-4H-pyran-4-one (259):<sup>602</sup>

**1H NMR** (600 MHz; CDCl<sub>3</sub>) δ: 4.99 (t, J = 7.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 2.90 (dd, J = 15.5, 7.6 Hz, 1H), 2.49 (dd, J = 15.5, 7.6 Hz, 1H), 1.69 (s, 3H), 1.63 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.15 (s, 9H).

**13C NMR** (125 MHz; CDCl<sub>3</sub>) δ: 180.6, 174.4, 171.0, 136.2, 135.2, 117.7, 73.1, 61.7, 59.6, 31.4, 28.4, 27.9, 26.1, 18.04, 14.4.

Ethyl 3-(tert-butyl)-2-methoxy-1-(3-methylbut-2-en-1-yl)-4-oxocyclobut-2-ene carboxylate (260):<sup>602</sup>

**1H NMR** (600 MHz; CDCl<sub>3</sub>) δ: 5.15 (t, J = 7.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.00 (d, J = 7.0 Hz, 2H), 1.69 (s, 3H), 1.65 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.36 (s, 9H).

**13C NMR** (125 MHz; CDCl<sub>3</sub>) δ: 182.4, 158.24, 158.17, 131.9, 122.3, 111.1, 104.0, 66.1, 55.9, 33.9, 30.5, 25.9, 21.2, 17.97, 15.0.

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<sup>602</sup> NMR assignments of the mixture were elucidated using heteronuclear 2D-NMR techniques.
S-Ethyl 2-(chlorocarbonyl)-3,3-dimethylbutanethioate (263):

A MeCN (4 mL) solution of \(262^{594}\) (813 mg, 4.06 mmol, 1 equiv) in a 20-mL scintillation vial was cooled to 0 ºC. Hünig’s base (777 µL, 4.47 mmol, 1.1 equiv) followed by chlorotrimethylsilane (567 µL, 4.47 mmol, 1.1 equiv) were added dropwise over 10 min. After stirring an additional 10 min at 0 ºC, ethanethiol (316 µL, 4.26 mmol, 1.05 equiv) was added. The resulting white slurry was warmed to 43 ºC, whereupon a colorless solution formed. After stirring at 43 ºC for 4.5 h, the solution was cooled to rt, quenched with 0.3 M HCl, and extracted thrice with Et₂O. The organic extracts were combined and extracted once with sat. aq. NaHCO₃. This aqueous extract was stirred vigorously while an aqueous 10% HCl solution was added dropwise until the pH of the solution was < 2. This solution was extracted thrice with Et₂O. These organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated to a colorless oil, which solidified upon cooling. An Et₂O (12 mL) solution of this material and phosphorous(V) chloride (1.46 g, 6.99 mmol, 2 equiv) in a 2-neck 25-mL round-bottom flask outfitted with a reflux condenser was refluxed for 2.5 h. After cooling the solution to rt, it was transferred via cannula to a Schlenk filter funnel and filtered under a positive pressure of N₂ followed by one Et₂O rinse. The filtrate was concentrated under a stream of N₂ and distilled directly. Short-path distillation (6 mmHg, 65-70 ºC) afforded 604 mg (2.71 mmol, 77% yield over 2 steps) of \(263\) as a colorless oil.

\(^1\)H NMR (600 MHz; CDCl₃) δ: 3.98 (s, 1H), 2.97 (m, 2H), 1.29 (t, \(J = 7.4 \text{ Hz}, 3\)H), 1.15 (s, 9H).

\(^13\)C NMR (125 MHz; CDCl₃) δ: 191.1, 167.1, 80.5, 36.8, 28.3, 24.9, 14.5.
**S-Ethyl 3,3-dimethyl-2-oxomethylidenebutanethioate (261):**

A PhH (3.8 mL) solution of 263 (593 mg, 2.66 mmol, 1 equiv) in a 10-mL pear-shaped flask was treated with triethylamine (0.74 mL, 5.3 mmol, 2 equiv), immediately causing a white precipitate to form. After allowing the flask to stand for 16 h at rt, the reaction was diluted with PhH and filtered through a Schlenk filter funnel under a positive pressure of N₂. The pale yellow precipitate was washed twice with PhH. The resulting pale yellow filtrate was concentrated *in vacuo*. Short-path distillation (6 mmHg, 45-50 °C) afforded 195 mg (1.05 mmol, 39% yield) of 261 as a colorless oil.

**1H NMR** (500 MHz; CDCl₃) δ: 2.96 (q, *J* = 7.4 Hz, 2H), 1.28 (t, *J* = 7.4 Hz, 3H), 1.26 (s, 9H).

**13C NMR** (125 MHz; CDCl₃) δ: 189.5, 110.9, 62.9, 32.8, 29.8, 23.8, 15.4.

**FTIR** (thin film) ν_max: 2965, 2919, 2874, 2108, 1661, 1241, 1158, 864, 773 cm⁻¹.
5-(tert-Butyl)-6-(ethylthio)-4-methoxy-3-(3-methylbut-2-en-1-yl)-2H-pyran-2-one (264):

A PhMe (3.2 mL) solution of 261 (30. mg, 0.16 mmol, 1 equiv) and 246 (100 mg, 0.81 mmol, 5 equiv) was heated to 110 ºC in a 10-mL sealed tube. After stirring at 110 ºC for 11 h, the reaction was cooled to rt and concentrated in vacuo. Flash column chromatography (30 mL SiO₂, 95:5 hexane:EtOAc) afforded 19.0 mg (0.061 mmol, 38% yield) of 264 as a colorless residue.

1H NMR (600 MHz; CDCl₃) δ: 5.04 (t, J = 6.2 Hz, 1H), 3.65 (s, 3H), 3.07 (m, 4H), 1.71 (s, 3H), 1.70 (s, 3H), 1.40 (s, 9H), 1.35 (t, J = 7.4 Hz, 3H).

13C NMR (125 MHz; CDCl₃) δ: 168.0, 163.9, 155.9, 133.3, 121.6, 120.0, 115.2, 62.3, 35.7, 30.4, 25.8, 25.2, 18.3, 15.5.

**Key 1D nOe correlations.**

FTIR (thin film) νmax: 2964, 2930, 1717, 1597, 1509, 1343, 1118, 1008, 942 cm⁻¹.


TLC Rₜ = 0.30 (9:1 hexane:EtOAc).
A PhH (2 mL) solution of 238 (171 mg, 0.65 mmol, 1 equiv) and 265 (100 mg, 0.65 mmol, 1 equiv) was stirred at rt in a sealed tube for 9.5 h. The reaction was then heated to 40 °C for 1 d. The reaction was subsequently cooled to rt and concentrated in vacuo to a red oil. Flash column chromatography (100 mL SiO₂, 95:5 → 9:1 → 8:2 hexane:EtOAc) afforded 32 mg (0.077 mmol, 12% yield) of 266 as a pale yellow oil and 183 mg (0.44 mmol, 68% yield) of 267 as a pale yellow oil.

\[ E-2-((3-\text{Butyl}-2-(\text{diethylamino})-1-(3\text{-methylbut-2-en-1-yl})-4\text{-oxocyclobut-2-en-1-yl})(\text{ethoxy})\text{methylene})-3,3\text{-dimethylbutanenitrile} \text{ (266):} \]

\[ \text{1H NMR} \ (600 \text{ MHz; CDCl}_3 \) δ: 4.97 \text{(t,} \ J = 7.2 \text{ Hz,} \ 1\text{H}), \ 4.58 \text{(dq,} \ J = 10.0, \ 7.1 \text{ Hz,} \ 1\text{H}), \ 3.61-3.53 \text{ (m,} \ 2\text{H}), \ 3.28-3.21 \text{ (m,} \ 3\text{H}), \ 2.64 \text{(dd,} \ J = 15.9, \ 7.2 \text{ Hz,} \ 1\text{H}), \ 2.31 \text{(dd,} \ J = 15.9, \ 7.2 \text{ Hz,} \ 1\text{H}), \ 2.19-2.10 \text{ (m,} \ 2\text{H}), \ 1.66 \text{(s,} \ 3\text{H}), \ 1.62 \text{(s,} \ 3\text{H}), \ 1.57 \text{(m,} \ 2\text{H}), \ 1.36 \text{(m,} \ J = 2.9 \text{ Hz,} \ 2\text{H}), \ 1.32 \text{(t,} \ J = 7.1 \text{ Hz,} \ 3\text{H}), \ 1.25 \text{(s,} \ 9\text{H}), \ 1.22 \text{(m,} \ 6\text{H}), \ 0.90 \text{(t,} \ J = 7.4 \text{ Hz,} \ 3\text{H)}. \]

\[ \text{13C NMR} \ (125 \text{ MHz; CDCl}_3 \) δ: 180.8, 168.9, 165.0, 134.7, 118.64, 118.57, 117.9, 110.3, 72.0, 67.8, 45.9, 42.6, 35.3, 31.1, 30.9, 27.4, 26.2, 23.7, 22.9, 18.4, 14.9, 14.1, 13.8, 12.7.

Key 1D nOe correlations.

\[ \text{HRMS–ESI (m / z): [M+Na]⁺ calculated for C}_{26}\text{H}_{42}\text{N}_{2}\text{O}_{2}, \ 437.3139; \text{found,} \ 437.3150. \]

\[ \text{FTIR (thin film) ν}_{\text{max}}: \ 2962, 2933, 2873, 2198, 1744, 1586, 1451 \text{ cm}^{-1}. \]

\[ \text{TLC} \ R_f = 0.51 \ (8:2 \text{ hexane:EtOAc}). \]
**E-2-Butyl-6-cyano-5-ethoxy-N,N-diethyl-7,7-dimethyl-4-(3-methylbut-2-en-1-yl)octa-2,3,5-trienamide (267):**

**1H NMR** (500 MHz; CDCl₃) δ: 5.14 (t, J = 7.3 Hz, 1H), 3.89-3.79 (m, 2H), 3.39-3.28 (m, 4H), 2.90 (dd, J = 16.1, 7.3 Hz, 1H), 2.81 (dd, J = 16.1, 7.3 Hz, 1H), 2.38-2.30 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.43-1.38 (m, 2H), 1.36-1.28 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H), 1.15 (s, 9H), 1.07 (t, J = 7.1 Hz, 6H), 0.85 (t, J = 7.2 Hz, 3H).

**13C NMR** (125 MHz; CDCl₃) δ: 200.4, 166.3, 163.7, 135.0, 119.46, 119.33, 104.7, 103.6, 100.9, 65.8, 42.8 (br), 39.5 (br), 33.0, 30.8, 30.59, 30.47, 29.8, 25.8, 22.4, 17.9, 15.3, 14.6 (br), 13.9, 12.9 (br).

Key 1D nOe correlations.

**FTIR** (thin film) v_max: 2967, 2934, 2873, 2201, 1595, 1539, 1458, 1429, 1274, 1220, 739 cm⁻¹.

**HRMS–ESI** (m/z): [M+H]+ calculated for C₂₆H₄₂N₂O₂, 415.3319; found, 415.3321.

**TLC** Rₜ = 0.31 (8:2 hexane:EtOAc).
3-Butyl-4-(diethylamino)-6-ethoxy-2-hydroxy-5-(3-methylbut-2-en-1-yl)benzonitrile (272):

A PhH (1 mL) solution of 266 (6.0 mg, 14 µmol) was heated to 140 °C for 15 min in a 10-mL sealed tube. The reaction was subsequently cooled to rt and concentrated in vacuo to an orange oil. Preparatory thin-layer chromatography (1 × 98:2 hexane:EtOAc) afforded 2.4 mg (6.7 µmol, 48% yield) of 272 as a pale yellow oil and 1.6 mg (3.9 µmol, 27% recovery) of 266 as a pale yellow oil.

$^1$H NMR (600 MHz; CDCl$_3$) δ: 5.39 (br s, 1H), 4.99 (t, $J = 6.1$ Hz, 1H), 4.12 (q, $J = 7.0$ Hz, 2H), 3.30 (d, $J = 6.1$ Hz, 2H), 3.06 (q, $J = 7.1$ Hz, 4H), 2.61-2.58 (m, 2H), 1.73 (s, 3H), 1.67 (s, 3H), 1.52-1.46 (m, 3H), 1.44-1.40 (m, 5H), 1.02 (t, $J = 7.1$ Hz, 6H), 0.96 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (125 MHz; CDCl$_3$) δ: 155.8, 155.5, 154.6, 131.0, 128.9, 126.2, 124.3, 115.5, 91.4, 70.8, 48.4, 31.5, 26.7, 25.84, 25.73, 23.8, 18.3, 15.9, 14.8, 14.2.

FTIR (thin film) $\nu_{\text{max}}$: 3323 (br), 2965, 2929, 2855, 2228, 1592, 1556, 1447, 1378, 1119 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{22}$H$_{34}$N$_2$O$_2$, 381.2512; found, 381.2505.

TLC $R_f=0.65$ (95:5 hexane:EtOAc).
Z-2-((3-Butyl-2-(diethylamino)-1-(3-methylbut-2-en-1-yl)-4-oxocyclobut-2-en-1-yl)(ethoxy)methylene)-3,3-dimethylbutanenitrile (273):

A PhH (1 mL) solution of 266 (5.0 mg, 12 µmol) in a 12-mL quartz test tube was irradiated in a continuous flow rt H2O bath for 4 h. The reaction was then concentrated in vacuo to an orange-yellow oil. Preparatory thin-layer chromatography (1 × 95:5 hexane:EtOAc → 1 × 9:1 hexane:EtOAc) afforded 1.3 mg (3.1 µmol, 26% yield) of 273 as a pale yellow residue and 1.6 mg (3.9 µmol, 32% recovery) of 266 as a pale yellow residue.

**1H NMR** (600 MHz; CDCl3) δ: 5.01 (t, J = 7.0 Hz, 1H), 4.24 (dq, J = 9.0, 7.0 Hz, 1H), 3.84 (dq, J = 9.0, 7.0 Hz, 1H), 3.38 (m, 2H), 3.23-3.18 (m, 2H), 3.03 (dd, J = 15.6, 7.0 Hz, 1H), 2.44 (dd, J = 15.6, 7.0 Hz, 1H), 2.16-2.05 (m, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.52-1.45 (m, 2H), 1.42 (s, 9H), 1.37-1.32 (m, 2H), 1.30-1.28 (m, 3H), 1.23-1.18 (m, 6H), 0.90 (t, J = 7.3 Hz, 3H).

**13C NMR** (125 MHz; CDCl3) δ: 179.7, 171.4, 165.9, 134.8, 118.7, 115.9, 114.1, 110.2, 74.6, 73.5, 46.3, 42.0, 33.5, 32.16, 32.12, 31.94, 26.1, 23.5, 22.9, 18.6, 16.0, 14.3, 14.1, 13.5.

**FTIR** (thin film) νmax: 2959, 2926, 2854, 2207, 1736, 1591, 1459, 1377 cm⁻¹.

**HRMS–ESI** (m / z): [M+H]⁺ calculated for C26H42N2O2, 415.3319; found, 415.3307.

**TLC** Rₜ = 0.37 (8:2 hexane:EtOAc).
4-(tert-Butyl)-4-chloro-3-methoxy-2-(3-methylbut-2-en-1-yl)cyclobut-2-enone (276):

A PhH (5 mL) solution of 275 (500 mg, 2.96 mmol 1 equiv) was added dropwise via cannula to a PhH (20 mL) solution of triethylamine (412 µL, 2.96 mmol, 1 equiv) and 246 (771 mg, 6.21 mmol, 2.1 equiv) in a 50-mL recovery flask. The resulting yellow solution was stirred at rt for 80 min. A reflux condenser was then attached to the recovery flask, and the reaction was refluxed for 90 min. The reaction was then cooled to rt and concentrated in vacuo to a red-orange oil. This oil was taken up in 9:1 hexane:EtOAc and filtered to remove an off-white solid. The filtrate was concentrated in vacuo to a red-orange oil. Flash column chromatography (100 mL SiO₂, 95:5 → 9:1 hexane:EtOAc) afforded 209 mg (0.81 mmol, 27% yield) of 276 as a pale yellow oil.

°H NMR (600 MHz; CDCl₃) δ: 5.04 (t, J = 7.0 Hz, 1H), 4.09 (s, 3H), 2.86-2.78 (m, 2H), 1.61 (s, 3H), 1.56 (s, 3H), 1.02 (s, 9H).

¹³C NMR (125 MHz; CDCl₃) δ: 185.7, 178.7, 133.9, 124.2, 119.4, 89.9, 60.3, 36.6, 26.3, 25.5, 21.4, 17.8.

FTIR (thin film) νmax: 2974, 1771, 1622, 1457, 1356, 1258, 991 cm⁻¹.

HRMS–ESI (m / z): [M+H]+ calculated for C₁₄H₂₁ClO₂, 257.1303; found, 257.1314.

TLC Rf = 0.18 (95:5 hexane:EtOAc).
A PhMe (3 mL) solution of 276 (50 mg, 0.19 mmol, 1 equiv) and 246 (48 mg, 0.39 mmol, 2 equiv) was heated to 140 °C in a 10-mL sealed tube. After stirring at 140 °C for 18.5 h, the reaction was cooled to rt and concentrated in vacuo to a yellow-orange oil. Flash column chromatography (30 mL SiO₂, 95:5 → 9:1 hexane:EtOAc) afforded 24 mg (0.094 mmol, 49% yield) of 277 as a pale yellow oil along with 8 mg (0.03 mmol, 16% recovery) of 276 as a pale yellow oil.

**1H NMR** (600 MHz; CDCl₃) δ: 4.99 (t, \( J = 7.5 \) Hz, 1H), 4.15 (s, 3H), 3.02 (dd, \( J = 15.5, 7.5 \) Hz, 1H), 2.71 (dd, \( J = 15.5, 7.5 \) Hz, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.14 (s, 9H).

**13C NMR** (125 MHz; CDCl₃) δ: 183.2, 176.3, 137.1, 135.3, 117.4, 82.1, 59.2, 35.7, 31.3, 28.1, 26.0, 18.1.

**FTIR** (thin film) \( \nu _{\text{max}} \): 2967, 2870, 1769, 1624, 1480, 1459, 1356 cm⁻¹.

**HRMS–ESI** (m / z): [M+H]^+ calculated for C₁₄H₂₁ClO₂, 257.1303; found, 257.1302.

**TLC** \( R_f = 0.44 \) (9:1 hexane:EtOAc).
Chapter 3

Total Synthesis of Hyperforin
Synthesis Overview

Given the inability of prior strategies to construct model systems resembling the core of hyperforin, we pursued an alternative strategy that addressed previously experienced shortcomings. One particular difficulty we encountered was the cyclization to form the phloroglucinol-derived carbocycle component of the bicyclo[3.3.1]nonane core of hyperforin. As previously elaborated, these cyclization strategies often afforded heterocyclic rings, such as pyrones. Further, when such a carbocycle was constructed, a very favorable elimination of a tert-butyl group was observed, producing a very stable aromatic product. Given the difficulties with pursuing an intermediate such as alkyl halide 200, which involves strategic cleavage of the C5–C6 bond of hyperforin (1), we elected to pursue an alternative strategy involving cleavage of the extremely hindered C1–C8 bond (Scheme 3.1). At first glance, such an approach would not take advantage of latent symmetry elements that would potentially shorten the synthesis sequence, considering that the C5 position of 281 is stereogenic owing to differential substitution at C1 and at C3. In addition, a nucleophilic displacement strategy would not be feasible, considering the hindered nature of the C8 position.603

Scheme 3.1. Retrosynthetic disconnection of hyperforin at two key positions.

603 SN1-type cyclization to form the C1–C8 bond of PPAPs has been explored (see ref. 534). When the C8 position contains differential substitution, as in the case of hyperforin, this cyclization mode produced a 1:1 mixture of diastereomers at the C8 position.
To reconcile these challenges, we developed a new synthesis strategy for hyperforin (Scheme 3.2a). In order to engender prostereogenicity at the key C5 position during a key cyclization event, the C1 isopropyl ketone and the C3 prenyl group were removed to afford intermediate 282. These substituents may be installed late in the synthesis sequence via precedentened bridgehead acylation and metalation-prenylation protocols, respectively. In addition, the C7 prenyl group was replaced with an alcohol functionality. This functional group exchange in 282 facilitates a mechanistic development of a transform, whereby the C7 alcohol would form an epoxide with the C8 position. The formation of the C1–C8 bond would now be reduced to a 6-endo-tet epoxide-opening cyclization reaction of 283, a reaction that has been utilized previously to form carbon-carbon bonds at hindered positions.

604 For examples of PPAP total syntheses that employ these reactions at a late stage, see refs. 510 and 527.

Scheme 3.2. (a) Retrosynthesis of hyperforin involving C1–C8 bond cleavage and (b) transition-state analysis of the key cyclization reaction.

An analysis of this key cyclization event is depicted in Scheme 3.2b. Owing to a plane of symmetry in the cyclohexadienone ring, the C5 position of 283 is prostereogenic. During the key epoxide-opening cyclization involving this intermediate, two diastereotopic nucleophilic enol ethers, at C1 and at C3, may engage in bonding interaction with the epoxide when activated with a Lewis acid. Transition state 284 is favored to yield 282 over its diastereomeric transition state 285, which must adopt a boat-like conformation containing two severe eclipsing interactions in forming 286. Additionally, due to geometric constraints of orbital overlap, a 6-(enolendo)-tet cyclization should be favored over a 5-(enolendo)-tet cyclization. Ultimately, the combinations of these factors culminate in: (1) the construction of the bicyclo[3.3.1]nonane core of hyperforin; (2) the introduction of stereochemistry at the previously prostereogenic C5 position; (3) the creation of a stereogenic quaternary center at C8; and (4) the formation of a conformationally rigid tertiary stereogenic center at C1. Additionally, given our

interests in creating a library of hyperforin analogs, alcohol 282 is also an ideal intermediate for
diversification, in which a variety of groups may be appended at the C1, C3, and C7 positions.

**Dearomative Allylation Approach**

Given the difficulties we encountered while attempting to synthesize cyclohexadienones, we
chose a well-precedented approach to an intermediate very similar to key cyclization precursor 283. A
Sharpless epoxidation of geraniol607 (287) afforded (S,S)-2,3-epoxygeraniol (288) in 91% ee, which upon
mesylation and Finkelstein bromination gave epoxygeranyl bromide 289 (Scheme 3.3).608 Large
quantities of 289 (120-130 g per batch of material) were processed through this three-step protocol, which
involved only a single distillation and no silica gel chromatography. Regioselective lithiation of
phloroglucinol triether 146528 followed by coupling with 289 afforded alkylation product 290. After
desilylation to reveal phenol 291, a Pd- and Ti-catalyzed dearomative allylation reaction, using a protocol
developed for the total synthesis of (+)-garsubellin A by Danishefsky,527,529 produced cyclohexadienone
292. This allylation was highly regioselective, and only trace amounts of aromatic allylation products
were observed.

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We then screened a variety of acids to promote the conversion of 292 to the desired cyclization product 293 (Table 3.1). Unfortunately, both Lewis (entries 1-12) and Bronsted (entries 13-15) acids failed to produce even trace amounts of our desired product. In many instances (entries 1, 3, 5, 6, 12, and 14), we isolated ketone 294, the result of acid-mediated epoxide-ketone rearrangement (Figure 3.1). In other cases (entries 2, 10, and 13), acid activation of the epoxide promoted elimination to form allylic alcohols and allylic silyl ethers, such as 295, 296, 297, and 298. Byproducts 299 and 300 originated from exogenous nucleophilic opening of the epoxide (entries 5 and 15). The only cyclization product observed was cyclopentanol 301 (entry 7), the result of 5-exo-tet opening of the epoxide by the pendant homoprenyl sidechain in 292.

609 These byproducts were not rigorously characterized; we surmised the structure of these compounds via comparison to 292 as well as spectroscopic analysis of reaction mixtures.
Table 3.1. Attempted conversion of cyclohexadienone 292 to bicyclo[3.3.1]nonane 293.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf</td>
<td>CHCl₂, –78 to 0 °C, 5 h</td>
<td>294, decomposition</td>
</tr>
<tr>
<td>2</td>
<td>TMSOTf</td>
<td>DTBMP, CHCl₂, –78 to 0 °C, 1 d</td>
<td>295 and 296 are the only observed products</td>
</tr>
<tr>
<td>3</td>
<td>BF₃·Et₂O</td>
<td>CHCl₂, –78 °C to rt, 2 h</td>
<td>294 (43%)</td>
</tr>
<tr>
<td>4</td>
<td>Et₂AlCl</td>
<td>CHCl₂, –78 °C to rt, 3 d</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>AlCl₃</td>
<td>CHCl₂, –78 °C to rt, 3 d</td>
<td>294 is the only observed product</td>
</tr>
<tr>
<td>6</td>
<td>SnCl₄</td>
<td>CH₂Cl₂, –78 to 0 °C, 4 h</td>
<td>301 is the only observed product</td>
</tr>
<tr>
<td>7</td>
<td>MgBr₂·Et₂O</td>
<td>CH₂Cl₂, –78 °C to rt, 1 d</td>
<td>299 is the only observed product</td>
</tr>
<tr>
<td>8</td>
<td>TiCl₄</td>
<td>CH₂Cl₂, –78 °C, 75 min</td>
<td>294 is the only observed product</td>
</tr>
<tr>
<td>9</td>
<td>HCl (pH 2)</td>
<td>H₂O, 0 °C to rt, 1 d</td>
<td>300 is the only observed product</td>
</tr>
<tr>
<td>10</td>
<td>p-TsOH·H₂O</td>
<td>CH₂Cl₂, –78 °C to rt, 3 d</td>
<td>297 and 298 are the only observed products</td>
</tr>
<tr>
<td>11</td>
<td>CSA</td>
<td>CH₂Cl₂, –78 °C to rt, 1 d</td>
<td>297 is the only observed product</td>
</tr>
<tr>
<td>12</td>
<td>Zn(OTf)₂</td>
<td>CH₂Cl₂, –78 °C to rt, 3.5 h</td>
<td>&gt;99% conversion to 294</td>
</tr>
<tr>
<td>13</td>
<td>HCl (pH 2)</td>
<td>H₂O, 0 °C to rt, 1 d</td>
<td>294 and 298 are the only observed products</td>
</tr>
<tr>
<td>14</td>
<td>p-TsOH·H₂O</td>
<td>CH₂Cl₂, –78 °C to rt, 3.5 h</td>
<td>&gt;99% conversion to 294</td>
</tr>
</tbody>
</table>

Figure 3.1. Various byproducts formed during attempted conversion of 292 to 293.

From these studies, we concluded that the cyclohexadienone did not bear sufficient nucleophilic character to engage the activated epoxide. The byproducts obtained involved exogenous nucleophile delivery to the epoxide or even participation of the homoprenyl olefin in the formation of 301, whereas the cyclohexadienone portion of the molecule remained unchanged. In order to increase the nucleophilic character of the enol ether functionality present in 292, we attempted to excise the carbonyl group. While several attempts to form a hydrazone failed, hydride reduction of 292 afforded cyclohexadiene 302.
Gratifyingly, exposure of this compound to TMSOTf in the presence of DTBMP afforded cyclization product 303 as a single diastereomer in 85% yield.  

Scheme 3.4. Cascade cyclization of 302 to form 303.\textsuperscript{a}

\textsuperscript{a} Conditions: (a) LAH, CH\textsubscript{2}Cl\textsubscript{2}, Et\textsubscript{2}O, 0 °C, 44%; (b) TMSOTf, DTBMP, CH\textsubscript{2}Cl\textsubscript{2}, –78 °C, 85%; (c) Pearlman’s catalyst, TBHP, Cs\textsubscript{2}CO\textsubscript{3}, O\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, 0 to 4 °C, 17%; (e) TMSOTf, CH\textsubscript{2}Cl\textsubscript{2}, –78 °C, 52%.

In this reaction, the stereochemistry of two key quaternary centers of hyperforin were established: at the previously prostereogenic C5 carbon, and at the C8 position. In addition to the construction of the bicyclo[3.3.1]nonane framework, the formation of a cyclic methyl ketal bridging the C7 and C9 carbons was an unexpected outcome to this reaction, formed from the intramolecular interception of the C9 oxocarbenium ion by the C7 oxygen atom in intermediate 304 (Scheme 3.4). Nevertheless, the establishment of this cyclic ketal was fortuitous, safeguarding the C7 carbinol from oxidation during subsequent allylic oxidation to reestablish carbonyl functionality at the C2 position. This allylic oxidation of 303 was accomplished using Pearlman’s catalyst and TBHP\textsuperscript{610} to furnish β-methoxyenone 305. We also briefly screened several other Lewis acids for the conversion of 302 to 303; however, lower yields of 303 were observed with BF\textsubscript{3}·Et\textsubscript{2}O and SnCl\textsubscript{4}. Omission of DTBMP afforded ketone 306 as the only reaction product.

**Double Alkylation Approach**

Even though this route allowed us to access β-methoxyenone 305, we resolved to develop a more straightforward means of accessing advanced intermediates. Over the three-step sequence beginning with cyclohexadienone 292 and ending with 305, a carbonyl was reduced and subsequently reintroduced. Our solution involved direct, sequential coupling of a prenyl halide (307) and epoxygeranyl bromide (289) with 1,5-dimethoxy-1,4-cyclohexadiene (308)\(^{611}\) to form cyclization precursor 309 (Scheme 3.5). Cyclohexadiene 308 may be synthesized from the Birch reduction of 1,3-dimethoxybenzene,\(^{612}\) and numerous examples of regioselective alkylations at the methylene proximal to the methoxy groups in 308 have been reported.\(^{613}\)

![Scheme 3.5. Retrosynthesis of cyclization precursor 309.](image)

For the synthesis of 309, we investigated both sequences of additions: (1) coupling of 308 with 289 followed by alkylation with 307 and (2) coupling of 307 with 289 followed by alkylation with 289. Deprotonation of 308 was accomplished using t-BuLi, and subsequent trapping with bromide 289.

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\(^{611}\) We also briefly explored a route involving the Birch reduction of 1,3-dimethoxy-2-prenylbenzene; however, the conditions necessary for this reduction (i.e., Na, NH\(_3\), reflux, 12-18 h) also resulted in reduction of the prenyl olefin.


afforded 310 as a single regioisomer (Scheme 3.6). Unfortunately but not unexpectedly, deprotonation of this intermediate afforded bicyclo[5.1.0]octadiene 311, the product of internal trapping with concomitant opening of the epoxide functionality.

Scheme 3.6. Deprotonation of 310 led to isolation of 311.

Scheme 3.6. Deprotonation of 310 led to isolation of 311.

\(^a\) Conditions: (a) t-BuLi, THF, –78 °C; 289, –78 °C to rt, 45%; (b) t-BuLi, THF, –78 to –30 °C; prenyl bromide, –78 °C to rt, 27% (29% recovered 310).

Prenylation of cyclohexadiene 308 was surprisingly problematic. Initially, alkylation of metalated 308 with prenyl bromide was rather unselective, providing both the desired coupling product 312 as well as its regioisomer 313 in equal amounts (Scheme 3.7). These regioisomers were separated by treatment with SiO\(_2\); exposure of unprocessed reaction mixtures facilitated the selective conversion of 313 to the more-polar \(\beta\)-methoxyenones 314 and 315, while 312 remained unchanged.

Scheme 3.7. Nonselective prenylation of cyclohexadiene 308.

\(^a\) Conditions: (a) t-BuLi, THF, –78 °C; HMPA, –78 °C; prenyl–Br; MeO\_2; MeO\_2; H

Even though from a practical standpoint, large quantities of 312 were readily available through this selective hydrolysis protocol, we resolved to improve the overall selectivity of this reaction (Table 3.2). In the absence of HMPA, selectivity improved marginally (entry 2). While the addition of MgBr\(_2\)
reversed selectivity, the addition of BaI\textsubscript{2} improved selectivity for the formation of 313 (entries 4-5). Substituting \textit{t}-BuLi for \textit{s}-BuLi in the deprotonation step had no effect on regioselectivity (entry 5). When prenyl chloride was used instead of prenyl bromide in otherwise identical conditions to entry 1, regioselectivity improved to 2:1 in favor of the desired regioisomer (entry 6). Several additives were studied in the coupling 308 with prenyl chloride (entries 7-9): ZnCl\textsubscript{2} afforded significant amounts of 3-methoxycyclohex-2-enone, and while both CeCl\textsubscript{3} and BaI\textsubscript{2} \textsuperscript{614} further improved regioselectivity, the former additive caused a decrease in conversion. The method of preparing anhydrous BaI\textsubscript{2} also had a significant effect on this alkylation. Anhydrous BaI\textsubscript{2} made from drying commercially available BaI\textsubscript{2}\cdot2H\textsubscript{2}O under vacuum\textsuperscript{615} afforded a 3:1 ratio of 312:313 with a 61\% yield of 313 (entry 9). Preparing BaI\textsubscript{2} \textit{in situ} from the reaction of barium metal with I\textsubscript{2} \textsuperscript{616} provided complete regiocontrol for the synthesis of 312, which was isolated in 91\% yield (entry 10).


Table 3.2. Prenylation of cyclohexadiene 308.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metalation conditions</th>
<th>Alkylation conditions</th>
<th>312:313 ratio</th>
<th>312 yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuLi, THF, –78 ºC; HMPA</td>
<td>prenyl–Br, –78 ºC to rt</td>
<td>1:1</td>
<td>44%</td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi, THF, –78 ºC</td>
<td>prenyl–Br, –78 ºC to rt</td>
<td>1.3:1</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>t-BuLi, THF, –78 ºC; MgBr₂</td>
<td>prenyl–Br, –78 ºC to rt</td>
<td>1:2.2</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>t-BuLi, THF, –78 ºC; BaI₂</td>
<td>prenyl–Br, –78 ºC to rt</td>
<td>2:1</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>t-BuLi, THF, –78 ºC; TMEDA</td>
<td>prenyl–Br, –78 ºC to rt</td>
<td>1:1</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>t-BuLi, THF, –78 ºC; HMPA</td>
<td>prenyl–Cl, –78 ºC to rt</td>
<td>2:1</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>t-BuLi, THF, –78 ºC; CeCl₃</td>
<td>prenyl–Cl, –78 ºC to rt</td>
<td>2.5:1</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>t-BuLi, THF, –78 ºC; BaI₂</td>
<td>prenyl–Cl, –78 ºC to rt</td>
<td>3:1</td>
<td>61%</td>
</tr>
<tr>
<td>9</td>
<td>t-BuLi, THF, –78 ºC; BaI₂</td>
<td>prenyl–Cl, –78 ºC to –30 ºC</td>
<td>&gt;20:1</td>
<td>91%</td>
</tr>
</tbody>
</table>

a The conditions presented in entry 1 are depicted in Scheme 3.7.
b Afforded a 2:1 ratio of 312 to 3-methoxycyclohex-2-enone.
c Low amount of conversion observed.
d Anhydrous BaI₂ prepared from drying BaI₂·2H₂O at 150 ºC at 6 mmHg pressure for 15 h.
e Anhydrous BaI₂ prepared from the reaction of Ba with I₂. See experimental section for details.

We then explored the alkylation of 312 with epoxygenyl bromide 289 to form cyclization precursor 309. Deuterium quench studies revealed that exposure to tert-butyllithium at –78 ºC did not lead to deprotonation of 312. We therefore surveyed the use of several bases across a range of temperatures. In general, a major byproduct during this coupling reaction was 1,3-dimethoxy-2-prenylbenzene (316), an oxidation product of 312. Low levels of deprotonation were observed with t-BuLi at –45 ºC and –30 ºC, and increasing the stoichiometry of t-BuLi generally favored conversion to 316. Several additives, including HMPA, TMEDA, MgBr₂, and BaI₂ did not facilitate conversion to 309. The use of the lithium amide bases LDA and LiTMP did not lead to appreciable deprotonation, even when a solution of LDA and 312 was warmed to rt. Similar results were observed with BuLi when warmed to –30 ºC. Eventually, we discovered that optimal yields of 309 could be achieved through deprotonation of 312 with s-BuLi at –30 ºC followed by addition of 289 (Scheme 3.8). If a solution of 312 and s-BuLi was warmed above –30 ºC, significant amounts of 316 were produced.
The subsequent cyclization of 309 afforded cyclic ketal 317 using conditions identical to the conversion of 302 to 303 (Scheme 3.9). From a practical material throughput standpoint, we chose to replace DTBMP with 2,6-lutidine; no appreciable decline in yield was observed using the latter base, and it was a much easier reagent to obtain, implement, and separate from product with larger scale reactions. Using this new double alkylation strategy, we were able to access large quantities of 317 from 1,3-dimethoxybenzene in 4 steps, a significant improvement from the prior approach involving dearomative allylation of 291.

The next step in our synthesis sequence involved the allylic oxidation\(^{617}\) of 317 to \(\beta\)-methoxyenone 318 (Table 3.3). This was an exceptionally challenging transformation given the seven allylic sites present in 303 and the steric environment surrounding the desired oxidation site at the C2 position. Numerous allylic oxidation conditions were screened and can be classified into three distinct categories: (1) the combination of a high-valent metal species and TBHP (entries 1-22); (2) stoichiometric

\(^{617}\) For a recent review of allylic oxidations in total synthesis, see: Nakamura, A.; Nakada, M. *Synthesis* 2013, 45, 1421-1451.
metal oxidants (entries 23-32); and (3) the combination of hypervalent iodide species and TBHP (entries 33-65). In many cases, we observed several byproducts, including transposed *tert*-butyl peroxide 319, enone 320, and ketone 321 (Figure 3.2).

### Table 3.3. Allylic oxidation of enol ether 317.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidants (equiv)</th>
<th>Additives (equiv)</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OH)2 (0.1), TBHP (5)</td>
<td>K2CO3 (5)</td>
<td>CH2Cl2, 4 ºC, 12 h</td>
<td>318 (15%)</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OH)2 (0.1), TBHP (5)</td>
<td>K2CO3 (5)</td>
<td>CH2Cl2, 4 ºC, 4 h</td>
<td>318 (16%), 319 (1%)</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OH)2 (0.1), TBHP (5)</td>
<td>KOH (1.2)</td>
<td>CH2Cl2, 4 ºC, 7 h</td>
<td>318 (24%), 319 (1%)</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OH)2 (0.2), TBHP (5)</td>
<td>K2PO4 (1.2)</td>
<td>CH2Cl2, 4 ºC, 7 h</td>
<td>318 (26%)</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OH)2 (0.2), TBHP (5)</td>
<td>K2CO3 (5)</td>
<td>CH2Cl2, 4 ºC, 20 h</td>
<td>low conversion to 319</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OH)2 (0.2), TBHP (5)</td>
<td>Cs2CO3 (5)</td>
<td>CH2Cl2/DMF, 4 ºC, 20 h</td>
<td>low conversion to 319</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OH)2 (0.1), TBHP (5)</td>
<td>none</td>
<td>CH2Cl2, 4 ºC, 3 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OH)2 (0.1), TBHP (5)</td>
<td>none</td>
<td>CH2Cl2, 4 ºC, 3 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)2 (0.25), TBHP (5)</td>
<td>Cs2CO3 (5)</td>
<td>CH2Cl2, 4 ºC, 3 h</td>
<td>318 (5%)</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)2 (1), TBHP (5)</td>
<td>Cs2CO3 (5)</td>
<td>CH2Cl2, 4 ºC, 3 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>11</td>
<td>Pd/C (0.2), TBHP (5)</td>
<td>none</td>
<td>CH2Cl2, 4 ºC, 17 h</td>
<td>318 (6%)</td>
</tr>
<tr>
<td>12</td>
<td>NaOAc (excess), TBHP (5)</td>
<td>none</td>
<td>EtOAc, rt, 3 h</td>
<td>selectively afforded 319</td>
</tr>
<tr>
<td>13</td>
<td>Cr(O2)(0.05), TBHP (5)</td>
<td>none</td>
<td>PhH, 75 ºC, 17 h</td>
<td>selectively afforded 319</td>
</tr>
<tr>
<td>14</td>
<td>PDC (2), TBHP (2)</td>
<td>none</td>
<td>PhH, 0 ºC to rt, 5 h</td>
<td>318 (14%), 320 (37%)</td>
</tr>
<tr>
<td>15</td>
<td>MnOAc (0.1), TBHP (4)</td>
<td>K2CO3 (0.5)</td>
<td>EtOAc, rt, 3.5 h</td>
<td>318 (11%)</td>
</tr>
<tr>
<td>16</td>
<td>Fe3+ - H2O (0.5), TBHP (5)</td>
<td>Cs2CO3 (5)</td>
<td>CH2Cl2, 4 ºC, 17 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>17</td>
<td>CuI (0.1), TBHP (10)</td>
<td>none</td>
<td>MeCN, 55 ºC, 16 h</td>
<td>319</td>
</tr>
<tr>
<td>18</td>
<td>CuI (0.1), TBHP (4)</td>
<td>none</td>
<td>MeCN, rt, 14 h</td>
<td>selectively afforded 319</td>
</tr>
<tr>
<td>19</td>
<td>SeI (0.1), TBHP (4)</td>
<td>none</td>
<td>MeCN, rt, 14 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>20</td>
<td>SeI (0.1), TBHP (4)</td>
<td>none</td>
<td>MeCN, rt, 1.5 h</td>
<td>selectively afforded 319 and 320</td>
</tr>
<tr>
<td>21</td>
<td>PhSeO (0.1), TBHP (6)</td>
<td>none</td>
<td>MeCN, rt, 12 h</td>
<td>low conversion to 319</td>
</tr>
<tr>
<td>22</td>
<td>CAN (0.1), TBHP (5)</td>
<td>none</td>
<td>MeCN, rt, 10 min</td>
<td>321 (20%)</td>
</tr>
<tr>
<td>23</td>
<td>CAN (0.1), TBHP (5)</td>
<td>none</td>
<td>CH2Cl2, rt, 10 min</td>
<td>321 (20%)</td>
</tr>
<tr>
<td>24</td>
<td>TEMPO (2.2), i-But (1.1)</td>
<td>none</td>
<td>THF, 78 ºC to rt, 12 h</td>
<td>320 (5%)</td>
</tr>
<tr>
<td>25</td>
<td>PDC (0.1)</td>
<td>none</td>
<td>PhH, rt, 30 h</td>
<td>very low conversion to 320</td>
</tr>
<tr>
<td>26</td>
<td>CrO2-DMP (20)</td>
<td>none</td>
<td>CH2Cl2, 0 ºC, 5 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>27</td>
<td>PhSeAc (2), PhH (10)</td>
<td>K2CO3 (0.5)</td>
<td>EtOAc, rt, 3.5 h</td>
<td>318 (27%), 319 (2%), 320 (26%)</td>
</tr>
<tr>
<td>28</td>
<td>Pd(OAc)2 (0.1), TBHP (5)</td>
<td>K2CO3 (0.5)</td>
<td>EtOAc, 4 ºC, 5 h</td>
<td>318 (27%), 319 (2%), 320 (26%)</td>
</tr>
<tr>
<td>29</td>
<td>Pd(OAc)2 (0.1), TBHP (5)</td>
<td>K2CO3 (0.5)</td>
<td>EtOAc, 4 ºC, 5 h</td>
<td>318 (27%), 319 (2%), 320 (26%)</td>
</tr>
<tr>
<td>30</td>
<td>Pd(OAc)2 (0.1), TBHP (5)</td>
<td>K2CO3 (0.5)</td>
<td>EtOAc, 4 ºC, 5 h</td>
<td>318 (27%), 319 (2%), 320 (26%)</td>
</tr>
</tbody>
</table>
Table 3.3 (continued). Allylic oxidation of enol ether 317.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidants (equiv)</th>
<th>Additives (equiv)</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC, 4 h</td>
<td>mixture of 318, 319, and 321</td>
</tr>
<tr>
<td>41</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>none</td>
<td>pentOAc, 4 ºC, 12 h</td>
<td>mixture of 318 and 321</td>
</tr>
<tr>
<td>42</td>
<td>PhIOAc, (2), TBHP (1.5)</td>
<td>CsCO3 (2)</td>
<td>EtOAc, 4 ºC, 75 min</td>
<td>318 (10%), 319 (24%), 320 (28%)</td>
</tr>
<tr>
<td>43</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>K2CO3 (0.5)</td>
<td>pentOAc, 4 ºC, 75 min</td>
<td>318 (23%), 320 (37%)</td>
</tr>
<tr>
<td>44</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>K2CO3 (0.5), 3Å MS</td>
<td>pentOAc, 4 ºC, 2 d</td>
<td>mixture of 318 and 320</td>
</tr>
<tr>
<td>45</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>KPO4 (4)</td>
<td>EtOAc, 4 ºC, 45 min</td>
<td>mixture of 318, 320, and 321</td>
</tr>
<tr>
<td>46</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, 4 ºC, 13 h</td>
<td>318 (21%), 320 (12%)</td>
</tr>
<tr>
<td>47</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –30 ºC, 90 min</td>
<td>318 (19%), 320 (28%)</td>
</tr>
<tr>
<td>48</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC, 1 h</td>
<td>318 (17%), 319 (4%)</td>
</tr>
<tr>
<td>49</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>CH2Cl2, –78 ºC, 1 h</td>
<td>318 (16%)</td>
</tr>
<tr>
<td>50</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>MeCN, –40 ºC, 2 h</td>
<td>mixture of 318, 319, 320, and 321</td>
</tr>
<tr>
<td>51</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, rt, 3 d</td>
<td>318 (17%)</td>
</tr>
<tr>
<td>52</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>K2CO3 (4)</td>
<td>EtOAc, –78 ºC, 1 h</td>
<td>318 (30%)</td>
</tr>
<tr>
<td>53</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC, 1 h</td>
<td>318 (16%)</td>
</tr>
<tr>
<td>54</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC, 2 h</td>
<td>318 (17%)</td>
</tr>
<tr>
<td>55</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC, 1 h</td>
<td>318 (14%), 319 (5%), 320 (15%)</td>
</tr>
<tr>
<td>56</td>
<td>PhIOAc, (3), BzOAc-Bu (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC to rt, 1 d</td>
<td>no reaction</td>
</tr>
<tr>
<td>57</td>
<td>PhIOAc, (3), BPX (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC, 90 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>58</td>
<td>PhIOAc, (5), TBHP (excess)</td>
<td>CsCO3 (10)</td>
<td>EtOAc, –78 ºC, 30 min</td>
<td>318 (17%), 320 (11%)</td>
</tr>
<tr>
<td>59</td>
<td>322 (2)</td>
<td>K2CO3 (4)</td>
<td>PhH, rt, 3 d</td>
<td>319 (26%), 320 (5%)</td>
</tr>
<tr>
<td>60</td>
<td>322 (2)</td>
<td>CsCO3 (4)</td>
<td>PhH, rt, 12 h</td>
<td>mixture of 318 and 319</td>
</tr>
<tr>
<td>61</td>
<td>322 (3), TBHP (4)</td>
<td>CsCO3 (4)</td>
<td>EtOAc, –78 ºC to rt, 1 d</td>
<td>mixture of 318, 320, and 321</td>
</tr>
<tr>
<td>62</td>
<td>322 (2), O2</td>
<td>K2CO3 (4)</td>
<td>PhH, rt, 1 d</td>
<td>318 (9%)</td>
</tr>
<tr>
<td>63</td>
<td>PhIOAc, (3), TBHP (4)</td>
<td>K2CO3 (4)</td>
<td>EtOAc, 4 ºC, 12 h</td>
<td>selectively afforded 319</td>
</tr>
<tr>
<td>64</td>
<td>IBX (3)</td>
<td>none</td>
<td>DMSO, 110 ºC, 14 h</td>
<td>mixture of 318, 320, and 321</td>
</tr>
<tr>
<td>65</td>
<td>DMP (3)</td>
<td>CsCO3 (4)</td>
<td>CH2Cl2, rt, 2 d</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Figure 3.2. Byproducts from the allylic oxidation of 317 and the structure of peroxyiodoxolone 322.

Given the early success with the allylic oxidation of 303 to afford 306, we first focused on the Pearlman’s catalyst-TBHP allylic oxidation system (Table 3.3, entries 1-8). Despite increases in catalyst stoichiometry, we typically observed a considerable conversion to enone 320 and variable conversion to peroxide 319. Additionally, while changing the identity of the base mitigated has enone formation in similar systems, we did not observe significant changes in product distribution through the

use of K₂CO₃, KOH, K₃PO₄, or Cs₂CO₃. Using different Pd catalysts had no positive effect on desired yield (entries 9-11). A variety of other known allylic oxidation systems, involving the combination of TBHP and: NaOCl, Cr(CO)₆, PDC, Mn(OAc)₃, FeCl₂·4H₂O, NiCl₂·6H₂O, CuI, SeO₂, RuCl₃, Rh₂(cap)₄, and CAN, also did not afford large proportions of 318 selectively (entries 12-22). When stoichiometric metal oxidants were used (entries 23-32), we did not observe any but rather enone 320 and ketone 321 in cases where significant decomposition was not observed.

In addition to the use of metal-based oxidants, we also investigated the use of hypervalent iodine reagents, both in the presence and in the absence of TBHP (Table 3.3, entries 33-65). Prior studies by the Yeung group illustrated the effectiveness of PhI(OAc)₂-TBHP for the allylic oxidation of a wide range of substrates. It is believed that exposure of iodosobenzene species 323 to TBHP generates [bis(tert-butylperoxy)iodo]benzene (324, Scheme 3.10). This is predicted to be a particularly unstable

intermediate, which undergoes reductive elimination to afford PhI and di-tert-butyl tetroxide (325), which decomposes into a variety of tert-butyl polyoxide radicals (326), eventually leading to oxygen evolution, and to formation of t-BuOH and t-BuOOt-Bu. These processes appear to be solvent dependent.

The rate at which 324 forms and decomposes to PhI and 325 is affected by several factors, including solvent and temperature. Exposure of PhI(TFA)₂ to TBHP forms 324 at temperatures as low as −30 ºC using CH₂Cl₂; the use of more Lewis basic solvents EtOAc, acetone, THF, and MeCN led to lower conversion rates in subsequent allylic oxidations at that temperature.⁶³¹ Solvent effects were also observed in the PhI(OAc)₂-TBHP allylic oxidation system.⁶²⁹a Use of ester solvents containing large alkyl substituents led to higher yields. This may be due to the solvent effects on the conversion of 323 to 324, with more sterically demanding Lewis basic solvents decreasing the rate of this reaction.

Several mechanisms may be proposed for the allylic oxidation of 317. One plausible mechanism involves three distinct stages: a radical abstraction; radical combination; and base-promoted elimination (Scheme 3.11). First, the radical abstraction of a hydrogen atom at the C2 position forms allylic radical 327. This radical may be intercepted to form peroxide 328, which then may eliminate alkoxide anion via methine deprotonation⁶³² at C2 to afford 318. This mechanistic proposal may also explain the formation of several byproducts. Interception of allylic radical 327 with a tert-buty peroxy radical may form 319.

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⁶³² For an early example of base-mediated cleavage of a dialkyl peroxide, see: Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, 73, 880-881.
In addition, E1cB-type expulsion of a peroxo anion from 328 may afford enoxonium 329, which upon demethylation would afford enone 320.

Scheme 3.11. A plausible radical-based mechanism for the formation of 318 and other oxidation products from 317.

In many allylic oxidation experiments, we isolated a significant amount of 319, and we investigated the possible conversion of this peroxide to the desired β-methoxyenone 318. Exposure of peroxide 319 to a variety of basic, acidic, and reducing conditions did not afford more than trace amounts of 318. Only upon exposure of 319 to FeCl2·4H2O633 in a Fenton-type reaction,634 appreciable (5-10% yield) amounts of β-methoxyenone 318 were produced. The inability to convert 319 to 318 meant that this peroxide was a detrimental byproduct in this reaction process, and we sought to mitigate its formation to improve the yield of 318. Since a peroxide would approach from outside the concavity of the bicyclic core of 327 to form the epimer shown in 328, subsequent C2 deprotonation would be exceedingly


difficult given the steric environment around this position.\textsuperscript{635} We hypothesized that if oxygen was present, it may intercept \textsuperscript{327} and subsequently form a hydroperoxide (\textsuperscript{328}, \( R = \text{H} \)), and this species may undergo more facile C2 deprotonation to form the desired \( \beta \)-methoxyenone \textsuperscript{318}.

Taking all these factors into consideration and screening a variety of conditions involving iodine(III) reagents (Table 3.3, entries 33-58), we were obtained \textsuperscript{318} in 30\% yield (entry 52). While the use of large ester solvents (i.e., amyl acetate and butyl butyrate) decreased the rate at which radical tert-butyl polyoxides formed, their relatively high melting points prevented the cooling of the reaction mixtures to further decrease the rate of radical formation. EtOAc was the solvent of choice, allowing reaction mixtures to be cooled to \(-78 \, ^\circ\text{C}\) while preventing fast decomposition of TBHP and the hypervalent iodine reagent. In addition, we found that PhI(TFA)\textsubscript{2} was optimal relative to PhI(OAc)\textsubscript{2} and PhIO, and the addition of a vigorous stream of oxygen into the reaction mixture caused a significant increase in product yield. We also assessed the use of several iodine(V) reagents, such as peroxiodoxolone \textsuperscript{322},\textsuperscript{636} PhIO\textsubscript{2}, IBX, and DMP (entries 59-65); however, the use of these reagents did not afford the desired allylic oxidation product selectively. Even though yields of the desired \( \beta \)-methoxyenone \textsuperscript{318} were not dramatically improved using the optimized PhI(TFA)\textsubscript{2}-TBHP-O\textsubscript{2} system, the use of hypervalent iodine reagents were more conducive for large scale allylic oxidations of \textsuperscript{317}, necessary for processing large quantities of material for the total synthesis endeavor.

With access to large amounts of \( \beta \)-methoxyenone \textsuperscript{318}, we developed a synthesis strategy that would allow us to quickly access hyperforin. We hypothesized that hyperforin (\textsuperscript{1}) may be accessed from cyclopropane \textsuperscript{330} (Scheme 3.12a). The cyclopropane present in \textsuperscript{330} is activated by both the C1 and C9 carbonyl groups,\textsuperscript{637} and nucleophilic addition of a prenylmetal species may occur selectively at the C7

\textsuperscript{635} The difficulty with C2 deprotonation of \textsuperscript{328} may favor enone \textsuperscript{320} formation via enoxonium \textsuperscript{329}.


\textsuperscript{637} It should be noted that there is very little orbital overlap between the C9–O \( \pi^* \) orbital and the C7–C9 \( \sigma \) orbital.
position and not at the C8 quaternary center. This addition would result in an intermediate C1 bridgehead organometallic 331, which upon exposure to isobutryl chloride may directly provide the methyl ether of hyperforin (60, Scheme 3.12b). In one single operation, two of the three key remaining C–C bonds of hyperforin would be established: prenylation at the C7 position and acylation at the C1 position (highlighted in Scheme 3.12b). The remaining C3 prenyl group would be installed via a preceded tandem deprotonation-transmetalation-alkylation protocol of 318 to afford 332, the precursor to 330 via sequential bridgehead lithiation and intramolecular cyclization.

Scheme 3.12. (a) Retrosynthesis of hyperforin (1) from β-methoxyenone 318 via cyclopropane 330, and (b) a proposed tandem 1,5-addition-bridgehead acylation of 330 to form O-methyl hyperforin (60).

Prenylation at the C3 position of 318 was accomplished through the previously mentioned sequential LiTMP-mediated deprotonation, transmetalation with Li(2-Th)CuCN, and trapping with prenyl bromide to afford 333 (Scheme 3.13a). A variety of Lewis and Brønsted acidic conditions were then screened for the hydrolysis of the cyclic ketal present in 333. No reactivity was observed using

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aqueous HOAc, LiBF₄, Sc(OTf)₃, CuCl₂·2H₂O, or InCl₃, or anhydrous conditions involving Ti(O-i-Pr)₄/MeOH or SmCl₃/TMSCl. Loss of the C3, C5, and C8 olefin functionality was observed when p-TsOH·H₂O, TFA, Amberlyst-15 acidic resin, or CAN was employed. While no reactivity was observed with aqueous HCl, PPTS, or BF₃·Et₂O/TBAI at rt, decomposition was observed upon heating. Several reagents led to selective cleavage of the C4 O-methyl ether, including HBr, BBr₃, TMSI, and FeCl₃·6H₂O. Selective cyclic ketal hydrolysis was ultimately accomplished using BrBMe₂.⁶³⁹ exposure of 333 to this reagent at –78 ºC led to hemiketal 334. The conversion of 333 to 334 may proceed via coordination of the Lewis acidic reagent to the Lewis basic cyclic ketal oxygen to give intermediate 335, which may undergo ketal cleavage to form oxocarbenium ion 336 (Scheme 3.13b). The displaced bromide anion may then intercept the oxocarbenium ion to form the unstable geminal bromoether 337, a species we observed spectroscopically but did not isolate. Upon exposure of 337 to H₂O upon reaction quench, the product hemiketal 334 is formed. The reaction was chemoselective for cyclic ketal cleavage at –78 ºC; at higher temperatures, C4 O-methyl ether cleavage was also observed. Hydrolysis of 334 was accomplished by refluxing in wet acetone with PPTS to afford 332.

Scheme 3.13. (a) Prenylation and cyclic ketal hydrolysis of 318, and (b) a possible mechanism for the conversion of 333 to 334.\(^a\)

\(^a\) Conditions: (a) LiTMP, THF, –78 °C; Li(2-Th)CuCN, THF, –78 to –40 °C; prenyl–Br, –78 to –40 °C, 71%; (b) BrBMe₂, CH₂Cl₂, –78 °C; NEt₃; NaHCO₃, H₂O, 89%; (c) PPTS, acetone/H₂O, reflux, 92%.

We then attempted to synthesize cyclopropane 330 from alcohol 332; however, we did not obtain this desired product (Scheme 3.14). After conversion to triflate 338, exposure to LDA led to decomposition, including LDA-mediated hydride transfer to the C9 ketone.\(^640\) Treatment with NaOMe in MeOH, conditions known to promote bridgehead functionalization,\(^641\) led to quantitative conversion to methanopentalene 339, the product of methoxide addition to the C4 position followed by cyclization of the resulting C3 enolate to the C7 position. Studies with mesylate 340 were also unsuccessful. While


\(^{641}\) Nickon, A.; Covey, D. F.; Huang, F.-C.; Kuo, Y.-N. J. Am. Chem. Soc. 1975, 97, 904-905.
treatment with LDA also resulted in decomposition, exposure to NaOMe/MeOH afforded rearranged cyclopropane 341. This product may have formed via initial cleavage of the C1–C2 bond with concomitant C1–C7 bond formation from C2 hemiketal anion 342, followed by lactone formation upon aqueous workup.

Scheme 3.14. Byproducts isolated from attempted bridgehead lithiations of 338 and 340.¹

¹ Conditions: (a) Tf₂O, pyr, CH₂Cl₂, −43 to 0 ºC, 84%; (b) NaOMe, MeOH, 0 ºC to rt, >99%; (c) MsCl, NEt₃, CH₂Cl₂, 0 ºC, 82%; (d) NaOMe, MeOH, 0 to 70 ºC, 15%.

Since there is very poor overlap of the C9 ketone π orbital with the C1–H methine σ* orbital and that a major source of byproducts was hydride addition to the C9 ketone, we also explored the bridgehead lithiation chemistry of a series of intermediates bearing a C9 dimethyl ketal (Scheme 3.15). By quenching the BrBMe₂-mediated reaction of 333 with MeOH before introduction of H₂O, dimethyl ketal 343 was isolated instead of hemiketal 334. Reactions of the triflate 344 derived from this intermediate were investigated; however, we did not observe desired cyclopropane formation. Exposure of 344 to LDA afforded tricyclononane 345, which may have formed via deprotonation of the C3 prenyl methylene with subsequent C4–C7 bond formation, yielding intermediate 346. After formation of extended enolate
Treatment of 344 with s-BuLi led to 348, the result of 1,2-addition of s-Bu anion to the C2 ketone followed by displacement of the C7 triflate with the resulting alkoxide. Reactions of mesylate 349 and pivalate 350 were also fruitless; when reactivity was observed, it was typically due to C3 prenyl methylene deprotonation.

Scheme 3.15. Synthesis and reactivity of 343 derivatives.

Given the enhanced acidity of the bisallylic methylene attached to C3, we elected to pursue a synthesis strategy in which cyclopropation to form the C1–C7 bond would precede C3 prenylation. BrBMe₂-mediated cyclic ketal hydrolysis of 318 afforded hemiketal 351, and subsequent hydrolysis afforded alcohol 282 (Scheme 3.16). Triflation of 282 yielded 352. Gratifyingly, exposure of this triflate
to LDA in the presence of TMSCl produced cyclopropane 353. In this reaction, silylation of the C3 position accompanied C1 bridgehead lithiation with subsequent C1–C7 bond formation, providing 353. An observed, unstable byproduct in this reaction was the result of LDA-mediated C9 ketone reduction, which was isolated in variable amounts.

Scheme 3.16. Synthesis of cyclopropane 353.\textsuperscript{a}

\textsuperscript{a} Conditions: (a) BrBMe\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, –78 °C; NEt\textsubscript{3}, –78 °C; NaHCO\textsubscript{3}, H\textsubscript{2}O, –78 °C to rt, 79%; (b) PPTS, H\textsubscript{2}O/acetone, reflux, 90%; (c) Tf\textsubscript{2}O, pyr, CH\textsubscript{2}Cl\textsubscript{2}, –43 to 5 °C, 80%; (d) LDA, TMSCl, THF, –78 °C, 49%.

We then attempted 1,5-addition of a variety of nucleophiles to the activated cyclopropane present in 353; however, under all conditions screened, we did not isolate any desired products (354, Table 3.4). In general, we explored the use of organocuprates\textsuperscript{642} as nucleophiles, given past precedent of the use of these reagents for cyclopropane opening.\textsuperscript{643} We utilized the Lewis acids TMSCl and BF\textsubscript{3}·Et\textsubscript{2}O in an attempt to further activate the cyclopropane for nucleophilic attack.\textsuperscript{644,645} The 1,5-addition of

\textsuperscript{642} For reviews of organocuprate chemistry, see: (a) Posner, G. H. Org. React. 1975, 22, 253-400. (b) Lipshutz, B. H. Synlett 1990, 119-128.


alkylcuprates to activated cyclopropanes may also be catalyzed by PbU3. Due to the inability of accessing prenyllithium from lithium insertion into a prenyl halide, several modes of prenyl cuprate formation were explored. In entry 1, Rieke copper(0) was generated, but the reagent derived from Cu* and prenyl chloride did not react with the substrate. The only product we observed in this reaction was (Figure 3.3), the result of nucleophilic opening of THF solvent. No reactivity was observed with prenylcuprates derived from: (a) prenyl–MgBr and CuI (entries 2-3) and (b) prenyl–Li and CuI (entries 4-5). The generation of prenylcuprate from prenyl–SnBu3, BuLi, and CuI afforded iodide and proteodesilylation product. Iodide was the only product obtained in these

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651 Prenyllithium was generated from the reaction of phenyl prenyl ether with Li. For more information, see: Eisch, J. J.; Jacobs, A. M. J. Org. Chem. 1963, 28, 2145-2146.


654 For the generation of allyllithium reagents from the reaction of allyltributylstannanes and BuLi, see: Desponds, O.; Schlosser, M. J. Organomet. Chem. 1991, 409, 93-101.

655 357 and 358 were not rigorously characterized; we surmised the structure of these compounds via comparison to 353 as well as spectroscopic analysis of reaction mixtures.
studies in which the cyclopropane ring of 353 was opened. We also briefly explored the TMSOTf-mediated addition of allyltrimethylsilane (entry 14), but the only product observed was 357.

Table 3.4. Attempted formation of 354 from nucleophilic 1,5-additions to 353.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Reagent formation</th>
<th>Additives</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>prenyl-Cu* (10)</td>
<td>LiNap; CuCN, LiBr; prenyl–Cl</td>
<td>TMSCl</td>
<td>THF</td>
<td>–78 to 0 °C</td>
<td>355 is only product</td>
</tr>
<tr>
<td>2</td>
<td>prenyl-Cu (2.2)</td>
<td>prenyl–MgBr; Cul</td>
<td>TMSCl</td>
<td>THF</td>
<td>–78 to 40 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>prenyl-Cu (10)</td>
<td>prenyl–MgBr; Cul</td>
<td>TMSCl</td>
<td>THF</td>
<td>–78 °C to rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>prenyl–Cu (5)</td>
<td>prenyl–OPh, Li; Cul</td>
<td>BF₃·Et₂O, PBu₃, Et₂O/THF</td>
<td>THF</td>
<td>–78 °C to rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>prenyl–Cu (25)</td>
<td>prenyl–OPh, Li; Cul</td>
<td>BF₃·Et₂O, PBu₃, Et₂O/THF</td>
<td>THF</td>
<td>–78 °C to rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>prenyl–Cu (5)</td>
<td>prenyl–SnBu₃, BuLi; Cul, LiCl</td>
<td>TMSCl</td>
<td>THF</td>
<td>–78 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>prenyl–Cu (30)</td>
<td>prenyl–SnBu₃, BuLi; Cul, LiCl</td>
<td>TMSCl</td>
<td>THF</td>
<td>–78 °C to rt</td>
<td>356 (50%), 357 (50%)</td>
</tr>
<tr>
<td>8</td>
<td>Bu₂CuLi (5)</td>
<td>BuLi, Cul</td>
<td>none</td>
<td>Et₂O</td>
<td>–78 to 0 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>9</td>
<td>Bu₂CuLi (5)</td>
<td>BuLi, Cul</td>
<td>BF₃·Et₂O, Et₂O</td>
<td>Et₂O</td>
<td>–78 °C</td>
<td>358 is only product</td>
</tr>
<tr>
<td>10</td>
<td>Bu₂CuLi (5)</td>
<td>BuLi, Cul</td>
<td>TMSCl</td>
<td>Et₂O</td>
<td>–78 °C</td>
<td>358 is only product</td>
</tr>
<tr>
<td>11</td>
<td>Bu₂CuCNLi₂ (5)</td>
<td>BuLi, Cul</td>
<td>TMSCl</td>
<td>Et₂O</td>
<td>–78 °C</td>
<td>358 is only product</td>
</tr>
<tr>
<td>12</td>
<td>Bu₂CuCNLi₂ (5)</td>
<td>BuLi, Cul</td>
<td>none</td>
<td>THF</td>
<td>–78 °C to rt</td>
<td>358 is only product</td>
</tr>
<tr>
<td>13</td>
<td>Bu₂CuCNLi₂ (5)</td>
<td>BuLi, Cul</td>
<td>none</td>
<td>THF</td>
<td>–78 °C to rt</td>
<td>358 is only product</td>
</tr>
<tr>
<td>14</td>
<td>allyl–TMS</td>
<td>--</td>
<td>TMSOTf</td>
<td>CH₂Cl₂</td>
<td>–78 °C to rt</td>
<td>357 is only product</td>
</tr>
</tbody>
</table>

Figure 3.3. Byproducts obtained from the reaction of 353 with various nucleophiles.

Owing to the variability of prenyl–metal formation, we also assessed the reactivity of butyl-derived cuprate species for this cyclopropane-opening reaction (Table 3.4, entries 8-13). The preparation

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of these reagents was much more straightforward than the preparation of prenylcuprates. Both Gilman and Lipshutz-type higher order cuprates were examined. In these cases, the only product we isolated was 358, the result of 1,2-addition to the C9 ketone (Figure 3.3).

Given the propensity of nucleophilic 1,2-addition to the C9 ketone, we also synthesized and explored the chemistry of cyclopropane 359, in which the reactive ketone was masked as a dimethyl ketal. BrBMe2-mediated cyclic ketal opening of 318 followed by a methanol quench afforded alcohol 360 (Scheme 3.17). A variety of conditions were screened for the synthesis of 359 from the derived triflate 361. Exposure of 361 to LDA and TMSCl only afforded vinylsilane 362. We rationalized that a smaller lithium amide base may promote bridgehead deprotonation, since the presence of the C9 dimethyl ketal significantly increased the steric environment surrounding the C1 methine. Exposure of 362 to excess LiNEt2 provided the desired cyclopropane 359 along with sulfamate 363, the product of diethylamide displacement of trifluoromethide from 361. To the best of our knowledge, this is the only known example of trifluoromethide displacement from an alkyl triflate to form a sulfamate. Such a displacement is thermodynamically tenable, given the relative acidity of fluoroform ($pK_a \approx 25-28$) versus diethylamine ($pK_a \approx 31$). Upon reexposure of 363 to LDA or LiNEt2, only trace amounts of 359 were produced. Interestingly, upon exposure of 361 to LiNEt2, rearranged cyclopropane 364 was

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660 All intermediates bearing both a C9 dimethyl ketal and a C7 triflate were particularly unstable and were not fully characterized.

661 Reexposure of this product to LDA did not afford cyclopropane 359.


isolated. This rearrangement product may arise from 1,2-alkyl shift of carbenoid intermediate 365. This reaction is remarkable given the contrasting reactivity of closely related triflate 362.


° Conditions: (a) BrBMe₂, NEt₃, CH₂Cl₂, –78 ºC; MeOH, NEt₃; NaHCO₃, H₂O, 61%; (b) Tf₂O, CH₂Cl₂, –40 to 0 ºC; (c) LDA, TMSCl, HMPA, THF, –78 to 0 ºC; (d) LiNEt₂, THF, –78 ºC to rt, 14% 359, 42% 363 (both yields from 360); (e) LiNEt₂, THF, –78 ºC to rt, 44% (from 360).

We then sought to improve the yield of 359 through the intermediacy of benzenesulfonate 366, since displacement of a phenyl anion would be highly unlikely. Treatment of alcohol 360 with BsCl afforded 366 (Scheme 3.18). Exposure of this sulfonate to LDA and TMSCl afforded vinylsilanes 367 and 368, in which the sulfonate functionality directed lithiation and subsequent silylation upon the attached phenyl ring. Exposure of both of these products to LiNEt₂ afforded 359 in identical yield. Unfortunately, we were unable to successfully convert cyclopropane 359 to a desired ring-opened product

664 The structure of 364 was elucidated from the appearance of nOe correlations between the cyclopropyl methine to both ketal methyl groups, circumstances that would be highly unlikely in the desired cyclopropane.
A variety of conditions were screened, similar to those found in Table 3.4. Proteodesilylation at the C3 position and hydrolysis of the C9 ketal were the only products we isolated in this endeavor.

Scheme 3.18. Synthesis of 359 via benzenesulfonate 366 and unsuccessful formation of 369 from 359.665

\[ \text{Conditions: (a) } \text{BsCl, pyr, CH}_2\text{Cl}_2, -40 \degree \text{C to rt, 48\% yield; (b) } \text{LDA, TMSCl, THF, -78 to 0 \degree \text{C, 29\% 367, 41\% 368; (c) LiNEt}_2, THF, -78 \degree \text{C to rt, 47\% (from either 367 or 368).} \]

In summary, we did not observe desired 1,5-addition to both 353 and 359 despite screening a variety of nucleophiles under a litany of reaction conditions. Iodide 356 was the only product isolated in which 1,5-addition occurred. Given the ability of an iodide to act as a functional handle, we briefly explored the reactivity of this compound (Scheme 3.19).666 Attempted metal-iodine exchange of 356 afforded cyclohexenedione 370.666 The formation of this ring-opened product is unsurprising considering the orbital overlap between the \( \sigma(\text{C7-M}) \) and the \( \sigma^*(\text{C1-C8}) \) bonds of possible intermediate 371. Keck allylation530 of 356 very cleanly afforded 372. Upon radical formation at the C7 position, a facile 5-exo-

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665 Due to the paucity of iodide 356, the products of these reactions were not fully characterized; however, spectroscopic analysis provided sufficient evidence to support the structural assertions made herein.

trig radical cyclization preceded intermolecular allylation. Similar cyclization products were obtained from attempted Ni-catalyzed Fu–Negishi couplings of 356.\textsuperscript{667}

![Scheme 3.19. Reactions of iodide 356.\textsuperscript{a}](image)

\textsuperscript{a} Conditions: (a) ZnBr\textsubscript{2}, i-PrMgCl, Et\textsubscript{2}O, THF, rt; 356; CuCN, LiCl, –78 ºC; prenyl bromide, –78 ºC to rt, 40%; (b) AIBN, allyltributylstannane, PhH, 80 ºC, >99%.

**Total Synthesis of Hyperforin**

Even though Keck coupling of 356 provided the undesired cyclization product 372, we were intrigued by the facility of this radical-based transformation. We resolved to utilize a Keck allylation strategy for the installation of the C7 prenyl group, given the aforementioned result and the successful implementation of a Keck allylation strategy in the total synthesis of (±)-garsubellin A by Danishefsky.\textsuperscript{668} In order to prevent cyclization prior to intermolecular allylation, masking the olefin present in the C8 side chain was required. A similar strategy was utilized in the total synthesis of \textit{ent}-hyperforin by Shibasaki, in which formal methanolysis provided a temporary means of veiling the C8 olefin.\textsuperscript{669} We rationalized


\textsuperscript{668} See discussion on page 120 and ref. 527.

\textsuperscript{669} Specifically, the strategy was implemented in the sequence starting with intermediate 115 and ending with 122. See the discussion starting on page 113 and ref. 512.
that a similar protecting group strategy would minimally affect existing methodology while providing a practical and prudent means of achieving a total synthesis of hyperforin.

We began implementing this strategy by synthesizing methyl ether 373 from the methoxymercuration of epoxygeranyl bromide 289 (Scheme 3.20). Coupling of 373 with cyclohexadiene 312 afforded cyclization precursor 374, and exposure of this intermediate to TMSOTf provided the expected enol ether 375. Subsequent allylic oxidation using our optimized PhI(TFA)$_2$–TBHP–O$_2$ system provided β-methoxyenone 376. However, treatment with BrBMe$_2$ not only hydrolyzed the cyclic ketal of 376 but also displaced the tertiary methyl ether functionality to form bromide 377 as the only isolated product. Decreasing the BrBMe$_2$ stoichiometry afforded bromide 378, indicating that methyl ether cleavage preceded cyclic ketal hydrolysis.

**Scheme 3.20.** Synthesis and reactivity of methyl ether 376.$^d$

$d$ Conditions: (a) Hg(OAc)$_2$, MeOH; NaOH, H$_2$O, 0 °C; NaBH$_4$, 0 °C; 88%, 4% recovered 289; (b) s-BuLi, THF, −78 to −30 °C; 289, −78 to 0 °C, 67%; (c) TMSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 76%; (d) PhI(TFA)$_2$, TBHP, Cs$_2$CO$_3$, O$_2$, EtOAc, −78 to 0 °C, 29%; (e) BrBMe$_2$ (5 equiv), NEt$_3$, CH$_2$Cl$_2$, −78 °C; NEt$_3$; H$_2$O, NaHCO$_3$, 37%; (f) BrBMe$_2$ (2 equiv), NEt$_3$, CH$_2$Cl$_2$, −78 °C; NEt$_3$; H$_2$O, NaHCO$_3$, >90% conversion.
Since Lewis acid coordination was a likely cause of this unintended reactivity, we hypothesized that a more sterically encumbered ether would be less prone to cleavage during the ketal hydrolysis step. Accordingly, triethylsilyl ether 379 was synthesized in two steps from epoxygeranyl bromide 289: (1) oxymercuration of 289, and (2) silylation of the resulting alcohol 380 (Scheme 3.21). We attempted to append other, more sterically demanding silyl moieties to 380; however, intramolecular epoxide-opening cyclization preceded silylation. Coupling of 379 with cyclohexadiene 312 yielded 381, which upon exposure to TMSOTf generated enol ether 382. Allylic oxidation, using aforementioned conditions with minor modifications, afforded β-methoxyenone 383 in a significantly higher yield than previous, similar allylic oxidations. Unfortunately, exposure of this compound to BrBMe₂ at –78 °C produced the tertiary bromide 377, previously observed in the reaction of 376. Nevertheless, we discovered that if the reaction was cooled to below –90 °C, silyl ether cleavage was avoided while negligibly affecting the cyclic ketal hydrolysis, and we obtained the desired hemiketal 384. LiTMP-mediated methanol extrusion from 384 yielded 385.

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670 Methyl ether cleavage was still observed in the reaction of 376 and BrBMe₂ when performed below –90 °C.
Scheme 3.21. Synthesis of triethylsilyl ether 385.\(^a\)

\(^a\) Conditions: (a) Hg(OAc)\(_2\), acetone, H\(_2\)O; NaOH, 0 °C; NaBH\(_4\), 0 °C, 91%; (b) TESCl, imid, DMF, 97%; (c) s-BuLi, THF, –78 to –30 °C; (d) TMSOTf, 2,6-lutidine, CH\(_2\)Cl\(_2\), –78 °C, 79%; (e) PhI(TFA)\(_2\), TBHP, Cs\(_2\)CO\(_3\), 4Å MS, EtOAc, O\(_2\), –78 to 0 °C, 44%; (f) BrBMe\(_2\), NEt\(_3\), CH\(_2\)Cl\(_2\), –78 °C; NEt\(_3\), NaHCO\(_3\), H\(_2\)O, 48%; (g) BrBMe\(_2\), NEt\(_3\), CH\(_2\)Cl\(_2\), –95 °C; NEt\(_3\), NaHCO\(_3\), H\(_2\)O, 57%; (h) LiTMP, THF, –78 to 0 °C, 97%.

Installation of the key C7 prenyl group was accomplished in three steps from 385 via a Keck allylation strategy. A variety of radical initiating functional groups were screened in the radical allylation reaction step to afford 386, including phenyl thiocarbonate 387,\(^{671}\) pentafluorophenyl thiocarbonate 388,\(^{672}\) methyl xanthate 389, and imidazole carbothioate 390 (Scheme 3.22). In addition, we screened several methods of radical generation, including: (1) the use of AIBN, activated both thermally and photochemically; (2) photochemical radical generation (in the absence of a radical promotor); and (3) the combination of BEt\(_3\) and air. A major byproduct in these studies was 391, the result of reductive deoxygenation. Ultimately, we found that the activation of 388 with BEt\(_3\) and air afforded 386 in

\(^{671}\) 387 was synthesized in one step from hemiketal 384 rather than from 385. See experimental section for details.

\(^{672}\) N-Hydroxysuccinimide (NHS) was utilized in the formation of 388 from 385. For more information on the use of NHS in the synthesis of thiocarbonates, see: Barton, D. H. R.; Jaszberenyi, J. C. Tetrahedron Lett. 1989, 30, 2619-2622.
consistently good yield. Past studies have found that the pentafluorophenyl thiocarbonate radical precursor functionality has a relatively long half-life for radical generation;\textsuperscript{673} this prolonged half-life may prevent the formation of unintended byproducts and favor the selective formation of the intended allylation product. Cross metathesis of 386 with 2-methyl-2-butene catalyzed by Hoveyda–Grubbs second-generation catalyst (117) yielded 392, a product containing the requisite C7 prenyl moiety. Exposure of 392 to LiTMP and TMSCl afforded vinylsilane 393.

We then investigated the C1 bridgehead functionalization of 393. This was an extremely challenging transformation, given the steric environment around the intended reaction center. In addition, considering that we intended to functionalize the C1 position with an isopropyl ketone, this meant that an electrophile bearing an acidic $\alpha$-proton needed to be employed. In general, we focused our attention on

several variables in screening this bridgehead functionalization reaction, including: (1) choice of base; (2) deprotonation time and temperature; (3) quenching temperature; (4) choice of electrophile; (5) various additives; and (6) reaction concentration. Specifically, we screened various amide bases, including LDA, LiNEt$_2$, LiTMP, and various other TMP-derived organometallics (e.g., TMP–MgX, TMP–ZnCl).$^{674}$ In general, reduction of the C9 ketone was observed with LDA and LiNEt$_2$, and non-lithium TMP organometallics failed to deprotonate the C1 methine. MeCu(TMP)CNLi$_2$$^{675}$ was the only such base to react with $^{393}$, providing alcohol $^{394}$ as the result of methyl addition to the C9 ketone (Scheme 3.23). Appreciable deprotonation using LiTMP was not observed below −20 °C in THF solution; however, prolonged exposure of $^{393}$ to LiTMP above −20 °C caused significant decomposition. Eventually, we discovered that optimal deprotonation of $^{393}$ with LiTMP was accomplished in 5 min at 0 °C. Likewise, quenching temperature was also an important parameter in LiTMP-mediated reactions owing to the instability of $^{393}$ and its coupling products at relatively elevated temperatures. Significant increases in material recovery were observed when reactions were quenched at −20 °C and lower.

Scheme 3.23. Reaction of $^{393}$ with MeCu(TMP)CNLi$_2$.a

spoken Conditions: (a) MeCu(TMP)CNLi$_2$, THF, −78 to 0 °C; i-PrC(O)Cl, −78 °C to rt, 49%, 15% recovered $^{393}$.


We also examined the use of several electrophiles. A reaction between the 393 and \( i-\text{PrCHO} \) was observed, but the product obtained in these reactions also contained C9 ketone reduction, possibly through internal hydride transfer. Dimethyl ketene was an ideal coupling partner, having no acidic \( \alpha \)-proton, but we were not able to isolate any coupling products from reactions using this electrophile. Coupling reactions with \( I_2 \) resulted in decomposition. In the end, we observed our desired product through the use of either isobutyryl chloride or cyanide, the latter providing marginally improved yields on a consistent basis. In addition, reaction concentration was an important factor for this reaction. Optimal yields were observed with concentrations above 0.05 M. As a result of these findings, the optimized bridgehead acylation of 393 to afford 395 is depicted in Scheme 3.24. This is a significant improvement over prior PPAP total syntheses involving C1 bridgehead acylation, which required multiple steps involving a bridgehead iodide to synthesize similar intermediates.

Scheme 3.24. Bridgehead acylation of 393.\textsuperscript{a}

\textsuperscript{a} Conditions: (a) LiTMP, THF, \(-78 \, ^\circ\text{C}, 10\) min; 0 \( ^\circ\text{C}, 5\) min; \( i-\text{PrC(O)CN}, -78\) to \(-30\) \( ^\circ\text{C}, 49\%\).

It should be noted that we also briefly explored the bridgehead lithiation chemistry of 396 and 397 (Figure 3.4). Under a variety of conditions, C1 functionalization was not observed in reactions involving 396. Unsurprisingly, we observed products arising from C3 bisallylic methylene deprotonation upon exposure of 397 to lithium amide bases.
Having achieved bridgehead acylation, we investigated the desilylation and dehydration of 395. We hypothesized that under certain conditions, both tasks may be accomplished in a single step to afford 398. Heating 395 in the presence of strong acids, such as CSA and p-TsOH, caused slow decomposition of the starting material, and in the presence of weaker acids, desilylation was observed but not elimination of the resulting tertiary carbinol. If microwave irradiation was utilized as the source of heat and using both p-TsOH and HOAc, we were able to access our desired product 398 (Scheme 3.25). In addition to 398, we also isolated variable amounts of double-bond isomer 399. 2-Methyl-2-butene was used as an additive to this reaction to prevent the isomerization of the other olefins present in 395.

Scheme 3.25. Desilylation and dehydration of 395 to form 398, and the structure of double bond isomer 399.\(^a\)

\(^a\) Conditions: (a) p-TsOH H$_2$O, HOAc, 2-methyl-2-butene, PhMe, \(\mu\)wave, 100 °C, 65%.

Total synthesis of hyperforin was accomplished in two steps from 398 (Scheme 3.26). First, C3 prenylation was accomplished using stepwise lithiation, transmetalation with Lipshutz’s cuprate,\(^5\) and prenyl bromide alkylation to afford hyperforin O-methyl ether (60). This compound was
spectroscopically identical to 60 semisynthetically derived from hyperforin. Finally, demethylation under Krapcho conditions provided hyperforin (I). The hyperforin obtained from this synthesis was spectroscopically indistinguishable from hyperforin that we isolated from SJW as well as published data on the natural product.

Two other rearranged products were isolated in this final deprotection step, 400 and 401. A possible mechanism for the formation of these byproducts involves formal C-to-O acyl migration of hyperforin, which may be facilitated by cleavage of the C1–C2 bond to form an intermediate ketene 402 (Scheme 3.27). Chloromethane, a byproduct of the demethylation reaction, may react with 400 to form

\[ \text{Scheme 3.26. Completion of the total synthesis of hyperforin.}^{a} \]

\[ ^{a} \text{Conditions: (a) LDA, THF, –78 °C; Li(2-Th)CuCN, –78 to –40 °C; prenyl–Br (98%); (b) LiCl, DMSO, 120 °C, 55% I, 14% 400, 23% 401.} \]

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676 See experimental section for more details.

677 See experimental section for more details. A detailed procedure for the isolation of hyperforin from St. John’s wort extract is also provided.
A similar C-to-O migration has been observed previously by Plietker. Interestingly, the PPAP laxifloranone and the chromenone-type acylphoroglucinol mahureone A are analogously related despite being isolated from two disparate plant species.

Scheme 3.27. A possible mechanism for the formation of 400 and 401 from 1, and structures of laxifloranone and mahureone A.

Overall, these efforts culminated in a total synthesis of the naturally occurring enantiomer of hyperforin. The synthesis is 18 steps at its longest linear sequence, starting from geraniol. Relative and absolute stereochemistry in the synthesis is established through a Sharpless epoxidation reaction. The route is also considerably scalable; more than 40 mg of synthetic hyperforin were generated in a single batch. By recognizing latent symmetry elements embedded in the hyperforin core, we quickly established


the bicyclo[3.3.1]nonane core of hyperforin through a diastereoselective epoxide-opening cascade cyclization reaction. In this key conversion of 381 to 382, the stereochemical identity of three key carbon centers were established including two quaternary centers. Further, the practicality and modularity of this synthesis may be exploited to quickly access a library of hyperforin analogs.
**Experimental Section**

**General Procedures.** All reactions were performed in oven-dried or flame-dried glassware under a positive pressure of argon unless otherwise noted. Flash column chromatography was performed as described by Still et al.\textsuperscript{599} employing silica gel 60 (40-63 µm, Whatman). Both preparatory and analytical thin-layer chromatography (TLC) were performed using 0.25 mm silica gel 60 F\textsubscript{254} plates.

**Materials.** Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran, diethyl ether, dichloromethane, toluene, benzene, hexane, acetonitrile, and N,N-dimethylformamide were degassed with argon and passed through a solvent purification system (designed by J. C. Meyer of Glass Contour) utilizing alumina columns as described by Grubbs et al.\textsuperscript{600} unless otherwise noted. Diethylamine, triethylamine, diisopropylamine, pyridine, 2,2,6,6-tetramethylpiperidine, dimethyl sulfoxide, and chlorotrimethylsilane were distilled over calcium hydride. Hexamethylphosphoramide was distilled over calcium hydride under reduced pressure. Geraniol, titanium(IV) isopropoxide, prenyl chloride, prenyl bromide, allyltributylstannane, and trimethylsilyl trifluoromethanesulfonate were distilled under reduced pressure. N-Hydroxysuccinimide was recrystallized using ethanol. [bis(Trifluoroacetoxy)iodo]benzene was crystallized from the reaction of (diacetoxyiodo)benzene with trifluoroacetic acid and subsequently dried under reduced pressure (1 mmHg). Cesium carbonate was dried for at least 12 h at 150 °C under reduced pressure (1 mmHg). Lithium bromide, lithium chloride, and molecular sieves were stored in a vacuum oven for at least 24 h. The molarities of butyllithium, sec-butyllithium, and tert-butyllithium solutions were determined by titration with 1,10-phenanthroline as an indicator (average of three determinations). THF solutions of lithium diethylamide, lithium diisopropylamide, and lithium 2,2,6,6-tetramethylpiperidide were prepared by addition of a hexane solution of butyllithium (1 equiv) to a THF solution of the appropriate amine (1.1 equiv) cooled to –78 °C and stirring the solution for 30 min at 0 °C. PhH solutions of triethylborane were prepared by addition of neat triethylborane to PhH.

**Instrumentation.** \textsuperscript{1}H NMR spectra were recorded with Varian INOVA-600, Varian INOVA-500, and Varian Mercury 400 spectrometers, are reported in parts per million (δ), and are calibrated using...
residual non-deuterated solvent as an internal reference: CDCl₃, δ 7.26 (CHCl₃); C₆D₆, δ 7.16 (C₆D₅H); CD₃OD, δ 3.31 (CD₂HOD). Data for ¹H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, integration). Multiplicities are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; septet = septet; m = multiplet; br = broad, or combinations thereof. ¹³C NMR spectra were recorded with a Varian INOVA-500 spectrometer, are reported in parts per million (δ), and are referenced from the central peak of the carbon resonance of the solvent: CDCl₃, δ 77.23; C₆D₆, δ 128.06; CD₃OD, δ 49.00. Infrared (IR) data were recorded on a Varian 1000 FT-IR using NaCl plates or on a Bruker Alpha FT-IR spectrometer outfitted with an Eco-ATR sampling module. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectroscopy on an Agilent 6210 TOF LC/MS or a Bruker q-TOF Maxis Impact mass spectrometer. Gas chromatography mass spectra (GCMS) were performed on a Shimadzu GC-2014 equipped with an AOC-20i auto-injector. Microwave irradiation was accomplished using a CEM Discover microwave reactor. High-performance liquid chromatography was performed on a Agilent 1100 series HPLC. Chiral high performance liquid chromatography (HPLC) was performed on an Agilent 1200 series HPLC.

**Note:** For clarity, intermediates that have are not explicitly mentioned in this chapter are numbered sequentially in the experimental section beginning with 405.
A CH$_2$Cl$_2$ solution of tert-butyl hydroperoxide (4.0 M, 410 mL, 1.64 mol, 1.5 equiv) was added via cannula over 1 h to a CH$_2$Cl$_2$ (850 mL) slurry of 4Å molecular sieves (30.43 g, powdered), L-(+)-diethyl tartrate (28.2 mL, 164 mmol, 0.15 equiv), and titanium(IV) isopropoxide (32.5 mL, 110 mmol, 0.1 equiv) in a 3-neck 5-L round-bottom flask cooled to an internal reaction temperature of –25 ºC. The resulting yellow slurry was stirred at –25 ºC for 30 min and then cooled to an internal reaction temperature of –30 ºC. A CH$_2$Cl$_2$ (175 mL) solution of geraniol (287, 169.08 g, 1.0961 mol, 1 equiv) was added via cannula, followed by a CH$_2$Cl$_2$ (50 mL) rinse. Throughout this addition, the internal reaction temperature of the reaction was maintained ≤ –20 ºC. After stirring at –30 ºC for 75 min, the reaction was warmed to –10 ºC over 2 h. The reaction was then quenched at –10 ºC with H$_2$O (500 mL) followed by a 30 wt% H$_2$O solution of NaOH saturated in NaCl (300 mL). After stirring vigorously at rt for 45 min, the emulsion was diluted with MeOH (1.5 L) and brine (300 mL), and the layers were separated. The aqueous layer was washed thrice with CH$_2$Cl$_2$. The organic extracts were combined, washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo to an opaque yellow oil. Short-path distillation (6 mmHg, 90-93 ºC) afforded 171.05 g (1.0045 mol, 92% yield) of 288 as a pale yellow oil.

$^{1}$H NMR (600 MHz; CDCl$_3$) δ: 5.08 (t, J = 7.1 Hz, 1H), 3.82 (ddd, J = 11.8, 6.9, 4.7 Hz, 1H), 3.68 (ddd, J = 11.7, 6.8, 4.6 Hz, 1H), 2.97 (dd, J = 6.6, 4.3 Hz, 1H), 2.12-2.04 (m, 2H), 1.70-1.65 (m, 5H), 1.61 (s, 3H), 1.50-1.45 (m, 1H), 1.30 (s, 3H).

$^{13}$C NMR (125 MHz; CDCl$_3$) δ: 132.3, 123.5, 63.2, 61.6, 61.4, 38.7, 25.9, 23.9, 17.8, 16.9.

This procedure was adapted from ref. 607.

The CH$_2$Cl$_2$ used in this procedure was dried through storage over 3Å molecular sieves (pelleted) for at least 24 h.

See ref. 607 for preparation of a CH$_2$Cl$_2$ solution of tert-butyl hydroperoxide.
**FTIR** (thin film) $\nu_{\text{max}}$: 3420 (br), 2968, 2928, 2859, 1455, 1385, 1077, 1036, 865 cm$^{-1}$.

**HRMS–ESI** (m/z): [M+Na]$^+$ calculated for C$_{10}$H$_{18}$O$_2$, 193.1199; found, 193.1200.

$[\alpha]_D^{23} = -5.36^\circ$ (c 3.04, CHCl$_3$); [91% ee sample from literature]: $[\alpha]_D^{25} = -5.3^\circ$ (c 3.0, CHCl$_3$).

**TLC** $R_f = 0.45$ (1:1 hexane:EtOAc).
Chiral HPLC Trace of 288

**Racemic sample:** HPLC (ChiralPak AS-H, 9:1 isopropanol:hexane, 1 mL/min, 210 nm)

![Racemic sample HPLC trace](image1)

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**Scalemic sample:** HPLC (ChiralPak AS-H, 9:1 isopropanol:hexane, 1 mL/min, 210 nm)

![Scalemic sample HPLC trace](image2)

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Totals:
- Racemic: 2518.27002, 229.46797
- Scalemic: 3737.98067, 330.47387
((2S,3S)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl methanesulfonate (405)\textsuperscript{684}

A CH\textsubscript{2}Cl\textsubscript{2} \textsuperscript{685} (1.2 L) solution of 288 (100.00 g, 587.37 mmol, 1 equiv) and triethylamine (123 mL, 881 mmol, 1.5 equiv) in a 2-neck 2-L round-bottom flask outfitted with an equal pressure dropping funnel was cooled to an internal reaction temperature of –10 ºC, and methanesulfonyl chloride (59.5 mL, 763 mmol, 1.3 equiv) was added dropwise via the equal pressure dropping funnel over 30 min, maintaining an internal reaction temperature \( \leq 0 \) ºC. After the addition was complete, the yellow slurry was stirred at 0 ºC for 15 min, and then quenched at 0 ºC with H\textsubscript{2}O. The layers were separated, and the aqueous layer was washed thrice with CH\textsubscript{2}Cl\textsubscript{2}. The organic extracts were combined, washed sequentially with 2 N HCl, brine, and sat. aq. NaHCO\textsubscript{3}, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. The resulting yellow oil was dissolved in 95:5 hexane:EtOAc and passed through a plug of SiO\textsubscript{2}, rinsing with 95:5 hexane:EtOAc. Concentration of the filtrate \textit{in vacuo} yielded 142.19 g (572.56 mmol, 97% yield) of 405 as a yellow oil that was used without further purification.

\textsuperscript{1}H NMR (600 MHz; CDCl\textsubscript{3}) \( \delta \): 5.07 (t, \( J = 7.0 \) Hz, 1H), 4.42 (dd, \( J = 11.7, 4.1 \) Hz, 1H), 4.25 (dd, \( J = 11.7, 7.1 \) Hz, 1H), 3.09-3.07 (m, 4H), 2.12-2.05 (m, 2H), 1.71-1.66 (m, 4H), 1.61 (s, 3H), 1.52-1.47 (m, 1H), 1.33 (s, 3H).

\textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) \( \delta \): 132.6, 123.1, 68.9, 61.3, 59.3, 38.3, 38.0, 25.8, 23.7, 17.8, 17.0.

FTIR (thin film) \( \nu_{\text{max}} \): 2969, 2931, 2860, 1456, 1358, 1176, 981, 957, 833 cm\textsuperscript{-1}.

HRMS–ESI (m / z): [M+H]\textsuperscript{+} calculated for C\textsubscript{11}H\textsubscript{20}O\textsubscript{4}S, 249.1155; found, 249.1157.

\([\alpha]_{D}^{23} = -13.9^{\circ} \) (c 4.08, CHCl\textsubscript{3}).

TLC \( R_{f} = 0.55 \) (1:1 hexane:EtOAc).

\textsuperscript{684} This procedure was adapted from ref. 608.

\textsuperscript{685} The CH\textsubscript{2}Cl\textsubscript{2} used in this procedure was dried through storage over 3Å molecular sieves (pelleted) for at least 24 h.
(2S,3R)-3-(Bromomethyl)-2-methyl-2-(4-methylpent-3-en-1-yl)oxirane (289)\textsuperscript{686}

A Me2CO (1 L) slurry of 405 (141.96 g, 571.64 mmol, 1 equiv) and lithium bromide (99.29 g, 1.143 mol, 2 equiv) was heated to reflux in a 2-L recovery flask outfitted with a reflux condenser. After refluxing for 90 min, the slurry was cooled to rt and filtered. The yellow filtrate was concentrated \textit{in vacuo}. The resulting yellow oil was diluted with H2O and extracted thrice with 9:1 hexane:EtOAc. The organic extracts were combined, washed sequentially with H2O, sat. aq. NaHCO3, and brine, dried over Na2SO4, filtered, and concentrated \textit{in vacuo}. The resulting pale yellow oil was dissolved in 9:1 hexane:EtOAc, and passed through a plug of SiO2, rinsing with 9:1 hexane:EtOAc. Concentration of the filtrate \textit{in vacuo} yielded 125.35 g (537.64 mmol, 94% yield) of 289 as a pale yellow oil that was used without further purification.

\textbf{1H NMR} (600 MHz; CDCl3) \(\delta\): 5.10 (t, \(J = 7.1\) Hz, 1H), 3.54 (dd, \(J = 10.4, 5.9\) Hz, 1H), 3.24 (dd, \(J = 10.4, 7.8\) Hz, 1H), 3.08 (dd, \(J = 7.8, 5.9\) Hz, 1H), 2.13-2.05 (m, 2H), 1.74-1.70 (m, 4H), 1.61 (s, 3H), 1.45 (ddd, \(J = 13.7, 9.3, 7.1\) Hz, 1H), 1.31 (s, 3H).

\textbf{13C NMR} (125 MHz; CDCl3) \(\delta\): 132.5, 123.4, 63.2, 61.7, 38.6, 29.9, 25.9, 24.0, 17.9, 16.3.

\textbf{FTIR} (thin film) \(\nu_{\text{max}}\): 2969, 2928, 2859, 1451, 1385, 1217, 1112, 1071, 890, 652 cm\textsuperscript{-1}.

\textbf{PCI-GC/MS} (m / z): [M+NH4\textsuperscript{+}] 250 (100%), 252 (97.7%).

\([\alpha]_D^{23} = +22.6^\circ\) (c 4.34, CHCl3).

\textbf{TLC} \(R_f = 0.72\) (1:1 hexane:EtOAc).

\textsuperscript{686} This procedure was adapted from ref. 608.
(3,5-Dimethoxy-4-(((2S,3S)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl)phenoxy)triisopropylsilane (290):

A THF (54 mL) solution of 146 (3.169 g, 10.8 mmol, 1 equiv) in a 200-mL recovery flask was cooled to 0 ºC, and a hexane solution of butyllithium (2.60 M, 4.6 mL, 12 mmol, 1.1 equiv) was added dropwise over 5 min. The cooling bath was then removed, and the resulting yellow solution was stirred at rt for 1 h. After cooling the reaction to 0 ºC and stirring at that temperature for 30 min, 289 (2.76 g, 11.8 mmol, 1.1 equiv) was added dropwise. The cooling bath was subsequently removed, and the resulting colorless solution was stirred at rt for 3 h. The reaction was then quenched at rt with sat. aq. NH₄Cl, diluted with H₂O, and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (500 mL SiO₂, 95:5 hexane:EtOAc) afforded 4.034 g (8.72 mmol, 81% yield) of 290 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 6.10 (s, 2H), 5.29 (s, 1H), 5.00 (t, J = 7.1 Hz, 1H), 3.75 (s, 6H), 2.98 (dd, J = 13.6, 4.4 Hz, 1H), 2.88 (dd, J = 7.6, 4.4 Hz, 1H), 2.68 (dd, J = 13.6, 7.6 Hz, 1H), 1.61 (m, 1H), 1.59 (s, 3H), 1.54 (s, 3H), 1.37 (s, 3H), 1.34 (td, J = 6.8, 3.2 Hz, 1H), 1.26 (septet, J = 7.4 Hz, 3H), 1.12 (d, J = 7.4 Hz, 18H).

¹³C NMR (125 MHz; CDCl₃) δ: 159.1, 156.2, 131.7, 124.0, 107.2, 96.4, 63.5, 61.7, 55.7, 39.2, 25.8, 24.1, 22.5, 18.2, 17.7, 16.9, 12.9.

FTIR (thin film) ν_max: 2961, 2945, 2868, 1606, 1593, 1496, 1463, 1414, 1200, 1158, 1134, 1021, 883, 686 cm⁻¹.


TLC Rₖ = 0.55 (8:2 hexane:EtOAc).
3,5-Dimethoxy-4-(((2S,3S)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl)phenol (291):

A THF (30 mL) solution of 290 (3.97 g, 8.58 mmol, 1 equiv) in a 100-mL recovery flask was treated with a THF solution of tetrabutylammonium fluoride (1.0 M, 9.0 mL, 9.0 mmol, 1.05 equiv). After stirring at rt for 1 h, the reaction was quenched at rt with sat. aq. NH₄Cl, extracted once with hexane, and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow oil. Flash column chromatography (400 mL SiO₂, 7:3 → 1:1 hexane:EtOAc) afforded 2.200 g (7.18 mmol, 84% yield) of 291 as a colorless oil.

¹H NMR (500 MHz; CDCl₃) δ: 6.06 (s, 2H), 5.11 (s, 1H), 4.99 (t, J = 7.1 Hz, 1H), 3.76 (s, 6H), 2.97 (dd, J = 13.5, 4.6 Hz, 1H), 2.91 (dd, J = 7.3, 4.6 Hz, 1H), 2.69 (dd, J = 13.5, 7.3 Hz, 1H), 2.07-1.95 (m, 2H), 1.63 (m, J = 5.2 Hz, 1H), 1.59 (s, 3H), 1.54 (s, 3H), 1.38 (s, 3H), 1.37-1.33 (m, 1H).

¹³C NMR (125 MHz; CDCl₃) δ: 159.3, 156.4, 131.9, 123.8, 106.0, 92.1, 64.1, 62.6, 55.7, 39.1, 25.8, 24.1, 22.3, 17.7, 16.9.

FTIR (thin film) ν max: 3368 (br), 2936, 2840, 1618, 1603, 1475, 1431, 1206, 1134, 999 cm⁻¹.


TLC Rₜ = 0.50 (1:1 hexane:EtOAc).
4-Allyl-3,5-dimethoxy-4-(((2S,3S)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl)cyclohexa-2,5-dienone (292):

A PhH (36 mL) solution of 291 (2.189 g, 7.14 mmol, 1 equiv), triphenylphosphine (150 mg, 0.572 mmol, 0.08 equiv), and palladium(II) acetate (32 mg, 0.14 mmol, 0.02 equiv) in a 100-mL recovery flask was treated sequentially with allyl methyl carbonate (2.0 mL, 18 mmol, 2.5 equiv) and titanium(IV) isopropoxide (423 µL, 1.43 mmol, 0.2 equiv). The resulting dark red solution was heated to 50 ºC and stirred at that temperature for 2 h. The resulting orange-red solution was subsequently cooled to rt and quenched with sat. aq. NH₄Cl. After stirring at rt for 5 min, 1 N HCl was added, and the mixture was extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a orange slurry. Flash column chromatography (250 mL SiO₂, 7:3 → 6:4 → 1:1 hexane:EtOAc) afforded 1.148 g (3.31 mmol, 46% yield) of 292 as a pale yellow oil and 1.060 g (3.46 mmol, 48% recovery) of 291 as a pale yellow oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.59 (s, 1H), 5.58 (s, 1H), 5.39 (ddt, J = 17.1, 10.0, 7.2 Hz, 1H), 5.00-4.92 (m, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 2.61-2.54 (m, 2H), 2.40 (t, J = 5.9 Hz, 1H), 2.14 (dd, J = 13.9, 5.9 Hz, 1H), 2.04 (dd, J = 13.9, 5.9 Hz, 1H), 1.98-1.88 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H), 1.50 (ddd, J = 13.7, 9.7, 6.3 Hz, 1H), 1.27 (ddd, J = 13.7, 10.0, 6.5 Hz, 1H), 1.17 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 188.0, 173.1, 172.6, 132.2, 131.9, 123.6, 118.4, 103.55, 103.45, 60.7, 59.3, 56.2, 56.0, 49.7, 41.7, 38.9, 35.7, 25.8, 23.9, 17.8, 16.7.

FTIR (thin film) ν_max: 2928 (br), 1654, 1627, 1592, 1384, 1233, 1206, 1144 cm⁻¹.


TLC R_f = 0.20 (1:1 hexane:EtOAc).
4- Allyl-4-(3,7-dimethyl-2-oxooct-6-en-1-yl)-3,5-dimethoxycyclohexa-2,5-dienone (294):

A CH₂Cl₂ (1 mL) solution of 292 (3.3 mg, 9.5 µmol, 1 equiv) in a 10-mL pear-shaped flask was cooled to –78 ºC, and 1 drop of boron trifluoride ethyl etherate was added. After stirring the reaction for 10 min at –78 ºC, it was placed in a 0 ºC bath. After stirring the reaction at 0 ºC for 2 h, it was quenched at 0 ºC with brine, diluted with sat. aq. NH₄Cl, and extracted five times with EtOAc. The organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow residue. Flash column chromatography (4 mL SiO₂, 2:8 hexane:EtOAc) afforded 1.4 mg (4.0 µmol, 43% yield) of 294 as a colorless residue.

**¹H NMR** (500 MHz; CDCl₃) δ: 5.55 (s, 2H), 5.48-5.40 (m, 1H), 5.04 (t, J = 6.4 Hz, 1H), 4.96 (dd, J = 10.3, 1.3 Hz, 1H), 4.94 (dd, J = 17.2, 1.3 Hz, 1H), 3.67 (s, 6H), 3.07 (d, J = 16.8 Hz, 1H), 3.03 (d, J = 16.8 Hz, 1H), 2.45 (d, J = 7.5 Hz, 2H), 2.41 (q, J = 6.9 Hz, 1H), 1.89 (q, J = 7.5 Hz, 2H), 1.68 (s, 3H), 1.66-1.60 (m, 1H), 1.58 (s, 3H), 1.30-1.24 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 210.5, 188.4, 172.71, 172.62, 132.5, 131.5, 123.9, 118.8, 102.90, 102.86, 56.08, 56.06, 48.3, 46.3, 45.9, 43.2, 32.9, 25.93, 25.76, 17.9, 16.2.

**FTIR** (thin film) νmax: 2965, 2922, 2853, 1715, 1654, 1622, 1446, 1388, 1234, 1205, 1147, 851 cm⁻¹.


**TLC** Rₜ = 0.44 (EtOAc).
(2S,3S)-3-((1- Allyl-2,6-dimethoxycyclohexa-2,5-dien-1-yl)methyl)-2-methyl-2-(4-methylpent-3-en-1-yl)oxirane (302):

A CH₂Cl₂ (0.5 mL) solution of 292 (106 mg, 0.31 mmol, 1 equiv) was transferred via cannula to a CH₂Cl₂ (0.5 mL) slurry of lithium aluminum hydride (23 mg, 0.61 mmol, 2 equiv) in a 10-mL pear-shaped flask cooled to –78 ºC, followed by a CH₂Cl₂ (0.5 mL) rinse. After stirring for 30 min at –78 ºC, Et₂O (0.5 mL) was added, and the reaction was placed in a 0 ºC bath. After stirring at 0 ºC for 75 min, the reaction was quenched sequentially at 0 ºC with H₂O (23 µL), 15% (w/v) NaOH (23 µL), and H₂O (69 µL). The mixture was warmed to rt, diluted with H₂O, and extracted four times with EtOAc. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a brown residue. Flash column chromatography (30 mL SiO₂, 95:5 hexane:EtOAc) afforded 45 mg (0.14 mmol, 44% yield) of 302 as a colorless residue.

¹H NMR (600 MHz; CDCl₃) δ: 5.57 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H), 5.05 (t, J = 7.1 Hz, 1H), 4.94-4.88 (m, 2H), 4.80 (t, J = 3.5 Hz, 1H), 4.76 (t, J = 3.5 Hz, 1H), 3.54 (s, 3H), 3.49 (s, 3H), 2.78 (q, J = 3.5 Hz, 2H), 2.64 (dd, J = 8.0, 4.0 Hz, 1H), 2.39 (qd, J = 12.7, 7.2 Hz, 2H), 2.03 (dd, J = 13.7, 4.0 Hz, 1H), 1.97 (q, J = 7.9 Hz, 2H), 1.76 (dd, J = 13.7, 8.0 Hz, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.57-1.54 (m, 1H), 1.29 (dt, J = 13.5, 8.4 Hz, 1H), 1.18 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 153.80, 153.73, 135.3, 131.8, 124.2, 116.1, 93.23, 93.17, 61.25, 61.09, 54.6, 54.2, 46.2, 40.2, 39.4, 34.2, 25.8, 24.2, 24.0, 17.8, 16.8.

FTIR (thin film) νmax: 2932, 2831, 1694, 1659, 1451, 1381, 1223, 1206, 1139, 908 cm⁻¹.

HRMS–ESI (m / z): [M+H]⁺ calculated for C₂₁H₃₂O₃, 333.2424; found, 333.2425.

TLC Rf = 0.78 (1:1 hexane:EtOAc).
(2S,3S,3aR,7R,7aS)-7-allyl-6,7a-dimethoxy-3-methyl-3-(4-methylpent-3-en-1-yl)-2,3,3a,4,7,7a-hexahydro-2,7-methanobenzofuran (303):

A CH₂Cl₂ (6 mL) solution of 302 (100. mg, 0.301 mmol, 1 equiv) and 2,6-di-tert-butyl-4-methylpyridine (124 mg, 0.602 mmol, 2 equiv) in a 20-mL scintillation vial was cooled to –78 ºC, and trimethylsilyl trifluoromethanesulfonate (65 µL, 0.36 mmol, 1.2 equiv) was added dropwise. After stirring the bright yellow solution at –78 ºC for 30 min, it was quenched at –78 ºC with sat. aq. NaHCO₃ and extracted four times with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow oil. Flash column chromatography (50 mL SiO₂; 99:1 hexane:EtOAc) afforded 85 mg (0.26 mmol, 85% yield) of 303 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 6.02 (ddt, J = 17.2, 10.1, 7.1 Hz, 1H), 5.04 (t, J = 7.1 Hz, 1H), 5.01-4.95 (m, 2H), 4.54 (dd, J = 5.7, 2.1 Hz, 1H), 3.75 (d, J = 5.3 Hz, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 2.42 (dd, J = 14.1, 7.1 Hz, 1H), 2.29 (dd, J = 14.1, 7.1 Hz, 1H), 2.19 (ddd, J = 18.1, 6.7, 2.2 Hz, 1H), 2.07-2.02 (m, 2H), 2.01-1.93 (m, 1H), 1.86 (dd, J = 12.5, 5.3 Hz, 1H), 1.81 (d, J = 12.5 Hz, 1H), 1.72-1.65 (m, 4H), 1.58 (s, 3H), 1.47-1.42 (m, 1H), 1.25-1.20 (m, 1H), 1.14 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 158.1, 138.3, 131.7, 124.9, 115.8, 112.5, 90.8, 79.1, 54.6, 51.3, 46.3, 44.4, 42.0, 38.88, 38.73, 33.6, 28.1, 25.9, 22.9, 20.1, 17.8.

FTIR (thin film) νmax: 2966, 2930, 1671, 1578, 1460, 1439, 1376, 1304, 1215, 1168, 1136, 1062, 1001, 906 cm⁻¹.
HRMS–ESI (m/z): [M+Na]^+ calculated for C_{21}H_{32}O_{3}, 355.2244; found, 355.2245.

TLC R_f = 0.53 (9:1 hexane:EtOAc).
(2S,3S,3aS,7R,7aS)-7-Allyl-6,7a-dimethoxy-3-methyl-3-(4-methylpent-3-en-1-yl)-3,3a,7,7a-
tetrahydro-2,7-methanobenzofuran-4(2H)-one (305):

A CH2Cl2 (1.7 mL) slurry of 303 (55 mg, 0.17 mmol, 1 equiv) and cesium carbonate (292 mg, 0.83 mmol, 5 equiv) in a 10-mL pear-shaped flask was cooled to 0 ºC open to air, and Pearlman’s catalyst (4.4 mg, 0.0082 mmol based on Pd, 0.05 equiv) and a decane solution of tert-butyl hydroperoxide (5.5 M, 150 µL, 0.83 mmol, 5 equiv) were added in sequence. The flask was sealed, purged with O2 via O2 balloon, and stirred at 4 ºC for 13 h. The slurry was subsequently diluted with CH2Cl2 and filtered through a short plug of SiO2, rinsing with CH2Cl2 followed by EtOAc. The filtrate was concentrated in vacuo to a colorless oil. Flash column chromatography (20 mL SiO2, 8:2 hexane:EtOAc) afforded 10.4 mg (0.030 mmol, 17% yield) of 305 as a colorless residue.

1H NMR (600 MHz; CDCl3) δ: 5.98 (m, 1H), 5.35 (s, 1H), 5.06-5.01 (m, 2H), 4.99 (t, J = 7.1 Hz, 1H), 3.91 (d, J = 5.5 Hz, 1H), 3.71 (s, 3H), 3.48 (s, 3H), 2.69 (s, 1H), 2.53 (dd, J = 14.2, 6.7 Hz, 1H), 2.39 (dd, J = 14.2, 7.9 Hz, 1H), 2.06 (d, J = 13.1 Hz, 1H), 2.04-1.98 (m, 2H), 1.73-1.67 (m, 1H), 1.64 (s, 3H), 1.55 (s, 3H), 1.43-1.36 (m, 1H), 1.34-1.28 (m, 1H), 1.25 (s, 3H).

13C NMR (125 MHz; CDCl3) δ: 197.8, 180.7, 136.8, 132.1, 124.2, 117.3, 115.2, 100.9, 81.0, 56.9, 56.5, 52.1, 48.3, 48.1, 38.3, 38.0, 34.1, 27.9, 25.9, 22.8, 17.8.

FTIR (thin film) v max: 2964, 2923, 2850, 1652, 1604, 1459, 1373, 1228, 1046, 1001 cm⁻¹.


TLC Rf = 0.46 (6:4 hexane:EtOAc).
A CH₂Cl₂ (1 mL) solution of 302 (2.6 mg, 7.8 µmol, 1 equiv) in a 10-mL pear-shaped flask was cooled to –78 ºC, and trimethylsilyl trifluoromethanesulfonate (2 µL, 10 µmol, 1.5 equiv) was added. After stirring the resulting yellow solution at –78 ºC for 10 min, it was quenched at –78 ºC with sat. aq. NaHCO₃, diluted with H₂O, and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a white residue. Flash column chromatography (4 mL SiO₂, 9:1 hexane:EtOAc) afforded 1.3 mg (4.1 µmol, 52% yield) of 306 as a white residue.

¹H NMR (600 MHz; CDCl₃) δ: 5.87 (dddd, J = 17.1, 10.2, 8.9, 5.7 Hz, 1H), 5.07 (t, J = 7.2 Hz, 1H), 5.05-4.99 (m, 2H), 3.92 (d, J = 5.6 Hz, 1H), 3.46 (s, 3H), 2.58 (dd, J = 14.0, 5.7 Hz, 1H), 2.52 (ddd, J = 15.1, 10.9, 7.6 Hz, 1H), 2.38 (ddd, J = 15.1, 7.4, 4.1 Hz, 1H), 2.16-2.10 (m, 2H), 2.10-2.04 (m, 1H), 2.01 (dd, J = 13.7, 5.6 Hz, 1H), 1.95 (d, J = 13.7 Hz, 1H), 1.92-1.87 (m, 1H), 1.86-1.76 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.49 (m, 1H), 1.42 (ddd, J = 13.7, 11.9, 4.9 Hz, 1H), 1.20 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 212.9, 136.4, 132.3, 124.3, 117.7, 116.4, 79.1, 58.4, 52.2, 45.9, 41.6, 36.3, 36.0, 35.1, 33.8, 28.1, 25.9, 23.3, 19.0, 17.9.

**FTIR** (thin film) ν max: 2972, 2924, 1702, 1467, 1439, 1328, 1312, 1219, 1180, 1148, 995, 908 cm⁻¹.
**HRMS–ESI** (m/z): [M+H]$^+$ calculated for C$_{20}$H$_{30}$O$_3$, 319.2268; found, 319.2263.

**TLC** $R_f = 0.47$ (8:2 hexane:EtOAc).
(2S,3S)-3-((2,6-Dimethoxycyclohexa-2,5-dien-1-yl)methyl)-2-methyl-2-(4-methylpent-3-en-1-yl)oxirane (310):

A THF (6 mL) solution of 308 (250 mg, 1.78 mmol, 1 equiv) in a 25-mL recovery flask was cooled to –78 °C, and a pentane solution of tert-butyllithium (1.70 M, 2.2 mL, 3.8 mmol, 2.1 equiv) was added dropwise. After stirring the dark yellow solution at –78 °C for 1 h, 289 (873 mg, 3.75 mmol, 2.1 equiv) was added dropwise. The resulting colorless solution was allowed to slowly warm to rt. After stirring for 7 h, the resulting yellow solution was quenched at rt with H₂O and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (150 mL SiO₂, 99:1 → 98:2 → 95:5 → 9:1 → 8:2 hexane:EtOAc) afforded 234 mg (0.80 mmol, 45% yield) of 310 as a colorless oil.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.07 (t, J = 7.4 Hz, 1H), 4.73 (t, J = 3.6 Hz, 1H), 4.71 (t, J = 3.6 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 3.01 (quintet, J = 5.3 Hz, 1H), 2.87-2.76 (m, 2H), 2.72 (dd, J = 8.1, 4.4 Hz, 1H), 2.12 (dt, J = 14.0, 4.9 Hz, 1H), 2.01 (q, J = 7.4 Hz, 2H), 1.81 (ddd, J = 14.0, 8.1, 4.6 Hz, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.58-1.53 (m, 1H), 1.39-1.33 (m, 1H), 1.19 (s, 3H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 154.2, 131.9, 124.2, 91.77, 91.73, 77.2, 61.3, 61.1, 54.6, 54.3, 39.22, 39.14, 29.3, 25.9, 24.7, 23.9, 17.8, 16.7.

**FTIR** (thin film) νₘₐₓ: 2963, 2931, 2856, 1693, 1596, 1474, 1383, 1258, 1204, 1146, 1120, 774 cm⁻¹.

**HRMS–ESI** (m/z): [M+Na]⁺ calculated for C₁₈H₂₈O₃, 315.1931; found, 315.1927.

**TLC** Rₜ = 0.53 (8:2 hexane:EtOAc).
(S)-2-((S)-4,8-Dimethoxyspiro[2.5]octa-4,7-dien-1-yl)-6-methylhept-5-en-2-ol (311):

A THF (0.8 mL) solution of 310 (50 mg, 0.17 mmol, 1 equiv) in a 10-mL pear-shaped flask was cooled to –78 °C, and a pentane solution of tert-butyllithium (1.70 M, 111 µL, 0.19 mmol, 1.1 equiv) was added dropwise. The reaction was allowed to slowly warm to –30 °C over 1 h. The reaction was subsequently cooled to –78 °C, and prenyl bromide (40. µL, 0.34 mmol, 2 equiv) was added. After warming the reaction to rt over 2.5 h, it was quenched at rt with H2O and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow oil. Flash column chromatography (30 mL SiO₂, 98:2 → 95:5 hexane:EtOAc) afforded 13.6 mg (47 µmol, 27% yield) of 311 as a colorless oil as well as 14.4 mg (49 µmol, 29% recovery) of 310 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.14 (t, J = 7.1 Hz, 1H), 4.96 (t, J = 3.8 Hz, 1H), 4.64 (t, J = 3.6 Hz, 1H), 3.98 (s, 1H), 3.58 (s, 3H), 3.47 (s, 3H), 3.00 (dt, J = 21.2, 2.9 Hz, 1H), 2.93 (dt, J = 21.2, 4.6 Hz, 1H), 2.21-2.11 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.55 (t, J = 8.5 Hz, 2H), 1.49-1.45 (m, 2H), 1.39-1.35 (m, 1H), 1.17 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 154.0, 152.1, 131.3, 125.3, 95.9, 90.2, 69.7, 54.84, 54.69, 45.1, 35.7, 28.4, 25.93, 25.90, 24.0, 22.7, 17.9, 11.4.

FTIR (thin film) νmax: 3506, 2964, 2928, 2833, 1683, 1651, 1595, 1464, 1446, 1394, 1375, 1228, 1206, 1135, 1105, 1042, 979, 770 cm⁻¹.


FTIR (thin film) νmax: 0.43 (8:2 hexane:EtOAc).
1,5-Dimethoxy-6-(3-methylbut-2-en-1-yl)cyclohexa-1,4-diene (312):

*Preparation of barium iodide.* Using a hand drill hammer, a chisel, and a lead brick positioned on the laboratory floor, mineral oil-coated barium rod was portioned into approximately 25 mm segments. Each segment was flattened using the hammer to yield a barium pancake no thicker than 3 mm. A well-sharpened pair of metal cutting snips was used to cut each pancake into 1 mm × 2 mm × 10 mm slivers, which were washed with hexane. A 2-neck 2-L round-bottom flask outfitted with a reflux condenser was charged with barium slivers (63.7 g, 464 mmol, 1.3 equiv) and THF (500 mL). The flask was placed in a rt H2O bath, and iodine (99.6 g, 392 mmol, 1.1 equiv) was added in four portions over 20 min with vigorous stirring. After subsequently stirring vigorously for 4 d at reflux, a white-gray slurry of barium iodide was produced.

A THF (800 mL) solution of 308 (50.0 g, 357 mmol, 1 equiv) in a 2-neck 3-L round-bottom flask outfitted with an equal pressure dropping funnel was cooled using a –78 ºC dry ice/acetone bath. The dropping funnel was charged with a pentane solution of tert-butyllithium (1.56 M, 250. mL, 392 mmol, 1.1 equiv), and this solution was added in portions over 1 h, maintaining an internal reaction temperature ≤ –65 ºC. The resulting yellow slurry was stirred for an additional 45 min at –78 ºC. The THF slurry of barium iodide (preparation described above) was poured into this solution under a heavy stream of Ar, and the resulting yellow-green slurry was stirred at –78 ºC for 45 min. A THF (50 mL) solution of prenyl chloride (44.2 mL, 392 mmol, 1.1 equiv) was added via cannula over 10 min, maintaining an internal reaction temperature ≤ –60 ºC, and the yellow-green slurry was allowed to slowly warm to –30 ºC over 45 min. The resulting green-gray slurry was then quenched at –30 ºC with H2O. After warming

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687 If a hand drill hammer and chisel are unavailable, a standard claw hammer and an appropriately-shaped shelving bracket may be employed in this step.

688 Directly following the barium iodide addition, the internal reaction temperature rose to –30 ºC but returned to –70 ºC within 10 min.
to room temperature, the mixture was diluted with hexane and extracted thrice with 9:1 hexane:EtOAc. The organic extracts were combined, sequentially washed twice with H₂O and once with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to a pale yellow oil. Short-path distillation (6 mmHg, 76-82 °C) afforded 67.46 g (323.9 mmol, 91% yield) of **312** as a colorless oil.

**1H NMR** (600 MHz; CDCl₃) δ: 4.99 (t, *J* = 7.4 Hz, 1H), 4.68 (dd, *J* = 4.6, 3.0 Hz, 2H), 3.53 (s, 6H), 2.94–2.91 (m, 1H), 2.78 (ddt, *J* = 20.7, 6.0, 3.0 Hz, 1H), 2.72 (dq, *J* = 20.7, 4.6 Hz, 1H), 2.41 (dd, *J* = 7.4, 4.7 Hz, 2H), 1.64 (s, 3H), 1.55 (s, 3H).

**13C NMR** (125 MHz; CDCl₃) δ: 154.5, 132.8, 120.6, 91.9, 54.4, 41.3, 28.5, 26.1, 24.7, 17.8.

**FTIR** (thin film) ν<sub>max</sub>: 2995, 2933, 2910, 2825, 1695, 1663, 1446, 1394, 1230, 1206, 1148, 1048, 965, 775 cm<sup>-1</sup>.

**HRMS–ESI** (m/z): [M+Na]<sup>+</sup> calculated for C₁₃H₂₀O₂, 231.1356; found, 231.1350.

**TLC** *R*ₜ = 0.77 (9:1 hexane:EtOAc).
(2S,3S)-3-((2,6-Dimethoxy-1-(3-methylbut-2-en-1-yl)cyclohexa-2,5-dien-1-yl)methyl)-2-methyl-2-(4-methylpent-3-en-1-yl)oxirane (309):

A THF (140 mL) solution of 312 (5.68 g, 27.3 mmol, 1 equiv) in a 500-mL recovery flask was cooled to –78 ºC, and a c-Hex solution of sec-butyllithium (1.43 M, 28.6 mL, 40.9 mmol, 1.5 equiv) was added portionwise over 10 min. After stirring the bright orange solution at –78 ºC for 1 h, it was warmed to –30 ºC over 90 min and maintained at –30 ºC for an additional 30 min. The dark red solution was then cooled to –78 ºC, and a THF (25 mL) solution of 289 (9.54 g, 40.9 mmol, 1.5 equiv) was added over 2 min. The resulting bright yellow solution was allowed to slowly warm to rt. After stirring for 3 h, the reaction was quenched at rt with H₂O and extracted thrice with EtOAc. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (300 mL SiO₂, 98:2 → 95:5 hexane:EtOAc) afforded 4.97 (13.8 mmol, 51% yield) of 309 as a pale yellow oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.05 (t, J = 6.7 Hz, 1H), 4.90 (t, J = 7.1 Hz, 1H), 4.76 (t, J = 3.5 Hz, 1H), 4.72 (t, J = 3.5 Hz, 1H), 3.51 (s, 3H), 3.47 (s, 3H), 2.75 (m, 2H), 2.63 (dd, J = 8.1, 3.9 Hz, 1H), 2.35-2.28 (m, 2H), 2.04 (dd, J = 13.7, 3.9 Hz, 1H), 1.97 (q, J = 7.9 Hz, 2H), 1.76 (dd, J = 13.7, 8.1 Hz, 1H), 1.66 (s, 3H), 1.62 (s, 3H), 1.58-1.56 (m, 4H), 1.54 (s, 3H), 1.27 (dt, J = 13.6, 8.3 Hz, 1H), 1.18 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 13-C NMR (126 MHz; CDCl₃): δ 154.11, 154.05, 132.5, 131.8, 124.2, 120.7, 93.02, 92.92, 61.4, 61.1, 54.5, 54.1, 46.2, 39.5, 34.6, 34.1, 26.1, 25.9, 24.3, 24.1, 17.85, 17.79, 16.8.

FTIR (thin film) νmax: 2965, 2924, 2855, 2930, 1693, 1658, 1450, 1380, 1205, 1151, 1122, 1075, 973, 778, 688 cm⁻¹.

HRMS–ESI (m / z): [M+Na]⁺ calculated for C₂₃H₃₆O₃, 383.2557; found, 383.2554.
TLC $R_f = 0.54$ (8:2 hexane:EtOAc).
(2S,3S,3aR,7R,7aS)-6,7a-Dimethoxy-3-methyl-7-(3-methylbut-2-en-1-yl)-3-(4-methylpent-3-en-1-yl)-2,3,3a,4,7,7a-hexahydro-2,7-methanobenzofuran (317):

Method A, using 2,6-di-tert-butyl-4-methylpyridine:

A CH₂Cl₂ (100 mL) solution of 309 (1.88 g, 5.21 mmol, 1 equiv) and 2,6-di-tert-butyl-4-methylpyridine (2.14 g, 10.4 mmol, 2 equiv) in a 250-mL round-bottom flask was cooled to –78 ºC, and trimethylsilyl trifluoromethanesulfonate (1.13 mL, 6.26 mmol, 1.2 equiv) was added. After stirring the golden yellow solution at –78 ºC for 45 min, it was quenched at –78 ºC with sat. aq. NaHCO₃. After warming the mixture to rt, it was diluted with H₂O and brine, and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil.

Flash column chromatography (400 mL SiO₂, 99:1 → 95:5 hexane:EtOAc) afforded 1.70 g (4.72 mmol, 90% yield) of 317 as a colorless oil.

Method B, using 2,6-lutidine:

A CH₂Cl₂ (50 mL) solution of 309 (3.62 g, 10.0 mmol, 1 equiv) and 2,6-lutidine (2.4 mL, 30. mmol, 3 equiv) in a 200-mL round-bottom flask was cooled to –78 ºC, and trimethylsilyl trifluoromethanesulfonate (3.6 mL, 20. mmol, 2 equiv) was added. After stirring the golden yellow solution at –78 ºC for 45 min, it was quenched at –78 ºC with sat. aq. NaHCO₃, warmed to rt, and extracted thrice with EtOAc. The organic extracts were combined, washed sequentially with 2 N HCl, H₂O, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale orange oil. Flash column chromatography (250 mL SiO₂, 1:1 → 1:3 hexane:CH₂Cl₂) afforded 2.84 g (7.88 mmol, 79% yield) of 317 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.34 (t, J = 7.1 Hz, 1H), 5.03 (t, J = 7.1 Hz, 1H), 4.52 (dd, J = 5.6, 2.2 Hz, 1H), 3.74 (d, J = 5.1 Hz, 1H), 3.48 (s, 3H), 3.46 (s, 3H), 2.36 (dd, J = 14.8, 6.8 Hz, 1H), 2.22-2.17
(m, 2H), 2.05-2.01 (m, 2H), 1.98-1.96 (m, 1H), 1.82 (d, J = 12.4 Hz, 1H), 1.78 (dd, J = 12.4, 5.1 Hz, 1H), 1.70 (s, 3H), 1.69-1.65 (m, 4H), 1.61 (s, 3H), 1.58 (s, 3H), 1.45 (td, J = 13.1, 4.7 Hz, 1H), 1.22 (td, J = 13.1, 4.6 Hz, 1H), 1.14 (s, 3H).

$^1$H NMR (125 MHz; CDCl₃) δ: 13-C NMR (126 MHz; CDCl₃): δ 158.5, 131.6, 131.1, 124.9, 123.6, 112.7, 90.6, 78.9, 54.6, 51.4, 46.5, 44.4, 42.0, 39.4, 33.6, 32.8, 28.2, 26.4, 25.9, 22.9, 20.1, 17.99, 17.85.

FTIR (thin film) $\nu_{\text{max}}$: 2965, 2931, 1670, 1451, 1374, 1214, 1165, 1126, 1079, 1003, 945, 839, 804 cm⁻¹.

HRMS–ESI (m / z): [M+H]$^+$ calculated for C₂₃H₃₆O₃, 361.2737; found, 361.2730.

TLC $R_f = 0.50$ (9:1 hexane:EtOAc).
(2S,3S,3aS,7R,7aS)-6,7a-Dimethoxy-3-methyl-7-(3-methylbut-2-en-1-yl)-3-(4-methylpent-3-en-1-yl)-3,3a,7,7a-tetrahydro-2,7-methanobenzofuran-4(2H)-one (318):

An EtOAc (30 mL) slurry of 317 (3.30 g, 9.15 mmol, 1 equiv), cesium carbonate (12.9 g, 36.6 mmol, 4 equiv), and a nonane solution of tert-butyl hydroperoxide (5.5 M, 6.7 mL, 27 mmol, 4 equiv) in a 3-neck 200-mL round-bottom flask was sparged for 10 min with O₂ and subsequently cooled to –78 ºC with vigorous O₂ bubbling. An EtOAc (25 mL) solution of [bis(trifluoroacetoxy)iodo]benzene (11.8 g, 27.5 mmol, 3 equiv) was added dropwise over 8 min, followed by an EtOAc (5 mL) rinse. After stirring the resulting yellow slurry at –78 ºC for 1 h, it was quenched at –78 ºC with sat. aq. Na₂S₂O₃ and warmed to rt with vigorous stirring over 45 min. The mixture was then extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (250 mL SiO₂, 98:2 CH₂Cl₂:Et₂O) afforded 1.01 g (2.69 mmol, 30% yield) of 318 as a pale yellow oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.34 (s, 1H), 5.29 (t, J = 6.4 Hz, 1H), 4.98 (t, J = 7.1 Hz, 1H), 3.89 (d, J = 5.8 Hz, 1H), 3.70 (s, 3H), 3.47 (s, 3H), 2.68 (s, 1H), 2.42 (dd, J = 14.9, 6.3 Hz, 1H), 2.35 (dd, J = 14.9, 8.0 Hz, 1H), 2.06 (d, J = 13.0 Hz, 1H), 2.03-1.97 (m, 1H), 1.93 (dd, J = 13.0, 5.8 Hz, 1H), 1.74-1.67 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.38 (ddd, J = 14.0, 12.1, 4.8 Hz, 1H), 1.34-1.29 (m, 1H), 1.27 (s, 3H).

¹³C NMR (125 MHz; CDCl₃) δ: 197.9, 181.2, 132.9, 132.0, 124.2, 122.1, 115.4, 100.8, 80.8, 56.8, 56.4, 52.2, 48.6, 48.1, 38.8, 34.2, 32.2, 27.9, 26.3, 25.8, 22.8, 17.97, 17.84.

FTIR (thin film) νmax: 2970, 2927, 1651, 1604, 1452, 1374, 1228, 1071, 1003 cm⁻¹.

HRMS–ESI (m / z): [M+H]⁺ calculated for C₂₅H₃₄O₄, 375.2530; found, 375.2528.

TLC Rₜ = 0.25 (7:3 hexane:EtOAc).
(2S,3aR,6R,7S,7aS,8S)-6-(tert-Butylperoxy)-7a-methoxy-8-methyl-3a-(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)hexahydro-2,7-methanobenzofuran-4(2H)-one (319):

A PhH (2 mL) solution of 317 (21.4 mg, 59 µmol, 1 equiv) in a 2-dram scintillation vial was treated with 322 (40 mg, 0.12 mmol, 2 equiv) and potassium carbonate (33 mg, 0.24 mmol, 4 equiv). After stirring the reaction at rt for 3 d, it was diluted with 1:1 hexane:EtOAc and filtered through a short plug of SiO₂, rinsing with 1:1 hexane:EtOAc. The filtrate was concentrated in vacuo to a white residue. Flash column chromatography (25 mL SiO₂, 992:8 CH₂Cl₂:Et₂O) afforded 7 mg (20 µmol, 26% yield) of 319 as a colorless oil and 1 mg (3 µmol, 5% yield) of 320 as a colorless residue.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.39 (t, J = 7.2 Hz, 1H), 5.02 (t, J = 6.9 Hz, 1H), 4.73 (d, J = 5.3 Hz, 1H), 4.46 (dd, J = 5.3, 1.1 Hz, 1H), 3.75 (d, J = 5.3 Hz, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 2.46 (s, 1H), 2.37 (dd, J = 14.7, 6.9 Hz, 1H), 2.28 (dd, J = 14.7, 7.3 Hz, 1H), 2.04-1.93 (m, 1H), 1.82 (dd, J = 12.6, 5.3 Hz, 1H), 1.77 (d, J = 12.6 Hz, 1H), 1.69 (s, 3H), 1.68 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.36 (td, J = 12.8, 4.9 Hz, 1H), 1.29-1.26 (m, 1H), 1.25 (s, 9H), 1.21 (s, 3H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 164.9, 131.84, 131.68, 124.6, 123.4, 112.3, 89.0, 80.1, 79.1, 77.4, 55.0, 52.2, 47.0, 44.14, 43.95, 38.3, 34.0, 32.1, 27.9, 26.9, 26.4, 25.9, 23.0, 17.99, 17.89.

Key 1D nOe correlation.

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689 322 was prepared as described in ref. 636.
FTIR (thin film) $v_{\text{max}}$: 2970, 2925, 2869, 1657, 1450, 1374, 1363, 1225, 1196, 1169, 1069, 1005, 990, 880 cm$^{-1}$.

HRMS–ESI (m/z): [M+H]$^+$ calculated for C$_{27}$H$_{44}$O$_5$, 449.3262; found, 449.3248.

TLC $R_f = 0.25$ (7:3 hexane:EtOAc).
**3,3a,7,7a-tetrahydro-2,7-methanobenzofuran-4(2H)-one (320):**

A PhH (1 mL) solution of 317 (17.6 mg, 49 µmol, 1 equiv) in a 10-mL pear-shaped flask was cooled to 0 °C, and an aqueous solution of tert-butyl hydroperoxide (70% by weight, 14 µL, 98 µmol, 2 equiv) and pyridinium dichromate (37 mg, 98 µmol, 2 equiv) were added in sequence. The reaction was allowed to slowly warm to rt over 5 h, whereupon it was passed through a short plug of SiO₂, rinsing with EtOAc. The filtrate was concentrated in vacuo to an orange oil. Flash column chromatography (30 mL SiO₂, 9:1 → 8:2 hexane:EtOAc) afforded 6.2 mg (18 µmol, 37% yield) of 320 as a pale yellow residue and 2.5 mg (6.7 µmol, 14% yield) of 318 as a pale yellow residue.

**1H NMR** (600 MHz; CDCl₃) δ: 6.74 (dd, J = 10.2, 7.0 Hz, 1H), 6.06 (d, J = 10.2 Hz, 1H), 5.37 (t, J = 7.2 Hz, 1H), 5.01 (t, J = 7.2 Hz, 1H), 3.88 (d, J = 6.0 Hz, 1H), 3.47 (s, 3H), 2.59 (d, J = 7.0 Hz, 1H), 2.46 (dd, J = 14.7, 6.2 Hz, 1H), 2.34 (dd, J = 14.7, 8.2 Hz, 1H), 1.98 (d, J = 13.6 Hz, 1H), 1.95-1.92 (m, 1H), 1.89 (dd, J = 13.6, 6.0 Hz, 1H), 1.84-1.77 (m, 1H), 1.71 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.44-1.39 (m, 1H), 1.31-1.23 (m, 4H).

**13C NMR** (125 MHz; CDCl₃) δ: 201.5, 146.4, 132.9, 132.3, 129.2, 124.0, 122.3, 116.2, 80.8, 55.5, 52.5, 48.5, 46.1, 35.6, 34.8, 30.5, 27.0, 26.3, 25.9, 23.4, 18.00, 17.87.

**FTIR** (thin film) νₘₐₓ: 2966, 2925, 2870, 1728, 1673, 1449, 1375, 1220, 1005, 833 cm⁻¹.


**TLC** Rₜ = 0.38 (8:2 hexane:EtOAc).
(2S,3aR,7R,7aS,8S)-7a-Methoxy-8-methyl-3a-(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)hexahydro-2,7-methanobenzofuran-4(2H)-one (321): A MeCN (0.4 mL) solution of 317 (14.0 mg, 39 µmol, 1 equiv) and a nonane solution of tert-butyl hydroperoxide (5.5 M, 35 µL, 0.19 mmol, 5 equiv) in a 2-dram scintillation vial was treated with ceric ammonium nitrate (43 mg, 78 µmol, 2 equiv). After stirring the reaction for 10 min at rt, it was quenched with sat. aq. NaHCO$_3$, diluted with H$_2$O, and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a colorless oil. Flash column chromatography (25 mL SiO$_2$, 95:5 → 9:1 hexane:EtOAc) afforded 3.9 mg (11 µmol, 29% yield) of 321 as a white flocculent solid.

$^1$H NMR (600 MHz; CDCl$_3$) δ: 5.16 (t, $J$ = 7.3 Hz, 1H), 5.06 (t, $J$ = 7.1 Hz, 1H), 3.91 (d, $J$ = 5.7 Hz, 1H), 3.46 (s, 3H), 2.52 (ddd, $J$ = 14.8, 11.0, 7.6 Hz, 1H), 2.43-2.35 (m, 2H), 2.20 (dd, $J$ = 14.5, 9.2 Hz, 1H), 2.12-2.04 (m, 2H), 1.97 (d, $J$ = 13.7 Hz, 1H), 1.92-1.86 (m, 2H), 1.85-1.75 (m, 2H), 1.69 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.49 (td, $J$ = 12.8, 5.1 Hz, 1H), 1.41 (td, $J$ = 12.8, 4.8 Hz, 1H), 1.20 (s, 3H).

$^{13}$C NMR (125 MHz; CDCl$_3$) δ: 213.2, 133.8, 132.2, 124.3, 121.5, 116.7, 79.0, 59.1, 52.2, 46.0, 41.5, 36.1, 35.5, 33.8, 29.9, 28.2, 26.3, 25.9, 23.3, 19.1, 18.06, 17.90.

FTIR (thin film) $v_{max}$: 2966, 2929, 2859, 1707, 1449, 1375, 1325, 1227, 1150, 1103, 999 cm$^{-1}$.

HRMS–ESI (m/z): [M+Na]$^+$ calculated for C$_{22}$H$_{34}$O$_3$, 369.2400; found, 369.2412.

TLC $R_f$ = 0.65 (7:3 hexane:EtOAc).
(2S,3S,3aS,7R,7aS)-6,7a-Dimethoxy-3-methyl-5,7-bis(3-methylbut-2-en-1-yl)-3-(4-methylpent-3-en-1-yl)-3,3a,7,7a-tetrahydro-2,7-methanobenzofuran-4(2H)-one (333): A THF (19 mL) solution of 318 (697 mg, 1.86 mmol, 1 equiv) in a 100-mL recovery flask was cooled to –78 ºC, and a freshly prepared THF solution of lithium 2,2,6,6-tetramethylpiperidide (0.53 M, 7.0 mL, 3.7 mmol, 2 equiv) was added. After stirring the resulting yellow-orange solution at –78 ºC for 20 min, a THF solution of lithium (2-thienyl)cyanocopper(I) (0.22 M, 17 mL, 3.7 mmol, 2 equiv) was added slowly over 10 min. The resulting brown slurry was allowed to slowly warm to –40 ºC over 20 min. After stirring the brown slurry at –40 ºC for an additional 30 min, it was cooled to –78 ºC, and prenyl bromide (1.1 mL, 9.3 mmol, 5 equiv) was added. The reaction was allowed to slowly warm to –40 ºC over 45 min, maintained at that temperature for 15 min, and subsequently quenched at –40 ºC with sat. aq. NH₄Cl. The mixture was warmed to rt and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a brown oil. Flash column chromatography (200 mL SiO₂, 95:5 hexane:EtOAc) afforded 586 mg (1.32 mmol, 71% yield) of 333 as a pale yellow oil.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.30 (t, J = 6.9 Hz, 1H), 4.99 (t, J = 6.7 Hz, 1H), 4.97 (t, J = 7.1 Hz, 1H), 3.87 (d, J = 5.7 Hz, 1H), 3.81 (s, 3H), 3.45 (s, 3H), 3.03-3.01 (m, 2H), 2.72 (s, 1H), 2.47 (dd, J = 15.2, 6.9 Hz, 1H), 2.31 (dd, J = 15.2, 6.9 Hz, 1H), 2.14 (d, J = 12.7 Hz, 1H), 1.99-1.95 (m, 1H), 1.92 (dd, J = 12.7, 5.7 Hz, 1H), 1.74-1.70 (m, 4H), 1.68 (s, 3H), 1.65 (s, 9H), 1.55 (s, 3H), 1.33-1.28 (m, 2H), 1.26 (s, 3H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 198.6, 176.3, 132.2, 131.88, 131.80, 124.2, 122.8, 122.34, 122.28, 114.6, 81.0, 61.0, 56.7, 52.1, 49.3, 48.4, 39.3, 34.3, 32.8, 27.9, 26.3, 25.84, 25.81, 22.75, 22.65, 18.10, 18.04, 17.8.
**FTIR** (thin film) $v_{\text{max}}$: 2968, 2925, 1655, 1617, 1449, 1375, 1345, 1331, 1233, 1074, 1009, 941, 829 cm$^{-1}$.

**HRMS–ESI** (m/z): [M+H]$^+$ calculated for C$_{28}$H$_{42}$O$_4$, 443.3156; found, 443.3150.

**TLC** $R_f = 0.65$ (7:3 hexane:EtOAc).
(15R,7S,8S,9S)-7,9-Dihydroxy-4,9-dimethoxy-8-methyl-3,5-bis(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-en-2-one (334):

A CH$_2$Cl$_2$ (5 mL) solution of 333 (91 mg, 0.21 mmol, 1 equiv) in a 10-mL recovery flask was cooled to –78 ºC, and a CH$_2$Cl$_2$ solution of bromodimethylborane (2.65 M, 0.78 mL, 2.1 mmol, 10 equiv) was added dropwise. The resulting yellow solution was stirred at –78 ºC for 20 min and sequentially quenched at –78 ºC with NEt$_3$ (2 mL) and sat. aq. NaHCO$_3$. The mixture was warmed to rt and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H$_2$O, sat. aq. NH$_4$Cl, and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a viscous yellow oil. Flash column chromatography (50 mL SiO$_2$, 9:1 → 8:2 hexane:EtOAc) afforded 85 mg (0.18 mmol, 89% yield) of 334 as a pale yellow oil.

$^1$H NMR (600 MHz; C$_6$D$_6$) δ: 5.56 (d, $J = 11.5$ Hz, 1H), 5.36 (t, $J = 7.3$ Hz, 1H), 5.29 (t, $J = 6.6$ Hz, 1H), 3.72 (s, 1H), 3.68 (dd, $J = 11.9$, 5.3 Hz, 1H), 3.54 (s, 3H), 3.35 (dd, $J = 15.2$, 6.4 Hz, 1H), 3.19-3.15 (m, 2H), 3.07 (s, 3H), 2.93 (dd, $J = 14.1$, 11.5 Hz, 1H), 2.91-2.84 (m, 1H), 2.27 (d, $J = 14.1$ Hz, 1H), 2.11-2.06 (m, 1H), 2.01 (dd, $J = 12.8$, 11.9 Hz, 1H), 1.85 (d, $J = 0.6$ Hz, 3H), 1.73 (s, 3H), 1.73-1.69 (m, 1H), 1.65-1.60 (m, 7H), 1.57 (s, 3H), 1.43 (s, 3H), 1.28 (td, $J = 12.7$, 4.4 Hz, 1H), 1.13 (s, 3H).

$^{13}$C NMR (125 MHz; C$_6$D$_6$) δ: 197.4, 171.2, 136.5, 131.9, 131.2, 125.8, 124.5, 123.44, 123.31, 100.3, 73.5, 61.9, 57.6, 52.5, 48.2, 41.0, 39.8, 37.5, 30.9, 26.1, 25.84, 25.80, 23.8, 22.3, 18.08, 17.97, 17.7, 17.4.
Key 1D nOe correlations.

**FTIR** (thin film) $\nu_{\text{max}}$: 3464 (br), 2969, 2928, 2859, 1665, 1615, 1450, 1376, 1329, 1235, 1087, 1040, 986, 928, 907, 858, 737 cm$^{-1}$.

**HRMS–ESI** ($m/z$): [M+H]$^+$ calculated for C$_{28}$H$_{44}$O$_5$, 461.3262; found, 461.3254.

**TLC** $R_f = 0.40$ (7:3 hexane:EtOAc).
(1S,5R,7S,8S)-7-Hydroxy-4-methoxy-8-methyl-3,5-bis(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (332):

A 4:1 acetone:H₂O (10 mL) solution of 334 (84.8 mg, 0.184 mmol, 1 equiv) in a 25-mL recovery flask was treated with pyridinium *para*-toluenesulfonate (231 mg, 0.920 mmol, 5 equiv). The flask was outfitted with a reflux condenser, and the reaction was heated to reflux. After refluxing for 11 h, the reaction was cooled to rt, diluted with H₂O, and extracted thrice with 1:1 hexane:EtOAc. The organic extracts were combined, sequentially washed with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to a colorless oil. Flash column chromatography (35 mL SiO₂, 8:2 hexane:EtOAc) afforded 72.8 mg (0.17 mmol, 92% yield) of 332 as a colorless oil.

**¹H NMR** (600 MHz; C₆D₆) δ: 5.37 (t, *J* = 6.9 Hz, 1H), 5.27 (t, *J* = 7.2 Hz, 1H), 5.19 (t, *J* = 6.5 Hz, 1H), 3.63 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.52 (s, 1H), 3.40 (s, 3H), 3.18 (dd, *J* = 15.4, 6.4 Hz, 1H), 3.10 (dd, *J* = 15.4, 6.7 Hz, 1H), 2.67-2.57 (m, 2H), 2.44 (dd, *J* = 14.5, 7.3 Hz, 1H), 1.92-1.87 (m, 2H), 1.75 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.64-1.60 (m, 5H), 1.58 (s, 6H), 1.39 (td, *J* = 12.9, 4.8 Hz, 2H), 0.84 (s, 3H), 0.64 (br s, 1H).

**¹³C NMR** (125 MHz; C₆D₆) δ: 204.5, 193.6, 173.6, 133.5, 132.3, 131.6, 126.1, 125.1, 123.0, 120.6, 72.1, 69.8, 61.7, 57.8, 46.3, 39.8, 38.4, 30.7, 26.00, 25.98, 25.7, 23.7, 22.1, 18.14, 18.01, 17.90, 15.7.

**FTIR** (thin film) ν max: 3488 (br), 2968, 2922, 2856, 1736, 1656, 1649, 1593, 1447, 1376, 1341, 1236, 1059 cm⁻¹.


**TLC** Rₚ = 0.36 (7:3 hexane:EtOAc).
(1S,2S,3S,5R)-6-Methoxy-2-methyl-5,7-bis(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-en-3-yl trifluoromethanesulfonate (338):

A CH₂Cl₂ (3 mL) solution of 332 (33.5 mg, 78.2 mmol, 1 equiv) in a 10-mL test tube was cooled to –43 ºC, and pyridine (44 µL, 0.54 mmol, 7 equiv) and trifluoromethanesulfonic anhydride (76 µL, 0.45 mmol, 6 equiv) were added sequentially. The resulting white slurry was allowed to slowly warm to 0 ºC over 100 min. The reaction was subsequently quenched at 0 ºC with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to an orange oil. Flash column chromatography (40 mL SiO₂, 9:1 hexane:EtOAc) afforded 36.8 mg (65.6 µmol, 84% yield) of 338 as a colorless oil.

¹H NMR (600 MHz; C₆D₆) δ: 5.22 (t, J = 6.9 Hz, 1H), 5.16-5.10 (m, 3H), 3.49 (s, 1H), 3.41 (s, 3H), 3.17 (dd, J = 15.3, 7.1 Hz, 1H), 2.97 (dd, J = 15.3, 6.5 Hz, 1H), 2.59-2.49 (m, 2H), 2.35 (dd, J = 13.1, 5.4 Hz, 1H), 2.29 (dd, J = 14.5, 7.5 Hz, 1H), 1.84 (dd, J = 13.1, 11.8 Hz, 1H), 1.80-1.73 (m, 1H), 1.72 (s, 3H), 1.64-1.62 (m, 4H), 1.61 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.49 (td, J = 12.9, 4.6 Hz, 1H), 0.75 (s, 3H).

¹³C NMR (125 MHz; C₆D₆) δ: 201.6, 191.8, 172.2, 134.5, 133.7, 132.6, 126.7, 123.7, 121.7, 119.5, 90.9, 69.4, 62.1, 57.4, 45.6, 37.8, 37.0, 30.3, 25.92, 25.86, 25.6, 23.5, 21.6, 18.13, 17.96, 17.87, 16.3.

¹⁹F NMR (470 MHz; C₆D₆) δ: −75.54 (s, 3F).

FTIR (thin film) νmax: 2972, 2916, 2860, 1741, 1661, 1597, 1414, 1244, 1210, 1146, 918 cm⁻¹.

HRMS–ESI (m / z): [M+Na]^+ calculated for C₂₈H₃₉F₃O₆S, 583.2312; found, 583.2293.

TLC Rₜ = 0.50 (9:1 hexane:EtOAc).
(2R,3R,3aR,5S,6aR)-6,6-Dimethoxy-3-methyl-5,6a-bis(3-methylbut-2-en-1-yl)-3-(4-methylpent-3-en-1-yl)hexahydro-2,5-methanopentalene-1,7(2H)-dione (339):

A MeOH (0.25 mL) solution of 338 (12 mg, 21 µmol) in a 10-mL test tube was cooled to 0 ºC, and a MeOH solution of sodium methoxide (0.5 M, 1 mL) was slowly added. The reaction was allowed to slowly warm to rt. After stirring for 20 h, the reaction was quenched at rt with sat. aq. NaHCO₃ and extracted thrice with 1:1 hexane:EtOAc. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 9.1 mg (21 µmol, >99% yield) of 339 as a white flocculent solid.

¹H NMR (600 MHz; C₆D₆) δ: 5.72 (t, J = 7.0 Hz, 1H), 5.45 (t, J = 7.9 Hz, 1H), 5.03 (t, J = 6.9 Hz, 1H), 3.20 (d, J = 2.0 Hz, 1H), 3.12 (s, 3H), 3.04 (s, 3H), 2.81-2.76 (m, 2H), 2.71 (dd, J = 14.8, 7.7 Hz, 1H), 2.39 (dd, J = 14.6, 7.9 Hz, 1H), 2.17 (dd, J = 12.4, 5.8 Hz, 1H), 2.10 (dd, J = 5.8, 1.9 Hz, 1H), 1.92 (d, J = 12.4 Hz, 1H), 1.87 (dt, J = 15.7, 7.5 Hz, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.63-1.61 (m, 4H), 1.52 (s, 3H), 1.18 (t, J = 8.5 Hz, 2H), 0.77 (s, 3H).

¹³C NMR (125 MHz; C₆D₆) δ: 203.7, 202.5, 133.6, 132.1, 131.6, 124.5, 122.3, 121.8, 107.7, 75.5, 66.24, 66.07, 51.9, 51.2, 47.0, 44.8, 38.9, 35.0, 27.0, 26.6, 26.07, 26.02, 25.8, 22.2, 19.3, 18.10, 18.01, 17.7.
Key 1D nOe correlations.

**FTIR** (thin film) $v_{\text{max}}$: 2968, 2926, 2856, 1754, 1706, 1443, 1375, 1308, 1195, 1171, 1141, 1097, 1072, 1046, 858 cm$^{-1}$.

**HRMS–ESI** ($m / z$): [M+H]$^+$ calculated for C$_{28}$H$_{42}$O$_4$, 443.3156; found, 443.3148.

**TLC** $R_f = 0.41$ (9:1 hexane:EtOAc).
(1S,2S,3S,5R)-6-Methoxy-2-methyl-5,7-bis(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-en-3-yl methanesulfonate (340):

A CH₂Cl₂ (3 mL) solution of 332 (38.7 mg, 90.3 µmol, 1 equiv) in a 10-mL test tube was cooled to 0 ºC, and triethylamine (65 µL, 0.47 mmol, 5.2 equiv) and methanesulfonyl chloride (30 µL, 0.39 mmol, 4.3 equiv) were added sequentially. After stirring the reaction at 0 ºC for 10 min, it was quenched with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a colorless residue. Flash column chromatography (40 mL SiO₂, 9:1 hexane:EtOAc) afforded 37.5 mg (74.0 µmol, 82% yield) of 340 as a colorless oil.

¹H NMR (600 MHz; C₆D₆) δ: 5.31 (t, J = 6.9 Hz, 1H), 5.24-5.19 (m, 2H), 4.92 (dd, J = 11.6, 5.3 Hz, 1H), 3.54 (s, 1H), 3.54 (s, 3H), 3.16 (dd, J = 15.4, 6.9 Hz, 1H), 3.10 (dd, J = 15.4, 6.5 Hz, 1H), 2.64-2.59 (m, 2H), 2.55 (dd, J = 13.3, 5.3 Hz, 1H), 2.38 (dd, J = 14.5, 7.5 Hz, 1H), 2.07 (s, 3H), 1.92 (dd, J = 13.3, 11.6 Hz, 1H), 1.85 (tt, J = 12.6, 6.2 Hz, 1H), 1.75 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.59-1.56 (m, 4H), 1.52 (td, J = 12.8, 4.9 Hz, 1H), 0.87 (s, 3H).

¹³C NMR (125 MHz; C₆D₆) δ: 202.9, 192.6, 173.3, 134.1, 133.2, 132.2, 127.0, 124.4, 122.2, 119.9, 81.5, 69.8, 62.2, 57.6, 45.7, 38.2, 37.73, 37.69, 30.3, 25.99, 25.95, 25.75, 23.6, 21.8, 18.15, 18.00, 17.94, 16.5.
Key 1D nOe correlations.

**FTIR** (thin film) $\nu_{\text{max}}$: 2968, 2918, 2857, 1738, 1658, 1597, 1449, 1360, 1342, 1236, 1178, 1061, 945, 862 cm$^{-1}$.

**HRMS–ESI** (m / z): [M+H]$^+$ calculated for C$_{28}$H$_{42}$O$_6$S, 507.2775; found, 507.2781.

**TLC** $R_f = 0.50$ (7:3 hexane:EtOAc).
(4aR,5aS,6S,6aR,6bR)-6b-Hydroxy-4-methoxy-6-methyl-3,4a-bis(3-methylbut-2-en-1-yl)-6-(4-methylpent-3-en-1-yl)-4a,5,5a,6,6a,6b-hexahydro-2H-cyclopropa[4,5]cyclopenta[1,2-b]pyran-2-one (341):

A MeOH solution of sodium methoxide (0.5 M, 1 mL) was slowly added to a 10-mL test tube cooled to 0 ºC containing 340 (5.5 mg, 11 µmol). The reaction was allowed to slowly warm to rt. After 18 h, the test tube was sealed and heated to 70 ºC. After stirring the reaction at 70 ºC for 9 h, it was cooled to rt, quenched with sat. aq. NaHCO₃, and extracted thrice with 1:1 hexane:EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow residue. Preparatory thin-layer chromatography (1 × 8:2 hexane:EtOAc) afforded 0.7 mg (1.6 µmol, 15% yield) of 341 as a colorless residue.

¹H NMR (600 MHz; C₆D₆) δ: 5.46 (t, J = 6.4 Hz, 1H), 5.39 (t, J = 6.4 Hz, 1H), 5.06 (t, J = 7.0 Hz, 1H), 3.47 (s, 3H), 3.37 (dd, J = 15.5, 6.5 Hz, 1H), 3.23 (dd, J = 15.5, 5.9 Hz, 1H), 3.13-3.13 (br s, 1H), 2.48 (dd, J = 14.5, 7.7 Hz, 1H), 2.44 (dd, J = 14.7, 5.6 Hz, 1H), 2.29 (dd, J = 14.7, 7.7 Hz, 1H), 1.99 (dt, J = 11.4, 5.6 Hz, 2H), 1.65 (s, 3H), 1.63 (s, 3H), 1.63 (s, 3H), 1.58 (d, J = 8.0 Hz, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.49 (dd, J = 14.5, 4.7 Hz, 1H), 1.45 (s, 3H), 1.27 (s, 3H), 1.13 (td, J = 7.8, 4.8 Hz, 1H), 0.99-0.96 (m, 2H).

¹³C NMR (125 MHz; C₆D₆) δ: 170.3, 165.1, 133.6, 132.2, 131.2, 124.9, 123.2, 120.2, 115.0, 108.0, 65.0, 61.6, 42.7, 41.8, 33.4, 31.9, 30.7, 28.1, 25.84, 25.81, 25.77, 25.6, 25.3, 18.1, 17.88, 17.71, 14.1.

FTIR (thin film) v_max: 3308 (br), 2964, 2920, 2854, 1677, 1631, 1452, 1376, 1342, 1224, 1190, 1093, 1005 cm⁻¹.

HRMS–ESI (m / z): [M+H]+ calculated for C₂₇H₄₀O₄, 429.2999; found, 429.2991.
TLC $R_f = 0.61$ (8:2 hexane:EtOAc).
(1\,S,5\,R,7\,S,8\,S)-7-Hydroxy-4,9,9-trimethoxy-8-methyl-3,5-bis(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-en-2-one (343):

A CH₂Cl₂ (12 mL) solution of 333 (210 mg, 0.47 mmol, 1 equiv) in a 25-mL recovery flask was cooled to –78 ºC, and a CH₂Cl₂ solution of bromodimethylborane (2.65 M, 1.8 mL, 4.7 mmol, 10 equiv) was added. The resulting yellow solution was stirred at –78 ºC for 10 min and sequentially quenched at –78 ºC with 1:1 NEt₃:MeOH (10 mL) and sat. aq. NaHCO₃. The mixture was warmed to rt and extracted thrice with EtOAc. The organic extracts were combined, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a brown oil. Flash column chromatography (100 mL SiO₂, 9:1 hexane:EtOAc) afforded 149 mg (0.31 mmol, 67% yield) of 343 as a pale yellow oil.

\(^1\)H NMR (600 MHz; C₆D₆) δ: 5.27 (t, \(J = 7.1\) Hz, 1H), 4.94 (t, \(J = 7.2\) Hz, 1H), 4.90 (t, \(J = 6.5\) Hz, 1H), 3.76 (s, 3H), 3.47 (ddd, \(J = 11.9, 6.5, 5.4\) Hz, 1H), 3.23 (s, 3H), 3.10 (s, 3H), 3.02 (dd, \(J = 15.3, 6.5\) Hz, 1H), 2.89 (dd, \(J = 15.3, 6.5\) Hz, 1H), 2.82 (s, 1H), 2.57 (dd, \(J = 15.4, 7.6\) Hz, 1H), 2.26-2.21 (m, 2H), 1.82-1.74 (m, 2H), 1.68 (dd, \(J = 13.2, 5.4\) Hz, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.55 (s, 6H), 1.54 (s, 3H), 1.52 (s, 3H), 1.30 (td, \(J = 12.8, 4.7\) Hz, 1H), 1.17-1.13 (m, 1H), 1.00 (s, 3H), 0.87 (td, \(J = 12.8, 4.6\) Hz, 1H).

\(^13\)C NMR (125 MHz; CDCl₃) δ: 198.7, 174.5, 132.3, 131.8, 131.4, 125.1, 123.6, 122.51, 122.39, 103.1, 74.0, 62.3, 59.2, 53.7, 51.1, 50.5, 40.5, 39.8, 36.1, 30.7, 26.2, 25.93, 25.86, 23.4, 21.8, 18.2, 17.95, 17.89.
Key 1D nOe correlations.

**FTIR** (thin film) $\nu_{\text{max}}$: 3468 (br), 2965, 2925, 2857, 1683, 1613, 1451, 1376, 1336, 1225, 1153, 1100, 1065 cm$^{-1}$.

**HRMS–ESI** (m / z): [M+H]$^+$ calculated for C$_{29}$H$_{46}$O$_5$, 475.3418; found, 475.3406.

**TLC** $R_f = 0.47$ (8:2 hexane:EtOAc).
(1S,2S,3S,5R)-6,9,9-Trimethoxy-2-methyl-5,7-bis(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8-oxobicyclo[3.3.1]non-6-en-3-yl trifluoromethanesulfonate (344):

A CH$_2$Cl$_2$ (2 mL) solution of 343 (42 mg, 88 µmol, 1 equiv) and pyridine (43 µL, 0.53 mmol, 6 equiv) in a 10-mL recovery flask was cooled to –40 ºC, and trifluoromethanesulfonic anhydride (74 µL, 0.44 mmol, 5 equiv) was added. After allowing the reaction to slowly warm from –40 ºC to –10 ºC over 75 min, it was quenched at –10 ºC with sat. aq. NaHCO$_3$ and extracted thrice with EtOAc. The organic extracts were combined, washed sequentially with H$_2$O, sat. aq. NH$_4$Cl, and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a brown residue. Flash column chromatography (30 mL SiO$_2$, 95:5 hexane:EtOAc) afforded 37 mg (63 µmol, 71% yield) of 344 as a colorless oil.

$^1$H NMR (600 MHz; C$_6$D$_6$) δ: 5.56 (t, J = 6.9 Hz, 1H), 5.27-5.22 (m, 2H), 5.19 (dd, J = 12.0, 5.3 Hz, 1H), 3.58 (s, 3H), 3.33 (dd, J = 14.9, 7.4 Hz, 1H), 3.09 (s, 1H), 3.02 (dd, J = 14.9, 6.4 Hz, 1H), 2.95 (s, 3H), 2.91 (s, 3H), 2.80-2.78 (m, 1H), 2.63 (dd, J = 15.7, 7.2 Hz, 1H), 2.37-2.30 (m, 2H), 2.18 (dd, J = 12.9, 5.3 Hz, 1H), 1.99 (tt, J = 12.5, 6.1 Hz, 1H), 1.80 (s, 3H), 1.70 (s, 3H), 1.68-1.64 (m, 10H), 1.57 (s, 3H), 1.37 (td, J = 12.9, 4.3 Hz, 1H), 1.19 (s, 3H).

$^{13}$C NMR (125 MHz; C$_6$D$_6$) δ: 196.2, 172.5, 133.3, 132.0, 131.6, 128.4, 124.5, 122.37, 122.18, 102.5, 94.7, 62.1, 59.7, 54.3, 50.46, 50.42, 40.3, 39.8, 34.1, 31.3, 25.98, 25.94, 25.7, 23.5, 21.7, 19.3, 18.03, 17.90, 17.82.

$^{19}$F NMR (470 MHz; C$_6$D$_6$) δ: –75.71 (s, 3F).

FTIR (thin film) $\nu_{\text{max}}$: 2973, 2917, 2859, 1739, 1659, 1596, 1413, 1243, 1207, 1145, 915, 881, 626 cm$^{-1}$.

HRMS–ESI (m / z): [M+H]$^+$ calculated for C$_{30}$H$_{45}$F$_3$O$_7$S, 607.2911; found, 607.2892.

TLC $R_f$ = 0.61 (8:2 hexane:EtOAc).
A THF (1.2 mL) solution of 344 (7.0 mg, 12 mmol, 1 equiv) in a 10-mL pear-shaped flask was cooled to –78 °C, and a freshly prepared THF solution of lithium diisopropylamide (0.088 M, 0.52 mL, 46 µmol, 4 equiv) was added. After stirring the reaction at –78 °C for 1 h, it was allowed to slowly warm to –20 °C over 1 h. The reaction was quenched at –20 °C with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow residue. Preparatory thin-layer chromatography (2 × 9:1 hexane:EtOAc) afforded 2.3 mg (5.0 µmol, 42% yield) of 345 as a colorless residue and 0.1 mg (0.2 µmol, 10% recovery) of 345 as a colorless residue.

¹H NMR (600 MHz; C₆D₆) δ: 6.19 (t, J = 7.9 Hz, 1H), 5.59 (t, J = 7.4 Hz, 1H), 5.15 (t, J = 7.4 Hz, 1H), 4.85 (s, 1H), 4.81 (s, 1H), 3.78 (dd, J = 15.6, 8.2 Hz, 1H), 3.69 (dd, J = 15.6, 7.4 Hz, 1H), 3.18 (s, 3H), 3.06 (s, 3H), 3.00 (s, 3H), 2.87 (s, 1H), 2.73 (dd, J = 16.0, 8.5 Hz, 1H), 2.49 (dd, J = 16.0, 6.4 Hz, 1H), 2.38 (dd, J = 10.1, 7.7 Hz, 1H), 2.32 (dtd, J = 19.2, 6.8, 5.4 Hz, 1H), 2.18 (d, J = 7.7 Hz, 1H), 2.01 (tt, J = 12.8, 6.2 Hz, 1H), 1.90 (d, J = 10.1 Hz, 1H), 1.77 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.62 (s, 4H), 1.43 (td, J = 13.1, 4.4 Hz, 1H), 1.26 (s, 3H), 1.09 (dd, J = 13.1, 12.4, 4.5 Hz, 1H).

¹³C NMR (125 MHz; C₆D₆) δ: 196.9, 144.5, 138.4, 131.9, 131.4, 130.8, 125.1, 123.4, 111.2, 103.9, 87.4, 62.2, 57.6, 52.5, 49.8, 48.1, 44.6, 41.3, 37.1, 36.0, 27.8, 26.3, 25.9, 25.3, 22.8, 22.1, 21.4, 18.0, 17.7.
FTIR (thin film) $\nu_{\text{max}}$: 2965, 2933, 2857, 1708, 1440, 1376, 1354, 1204, 1123, 1079, 1057, 888 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{29}$H$_{44}$O$_4$, 479.3132; found, 479.3133.

TLC $R_f = 0.49$ (9:1 hexane:EtOAc).
(2R,3S,3aS,5R,7aR)-7a-(sec-Butyl)-6-methoxy-3-methyl-5,7-bis(3-methylbut-2-en-1-yl)-3-(4-methylpent-3-en-1-yl)-3,3a,5,7a-tetrahydro-2,5-methanobenzofuran-4(2H)-one (348):

A THF (1 mL) solution of 344 (15 mg, 25 µmol, 1 equiv) in a 10-mL pear-shaped flask was cooled to –78 ºC, and a c-Hex solution of sec-butyllithium (1.43 M, 69 µL, 99 µmol, 4 equiv) was added dropwise. After stirring the resulting yellow-green solution at –78 ºC for 30 min, it was quenched at –78 ºC with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a white residue. Preparatory thin-layer chromatography (1 × 1:1 CH₂Cl₂:hexane) afforded 3.9 mg (8.3 µmol, 33% yield) of 348 as a white residue.

¹H NMR (600 MHz; C₆D₆) δ: 5.73-5.67 (m, 1H), 5.65-5.62 (m, 1H), 5.14 (t, J = 6.5 Hz, 1H), 3.85 (d, J = 16.0 Hz, 1H), 3.38 (s, 3H), 3.32-3.25 (m, 1H), 2.88-2.78 (m, 2H), 2.56-2.43 (m, 1H), 2.02-1.83 (m, 5H), 1.68 (s, 6H), 1.65 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H), 1.45-1.36 (m, 3H), 1.35 (d, J = 7.3 Hz, 3H, diastereomer A), 0.98 (d, J = 7.1 Hz, 1H, diastereomer B), 0.92 (t, J = 7.4 Hz, 3H diastereomer A), 0.87 (s, 3H), 0.85 (d, J = 7.5 Hz, 3H, diastereomer B).

¹³C NMR (125 MHz; C₆D₆) δ: 206.40, 206.36, 161.2, 161.0, 134.2, 133.4, 133.11, 133.09, 131.6, 131.3, 130.05, 130.02, 125.63, 125.53, 124.6, 121.1, 89.8, 89.36, 89.35, 84.97, 84.81, 81.7, 61.18, 61.14, 54.79, 54.74, 51.78, 51.75, 44.9, 44.6, 38.62, 38.50, 34.99, 34.91, 28.2, 27.39, 27.30, 26.05, 25.89, 25.85, 25.79, 25.75, 25.4, 23.8, 22.96, 22.89, 18.02, 17.99, 17.80, 17.77, 17.44, 17.43, 17.36, 14.9, 14.7, 13.99, 13.98, 13.2 (mixture of two diastereomers).

FTIR (thin film) ν max: 2966, 2929, 2874, 1724, 1634, 1451, 1376, 1231, 1124, 1042, 970 cm⁻¹.

HRMS–ESI (m / z): [M+H]⁺ calculated for C₃₁H₄₈O₃, 469.3676; found, 469.3677.
TLC $R_f = 0.55$ (1:1 hexane:EtOAc).
(1S,2S,3S,5R)-6,9,9-Trimethoxy-2-methyl-5,7-bis(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8-oxobicyclo[3.3.1]non-6-en-3-yl methanesulfonate (349):

A CH$_2$Cl$_2$ (2 mL) solution of 343 (30. mg, 63 µmol, 1 equiv) and pyridine (31 µL, 0.38 mmol, 6 equiv) in a 10-mL pear-shaped flask was cooled to 0 ºC, and methanesulfonyl chloride (25 µL, 0.32 mmol, 5 equiv) was added. The reaction was allowed to slowly warm to rt. After 1 d, the reaction was quenched at rt with sat. aq. NaHCO$_3$ and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a pale yellow oil. Flash column chromatography (30 mL SiO$_2$, 9:1 hexane:EtOAc) afforded 13.7 mg (25 µmol, 39% yield) of 349 as a pale yellow oil.

$^{1}$H NMR (600 MHz; C$_6$D$_6$) δ: 5.65 (t, $J = 6.8$ Hz, 1H), 5.36 (t, $J = 6.8$ Hz, 1H), 5.30 (t, $J = 7.2$ Hz, 1H), 4.93 (dd, $J = 11.5$, 5.8 Hz, 1H), 3.74 (s, 3H), 3.35 (dd, $J = 15.0$, 7.2 Hz, 1H), 3.14-3.11 (m, 2H), 3.03 (s, 3H), 2.97 (s, 3H), 2.91-2.83 (m, 1H), 2.70 (dd, $J = 15.8$, 6.9 Hz, 1H), 2.44 (dd, $J = 15.8$, 6.6 Hz, 1H), 2.37-2.29 (m, 2H), 2.18 (s, 3H), 2.11-2.05 (m, 1H), 1.83 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 1.70-1.63 (m, 7H), 1.59 (s, 3H), 1.40 (td, $J = 13.0$, 4.2 Hz, 1H), 1.29 (s, 3H).

$^{13}$C NMR (125 MHz; C$_6$D$_6$) δ: 196.9, 173.5, 132.7, 131.7, 130.9, 125.1, 124.7, 122.85, 122.67, 103.0, 84.5, 62.4, 59.7, 54.1, 50.41, 50.34, 40.8, 39.6, 37.9, 34.7, 31.5, 26.07, 26.03, 25.85, 23.6, 21.9, 19.5, 18.08, 17.98, 17.84.

FTIR (thin film) $\nu_{\text{max}}$: 2968, 2925, 2858, 1668, 1615, 1450, 1358, 1336, 1226, 1177, 1065, 933, 862 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{39}$H$_{48}$O$_7$S, 575.3013; found, 575.3017.

TLC $R_f = 0.39$ (8:2 hexane:EtOAc).
(1S,2S,3S,5R)-6,9,9-Trimethoxy-2-methyl-5,7-bis(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8-oxobicyclo[3.3.1]non-6-en-3-yl pivalate (350):

A CH$_2$Cl$_2$ (2 mL) solution of 343 (30 mg, 63 µmol, 1 equiv), pyridine (31 µL, 0.38 mmol, 6 equiv), and 4-(dimethylamino)pyridine (46 mg, 0.38 mmol, 6 equiv) in a 10-mL pear-shaped flask was cooled to 0 ºC, and pivaloyl chloride (39 µL, 0.32 mmol, 5 equiv) was added. The resulting colorless solution was allowed to slowly warm to rt. After stirring for 4.5 h, the reaction was quenched at rt with sat. aq. NaHCO$_3$ and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to an oily white residue. Flash column chromatography (25 mL SiO$_2$, 95:5 hexane:EtOAc) afforded 29 mg (52 µmol, 82% yield) of 350 as a colorless oil.

$^1$H NMR (600 MHz; C$_6$D$_6$) δ: 5.70 (t, $J = 6.7$ Hz, 1H), 5.40 (t, $J = 6.6$ Hz, 1H), 5.33 (t, $J = 7.3$ Hz, 1H), 5.18 (dd, $J = 11.4$, 5.5 Hz, 1H), 3.87 (s, 3H), 3.36 (dd, $J = 15.2$, 6.8 Hz, 1H), 3.17 (s, 2H), 3.09 (s, 3H), 3.04 (s, 3H), 2.75 (dd, $J = 15.9$, 6.8 Hz, 1H), 2.52 (dd, $J = 15.9$, 6.6 Hz, 1H), 2.14-2.05 (m, 3H), 1.82 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.65 (s, 3H), 1.61 (s, 6H), 1.55 (td, $J = 13.1$, 4.4 Hz, 1H), 1.45-1.36 (m, 4H), 1.11 (s, 9H).

$^{13}$C NMR (125 MHz; C$_6$D$_6$) δ: 197.3, 177.6, 174.4, 132.4, 131.5, 130.4, 125.4, 124.6, 123.3, 122.9, 103.5, 76.3, 62.5, 59.9, 53.9, 50.44, 50.35, 41.1, 39.17, 39.05, 32.9, 31.7, 27.2, 26.10, 26.01, 25.8, 23.8, 22.1, 20.2, 18.1, 17.89, 17.84.

FTIR (thin film) $\nu_{max}$: 2971, 2928, 2877, 1726, 1666, 1615, 1460, 1376, 1335, 1283, 1160, 1063 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{34}$H$_{54}$O$_6$, 581.3813; found, 581.3812.

TLC $R_f = 0.66$ (8:2 hexane:EtOAc).
(1S,5R,7S,8S,9S)-7,9-Dihydroxy-4,9-dimethoxy-8-methyl-5-(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-en-2-one (351):

A CH$_2$Cl$_2$ (3 mL) solution of 318 (99 mg, 0.26 mmol, 1 equiv) and triethylamine (22 µL, 0.16 mmol, 0.6 equiv) in a 25-mL recovery flask was cooled to –78 ºC, and a CH$_2$Cl$_2$ solution of bromodimethylborane (1.54 M, 1.0 mL, 1.6 mmol, 6 equiv) was added slowly. After stirring the reaction at –78 ºC for 15 min, it was sequentially quenched at –78 ºC with NEt$_3$ (1 mL) and sat. aq. NaHCO$_3$. After warming the mixture to rt, it was extracted thrice with EtOAc. The organic extracts were combined, washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a yellow-orange oil. Flash column chromatography (30 mL SiO$_2$, 8:2 $\rightarrow$ 7:3 hexane:EtOAc) afforded 81 mg (0.21 mmol, 79% yield) of 351 as a flocculent white solid.

$^1$H NMR (600 MHz; CDCl$_3$) $\delta$: 5.48 (s, 1H), 5.26 (d, $J = 11.5$ Hz, 1H), 5.05 (t, $J = 7.2$ Hz, 1H), 3.75 (s, 3H), 3.62 (dd, $J = 12.1$, 5.3 Hz, 1H), 3.57 (s, 1H), 3.26 (s, 3H), 2.88-2.83 (m, 2H), 2.36 (tt, $J = 12.7$, 6.2 Hz, 1H), 2.25 (d, $J = 14.3$ Hz, 1H), 1.96 (t, $J = 12.1$ Hz, 1H), 1.90 (ddd, $J = 19.4$, 13.1, 6.7 Hz, 1H), 1.73 (s, 3H), 1.71-1.67 (m, 4H), 1.65 (s, 6H), 1.46 (td, $J = 12.9$, 4.7 Hz, 1H), 1.31-1.22 (br s, 1H), 1.12 (s, 3H), 1.06 (td, $J = 12.9$, 4.4 Hz, 1H).

$^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 198.2, 176.1, 137.4, 131.4, 125.0, 122.1, 104.1, 100.6, 73.2, 57.6, 56.6, 51.1, 48.6, 40.5, 39.2, 37.0, 30.0, 26.3, 25.9, 21.9, 18.01, 17.89, 17.0.

FTIR (thin film) $\nu_{\text{max}}$: 3460 (br), 2969, 2928, 2859, 1648, 1602, 1451, 1375, 1221, 1084, 908, 731 cm$^{-1}$.

HRMS–ESI (m / z): [M+H]$^+$ calculated for C$_{23}$H$_{36}$O$_5$, 393.2636; found, 393.2632.

TLC $R_f$ = 0.50 (1:1 hexane:EтOAc).

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$^{690}$ A CH$_2$Cl$_2$ solution of bromodimethylborane was prepared as described in ref. 639b.
(1S,5R,7S,8S)-7-Hydroxy-4-methoxy-8-methyl-5-(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (282):

A 4:1 acetone:H₂O (4 mL) solution of 351 and pyridinium para-toluenesulfonate (208 mg, 0.83 mmol, 5 equiv) in a 10-mL recovery flask outfitted with a reflux condenser was heated to reflux. After stirring at reflux for 15.5 h, the reaction was cooled to rt, diluted with H₂O, and extracted thrice with 1:1 hexane:EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow oil. Flash column chromatography (20 mL SiO₂, 7:3 hexane:EtOAc) afforded 54 mg (0.15 mmol, 90% yield) of 282 as a white flocculent solid.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.68 (s, 1H), 5.09 (t, J = 7.2 Hz, 1H), 4.98 (t, J = 7.0 Hz, 1H), 3.83-3.81 (m, 1H), 3.75 (s, 3H), 3.19 (s, 1H), 2.50 (dd, J = 14.6, 6.4 Hz, 1H), 2.40 (dd, J = 14.6, 7.6 Hz, 1H), 2.35 (tt, J = 12.6, 6.8 Hz, 1H), 2.12 (dd, J = 13.3, 5.4 Hz, 1H), 1.92 (tt, J = 12.6, 6.5 Hz, 1H), 1.76 (dd, J = 13.3, 11.6 Hz, 1H), 1.67 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.56 (td, J = 12.9, 4.8 Hz, 1H), 1.32 (td, J = 12.8, 4.7 Hz, 1H), 0.91 (s, 3H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 205.2, 193.1, 177.5, 134.6, 132.2, 124.3, 119.0, 106.1, 72.1, 69.2, 57.1, 56.1, 45.9, 39.4, 38.1, 29.5, 26.1, 25.9, 21.8, 18.1, 17.9, 15.7.

**FTIR** (thin film) ν_max: 3433 (br), 2969, 2915, 2858, 1735, 1649, 1589, 1448, 1352, 1228, 1193, 1052, 1034, 843, 732 cm⁻¹.

**HRMS–ESI** (m/z): [M+H]⁺ calculated for C₂₂H₃₂O₄, 361.2373; found, 361.2378.

**TLC** Rᵣ = 0.41 (1:1 hexane:EtOAc).
(1S,2S,3S,5R)-6-Methoxy-2-methyl-5-(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-en-3-yl trifluoromethanesulfonate (352):

A CH$_2$Cl$_2$ (20 mL) solution of 282 (253 mg, 0.702 mmol, 1 equiv) and pyridine (341 µL, 4.21 mmol, 6 equiv) in a 50-mL recovery flask was cooled to –43 ºC, and trifluoromethanesulfonic anhydride (0.59 mL, 3.5 mmol, 5 equiv) was added. The resulting yellow slurry was allowed to slowly warm to 5 ºC over 2 h, whereupon it was quenched with sat. aq. NaHCO$_3$ and extracted thrice with EtOAc. The organic extracts were combined, washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a yellow oil. The oil was retaken in 8:2 hexane:EtOAc and passed through a plug of SiO$_2$, rinsing with 8:2 hexane:EtOAc. The filtrate was concentrated in vacuo to afford 277 mg (0.562 mmol, 80% yield) of 352 as a yellow-orange oil.

$^1$H NMR (600 MHz; C$_6$D$_6$) δ: 5.32 (s, 1H), 5.19-5.15 (m, 2H), 5.07 (dd, $J =$ 11.6, 5.5 Hz, 1H), 3.41 (s, 1H), 2.66 (s, 3H), 2.64-2.57 (m, 1H), 2.45 (dd, $J =$ 14.4, 6.6 Hz, 1H), 2.30-2.25 (m, 2H), 1.85 (dd, $J =$ 12.9, 11.9 Hz, 1H), 1.81-1.76 (m, 1H), 1.74 (t, $J =$ 8.4 Hz, 2H), 1.65 (t, $J =$ 8.4 Hz, 2H), 1.62 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H), 0.75 (s, 3H).

$^{13}$C NMR (125 MHz; C$_6$D$_6$) δ: 201.6, 189.9, 175.4, 134.9, 132.6, 123.6, 118.8, 106.3, 90.6, 68.8, 56.4, 55.3, 45.3, 37.8, 36.6, 29.5, 25.86, 25.80, 21.7, 17.91, 17.82, 16.3.

$^{19}$F NMR (470 MHz; C$_6$D$_6$) δ: –75.61 (s, 3F).

FTIR (thin film) $\nu_{\text{max}}$: 2969, 2925, 2858, 1738, 1654, 1636, 1592, 1434, 1214, 1138, 922, 820, 602 cm$^{-1}$.

HRMS–ESI (m / z): [M+H]$^+$ calculated for C$_{23}$H$_{31}$F$_3$O$_6$S, 493.1866; found, 493.1865.
(1S,2S,3R,5R)-6-Methoxy-2-methyl-5-(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-7-
(trimethylsilyl)tricyclo[3.3.1.01,3]non-6-ene-8,9-dione (353):

A THF (12 mL) solution of 352 (277 mg, 0.562 mmol, 1 equiv) in a 25-mL recovery flask was cooled to
–78 ºC, and chlorotrimethylsilane (3.6 mL, 28 mmol, 50 equiv) and a THF solution of lithium
diisopropylamide (0.50 M, 5.6 mL, 2.8 mmol, 5 equiv) were added sequentially. After stirring the
resulting orange solution at –78 ºC for 45 min, it was quenched at –78 ºC with sat. aq. NaHCO₃. The
mixture was warmed to rt and extracted thrice with EtOAc. The organic extracts were combined,
sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo
to a yellow oil. Flash column chromatography (75 mL SiO₂, 95:5 hexane:EtOAc) afforded 114 mg (0.27
mmol, 49% yield) of 353 as a pale yellow oil.

¹H NMR (600 MHz; C₆D₆) δ: 5.42 (t, J = 7.4 Hz, 1H), 5.29 (t, J = 7.1 Hz, 1H), 3.23 (s, 3H), 2.60 (dd, J =
15.1, 6.4 Hz, 1H), 2.51-2.47 (m, 2H), 2.19 (tt, J = 12.5, 6.2 Hz, 1H), 1.87 (ddd, J = 13.0, 12.5, 5.2 Hz,
1H), 1.80 (ddd, J = 13.5, 11.2, 6.2 Hz, 1H), 1.75 (dd, J = 14.0, 5.4 Hz, 1H), 1.69-1.67 (m, 4H), 1.66 (s,
3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.08 (s, 3H), 0.99 (dd, J = 7.9, 5.4 Hz, 1H), 0.36 (s, 9H).

¹³C NMR (125 MHz; C₆D₆) δ: 200.3, 194.8, 184.3, 134.5, 131.64, 131.63, 124.7, 119.6, 74.2, 61.9, 56.9,
48.1, 38.8, 37.7, 27.8, 26.29, 26.18, 25.905, 25.898 18.00, 17.85, 16.4, 0.8.
**Key 1D nOe correlations.**

**FTIR** (thin film) $\nu_{\text{max}}$: 2968, 2918, 2860, 1764, 1664, 1523, 1451, 1438, 1386, 1233, 1201, 1157, 1042, 962, 845, 761, 691 cm$^{-1}$.

**HRMS–ESI** (m/z): [M+H]$^+$ calculated for C$_{25}$H$_{38}$O$_3$Si, 415.2663; found, 415.2650.

**TLC** $R_f = 0.64$ (9:1 hexane:EtOAc).
(1S,5R,7S,8S)-7-Iodo-4-methoxy-8-methyl-5-(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (357):

A mixture of copper(I) iodide (20. mg, 0.10 mmol, 30.7 equiv) and lithium chloride (5.3 mg, 0.12 mmol, 36.7 equiv) in a 10-mL recovery flask was subjected to three cycles of heat gun drying under vacuum and purging with Ar. The mixture was subsequently taken up in THF (0.5 mL) and stirred at rt for 3 min. Meanwhile, a THF (1 mL) solution of tributylprenylstannane (37 mg, 0.10 mmol, 30.4 equiv) in a 10-mL pear-shaped flask was cooled to –78 ºC, and a hexane solution of butyllithium (1.56 M, 63 µL, 99 µmol, 29.2 equiv) was added. After stirring the resulting bright yellow solution at –78 ºC for 15 min, it was transferred via dry ice-cooled cannula to the copper(I) iodide-lithium chloride solution cooled to –78 ºC. After stirring the resulting brown-red solution at –78 ºC for 10 min, chlorotrimethylsilane (22 µL, 0.17 mmol, 51.0 equiv), a THF (0.25 mL) solution of 353 (1.4 mg, 3.4 µmol, 1 equiv), and a THF (0.25 mL) rinse of the flask that contained 353 were added in quick succession. The reaction was then allowed to slowly warm to 0 ºC over 90 min and was stirred at 0 ºC for 2 h, at which point the reaction turned black. After stirring for an additional 1 h at 0 ºC, the resulting colorless solution was quenched at 0 ºC with sat. aq. NH₄Cl and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow residue. Preparatory thin-layer chromatography (1 × 8:2 hexane:EtOAc) afforded 0.8 mg (2 µmol, 50% yield) of 357 as a colorless residue.

¹H NMR (600 MHz; CDCl₃) δ: 5.76 (s, 1H), 5.08 (t, J = 7.1 Hz, 1H), 4.97 (t, J = 6.9 Hz, 1H), 4.35 (dd, J = 12.8, 5.0 Hz, 1H), 3.77 (s, 3H), 3.39 (s, 1H), 2.52-2.46 (m, 2H), 2.44-2.36 (m, 3H), 1.89 (tt, J = 12.4,
6.0 Hz, 1H), 1.68 (s, 3H), 1.68 (s, 3H), 1.65 (s, 6H), 1.60 (td, J = 12.9, 4.3 Hz, 1H), 1.55 (s, 3H), 1.28 (td, J = 12.9, 4.3 Hz, 1H), 1.05 (s, 3H).

$^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 203.7, 192.6, 176.1, 134.9, 132.4, 123.7, 118.7, 106.6, 67.7, 59.5, 57.2, 46.8, 45.1, 41.9, 37.1, 29.2, 26.15, 25.95, 21.9, 21.0, 18.2, 17.9.

FTIR (thin film) $\nu_{max}$: 2962, 2919, 2853, 1736, 1655, 1595, 1453, 1368, 1223, 1191 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{22}$H$_{31}$IO$_3$, 493.1210; found, 493.1193.

TLC $R_f = 0.41$ (8:2 hexane:EtOAc).
(1S,5R,7S,8S)-7-Hydroxy-4,9,9-trimethoxy-8-methyl-5-(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-en-2-one (360):

A CH₂Cl₂ (6 mL) solution of 318 (456 mg, 1.22 mmol, 1 equiv) and triethylamine (102 µL, 0.731 mmol, 0.6 equiv) in a 20-mL scintillation vial was cooled to −78 ºC, and a CH₂Cl₂ solution of bromodimethylborane (1.26 M, 5.8 mL, 7.3 mmol, 6 equiv) was added slowly. The resulting orange-red solution was stirred at −78 ºC for 45 min and subsequently quenched at −78 ºC through the addition of 1:1 MeOH:NEt₃ (8 mL). The reaction was then poured onto sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with 2 N HCl, sat. aq. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (150 mL SiO₂, 8:2 hexane:EtOAc) afforded 303 mg (0.745 mmol, 61% yield) of 360 as a flocculent yellow solid.

¹H NMR (600 MHz; CDCl₃) δ: 5.40 (s, 1H), 5.34 (t, J = 7.2 Hz, 1H), 5.04 (t, J = 7.2 Hz, 1H), 3.67 (s, 3H), 3.57-3.54 (m, 1H), 3.35 (s, 3H), 3.23 (s, 3H), 2.89 (s, 1H), 2.68 (dd, J = 15.3, 8.0 Hz, 1H), 2.39-2.33 (m, 2H), 1.92-1.88 (m, 1H), 1.84 (dd, J = 13.1, 12.1 Hz, 1H), 1.72 (dd, J = 13.1, 5.2 Hz, 1H), 1.68 (s, 3H), 1.64 (s, 6H), 1.61 (s, 3H), 1.45 (td, J = 12.9, 4.8 Hz, 1H), 1.37 (m, 1H), 1.11 (s, 3H), 1.04 (td, J = 12.9, 4.5 Hz, 1H).

¹³C NMR (125 MHz; CDCl₃) δ: 198.1, 179.0, 131.9, 131.4, 125.1, 122.1, 103.9, 103.0, 73.5, 59.0, 56.5, 52.4, 51.2, 50.6, 40.6, 39.5, 36.8, 35.9, 30.4, 26.2, 25.9, 21.9, 18.1, 17.9.

FTIR (thin film)νmax: 3455 (br), 2967, 2925, 2859, 1654, 1600, 1454, 1374, 1350, 1224, 1060 cm⁻¹.

HRMS–ESI (m/z): [M+Na]⁺ calculated for C₂₅H₃₈O₅, 429.2611; found, 429.2609.

TLC Rf = 0.49 (1:1 hexane:EtOAc).

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⁶⁹¹ A CH₂Cl₂ solution of bromodimethylborane was prepared as described in ref. 639b.
A CH$_2$Cl$_2$ (3 mL) solution of 360 (56.8 mg, 0.140 mmol, 1 equiv) and pyridine (68 µL, 0.84 mmol, 6 equiv) in a 10-mL recovery flask was cooled to –40 ºC, and trifluoromethanesulfonic anhydride (118 µL, 0.699 mmol, 5 equiv) was added. The resulting yellow slurry was allowed to slowly warm to 0 ºC over 90 min, whereupon it was quenched at 0 ºC with sat. aq. NaHCO$_3$ and extracted thrice with 8:2 hexane:EtoAc. The organic extracts were combined, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated to an orange-brown oil. A portion of this oil (30. mg, 56 µmol, 1 equiv) was dissolved in THF (1 mL) in a 10-mL test tube, cooled to –78 ºC, and treated sequentially with chlorotrimethylsilane (353 µL, 2.7 mmol, 50 equiv), a freshly prepared THF solution of lithium diisopropylamide (0.50 M, 0.56 mL, 0.28 mmol, 5 equiv), and hexamethylphosphoramide (53 µL, 0.31 mmol, 5.5 equiv). The orange slurry was stirred at –78 ºC for 1 h and was then allowed to warm to 0 ºC over 4 h. The reaction was then quenched at 0 ºC with sat. aq. NaHCO$_3$ and extracted thrice with 8:2 hexane:EtoAc. The organic extracts were combined, sequentially washed five times with H$_2$O and once with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to an orange oil. This oil was dissolved in THF (1 mL) in a 10-mL test tube, cooled to –78 ºC, and treated with a freshly prepared THF solution of lithium diethylamide (0.50 M, 1.1 mL, 0.56 mmol, 10 equiv). The brown-orange solution was stirred at –78 ºC for 45 min and subsequently allowed to slowly warm to –10 ºC over 45 min. The resulting red solution was then quenched at –10 ºC with sat. aq. NaHCO$_3$ and extracted thrice with EtoAc. The organic extracts were combined, sequentially washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a brown oil. Preparatory thin-layer chromatography (1 × 9:1 hexane:EtoAc containing 1% NEt$_3$) afforded 3.5 mg (7.6 µmol, 14% yield from 360) of 359 as a colorless oil and 14.5 mg (23.6 µmol, 42% yield from 360) of 363 as a pale yellow oil.
(1S,2R,3S,5R)-6,9,9-Trimethoxy-2-methyl-5-(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-7-(trimethylsilyl)tricyclo[3.3.1.01,3]non-6-en-8-one (359):

**1H NMR** (600 MHz; C₆D₆) δ: 5.54 (t, J = 7.1 Hz, 1H), 5.47 (t, J = 7.2 Hz, 1H), 3.37 (s, 3H), 2.99 (s, 3H), 2.97 (s, 3H), 2.77-2.71 (m, 2H), 2.42 (dd, J = 15.0, 7.0 Hz, 1H), 2.41-2.34 (m, 1H), 2.06 (dd, J = 13.3, 6.6 Hz, 1H), 1.84 (td, J = 12.3, 5.2 Hz, 1H), 1.74 (s, 3H), 1.73-1.68 (m, 4H), 1.68 (m, 4H), 1.62 (s, 3H), 1.54 (s, 3H), 0.84 (t, J = 7.0 Hz, 1H), 0.48 (s, 9H).

**13C NMR** (125 MHz; C₆D₆) δ: 199.0, 184.4, 131.2, 131.0, 129.3, 125.6, 123.2, 110.1, 74.2, 64.1, 53.6, 52.3, 51.1, 50.6, 41.8, 38.1, 31.7, 28.3, 26.7, 26.00, 25.95, 17.89, 17.87, 16.5, 1.0.

**FTIR** (thin film) νₘₐₓ: 2965, 2924, 2854, 1669, 1577, 1453, 1340, 1207, 1145, 1080 cm⁻¹.

**HRMS–ESI** (m / z): [M+Na]⁺ calculated for C27H44O4Si, 483.2901; found, 483.2908.

**TLC** Rₚ = 0.68 (8:2 hexane:EtOAc).

(1S,2S,3S,5R)-6,9,9-Trimethoxy-2-methyl-5-(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8-oxo-7-(trimethylsilyl)bicyclo[3.3.1]non-6-en-3-yl diethylsulfamate (363):

**1H NMR** (500 MHz; C₆D₆) δ: 5.66 (t, J = 6.8 Hz, 1H), 5.40 (t, J = 7.2 Hz, 1H), 4.82 (dd, J = 12.0, 5.2 Hz, 1H), 3.79 (s, 3H), 3.08-2.94 (m, 12H), 2.74 (dd, J = 15.8, 7.0 Hz, 1H), 2.55-2.51 (m, 2H), 2.42 (t, J = 12.6 Hz, 1H), 2.15 (tt, J = 12.3, 6.0 Hz, 1H), 1.91 (td, J = 13.2, 4.4 Hz, 1H), 1.83 (s, 3H), 1.70 (s, 3H), 1.68 (s, 3H), 1.59-1.51 (m, 4H), 1.34 (s, 3H), 0.85 (t, J = 7.1 Hz, 6H), 0.42 (s, 9H).

**13C NMR** (125 MHz; C₆D₆) δ: 201.1, 187.2, 131.6, 131.1, 128.6, 125.2, 122.7, 103.3, 84.3, 65.0, 60.10, 60.07, 55.0, 50.4, 42.7, 41.0, 39.9, 34.0, 31.4, 26.08, 25.99, 22.1, 20.6, 19.7, 17.97, 17.87, 14.2, 13.3, 1.0.

**FTIR** (thin film) νₘₐₓ: 2971, 2937, 1660, 1600, 1458, 1358, 1345, 1222, 1206, 1165, 1102, 1061, 929, 830 cm⁻¹.

**HRMS–ESI** (m / z): [M+Na]⁺ calculated for C₃₁H₅₅NO₇SSi, 636.3361; found, 636.3371.

**TLC** Rₚ = 0.55 (8:2 hexane:EtOAc).
(1R,2S,3R,5R)-4,4,6-Trimethoxy-2-methyl-5-(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)tricyclo[3.3.1.0¹,3]non-6-en-8-one (364):

A CH₂Cl₂ (3 mL) solution of 360 (56.8 mg, 0.140 mmol, 1 equiv) and pyridine (68 µL, 0.84 mmol, 6 equiv) in a 10-mL recovery flask was cooled to –40 ºC, and trifluoromethanesulfonic anhydride (118 µL, 0.699 mmol, 5 equiv) was added. The resulting yellow slurry was allowed to slowly warm to 0 ºC over 90 min whereupon it was quenched at 0 ºC with sat. aq. NaHCO₃ and extracted thrice with 8:2 hexane:EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated to an orange-brown oil. A portion of this oil (23 mg, 43 µmol, 1 equiv) was dissolved in THF (1 mL) in a 10-mL test tube, cooled to –78 ºC, and treated with a freshly prepared THF solution of lithium diisopropylamide (0.50 M, 0.85 mL, 0.43 mmol, 10 equiv). The resulting brown-orange solution was stirred at –78 ºC for 45 min and then allowed to slowly warm to rt. After stirring the resulting dark red solution for 16.5 h, it was quenched at rt with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a brown oil. Preparatory thin-layer chromatography (1 × 8:2 hexane:EtOAc) afforded 7.4 mg (19 µmol, 44% yield from 360) of 364 as a pale yellow oil.

¹H NMR (600 MHz; C₆D₆) δ: 5.33 (s, 1H), 5.31 (t, J = 7.2 Hz, 1H), 5.11 (t, J = 7.4 Hz, 1H), 3.24 (s, 3H), 3.05 (s, 3H), 3.03 (s, 3H), 2.84 (dd, J = 14.6, 7.2 Hz, 1H), 2.80 (dd, J = 14.6, 9.0 Hz, 1H), 2.60-2.52 (m, 1H), 2.24-2.18 (m, 1H), 2.00 (d, J = 12.8 Hz, 1H), 1.95-1.86 (m, 2H), 1.78 (d, J = 12.8 Hz, 1H), 1.67 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H), 1.29 (s, 3H), 1.16 (d, J = 0.9 Hz, 1H).

¹³C NMR (125 MHz; C₆D₆) δ: 13-C NMR (126 MHz; Benzene): δ 195.9, 179.9, 132.5, 131.2, 125.1, 121.8, 111.6, 105.4, 72.2, 55.7, 50.9, 50.0, 48.6, 44.5, 43.8, 39.3, 38.5, 28.6, 26.2, 25.97, 25.91, 18.0, 17.8, 14.7.
**Key 1D nOe correlations.**

**FTIR** (thin film) $\nu_{\text{max}}$: 2965, 2926, 2857, 1675, 1575, 1440, 1339, 1225, 1173, 1141, 1063, 997, 834 cm$^{-1}$.

**HRMS–ESI** (m / z): [M+Na]$^+$ calculated for C$_{24}$H$_{36}$O$_4$, 411.2506; found, 411.2512.

**TLC** $R_f = 0.34$ (8:2 hexane:EtOAc).
**295**

(1S,2S,3S,5R)-6,9,9-Trimethoxy-2-methyl-5-(3-methylbut-2-en-1-yl)-2-(4-methylpent-3-en-1-yl)-8-oxobicyclo[3.3.1]non-6-en-3-yl benzenesulfonate (366):

A CH₂Cl₂ (1 mL) solution of 360 (16.1 mg, 39.6 µmol, 1 equiv) and pyridine (19 µL, 0.24 mmol, 6 equiv) in a 10-mL recovery flask was cooled to –40 ºC, and benzenesulfonyl chloride (25 µL, 0.20 mmol, 5 equiv) was added. The resulting yellow solution was allowed to slowly warm to rt. After stirring for 1 d, the reaction was quenched at rt with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to a pale yellow oil. Flash column chromatography (30 mL SiO₂, 96:4 PhH:EtOAc) afforded 10.5 mg (19.2 µmol, 48% yield) of 366 as a colorless oil.

**¹H NMR** (600 MHz; C₆D₆) δ: 7.79 (d, J = 7.9 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.84 (t, J = 7.7 Hz, 2H), 5.44 (t, J = 6.9 Hz, 1H), 5.37 (s, 1H), 5.16 (t, J = 7.2 Hz, 1H), 4.84 (dd, J = 12.0, 5.3 Hz, 1H), 3.05 (s, 1H), 2.97 (s, 3H), 2.92 (s, 3H), 2.87-2.79 (m, 1H), 2.64 (dd, J = 15.6, 7.6 Hz, 1H), 2.32 (dd, J = 15.6, 6.3 Hz, 1H), 2.19 (dd, J = 14.5, 10.6 Hz, 1H), 2.01-1.93 (m, 2H), 1.79 (s, 3H), 1.66 (s, 6H), 1.50-1.46 (m, 4H), 1.32-1.24 (m, 4H).

**¹³C NMR** (125 MHz; C₆D₆) δ: 195.4, 177.3, 138.3, 133.1, 131.29, 131.14, 129.0, 125.2, 122.5, 103.68, 103.56, 85.7, 59.3, 55.9, 52.6, 50.7, 50.4, 40.8, 39.4, 33.9, 30.8, 26.10, 25.97, 21.9, 19.4, 17.9, 17.7.

**FTIR** (thin film) νₘₐₓ: 2965, 2925, 2857, 1655, 1599, 1448, 1363, 1223, 1186, 1097, 1186, 1097, 1050, 940, 853, 723, 689, 590 cm⁻¹.

**HRMS–ESI** (m / z): [M+H]⁺ calculated for C₃₀H₄₂O₇S, 547.2724; found, 547.2718.

**TLC** Rₙ = 0.30 (95:5 PhH:EtOAc).
**2S,3R)-3-(Bromomethyl)-2-(4-methoxy-4-methylpentyl)-2-methyloxirane (373):**

A MeOH (110 mL) solution of mercury(II) acetate (10.3 g, 32.2 mmol, 1.5 equiv) in a 250-mL round-bottom flask was treated with 289 (5.00 g, 21.4 mmol, 1 equiv). After stirring the resulting white slurry at rt for 15 min, it was cooled to 0 ºC and was treated with an aqueous solution of NaOH (3 M, 35 mL). After stirring the resulting bright orange slurry at 0 ºC for 2 min, and a basic, aqueous solution of NaBH₄ (0.5 M NaBH₄ in 3 M NaOH aqueous solution, 35 mL) was added. The resulting gray slurry was stirred at 0 ºC for 15 min, diluted with H₂O, and extracted thrice with 8:2 hexane:EtOAc. The organic extracts were combined, sequentially washed thrice with H₂O and once with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to a colorless oil. Flash column chromatography (250 mL SiO₂, 9:1 → 8:2 hexane:EtOAc) afforded 4.98 g (18.8 mmol, 88% yield) of 373 as a colorless oil as well as 187 mg (0.802 mmol, 3.7% recovery) of 289 as a colorless oil.

**1H NMR** (600 MHz; CDCl₃) δ: 3.53 (dd, J = 10.4, 5.9 Hz, 1H), 3.24 (dd, J = 10.4, 7.7 Hz, 1H), 3.16 (s, 3H), 3.08 (dd, J = 7.7, 5.9 Hz, 1H), 1.67-1.62 (m, 1H), 1.48-1.40 (m, 5H), 1.30 (s, 3H), 1.13 (s, 6H).

**13C NMR** (125 MHz; CDCl₃) δ: 74.6, 63.3, 61.6, 49.4, 39.9, 38.8, 30.0, 25.1, 19.6, 16.3.

**FTIR** (thin film) νₘₐₓ: 2971, 2948, 2915, 2826, 1465, 1432, 1382, 1364, 1253, 1221, 1205, 1148, 1083, 891, 652 cm⁻¹.

**HRMS–ESI** (m / z): [M+Na]⁺ calculated for C₁₁H₂₁BrO₂, 287.0617; found, 287.0621.

**TLC** Rₜ = 0.18 (9:1 hexane:EtOAc).
(2S,3S)-3-((2,6-Dimethoxy-1-(3-methylbut-2-en-1-yl)cyclohexa-2,5-dien-1-yl)methyl)-2-(4-methoxy-4-methylpentyl)-2-methyloxirane (374):

A THF (100 mL) solution of 312 (4.35 g, 20.9 mmol, 1 equiv) in a 250-mL round-bottom flask was cooled to –78 ºC, and a c-Hex solution of sec-butyllithium (1.21 M, 21.6 mL, 26.1 mmol, 1.25 equiv) was added slowly over 5 min. The resulting yellow slurry was allowed to slowly warm from –78 ºC to –30 ºC over 40 min and then stirred at –30 ºC for 15 min. The resulting red-orange slurry was cooled to –78 ºC, and a THF (20 mL) solution of 373 (4.98 g, 18.8 mmol, 0.9 equiv) was added followed by two THF (10 mL each) rinses. The resulting cream-colored slurry was allowed to slowly warm to 0 ºC. After stirring for 3.5 h, the reaction was quenched at 0 ºC with H₂O and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (400 mL SiO₂, 9:1 → 8:2 hexane:EtOAc) afforded 4.95 g (12.6 mmol, 67% yield) of 374 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 4.89 (t, J = 7.3 Hz, 1H), 4.76 (t, J = 3.6 Hz, 1H), 4.72 (t, J = 3.6 Hz, 1H), 3.51 (s, 3H), 3.46 (s, 3H), 3.15 (s, 3H), 2.75 (t, J = 3.6 Hz, 2H), 2.61 (dd, J = 8.0, 3.9 Hz, 1H), 2.34-2.27 (m, 2H), 2.03 (dd, J = 13.7, 3.9 Hz, 1H), 1.76 (dd, J = 13.7, 8.0 Hz, 1H), 1.62 (s, 3H), 1.54 (s, 3H), 1.54-1.49 (m, 1H), 1.42-1.37 (m, 2H), 1.35-1.30 (m, 2H), 1.27-1.22 (m, 1H), 1.17 (s, 3H), 1.12 (s, 6H).

¹³C NMR (125 MHz; CDCl₃) δ: 154.09, 154.02, 132.5, 120.7, 93.05, 92.94, 74.7, 61.47, 61.27, 54.5, 54.1, 49.3, 46.2, 40.11, 39.91, 34.6, 34.1, 26.1, 25.23, 25.17, 24.2, 19.8, 17.9, 16.8.

FTIR (thin film) ν max: 2972, 2912, 2828, 1695, 1659, 1453, 1381, 1364, 1223, 1206, 1151, 1124, 1084, 1033, 973, 952, 849, 779, 689 cm⁻¹.

HRMS–ESI (m/z): [M+H]⁺ calculated for C₂₄H₄₀O₄, 393.2999; found, 393.3000.

TLC Rₜ = 0.37 (8:2 hexane:EtOAc).
(2S,3S,3aR,7R,7aS)-6,7a-Dimethoxy-3-(4-methoxy-4-methylpentyl)-3-methyl-7-(3-methylbut-2-en-1-yl)-2,3,3a,4,7,7a-hexahydro-2,7-methanobenzofuran (375):

A THF (63 mL) solution of 374 (4.91 g, 12.5 mmol, 1 equiv) and 2,6-lutidine (3.0 mL, 38 mmol, 3 equiv) in a 200-mL round-bottom flask was cooled to –78 °C, and trimethylsilyl trifluoromethanesulfonate (4.5 mL, 25 mmol, 2 equiv) was added. The resulting golden yellow solution was stirred at –78 °C for 45 min and subsequently quenched at –78 °C with sat. aq. NaHCO₃. The mixture was warmed to rt and extracted thrice with CH₂Cl₂. The organic extracts were combined, sequentially washed with 1 N HCl, H₂O, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow oil. Flash column chromatography (300 mL SiO₂, 95:5 → 9:1 hexane:EtOAc) afforded 3.74 g (9.52 mmol, 76% yield) of 375 as a pale yellow oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.33 (t, J = 7.1 Hz, 1H), 4.51 (dd, J = 5.5, 2.1 Hz, 1H), 3.74 (d, J = 4.6 Hz, 1H), 3.47 (s, 3H), 3.45 (s, 3H), 3.15 (s, 3H), 2.34 (dd, J = 14.7, 6.8 Hz, 1H), 2.21 (dd, J = 6.8, 1.8 Hz, 1H), 2.18 (dd, J = 6.7, 2.3 Hz, 1H), 2.03 (m, 1H), 2.02-1.99 (m, 1H), 1.77 (dd, J = 12.0, 4.6 Hz, 1H), 1.75 (d, J = 12.0 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.42-1.28 (m, 4H), 1.18 (td, J = 12.6, 3.0 Hz, 1H), 1.12 (s, 3H), 1.11 (s, 3H), 1.03-0.95 (m, 1H).

¹³C NMR (125 MHz; CDCl₃) δ: 158.6, 131.2, 123.6, 112.6, 90.5, 79.0, 74.6, 54.6, 51.4, 49.3, 46.5, 44.5, 41.9, 41.2, 39.3, 34.0, 32.8, 28.2, 26.4, 25.23, 25.15, 20.1, 18.5, 18.0.

Key 1D nOe correlations.
FTIR (thin film) $\nu_{\text{max}}$: 2968, 2839, 1670, 1451, 1374, 1363, 1208, 1166, 1078, 1006, 843, 805, 785 cm$^{-1}$.

HRMS–ESI (m/z): [M+Na]$^+$ calculated for C$_{24}$H$_{40}$O$_4$, 415.2819; found, 415.2832.

TLC $R_f = 0.49$ (8:2 hexane:EtOAc).
(2S,3S,3aS,7R,7aS)-6,7a-Dimethoxy-3-(4-methoxy-4-methylpentyl)-3-methyl-7-(3-methylbut-2-en-1-yl)-3,3a,7,7a-tetrahydro-2,7-methanobenzofuran-4(2H)-one (376):

An EtOAc\(^{692}\) (30 mL) slurry of cesium carbonate (12.76 g, 36.2 mmol, 4 equiv), 375 (3.55 g, 9.04 mmol, 1 equiv), and a nonane solution of tert-butyl hydroperoxide (5.5 M, 6.6 mL, 36 mmol, 4 equiv) in a 3-neck 300-mL round-bottom flask was cooled to –78 ºC with rapid O\(_2\) bubbling, and an EtOAc (25 mL) solution of [bis(trifluoroacetoxy)iodo]benzene (11.67 g, 27.1 mmol, 3 equiv) was added dropwise over 30 min followed by an EtOAc (5 mL) rinse. After stirring the reaction at –78 ºC for 2 h, it was allowed to slowly warm to 0 ºC. After stirring the pink slurry for 2.25 h, O\(_2\) bubbling was suspended, and the reaction was quenched at 0 ºC with sat. aq. Na\(_2\)S\(_2\)O\(_3\). The resulting yellow slurry was stirred vigorously at rt for 45 min and then extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H\(_2\)O and brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo} to a yellow oil. Flash column chromatography (300 mL SiO\(_2\), 7:3 hexane:EtOAc) afforded 1.069 g (2.629 mmol, 29% yield) of 376 as a pale yellow oil.

\(^1\)H NMR (600 MHz; CDCl\(_3\)) \(\delta\): 5.33 (s, 1H), 5.29 (t, \(J = 7.2\) Hz, 1H), 3.90 (d, \(J = 5.7\) Hz, 1H), 3.70 (s, 3H), 3.46 (s, 3H), 3.12 (s, 3H), 2.67 (s, 1H), 2.41 (dd, \(J = 14.9, 6.1\) Hz, 1H), 2.34 (dd, \(J = 14.9, 8.0\) Hz, 1H), 2.00 (d, \(J = 13.0\) Hz, 1H), 1.93 (dd, \(J = 13.0, 5.7\) Hz, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.39-1.29 (m, 4H), 1.26 (s, 3H), 1.23-1.11 (m, 2H), 1.09 (s, 6H).

\(^13\)C NMR (125 MHz; CDCl\(_3\)) \(\delta\): 198.0, 181.3, 133.0, 122.1, 115.4, 100.8, 80.7, 74.5, 56.8, 56.4, 52.2, 49.3, 48.6, 48.1, 40.9, 38.8, 34.6, 32.1, 28.0, 26.3, 25.3, 25.0, 18.2, 17.9.

FTIR (thin film) \(\nu_{\text{max}}\): 2969, 2943, 2873, 1720, 1649, 1602, 1453, 1372, 1227, 1070, 1003, 681 cm\(^{-1}\).

HRMS–ESI (m / z): [M+Na]\(^+\) calculated for C\(_{24}\)H\(_{38}\)O\(_5\), 429.2611; found, 429.2614.

TLC \(R_t = 0.18\) (1:1 hexane:EtOAc).

\(^{692}\) The EtOAc used in this procedure was sparged with O\(_2\) for 30 min directly prior to use.
**5-((2S,3R)-3-(Bromomethyl)-2-methyloxiran-2-yl)-2-methylpentan-2-ol (380):**

A 1:1 THF/H$_2$O (1 L) slurry of mercury(II) acetate (255.52 g, 801.82 mmol, 1.5 equiv) in a 2-L recovery flask was treated with 289 (124.63 g, 534.55 mmol, 1 equiv), and the resulting yellow solution was stirred at rt for 10 min. The solution was then cooled using a 0 ºC ice bath, and an aqueous solution of NaOH (3 M, 900 mL) was added. The resulting bright yellow-orange slurry was stirred at 0 ºC for 2 min, and a basic, aqueous solution of NaBH$_4$ (0.5 M NaBH$_4$ in 3 M NaOH aqueous solution, 900 mL) was added, immediately producing a gray slurry. After stirring an additional 10 min at 0 ºC, the slurry was extracted thrice with EtOAc. The organic extracts were combined, sequentially washed thrice with H$_2$O and once with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resulting yellow oil was dissolved in 1:1 hexane:EtOAc and passed through a plug of SiO$_2$, rinsing with 1:1 hexane:EtOAc. Concentration of the filtrate in vacuo yielded 122.21 g (486.58 mmol, 91% yield) of 380 as a pale yellow oil that was used without further purification.

**1H NMR** (600 MHz; CDCl$_3$) $\delta$: 3.53 (dd, $J = 10.4, 5.9$ Hz, 1H), 3.24 (dd, $J = 10.4, 7.8$ Hz, 1H), 3.07 (dd, $J = 7.7, 6.0$ Hz, 1H), 1.67-1.63 (m, 1H), 1.51-1.44 (m, 5H), 1.43-1.39 (m, 5H), 1.31-1.29 (s, 3H), 1.20 (s, 6H).

**13C NMR** (125 MHz; CDCl$_3$) $\delta$: 71.0, 63.3, 61.5, 43.6, 38.7, 29.9, 29.51, 29.42, 20.0, 16.2.

**FTIR** (thin film) $\nu_{\text{max}}$: 3458 (br), 2971, 2947, 2872, 1471, 1386, 1222, 1153, 1073, 891 cm$^{-1}$.

**HRMS–ESI** (m / z): [M+Na]$^+$ calculated for C$_{10}$H$_{19}$BrO$_2$, 273.0461; found, 273.0457.

$[\alpha]_D^{23} = +23.1^\circ$ (c 1.83, CHCl$_3$).

**TLC** R$_f = 0.32$ (1:1 hexane:EtOAc).
((5-((2S,3R)-3-(Bromomethyl)-2-methyloxiran-2-yl)-2-methylpentan-2-yl)oxy)triethylsilane (379):  
A DMF (1 L) solution of 380 (121.84 g, 485.11 mmol, 1 equiv) and imidazole (132.10 g, 1.940 mol, 4 equiv) in a 2-L recovery flask was placed in a rt H2O bath and treated with chlorotriethylsilane (163 mL, 0.970 mol, 2 equiv). After stirring the resulting yellow solution at rt for 105 min, the flask was cooled using a 0 ºC ice bath and slowly quenched with sat. aq. NaHCO3. After effervescence ceased, the mixture was extracted thrice with 9:1 hexane:EtOAc. The organic extracts were combined, sequentially washed thrice with H2O and once with brine, dried over Na2SO4, filtered, and concentrated in vacuo. The resulting colorless oil was dissolved in 95:5 hexane:EtOAc and passed through a plug of SiO2, rinsing with 95:5 hexane:EtOAc. Concentration of the filtrate in vacuo yielded 171.69 g (469.84 mmol, 97% yield) of 379 as a colorless oil that was used without further purification.

1H NMR (600 MHz; CDCl3) δ: 3.55 (dd, J = 10.4, 5.9 Hz, 1H), 3.25 (dd, J = 10.4, 7.9 Hz, 1H), 3.07 (dd, J = 7.8, 5.9 Hz, 1H), 1.66 (ddd, J = 13.2, 9.3, 5.3 Hz, 1H), 1.52-1.37 (m, 5H), 1.30 (s, 3H), 1.20 (s, 6H), 0.94 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H).

13C NMR (125 MHz; CDCl3) δ: 73.3, 63.4, 61.6, 45.0, 38.9, 30.11, 30.02, 20.2, 16.2, 7.3, 7.0.

FTIR (thin film) νmax: 2953, 2912, 2876, 1462, 1383, 1364, 1233, 1155, 1042, 1017, 743, 724 cm⁻¹.

HRMS–ESI (m / z): [M+Na]+ calculated for C16H33BrO2Si, 387.1325; found, 387.1326.

[α]D²³ = +16.8° (c 6.20, CHCl3).

TLC Rf = 0.83 (1:1 hexane:EtOAc).
((5-((2S,3S)-3-((2,6-Dimethoxy-1-(3-methylbut-2-en-1-yl)cyclohexa-2,5-dien-1-yl)methyl)-2-methyloxiran-2-yl)-2-methylpentan-2-yl)oxy)triethylsilane (381):

A THF (1 L) solution of 312 (46.52 g, 223.3 mmol, 1 equiv) in a 2-neck 3-L round-bottom flask outfitted with an equal pressure dropping funnel was cooled using a –78 ºC dry ice/acetone bath, and a c-Hex solution of sec-butyllithium (1.56 M, 170. mL, 235 mmol, 1.05 equiv) was added dropwise over 30 min via the equal pressure dropping funnel, maintaining an internal reaction temperature ≤ –65 ºC. The resulting yellow-orange slurry was allowed to slowly warm to –30 ºC over 90 min, and the resulting deep red slurry was stirred at –30 ºC for 15 min. The reaction was then cooled using a –78 ºC dry ice/acetone bath, and a THF (200 mL) solution of 379 (73.45 g, 201.0 mmol, 0.9 equiv) was added dropwise via cannula, followed by two THF (50 mL each) rinses, maintaining an internal reaction temperature ≤ –65 ºC throughout the addition. The resulting pale yellow solution was allowed to slowly warm to –40 ºC over 1 h and quenched at –40 ºC with sat. aq. NaHCO₃, which produced a small amount of effervescence. The mixture was warmed to rt and extracted thrice with 1:1 hexane:EtOAc. The organic extracts were combined, sequentially washed sequentially with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow oil. Flash column chromatography (1 L SiO₂, 98:2 hexane:EtOAc) afforded 83.99 g (170.4 mmol, 85% yield) of 381 as a colorless oil.

1H NMR (600 MHz; CDCl₃) δ: 4.90 (t, J = 7.3 Hz, 1H), 4.77 (t, J = 3.5 Hz, 1H), 4.72 (t, J = 3.6 Hz, 1H), 3.52 (s, 3H), 3.47 (s, 3H), 2.76 (t, J = 3.6 Hz, 2H), 2.62 (dd, J = 8.0, 4.0 Hz, 1H), 2.31 (qd, J = 10.8, 7.6 Hz, 2H), 2.03 (dd, J = 13.7, 3.9 Hz, 1H), 1.77 (dd, J = 13.7, 7.9 Hz, 1H), 1.63 (s, 3H), 1.55 (s, 3H), 1.53-1.48 (m, 1H), 1.41-1.31 (m, 4H), 1.28-1.21 (m, 1H), 1.18 (s, 3H), 1.17 (s, 6H), 0.94 (t, J = 7.9 Hz, 9H), 0.55 (q, J = 7.9 Hz, 6H).
$^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 154.09, 154.04, 132.5, 120.7, 93.02, 92.90, 73.5, 61.45, 61.32, 54.5, 54.1, 46.2, 45.4, 39.9, 34.6, 34.2, 30.2, 30.0, 26.1, 24.3, 20.2, 17.9, 16.8, 7.3, 7.0.

FTIR (thin film) $\nu_{\text{max}}$: 2953, 2913, 2831, 1695, 1660, 1458, 1382, 1224, 1206, 1152, 1124, 1041, 778, 742, 723 cm$^{-1}$.

HRMS–ESI (m / z): [M+H]$^+$ calculated for C$_{29}$H$_{52}$O$_4$Si, 493.3708; found, 493.3708.

$[\alpha]_D^{23} = +22.1^\circ$ (c 0.58, CHCl$_3$).

TLC $R_f = 0.27$ (95:5 hexane:EtOAc).
A CH$_2$Cl$_2$ (30 mL) solution of 381 (2.73 g, 5.54 mmol, 1 equiv) in a 100-mL recovery flask was cooled using a –78 ºC dry ice/acetone bath, and 2,6-lutidine (1.3 mL, 17 mmol, 3 equiv) and trimethylsilyl trifluoromethanesulfonate (2.46 g, 11.1 mmol, 2 equiv) were added sequentially. The resulting yellow solution was stirred at –78 ºC for 45 min and subsequently quenched at –78 ºC with sat. aq. NaHCO$_3$. After warming the mixture to rt, it was extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with 2 N HCl, H$_2$O, sat. aq. NaHCO$_3$, and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a colorless oil. Flash column chromatography (200 mL SiO$_2$, 99:1 → 98:2 hexane:EtOAc) afforded 2.15 g (4.35 mmol, 79% yield of 382 as a pale yellow oil.

$^1$H NMR (600 MHz; CDCl$_3$) $\delta$: 5.33 (t, $J = 7.1$ Hz, 1H), 4.51 (dd, $J = 5.5$, 2.0 Hz, 1H), 3.72 (t, $J = 2.7$ Hz, 1H), 3.47 (s, 3H), 3.45 (s, 3H), 2.34 (dd, $J = 14.7$, 6.8 Hz, 1H), 2.21-2.16 (m, 1H), 2.04-2.00 (m, 1H), 2.04-2.00 (m, 1H), 2.16 (d, $J = 2.7$ Hz, 1H), 2.16 (s, 3H), 1.37 (m, 1H), 1.35-1.34 (m, 1H), 1.34-1.31 (m, 1H), 1.31-1.29 (m, 1H), 1.19 (m, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 0.93 (t, $J = 7.9$ Hz, 9H), 0.54 (q, $J = 7.9$ Hz, 6H).

$^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 158.6, 131.1, 123.6, 112.6, 90.5, 79.0, 73.4, 54.5, 51.4, 46.49, 46.34, 44.5, 41.9, 39.3, 34.0, 32.7, 30.2, 30.0, 28.2, 26.3, 20.1, 18.9, 17.9, 7.3, 7.0.

FTIR (thin film) $\nu_{\text{max}}$: 2960, 2876, 2839, 1669, 1456, 1375, 1240, 1166, 1007, 853, 803, 743, 722 cm$^{-1}$.

HRMS–ESI (m / z): [M+H]$^+$ calculated for C$_{29}$H$_{32}$O$_4$Si, 493.3708; found, 493.3716.

$[\alpha]_D^{22} = +17.6^\circ$ (c 2.76, CHCl$_3$).

TLC $R_f = 0.50$ (9:1 hexane:EtOAc).
(3S,3aS,7R,7aS)-6,7a-Dimethoxy-3-methyl-3-(4-methyl-4-((triethylsilyl)oxy)pentyl)-7-(3-methylbut-2-en-1-yl)-3,3a,7,7a-tetrahydro-2,7-methanobenzofuran-4(2H)-one (383):

An EtOAc\(^{693}\) (500 mL) slurry of [bis(trifluoroacetoxy)iodo]benzene (133.9 g, 311.4 mmol, 3 equiv), cesium carbonate (146.5 g, 415.3 mmol, 4 equiv), 4Å molecular sieves (8.0 g, powdered), and \( \text{382} \) (51.16 g, 103.8 mmol, 1 equiv) in an open 2-L recovery flask was cooled using a –78 ºC dry ice/acetone bath with vigorous O\(_2\) bubbling through the slurry via three foreshortened glass pipettes. An EtOAc (200 mL, sparged for 1 h with O\(_2\) directly prior to the reaction) dilution of a nonane solution of tert-butyl hydroperoxide (5.5 M, 38 mmol, 210 mmol, 2 equiv) was added via cannula over 20 min. The resulting yellow slurry was allowed to slowly warm to –15 ºC over 2.5 h, at which point O\(_2\) bubbling was suspended. The reaction was then quenched at –15 ºC with sat. aq. Na\(_2\)S\(_2\)O\(_3\). After warming the slurry to rt, the layers were separated. The aqueous layer was extracted thrice with H\(_2\)O and once with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo to a red oil. Flash column chromatography (850 mL SiO\(_2\), 9:1 → 8:2 hexane:EtOAc) afforded 22.92 g (45.23 mmol, 44% yield) of 383 as a viscous yellow syrup.

\(^{1}\text{H NMR}\) (500 MHz; CDCl\(_3\)) \( \delta \): 5.28 (s, 1H), 5.24 (t, \( J = 7.1 \) Hz, 1H), 3.82 (d, \( J = 5.7 \) Hz, 1H), 3.64 (s, 3H), 3.40 (s, 3H), 2.61 (s, 1H), 2.36 (dd, \( J = 14.8, 6.2 \) Hz, 1H), 2.28 (dd, \( J = 14.8, 8.1 \) Hz, 1H), 1.95 (d, \( J = 13.0 \) Hz, 1H), 1.86 (dd, \( J = 13.0, 5.7 \) Hz, 1H), 1.63 (s, 3H), 1.56 (s, 3H), 1.26 (m, 1H), 1.24 (m, 1H), 1.21 (m, 1H), 1.20 (m, 1H), 1.19 (s, 3H), 1.09 (s, 6H), 1.04-0.96 (m, 1H), 0.85 (t, \( J = 7.9 \) Hz, 9H), 0.47 (q, \( J = 7.9 \) Hz, 6H).

\(^{13}\text{C NMR}\) (125 MHz; CDCl\(_3\)) \( \delta \): 197.8, 181.1, 132.6, 122.0, 115.2, 100.6, 80.6, 73.1, 56.7, 56.2, 52.0, 48.4, 48.0, 45.7, 38.7, 34.5, 32.0, 30.1, 29.7, 27.8, 26.1, 18.5, 17.8, 7.1, 6.8.

\(^{693}\) The EtOAc used in this procedure was sparged with O\(_2\) for 1 h directly prior to use.
HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{29}$H$_{50}$O$_5$Si, 529.3320; found, 529.3304.

$[\alpha]_{D}^{23} = +30.6^{\circ}$ (c 3.22, CHCl$_3$).

TLC R$_f$ = 0.50 (7:3 hexane:EtOAc).
(1S,5R,7S,8S,9S)-7,9-Dihydroxy-4,9-dimethoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-en-2-one (384):  
A CH₂Cl₂ (20 mL) solution of 383 (794 mg, 1.57 mmol, 1 equiv) and triethylamine (131 µL, 0.940 mmol, 6 equiv) in a 25-mL recovery flask was cooled using a –95 ºC ethanol/liquid nitrogen bath, and a CH₂Cl₂ solution of bromodimethylborane⁶⁹⁴ (1.59 M, 5.9 mL, 0.94 mmol, 6 equiv) was added slowly over 5 min, maintaining a bath temperature below –90 ºC. The resulting bright yellow solution was stirred at –95 ºC for an additional 10 min and sequentially quenched at –95 ºC with 6 mL NEt₃ and sat. aq. NaHCO₃. After warming the mixture to rt, it was extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with 2 N HCl, H₂O, sat. aq. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow-orange oil. Flash column chromatography (150 mL SiO₂, 8:2 → 7:3 hexane:EtOAc) afforded 471 mg (0.897 mmol, 57% yield) of 384 as a white flocculent solid.  

**¹H NMR** (600 MHz; CDCl₃) δ: 5.48 (s, 1H), 5.26 (d, J = 8.9 Hz, 1H), 5.05 (t, J = 7.1 Hz, 1H), 3.74 (s, 3H), 3.63-3.59 (m, 1H), 3.57 (s, 1H), 3.26 (s, 3H), 2.87-2.83 (m, 2H), 2.36 (tt, J = 12.5, 6.2 Hz, 1H), 2.25 (d, J = 14.0 Hz, 1H), 2.01-1.93 (m, 2H), 1.92-1.86 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.65 (s, 6H), 1.46 (td, J = 13.0, 4.8 Hz, 1H), 1.32 (d, J = 5.9 Hz, 1H), 1.11 (s, 3H), 1.05 (td, J = 12.9, 4.4 Hz, 1H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 198.2, 176.1, 137.4, 131.4, 125.0, 122.1, 104.1, 100.6, 73.2, 57.6, 56.6, 51.1, 48.5, 40.5, 39.2, 36.9, 30.0, 26.2, 25.9, 21.9, 18.00, 17.88, 17.0.

**FTIR** (thin film) νmax: 3465(br), 2954, 2913, 2876, 1659, 1645, 1606, 1456, 1365, 1225, 1173, 1087, 1044, 1016, 742, 725 cm⁻¹.

**HRMS–ESI** (m/z): [M+H]⁺ calculated for C₂₃H₃₆O₅, 393.2636; found, 393.2632.

[α]D²³ = –24º (c 0.70, CHCl₃).

⁶⁹⁴ A CH₂Cl₂ solution of bromodimethylborane was prepared as described in ref. 639b.
TLC $R_f = 0.50$ (1:1 hexane:EtOAc).
(1S,5R,7S,8S)-7-Hydroxy-4-methoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (385):

A THF (8 mL) solution of 384 (419.9 mg, 0.8001 mmol, 1 equiv) in a 50-mL recovery flask was cooled using a −78 ºC dry ice/acetone bath, and a freshly prepared THF solution of lithium 2,2,6,6-tetramethylpiperidide (0.50 M, 4.0 mL, 2.0 mmol, 2.5 equiv) was added. The resulting orange solution was allowed to warm to 0 ºC over 50 min. The reaction was then quenched at 0 ºC with sat. aq. NaHCO₃ at 0 ºC. The mixture was warmed to rt and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to an orange oil. Flash column chromatography (100 mL SiO₂, 7:3 hexane:EtOAc) afforded 381.6 mg (0.7744 mmol, 97% yield) of 385 as a viscous yellow oil.

1H NMR (600 MHz; CDCl₃) δ: 5.63 (s, 1H), 4.95 (t, J = 7.0 Hz, 1H), 3.78 (d, J = 7.8 Hz, 1H), 3.73 (s, 3H), 3.15 (s, 1H), 2.47 (dd, J = 14.5, 6.4 Hz, 1H), 2.37 (dd, J = 14.5, 7.6 Hz, 1H), 2.09 (dd, J = 13.4, 5.4 Hz, 1H), 1.88 (s, 1H), 1.73 (dd, J = 13.3, 11.6 Hz, 1H), 1.65 (m, 7H), 1.52 (td, J = 12.6, 3.5 Hz, 1H), 1.39 (td, J = 12.5, 4.1 Hz, 1H), 1.34-1.27 (m, 2H), 1.23 (m, 4H), 1.18 (s, 3H), 0.92 (t, J = 7.9 Hz, 9H), 0.86 (s, 3H), 0.54 (q, J = 7.8 Hz, 6H).

13C NMR (125 MHz; CDCl₃) δ: 205.4, 193.1, 177.4, 134.4, 119.0, 105.9, 73.6, 72.0, 69.2, 57.0, 56.0, 46.2, 45.6, 39.4, 38.4, 30.6, 29.50, 29.48, 26.1, 18.1, 17.9, 15.7, 7.3, 6.9.

FTIR (thin film) νmax: 3458(br), 2953, 2876, 1740, 1733, 1661, 1594, 1454, 1364, 1231, 1038, 842, 743, 724 cm⁻¹.

HRMS–ESI (m/z): [M+Na]⁺ calculated for C₂₉H₄₈O₅Si, 515.3163; found, 515.3170.

[α]D²³ = +32.1° (c 2.30, CHCl₃).

TLC Rₜ = 0.56 (1:1 hexane:EtOAc).
**O-(1S,2S,3S,5R)-6-Methoxy-2-methyl-2-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-yl) O-phenyl carbonothioate (387):**

A THF solution of 384 (71 mg, 0.14 mmol, 1 equiv) in a 10-mL recovery flask was cooled to –78 ºC, and a hexane solution of butyllithium (2.02 M, 141 µL, 0.28 mmol, 2.1 equiv) was added dropwise over 5 min. After stirring the reaction at –78 ºC for 20 min, O-phenyl chlorothionoformate (39 µL, 0.28 mmol, 2.1 equiv) was added in one portion. The resulting yellow solution was allowed to slowly warm to rt. After stirring for 90 min, the reaction was quenched at rt with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to an orange oil. Flash column chromatography (50 mL SiO₂, 95:5 hexane:EtOAc) afforded 51 mg (81 µmol, 60% yield) of 387 as a yellow oil.

**1H NMR** (600 MHz; CDCl₃) δ: 7.41 (dd, J = 8.4, 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.08-7.06 (m, 2H), 5.74 (s, 1H), 5.53 (dd, J = 11.5, 5.4 Hz, 1H), 4.99 (t, J = 7.0 Hz, 1H), 3.80 (s, 3H), 3.25 (s, 1H), 2.56-2.53 (m, 2H), 2.44 (dd, J = 14.6, 7.4 Hz, 1H), 1.86 (dd, J = 12.9, 11.7 Hz, 1H), 1.69-1.65 (m, 7H), 1.58-1.56 (m, 1H), 1.47-1.41 (m, 2H), 1.37 (m, 2H), 1.23 (s, 3H), 1.23 (s, 3H), 1.03 (s, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.9 Hz, 6H).

**13C NMR** (125 MHz; CDCl₃) δ: 204.2, 194.6, 192.2, 177.0, 153.4, 134.9, 129.8, 126.9, 122.0, 118.7, 106.3, 84.6, 73.6, 69.8, 57.4, 55.7, 45.66, 45.60, 38.1, 34.3, 30.5, 29.7, 29.4, 26.2, 18.2, 17.8, 17.5, 7.4, 7.0.

**FTIR** (thin film) νmax: 2958, 2911, 2874, 1739, 1659, 1594, 1490, 1275, 1206, 1034, 1017, 743 cm⁻¹.

**HRMS–ESI** (m / z): [M+Na]⁺ calculated for C₃₅H₅₂O₇SSi, 651.3152; found, 651.3130.

**TLC** Rₛ = 0.57 (7:3 hexane:EtOAc).
**O-((1S,2S,3S,5R)-6-Methoxy-2-methyl-2-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-en-3-yl)-O-(perfluorophenyl) carbonothioate (388):**

A PhMe (100 mL) solution of 385 (5.40 g, 11.0 mmol, 1 equiv), N-hydroxysuccinimide (1.26 g, 11.0 mmol, 1 equiv), and pyridine (4.4 mL, 55 mmol, 5 equiv) in a 200-mL recovery flask was treated with pentafluorophenyl chlorothionoformate (8.8 mL, 55 mmol, 5 equiv), and the resulting yellow-orange slurry was stirred at 80 ºC for 2 h. After cooling the resulting orange slurry to rt, it was diluted with EtOAc and sequentially washed twice with H2O and once with brine, dried over Na2SO4, filtered, and concentrated in vacuo to a black oil. Flash column chromatography (700 mL SiO2, 98:2 → 9:1 hexane:EtOAc) afforded 6.47 g (9.00 mmol, 82% yield) of 388 as viscous brown-orange syrup.

**1H NMR** (600 MHz; CDCl3) δ: 5.74 (s, 1H), 5.45 (dd, J = 11.6, 5.4 Hz, 1H), 4.98 (t, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.27 (s, 1H), 2.55 (dd, J = 14.5, 6.3 Hz, 1H), 2.50 (dd, J = 13.0, 5.4 Hz, 1H), 2.45 (dd, J = 14.5, 7.5 Hz, 1H), 1.92 (t, J = 12.3 Hz, 1H), 1.69-1.68 (m, 7H), 1.42-1.29 (m, 5H), 1.21 (s, 6H), 1.07 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 8.0 Hz, 6H).

**13C NMR** (125 MHz; CDCl3) δ: 203.7, 191.8, 176.8, 135.1, 118.4, 106.3, 87.2, 73.5, 69.6, 57.4, 55.6, 45.64, 45.45, 38.0, 34.0, 30.4, 29.7, 29.3, 26.1, 18.2, 17.7, 17.4, 7.3, 7.0.

**19F NMR** (282 MHz; CDCl3) δ: −152.71 (d, J = 18.1 Hz, 2F), −156.71 (t, J = 21.9 Hz, 1F), −162.21 (t, J = 19.8 Hz, 2F).

**FTIR** (thin film) v max: 2960, 2914, 2876, 1742, 1668, 1599, 1523, 1456, 1380, 1312, 1222, 1158, 1043, 966, 845, 743, 725 cm−1.

**HRMS–ESI** (m / z): [M+Na]+ calculated for C34H47F5O6SSi, 741.2675; found, 741.2667.

[α]D23 = +5.16° (c 2.28, CHCl3).
TLC $R_f = 0.69$ (7:3 hexane:EtOAc).
**O-((1S,2S,3S,5R)-6-Methoxy-2-methyl-2-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-3-yl) S-methyl carbonodithioate (389):**

A THF (2 mL) solution of 385 (18.0 mg, 36.5 µmol, 1 equiv) and carbon disulfide (22 µL, 0.37 mmol, 10 equiv) in a 10-mL recovery flask was cooled to 0 ºC, and sodium hydride (60% suspension in mineral oil, 15 mg, 0.37 mmol, 10 equiv) was added. After stirring the resulting white slurry at 0 ºC for 30 min, iodomethane (23 µL, 0.37 mmol, 10 equiv) was added. The resulting yellow slurry was allowed to slowly warm to rt. After stirring for 15.5 h, the reaction was quenched at rt with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to a yellow oil. Flash column chromatography (20 mL SiO₂, 98:2 → 95:5 → 9:1 hexane:EtOAc) afforded 16.8 mg (28.8 µmol, 79% yield) of 389 as a colorless oil.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.88 (dd, J = 11.6, 5.4 Hz, 1H), 5.73 (s, 1H), 4.97 (t, J = 7.0 Hz, 1H), 3.80 (s, 3H), 3.23 (s, 1H), 2.55-2.50 (m, 4H), 2.48 (dd, J = 13.0, 5.4 Hz, 1H), 2.40 (dd, J = 14.6, 7.3 Hz, 1H), 1.76 (dd, J = 13.0, 11.6 Hz, 1H), 1.62-1.60 (m, 7H), 1.40-1.22 (m, 5H), 1.19 (s, 6H), 1.07 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 215.8, 204.3, 192.2, 177.1, 134.8, 118.7, 106.2, 83.2, 73.5, 70.1, 57.3, 55.7, 45.8, 45.5, 38.3, 34.5, 30.5, 29.7, 29.3, 26.1, 19.2, 18.2, 17.86, 17.74, 7.4, 7.0

**FTIR** (thin film) νₘₐₓ: 2956, 2911, 2874, 1739, 1658, 1595, 1458, 1353, 1231, 1208, 1050, 742, 724 cm⁻¹.

**HRMS–ESI** (m / z): [M+Na]⁺ calculated for C₃₀H₅₀O₆S₂Si, 605.2761; found, 605.2737.

**TLC** Rₕ = 0.28 (9:1 hexane:EtOAc).
O-((1S,2S,3S,5R)-6-Methoxy-2-methyl-2-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-en-3-yl) 1H-imidazole-1-carbothioate (390):

A CH₂Cl₂ (1 mL) solution of 385 (19.2 mg, 39.0 µmol, 1 equiv), 1,1′-thiocarbonyldiimidazole (69 mg, 0.390 mmol, 10 equiv), and 4-(dimethylamino)pyridine (5 mg, 40 µmol, 1 equiv) in a 10-mL test tube was sealed and heated to 40 ºC. After stirring the brown-orange solution at 40 ºC for 30 h, it was cooled to rt, and quenched with a few drops of MeOH. The mixture was diluted with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to an orange oil. Flash column chromatography (25 mL SiO₂, 8:2 → 7:3 hexane:EtOAc) afforded 12.8 mg (21.2 µmol, 54% yield) of 390 as a colorless oil.

**¹H NMR** (600 MHz; CDCl₃) δ: 8.28 (s, 1H), 7.55 (s, 1H), 7.05 (s, 1H), 5.80-5.75 (m, 2H), 4.99 (t, J = 7.0 Hz, 1H), 3.85 (s, 3H), 3.29 (s, 1H), 2.56-2.51 (m, 2H), 2.44 (dd, J = 14.6, 7.5 Hz, 1H), 1.85 (t, J = 12.3 Hz, 1H), 1.71-1.64 (m, 7H), 1.40-1.23 (m, 5H), 1.17 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H), 0.91 (t, J = 7.9 Hz, 9H), 0.53 (q, J = 7.9 Hz, 6H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 203.7, 191.8, 183.4, 176.9, 137.0, 135.2, 131.4, 118.4, 117.9, 106.3, 83.8, 73.4, 69.6, 57.5, 55.6, 45.6, 45.4, 38.4, 34.2, 30.5, 29.6, 29.3, 26.2, 18.18, 18.04, 17.8, 7.4, 7.0.

**FTIR** (thin film) ν max: 2957, 2913, 2874, 1740, 1656, 1595, 1460, 1390, 1332, 1285, 1221, 1108, 1042, 986, 742, 724 cm⁻¹.

**HRMS–ESI** (m / z): [M+Na]⁺ calculated for C₃₂H₅₀N₂O₅SSi, 625.3102; found, 625.3082.

**TLC** Rₜ = 0.58 (1:1 hexane:EtOAc).
(15S,7S,8R)-7- Allyl-4-methoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-en-2,9-dione (386):

1H NMR (600 MHz; CDCl₃) δ: 5.69 (s, 1H), 5.65 (dddd, J = 16.8, 10.3, 8.5, 5.5 Hz, 1H), 5.01 (dd, J = 4.9, 0.8 Hz, 1H), 4.99 (dd, J = 11.7, 0.8 Hz, 1H), 4.96 (t, J = 7.0 Hz, 1H), 3.73 (s, 3H), 3.13 (s, 1H), 2.46 (dd, J = 14.4, 5.9 Hz, 1H), 2.36 (dd, J = 14.7, 7.8 Hz, 1H), 2.34-2.30 (m, 1H), 1.97 (dd, J = 13.9, 4.6 Hz, 1H), 1.77-1.69 (m, 2H), 1.67-1.64 (m, 4H), 1.63 (s, 3H), 1.48-1.38 (m, 3H), 1.34-1.32 (m, 1H), 1.27 (m, 1H), 1.24-1.22 (m, 4H), 1.21 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.81 (s, 3H), 0.57 (q, J = 7.8 Hz, 6H).

13C NMR (125 MHz; CDCl₃) δ: 207.2, 193.9, 177.5, 137.2, 133.9, 119.5, 116.8, 106.5, 73.7, 70.8, 56.98, 56.95, 46.2, 45.7, 39.8, 39.29, 39.16, 33.9, 30.6, 29.8, 29.6, 26.1, 18.13, 18.06, 17.90, 7.4, 7.0.

FTIR (thin film) νmax: 2961, 2917, 2876, 1733, 1657, 1599, 1599, 1460, 1315, 1227, 1171, 1042, 1017, 743, 724 cm⁻¹.

HRMS–ESI (m / z): [M+Na]⁺ calculated for C₃₁H₅₂O₄Si, 539.3527; found, 539.3521.

[α]D²³ = +23.5° (c 0.54, CHCl₃).

TLC Rf = 0.45 (8:2 hexane:EtOAc).

388 (6.46 g, 8.99 mmol, 1 equiv) was taken up in PhH (10 mL) and allyltributylstannane (30 mL) in a 200-mL recovery flask open to air, and a PhH solution of triethylborane (5.0 M, 0.90 mL, 4.5 mmol, 0.5 equiv) was added. The resulting golden yellow solution was stirred vigorously open to air for 30 min, and a PhH solution of triethylborane (5.0 M, 0.90 mL, 4.5 mmol, 0.5 equiv) was added. After stirring an additional 40 min, the solution was concentrated partially *in vacuo* and purified using flash column chromatography (700 mL SiO₂, 98:2 → 95:5 hexane:EtOAc) to afford 3.35 g (6.48 mmol, 72% yield) of 386 as a colorless oil and 701 mg (1.47 mmol, 16% yield) of 391 as a pale yellow oil.
(1S,5S,8R)-4-Methoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (391): 

$^1$H NMR (500 MHz; CDCl$_3$) δ: 5.72 (s, 1H), 4.96 (t, $J = 7.0$ Hz, 1H), 3.74 (s, 3H), 2.97 (s, 1H), 2.50 (dd, $J = 14.5$, 6.0 Hz, 1H), 2.38 (dd, $J = 14.5$, 7.8 Hz, 1H), 1.84-1.80 (m, 1H), 1.77 (dd, $J = 13.7$, 4.2 Hz, 1H), 1.69-1.67 (m, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 1.52-1.27 (m, 7H), 1.25-1.20 (m, 3H), 1.18 (s, 6H), 0.92 (t, $J = 7.9$ Hz, 9H), 0.54 (q, $J = 7.9$ Hz, 6H).

$^{13}$C NMR (125 MHz; CDCl$_3$) δ: 207.1, 194.1, 177.1, 133.9, 128.5, 119.5, 106.4, 73.6, 72.3, 56.9, 45.6, 43.5, 42.3, 33.4, 31.8, 30.5, 29.80, 29.76, 26.1, 22.0, 18.16, 18.12, 7.3, 7.0.

FTIR (thin film) $\nu_{\text{max}}$: 2954, 2911, 2875, 1733, 1655, 1597, 1458, 1365, 1224, 1044, 1015, 743, 724 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{28}$H$_{48}$O$_4$Si, 499.3214; found, 499.3204.

TLC $R_f = 0.38$ (8:2 hexane:EtOAc).
(1S,5R,7S,8R)-4-Methoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5,7-bis(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (392):

A CH$_2$Cl$_2$ (0.5 mL) and 2-methyl-2-butene (0.5 mL) solution of 386 (18.4 mg, 35.6 µmol, 1 equiv) and Hoveyda–Grubbs 2nd generation catalyst 117 (3.3 mg, 5.3 µmol, 0.15 equiv) in a sealed 10-mL test tube was stirred at 40 ºC for 2 h. The olive-black solution was subsequently cooled to rt and concentrated in vacuo. Flash column chromatography (50 mL SiO$_2$, 95:5 hexane:EtOAc) afforded 16.7 mg (30.6 µmol, 86% yield) of 392 as a colorless oil.

$^1$H NMR (600 MHz; CDCl$_3$) $\delta$: 5.69 (s, 1H), 4.98-4.94 (m, 2H), 3.73 (s, 3H), 3.12 (s, 1H), 2.45 (dd, $J = 14.2, 6.0$ Hz, 1H), 2.36 (dd, $J = 14.6, 7.7$ Hz, 1H), 2.14-2.11 (m, 1H), 1.93 (dd, $J = 14.0, 4.1$ Hz, 1H), 1.69 (s, 3H), 1.67-1.65 (m, 4H), 1.63 (s, 3H), 1.58-1.54 (m, 4H), 1.50-1.45 (m, 2H), 1.44-1.38 (m, 3H), 1.34-1.30 (m, 2H), 1.22 (s, 3H), 1.21 (s, 3H), 0.94 (t, $J = 7.9$ Hz, 9H), 0.82 (s, 3H), 0.57 (q, $J = 7.8$ Hz, 6H).

$^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 207.4, 194.0, 177.5, 133.8, 133.3, 122.9, 119.7, 106.5, 73.7, 70.9, 57.1, 56.9, 46.4, 45.7, 40.9, 39.5, 39.2, 30.6, 29.9, 29.6, 27.9, 26.10, 26.05, 18.16, 18.13, 18.06, 17.92, 7.4, 7.0.

FTIR (thin film) $v_{max}$: 2964, 2914, 2876, 1733, 1659, 1656, 1600, 1453, 1368, 1227, 1045, 1017, 723 cm$^{-1}$.

HRMS–ESI (m/z): [M+Na]$^+$ calculated for C$_{33}$H$_{56}$O$_4$Si, 567.3840; found, 567.3831.

$[\alpha]_{D}^{22} = +27.2^\circ$ (c 3.61, CHCl$_3$).

TLC $R_f = 0.49$ (9:1 hexane:EtOAc).
(1R,5R,7S,8R)-4-Methoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5,7-bis(3-methylbut-2-en-1-yl)-3-(trimethylsilyl)bicycle[3.3.1]non-3-ene-2,9-dione (393):

A THF (1 mL) solution of 392 (22.9 mg, 42.0 µmol, 1 equiv) in a 10-mL test tube was cooled to –78 ºC, and chlorotrimethylsilane (53 µL, 420 µmol, 10 equiv) and a freshly prepared THF solution of lithium 2,2,6,6-tetramethylpiperidide (0.50 M, 420 µL, 210 µmol, 5 equiv) were added sequentially. After allowing the resulting golden yellow solution to slowly warm to 0 ºC over 1 h, it was quenched at 0 ºC with sat. aq. NaHCO₃. The mixture was then extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (20 mL SiO₂, 98:2 hexane:EtOAc) afforded 23.4 mg (37.9 µmol, 90% yield) of 393 as a viscous yellow syrup.

¹H NMR (600 MHz; CDCl₃) δ: 5.02-4.97 (m, 2H), 3.83 (s, 3H), 3.11 (s, 1H), 2.51 (dd, J = 14.4, 6.3 Hz, 1H), 2.37 (dd, J = 14.5, 7.5 Hz, 1H), 2.15-2.11 (m, 1H), 1.99 (dd, J = 14.0, 3.7 Hz, 1H), 1.69 (s, 3H), 1.68-1.63 (m, 9H), 1.57 (s, 3H), 1.48 (td, J = 12.7, 3.9 Hz, 1H), 1.46-1.37 (m, 2H), 1.30 (td, J = 12.2, 4.1 Hz, 1H), 1.26-1.24 (m, 1H), 1.21 (s, 3H), 1.21 (s, 3H), 1.14 (td, J = 12.6, 4.2 Hz, 1H), 0.94 (t, J = 7.9 Hz, 9H), 0.80 (s, 3H), 0.57 (q, J = 8.1 Hz, 6H), 0.23 (s, 9H).

¹³C NMR (125 MHz; CDCl₃) δ: 207.9, 198.6, 185.7, 133.70, 133.59, 127.7, 122.8, 120.0, 73.7, 72.6, 64.1, 59.7, 46.7, 45.7, 41.8, 39.29, 39.27, 30.6, 30.0, 29.7, 27.6, 26.02, 25.97, 18.21, 18.14, 17.88, 17.83, 7.4, 7.0, 0.8.

FTIR (thin film) ν_max: 2962, 2914, 2876, 1729, 1652, 1556, 1461, 1440, 1382, 1247, 1216, 1045, 845, 743, 724 cm⁻¹.

HRMS–ESI (m / z): [M+H]⁺ calculated for C₃₆H₆₄O₄Si₂, 617.4416; found, 617.4395.

[α]D²³ = +29.8º (c 1.24, CHCl₃).
TLC $R_f = 0.40$ (95:5 hexane:EtOAc).
(1R,5S,7S,8R,9S)-9-Hydroxy-4-methoxy-8,9-dimethyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5,7-
bis(3-methylbut-2-en-1-yl)-3-(trimethylsilyl)bicyclo[3.3.1]non-3-en-2-one (394):

A THF (0.5 mL) solution of 393 (7.4 mg, 12 µmol, 1 equiv) in a 10-mL test tube was cooled to –78 ºC, and a freshly prepared THF solution of dilithium (cyano-κC)methyl(2,2,6,6-tetramethyl-1-piperidinyl)copper\textsuperscript{695} (0.17 M, 353 µL, 60. µmol, 5 equiv) was added dropwise. The resulting pale yellow solution was stirred at –78 ºC for 10 min and at 0 ºC for 15 min. The resulting yellow solution was subsequently cooled to –78 ºC, and a THF solution of isobutyryl chloride (1.0 M, 60. µL, 60. µmol, 5 equiv) was added. The reaction was stirred at –78 ºC for 30 min and then allowed to slowly warm to rt. After stirring an additional 2.5 h, the reaction was quenched at rt with sat. aq. NH₄Cl and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O, sat. aq. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated \textit{in vacuo} to a yellow residue. Preparatory thin-layer chromatography (1 × 95:5 hexane:EtOAc) afforded 3.7 mg (5.8 µmol, 49% yield) of 394 as a white flocculent solid and 1.1 mg (1.8 µmol, 15% recovery) of 393 as a pale yellow residue.

\textbf{1H NMR} (600 MHz; CDCl₃) δ: 5.40 (t, \(J = 6.8\) Hz, 1H), 5.05 (t, \(J = 7.3\) Hz, 1H), 3.73 (s, 3H), 2.43-2.41 (m, 2H), 2.27 (s, 1H), 2.14 (dd, \(J = 13.2, 5.4\) Hz, 1H), 2.02 (t, \(J = 13.2\) Hz, 1H), 1.80-1.75 (m, 1H), 1.74-1.72 (m, 4H), 1.67-1.63 (m, 7H), 1.61 (s, 3H), 1.50-1.36 (m, 4H), 1.34-1.24 (m, 5H), 1.23 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.06 (s, 3H), 0.94 (t, \(J = 7.9\) Hz, 9H), 0.56 (q, \(J = 7.9\) Hz, 6H), 0.22 (s, 9H).

\textbf{13C NMR} (125 MHz; CDCl₃) δ: 205.2, 187.1, 133.3, 132.8, 125.8, 124.1, 122.0, 100.3, 75.9, 74.0, 66.7, 63.7, 52.6, 46.1, 42.9, 41.9, 38.0, 31.02, 30.83, 30.66, 29.4, 28.5, 27.3, 26.4, 26.0, 22.1, 18.2, 17.8, 7.4, 7.0, 0.9.

\textsuperscript{695} For the preparation of a THF solution of dilithium (cyano-κC)methyl(2,2,6,6-tetramethyl-1-piperidinyl)copper, see ref. 675.
**FTIR** (thin film) $\nu_{\text{max}}$: 3503 (br), 2957, 2913, 1651, 1564, 1459, 1380, 1244, 1050, 843, 742, 723 cm$^{-1}$.

**HRMS–ESI** ($m/z$): [M+H]$^+$ calculated for $C_{37}H_{68}O_4Si_2$, 633.4729; found, 633.4726.

**TLC** $R_f = 0.18$ (95:5 hexane:EtOAc).
(1S,5R,7S,8R)-1-Isobutyryl-4-methoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-5,7-bis(3-methylbut-2-en-1-yl)-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione (395):

A THF (200 µL) solution of 393 (15.9 mg, 25.8 µmol, 1 equiv) in a 10-mL pear-shaped flask was cooled to –78 ºC, and a freshly prepared THF solution of lithium 2,2,6,6-tetramethylpiperidide (0.50 M, 155 µL, 77.3 µmol, 3 equiv) was added dropwise. The resulting yellow solution was stirred at –78 ºC for 10 min and at 0 ºC for 5 min. The resulting orange solution was then cooled to –78 ºC, and isobutyryl cyanide (12.5 mg, 129 µmol, 5 equiv) was added. The resulting yellow solution was slowly warmed to –30 ºC over 35 min and subsequently quenched with sat. aq. NaHCO₃. The mixture was warmed to rt and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow residue. Preparatory thin-layer chromatography (3 × 98:2 hexane:EtOAc) afforded 8.6 mg (13 µmol, 49% yield) of 395 as a colorless residue.

**1H NMR** (600 MHz; CDCl₃) δ: 4.98 (m, 1H), 4.97 (m, 1H), 3.91-3.88 (s, 3H), 2.55 (dd, J = 14.5, 6.2 Hz, 1H), 2.41 (dd, J = 14.4, 7.6 Hz, 1H), 2.08 (d, J = 13.5 Hz, 1H), 1.97 (septet, J = 6.5 Hz, 1H), 1.92-1.89 (m, 1H), 1.89-1.85 (m, 1H), 1.78-1.70 (m, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 1.66 (s, 3H), 1.60-1.59 (m, 1H), 1.57-1.56 (s, 3H), 1.50-1.45 (m, 1H), 1.45-1.42 (m, 1H), 1.38-1.35 (m, 1H), 1.34-1.33 (m, 1H), 1.33-1.30 (m, 1H), 1.29-1.25 (m, 1H), 1.17 (s, 3H), 1.16 (s, 3H), 1.13 (d, J = 6.5 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H), 0.98 (s, 3H), 0.92 (t, J = 7.9 Hz, 9H), 0.54 (q, J = 8.0 Hz, 6H), 0.26 (s, 9H).

**13C NMR** (125 MHz; CDCl₃) δ: 209.4, 197.6, 187.3, 134.4, 133.7, 128.3, 122.9, 119.4, 85.2, 73.6, 64.8, 59.6, 49.5, 46.1, 44.4, 43.0, 38.4, 37.4, 30.4, 30.0, 27.3, 26.13, 25.96, 21.7, 21.1, 20.7, 18.28, 18.12, 13.8, 7.4, 7.0, 0.7.

For the preparation of isobutyryl cyanide, see ref. 520.
FTIR (thin film) νₘₚₐₓ: 2965, 2914, 2876, 1730, 1565, 1561, 1456, 1379, 1315, 1249, 1220, 1156, 1049, 845, 743, 724 cm⁻¹.

HRMS–ESI (m/z): [M+Na]⁺ calculated for C₄₀H₇₀O₅Si₂, 709.4654; found, 709.4626.

[α]²²_D = –42.9° (c 0.46, CH₂Cl₂).

TLC Rᶠ = 0.47 (95:5 hexane:EtOAc).
(2S,3S,3aS,7R,7aS)-6,7a-Dimethoxy-3-methyl-3-(4-methyl-4-((triethylsilyl)oxy)pentyl)-7-(3-methylbut-2-en-1-yl)-5-(trimethylsilyl)-3,3a,7,7a-tetrahydro-2,7-methanobenzofuran-4(2H)-one (396):

A THF (3 mL) solution of 383 (147 mg, 0.290 mmol, 1 equiv) in a 10-mL test tube was cooled to –78 ºC, and chlorotrimethylsilane (184 µL, 1.45 mmol, 5 equiv) and a freshly prepared THF solution of lithium 2,2,6,6-tetramethylpiperidide (0.50 M, 1.7 mL, 0.87, 3 equiv) were added sequentially. The resulting bright yellow solution was stirred at –78 ºC for 10 min and then allowed to slowly warm to –35 ºC over 25 min. The reaction was subsequently quenched at –35 ºC with sat. aq. NaHCO₃ and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (50 mL SiO₂, 95:5 hexane:EtOAc) afforded 114 mg (0.197 mmol, 68% yield) of 396 as a colorless oil.

**¹H NMR** (600 MHz; CDCl₃) δ: 5.27 (t, J = 6.9 Hz, 1H), 3.85 (d, J = 5.6 Hz, 1H), 3.72 (s, 3H), 3.43 (s, 3H), 2.62 (s, 1H), 2.51 (dd, J = 15.3, 6.9 Hz, 1H), 2.28 (dd, J = 15.3, 6.9 Hz, 1H), 2.12 (d, J = 12.6 Hz, 1H), 1.90 (dd, J = 12.6, 5.6 Hz, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.40-1.23 (m, 4H), 1.25-1.17 (m, 5H), 1.16 (s, 3H), 1.14 (s, 3H), 0.90 (t, J = 7.8 Hz, 9H), 0.52 (q, J = 7.8 Hz, 6H), 0.19 (s, 9H).

**¹³C NMR** (125 MHz; CDCl₃) δ: 202.7, 187.3, 132.1, 122.2, 121.6, 115.2, 80.7, 73.3, 61.2, 57.5, 52.2, 49.1, 48.1, 46.0, 39.4, 35.1, 32.7, 30.6, 29.6, 28.0, 26.2, 18.7, 18.0, 7.3, 7.0, 1.1.

**FTIR** (thin film) νₘₐₓ: 2953, 2910, 2875, 1646, 1571, 1458, 1311, 1244, 1224, 1070, 1045, 1011, 843, 723 cm⁻¹.

**HRMS–ESI** (m / z): [M+K]⁺ calculated for C₃₂H₅₈O₅Si₂, 617.3454; found, 617.3437.

**TLC** Rₜ = 0.67 (8:2 hexane:EtOAc).
(1S,5R,7S,8R)-4-Methoxy-8-methyl-8-(4-methyl-4-((triethylsilyl)oxy)pentyl)-3,5,7-tris(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (397):

A THF (0.5 mL) solution of 392 (7.2 mg, 13 µmol, 1 equiv) in a 10-mL test tube was cooled to –78 ºC, and a freshly prepared THF solution of lithium 2,2,6,6-tetramethylpiperidide (0.50 M, 53 µL, 26 µmol, 2 equiv) was added dropwise. After stirring the resulting bright yellow solution at –78 ºC for 20 min, a THF solution of lithium (2-thienyl)cyanocopper(I) 511 (0.10 M, 264 µL, 26.4 mmol, 2 equiv) was added. The resulting brown slurry was allowed to slowly warm to –40 ºC over 20 min and subsequently stirred at –40 ºC for 30 min. The resulting pale yellow solution was cooled to –78 ºC, and prenyl bromide (7.6 µL, 66 µmol, 5 equiv) was added. The reaction was allowed to slowly warm to 0 ºC over 2 h, and was then quenched at 0 ºC with sat. aq. NH₄Cl and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O, sat. aq. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a brown oil. Flash column chromatography (20 mL SiO₂, 98:2 hexane:EtOAc) afforded 7.0 mg (11 µmol, 86% yield) of 397 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.03-4.99 (m, 2H), 4.97 (t, J = 7.4 Hz, 1H), 3.88 (s, 3H), 3.17 (s, 1H), 3.11 (d, J = 6.3 Hz, 2H), 2.47 (dd, J = 14.7, 6.0 Hz, 1H), 2.34 (dd, J = 14.7, 7.1 Hz, 1H), 2.15-2.10 (m, 1H), 1.98 (dd, J = 14.0, 3.9 Hz, 1H), 1.71-1.68 (m, 4H), 1.67 (s, 6H), 1.66-1.65 (m, 4H), 1.65 (s, 3H), 1.57 (s, 3H), 1.47 (td, J = 12.7, 4.1 Hz, 1H), 1.43-1.36 (m, 3H), 1.36-1.28 (m, 2H), 1.22 (s, 3H), 1.21 (s, 3H), 1.11 (td, J = 12.7, 4.0 Hz, 1H), 0.94 (t, J = 7.8 Hz, 9H), 0.80 (s, 3H), 0.57 (q, J = 7.8 Hz, 6H).

¹³C NMR (125 MHz; CDCl₃) δ: 207.5, 195.0, 174.3, 133.51, 133.37, 132.6, 126.9, 122.9, 122.5, 120.2, 73.7, 71.3, 62.3, 58.8, 46.7, 45.8, 41.3, 39.27, 39.07, 30.7, 30.3, 29.5, 27.7, 26.05, 26.00, 25.84, 23.5, 18.23, 18.19, 18.12, 17.99, 17.82, 7.4, 7.0.
FTIR (thin film) $\nu_{\text{max}}$: 2963, 2914, 2875, 1732, 1655, 1601, 1452, 1382, 1340, 1233, 1170, 1043, 1016, 743, 723 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{38}$H$_{64}$O$_4$Si, 635.4466; found, 635.4449.

TLC $R_f = 0.45$ (9:1 hexane:EtOAc).
(1R,5R,7S,8R)-1-Isobutyryl-4-methoxy-8-methyl-5,7-bis(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)bicyclo[3.3.1]non-3-en-2,9-dione (398):

A PhMe (0.5 mL) solution of 395 (2.2 mg, 3.2 µmol, 1 equiv) in a 7-mL microwave vial was treated with 2-methyl-2-butene (100 µL), HOAc (50 µL), and a HOAc solution of para-toluenesulfonic acid monohydrate (1.0 M, 6.4 µL, 6.4 µmol, 2 equiv). The vial was sealed and irradiated in a microwave reactor (200 watt power) to 100 ºC and held at that temperature for 15 min. The resulting yellow solution was cooled to rt, quenched with sat. aq. NaHCO₃, and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow residue. Preparatory thin-layer chromatography (3 × 1:1 hexane:CH₂Cl₂) afforded 1.0 mg (2.1 µmol, 65% yield) of 398 as a colorless residue.

**1H NMR** (600 MHz; CDCl₃) δ: 5.89 (s, 1H), 5.04 (t, J = 6.8 Hz, 1H), 4.98 (t, J = 6.8 Hz, 1H), 4.93 (t, J = 6.3 Hz, 1H), 3.80 (s, 3H), 2.49 (dd, J = 14.8, 6.5 Hz, 1H), 2.42 (dd, J = 14.7, 7.6 Hz, 1H), 2.15-2.07 (m, 3H), 1.95-1.82 (m, 3H), 1.78-1.73 (m, 1H), 1.69 (s, 3H), 1.72-1.64 (m, 1H), 1.663 (s, 3H), 1.661 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.46-1.40 (m, 2H), 1.13 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 6.5 Hz, 3H), 1.00 (s, 3H).

**13C NMR** (125 MHz; CDCl₃) δ: 209.5, 207.1, 193.0, 177.4, 134.4, 133.5, 131.3, 124.9, 122.6, 119.3, 107.0, 84.4, 57.30, 57.12, 49.1, 43.2, 42.7, 39.4, 36.8, 29.7, 27.5, 26.18, 26.08, 25.91, 25.2, 21.7, 20.7, 18.21, 18.19, 17.9, 13.8.

**FTIR** (thin film) νmax: 2967, 2926, 2855, 1728, 1722, 1645, 1601, 1456, 1376, 1227 cm⁻¹.

**HRMS–ESI** (m / z): [M+H]⁺ calculated for C₃₁H₄₆O₄, 483.3468; found, 483.3469.

\[ [\alpha]_{D}^{22} = +37.0° \] (c 0.13, CHCl₃).

**TLC** Rₜ = 0.26 (9:1 hexane:EtOAc).
(1R,5R,7S,8R)-1-Isobutyryl-4-methoxy-8-methyl-5,7-bis(3-methylbut-2-en-1-yl)-8-(4-methylpent-4-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (399):

A PhMe (3 mL) solution of 395 (58.0 mg, 84.4 µmol, 1 equiv) in a 7-mL microwave vial was treated with 2-methyl-2-butene (100 µL), HOAc (100 µL), magnesium sulfate (51 mg, 0.42 mmol, 5 equiv), and a HOAc solution of para-toluene sulfonic acid monohydrate (1.0 M, 60. µL, 60. µmol, 0.7 equiv). The vial was sealed and irradiated in a microwave reactor (200 watt power) to 100 ºC and held at that temperature for 15 min. The resulting yellow slurry was cooled to rt, quenched with sat. aq. NaHCO₃, and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. The oil was split into two samples and purified using preparatory high-performance liquid chromatography with a 30 mm × 250 mm Agilent Prep-SIL 10 µm column (injection volume: 500 µL each, hexane; detection at 254 nm; 23 ºC ± 2 ºC column temperature; 40 mL/min flow rate; gradient elution from 100:0 → 60:40 hexane:CH₂Cl₂ over 45 min). The fractions eluting at 34-37 min were collected and concentrated in vacuo to afford 6.2 mg (13 µmol, 15% yield) of 399 as a colorless oil. The fractions eluting at 28-33 min were collected and concentrated in vacuo to afford 19.3 mg (39.8 µmol, 47% yield) of 398 as a colorless oil.

¹H NMR (600 MHz; CDCl₃) δ: 5.89 (s, 1H), 4.98 (t, J = 6.9 Hz, 1H), 4.93 (t, J = 6.8 Hz, 1H), 4.71-4.59 (m, 2H), 3.80 (s, 3H), 2.48 (dd, J = 14.5, 6.0 Hz, 1H), 2.42 (dd, J = 14.5, 7.8 Hz, 1H), 2.11 (septet, J = 6.5 Hz, 1H), 2.06 (dd, J = 13.9, 5.3 Hz, 1H), 1.96-1.83 (m, 4H), 1.76-1.72 (m, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.66 (s, 6H), 1.59-1.55 (m, 5H), 1.45-1.34 (m, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 6.5 Hz, 3H), 0.99 (s, 3H).
$^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 209.6, 207.1, 193.0, 177.4, 146.3, 134.4, 133.5, 122.7, 119.3, 110.0, 107.0, 84.4, 57.32, 57.12, 49.1, 43.3, 42.7, 39.4, 38.8, 36.8, 29.7, 27.5, 26.19, 26.10, 24.5, 22.7, 21.7, 20.7, 18.22, 18.17, 13.8.

FTIR (thin film) $\nu_{\text{max}}$: 2968, 2927, 2872, 1729, 1645, 1601, 1449, 1374, 1231 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{31}$H$_{46}$O$_4$, 505.3288; found, 505.3278.

TLC $R_f = 0.26$ (9:1 hexane:EtOAc).
A THF (5 mL) solution of 398 (107.4 mg, 222.5 µmol, 1 equiv) in a 50-mL pear-shaped flask was cooled using a –78 ºC dry ice/acetone bath, and a freshly prepared THF solution of lithium diisopropylamide (0.50 M, 1.3 mL, 670 µmol, 3 equiv) was added dropwise. After stirring the resulting yellow solution at –78 ºC for 20 min, a freshly prepared THF solution of 2-thienyl(cyano)copper lithium (0.10 M, 6.7 mL, 0.67 mmol, 3 equiv) was added dropwise. The resulting light brown solution was stirred at –78 ºC for 5 min and at –40 ºC for 30 min. The solution was then cooled using a –78 ºC dry ice/acetone bath, and prenyl bromide (437 µL, 3.34 mmol, 15 equiv) was added dropwise. After slowly warming the golden yellow solution to –30 ºC over 90 min, it was quenched at –30 ºC with sat. aq. NH₄Cl, warmed to rt, and extracted thrice with EtOAc. The organic extracts were combined, sequentially washed with H₂O, sat. aq. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to a yellow oil. Flash column chromatography (75 mL SiO₂, 98:2 hexane:EtOAc) afforded 120.6 mg (219.0 µmol, 98% yield) of 60 as a colorless oil.

**1H NMR** (500 MHz; CDCl₃) δ: 5.07-5.02 (m, 2H), 4.99 (t, J = 6.7 Hz, 1H), 4.95 (t, J = 7.1 Hz, 1H), 3.92 (s, 3H), 3.18 (d, J = 6.5 Hz, 2H), 2.50 (dd, J = 14.7, 6.0 Hz, 1H), 2.41 (dd, J = 14.7, 7.4 Hz, 1H), 2.11-2.06 (m, 2H), 1.99 (septet, J = 6.5 Hz, 1H), 1.92-1.84 (m, 3H), 1.77-1.70 (m, 1H), 1.69-1.66 (m, 15H), 1.64 (s, 3H), 1.63-1.62 (m, 1H), 1.59 (s, 3H), 1.56 (s, 3H), 1.44-1.41 (m, 1H), 1.39-1.37 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H), 0.99 (s, 3H).
\(^{13}\text{C NMR}\) (125 MHz; CDCl\(_3\)) \(\delta\): 209.3, 207.3, 194.1, 174.1, 134.0, 133.5, 133.2, 131.2, 127.6, 125.0, 122.7, 121.9, 119.9, 84.3, 62.6, 58.9, 49.4, 43.4, 42.8, 39.1, 36.7, 30.3, 27.3, 26.10, 26.01, 25.88, 25.80, 25.1, 23.6, 21.5, 20.6, 18.27, 18.14, 18.12, 17.9, 13.8.

\textbf{FTIR} (thin film) \(\nu_{\text{max}}\): 2968, 2927, 2874, 1730, 1725, 1645, 1601, 1447, 1377, 1338, 1236, 1100, 1079, 1060 cm\(^{-1}\).

\textbf{HRMS–ESI} (m / z): [M+H]\(^+\) calculated for C\(_{36}\)H\(_{54}\)O\(_4\), 551.4095; found, 551.4102.

\([\alpha]_{D}^{22} = +49.6^\circ\) (c 0.33, CHCl\(_3\)).

\textbf{TLC} : \(R_f = 0.52\) (9:1 hexane:EtOAc).
Table 3.5. NMR data comparison of synthetic 60 with 60 derived from natural hyperforin (ref. 309).

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<td><strong>13C NMR (125 MHz, CDCl&lt;sub&gt;3&lt;/sub&gt;)</strong></td>
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<th>Synthetic&lt;sup&gt;b&lt;/sup&gt;</th>
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<td><strong>13C NMR (125 MHz, CDCl&lt;sub&gt;3&lt;/sub&gt;)</strong></td>
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</table>

<sup>a</sup> Several NMR signals for 60 are not reported in ref. 309. In particular, there are only 50 protons reported for 60, which contains 54 protons. Also, the shift of the O-methyl group is not reported in the 13C NMR data.

<sup>b</sup> For the purpose of this analysis, the CDCl<sub>3</sub> signal in the 13C NMR of synthetic 60 was re-referenced to 77.00 ppm to match the reported chemical shift reference in ref. 309.
Note: All manipulations for the following procedure were conducted in the dark. Solvents used during the workup procedure were sparged for at least 15 min with N\textsubscript{2} prior to use.

A DMSO (3 mL) slurry of 60 (74.9 mg, 136 \( \mu \text{mol} \), 1 equiv) and lithium chloride (58 mg, 1.4 mmol, 10 equiv) in a 15-mL round-bottom flask was heated to 120 °C. After stirring the pale yellow solution for 30 min at 120 °C, it was cooled to rt, diluted with H\textsubscript{2}O, and extracted thrice with 1:1 hexane:EtOAc. The organic extracts were combined, sequentially washed thrice with H\textsubscript{2}O and once with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated \textit{in vacuo} to afford a yellow oil. Flash column chromatography (30 mL SiO\textsubscript{2}, 95:5 hexane:EtOAc) afforded 40.0 mg (74.5 \( \mu \text{mol} \), 55% yield) of 1 as a colorless oil, 10.8 mg (19.6 \( \mu \text{mol} \), 14% yield) of 400 as a colorless oil, and 12.5 mg (23.3 \( \mu \text{mol} \), 23% yield) of 401 as a colorless oil.

\textbf{Hyperforin (1):}

\textbf{\textit{\textsuperscript{1}H NMR}} (500 MHz; CD\textsubscript{3}OD) \( \delta \): 5.12 (t, \( J = 7.0 \text{ Hz} \), 1H), 5.04-4.95 (m, 3H), 3.12 (dd, \( J = 14.6, 7.2 \text{ Hz}, 1\text{H} \)), 3.07 (dd, \( J = 14.7, 7.1 \text{ Hz}, 1\text{H} \)), 2.49 (dd, \( J = 14.4, 6.9 \text{ Hz}, 1\text{H} \)), 2.40 (dd, \( J = 14.6, 6.8 \text{ Hz}, 1\text{H} \)), 2.14 (septet, \( J = 6.5 \text{ Hz}, 1\text{H} \)), 2.10-2.02 (m, 1H), 2.02-1.87 (m, 3H), 1.78-1.72 (m, 3H), 1.71 (s, 3H), 1.68 (s, 6H), 1.66 (s, 3H), 1.66-1.63 (m, 1H), 1.64 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.37 (dd, \( J = 13.3, 12.2 \text{ Hz}, 1\text{H} \)), 1.09 (d, \( J = 6.5 \text{ Hz}, 3\text{H} \)), 1.04 (d, \( J = 6.5 \text{ Hz}, 3\text{H} \)), 0.97 (s, 3H).

\textbf{\textit{\textsuperscript{13}C NMR}} (125 MHz; CD\textsubscript{3}OD) \( \delta \): 211.7, 208.8, 134.6, 134.2, 133.5, 131.8, 126.1, 123.8, 122.6, 122.1, 120.9, 82.6, 60.7, 49.5, 43.05, 43.02, 40.8, 37.9, 30.7, 28.6, 26.16, 26.06, 25.99, 25.92, 25.4, 22.5, 22.0, 21.2, 18.27, 18.16, 18.11, 17.86, 15.3.

\textbf{FTIR} (thin film) \( \nu_{\text{max}} \): 3326 (br), 2969, 2925, 2876, 1725, 1601, 1447, 1377, 1232, 838 cm\textsuperscript{-1}.

\textbf{HRMS–ESI} (m / z): [M+H]\(^+\) calculated for C\textsubscript{33}H\textsubscript{52}O\textsubscript{4}, 537.3938; found, 537.3937.
\[ \alpha \]_D^{23} = +39.5^\circ \text{ (c 3.02, EtOH)}; \text{ [natural sample from literature:} \]_D^{18} = +41^\circ \text{ (c 5, EtOH)}].

**TLC** \( R_f = 0.26 \) (9:1 hexane:EtoAc).

(35,4aS,65,7R)-8-Isobutyryl-3,7-dimethyl-3,4a,6-tris(3-methylbut-2-en-1-yl)-7-(4-methylpent-3-en-1-yl)-4a,5,6,7-tetrahydro-2H-chromene-2,4(3H)-dione (400):

\(^1H\) NMR (500 MHz; CDCl\(_3\)) \( \delta \): 5.09 (t, \( J = 6.1 \text{ Hz}, 1\text{H} \)), 5.01-4.96 (m, 2H), 4.93 (t, \( J = 6.4 \text{ Hz}, 1\text{H} \)), 2.71 (septet, \( J = 6.9 \text{ Hz}, 1\text{H} \)), 2.64 (dd, \( J = 13.7, 8.1 \text{ Hz}, 1\text{H} \)), 2.57 (dd, \( J = 13.7, 7.1 \text{ Hz}, 1\text{H} \)), 2.46 (dd, \( J = 13.5, 2.7 \text{ Hz}, 1\text{H} \)), 2.25 (dd, \( J = 14.5, 7.0 \text{ Hz}, 1\text{H} \)), 2.06 (dd, \( J = 13.8, 4.9 \text{ Hz}, 1\text{H} \)), 1.84-1.76 (m, 5H), 1.74-1.69 (m, 4H), 1.69-1.63 (m, 4H), 1.62 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.52-1.49 (m, 1H), 1.47 (s, 3H), 1.37 (t, \( J = 13.3 \text{ Hz}, 1\text{H} \)), 1.31-1.25 (m, 1H), 1.21 (d, \( J = 6.9 \text{ Hz}, 3\text{H} \)), 1.15 (d, \( J = 6.9 \text{ Hz}, 3\text{H} \)), 1.14 (s, 3H), 1.11-1.07 (m, 1H).

\(^13C\) NMR (125 MHz; CDCl\(_3\)) \( \delta \): 209.0, 205.2, 169.8, 144.5, 137.2, 136.25, 136.11, 133.4, 132.0, 124.0, 122.5, 119.3, 117.1, 56.8, 52.3, 42.6, 40.9, 37.51, 37.37, 34.3, 31.5, 27.27, 27.15, 26.24, 26.14, 26.10, 25.9, 25.2, 23.2, 22.8, 18.7, 18.31, 18.28, 18.25, 17.8, 17.5.

**FTIR** (thin film) \( \nu_{\max} \): 2971, 2930, 2875, 1778, 1724, 1699, 1665, 1451, 1377, 1255, 1237, 1136, 1094, 1056, 844 cm\(^{-1}\).

**HRMS–ESI** (m / z): [M+H]+ calculated for C\(_{36}\)H\(_{54}\)O\(_4\), 551.4096; found, 551.4095.

**TLC** \( R_f = 0.66 \) (9:1 hexane:EtoAc).

(4aR,6S,7R)-4-Hydroxy-8-isobutyryl-7-methyl-3,4a,6-tris(3-methylbut-2-en-1-yl)-7-(4-methylpent-3-en-1-yl)-4a,5,6,7-tetrahydro-2H-chromen-2-one (401):

\(^1H\) NMR (500 MHz; CDCl\(_3\)) \( \delta \): 5.11-4.98 (m, 3H), 4.93 (t, \( J = 6.5 \text{ Hz}, 1\text{H} \)), 3.35-3.33 (m, \( \sim 0.7\text{H} \)), 3.22 (dd, \( J = 8.3, 5.8 \text{ Hz}, \sim 0.3\text{H} \)), 2.77-2.56 (m, 3H), 2.52-2.42 (m, 1H), 2.25 (dd, \( J = 14.2, 6.3 \text{ Hz}, \sim 0.3\text{H} \)), 2.17-2.02 (m, 2H), 1.91 (dd, \( J = 14.5, 8.2 \text{ Hz}, \sim 0.7\text{H} \)), 1.88-1.80 (m, 1H), 1.76 (s, \( \sim 1\text{H} \)), 1.75 (s, \( \sim 2\text{H} \)), 1.72 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.63-1.62 (m, 4H), 1.62-1.61 (m, 4H), 1.60 (s, 3H), 1.60-1.44 (m, 7H), 1.44-1.25 (m, 3H), 1.23 (s, 3H), 1.15-1.11 (m, 3H) (mixture of tautomers and diastereomers).
$^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 208.9, 202.3, 201.7, 167.2, 166.2, 145.3, 144.9, 137.75, 137.65, 137.4
136.9, 135.3, 133.50, 133.40, 132.00, 131.94, 124.03, 123.93, 122.49, 122.37, 119.7, 118.0, 116.97,
116.88, 55.2, 54.6, 53.1, 52.6, 42.78, 42.64, 41.1, 37.9, 37.63, 37.46, 37.32, 34.1, 32.7, 29.6, 28.1, 27.34,
27.31, 27.27, 26.24, 26.09, 26.07, 26.04, 25.90, 23.41, 23.21, 23.06, 22.97, 22.85, 18.95, 18.76, 18.35,
18.28, 18.24, 18.22, 18.10, 17.86, 17.83, 17.81, 17.63 (mixture of tautomers and diastereomers).

FTIR (thin film) $\nu_{\max}$: 2969, 2916, 2875, 1781, 1728, 1697, 1665, 1447, 1377, 1254, 1223, 1142, 1102,
1050 cm$^{-1}$.

HRMS–ESI (m / z): [M+Na]$^+$ calculated for C$_{35}$H$_{52}$O$_4$, 559.3758; found, 559.3756.

TLC $R_f = 0.51$ (9:1 hexane:EtOAc).
Figure 3.5. $^1$H NMR spectra comparison of natural and synthetic hyperforin (1).
NMR Data Comparison of Synthetic and Natural Hyperforin (1).

On the following pages, the $^1$H and $^{13}$C NMR data for synthetic 1 are compared to published data for natural 1 as well as synthetic ent-1. All NMR data have been acquired using CD$_3$OD solvent. NMR spectrometer frequencies are noted.

The references from which NMR data for natural 1 are presented include:


The reference from which NMR data for ent-1 are presented:


The positional numbering scheme used for these tables is shown below.
As previously noted, small deviations in the NMR data from the different references may be attributed to not only different chemical shift references but also to the concentration of I and to the water content in the NMR sample, which influence the keto-enol tautomerization at the hyperforin C2–C4 position. In the $^1$H NMR analysis of I, we observed concentration- and water-dependent changes in the lineshape of the C26 proton signals and in the chemical shifts of the C11, C12, and C13 proton signals. We also observed broadening of the C1 and C5 signals and an absence of the C2 and C4 signals in the $^{13}$C NMR spectrum of I.
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<th>Ref. B (500 MHz)</th>
<th>Ref. C (600 MHz)</th>
<th>Ref. D (600 MHz)</th>
<th>Ref. E (600 MHz)</th>
<th>Ref. F (500 MHz)</th>
<th>This work (500 MHz)</th>
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Table 3.6. $^1$H NMR data comparison of synthetic and natural hyperforin (1).
Table 3.7. $^{13}$C NMR data comparison of synthetic and natural hyperforin (1).

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Isolation of hyperforin (1) from St. John’s Wort extract.\textsuperscript{697}

Supercritical CO\textsubscript{2} extract of St. John’s wort was obtained from Flavex Naturextrakte GmbH as a generous gift or was purchased from “From Nature with Love.” The brown resinous extract (1.468 g) was dissolved in MeOH (150 mL, saturated in heptane) and heptane (50 mL, saturated in MeOH) with the aid of sonication. The layers were separated, and the heptane fraction was extracted twice with MeOH (75 mL each, saturated in heptane). The MeOH extracts were combined, washed twice with heptane (50 mL, saturated in MeOH), and concentrated \textit{in vacuo} to a brown-yellow syrup. Flash column chromatography (500 mL SiO\textsubscript{2}, 98:2 → 95:5 → 9:1 hexane:EtOAc) afforded 572 mg (1.07 mmol, 38% yield by weight of initial extract) of 1 as a pale yellow syrup.

\textsuperscript{697} This procedure was adapted from ref. 44.
Appendix A

A Comprehensive Listing of all Polycyclic Polyrenylated Acylphloroglucoinols
In the table below, all known 260 PPAPs are listed. The PPAPs are presented in alphabetical order, except for certain instances (e.g., epimers, ethers). Along with the name and structure of each PPAP, the plant species and geographical location from which that PPAP has been isolated is listed. In cases where a PPAP has been isolated from multiple species, the species from which the PPAP was initially isolated is listed in boldface text. In addition, references to spectroscopic data (i.e., NMR, UV, IR) and relevant crystal structure refinements are provided. Optical rotation data is also listed. Unless indicated by an explicit reference to an absolute configuration determination, an arbitrary enantiomer is depicted for each PPAP. For certain PPAPs, multiple names have been given, mostly due to simultaneous discovery of the PPAP by several groups. All alternative names are provided in italicized text below name that was provided by the initial published report. If a PPAP has been isolated in both enantiomeric forms, the name of its corresponding enantiomeric PPAP is also found below its name. All references herein are found at the end of this appendix.

<table>
<thead>
<tr>
<th>PPAP Name</th>
<th>Structure</th>
<th>Plant Species and Location</th>
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| acuminophenone A         | ![Structure](https://example.com/structure1.png) | Rheedia acuminata (La Paz, Bolivia)\(^1\)  
                             (NMR, UV, IR)\(^1\) \([\alpha]_D = +208^\circ \text{ (CHCl}_3\)\(^1\) |
| adhyperfirin             | ![Structure](https://example.com/structure2.png) | Hypericum empetrifolium (northern Jordan)\(^3\)  
                             H. perforatum  
                             Epirus, Greece\(^4\)  
                             Cemernik Mountain, southern Serbia\(^5\)  
                             H. reflexum (Halle-Wittenberg, Germany)\(^3\)  
                             H. triquetrifolium (Al-Mafraq, Jordan)\(^9\)  
                             \(^1\)H NMR\(^4\) |
**adhyperforin (3)**

Hypericum calycinum (Bonn, Germany)
H. elodes (Umbrian-Marchean Apennines, Italy)
H. maculatum (Prakovce, Slovakia)
H. perforatum (El Feidja, northwestern Tunisia)

**H. helodes** (Umbrian-Marchean Apennines, Italy)
H. maculatum (Prakovce, Slovakia)
H. perforatum (Mt. Taylor, Canberra, Australia)
Alpirsbach, Black Forest, Germany
Epirus, Greece
Cemernik Mountain, southern Serbia
Nová Ľubovňa, Slovakia
El Feidja, northwestern Tunisia
H. ericoides (El Feidja, northwestern Tunisia)

1H NMR, 13C NMR, UV, IR

---

**androforin A (4)**

Hypericum androsaemum (Yunnan, China)

(NMR, UV, IR) $[\alpha]_D = -59.3^\circ$ (MeOH)

---

**aristophenone 18,19-dihydroxy-clusianone (5)**

Clusia torresii (Turrialba, Cartago, Costa Rica)
Garcinia aristata (Havana, Cuba)
G. multiflora (Diaoluo Mountain, Hainan, China)
G. xanthochymus (Homestead, Florida, USA)
propolis (Manaus, Brazil)

(NMR, UV, IR) $[\alpha]_D = +58^\circ$ (CHCl$_3$)

---

**chamone I (6)**

Clusia grandiflora (Canaima, Venezuela)

O-Me ether (NMR, IR)

---

**chamone II (7)**

Clusia grandiflora (Canaima, Venezuela)

(NMR, IR)
chamuangone  
cowanone  
ext-guttiferone Q
(8)

Garcinia cowa  
Hat-Yai, Songkhla, Thailand
Nong Khai, Thailand

(NMR, UV, IR)\(^{22,23}\) \([\alpha]_D = +5.3^\circ (\text{CHCl}_3)\)

clusianone
(9)

Clusia burchellii (Campinas, São Paulo, Brazil)\(^{24}\)
\(C.\) congestiflora (Fresno, Colombia)\(^{25}\)
\(C.\) fluminensis
Campinas, São Paulo, Brazil\(^{24}\)
Viçosa, São Paulo, Brazil\(^{36}\)
C. lanceolata (Campinas, São Paulo, Brazil)\(^{24}\)
C. pana-panari (Campinas, São Paulo, Brazil)\(^{24}\)
C. paralicola (Campinas, São Paulo, Brazil)\(^{24}\)
C. pernambucensis (Campinas, São Paulo, Brazil)\(^{24}\)
C. sandiensis (Campinas, São Paulo, Brazil)\(^{24}\)
C. pernambucensis (Campinas, São Paulo, Brazil)\(^{24}\)
C. assigui (Central Province, Papua New Guinea)\(^{29}\)
G. brevipedicellata (Cameroon)\(^{30}\)
G. preussii (Cameroon)\(^{30}\)
Hypericum hypericoides (St. Andrew, Jamaica)\(^{31}\)
H. sampsonii (Jinhua, Zhejiang, China)\(^{32}\)
propolis (Campinas, São Paulo, Brazil)\(^{24}\)

NMR\(^{26,27,16}\) (UV, IR)\(^{27,16}\) \([\alpha]_D = +60^\circ, +58.3^\circ (\text{CHCl}_3)\)
O-Me ether (NMR, IR, UV)\(^{23}\) \([\alpha]_D = +60.7^\circ (\text{CHCl}_3)\)
structural revision;\(^{16}\) crystal structure;\(^{25}\)
O-Me ether crystal structure\(^{28}\)

7-epi-clusianone
(10)

Calophyllum thorelii (central Vietnam)\(^{33}\)
Clusia torresii (Turrialba, Cartago, Costa Rica)\(^{16}\)
Garcinia brasiliensis (Viçosa, Minas Gerais, Brazil)\(^{34,35,36}\)
G. brevipedicellata (Cameroon)\(^{30}\)
G. preussii (Cameroon)\(^{30}\)
Hypericum hypericoides (St. Andrew, Jamaica)\(^{31}\)
H. sampsonii (Hunan, China)\(^{37}\)
H. scabrum (Chimgan, Uzbekistan)\(^{38}\)
H. elegans (Balgarevo, Kavarna, Bulgaria)\(^{39}\)
Rheedia brasiliensis (Viçosa, Minas Gerais, Brazil)\(^{40}\)
R. edulis (Broward County, Florida, USA)\(^{41}\)
R. gardneriana (Viçosa, Minas Gerais, Brazil)\(^{42,43}\)
propolis (Manaus, Brazil)\(^{39}\)

NMR\(^{16,34,44}\) IR\(^{16,44}\) (UV)\(^{16,41,44}\)
\([\alpha]_D = +60^\circ, +62.3^\circ, +66^\circ (\text{CHCl}_3)\)
+15.6^\circ (\text{MeOH})\(^{41}\)
structural revision;\(^{16}\) crystal structure;\(^{37,42,45}\)
absolute configuration\(^{45}\)
18-hydroxclusianone (11) *Hypericum hypericoides* (St. Andrew, Jamaica)\(^{31}\) (NMR, UV, IR)\(^{31}\)

18-hydroxy-7-epi-clusianone (12) *Hypericum hypericoides* (St. Andrew, Jamaica)\(^{31}\) (NMR, UV, IR)\(^{31}\) \([\alpha]_D = +64^\circ (\text{CHCl}_3)\)\(^{31}\)

coccinone B (13) *Moronoea coccinea* (dense rain forest, French Guyana)\(^{16}\) (NMR, UV, IR)\(^{46}\) \([\alpha]_D = -55^\circ (\text{CHCl}_3)\)\(^{46}\)

7-epi-coccinone B (14) *Symphonia globulifera* (dense rain forest, French Guyana)\(^{47}\) (NMR, UV, IR)\(^{47}\) \([\alpha]_D = -50^\circ (\text{CHCl}_3)\)\(^{47}\)

coccinone C (15) *Moronoea coccinea* (dense rain forest, French Guyana)\(^{16}\) (NMR, UV, IR)\(^{46}\) \([\alpha]_D = -60^\circ (\text{CHCl}_3)\)\(^{46}\)
**coccinone D** (16)  
*Moronobea coccinea* (dense rain forest, French Guyana)\(^{46}\)  
(NMR, UV, IR)\(^{46}\) \([\alpha]_D = -76^\circ (\text{CHCl}_3)\)

**coccinone E** (17)  
*Moronobea coccinea* (dense rain forest, French Guyana)\(^{46}\)  
(NMR, UV, IR)\(^{46}\) \([\alpha]_D = -70^\circ (\text{CHCl}_3)\)

**coccinone F** (18)  
*Moronobea coccinea* (dense rain forest, French Guyana)\(^{46}\)  
(NMR, UV, IR)\(^{46}\) \([\alpha]_D = -32^\circ (\text{CHCl}_3)\)

**coccinone G** (19)  
*Moronobea coccinea* (dense rain forest, French Guyana)\(^{46}\)  
(NMR, UV, IR)\(^{46}\) \([\alpha]_D = -16^\circ (\text{CHCl}_3)\)

**coccinone H** (20)  
*Moronobea coccinea* (dense rain forest, French Guyana)\(^{46}\)  
(NMR, UV, IR)\(^{46}\) \([\alpha]_D = +2^\circ (\text{CHCl}_3)\)

**cycloxanthochymol** (21)  
*Garcinia livingstonei* (Homestead, Florida, USA)\(^{48}\)  
*G. nuijiangensis* (Nuijiang, Yunnan, China)\(^{49}\)  
*G. pyrifera* (Sungai Petani, Kedah, Malaysia)\(^{50}\)  
*G. subelliptica* (Okinawa, Japan)\(^{51}\)  
*G. xanthochymus* (Homestead, Florida, USA)\(^{19}\)  
*Moronobea coccinea* (dense rain forest, French Guyana)\(^{46}\)  
(UV, IR)\(^{46}\) \([\alpha]_D = +112^\circ (\text{CHCl}_3)\)  
characterized as mixture with 153 (NMR, UV, IR)\(^{50,51}\)  
\([\alpha]_D = +142^\circ (\text{CHCl}_3)\) \([\alpha]_D = +158^\circ (\text{MeOH})\)

---

---
**ent-cycloanthchymol**

*(22)*

*Garcinia nuijjangensis* (Nuijiang, Yunnan, China)\(^49\)
*G. subelliptica* (northern mountains, Taiwan)\(^52\)

(NMR, UV, IR)\(^52\) \([\alpha]_D = -80.9^\circ\) (MeOH)\(^52\)

---

**dorstenpictanone**

*(23)*

*Dorstenia picta* (Moraceae; Nkolbibanda, Cameroon)\(^55\)

(NMR, IR)\(^55\)

---

**enervosanone**

*(24)*

*Calophyllum enervosum* (Bukitinggi, West Sumatra, Indonesia)\(^54,55\)

(NMR, UV, IR)\(^54\) \([\alpha]_D = +10^\circ\) (MeOH)\(^54\)

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**eugeniaphenone**

*(25)*

*Garcinia eugeniaefolia* (Riau Islands, Indonesia)\(^56\)

(NMR, IR);\(^56\) crystal structure\(^56\)

---

**furoadhyperforin**

*(26)*

*Hypericum perforatum*

Mt. Taylor, Canberra, Australia\(^11\)
Mt. Orzen, southeast Serbia\(^27,58\)

\(^1\)H NMR\(^11,57\), \(^13\)C NMR\(^51\)

---

**furoadhyperforin isomer A**

*(27)*

*Hypericum perforatum* (Tokushima, Japan)\(^59\)

(NMR, IR)\(^59\) \([\alpha]_D = +33.8\) (CHCl\(_3\))\(^59\)
Furoadhyperforin isomer B
(28)  

Hypericum perforatum (Tokushima, Japan)\(^{59}\)  
(NMR, IR)\(^{59}\) \([\alpha]\_D = +13.8 \text{ (CHCl}_3)\)\(^{59}\)

Furohyperforin
(29)  

Hypericum henryi (Lünchun, Yunnan, China)\(^{60}\)  
Hypericum perforatum  
Mt. Taylor, Canberra, Australia\(^{11}\)  
Chile\(^{61}\)  
China\(^{62}\)  
Italy\(^{13}\)  
Tokushima, Japan\(^{59}\)  
Mt. Orzen, southeast Serbia\(^{57,58,63}\)  

NMR\(^{11,58,61,62}\) (UV, IR)\(^{58,61}\) \([\alpha]\_D = +68^{\circ}, +62.4^{\circ} \text{ (CHCl}_3) \)\([\alpha]\_D = +81.9^{\circ} \text{ (MeOH)}\)\(^{61}\)

33-deoxy-33-hydroperoxy-
furohyperforin
(30)  

Hypericum perforatum  
Chile\(^{64}\)  
Tokushima, Japan\(^{59}\)  

(NMR, UV, CD)\(^{64}\) \([\alpha]\_D = +75.0^{\circ} \text{ (CHCl}_3)\)\(^{64}\)

Furohyperforin A
(31)  

Hypericum perforatum (Mt. Orzen, southeast Serbia)\(^{58,63}\)  
(NMR, UV, IR)\(^{63}\)

Deoxyfurohyperforin A
(32)  

Hypericum perforatum (Mt. Orzen, southeast Serbia)\(^{58}\)  
(NMR, UV, IR)\(^{58}\) \([\alpha]\_D = +42 \text{ (CH}_2\text{Cl}_2)\)\(^{58}\)
furohyperforin isomer 1 (33)

Hypericum perforatum
Mt. Taylor, Canberra, Australia¹¹
Tokushima, Japan⁵⁹
NMR¹¹,⁵⁹ [α]₀ = +49.7 (CHCl₃)⁵⁹

27-epi-furohyperforin isomer 1 (34)

Hypericum perforatum (Tokushima, Japan)⁵⁹
NMR⁵⁹ [α]₀ = +14.5 (CHCl₃)⁵⁹

furohyperforin isomer 2 (35)

Hypericum perforatum
Mt. Taylor, Canberra, Australia¹¹
Tokushima, Japan⁵⁹
NMR¹¹

garcicowin A (36)

Garcinia cowa (Yunnan, China)⁶⁵
(NMR, UV, IR)⁶⁵ [α]₀ = −219.0º (CHCl₃)⁶⁵

garcicowin B (37)

Garcinia cowa (Yunnan, China)⁶⁵,⁶⁶
G. lancilimba (Xishuangbanna, Yunnan, China)⁶⁶
G. yunnanensis (Dehong, Yunnan, China)⁶⁶
(NMR, UV, IR)⁶⁵ [α]₀ = −16.0º (CHCl₃)⁶⁵
**Garcinia cowa (Yunnan, China)**\(^{65,66}\)

- *G. lancilimba* (Xishuangbanna, Yunnan, China)\(^{66}\)
- *G. oblongifolia* (Bobai, Guangxi, China)\(^{66}\)
- *G. paucinervis* (Xishuangbanna, Yunnan, China)\(^{67}\)
- *G. xanthochymus* (Xishuangbanna, Yunnan, China)\(^{66}\)

(NMR, UV, IR)\(^{65}\) [\(\alpha\)]\(_D\) = −72.1° (CHCl\(_3\))\(^{65}\)

**Garcinia cowa (Yunnan, China)**\(^{65,66}\)

- *G. lancilimba* (Xishuangbanna, Yunnan, China)\(^{66}\)
- *G. multiliora* (Wanning, China)\(^{66}\)
- *G. oblongifolia* (Bobai, Guangxi, China)\(^{66}\)
- *G. paucinervis* (Xishuangbanna, Yunnan, China)\(^{66}\)
- *G. subelliptica* (Shenzhen, Guangdong, China)\(^{66}\)
- *G. xanthochymus* (Xishuangbanna, Yunnan, China)\(^{66}\)
- *G. xipshuangbananensis* (Xishuangbanna, Yunnan, China)\(^{66}\)
- *G. yunnanensis* (Dehong, Yunnan, China)\(^{66}\)

(NMR, UV, IR)\(^{65}\) [\(\alpha\)]\(_D\) = +336.0° (CHCl\(_3\))\(^{65}\)

**Garcinia multiflora (Mudan, Taiwan)**\(^{68}\)

- *G. multiflora* (Mudan, Taiwan)\(^{68}\)

(NMR, UV, IR, CD)\(^{68}\) [\(\alpha\)]\(_D\) = −173° (CHCl\(_3\))\(^{68}\)

**Garcinia multiflora (Mudan, Taiwan)**\(^{68}\)

- *G. multiflora* (Mudan, Taiwan)\(^{68}\)

(NMR, UV, IR, CD)\(^{68}\) [\(\alpha\)]\(_D\) = −132° (CHCl\(_3\))\(^{68}\)

**13-hydroxy-garcimultiflorone B (42)**

- *Garcinia multiflora* (Mudan, Taiwan)\(^{68}\)

(NMR, UV, IR, CD)\(^{68}\) [\(\alpha\)]\(_D\) = −115° (CHCl\(_3\))\(^{68}\)
garcimultiflorone C
(43)

*Garcinia multiflora* (Mudan, Taiwan)\(^{68}\)
(NMR, UV, IR, CD)\(^{68}\) \([\alpha]_D = -25.3^\circ\) (CHCl\(_3\))^\(68\)

---

garcimultiflorone D
(44)

*Garcinia multiflora* (Diaoluo Mountain, Hainan, China)\(^{16}\)
(NMR, UV, IR)\(^{18}\) \([\alpha]_D = -53.6^\circ\) (MeOH)\(^{18}\)

---

garcimultiflorone D2
(45)

*Garcinia multiflora* (Mudan, Pingtung, Taiwan)\(^{69}\)
(NMR, UV, IR)\(^{69}\) \([\alpha]_D = +5.6^\circ\) (CHCl\(_3\))

---

18-hydroxy-garcimultiflorone D
(46)

*Garcinia multiflora* (Diaoluo Mountain, Hainan, China)\(^{18}\)
(NMR, UV, IR)\(^{18}\) \([\alpha]_D = -33.3^\circ\) (MeOH)\(^{18}\)

---

garcimultiflorone E
(47)

*Garcinia multiflora* (Diaoluo Mountain, Hainan, China)\(^{18}\)
(NMR, UV, IR)\(^{18}\) \([\alpha]_D = -43.6^\circ\) (MeOH)\(^{18}\)

---

garcimultiflorone F
(48)

*Garcinia multiflora* (Diaoluo Mountain, Hainan, China)\(^{18}\)
(NMR, UV, IR)\(^{18}\) \([\alpha]_D = -48.7^\circ\) (MeOH)\(^{18}\)
isogarcimultiflorone F
(49)

Garcinia multiflora (Diaoluo Mountain, Hainan, China)\(^{18}\)
(NMR, UV, IR)\(^{18}\) \([\alpha]_D = -46.0^\circ\) (MeOH)\(^{18}\)

garciniagifolone A
(50)

Garcinia oblongifolia (Hainan, China)\(^{70}\)
(NMR, UV, IR)\(^{70}\) \([\alpha]_D = +7.0^\circ\) (MeOH)\(^{70}\)

garcinialiptone A
(51)

Garcinia subelliptica (northern mountains, Taiwan)\(^{52}\)
(NMR, UV, IR)\(^{52}\) \([\alpha]_D = +12.1^\circ\) (MeOH)\(^{52}\)

ent-garcinialiptone A
(52)

Garcinia cochinichinensis (southern Vietnam)\(^{71}\)
G. nujangensis (Nuijiang, Yunnan, China)\(^{49}\)
G. subelliptica (northern mountains, Taiwan)\(^{52}\)
(NMR, UV, IR)\(^{52}\) \([\alpha]_D = -17.3^\circ\) (MeOH)\(^{52}\)

garcinialiptone B
(53)

Garcinia nujangensis (Nuijiang, Yunnan, China)\(^{49}\)
G. subelliptica (northern mountains, Taiwan)\(^{52}\)
(NMR, UV, IR)\(^{52}\) \([\alpha]_D = +84.8^\circ\) (MeOH)\(^{52}\)
garcinialiptone C
(54)

\[
\text{Garcinia subelliptica (northern mountains, Taiwan)}^{52}
\]
\[
\text{(NMR, UV, IR)}^{52} [\alpha]_D = -94.0^\circ \text{ (MeOH)}^{52}
\]

---

garcinialiptone D
(55)

\[
\text{Garcinia subelliptica (northern mountains, Taiwan)}^{52}
\]
\[
\text{(NMR, UV, IR)}^{52} [\alpha]_D = -79.1^\circ \text{ (MeOH)}^{52}
\]

---

garcinialone
(56)

\[
\text{Garcinia multiflora (Taiwan)}^{72}
\]
\[
\text{(NMR, UV, IR)}^{72} [\alpha]_D = -2.0^\circ \text{ (MeOH)}^{72}
\]

---

garciniaphenone
(57)

\[
\text{Garcinia brasiliensis (Viçosa, Minas Gerais, Brazil)}^{34,35}
\]
\[
\text{(NMR, UV, IR)}^{34} [\alpha]_D = -52.8 \text{ (CHCl}_3)^{34}
\]
\[
\text{crystal structure}^{35}
\]

---

garciinelliptone A
(58)

\[
\text{Garcinia subelliptica (Kaohsiung, Taiwan)}^{73,74}
\]
\[
\text{(NMR, UV, IR)}^{73} [\alpha]_D = -33^\circ \text{ (CHCl}_3)^{73}
\]
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structural Formula</th>
<th>Source</th>
<th>NMR, UV, IR</th>
<th>Optical Rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>garcinielliptone B (59)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><em>Garcinia subelliptica</em> (Kaohsiung, Taiwan)</td>
<td>(NMR, UV, IR)</td>
<td>$[\alpha]_D = -23^\circ$ (CHCl$_3$)</td>
</tr>
<tr>
<td>garcinielliptone C (60)</td>
<td><img src="image2.png" alt="Structure" /></td>
<td><em>Garcinia subelliptica</em> (Kaohsiung, Taiwan)</td>
<td>(NMR, UV, IR)</td>
<td>$[\alpha]_D = -40^\circ$ (CHCl$_3$)</td>
</tr>
<tr>
<td>garcinielliptone D (61)</td>
<td><img src="image3.png" alt="Structure" /></td>
<td><em>Garcinia subelliptica</em> (Kaohsiung, Taiwan)</td>
<td>(NMR, UV, IR)</td>
<td>$[\alpha]_D = -22^\circ$ (CHCl$_3$)</td>
</tr>
<tr>
<td>garcinielliptone F (62)</td>
<td><img src="image4.png" alt="Structure" /></td>
<td><em>Garcinia subelliptica</em> (Kaohsiung, Taiwan)</td>
<td>(NMR, UV, IR)</td>
<td>$[\alpha]_D = -23^\circ$ (CHCl$_3$)</td>
</tr>
<tr>
<td>garcinielliptone FB (63)</td>
<td><img src="image5.png" alt="Structure" /></td>
<td><em>Garcinia subelliptica</em> (Kaohsiung, Taiwan)</td>
<td>(NMR, UV, IR)</td>
<td>$[\alpha]_D = -66^\circ$ (CHCl$_3$)</td>
</tr>
<tr>
<td>garcinielliptone FC (64)</td>
<td><img src="image6.png" alt="Structure" /></td>
<td><em>Garcinia subelliptica</em> Kaohsiung, Taiwan, <em>Platonia insignis</em> Barras, Piaui, Brazil</td>
<td>NMR, UV, IR</td>
<td>$[\alpha]_D = +12.6^\circ$ (CHCl$_3$)</td>
</tr>
</tbody>
</table>
garcinielliptone H
(65)

*Garcinia subelliptica* (Kaohsiung, Taiwan)\(^{75}\)
(NMR, UV, IR)\(^{75}\) \([\alpha]_D = -143^\circ\) (CHCl\(_3\))\(^{75}\)

---

**garcinielliptone I
ent-hyperibone A**
(66)

*Clusia minor* (Havana, Cuba)\(^{79}\)
*Garcinia subelliptica* (Kaohsiung, Taiwan)\(^{75}\)
propolis (Guanatamo, Cuba)\(^{80}\)
NMR\(^{75,79}\) (UV, IR)\(^{75}\) \([\alpha]_D = +57^\circ, 75^\circ \pm 63.7^\circ\) (CHCl\(_3\))

---

**garcinielliptone K**
(67)

*Garcinia subelliptica* (Kaohsiung, Taiwan)\(^{81}\)
(NMR, UV, IR)\(^{81}\) \([\alpha]_D = +27^\circ\) (CHCl\(_3\))\(^{81}\)

---

**garcinielliptone L**
(68)

*Garcinia subelliptica* (Kaohsiung, Taiwan)\(^{81}\)
(NMR, UV, IR)\(^{81}\) \([\alpha]_D = -41^\circ\) (CHCl\(_3\))\(^{81}\)

---

**garcinielliptone M**
(69)

*Garcinia subelliptica* (Kaohsiung, Taiwan)\(^{81}\)
(NMR, UV, IR)\(^{81}\) \([\alpha]_D = +73^\circ\) (CHCl\(_3\))\(^{81}\)

---

**garcinielliptone P**
(70)

*Garcinia subelliptica* (Ping-Tung Hsien, Taiwan)\(^{82}\)
(NMR, UV, IR)\(^{82}\) \([\alpha]_D = -2^\circ\) (CHCl\(_3\))\(^{82}\)
garcinielliptone R
(71)

Garcinia subelliptica (Kaohsiung, Taiwan)\textsuperscript{74}

(NMR, UV, IR)\textsuperscript{74} [\alpha]_D = –38° (CHCl\textsubscript{3})\textsuperscript{74}

Allanblackia monticola (West Province, Cameroon)\textsuperscript{83}
Garcinia assigu (Central Province, Papua New Guinea)\textsuperscript{79}
G. bancana (Naratiwath, Thailand)\textsuperscript{84}
G. brevipedicellata (Cameroon)\textsuperscript{90}
G. cambogia
Dapoli, \textsuperscript{85} Maharastra, India\textsuperscript{86,87}
Sri Lanka\textsuperscript{88,89}
G. cowa (Yunnan, China)\textsuperscript{65,90}
G. dulcis (Songkhla, Thailand)\textsuperscript{91}
G. huillensis (western Democratic Republic of the Congo)\textsuperscript{92}
G. indica (Kerela, \textsuperscript{93,94} India)
G. maingayii (Riau Islands, Indonesia)\textsuperscript{95}
G. oblongifolia
Hainan, China\textsuperscript{70}
Nhu Xuan, Vietnam\textsuperscript{96}
G. paucinervis (Xishuangbanna, Yunnan, China)\textsuperscript{67}
G. pedunculata (Jorhat, Assam, India)\textsuperscript{97}
G. preussii (Cameroon)\textsuperscript{90}
G. purpurea (Japan)\textsuperscript{71}
G. tetrandra (West Kalimantan, Indonesia)\textsuperscript{98}
Moronobea cocinea (dense rain forest, French Guiana)\textsuperscript{46}

\textsuperscript{1}H NMR\textsuperscript{86,90,92,95,97,98,99} \textsuperscript{13}C NMR\textsuperscript{86,90,92,95,98,99}
(UV, IR)\textsuperscript{46,51,86,90,92,95,97,99} CD\textsuperscript{28,90}
[\alpha]_D = –135°, \textsuperscript{46} –138°, \textsuperscript{51} –132.9°, \textsuperscript{86} –143°, \textsuperscript{93} –125.3°, \textsuperscript{92}
–142\textsuperscript{97} (CHCl\textsubscript{3}) –192.0°, \textsuperscript{90} –128.5°, \textsuperscript{91} –149.2\textsuperscript{94} (MeOH)
–125.3° (EtOH)\textsuperscript{92}

garcinol camboginol
ent-guttiferone E
(72)

Garcinia assigu (Central Province, Papua New Guinea)\textsuperscript{79}

(NMR, UV, IR, CD)\textsuperscript{29} [\alpha]_D = –117° (CHCl\textsubscript{3})\textsuperscript{29}

13-\textit{O}-methyl ether
(73)
<table>
<thead>
<tr>
<th>Molecular Name</th>
<th>Source</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-epi-garcinol (74)</td>
<td><em>Garcinia brevipedicellata</em> (Cameroon)\textsuperscript{30}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>G. nuijiangensis</em> (Nujiang, Yunnan, China)\textsuperscript{49}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>G. preussii</em> (Cameroon)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Moronoba coccinea</em> (dense rain forest, French Guyana)\textsuperscript{46}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Symphonia globulifera</em> (dense rain forest, French Guyana)\textsuperscript{47}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NMR\textsuperscript{46} (UV, IR)\textsuperscript{46,47} $[\alpha]_D = -86^\circ$ (CHCl\textsubscript{3})\textsuperscript{46,47}</td>
</tr>
<tr>
<td>no name cyclogarcinol (75)</td>
<td><em>Garcinia indica</em> (Bengaluru, India)\textsuperscript{94}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NMR, UV, IR)\textsuperscript{94} $[\alpha]_D = +18.9$ (MeOH)\textsuperscript{94}</td>
</tr>
<tr>
<td>14-deoxygarcinol (76)</td>
<td><em>Moronoba coccinea</em> (dense rain forest, French Guyana)\textsuperscript{16}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NMR, UV, IR)\textsuperscript{46} $[\alpha]_D = -42^\circ$ (CHCl\textsubscript{3})\textsuperscript{46}</td>
</tr>
<tr>
<td>garciyunnanin B (77)</td>
<td><em>Garcinia lancilimba</em> (Xishuangbanna, Yunnan, China)\textsuperscript{56}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>G. multiflora</em> (Wanning, China)\textsuperscript{66}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>G. xanthochymus</em> (Xishuangbanna, Yunnan, China)\textsuperscript{66}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>G. yunnanensis</em> (Dehong, Yunnan, China)\textsuperscript{66,100}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NMR, UV, IR)\textsuperscript{100} $[\alpha]_D = +18.1^\circ$ (CHCl\textsubscript{3})\textsuperscript{100}</td>
</tr>
<tr>
<td>garsubellin A (78)</td>
<td><em>Garcinia subelliptica</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Ishigaki Island, Japan</em>\textsuperscript{101,102}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Kaohsiung, Taiwan</em>\textsuperscript{53,74}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NMR\textsuperscript{101,102} (UV, IR)\textsuperscript{101} $[\alpha]_D = -21.3^\circ$ (EtOH)\textsuperscript{101}</td>
</tr>
</tbody>
</table>
garsubellin B
(Garcinia subelliptica (Ishigaki Island, Japan)\textsuperscript{102}
(NMR, UV, IR)\textsuperscript{102} [\alpha]_{D} = –36º (EtOH)\textsuperscript{102}

garsubellin C
(Garcinia subelliptica (Ishigaki Island, Japan)\textsuperscript{102}
(NMR, UV, IR)\textsuperscript{102} [\alpha]_{D} = +39º (EtOH)\textsuperscript{102}

garsubellin D
(Garcinia subelliptica
Ishigaki Island, Japan\textsuperscript{102}
Kaohsiung, Taiwan\textsuperscript{53}
(NMR, UV, IR)\textsuperscript{102} [\alpha]_{D} = –12º (EtOH)\textsuperscript{102}

garsubellin E
(Garcinia subelliptica (Ishigaki Island, Japan)\textsuperscript{102}
(NMR, UV, IR)\textsuperscript{102} [\alpha]_{D} = –7º (EtOH)\textsuperscript{102}

guttiferone A
(Clusia rosea (Havana, Cuba)\textsuperscript{103}
Garcinia achachairu (Camboriú, Santa Catarina, Brazil)\textsuperscript{104}
G. aristata (Homestead, Florida, USA)\textsuperscript{105}
G. brasiliensis (Viçosa, Minas Gerais, Brazil)\textsuperscript{36,35}
G. cowa (Xishuangbanna, Yunnan, China)\textsuperscript{65}
G. intermedia (Ejido Benigno Mendoza, Veracruz, Mexico)\textsuperscript{105,106}
G. livingstonei
Iringa, Mufindi, Tanzania\textsuperscript{107}
Southeastern Florida, USA\textsuperscript{18,105}
G. macrophylla (Supaliwini, Suriname)\textsuperscript{108}
G. semseii (Morogoro, Tanzania)\textsuperscript{109}
G. spicata (Homestead, Florida, USA)\textsuperscript{105}
Rheedia edulis (Broward County, Florida, USA)\textsuperscript{41}
Symphonia globulifera
Fundong, Northwest Province, Cameroon\textsuperscript{110,111}
West Province, Cameroon\textsuperscript{93}
Ndakan Gorilla Study Area, Central African Republic\textsuperscript{107}

S. pauciflora (Zahamena National Park, Madagascar)\textsuperscript{112}

NMR\textsuperscript{107,113,114} IR\textsuperscript{107,113} UV\textsuperscript{41,107,113} \([\alpha]_D = +34^{\circ} \textsuperscript{107}, +32^{\circ} \textsuperscript{108}, +47.6^{\circ} \textsuperscript{113} (\text{CHCl}_3) +31.4^{\circ} (\text{MeOH})\textsuperscript{41}\]
crystal structure\textsuperscript{113,115}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{guttiferone_B}
\caption{Guttiferone B (84)}
\end{figure}

Garcinia cowa (Yunnan, China)\textsuperscript{65,66}
G. lancilimba (Xishuangbanna, Yunnan, China)\textsuperscript{66}
G. multiflora (Wanning, China)\textsuperscript{66}
G. oblongifolia
Bobai, Guangxi, China\textsuperscript{66,116}
Nhu Xuan, Vietnam\textsuperscript{66}
G. subelliptica (Shenzhen, Guangdong, China)\textsuperscript{66}
G. xanthochymus (Xishuangbanna, Yunnan, China)\textsuperscript{66}
G. xipsuaxhuangbannaensis (Xishuangbanna, Yunnan, China)\textsuperscript{66}
G. yunnanensis (Dehong, Yunnan, China)\textsuperscript{66}

Symphonia globulifera (Ndakan Gorilla Study Area, Central African Republic)\textsuperscript{107}

characterized as mixture with \textsuperscript{86} (NMR, UV, IR)\textsuperscript{107} \([\alpha]_D = -44^{\circ} (\text{CHCl}_3)\textsuperscript{107}\)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{guttiferone_C}
\caption{Guttiferone C (85)}
\end{figure}

Symphonia globulifera (Ndakan Gorilla Study Area, Central African Republic)\textsuperscript{107}

classified as mixture with \textsuperscript{86} (NMR, UV, IR)\textsuperscript{107} \([\alpha]_D = +92^{\circ} (\text{CHCl}_3)\textsuperscript{107}\)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{guttiferone_D}
\caption{Guttiferone D (86)}
\end{figure}

Symphonia globulifera (Ndakan Gorilla Study Area, Central African Republic)\textsuperscript{107}

classified as mixture with \textsuperscript{85} (NMR, UV, IR)\textsuperscript{107} \([\alpha]_D = +92^{\circ} (\text{CHCl}_3)\textsuperscript{107}\)
**Guttiferone E**
ent-garcinol (87)

**Clusia rosea** (Dominican Republic)\(^{107}\)
Garcinia afzelii (Mt. Eloumdem, Centre Province, Cameroon)\(^{127}\)
G. intermedia (Homestead, Florida, USA)\(^{105}\)
G. livingstonei (Homestead, Florida, USA)\(^{48}\)
G. multiflora (Diaoluo Mountain, Hainan, China)\(^{18}\)
G. ovalifolia (Ndakan Gorilla Study Area, Central African Republic)\(^{107}\)
G. paucinervis (Xishuangbanna, Yunnan, China)\(^{66}\)
G. pyrifera (Sungai Petani, Kedah, Malaysia)\(^{50}\)
G. spicata (Homestead, Florida, USA)\(^{105}\)
G. xanthochymus (Homestead, Florida, USA)\(^{19,105}\)
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China)\(^{18}\)
G. virgata (Aoupinié, New Caledonia)\(^{119}\)
**Allanblackia monticola** (West Province, Cameroon)\(^{83}\)
A. gabonensis (Mbankomo, Centre Province, Cameroon)\(^{122}\)
A. stuhlmannii (Mufundi, Tanzania)\(^{23}\)
A. ulugurensis (Morningside, Morogoro, Tanzania)\(^{124}\)
Calophyllum thorelii (central Vietnam)\(^{33}\)
Garcinia bancana (West Kalimantan, Indonesia)\(^{125}\)
G. cowa (Yunnan, China)\(^{65,66}\)
G. esculenta (Dehong, Yunnan, China)\(^{66}\)
G. multiflora
Diaoluo Mountain, Hainan, China\(^{18}\)
Wanning, China\(^{66}\)
G. lancilimba (Xishuangbanna, Yunnan, China)\(^{66}\)
G. oblongifolia
Bobai, Guangxi, China\(^{66}\)
Vietnam\(^{126}\)
G. paucinervis (Xishuangbanna, Yunnan, China)\(^{66}\)
G. subelliptica (Shenzhen, Guangdong, China)\(^{66}\)
G. xanthochymus (Xishuangbanna, Yunnan, China)\(^{66}\)
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China)\(^{66}\)
G. yunnanensis (Dehong, Yunnan, China)\(^{66}\)
(NMR, IR)\(^{123,125}\)
UV\(^{123}\) \([\alpha]_D = -293^\circ (\text{CHCl}_3)\)\(^{123}\)

**Guttiferone F**

(NR, IR)\(^{123,125}\)
UV\(^{123}\) \([\alpha]_D = -293^\circ (\text{CHCl}_3)\)\(^{123}\)
**Guttiferone G**

**Guttiferone I2**

**Ent-oblongifolin C**

(89)

---

*Calophyllum theorelii* (central Vietnam)\(^{33}\)
*Garcinia cambogia* (Sri Lanka)\(^{88}\)
*G. cochinchinensis* (southern Vietnam)\(^{71,127}\)
*G. griffithii* (Lembah Arau, West Sumatra, Indonesia)\(^{128}\)
*G. humilis* (Dominica)\(^{129}\)
*G. macrophylla* (Supaliwini, Suriname)\(^{108}\)
*G. paucinervis* (Xishuangbanna, Yunnan, China)\(^{67}\)
*G. smeathmannii* (Cheffou-Baham, West Province, Cameroon)\(^{30,131}\)
*G. virgata* (Aoupinié, New Caledonia)\(^{119}\)

(NMR, UV, IR)\(^{108,119,129}\) \([\alpha]_D = -25^\circ, 108 -14.3^\circ\)\(^{119}\)

(CHCl\(_3\))

+8.7 (MeOH)\(^{129}\)

structural revision\(^{132}\)

---

**Guttiferone H**

(90)

*Garcinia xanthochymus* (Homestead, Florida, USA)\(^{19}\)

(NMR, UV)\(^{19}\) \([\alpha]_D = +94^\circ\) (CHCl\(_3\))\(^{19}\) +57\(^\circ\) (MeOH)\(^{19}\)

---

**Guttiferone I**

(91)

*Garcinia cochinchenensis* (Dong Nai, Vietnam)\(^{133}\)
*G. griffithii* (Singapore)\(^{134}\)
*Symphonia pauciflora* (Zahamena National Park, Madagascar)\(^{112}\)

(NMR, UV, IR)\(^{134}\) \([\alpha]_D = -68^\circ\) (CHCl\(_3\))\(^{134}\)

---

**Oxy-guttiferone I**

(92)

*Garcinia cambogia* (Sri Lanka)\(^{135}\)

(NMR, UV, IR)\(^{135}\) \([\alpha]_D = +23.8^\circ\) (MeOH)\(^{134}\)
Garcinia cambogia (Sri Lanka) 88
Garcinia cowa (Yunnan, China) 66
G. lancilimba (Xishuangbanna, Yunnan, China) 66
G. multiflora (Wanning, China) 66
G. oblongifolia (Bobai, Guangxi, China) 66
G. paucinervis (Xishuangbanna, Yunnan, China) 66
G. subelliptica (Shenzhen, Guangdong, China) 66
G. xanthochymus (Xishuangbanna, Yunnan, China) 66
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China) 66
G. virgata (Aoupinic, New Caledonia) 119
G. yunnanensis (Yunnan, China) 66, 100

\[ \alpha_D = -3^\circ \text{ (CHCl}_3) \text{ and } -34.3^\circ \text{ (MeOH)} \] 119

Rheedia edulis (Broward County, Florida, USA) 41

7-epi-guttiferone J
(94)

Rheedia calcicola (Antsiranana, Madagascar) 136

\[ \alpha_D = -2^\circ \text{ (CHCl}_3) \] 136

Garcinia cambogia (Sri Lanka) 88, 90, 135
G. cowa (Yunnan, China) 65, 66
G. lancilimba (Xishuangbanna, Yunnan, China) 66
G. livingstonii (Homestead, Florida, USA) 48
G. multiflora (Wanning, China) 66
G. oblongifolia (Bobai, Guangxi, China) 66
G. paucinervis (Xishuangbanna, Yunnan, China) 66, 67
G. senssei (Morogoro, Tanzania) 109
G. subelliptica (Shenzhen, Guangdong, China) 66
G. xanthochymus (Xishuangbanna, Yunnan, China) 66
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China) 66
G. yunnanensis
Dehong, Yunnan, China 66
Luxi, Yunnan, China 100

Rheedia acuminata (La Paz, Bolivia) 1

\[ \alpha_D = +28^\circ \text{ (CHCl}_3) \text{ and } +106.45^\circ \text{ (MeOH)} \] 90

Garcinia cowa (Yunnan, China) 90
Moronobea coccinea (dense rain forest, French Guyana) 16

\[ \alpha_D = +28^\circ \text{ (CHCl}_3) \text{ and } +106.45^\circ \text{ (MeOH)} \] 90
oxy-guttiferone K
(97)

\[ \text{Garcinia cambogia (Sri Lanka)}^{88,135} \]

(NMR, UV, IR)\(^{88}\) \([\alpha]_D = +20.9^\circ (\text{CHCl}_3)^{88}\)

absolute configuration\(^{135}\)

oxy-guttiferone K2
(98)

\[ \text{Garcinia cambogia (Sri Lanka)}^{135} \]

(NMR, UV, IR)\(^{135}\) \([\alpha]_D = +12.2^\circ (\text{MeOH})^{135}\)

guttiferone L
(99)

\[ \text{Rheedia calcicola (Antsiranana, Madagascar)}^{136} \]

(NMR, UV, IR)\(^{136}\) \([\alpha]_D = -8^\circ (\text{CHCl}_3)^{136}\)

guttiferone M
(100)

\[ \text{Garcinia cambogia (Sri Lanka)}^{88,135} \]

(NMR, UV, IR)\(^{88}\) \([\alpha]_D = -29.8^\circ (\text{MeOH})^{88}\)

absolute configuration\(^{135}\)

oxy-guttiferone M
(101)

\[ \text{Garcinia cambogia (Sri Lanka)}^{135} \]

(NMR, UV, IR)\(^{135}\) \([\alpha]_D = -96.2^\circ (\text{MeOH})^{135}\)
32-hydroxy-ent-guttiferone M (102) 
*Rheedia edulis* (Broward County, Florida, USA)

(NMR, UV, IR, CD) $\alpha_D = +9.6^\circ$ (MeOH)

absolute configuration

---

guttiferone N (103) 
*Garcinia cambogia* (Sri Lanka)

(NMR, UV, IR) $\alpha_D = -34.5^\circ$ (MeOH)

---

guttiferone O (104) 
*Garcinia solomonensis* (Central Province, Papua New Guinea)

(NMR, UV, IR) $\alpha_D = +30.7^\circ$ (CHCl)

---

guttiferone O2 ent-oblongifolin F (105) 
*Garcinia afzelii* (Mt. Eloumdem, Centre Province, Cameroon)

(NMR, UV, IR) $\alpha_D = +45^\circ$ (acetone)

---

guttiferone P (106) 
*Garcinia solomonensis* (Central Province, Papua New Guinea)

(NMR, UV, IR) $\alpha_D = +18.2^\circ$ (CHCl)
guttiferone Q
ent-chamuangone
ent-cowanone (107)

Garcinia cochinchinensis (Dong Nai, Vietnam)\textsuperscript{133}
(NMR, UV, IR)\textsuperscript{133} \([\alpha]_D = -50.0^\circ\) (MeOH)\textsuperscript{133}

---

guttiferone R (108)

Garcinia cochinchinensis (Dong Nai, Vietnam)\textsuperscript{133}
(NMR, UV, IR)\textsuperscript{133} \([\alpha]_D = -57.5^\circ\) (MeOH)\textsuperscript{133}

---

guttiferone S (109)

Garcinia cochinchinensis (Dong Nai, Vietnam)\textsuperscript{133}
(NMR, UV, IR)\textsuperscript{133} \([\alpha]_D = -10.0^\circ\) (MeOH)\textsuperscript{133}

---

guttiferone T (110)

Garcinia cochinchinensis (southern Vietnam)\textsuperscript{71}
(NMR, UV, IR)\textsuperscript{71} \([\alpha]_D = -14.0^\circ\) (CHCl\textsubscript{3})\textsuperscript{71}

---

hydroperoxycadiforin (111)

Hypericum perforatum (Bonn-Beuel, Germany)\textsuperscript{138}
(NMR, UV, IR)\textsuperscript{138} \([\alpha]_D = +26.5^\circ\) (hexane)\textsuperscript{138}
hyperandrone A (112)

Hypericum androsaemum (Yunnan, China)\textsuperscript{15}
(NMR, UV, IR)\textsuperscript{15} $[\alpha]_D = +20.9^\circ$ (MeOH)\textsuperscript{15}

hyperatomarin (113)

Hypericum annulatum (Rhodope Mountains, Bulgaria)\textsuperscript{139,140}
$H. atomarium$ (Nišava District, Serbia)\textsuperscript{141}
(NMR, UV, IR)\textsuperscript{141} $[\alpha]_D = +19.4^\circ$ (CH$_2$Cl$_2$)\textsuperscript{141}

hyperevolutin A (114)

Hypericum revolutum (Zomba, Malawi)\textsuperscript{142}
(NMR, UV, IR)\textsuperscript{142} $[\alpha]_D = +84.4^\circ$ (MeOH)\textsuperscript{142}
crystal structure\textsuperscript{142}

hyperevolutin B (115)

Hypericum revolutum (Zomba, Malawi)\textsuperscript{142}
(NMR, UV)\textsuperscript{142}

hyperflrin (116)

Hypericum perforatum
Germany\textsuperscript{3}
Epirus, Greece\textsuperscript{4}
Cemernik Mountain, southern Serbia\textsuperscript{5}
$H. reflexum$ (Halle-Wittenberg, Germany)\textsuperscript{3}
$H. triquetrifolium$ (Al-Mafraq, Jordan)\textsuperscript{5}
$^1$H NMR\textsuperscript{4}

hyperfoliatin

Hypericum perforatum (Jijel, Algeria)\textsuperscript{143}
$H. perforatum$ (Tokushima, Japan)\textsuperscript{50}
$H. scabrum$ (Chimgan, Uzbekistan)\textsuperscript{38}
$H. tomentosum$ (Bekira-Constantine, eastern Algeria)\textsuperscript{144}
(NMR, IR)\textsuperscript{143,38} UV\textsuperscript{143}$[\alpha]_D = +17$ (MeOH)\textsuperscript{143} +16.9 (CHCl$_3$)\textsuperscript{38}
<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
<td><em>Hypericum androsaemum</em></td>
<td>(northern Turkey)</td>
</tr>
<tr>
<td><em>H. avicularifolium</em></td>
<td>(northern Turkey)</td>
</tr>
<tr>
<td><em>H. barbatum</em></td>
<td>(throughout Macedonia and Serbia)</td>
</tr>
<tr>
<td><em>H. bithynicum</em></td>
<td>(northern Turkey)</td>
</tr>
<tr>
<td><em>H. bupleuroides</em></td>
<td>(Maçka district, Trabzon, Turkey)</td>
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<tr>
<td><em>H. calabricum</em></td>
<td>(Calabria, Italy)</td>
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<tr>
<td><em>H. calycinum</em></td>
<td>(Bonn, Germany)</td>
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<tr>
<td><em>H. confertum</em></td>
<td>(Uludağ Mountain, Bursa, Turkey)</td>
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<tr>
<td><em>H. elodes</em></td>
<td>(Umbrian-Marchean Apennines, Italy)</td>
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<tr>
<td><em>H. empetrifolium</em></td>
<td>(Irbid, northern Jordan)</td>
</tr>
<tr>
<td><em>H. ericoides</em></td>
<td>(El Feidja, northwestern Tunisia)</td>
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<tr>
<td><em>H. grandifolium</em></td>
<td>(Pedro Álvarez, Tenerife, Canary Islands)</td>
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<tr>
<td><em>H. heterophyllum</em></td>
<td>(northern Turkey)</td>
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<td><em>H. hircinum</em></td>
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<td><em>H. hirsutum</em></td>
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<tr>
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<tr>
<td><em>H. lescenaultii</em></td>
<td>(Indonesia)</td>
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<td><em>H. leptophyllum</em></td>
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<tr>
<td><em>H. maculatum</em></td>
<td>(Prakovce, Slovakia)</td>
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<td><em>H. microsepalum</em></td>
<td>(southeastern USA)</td>
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<tr>
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<tr>
<td><em>H. montbretii</em></td>
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<td><em>H. nummularioides</em></td>
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<td><em>H. olympicum</em></td>
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<tr>
<td><em>H. orientale</em></td>
<td>(northern Turkey)</td>
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<tr>
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</tr>
<tr>
<td><em>H. perforatum</em></td>
<td>(Southeastern USA)</td>
</tr>
</tbody>
</table>

**Hyperforin (118)**

![Hyperforin Molecular Structure](image-url)
H. pruinatum (northern Turkey)\textsuperscript{145}

H. reflexum (Halle-Wittenberg, Germany)\textsuperscript{3}

H. richeri

Umbrian-Marchean Apennines, Italy\textsuperscript{151}

Throughout Macedonia and Serbia\textsuperscript{146,147}

H. rumeliacum (throughout Macedonia and Serbia)\textsuperscript{145,147}

H. scabrum (northern Turkey)\textsuperscript{145}

H. sinaicum (northern Jordan)\textsuperscript{2,152}

H. tetrapetrum

Umbrian-Marchean Apennines, Italy\textsuperscript{153,154}

Throughout Macedonia and Serbia\textsuperscript{146,147}

Nová Sedlica, Slovakia\textsuperscript{155}

H. triquetrifolium

Ajloun Nature Preserve, northern Jordan\textsuperscript{152}

Northern Turkey\textsuperscript{145,147}

H. venustum (throughout Turkey)\textsuperscript{145,171}

Apocynum venetum (Apocynaceae)\textsuperscript{172}

Scutellaria baicalensis (Lamiaceae)\textsuperscript{173}

\textsuperscript{1}H NMR\textsuperscript{9,167,174,175,176,177,177} \textsuperscript{13}C NMR\textsuperscript{114,174,175,176,177} (UV, IR)\textsuperscript{167,174} [\alpha]_D = +41° (EtOH)\textsuperscript{167}

structural elucidation;\textsuperscript{178,179} crystal structure\textsuperscript{179,180} absolute configuration\textsuperscript{180}

---

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}

propolis, type 6 (Atlantic forest, Bahia, Brazil)\textsuperscript{182}

(NMR, IR)\textsuperscript{181,182} UV\textsuperscript{181} [\alpha]_D = –37.7° (CHCl\textsubscript{3})\textsuperscript{181}

---

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}

propolis (Guantanamo, Cuba)\textsuperscript{181}

NMR\textsuperscript{79,181} (UV, IR)\textsuperscript{181} [\alpha]_D = –42.2°; \textsuperscript{79,80} –20.8°\textsuperscript{181} (CHCl\textsubscript{3})

---

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}

(NMR, UV, IR)\textsuperscript{181} [\alpha]_D = –27.3° (CHCl\textsubscript{3})\textsuperscript{181}

structural revision
hyperibone D
(122)

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}
(NMR, UV, IR)\textsuperscript{181} $[\alpha]_D = -61.9^\circ$ (CHCl\textsubscript{3})\textsuperscript{181}

---

hyperibone E
(123)

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}
(NMR, UV, IR)\textsuperscript{181} $[\alpha]_D = -56.0^\circ$ (CHCl\textsubscript{3})\textsuperscript{181}
structural revision\textsuperscript{132}

---

hyperibone F
(124)

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}
(NMR, UV, IR)\textsuperscript{181} $[\alpha]_D = -31.0^\circ$ (CHCl\textsubscript{3})\textsuperscript{181}
structural revision\textsuperscript{132}

---

hyperibone G
(125)

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}
(NMR, UV, IR)\textsuperscript{181} $[\alpha]_D = -29.3^\circ$ (CHCl\textsubscript{3})\textsuperscript{181}

---

hyperibone H
(126)

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}
(NMR, UV, IR)\textsuperscript{181} $[\alpha]_D = +12.4^\circ$ (CHCl\textsubscript{3})\textsuperscript{181}
structural revision\textsuperscript{132}

---

hyperibone I
(127)

Hypericum scabrum (Chimgan, Uzbekistan)\textsuperscript{181}
(NMR, UV, IR)\textsuperscript{181} $[\alpha]_D = +13.3^\circ$ (CHCl\textsubscript{3})\textsuperscript{181}
structural revision\textsuperscript{132}
hyperibone K
(128)

Hypericum scabrum (Chimgan, Uzbekistan) \(^{38}\)
(NMR, UV, IR) \(^{38}\) \([\alpha]_D = +22.3^\circ (\text{CHCl}_3)\) \(^{38}\)
absolute configuration \(^{183}\)

18-hydroxyhyperibone K
(129)

Hypericum hypericoides (St. Andrew, Jamaica) \(^{31}\)
(NMR, IR) \(^{31}\)

hyperibone L
(130)

Hypericum scabrum (Chimgan, Uzbekistan) \(^{38}\)
(NMR, UV, IR) \(^{38}\) \([\alpha]_D = +69.5^\circ (\text{CHCl}_3)\) \(^{38}\)

hyperpapuanone
(131)

Hypericum papuanum (Ialibu, Papua New Guinea) \(^{184}\)
(NMR, UV) \(^{184}\) \([\alpha]_D = +15^\circ (\text{MeOH})\) \(^{184}\)

hypersampsone A
(132)

Hypericum sampsonii (Chia-Yi, Taiwan) \(^{185}\)
(NMR, IR) \(^{185}\) \([\alpha]_D = +21^\circ (\text{CHCl}_3)\) \(^{185}\)

hypersampsone B
(133)

Hypericum sampsonii (Chia-Yi, Taiwan) \(^{185}\)
(NMR, IR) \(^{185}\) \([\alpha]_D = +12^\circ (\text{CHCl}_3)\) \(^{185}\)

hypersampsone C
(134)

Hypericum sampsonii (Chia-Yi, Taiwan) \(^{185}\)
(NMR, IR) \(^{185}\) \([\alpha]_D = +14.3^\circ (\text{CHCl}_3)\) \(^{185}\)
<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Additional Information</th>
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</thead>
<tbody>
<tr>
<td>hypersampsone D</td>
<td>Hypericum sampsonii (Chia-Yi, Taiwan)</td>
<td>(NMR, UV, IR) [\alpha]_D = −35º (CHCl)</td>
</tr>
<tr>
<td>(135)</td>
<td></td>
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</tr>
<tr>
<td>hypersampsone E</td>
<td>Hypericum sampsonii (Chia-Yi, Taiwan)</td>
<td>(NMR, UV, IR) [\alpha]_D = +39º (CHCl)</td>
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<td>(136)</td>
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<tr>
<td>hypersampsone F</td>
<td>Hypericum sampsonii (Chia-Yi, Taiwan)</td>
<td>(NMR, UV, IR) [\alpha]_D = +30.0º (CHCl)</td>
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<tr>
<td>(137)</td>
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<td>structural revision</td>
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<tr>
<td>hypersampsone G</td>
<td>Hypericum sampsonii (China)</td>
<td>IR [\alpha]_D = +10.25º (CHCl)</td>
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<td>(138)</td>
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<td>crystal structure</td>
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<tr>
<td>hypersampsone H</td>
<td>Hypericum sampsonii (China)</td>
<td>(NMR, IR) [\alpha]_D = +44.37º (CHCl)</td>
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<td>(139)</td>
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</tr>
<tr>
<td>hypersampsone I</td>
<td>Hypericum sampsonii (Chalin, Hunan, China)</td>
<td>(NMR, UV, IR) [\alpha]_D = +18.6º (CHCl)</td>
</tr>
<tr>
<td>(140)</td>
<td></td>
<td>crystal structure</td>
</tr>
<tr>
<td>hypersampsone J</td>
<td>Hypericum sampsonii (Chalin, Hunan, China)</td>
<td>(NMR, UV, IR) [\alpha]_D = +11.4º (CHCl)</td>
</tr>
<tr>
<td>(141)</td>
<td></td>
<td>crystal structure</td>
</tr>
</tbody>
</table>
hypersampsone K  
(142)  
Hypericum sampsonii (Chalin, Hunan, China) \(^{187}\)  
(NMR, UV, IR) \(^{187}\) \([\alpha]_D = +31.7^\circ \text{ (CHCl}_3\) \(^{187}\)

hypersampsone L  
(143)  
Hypericum sampsonii (Chalin, Hunan, China) \(^{187}\)  
(NMR, UV, IR) \(^{187}\) \([\alpha]_D = -67.4^\circ \text{ (CHCl}_3\) \(^{187}\)

insignone  
(144)  
Clusia insignis (Campinas, São Paulo, Brazil) \(^{24}\)  
O-Me ether \((^{1}H\text{ NMR, UV}) \(^{24}\) \([\alpha]_D = +92.7^\circ \text{ (CHCl}_3\) \(^{24}\)

methyl insignone  
(145)  
propolis (Manaus, Brazil) \(^{20}\)  
\((^{1}H\text{ NMR, UV}) \(^{24}\) \([\alpha]_D = +92.7^\circ \text{ (CHCl}_3\) \(^{24}\)
Allanblackia monticola (West Province, Cameroon)\textsuperscript{83}
Calophyllum enervosum (Bukittinggi, West Sumatra, Indonesia)\textsuperscript{14}
C. thorelii (central Vietnam)\textsuperscript{33}
Hypericum lanceolatum (Mt. Bambouts, West Province, Cameroon)\textsuperscript{188,189}
Garcinia assigu (Central Province, Papua New Guinea)\textsuperscript{29}
G. bancana (Naratiwath, Thailand)\textsuperscript{84}
G. brevipedicellata (Cameroon)\textsuperscript{30}
G. cambogia (India)\textsuperscript{86,87}
G. cowa (Yunnan, China)\textsuperscript{65,66}
G. esculenta (Dehong, Yunnan, China)\textsuperscript{66}
G. giffithii (Singapore)\textsuperscript{134}
G. indica (India)\textsuperscript{93,94}
G. lancelimba (Xishuangbanna, Yunnan, China)\textsuperscript{86}
G. latissimia (Central Province, Papua New Guinea)\textsuperscript{190}
G. multiflora
  Wanning, China\textsuperscript{65}
  Mudan, Taiwan\textsuperscript{68}
G. nuijiangensis (Nuijiang, Yunnan, China)\textsuperscript{49}
G. oblongifolia (Bobai, Guangxi, China)\textsuperscript{66}
G. paucinervis (Xishuangbanna, Yunnan, China)\textsuperscript{66}
G. pedunculata (Jorhat, Assam, India)\textsuperscript{97}
G. preussii (Cameroon)\textsuperscript{30}
G. purpurea (Japan)\textsuperscript{51}
G. subelliptica (Shenzhen, Guangdong, China)\textsuperscript{66}
G. tetrandra (West Kalimantan, Indonesia)\textsuperscript{98}
G. xanthochymus (Xishuangbanna, Yunnan, China)\textsuperscript{86}
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China)\textsuperscript{66}
G. yunnanensis (Dehong, Yunnan, China)\textsuperscript{66}
Moronobea coccinea (dense rain forest, French Guyana)\textsuperscript{16}
Rheedia acuminata (French Guyana)\textsuperscript{191}

\textsuperscript{1}H NMR\textsuperscript{46,97,98,191} \textsuperscript{13}C NMR\textsuperscript{46,86,98,191} 
(\textsuperscript{1}H, IR)\textsuperscript{46,51,93,94,97,191} \textsuperscript{13}C\textsuperscript{29} 
[\alpha]_D = -158^\circ, 46\textsuperscript{°} -160^\circ\textsuperscript{191} (\textsuperscript{1}HCl)\textsuperscript{-}224^\circ, 51\textsuperscript{°} -209.9^\circ,\textsuperscript{86} 
-269.8^\circ\textsuperscript{94} (\textsuperscript{1}HCl)\textsuperscript{-}203^\circ, 93\textsuperscript{°} -211^\circ\textsuperscript{97} (\textsuperscript{1}HCl) 
structural revision,\textsuperscript{192} crystal structure,\textsuperscript{192} absolute configuration,\textsuperscript{66}

Garcinia assigu (Central Province, Papua New Guinea)\textsuperscript{29}

(NMR, UV, IR, CD)\textsuperscript{29} [\alpha]_D = -199^\circ (\textsuperscript{1}HCl)\textsuperscript{29} 
absolute configuration,\textsuperscript{29}
7-epi-isogarcinol (148)

Garcinia nuijiangensis (Nuijiang, Yunnan, China)\textsuperscript{49}  
Moronobea coccinea (dense rain forest, French Guyana)\textsuperscript{46}  
Rheedia acuminata (French Guyana)\textsuperscript{191}  
Symphonia globulifera (dense rain forest, French Guyana)\textsuperscript{57}

(NMR, UV, IR)\textsuperscript{46,47,191} \([\alpha]_D = -158^\circ\) (CHCl\textsubscript{3})\textsuperscript{46,47,191}

30-epi-isogarcinol (149)

Allanblackia ulugurensis (Morningside, Morogoro, Tanzania)\textsuperscript{124}  
Garcinia cochinchinensis (southern Vietnam)\textsuperscript{71}  
G. cowa (Yunnan, China)\textsuperscript{63,66}  
G. esculenta (Dehong, Yunnan, China)\textsuperscript{66}  
G. lancilimba (Xishuangbanna, Yunnan, China)\textsuperscript{66}  
G. multiflora (Wanning, China)\textsuperscript{66}  
G. oblifolia (Vietnam)\textsuperscript{126}  
G. paucinervis (Xishuangbanna, Yunnan, China)\textsuperscript{66,67}  
G. subelliptica (Shenzhen, Guangdong, China)\textsuperscript{66}  
G. xanthochymus (Xishuangbanna, Yunnan, China)\textsuperscript{66}  
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China)\textsuperscript{66}  
G. yunnanensis (Dehong, Yunnan, China)\textsuperscript{66}

(NMR, UV)\textsuperscript{123} \([\alpha]_D = -125^\circ\) (CHCl\textsubscript{3})\textsuperscript{123}

14-deoxyisogarcinol (150)

Garcinia indica (Bengaluru, India)\textsuperscript{94}

(NMR, UV, IR)\textsuperscript{94} \([\alpha]_D = -178.0^\circ\) (MeOH)\textsuperscript{94}  
crystal structure\textsuperscript{193}

14-deoxy-7-epi-isogarcinol (151)

Symphonia globulifera (dense rain forest, French Guyana)\textsuperscript{57}

(NMR, UV, IR)\textsuperscript{47} \([\alpha]_D = -77^\circ\) (CHCl\textsubscript{3})\textsuperscript{57}

13,14-didehydroxyisogarcinol (152)

Garcinia multiflora (Mudan, Taiwan)\textsuperscript{68}

(NMR, UV, IR, CD)\textsuperscript{68} \([\alpha]_D = -185^\circ\) (CHCl\textsubscript{3})\textsuperscript{68}  
absolute configuration\textsuperscript{68}
**Isoxanthochymol**  

**Ent-isogarcinol**  

(153)  

**Garcinia afzelii** (Mt. Eloumdem, Centre Province, Cameroon)  
**G. cambogia** (Kerela, India)  
**G. griffithii** (Lembah Arau, West Sumatra, Indonesia)  
**G. indica** (Dapoli, Maharashtra, India)  
**G. livingstonei** (Homestead, Florida, USA)  
**G. maingayii**  
Riau Islands, Indonesia  
Pahang, Malaysia  
**G. multiflora**  
Diaoluo Mountain, Hainan, China  
Taiwan  
**G. ovalifolia**  
Douala-Edea Reserve, Cameroon  
Ndakan Gorilla Study Area, Central African Republic  
**G. polyantha** (Cheffou-Baham, West Province, Cameroon)  
**G. pyrifera** (Sungai Petani, Kedah, Malaysia)  
**G. smeathmannii** (Cheffou-Baham, West Province, Cameroon)  
**G. subelliptica** (Okinawa, Japan)  
**G. xanthochymus**  
South Canara, India  
Homestead, Florida, USA  
**G. xipshuangbannaensis** (Xishuangbanna, Yunnan, China)  
**Rheedia acuminata** (La Paz, Bolivia)  
**R. edulis** (Broward County, Florida, USA)  

\[
\alpha_D = +181^\circ \quad \text{MeOH} 
\]

\[
\alpha_D = +208^\circ \quad \text{EtOH} 
\]

characterized as mixture with  

(1H NMR, IR)  

\[
\alpha_D = +142^\circ \quad \text{CHCl}_3 
\]

\[
\alpha_D = +158^\circ \quad \text{MeOH} 
\]

absolute configuration; crystal structure  

structural revision

**Lathrophytoic acid B**  

(154)  

**Kielmeyera lathrophyton** (Chapada Diamantina, Brazil)  
O-Me ether (NMR, IR)

**Laxifloranone**  

(155)  

**Marila laxiflora** (Guatemala)  

(NMR, UV, IR)  

\[
\alpha_D = +23.6^\circ \quad \text{MeOH} 
\]
**makandechemone (156)**

*Garcinia punctata* (northern Gabon)

(NMR, UV)

---

**nemorosone (157)**

*Clusia rosea*

Campinas, São Paulo, Brazil

Havana, Cuba

*C. grandiflora*

Campinas, São Paulo, Brazil

Canaima, Venezuela

*C. hilariana*

Campinas, São Paulo, Brazil

Jurubatiba, Brazil

*C. insignis* (Campinas, São Paulo, Brazil)

*C. nemorosa* (Campinas, São Paulo, Brazil)

*C. rosea*

Campinas, São Paulo, Brazil

Havana, Cuba

brown propolis (throughout Cuba)

(NMR, UV, IR) [α]D = +112.8 (CHCl3) [α]D = +150º (MeOH) [α]D = +48.6º (CHCl3)

structural revision; crystal structure

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**hydroxynemorosone (158)**

*Clusia nemorosa* (Campinas, São Paulo, Brazil)

O-Me ether (NMR, IR) [α]D = +142.8º (MeOH)

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**nujiangefolin A (159)**

*Garcinia nujiangensis* (Nujiang, Yunnan, China)

(NMR, UV, IR) [α]D = −2º (MeOH)
<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>nujiangefolin B</td>
<td><em>Garcinia nujiangensis</em> (Nuijiang, Yunnan, China)</td>
<td>(NMR, UV, IR) ( [\alpha]_D = +5^\circ ) (MeOH) (^9)</td>
</tr>
<tr>
<td>nujiangefolin C</td>
<td><em>Garcinia nujiangensis</em> (Nuijiang, Yunnan, China)</td>
<td>(NMR, UV, IR) ( [\alpha]_D = +20^\circ ) (MeOH) (^9)</td>
</tr>
<tr>
<td>no name</td>
<td><em>Clusia obdeltifolia</em> (Chapada Diamantina, Brazil)</td>
<td>NMR (^{215} ) ( [\alpha]_D = +30.9^\circ ) (CHCl(_3)) (^{215})</td>
</tr>
<tr>
<td>no name</td>
<td><em>Clusia obdeltifolia</em> (Chapada Diamantina, Brazil)</td>
<td>NMR (^{215} ) ( [\alpha]_D = +10.0^\circ ) (CHCl(_3)) (^{215})</td>
</tr>
<tr>
<td>no name</td>
<td><em>Clusia obdeltifolia</em> (Chapada Diamantina, Brazil)</td>
<td>(NMR, IR) (^{216})</td>
</tr>
<tr>
<td>no name</td>
<td><em>Clusia obdeltifolia</em> (Chapada Diamantina, Brazil)</td>
<td>(NMR, IR) (^{216} ) ( [\alpha]_D = -5.1^\circ ) (CHCl(_3)) (^{216})</td>
</tr>
</tbody>
</table>
oblongifolin A
(166)

Garcinia cowa (Yunnan, China)\(^{65,66}\)
G. lancilimba (Xishuangbanna, Yunnan, China)\(^{66}\)
G. multiflora (Wanning, China)\(^{66}\)

**G. oblongifolia**
Bobai, Guangxi, China\(^{66,116}\)
Nhu Xuan, Vietnam\(^{96,126}\)

G. paucinervis (Xishuangbanna, Yunnan, China)\(^{66}\)
G. xanthochymus (Xishuangbanna, Yunnan, China)\(^{66}\)
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China)\(^{66}\)

G. yunnanensis
Dehong, Yunnan, China\(^{66}\)
Luxi, Yunnan, China\(^{100}\)

\((\text{NMR, UV, IR})\)^{96} \([\alpha]_D = +23^\circ (\text{CHCl}_3)\)

---

oblongifolin B
(167)

\((\text{NMR, UV, IR})\)^{96} \([\alpha]_D = +7.6^\circ (\text{CHCl}_3)\)

---

oblongifolin C
ent-guttiferone G
(168)

\((\text{NMR, UV, IR})\)^{96} \([\alpha]_D = +14.5^\circ (\text{CHCl}_3)\)

---

oblongifolin D
(169)

\((\text{NMR, UV, IR})\)^{96} \([\alpha]_D = +44.6^\circ (\text{CHCl}_3)\)
oblongifolin E
(170)

Garcinia oblongifolia (Bobai, Guangxi, China)\textsuperscript{116}
(NMR, UV, IR)\textsuperscript{116} [\alpha]_D = +65.1° (CHCl\textsubscript{3})\textsuperscript{116}

oblongifolin F
ent-guttiferone \textit{O2}
(171)

Garcinia multiflora (Wanning, China)\textsuperscript{66}
\textit{G. oblongifolia} (Bobai, Guangxi, China)\textsuperscript{116}
\textit{G. subelliptica} (Shenzhen, Guangdong, China)\textsuperscript{66}
\textit{G. xipshuangbannaensis} (Xishuangbanna, Yunnan, China)\textsuperscript{66}
\textit{G. yunnanensis} (Dehong, Yunnan, China)\textsuperscript{66}
(NMR, UV, IR)\textsuperscript{116} [\alpha]_D = –85.6° (CHCl\textsubscript{3})\textsuperscript{116}

oblongifolin G
(172)

Garcinia oblongifolia (Bobai, Guangxi, China)\textsuperscript{66}
\textit{G. oblongifolia} (Bobai, Guangxi, China)\textsuperscript{116}
\textit{G. paucinervis} (Xishuangbanna, Yunnan, China)\textsuperscript{66}
\textit{G. subelliptica} (Shenzhen, Guangdong, China)\textsuperscript{66}
\textit{G. xipshuangbannaensis} (Xishuangbanna, Yunnan, China)\textsuperscript{66}
\textit{G. yunnanensis} (Dehong, Yunnan, China)\textsuperscript{66}
(NMR, UV, IR)\textsuperscript{116} [\alpha]_D = +5.9° (CHCl\textsubscript{3})\textsuperscript{116}

oblongifolin H
(173)

Garcinia oblongifolia (Bobai, Guangxi, China)\textsuperscript{66}

oblongifolin I
(174)

Garcinia oblongifolia (Bobai, Guangxi, China)\textsuperscript{66}
ochrocarpinone A (175)

Ochrocarpos punctatus (Mahajanga, Madagascar)\textsuperscript{217}

(NMR, UV, IR)\textsuperscript{217} [\(\alpha\)]\textsubscript{D} = +8.7º (CHCl\textsubscript{3})\textsuperscript{217}

ochrocarpinone B (176)

Ochrocarpos punctatus (Mahajanga, Madagascar)\textsuperscript{217}

(NMR, UV, IR)\textsuperscript{217} [\(\alpha\)]\textsubscript{D} = -3.5º (CHCl\textsubscript{3})\textsuperscript{217}

ochrocarpinone C ent-hyperibone B (177)

Ochrocarpos punctatus (Mahajanga, Madagascar)\textsuperscript{217}

(NMR, UV, IR)\textsuperscript{217} [\(\alpha\)]\textsubscript{D} = +10.2º (CHCl\textsubscript{3})\textsuperscript{217}

otogirinin A (178)

Hypericum erectum (Japan)\textsuperscript{218}

(NMR, UV, IR, CD)\textsuperscript{218} [\(\alpha\)]\textsubscript{D} = -8.1º (MeOH)\textsuperscript{218}

otogirinin B (179)

Hypericum erectum (Japan)\textsuperscript{218}

(NMR, UV, IR, CD)\textsuperscript{218} [\(\alpha\)]\textsubscript{D} = +12.0º (MeOH)\textsuperscript{218}

otogirinin C (180)

Hypericum erectum (Japan)\textsuperscript{218}

NMR\textsuperscript{218}
otogirinin D (181)

Hypericum erectum (Japan)\(^{218}\)

(NMR, UV, IR)\(^{218}\) \([\alpha]_D = +160.0^\circ\) (MeOH)\(^{218}\)

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otogirinin E (182)

Hypericum erectum (Japan)\(^{218}\)

NMR\(^{218}\)

---

oxepahyperforin (183)

Hypericum perforatum (Chile)\(^{64}\)

(NMR, UV, IR, CD)\(^{64}\) \([\alpha]_D = -73.7^\circ\) (CHCl\(_3\))

---

oxyhyperforin 8-hydroxyhyperforin 8,1-hemiacetal (184)

Hypericum perforatum

Chile\(^{64}\)

Italy\(^{13}\)

Tokushima, Japan\(^{59}\)

(NMR, UV, IR, CD)\(^{64}\) \([\alpha]_D = +34.0^\circ\) (CHCl\(_3\))

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papuaforin A (185)

Hypericum papuanum (Ialibu, Papua New Guinea)\(^{184}\)

(NMR, UV)\(^{184}\) \([\alpha]_D = +13^\circ\) (MeOH)\(^{184}\)

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papuaforin B (186)

Hypericum papuanum (Ialibu, Papua New Guinea)\(^{184}\)

NMR\(^{184}\)
papuaforin C (187)

Hypericum papuanum (Ialibu, Papua New Guinea)\(^{184}\)

(NMR, UV)\(^{184}\) \(\lbrack \alpha \rbrack_D = +23^\circ \) (MeOH)\(^{184}\)

papuaforin D (188)

Hypericum papuanum (Ialibu, Papua New Guinea)\(^{184}\)

(NMR, UV)\(^{184}\) \(\lbrack \alpha \rbrack_D = +64^\circ \) (MeOH)\(^{184}\)

papuaforin E (189)

Hypericum papuanum (Ialibu, Papua New Guinea)\(^{184}\)

(NMR, UV)\(^{184}\) \(\lbrack \alpha \rbrack_D = +41^\circ \) (MeOH)\(^{184}\)

paucinone A (190)

Garcinia paucinervis (Xishuangbanna, Yunnan, China)\(^{219,220}\)

(NMR, UV, IR)\(^{219,220}\) \(\lbrack \alpha \rbrack_D = -6.2^\circ \) (MeOH)\(^{219,220}\)

paucinone B (191)

Garcinia paucinervis (Xishuangbanna, Yunnan, China)\(^{219,220}\)

(NMR, UV, IR)\(^{219,220}\) \(\lbrack \alpha \rbrack_D = +58.7^\circ \) (MeOH)\(^{219,220}\)

paucinone C (192)

Garcinia paucinervis (Xishuangbanna, Yunnan, China)\(^{219,220}\)

(NMR, UV, IR)\(^{219,220}\) \(\lbrack \alpha \rbrack_D = +19.2^\circ \) (MeOH)\(^{219,220}\)
**paucinone D** (193)  
*Garcinia paucinervis* (Xishuangbanna, Yunnan, China)\(^{219,220}\)  
(NMR, UV, IR)\(^{219,220}\) \([\alpha]_D = +41.6^\circ\) (MeOH)\(^{219,220}\)

**pedunculol** (194)  
*Garcinia pedunculata* (Jorhat, Assam, India)\(^97\)  
(NMR, UV, IR)\(^97\) \([\alpha]_D = -159^\circ\) (EtOH)\(^97\)

**peroxysampsone A** (195)  
*Hypericum sampsonii* (Cha Lin, Hunan, China)\(^221\)  
(NMR, UV, IR)\(^221\) \([\alpha]_D = +17.0^\circ\) (CHCl\(_3\))\(^221\)

**peroxysampsone B** (196)  
*Hypericum sampsonii* (Cha Lin, Hunan, China)\(^221\)  
(NMR, UV, IR)\(^221\) \([\alpha]_D = -41.2^\circ\) (CHCl\(_3\))\(^221\)

**plukenetione A** (197)  
*Clusia plukenetii* (Barbados)\(^222\) propolis (throughout Cuba)\(^212\)  
(NMR, UV, IR)\(^222\) \([\alpha]_D = +1^\circ\) (CHCl\(_3\))\(^222\)

**28,29-epoxyplukenetione A** (198)  
*Clusia havetiodes* (Ecclesdown, Portland, Jamaica)\(^223\)  
*C. obdeltifolia* (Chapada Diamantina, Brazil)\(^15\)  
(NMR, UV, IR)\(^223\) \([\alpha]_D = -4.4^\circ\) (CHCl\(_3\))\(^223\)

**plukenetione B** (199)  
*Clusia plukenetii* (St. Thomas, Barbados)\(^224\)  
(NMR, UV, IR)\(^224\) \([\alpha]_D = +17.2^\circ\) (CHCl\(_3\))\(^224\) structural revision\(^225\)
plukenetione C
(200)

Clusia havetiodes (Ecclesdown, Portland, Jamaica)\textsuperscript{223}

\textit{C. plukenetii} (St. Thomas, Barbados)\textsuperscript{224}

Hypericum sampsonii (Cha Lin, Hunan, China)\textsuperscript{221}

\((\text{NMR, UV, IR})\textsuperscript{221,223,224}\)

\([\alpha]_D = +27.5^\circ, \textsuperscript{221} +15.0^\circ, \textsuperscript{223} +65.9^\circ (\text{CHCl}_3)\)

33-hydroxyperoxyiso-
plukenetione C
(201)

Clusia havetiodes (Ecclesdown, Portland, Jamaica)\textsuperscript{223}

\((\text{NMR, UV, IR})\textsuperscript{223} [\alpha]_D = -3.9^\circ (\text{CHCl}_3)\textsuperscript{223}\)

plukenetione D/E
7-epi-nemorosone
(202)

Clusia hilariana (Campinas, São Paulo, Brazil)\textsuperscript{24}

\textit{C. nemorosa} (Campinas, São Paulo, Brazil)\textsuperscript{209}

\textit{C. plukenetii} (St. Thomas, Barbados)\textsuperscript{224}

\textit{C. rosea} (Florida, USA)\textsuperscript{226}

\textit{Tovomitopsis saldanhae} (southeastern Brazil)\textsuperscript{227}

\textit{Propolis Caribean} \textsuperscript{226}

\textit{Manaus, Brazil} \textsuperscript{20}

\((\text{NMR, UV, IR})\textsuperscript{20,227}\)

\textit{O-Me ether} (\text{NMR, IR})\textsuperscript{209} \([\alpha]_D = +140.7 (\text{CHCl}_3)\textsuperscript{209}\)

\textit{acetate ester} (\text{NMR, UV, IR})\textsuperscript{224} \([\alpha]_D = +34.5^\circ (D), -37.6^\circ (E) (\text{CHCl}_3)\textsuperscript{224}\)

\textit{structural revision}\textsuperscript{225,227}

plukenetione F
(203)

Clusia plukenetii (St. Thomas, Barbados)\textsuperscript{224}

\((\text{NMR, UV, IR})\textsuperscript{224} [\alpha]_D = -53.6^\circ (\text{CHCl}_3)\textsuperscript{224}\)

characterized as mixture with \textit{205} \((\text{NMR, UV, IR})\textsuperscript{223}\)

\textit{structural revision}\textsuperscript{132}

15,16-dihydro-16-hydroperoxy-
plukenetione F
(204)

Clusia havetiodes (Ecclesdown, Portland, Jamaica)\textsuperscript{223}

\textit{Ochrocarpos punctatus} (Mahajanga, Madagascar)\textsuperscript{217}

\((\text{NMR, UV, IR})\textsuperscript{223} [\alpha]_D = +24.7^\circ (\text{CHCl}_3)\textsuperscript{223}\)

\textit{structural revision}\textsuperscript{132}

plukenetione G
(205)

Clusia havetiodes (Ecclesdown, Portland, Jamaica)\textsuperscript{223}

\textit{C. plukenetii} (St. Thomas, Barbados)\textsuperscript{224}

\((\text{NMR, UV, IR})\textsuperscript{224}\)

characterized as mixture with \textit{203} \((\text{NMR, UV, IR})\textsuperscript{223}\)

\textit{structural revision}\textsuperscript{132}
prolifenone A (206)  
*Hypericum prolificum* (Lawrence County, Pennsylvania, USA)  
(NMR, UV, IR)\(^\text{228}\) \([\alpha]_D = +13.3^\circ\text{ (MeOH)}\)\(^{228}\)

prolifenone B (207)  
*Hypericum prolificum* (Lawrence County, Pennsylvania, USA)  
(NMR, UV, IR)\(^\text{228}\) \([\alpha]_D = -0.58^\circ\text{ (MeOH)}\)\(^{228}\)

propolone A (208)  
propolis (Nuevitas, Cuba)\(^\text{229}\)  
(NMR, UV, IR)\(^\text{229}\) \([\alpha]_D = +40^\circ\text{ (CHCl}\_3)\)\(^\text{229}\)

propolone B (209)  
propolis (Guantanamo, Cuba)\(^\text{80}\)  
(NMR, UV, IR)\(^\text{80}\) \([\alpha]_D = +38.2^\circ\text{ (CHCl}\_3)\)\(^\text{80}\)

propolone C (210)  
propolis (Guantanamo, Cuba)\(^\text{80}\)  
(NMR, UV, IR)\(^\text{80}\) \([\alpha]_D = +35.7^\circ\text{ (CHCl}\_3)\)\(^\text{80}\)

propolone D  
ent-hyperibone G (211)  
*Clusia minor* (Havana, Cuba)\(^\text{79}\)  
propolis (Guantanamo, Cuba)\(^\text{80}\)  
NMR\(^\text{79}\) \([\alpha]_D = +48.5^\circ\text{ (CHCl}\_3)\)\(^\text{79,80}\)
pyrohyperforin

Hypericum perforatum
Longxi, Gansu, China$^{162,230}$
Tokushima, Japan$^{59}$
Mt. Orzen, southeast Serbia$^{58}$

(NMR, UV, IR)$^{162,230} [\alpha]_D = +83.5$ (CHCl$_3$)$^{162,230}$

sampsonione A

Hypericum erectum (Japan)$^{218}$

H. sampsonii
Jinhua, Zhejiang, China$^{32,231}$
Yunnan, China$^{232}$

(NMR, UV, IR)$^{231,232} [\alpha]_D = -49.10^\circ$ (CHCl$_3$)$^{231}$

sampsonione B

Clusia obdeltifolia (Chapada Diamantina, Brazil)$^{216}$

Hypericum sampsonii
Hunan, China$^{37}$
Jinhua, Zhejiang, China$^{32,231}$

NMR$^{231}$ IR$^{216} [\alpha]_D = +10.0$ (CHCl$_3$)$^{216}$

sampsonione C

Hypericum sampsonii (Jinhua, Zhejiang, China)$^{32,233}$

(NMR, UV, IR)$^{233} [\alpha]_D = +13.39^\circ$ (CHCl$_3$)$^{233}$

sampsonione D

Hypericum sampsonii
Jinhua, Zhejiang, China$^{32,233}$
Chia-Yi, Taiwan$^{89}$

(NMR, UV, IR)$^{231} [\alpha]_D = +12.27^\circ$ (CHCl$_3$)$^{233}$

sampsonione E

Hypericum sampsonii
Jinhua, Zhejiang, China$^{32,233}$

(NMR, UV, IR)$^{231} [\alpha]_D = +57.69^\circ$ (CHCl$_3$)$^{233}$

sampsonione F

Hypericum sampsonii
Jinhua, Zhejiang, China$^{32,233}$
Yunnan, China$^{232}$

(NMR, UV, IR)$^{232,233} [\alpha]_D = +14.52^\circ$ (CHCl$_3$)$^{233}$
**sampsonione G**  
(219)  
Clusia obdeltifolia (Chapada Diamantina, Brazil)\(^{216}\)  
Hypericum sampsonii (Jinhua, Zhejiang, China)\(^{2,233}\)  
(NMR, UV)\(^{216,233}\) \([\alpha]_D = +10.00^\circ\) (CHCl\(_3\))\(^{233}\)

**ent-sampsonione G**  
(220)  
Clusia havetoides (Ecclesdown, Portland, Jamaica)\(^{223}\)  
(NMR, UV, IR)\(^{223}\) \([\alpha]_D = -3.5^\circ\) (CHCl\(_3\))\(^{223}\)

**sampsonione H**  
(221)  
Hypericum sampsonii  
Jinhua, Zhejiang, China\(^{233}\)  
Chia-Yi, Taiwan\(^{35}\)  
(NMR, UV, IR)\(^{233}\) \([\alpha]_D = +5.15^\circ\) (CHCl\(_3\))\(^{233}\)

**sampsonione I**  
(222)  
Hypericum sampsonii (Jinhua, Zhejiang, China)\(^{32,234}\)  
(NMR, UV, IR)\(^{234}\) \([\alpha]_D = +16.88^\circ\) (CHCl\(_3\))\(^{234}\)

**sampsonione J**  
(223)  
Garcinia multiflora (Mudan, Pingtung, Taiwan)\(^{69}\)  
Hypericum sampsonii (Jinhua, Zhejiang, China)\(^{32,234}\)  
(NMR, UV, IR)\(^{234}\) \([\alpha]_D = +1.48^\circ\) (CHCl\(_3\))\(^{234}\)

**sampsonione K**  
(224)  
Hypericum sampsonii  
Jinhua, Zhejiang, China\(^{32}\)  
Yunnan, China\(^{32}\)  
(NMR, UV, IR)\(^{32,232}\) \([\alpha]_D = -5.60^\circ\) (CHCl\(_3\))\(^{32}\)

**sampsonione L**  
(225)  
Hypericum sampsonii  
Hunan, China\(^{32}\)  
Jinhua, Zhejiang, China\(^{32}\)  
(NMR, UV, IR)\(^{32}\) \([\alpha]_D = +55.00^\circ\) (CHCl\(_3\))\(^{32}\)
**Sampsonione M**

*Hypericum sampsonii* (Jinhua, Zhejiang, China)\textsuperscript{32}

(NMR, UV, IR)\textsuperscript{32} \([\alpha]_D = +54.77^\circ\) (CHCl\textsubscript{3})\textsuperscript{32}

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**Sampsonione N**

*Hypericum sampsonii* (Hunan, China)\textsuperscript{37}

(NMR, UV, IR)\textsuperscript{37} \([\alpha]_D = +22.0^\circ\) (CHCl\textsubscript{3})\textsuperscript{37}

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**Sampsonione O**

*Hypericum sampsonii* (Hunan, China)\textsuperscript{37}

(NMR, UV, IR)\textsuperscript{37} \([\alpha]_D = +87.9^\circ\) (CHCl\textsubscript{3})\textsuperscript{37}

---

**Sampsonione P**

*Hypericum sampsonii* (Hunan, China)\textsuperscript{37}

(NMR, UV, IR)\textsuperscript{37} \([\alpha]_D = +18.6^\circ\) (CHCl\textsubscript{3})\textsuperscript{37}

---

**Sampsonione Q**

*Hypericum sampsonii* (Hunan, China)\textsuperscript{37}

(NMR, UV, IR)\textsuperscript{37} \([\alpha]_D = -9.65^\circ\) (CHCl\textsubscript{3})\textsuperscript{37}

Crystal structure\textsuperscript{37}

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**No name sampsonione R**

*Clusia obdeltifolia* (Chapada Diamantina, Brazil)\textsuperscript{216}

*Hypericum sampsonii* (Hunan, China)\textsuperscript{37}

(NMR, IR)\textsuperscript{216} \([\alpha]_D = +10.8^\circ\) (CHCl\textsubscript{3})\textsuperscript{216}
**Clusia scrobiculata** (Campinas, São Paulo, Brazil)\(^{24}\)
propolis (Andes Trujillo, Venezuela)\(^{235}\)
brown propolis (throughout Cuba)\(^{212}\)

\(\left[^1H\text{NMR, UV, IR}\right]D = +44.7^\circ \text{ (CHCl}_3)\)\(^{24}\)

**18-ethyloxy-17-hydroxy-17,18-dihydro-scrobiculatone A**

(233)

propolis (Andes Trujillo, Venezuela)\(^{235}\)
(NMR, UV)\(^{235}\)

**Clusia scrobiculata** (Campinas, São Paulo, Brazil)\(^{24}\)
propolis (Andes Trujillo, Venezuela)\(^{235}\)
brown propolis (throughout Cuba)\(^{212}\)

\(\left[^1H\text{NMR, UV, IR}\right]D = +44.7^\circ \text{ (CHCl}_3)\)\(^{24}\)

**18-ethyloxy-17-hydroxy-17,18-dihydro-scrobiculatone B**

(235)

**Propolis**
Manaus, Brazil\(^{20}\)
Andes Trujillo, Venezuela\(^{235}\)
(NMR, UV)\(^{235}\)

**secohyperforin**

(236)

**Hypericum perforatum** (Yerevan, Armenia)\(^{160}\)
NMR\(^{160}\)
semsinone A
(237)

\[
\text{Garcinia semseii (Morogoro, Tanzania)}^{109,236}

(NMR, UV, IR)^{236} [\alpha]_{D}^{236} = +52^\circ \text{ (CHCl}_3)^{236}
\]

sinaicinone
(238)

\[
\text{Hypericum sinaicum (Sinai peninsula, Egypt)}^{237}

(NMR, UV, IR)^{237} [\alpha]_{D}^{237} = +37.5^\circ \text{ (CH}_2\text{Cl}_2)^{237}
\]

absolute configuration

spiranthenone A
(239)

\[
\text{Spiranthera odoratissima (Rutaceae; Brasilia, Brazil)}^{238}

(NMR, IR)^{238} [\alpha]_{D}^{238} = +11^\circ \text{ (CHCl}_3)^{238}
\]

spiranthenone B
(240)

\[
\text{Spiranthera odoratissima (Rutaceae; Brasilia, Brazil)}^{238}

(NMR, IR)^{238} [\alpha]_{D}^{238} = +13^\circ \text{ (CHCl}_3)^{238}
\]

spiritone
(241)

\[
\text{Clusia burchellii (Campinas, São Paulo, Brazil)}^{24}
\]
\[
\text{C. flaminensis (Campinas, São Paulo, Brazil)}^{24}
\]
\[
\text{C. pana-panari (Campinas, São Paulo, Brazil)}^{24}
\]
\[
\text{C. pernambucensis (Campinas, São Paulo, Brazil)}^{24}
\]
\[
\text{C. spiritu-sanctensis (Campinas, São Paulo, Brazil)}^{24}
\]
\[
\text{C. weddelliana (Campinas, São Paulo, Brazil)}^{24}
\]

O-Me ether (\(^1\)H NMR, UV, IR)^{24}

subellinone
(242)

\[
\text{Garcinia subelliptica (Ishigaki Island, Japan)}^{239}

(NMR, IR)^{239} [\alpha]_{D}^{239} = -2.8^\circ \text{ (EtOH)}^{239}
\]
sundaicumone A (243)  
*Calophyllum sundaicum* (Singapore)\(^{240}\)  
(NMR, UV, IR)\(^{240}\) \([\alpha]_D = +52^o (\text{EtOH})\)\(^{240}\)

sundaicumone B (244)  
*Calophyllum sundaicum* (Singapore)\(^{240}\)  
(NMR, UV, IR)\(^{240}\) \([\alpha]_D = +48^o (\text{EtOH})\)\(^{240}\)

symphonone A (245)  
*Symphonia globulifera* (dense rain forest, French Guyana)\(^{47}\)  
(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -37^o (\text{CHCl}_3)\)\(^{47}\)

symphonone B (246)  
*Symphonia globulifera* (dense rain forest, French Guyana)\(^{47}\)  
(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -81^o (\text{CHCl}_3)\)\(^{47}\)

symphonone C (247)  
*Symphonia globulifera* (dense rain forest, French Guyana)\(^{47}\)  
(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -67^o (\text{CHCl}_3)\)\(^{47}\)
Symphonone D (248)

Symphonia globulifera (dense rain forest, French Guyana)

(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -41^\circ (\text{CHCl}_3)\)

Symphonone E (249)

Symphonia globulifera (dense rain forest, French Guyana)

(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -50^\circ (\text{CHCl}_3)\)

Symphonone F (250)

Symphonia globulifera (dense rain forest, French Guyana)

(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -9^\circ (\text{CHCl}_3)\)

Symphonone G (251)

Symphonia globulifera (dense rain forest, French Guyana)

(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -4^\circ (\text{CHCl}_3)\)

Symphonone H (252)

Symphonia globulifera (dense rain forest, French Guyana)

(NMR, UV, IR)\(^{47}\) \([\alpha]_D = -37^\circ (\text{CHCl}_3)\)
**Symphonone I**

*(253)*

*Symphonia globulifera* (dense rain forest, French Guyana)

(NMR, UV, IR) \( [\alpha]_D = -22^\circ \) (CHCl₃)

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**Thorelione A**

*(254)*

*Calophyllum thorelii* (central Vietnam)

(NMR, UV, IR) \( [\alpha]_D = +91.9^\circ \) (MeOH)

---

**Oxy-thorelione A**

*(255)*

*Calophyllum thorelii* (central Vietnam)

(NMR, UV, IR) \( [\alpha]_D = +323.0^\circ \) (MeOH)

---

**Thorelione B**

*(256)*

*Calophyllum thorelii* (central Vietnam)

(NMR, UV, IR) \( [\alpha]_D = +412.0^\circ \) (MeOH)

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**Uralodin A**

*(257)*

*Hypericum henryi*  
Jinping, Yunnan, China  
Lünchun, Yunnan, China

(NMR, UV, IR) \( [\alpha]_D = -55^\circ \) (MeOH)
uralodin B
(258)

Hypericum henryi (Lünchun, Yunnan, China)\(^6^0\)
(NMR, UV, IR)\(^6^0\) \([\alpha]_D = -24.6^\circ\) (MeOH)\(^6^0\)

uralodin C
(259)

Hypericum henryi (Lünchun, Yunnan, China)\(^6^0\)
(NMR, UV, IR)\(^6^0\) \([\alpha]_D = -55.0^\circ\) (MeOH)\(^6^0\)

xanthochymol
(260)

Clusia rosea
Dominican Republic\(^1^0^7\)
Hilo, Hawaii, USA\(^2^4^2\)
Endodesmia calophylloides (Calophyllaceae; Balmayo, Centre Province, Cameroon)\(^2^4^3\)
Garcinia densivenia (Douala-Edea Reserve, Cameroon)\(^1^9^8\)
G. indica (India)\(^1^9^5\)
G. intermedia (Homestead, Florida, USA)\(^1^0^5\)
G. livingstonei (Homestead, Florida, USA)\(^4^8\)
G. mannii (Douala-Edea Reserve, Cameroon)\(^1^9^8, 2^4^4\)
G. ovalifolia (Douala-Edea Reserve, Cameroon)\(^1^9^7, 1^9^8\)
G. pyrifera (Sungai Petani, Kedah, Malaysia)\(^5^0\)
G. spicata (Homestead, Florida, USA)\(^1^0^5\)
G. staudtii (Douala-Edea Reserve, Cameroon)\(^2^4^5\)
G. subelliptica
northern mountains, Taiwan\(^5^2\)
Okinawa, Japan\(^5^1\)
G. xanthochymus
South Canara,\(^2^0^0\) India\(^2^0^1, 2^0^2, 2^4^6\)
Homestead, Florida, USA\(^1^9, 1^0^5\)
G. xipshuangbannaensis (Xishuangbanna, Yunnan, China)\(^1^1^8, 2^0^3\)
G. virgata (Aoupiníë, New Caledonia)\(^1^1^9\)
Rheedia edulis (Broward County, Florida, USA)\(^4^1\)
R. madrunno (Caracas, Venezuela)\(^2^4^7\)
propolis
Manaus, Brazil\(^2^0\)
throughout Cuba\(^1^2^0\)
red propolis (Maceio City, Alagoas, Brazil)\(^1^2^1\)

\(^{1}^{1}H\) NMR\(^2^0, 5^0, 5^1, 2^0^1, 2^0^2, 2^0^3, 2^4^2, 2^4^8\)
\(^{1}^{3}C\) NMR\(^2^0, 5^0, 5^1, 2^0^1, 2^0^2, 2^4^8\)
UV\(^2^0, 4^1, 5^0, 5^1, 2^0^1, 2^0^2, 2^4^2\)
IR\(^2^0, 5^1, 2^0^1, 2^0^2, 2^4^2\)
\([\alpha]_D = +141.6^\circ\)\(^5^0\)
+138^\circ\)\(^5^1\)
+143.5^\circ\)\(^2^0^2, 2^0^5\)
(CHCl\(_3\)) +209.9^\circ\) (MeOH)\(^2^4^6\)
structural revision\(^2^4^8\)
crystal structure\(^2^4^8\)
absolute configuration\(^2^4^8\)

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Appendix A References


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Appendix B

Catalog of Spectra
The image contains a chemical structure and an 
NMR spectrum. The chemical structure shows a 
compound with various substituents such as 
$t$-Bu, Me, and EtO. The NMR spectrum is 
detailed with peaks at different ppm values, 
indicating the chemical's molecular properties.
Me\_2C\_\_C\_\_C\_\_C\_\_O\_\_C\_\_C\_\_C\_\_\_O\_\_\_\_C\_\_C\_\_C\_\_\_OH

ppm 0 20 40 60 80 100 120 140 160 180 200

ppm 0 20 40 60 80 100 120 140 160 180 200
391