Total Synthesis of Complex Natural Products: Cortistatin A, Vinigrol and Maoecrystal V

A thesis presented

by

Jun Shi

to

The Scripps Research Institute Graduate Program

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

for

The Scripps Research Institute

La Jolla, California

June 2011
Dedication

This thesis is dedicated to

my parents: Youqing Cai and Feng Shi,

and loving Fiancé Shun Su
ACKNOWLEDGEMENTS

First and foremost, I would like to thank my advisor, Professor Phil S. Baran for his continuous support and guidance during my Ph. D. study. It is difficult to overstate my gratitude to Phil. His enthusiasm towards science, his profound understanding of organic chemistry, his creative approaches for problem solving, and his determination and perseverance have set up a standard for me, a student still anxious to learn from him. A reflection of my past five years’ research work clearly reveals the imprint of Phil’s tactic in pursuing challenging problems in organic synthesis. The magic transformation from a first year graduate student who barely knew any organic reactions to a qualified synthetic chemist would never come to reality without his presence.

I am very grateful to my thesis committee: Professor K. C. Nicolaou, Professor Jin-Quan Yu, and Professor Floyd E. Romesberg for their guidance on my research projects over five years. I would like to thank Professor Emmanuel Theodorakis to be my external thesis committee advisor for the guidance on my thesis.

I could not expect better labmates than my knowledgeable and sharp colleagues: Dr. Ben Hafensteiner, Dr Noah Burns, Dr. Tom Maimone, Dr. Carlos A. Guerrero, Dr. Ryan A. Shenvi, Dr. Tim Newhouse, Dr Ian Young, Dr. Ke Chen, Dr. David Lin, Klement Foo, Rodrigo Rodriguez, Ian Seiple, Hans Renata, Paul Krawczuk, Emily Cherney, Ana-Florina Voica, Will Gutekunst, Quentin Michaudel, Dane Holte, Jonathan Lockner, Steve McKerrall and Yoshihiro Ishihara. The years we spent together will be the most valuable time in my life and I wish them the best in their future careers. I also am indebted to Yoshihiro Ishihara, Rodrigo Rodriguez, Hans Renata, Paul Krawczuk, Ana-
Florina Voica, Klement Foo for proof-reading my paper and thesis manuscripts. Special thanks to Dr. Ben Hafensteiner, Dr Noah Burns and Dr. Tom Maimone for their enormous help during the past years working in the same lab bay. Many thanks to Klement Foo and Emily Cherney for tolerating me as their hoodmate and baymate and their emotional support, camaraderie, and caring. In a strange sense I am sorry to see the thesis finished since we have had such good time in our lab. With the warmth of their friendship and their words of encouragement, this journey has been much easier for me. I am also grateful to former Baran group member Dr. Ke Chen for her valuable support and friendship over years.

I am indebted to Dr. Carlos A. Guerrero, Dr. Ryan A. Shenvi, Dr. Georg Manolikakes, Chien-Hung Yeh, Dr. Chuang-chuang Li and Dr. Hiroki Shigehisa for the collaboration in the cortistatin project. Special thanks to Dr. Tom Maimone for the collaboration in vinigrol project. Many thanks to Paul Krawczuk, for our collaboration on maocrystal V project and I wish him the best for his future career. It has been a great privilege for me to have the opportunity to work with these talented chemists, whose excellent work has shaped the course of my Ph. D. study.

I want to thank former and current Baran Lab members, Dr. Dan O'Malley, Dr. Jeremy Richter, Dr. Michael DeMartino, Dr. Tobias Brückl, Dr. Darryl Dixon, Dr. Yuta Fujiwara, Dr. Daniel Götz, Dr. Abraham Mendoza, Dr. Damien Thevenet, Dr. Ippei Usui, Dr. Moritz Biskup, Dr. Shinji Ashida, Dr. Kyle Eastman, Dr. Tanja Gaich, Dr. Tanja Gulder, Dr. Mike Luzung, Dr. Takeshi Masuda, Dr. Elena Petricci, Dr. Niklas Schöne, Dr. Junichiro Yamaguchi, Rune Risgaard, Matt Del Bel, Joe Nagamizo, Paul Hernandez, for providing a stimulating and fun environment in which to learn and grow.
I would also like to extend my sincere thanks to my friends outside Baran lab, especially to Dr. Donghui Wang, Dr. Yaping Sun, Dr. Jian Xie, Dr. Fei Xu, Dr. Guo Min, David Sarlah, Tyson Mei and Keary Eagle.

Many thanks to Taylor Cohen for managing our lab and it is her work over years to keep the lab in order. I also thank the graduate office (Diane Kreger, Marylyn Rinaldi, Stacy Evans and Miriam Davis) for the administrative assistance in my graduate study.

I am very grateful to Dr. C. Moore and Professor A. Rheingold for X-ray crystallographic measurements, Dr. G. Siuzdak for mass spectrometric assistance and Dr. D.-H. Huang and Dr. L. Pasternack for NMR assistance. Bristol-Myers Squibb, Novartis and Roche are acknowledged for their fellowship over the years.

I wish to thank my family, especially my parents Feng Shi and Youqing Cai. They are the reason I am here today and this thesis would not have been possible without their unconditional love, support, and encouragement throughout these years.

Lastly, and most importantly, I would like to thank my fiancé Shun, without whose unabated love and endless support none of this work would be possible. How wonderful it is to have a life-partner who shares my dreams and tolerates my moods. If Scripps has given me nothing more, it has brought Shun and I together, and I am most thankful for that.
## Table of Contents

Dedication .................................................. 1

Acknowledgements ............................................. 2

Table of Contents ............................................ 5

Abbreviations .................................................. 7

Abstract ....................................................... 11

Chapter 1: Syntheses of cortistatin A and related analogs .................. 13

Section 1.1: Introduction ...................................... 14

Section 1.2: Synthetic Strategy ................................ 18

Section 1.3: Scalable syntheses of cortistatin A and related structures ........ 20

Section 1.4: Stereodivergent synthesis of 17-α and -β aryl steroids ............ 38

Section 1.5: Synthesis of cortistatin analogs ............................... 46

Section 1.6: Conclusion and distribution of credit ................................ 48

Section 1.7: References ........................................ 49

Section 1.8: Experimental section .................................. 56

Section 1.9: Appendix to Chapter 1: Spectra ................................ 106

Chapter 2: Total synthesis of vinigrol .................................. 233

Section 2.1: Introduction ...................................... 234

Section 2.2: Synthetic Strategy .................................. 240

Section 2.3: Synthesis of vinigrol skeleton ............................. 242

Section 2.4: Synthesis of 2, 3-didrovinigrol .............................. 246

Section 2.5: Synthesis of vinigrol .................................... 249

Section 2.6: Conclusion and distribution of credit .......................... 254
List of Abbreviations

Ac = acetyl
acac = acetylacetonate
AIBN = azobis(\textit{iso}-butyronitrile)
9-BBN = 9-borabicyclo[3.3.1]octane
b = broad
BRSM = based on recovered starting material
CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine
cat. = catalyst
COD = cyclooctadiene
Cy = Cyl = cyclohexyl
Crabtree’s catalyst = (tricyclohexylphosphine)(1,5-cyclooctadiene)(pyridine)iridium(I)
hexafluorophosphate
d = doublet
dba = dibenzylideneacetone
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL = diisobutyl aluminum hydride
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCB = \textit{o}-dichlorobenzene
DCE = 1,2-dichloroethane
DCM = dichloromethane (\text{CH}_2\text{Cl}_2)
DEAD = diethylazodicarboxylate
DMAP = (4-dimethylamino)pyridine
DMDO = dimethyl dioxirane
DMF = N,N'-dimethylformamide
DMP = Dess-Martin periodinane
DMSO = dimethylsulfoxide
ESI-TOF = electrospray ionization-time of flight
EDC = 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide
equiv. = equivalents
Herrmann’s catalyst = \(\text{trans-di(\mu\text{-acetato})bis[o-(\text{di-o-tolylphosphino})benzyl]}\) dipalladium(II)
hv = UV irradiation
HMPA = hexamethylphosphoric triamide
HRMS = high resolution mass spectrometry
IBX = \(o\)-iodoxybenzoic acid
IR = infrared
imid = imidazole
KHMDSD = potassium hexamethydisilazide
LCMS = liquid chromatography mass spectrometry
LDA = lithium diisopropylamide
LAH = lithium aluminum hydride
LRMS = low resolution mass spectrometry
L-selectride = lithium tri-(sec-butyl)borohydride
m = multiplet
\(m\)-CPBA = \(m\)-chloroperoxybenzoic acid
Mont = montmorillonite

mp = melting point

Ms = methansulfonyl

MTAD = 4-methyl-1,2,4-triazoline-3,5-dione

Mukaiyama’s reagent = N-tert-butylbenzenesulfinimidoyl chloride

MWI = microwave irradiation

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

NMM = N-methylmorpholine

NMR = nuclear magnetic resonance

[O] = oxidant

PhH = benzene (C₆H₆)

PhMe = toluene (C₇H₈)

PMA = phosphomolybdic acid

PP = pyrophosphate

PTLC = preparative thin layer chromatography

Pyr. = pyridine (C₅H₅N)

p-ABSA = para-acetamidobenzenesulfonyl azide

prenyl = 3,3-dimethylallyl

reverse prenyl = 1,1-dimethylallyl

q = quartet

s = singlet

SET = single electron transfer
t = triplet
TBAB = tetrabutylammonium bromide
TBAC = tetrabutylammonium chloride
TBAI = tetrabutylammonium iodide
TBAF = tetrabutylammonium fluoride
TEA = triethylamine (Et$_3$N)
TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Tf = trifluoromethanesulfonate
TFA = trifluoroacetic acid
TFAA = trifluoroacetic anhydride
$p$-TsOH = para-toluenesulfonic acid
THF = tetrahydrofuran (C$_4$H$_8$O)
TLC = thin layer chromatography
TBS = tert-butyldimethylsilyl
TMSOTf = trimethylsilyltrifluoromethane sulfonate
Ts = para-toluenesulfonyl
ABSTRACT

Full details are provided for an improved synthesis of cortistatin A and related structures as well as the underlying logic and evolution of strategy. The highly functionalized cortistatin A-ring embedded with a key heteroadamantane was synthesized by a simple and scalable 5-step sequence. A chemoselective, tandem geminal dihalogenation of an unactivated methyl group, a reductive fragmentation/trapping/elimination of a bromocyclopropane, and a facile chemoselective etherification reaction afforded the cortistatin A core, dubbed “cortistatinone”. A selective Δ^{16}-alkene reduction with Raney Ni provided cortistatin A. With this scalable and practical route, copious quantities of cortistatinone, Δ^{16}-cortistatin A—the equipotent direct precursor to cortistatin A, and its related analogs were prepared for further biological studies.

Vinigrol, an unusual diterpenoid, was isolated from the fungal strain *Virgaria nigra* F-5408 in 1987 by Ando and co-workers. The unique architecture and promising biological profile of vinigrol has attracted significant attention from the synthetic community. Herein, a simple and efficient synthetic route to the unusual decahydro-1,5-butanonaphthalene ring system found in vinigrol is described. In addition, synthetic routes are described to several advanced intermediates containing the entire carbon skeleton and full stereogenicity of this intriguing natural product.

Maoecrystal V, a novel diterpenoid possessing a unique 6,7-seco-6-nor-15(8→9)-abeo-5,8-epoxy-ent-kaurane, was isolated from the leaves of a Chinese medicinal herb, *Isodon eriocalyx*, in 1994 by Sun and coworkers. In an effort to complete the total synthesis of Maoecrystal V, a number of synthetic routes, including oxygenations of C8
on highly functionalized A-ring substrates and retro-aldol/aldol strategy, to construct the THF ring of Maoecrystal V were explored and further attempts, such as directly reduction, semi-pinacol rearrangement and 1,3-dipolar cycloaddition, to synthesize the key diol were pursued was well.
Chapter 1

Syntheses of cortistatin A and related analogs
1.1. Introduction

Steroids are beyond “privileged” structures, playing a vital role not only in biology, medicine and society, but also in the origins and development of organic synthesis.\(^1\) In 1815, the first steroid, cholesterol (1.1, Figure 1), was isolated from gallstones by Chevreul.\(^2\) But the correct chemical structure of cholesterol was not elucidated until 1932. Subsequently, during the 1930s to the 1950s, the discovery of steroids’ useful biological activities coupled with the need for cortisone (1.2) specifically in World War II immensely stimulated the development of chemical syntheses of steroids in both academic and industrial settings. In 1939, the first total synthesis of a steroid, equilene, was accomplished by Bachmann.\(^3\) Meanwhile, the Robinson\(^4\), Fieser,\(^5\) Woodward,\(^6\) Barton,\(^7\) and Jones\(^8\) groups investigated numerous synthetic methods aimed at the synthesis of steroids and a number of total syntheses of cortisone (2) were reported. The mechanistic, stereochemical model for steroid biosynthesis proposed by Stork and Eschenmoser,\(^9\) and related studies on polyene cyclization, ultimately led to Johnson’s biomimetic steroid syntheses, including his landmark total synthesis of progesterone (3) in 1971.\(^10\) Academic inquiry into the synthesis of steroids has thus resulted in an immense body of knowledge both in the realm of fundamental organic chemistry and medicine.

**Figure 1.1.** Representative steroids
In parallel to academic endeavors on the synthesis of steroids, the need for commercialization of certain steroid targets steered the pharmaceutical industry towards more efficient and practical approaches to semisynthesis. Starting from diosgenin, an abundant ingredient in wild Mexican yams, Marker achieved the commercialization of progesterone at Syntex by a 6-step sequence (known as “Marker’s degradation”) in 1940. In 1946, Sarett at Merck accomplished the first semisynthesis of cortisone (1.2) from bile acid in 36 steps. In 1951, a group of chemists at Syntex, led by Carl Djerassi, achieved the semisynthesis of cortisone (1.2) from diosgenin in a 14-step sequence. In the same year, a highly innovative microbiological fermentation approach was disclosed by Upjohn to functionalize the C11 position of progesterone (1.3), which led to the successful commercialization of cortisone (1.2). Currently, most steroid-based medicines (Figure 1.2) are prepared by semisynthesis, including Deltasone™ (1.5, anti-inflammatory agent), Flovent™ (1.6, antiasthmatic and antiallergic agent), Lanoxin™ (1.7, cardiovascular agent), Mifepristone™ (1.8, pregnancy termination agent), Testosterone™ (1.9, treatment of male hypogonadism), and Mestranol™ (1.10, oral contraceptive).
In 2006 and 2007, the Kobayashi group elucidated structures of novel steroidal alkaloids, cortistatins A–J (1.11–1.21, Figure 1.3), and disclosed their highly selective antiangiogenic activity. Angiogenesis, a process that involves the formation of new capillary blood vessels from pre-existing ones, is fundamental and vital to growth, development, wound healing, as well as cancer metastasis. Currently, Avastin®, Erbitux®, Vectibix® and Herceptin® are the major monoclonal antibody drugs for cancer treatment based on the inhibition of this mechanism. Therefore, the isolation and study of new small molecule natural products with highly selective antiangiogenic activity is of great interest and significance. Interestingly, cortistatin A (1.11) showed antiproliferative activity against human umbilical vein endothelial cell (HUVECs) at a low concentration with an IC₅₀ = 1.8 nM, while it demonstrated a selectivity index of more than 3000 fold against HUVECs in comparison with NHDF (normal human dermal fibroblast), KB3-1
Figure 1.3. Cortistatin family members and their biological activities.

<table>
<thead>
<tr>
<th>Cortistatin</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>J</th>
<th>K</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>I&lt;sub&gt;50&lt;/sub&gt;</td>
<td>0.0018</td>
<td>1.1</td>
<td>0.019</td>
<td>0.15</td>
<td>0.45</td>
<td>1.9</td>
<td>0.80</td>
<td>0.35</td>
<td>0.008</td>
<td>0.04</td>
<td>0.023</td>
</tr>
</tbody>
</table>

<sup>IC<sub>50</sub> = μM</sup>

Structurally, all of the cortistatins possess an unusual 9(10,19)-abeo-androstane skeleton with an oxabicyclo[3.2.1]octene core. The combination of their exciting
bioactivity and scarce availability from Nature makes the cortistatins worthy candidates for synthesis. Indeed, these marine sponge (*corticium simplex*) derived molecules are so rare and valuable that the isolation chemists have reported efforts towards their total synthesis.¹⁹ Not surprisingly, the last three years have witnessed dozens of publications on the chemistry of the cortistatins.¹⁹–²⁴ Four elegant total syntheses of cortistatin A have emerged from the Nicolaou–Chen, Shair, Myers and Hirama laboratories and many approaches have been reported.²³ Our own efforts were inspired by the rich history of steroid semisynthesis and a desire to procure gram quantities of the cortistatins for biological evaluations.²⁴ Thus, a route was devised beginning from the abundant terrestrially-derived steroid prednisone (1.4) (available for $1.2/gram).

1.2 Synthetic Strategy

Given the tremendous success of steroid semisynthesis to prepare large quantities of biologically valuable compounds, we decided to explore this higher-level substructure search strategy to identify candidate steroid starting materials. In concert with this global search, an initial retrosynthetic excision of the isoquinoline allowed a bidirectional search for methods of heterocycle installation to the D-ring, as well as steroid scaffolds that lacked the C17 sidechain. Further considerations for the starting material derived from ‘ideality’ criteria,²⁵ particularly for an overall isohypsic (redox-neutral) conversion from commercial steroid to target.²⁶ Since there are few affordable steroids that bear the appropriate methine oxidation state at C19, a strategic sacrifice was made to introduce this oxidized carbon from the very common C19 methyl. A look-ahead search for appropriate A-ring precursors proved more straightforward, since the cortistatin A-ring is
in the same oxidation state as a cyclohexadienone, which is a common motif in commercial steroids. Similarly, the C-ring allylic ether motif corresponded in oxidation state to a C-ring cyclohexanone, a substructure that has been made available in commercial steroids by microbial oxidation. When these structures are amalgamated into an imaginary steroid, the result bears striking resemblance to prednisone, with the exception of the pregnane side-chain. Fortunately, there are several methods for oxidative cleavage of this sidechain to the corresponding cyclopentanone, which serves as a useful handle for appending the isoquinoline.

Further considerations that bolstered the proposal to begin from an abundant terrestrial steroid include: 1) the unique strategic opportunities that could arise from rendering a semisynthesis amenable to the construction of analogs with deep seated modification; 2) the occasion to develop new chemical methods and tactics to achieve such ends; and 3) the economies of using prednisone, which possesses ca. 70 % of the carbon atoms and the corresponding enantiopure chirality of the cortistatins. As discussed above, a crucial target structure became the cortistatin A ketonic core that we termed (+)-cortistatinone (1.22, Scheme 1.1). This key structure was anticipated to allow for straightforward elaboration to the natural product, as well as divergence to other family members and unnatural analogs. As part of this plan, numerous exciting challenges had to be addressed, including control of all four A-ring stereocenters, oxidation of the unfunctionalized C19 and C8 centers, expansion of the B-ring, and chemo/stereoselective installation of the isoquinolinone sidechain.


**Scheme 1.1.** A general retrosynthetic strategy to target the cortistatin A (1.11) core: cortistatinone (1.22).

1.3 Scalable syntheses of cortistatin A and related structures

**A-ring functionalization.** Our initial efforts for A-ring functionalization are depicted in Scheme 2. Starting from prednisone (1.4), side chain cleavage and subsequent ketalization led to the known steroid core 1.25 in 92% overall yield after recrystallization. Nucleophilic epoxidation of enone 1.25 generated epoxide 1.26 in 82% yield (>30g) under the mediation of t-BuOOH, a protocol that is operationally superior on a large scale to a reported DMDO procedure. For our first forays, a straightforward hydride reduction/activation/displacement sequence was pursued to install the C3 amino group. In the event, ketone reduction provided α-hydroxyl derivative 1.27 as a major diastereomer, which upon activation with p-TsCl led to allylic chloride 1.29 in 75% yield over 2 steps. Treatment of 1.29 with NaN₃ delivered the corresponding allylic azide 1.30 which was subjected to a Staudinger reduction with PPh₃, followed by formylation of the resulting amine, to afford epoxy alkenyl formamide 1.31 in 39% overall yield.
Scheme 1.2. Initial efforts to install the C3 amino group on the A-ring

Capitalizing on the observation that hydride attacks the β-face of ketone 1.26, a more concise route to epoxy alkenyl formamide 1.31 was formulated (Scheme 1.3). Thus, reductive amination of the C3 ketone moiety of 1.26 with NH₄OAc and NaBH₃CN furnished the corresponding allylic amine, which was directly formylated, to give formamide 1.31 in 73% overall yield. After extensive optimization, formamide 1.31 was obtained in 95% overall yield by using Ti(Oi-Pr)₄, NH₃ and NaBH₄ for reductive amination followed by formylation.

Scheme 1.3. Simplified route to epoxy alkenyl formamide 1.31

With a scalable (>25 g) route to the epoxy alkenyl formamide 1.31 secured, attention was turned to the C1, C2 trans-vicinal diol formation via epoxide opening. Acid
(TFA) mediated opening of the 1,2-epoxide was initially attempted, resulting in cyclization to the proximal C11 ketone and then dehydration to form dihydrofuran 1.32 in 93% yield. Solvolysis of 1.32 to the desired *trans*-diol 1.33 met with failure. Ultimately, it was found that the epoxide opening could be accomplished with complete positional selectivity using *n*-Bu₄NOAc as a soluble and highly nucleophilic source of acetate anion in the presence of catalytic amount of Co(acac)₂ as a Lewis acid additive.

Scheme 1.4. First approach to open epoxide 1.31

While the above mentioned epoxide-opening reaction provided a decent quantity (hundreds of milligrams) of material for our early stage studies, the moderate yield for this transformation deterred us from the preparation of alcohol 1.34 on a gram scale. A number of conditions were subsequently investigated and alternative epoxide-opening conditions were established (Scheme 1.5). By treatment of epoxide 1.31 with triethylamine in acetic acid, both C2 acetate 1.34 and C1 acetate 1.35 were obtained in a 2:1 ratio (1.34: 64%, 1.35: 32%). The undesired C1 regioisomer 1.35 can be recycled.
using DMAP in reflux toluene to deliver the same equilibrium mixture (1.34: 64%, 1.35: 31%, 34 : 35 = 2 : 1).

**Scheme 1.5.** Second approach to open epoxide 1.31

In parallel to the epoxide-opening studies, installation of the requisite C5 hydroxyl was investigated on several different intermediates (Scheme 1.6). For instance, displacement of allylic chloride 1.29 with PhSH under basic media followed by \textit{m}-CPBA oxidation delivered sulfoxide 1.36 in 90% overall yield. It was expected that sulfoxide 1.36 would undergo a Mislow–Evans rearrangement\textsuperscript{29} to furnish allylic alcohol 1.37. However, 1.37 was not observed under a variety of conditions, presumably due to the pseudo-equatorial orientation of the sulfoxide group which lacks the necessary proximity to C5 for the rearrangement to occur. An alternative approach for the installation of the C5 hydroxyl group was carried out by treating allylic alcohol 1.27 with \textit{m}-CPBA followed by Dess–Martin periodinane oxidation to generate bisepoxy ketone 1.38 (90% yield over 2 steps). However, the C4–C5 epoxide could not be opened to the desired C5 alcohol 1.39 under a variety of reductive conditions. Finally, Co-catalyzed Mukaiyama hydration\textsuperscript{30} of the C4–C5 olefin in 1.31 delivered the undesired β-oriented tertiary alcohol 1.40 in 75% yield. An X-ray crystallographic analysis of 1.40 confirmed its stereochemical assignment.
Scheme 1.6. Attempts at installing the requisite α-disposed C5-tertiary alcohol

The origin of this selectivity likely arises from the preference of the A-ring to adopt a half-chair conformation (1.41) with the C2 formamide group in an equatorial rather than an axial position (1.42) (Figure 1.4A). It was reasoned that a complete reversal of selectivity would arise if a tether was present between the C1 and C3 atoms as shown in Figure 1.4B. To test this hypothesis, the requisite substrate 1.48 was synthesized in 54% overall yield by the following sequence (Scheme 1.7A): 1) dehydration of formamide 1.34 to isonitrile 1.45 by using the Burgess reagent; and 2) Cu-catalyzed cyclization of the C1 hydroxyl onto the isonitrile. When subjecting imidate 1.48 to Mn(acac)₂, PhSiH₃ and O₂, the desired C5-oxygenated α-isomer 1.49 was produced in 78% yield. Subsequently, it was found that simply reacting 1.34 with
Co(acac)$_2$, PhSiH$_3$ and O$_2$ produced the desired C5-OH α-isomer 1.52, which can be rationalized as arising from the greater stability of the desired radical configuration 1.51 over 1.50 (Scheme 1.7B).

**Figure 1.4.** Rationale for the stereoselectivity of the C5 hydration

![Diagram showing the stereoselectivity of the C5 hydration](image)

**Scheme 1.7.** Successful installation of the requisite α-disposed C5-tertiary alcohol

A. First success to install C5 tertiary alcohol

![Diagram showing the first success to install C5 tertiary alcohol](image)

B. Improved installation of C5 tertiary alcohol

![Diagram showing the improved installation of C5 tertiary alcohol](image)

After extensive experimentation, C5-oxygenated orthoamide 1.24 was synthesized in one pot from intermediate 1.34 in 65 % yield via: 1) Mukaiyama hydration of the trisubstituted C4–C5 olefin; 2) condensation of the formamido-diol with trimethyl orthoformate; and 3) solvolysis of the C2 acetate (Scheme 1.8). Thus, the final optimized route to the fully functionalized cortistatin A-ring is described in Scheme 1.8. This simple
5-step sequence provides scalable entry to the highly functionalized A-ring steroid intermediate 1.24. The salient strategic aspect of this work involves the construction of the key “heteroadamantane” system expressed in ring A which served three pivotal roles: 1) it pre-organized the system for the ensuing B-ring expansion (vide infra); 2) it protected three of the four A-ring heteroatoms; and 3) its subsequent removal would, in principle, not necessitate additional concession steps25 since the orthoester and formamide carbons are oxidized forms of the C3 dimethylamino group found in the cortistatins.

Scheme 1.8. A simple 5-step stereoselective process for converting the known steroid core 1.25 into the fully A-ring functionalized intermediate 1.24

B-ring Expansion. The hallmark seven-membered B-ring of the cortistatins (9(10,19)-abeo-androstan which contains the 6-7-6-5 ring system) presented the exciting challenge of developing a practical and scalable method for B-ring expansion of a “normal” steroid (containing the 6-6-6-5 ring system). The presumed biosynthesis of the cortistatins, initially proposed by the Kobayashi group,15c was particularly path pointing to us (Scheme 1.9A). Inspired by the known biosynthesis of the Buxus alkaloids where both the 9β,19-cyclo system (1.54) and the abeo-9(10,19)-diene (1.55) are naturally occurring, 1.54 was proposed to be the biogenetic precursor of 1.55. Based on this
information, the Kobayashi group proposed that the cortistatin family might be generated from 3,29-diaminosterol (1.53), a hypothetical metabolite that bears resemblance to related natural products (Scheme 1.9A). Starting with this key precursor, cyclopropane formation via C19-methyl activation followed by subsequent ring expansion should produce 1.55. Dehydrogenation to triene 1.56 and oxidation would afford the unique THF (5,8-oxide) ring system in 1.57 and in all other members of the cortistatin family. This biosynthetic pathway has parallels in a number of early synthetic studies. For instance, in Martin and coworkers’ semisynthesis of the Buxus alkaloid cycloprotobuxine A (1.64) from lanosterol (1.60; Scheme 1.9B), the C19 methyl group in 1.61 was transformed into the alkyl iodide 1.62 via Barton nitrite photolysis and trapping with I2. Subsequent ketone formation and cyclopropanation delivered cyclopropane 1.63 in 60% yield over 4 steps. In other reports, B-ring expansions of steroids have also been documented (Scheme 1.9C), such as in the case of 1.65 which was smoothly transformed to abeo-9(10,19)-diene 1.66 in 82% yield under TFA mediation. Radical conditions (AIBN, Bu3SnH) have also been used in these types of fragmentations, as illustrated with the conversion of 1.67 to 1.69 via the cyclopropyl radical 1.68. It was within this context that a synthetic plan for cortistatin B-ring formation was devised, involving a remote C19 methyl group functionalization/cyclopropanation/ring expansion sequence.
Scheme 1.9. Key considerations and historical context for the B-ring expansion.

For the first stage of the planned B-ring expansion, a mild method was needed for C19 methyl functionalization. Conveniently, the rigidity imparted by the “heteroadamantane” A-ring forced the C2 hydroxyl and the C19 methyl groups into a pseudo-1,3-diaxial conformation and thus in very close proximity to one another (distance between C2-oxygen to C19 is 2.894 Å based on the X-ray crystal structure of 1.24). Several potential methods were therefore at our disposal for an alcohol-directed C–H functionalization. The Barton nitrite ester reaction was attempted first, but unfortunately, this chemistry failed to produce the desired result from 1.24. Subsequently, conditions for the controlled halogenation of C19 were explored. It was found that...
modification of Suárez’s conditions\textsuperscript{37} for remote methyl oxidation using PhI(OAc)\textsubscript{2} and Br\textsubscript{2} effected monobromination of C19 (Scheme 1.10A). The reaction proceeds by \textit{in situ} formation of AcOBr that most likely leads to formation of an O–Br bond at the C2 hydroxyl, subsequent O–Br bond homolysis, hydrogen atom abstraction, and recombination with bromine radical or Br\textsubscript{2} at C19. The intermediate hydroxy bromide was not isolated due to its rapid closure to a tetrahydrofuran; instead, immediate protection of the C2 alcohol as a trimethyl silyl ether and base-induced cyclopropanation afforded cyclopropane 1.72 in 64\% yield over 2 steps. It should be noted that the use of the well-precedented PhI(OAc)\textsubscript{2}/I\textsubscript{2} conditions for monoiiodination resulted in competitive THF formation, likely due to a much larger coefficient of the $\sigma^{*}_{C-I}$ orbital.\textsuperscript{38} For the subsequent B-ring expansion, selected attempts to open cyclopropane 1.72 are shown in Scheme 1.10B. AlH\textsubscript{3}-mediated reduction of the orthoamide moiety provided 1.73 in 74\% yield. Unfortunately, acid catalyzed fragmentation of cyclopropyl alcohol 1.73 to diene 1.74 was unsuccessful. After extensive experimentation, cyclopropyl ketone 1.72 could be efficiently fragmented to give cycloheptyl ketone 1.75 upon exposure to SmI\textsubscript{2} followed by acidic workup in 84\% yield. Alternatively, quenching the reaction with PhSeBr and subsequent oxidative elimination furnished conjugated enone 1.77 in 56\% over 2 steps. Clearly, the obtention of cycloheptyl ketones 1.75 and 1.77 marked a milestone in our studies since they were the first intermediates to bear a seven-membered B-ring. Cycloheptyl ketones 1.75 and 1.77 merely required a loss of four or two hydrogens, respectively, in order to arrive at the desired cycloheptyl dienone 1.76. The realization of this crucial dehydrogenation, however, proved challenging: no reaction
conditions were identified on these ketones to perform this transformation chemoselectively.

**Scheme 1.10.** Synthesis of cyclopropane 1.72 and its B-ring expansion

A. Synthesis of a cyclopropanated B-ring

B. Ring expansion studies

Since dehydrogenation at C10 and C19 following the B-ring expansion proved difficult, establishing the desired oxidation state on C19 prior to B-ring expansion was evaluated. Fortuitously, during our studies on the Suárez-type monobromination\(^\text{37}\) (Scheme 1.10A), small quantities of bis-brominated material were always isolated. It was reasoned that this geminal dibromide (see 1.79, Scheme 1.11) possessed the exact oxidation state required of the C19 carbon atom for its eventual expression in 1.76. After substantial optimization, 1.79 was obtained in 53 % yield via an iterative, double C–H activation process, while suppressing S\(_N\)2 attack of the alcohol on the \(\sigma^*\)C–Br orbital of monobromide 1.81. To the best of our knowledge, this is a rare example of an alcohol-
directed, geminal dihalogenation of an unactivated hydrocarbon. The unstable dibromo alcohol 1.83 was capped with a trimethylsilyl group to prevent an unwanted intramolecular cyclization. α-Alkylation of the C11 ketone with the proximal dibromomethyl group proceeded with DBU and LiCl to generate the exotic bromocyclopropane 1.80 as a single diastereomer in 48% yield over 2 steps, whose configuration was confirmed by X-ray crystallographic analysis.

Scheme 1.11. Synthesis of bromocyclopropane 1.80

Now that the desired oxidation state at C19 was obtained, bromocyclopropane 1.80 was subjected to the SmI$_2$ reductive fragmentation conditions. Pleasingly, 1.80 underwent B-ring expansion as anticipated and unconjugated enone 1.88 was isolated, bearing no bromine atom but rather a C10–C19 alkene (Scheme 1.12A). This product is presumably formed via radical-induced ring expansion from 1.85 to 1.86, extrusion of bromine radical, and quenching of dienolate 1.87 with H$_2$O. Reduction of the C11 ketone in 1.88, elimination of resulting hydroxyl group, and heteroadamantane reduction with AlH$_3$ afforded diene 1.89 in 23% yield over 3 steps. Thus, the oxidation state
deliberately embedded into C19-methyl dibromide 1.79 was translated smoothly into the olefinic C19-methine of the cortistatin core. In addition, 1.89 possessed all of the correct A-ring functionalities with their correct stereochemistry and the hallmark C10–C19/C9–C11 diene expressed in the natural product. However, thereafter, all attempts to oxidize the C8 position in order to form the THF ring unfortunately met with failure. In essence, what we hoped to achieve was an isohypsic reaction26 (in this case an isomerization) to convert bromocyclopropane 1.80 into the redox-isomeric dienone 1.76 in a single operation. Thus, a set of trapping experiments on the reactive samarium dienolate 1.87 was investigated as shown (Scheme 1.12B). Trapping dienolate 1.87 with O₂ afforded γ-hydroxy enone 1.91 in 72% yield, whose structure was identified by X-ray crystallographic analysis. Dehydration of 1.91 turned out to be difficult and the desired product was not observed. Eventually, it was found that trapping dienolate 1.87 with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCHD) delivered the α-disposed allylic C9-bromide 1.92 with high diastereoselectivity, which could be converted to the cross conjugated-dienone 1.76 on a gram-scale under mildly basic conditions (LiBr, Li₂CO₃). This two-step process took place in 65% overall yield and the structure of the coveted dienone 1.76 was verified by X-ray crystallographic analysis.
Scheme 1.12. Ring opening of the bromocyclopropane

**THF ring closure.** Dienone 1.76 represented a “point of no return” in our path to the cortistatins with carbons 8, 9, 10 and 19 having the correct oxidation state. All that remained in order to complete the core synthesis was a THF ring formation and a chemoselective dismantling of the heteroadamantane-cloaked A-ring. It was reasoned that the THF ring could be constructed by attack of the C5 tertiary alcohol onto the C8 position by an $S_N 1'$ or $S_N 2'$ mechanism. Treatment of dienone 1.76 with AlH$_3$ led to a notably clean and precise delivery of five hydrides to give an intermediate dimethylamino triol. Addition of MeOH to the reaction mixture served to quench any remaining hydride
and the addition of K$_2$CO$_3$ removed the TMS group on the C2 alcohol to afford tetraol 1.23 in 89% yield. Acetylation of tetraol 1.23 furnished triacetate 1.93 in 93% yield, which allowed us to test the hypothesis that the bicyclic ether in cortistatin A might be formed through selective ionization. After screening a number of conditions, it was found that MgBr$_2$·Et$_2$O and 2,6-di-tert-butylpyridine was an effective combination of reagents to perform the desired cyclization. Subsequent deketalization and saponification delivered cortistatinone (1.22) in 82% overall yield. Comparison of the $^1$H NMR data with that of cortistatin A (1.11) was encouraging, as all of the non-aliphatic carbons bore strong resemblance to the natural product spectra.

The three-step sequence from tetraol 1.23 to cortistatinone (1.22), while easy to perform, was not efficient in terms of step count and reaction time. Therefore a direct route from tetraol 1.23 to cortistatinone (1.22) was investigated. A variety of acids were screened to effect this transformation (Scheme 1.13B), upon which it was found that both Lewis and Brønsted acids (for example, HCl, entry 5) were able to produce the desired compound – cortistatinone (1.22). BiCl$_3$ was identified as the superior reagent to perform the cyclization and deketalization simultaneously in 73% yield. This improvement reduced the operations of the original route by three and enabled the preparation of multigram quantities of cortistatinone (1.22).
Scheme 1.13. THF ring closure

A. Stepwise THF ring closure

B. Direct THF ring closure

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)3</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>InCl3</td>
<td>56%</td>
</tr>
<tr>
<td>3</td>
<td>MgBr2•Et2O</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>BCl3</td>
<td>73%</td>
</tr>
<tr>
<td>5</td>
<td>HCl</td>
<td>40%</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)2</td>
<td>0%</td>
</tr>
</tbody>
</table>

The final optimized route from orthoamide 1.24 to cortistatinone (1.22) is shown in Scheme 1.14. It features a number of gram-scale transformations: 1) a newly invented alcohol directed dibromination; 2) an isohypsic cascade to access the 9(10,19)-abeo-androstane skeleton; 3) an olefin-sparing, heteroadamantane fragmentation to differentiate the tethered aminodiol; and 4) a mild S_N’ cyclization to close the THF ring. With this robust pathway developed, over two grams of cortistatinone (1.22) have been prepared to date.
Scheme 1.14. Final optimized route to cortistatinone (1.22)

Isoquinoline Installation. In parallel to our efforts to synthesize cortistatinone (1.22), methods were evaluated for the introduction of the C17 isoquinoline moiety at earlier stages in our synthesis (Scheme 1.15). The fundamental strategic problem with such an approach is that it prevents the desired late-stage diversification and the isoquinoline moiety itself poses incompatibilities with key reactions. For example, intermediate 1.24 could be transformed to isoquinoline-containing steroid 1.96 in 10% overall yield by a sequence employing ketal cleavage, Barton vinyl iodide formation (leading to 1.95), Stille coupling with stannane 1.105, and stereoselective hydrogenation with Pd/C. Unfortunately, the isoquinoline moiety was incompatible with Suárez conditions. In a similar vein, bromocyclopropane-isoquinoline conjugate 1.99 could be prepared in 16% overall yield, but again the isoquinoline heterocycle was not compatible with hydrogenation conditions. Therefore, the original plan for late-stage isoquinoline installation remained the most logical, and indeed the only viable option.

With two free alcohols, one tertiary amine, and a sensitive diene adjacent to a THF ring, cortistatinone (1.22) requires “gentle” chemistry for derivatization. Barton’s vinyl iodide preparation (vide supra) fulfills this requirement as does the Stille coupling. In the event, this reaction sequence works well to deliver Δ16-cortistatin A (1.101) in 53% isolated yield (on scales ranging from one to 300 mg). The final conversion of 1.101 to cortistatin A (1.11) required numerous screens in order to identify...
a suitably chemoselective reducing agent that could differentiate a styrene-like olefin from an isoquinoline and a diene and do so in the presence of numerous unprotected functionalities. Whereas Sm- and Pd-based agents led to over reduction (observed by LC-MS, uncharacterized), and Rh-mediated transfer hydrogenation or diimide methods did not work in our hands, Raney Ni led to an excellent conversion to 1.11, thus completing the synthesis. This reaction was never run beyond a 10 mg scale since it was soon found that 1.10 is nearly equipotent to 1.11 in all biological assays tested. In the next section, we will demonstrate the generality of this reaction and explored its mechanism.\textsuperscript{18d}

In passing, we note that although isoquinoline 1.104 is commercially available, it is prohibitively expensive (\textit{ca.} \$ 80 / 10 milligrams in 2007 when we started our studies). Furthermore, the existing method to synthesize 7-bromoisoquinoline by the Pomeranz–Fritsch reaction,\textsuperscript{44} gives 5-bromoisoquinoine as a byproduct that is difficult to separate. Therefore, a scalable and practical synthesis of 7-bromoisoquinoline was developed as shown in Scheme 1.16. Starting from tetrahydroisoquinoline 1.102, imine formation with NBS/NaOH,\textsuperscript{45} nitration at the C7 position\textsuperscript{46} and dehydrogenation with MnO\textsubscript{2} furnished 7-nitroisoquinoline 1.103 in 61\% yield over 3 steps. Subsequent reduction of the nitro group and Sandmeyer reaction afforded the desired 7-bromoisoquinoline 1.104 in 63\% yield over 2 steps. Lastly, stannylation of 7-bromoisoquinoline 1.104 delivered 7-trimethylstannylisoquinoline 1.105 in 88\% yield.
1.4. Stereodivergent synthesis of 17-α and -β aryl steroids

While the Kobayashi group has already delineated a preliminary SAR picture of the family (see Figure 1.5), their scarce natural supply renders chemical synthesis as the only means to decipher their medicinal potential. Particularly intriguing is the impact of the isoquinoline moiety on biological activity since its absence significantly lowers activity. This section illustrates the dramatic influence of D-ring stereochemistry on biological activity with the synthesis of 17-epi-cortistatin A (1.106). Specifically, we have found that the C17 stereochemistry may be removed all together as Δ16-cortistatin A (1.101) retains much of the potency of cortistain A (1.11). This line of chemical inquiry
has also led to the first useful method for the stereocontrolled preparation of other α-aryl-substituted D-ring steroids. In order to evaluate the importance of a β-oriented isoquinoline moiety, an estrone-derived model (1.107, Scheme 1.17) was employed as a testbed for a strategy that would deliver both epimers from a common intermediate.

**Figure 1.5.** Cortistatin A (1.11), its known SAR, and relationship to its 17-epi relative (1.106).

By analogy to the synthesis of 1.101, estrone model 1.107 was converted to the D-ring styrene 1.108a as depicted in Scheme 1.17. Regardless of the reducing conditions, the only observed product was the expected β-aryl substituted product 1.109a. Ra-Ni mediated reduction led to a 97% isolated yield of 1.109a. This is not surprising given the fact that an overwhelming majority of nucleophilic, electrophilic, and radical substitution reactions at C17 occur from the α-face. Attention was therefore turned to an alternative
approach that began with tertiary alcohol $1.110a$, derived from addition of PhLi to $1.107$. Based on preliminary evidence gathered in-house, $24b$, $24c$ and a report that Ra-Ni reductions of benzylic alcohols occurred with retention of configuration, $48$ alcohol $1.110a$ was subjected to Ra-Ni in toluene at reflux. To our delight, a diastereomeric pair of compounds was isolated in a 6.6:1 ratio, the major isomer of which bore the desired a-stereochemistry. The structures of $1.108a$-$1.111a$ were all verified by X-ray crystallography.

**Scheme 1.17.** Divergent access to α- and β- configured C17 aryl estrone derivatives.

The generality of this reagent system, a synthesis of 17-epi-cortistatin A, mechanistic analysis of these reductive processes, and biological evaluation of cortistatin analogs are presented below.
Table 1.1. Deoxygenation and hydrogenation mediated by Ra-Ni.

<table>
<thead>
<tr>
<th>Isolated Yield (%) and Diastereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>

As shown in Table 1.1, both pathways (1.108 to 1.109 and 1.110 to 1.111) are amenable to the incorporation of electron rich, neutral, and withdrawing arenes, as demonstrated by the successful deoxygenations and hydrogenations of C17 phenyl, p-tolyl, p-anisyl, and 3-pyridyl steroids. Hydrogenation of Δ^{16}-17-arylsteroids 1.108 was carried out in 10% toluene in isopropanol with Ra-Ni at 60°C for 2 h, providing 1.109 with yields varying between 68% and 98%. The diastereoselectivity of this transformation is generally over 20 : 1 (17-β : 17-α). Alternatively, deoxygenation of 17-β-hydroxy-17-α-arylsteroids 1.110 was carried out in toluene with Ra-Ni at 110°C for 5 h. Yields varied between 68% and 98% with moderate to good diastereoselectivities.

Deuterium labelling experiments were carried out as shown in Scheme 1.18. For Ra-Ni mediated transfer hydrogenation, the reaction of 1.108a was conducted in
deuterated isopropanol and toluene (toluene or toluene-$d_8$ gave identical results) with D$_2$O-washed Ra-Ni, affording 1.109a-d$_2$ with deuterium incorporation at C16 and C17. For Ra-Ni mediated deoxygenation, the reaction of 1.110a employed deuterated toluene with D$_2$O-washed Ra-Ni. Surprisingly, 1.111a-d$_4$ was obtained as the major product in 96% yield. However, 1.109a and 1.111a exhibited identical aromatic deuterium substitution when subjected to the same reduction conditions as 1.110a, demonstrating that this aromatic deuteration is independent of the deoxygenation process.

Scheme 1.18. Deuterium labelling of hydrogenation and deoxygenation.

The dichotomy in observed stereochemical outcome between 1.109 and 1.111 seemingly excludes the intermediacy of free-radicals in deoxygenation (1.110→1.111; radical deoxygenation produces β-stereochemistry at C17, vide supra). The differential stereoselectivity between 1.108 and 1.110 can be rationalized based on the facial selectivity of chemo-adsorption to the metal surface as depicted in Figure 1.6. Previous studies have demonstrated that a high degree of stereoselectivity can be incurred in Ra-Ni mediated reductions based on stereoselective adsorption. In the case of 1.108, adsorption likely occurs most favorably on the relatively flat a-face, away from the angular methyl group (C18). Hydrogens and/or electrons are then transferred from the
metal surface to the preferentially adsorbed face.\textsuperscript{49} In the case of 1.110, adsorption possibly takes place on the convex face, with interaction occurring between the surface and both the aromatic $\pi$-system and the benzylic hydroxyl, followed by metal oxidative addition to the C17–OH bond and subsequent hydrogen delivery from the metal.

**Figure 1.6.** Possible explanation for observed stereochemical dichotomy.

Finally, the mechanistic requirement of an aryl group at C17 during deoxygenation is supported by the fact that 17-$\beta$-hydroxy-17-$\alpha$-(n-butyl)-estrone (1.112) was inert to deoxygenation using Ra-Ni. In addition to submitting 1.112 to the reaction condition, a control experiment was carried out with an equimolar mixture of 1.112 and 1.110a premixed in the same reaction vessel and treated with Ra-Ni. While 1.110a was completely deoxygenated, 1.112 was quantitatively recovered.
Scheme 1.19. Control experiment of deoxygenation

The utility of the present invention is aptly demonstrated by the synthesis of 17-epi-cortistatin (1.106), as shown in Scheme 1.20. Thus, protection of the diol motif in cortistatinone (1.22) with TMS-imidazole, followed by treatment with an excess of 7-lithioisoquinoline in a THF/TMEDA solvent mixture at –78 °C generated an alkanolisoquinoline that was deoxygenated with Ra-Ni to deliver 17-epi-cortistatin A (1.106) in 16% yield over three steps.

This substance proved crucial in testing the substrate scope/specificity of cortistatin A’s biological target. The importance of this substrate cannot be understated since the greatest modulation of biological activity in the naturally occurring cortistatins stems from structure variations of the C17 substituent.15

Scheme 1.120. Synthesis of 17-epi-cortistatin A (1.106)
In an assay to determine activity against HUVECs (carried out by Pfizer Inc.), synthetic cortistatin A exhibited an IC$_{50}$ value of 2.43 nM, which is in good agreement with the reported value.$^{15a}$ Remarkably, 1.11 still retains high potency against HUVECs, with an IC$_{50}$ of 3.88 nM. This result is a significant step forward in the simplification of the overall cortistatin structure from a synthesis standpoint. However, 1.106 does not exhibit useful levels of activity (>1 mM). This profound difference of biological activity clearly indicates that the C17 stereochemistry is essential for biological behavior.

**Table 1.2.** Selective growth inhibition of cortistatins against HUVECs.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cortistatin A (1.11)</td>
<td>2.43$^a$, 1.8$^b$</td>
</tr>
<tr>
<td>Δ$^{16}$-cortistatin A (1.101)</td>
<td>3.88</td>
</tr>
<tr>
<td>17-epi-cortistatin A (1.106)</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>1.108d-g, 1.109a-f, 1.110e, 1.111a, 1.111d-e$^c$</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

[a] IC$_{50}$ of synthetic cortistatin A tested by Pfizer Inc.
[b] IC$_{50}$ of natural cortistatin A tested by Kobayashi group.$^{15a}$
[c] The TBS groups were removed prior to testing. The results of 1.108e and 1.109e are from ref. 18c.

Modeling studies (shown in Figure 1.7) suggested that 1.11, 1.101, and 1.106 exhibit rigid architectures that differ only in the angle in which the isoquinoline moiety would be presented to the active site. Not surprisingly, several estrone model compounds were also found to be inactive in the HUVEC screening.
**Figure 1.7.** Superimposed structures of the lowest energy conformation of 1.11 (blue), 1.101 (red), and 1.106 (green) by Schrödinger software dihedral drive macromodel.

1.5. Synthesis of cortistatin analogs

Due to the fascinating biological activity of cortistatins, more cortistatin analogs (114 a-b, 115 a-d) have been synthesized with our scalable route to explore its unique mechanism of action and to discover additional valuable bioactivities. Thus, biotin derivative 117 was attached to the C1 or C2 hydroxyl group of 116 to generate 114 a and 114b (Scheme 1.121A), in order to identify the protein that Δ^{16}-cortistatin A interacts with. In addition, to examine the effect of the sidechain aromatic ring with various nitrogen positioning, a collection of D-ring analogs (115 a-d, Scheme 1.121B) were synthesized via Suzuki coupling reactions. In collaboration with Professor Susana Valente at the Scripps Research Institute (Florida) and Leo® Phama, the biological evaluation of these cortistatin analogs are currently in progress. It is believed that these analogs may provide us a deeper understanding of the mechanism of action of cortistatins and help to disclose chemical structures with additional interesting biological activities.
**Scheme 1.121** Synthesis of cortistatin analogs

**A. Synthesis of biotylnlated cortistatins**

![Diagram of synthesis of cortistatin analogs](image)

**B. Synthesis of D-ring cortistatins analogs**

![Diagram of synthesis of D-ring cortistatins analogs](image)

<table>
<thead>
<tr>
<th>Isolation Yields (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R’</strong></td>
<td></td>
</tr>
<tr>
<td>![Diagram of R']</td>
<td></td>
</tr>
<tr>
<td><strong>1.115a:</strong> 19%</td>
<td></td>
</tr>
<tr>
<td><strong>1.115b:</strong> 22%</td>
<td></td>
</tr>
<tr>
<td><strong>1.115c:</strong> 22%</td>
<td></td>
</tr>
</tbody>
</table>
1.6. Conclusion and distribution of credit

A scalable synthesis of cortistatin A and related structures was described and several transformations were developed that either were not feasible or not possible prior to this work: the easily scalable side chain cleavage protocol; the chemoselective, tandem geminal dihalogenation of an unactivated methyl group; the reductive fragmentation/trapping/elimination of a bromocyclopropane to simultaneously establish both the $\Delta^{10(19)}$- and $\Delta^{8(9)}$-olefins and the 7-membered B-ring; the facile chemoselective etherification reaction for installation of the oxido bridge; and the remarkably selective $\Delta^{16}$-alkene reduction with Raney Ni. In addition, two processes were identified for the production of either $\alpha$- or $\beta$-oriented C17 aryl steroids, conveniently using the C17 ketone as a common starting material. Because of this divergence, it is now possible to efficiently produce both epimers of C17 aryl steroids, thus adding the $\alpha$-epimers to the cadre of unnatural biomolecules available for biological and other studies. The relevance and utility of such a transformation has been demonstrated by the synthesis of 1.11, its epimer 1.106, and biological evaluations thereof. Finally, the compelling finding that 1.101 retains much of the potency of 1.11 should considerably simplify SAR studies in this family.

For the distribution of credit related to our first generation route to cortistatin A, see reference 24b and 24c. For the distribution of credit for the scalable route of synthesis of cortistatin and related structures, Dr. Carlos Guerrero (a former graduate student in our lab), Dr. Ryan Shenvi (a former graduate student in our lab) and Dr. Chuang-Chuang Li (a former post-doc associate) conducted initial studies on A ring functionalization and dibrominated C19 methyl group. Dr. Georg Manolikakes (a former post-doc associate)
and Dr. Hiroki Shigehisa (a former post-doc associate) optimized and finalized a scalable route to A ring functionalization. Dr. Georg Manolikakes also helped to characterize some of intermediates from the failed routes. Chien-Hung Yeh, a visiting graduate student, synthesized some of the D-ring analogs. My contributions are listed below:

- finalized the scalable route to $^{16}\Delta$-cortistatin A
- discovered SmI$_2$ mediated trapping/elimination for B-ring expansion to the desired dienone
- investigated the scalable route to synthesize 7-subsituted isoquinoline
- studied the side installation
- discovered BiCl$_3$-mediated THF ring closure
- investigated Ra-Ni mediated reduction and deoxygenation
- synthesized 17-epi-cortistatin A
- synthesized analogs for the biological testing

1.7. References


(27) The Brooks–Norymberski method was found to be impractical on large scale, see: Brooks, C. J.; Norymberski, J. K. Biochem. J. 1953, 55, 371–370.


(31) Decalin-bridged radicals have been shown to deviate from planar geometry, see: Lloyd, R. V.; Williams, R. V. *J. Phys. Chem.* **1985**, 89, 5379-5381.


(40) It is also possible that 1.87 was formed via E1cB elimination of bromide in 1.86, followed by reaction of the π-conjugated carbon radical with an additional equivalent of SmI2.


1.8: Experimental section

**General procedures.** All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (CH$_2$Cl$_2$), benzene, toluene, methanol (MeOH), acetonitrile, 1,2-dimethoxyethane (DME), $N,N$-dimethylformamide (DMF), and triethylamine (Et$_3$N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO$_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl$_3$ @ 7.26 ppm $^1$H NMR, 77.0 ppm $^{13}$C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin
Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.

**Compounds 1.35:** Et$_3$N (76 mL, 550 mmol, 10 equiv) and HOAc (31.4 mL, 550 mmol, 10 equiv) were mixed in a sealed tube cooled with a water bath. The resulting solution was stirred for 10 min. Then the epoxide 1.31 (21.3 g, 55 mmol) was added, the tube sealed with a Teflon screwcap and the reaction heated to 130 °C for 16 h. After cooling to ambient temperature, the mixture was diluted with CH$_2$Cl$_2$ (500 mL) and washed with water (200 mL), 1 M HCl (200 mL), sat. aq. NaHCO$_3$ (200 mL), water (200 mL) and sat. aq. NaCl (200 mL). The organic portion was dried over MgSO$_4$ and concentrated. Purification of the crude residue by flash column chromatography (CH$_2$Cl$_2$:acetone 6:1 to 2:1) yielded the desired product 1.34 (15.75 g,) together with the undesired regioisomer 1.35 (7.85 g). 1.35 can be recycled by the following procedure. A mixture of the undesired regioisomer 1.35 (7.85 g, 17.6 mmol) and DMAP (220 mg, 1.8 mmol, 0.1 equiv) in toluene (88 ml, 0.2 M) was heated to reflux for 24 h. The reaction was allowed to cool and concentrated in vacuo. Purification of the crude residue by flash column chromatography (CH$_2$Cl$_2$:acetone 6:1 to 2:1) yielded the desired regioisomer 1.34 (5.0 g, 84% from 1.31) along with 1.35 (2.4 g, 10% from 1.31).

**Compound 1.35:**

$R_f$ = 0.43 (1:1 CH$_2$Cl$_2$:acetone)

$[\alpha]_D$ = 118 ° (c = 0.5, CHCl$_3$)

HRMS ($m/z$): calcd for C$_{24}$H$_{34}$NO$_7$ [M+H]$^+$, 448.233; found, 448.2320;

IR (film) $\nu_{\text{max}}$ = 3380, 2973, 2923, 2845, 1734, 1698, 1664, 1501, 1436, 1375, 1313, 1239, 1053, 1033 cm$^{-1}$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.10 (s, 1 H), 5.66 (d, $J = 3.9$ Hz, 1H), 5.64 – 5.60 (m, 1
(d, J = 4.8 Hz, 1 H), 4.54 – 4.49 (m, 1 H), 4.05 – 4.00 (m, 1 H), 3.96 – 3.88 (m, 2 H), 3.86 – 3.77 (m, 2 H), 3.03 (d, J = 4.7 Hz, 1 H), 2.51 (t, J = 11.4 Hz, 1 H), 2.41 – 2.33 (m, 1 H), 2.28 (t, J = 10.4 Hz, 1 H), 2.21 – 2.13 (m, 1 H), 2.08 – 1.97 (m, 3 H), 1.94 (s, 3 H), 1.94 – 1.86 (m, 2 H), 1.86 – 1.79 (m, 1 H), 1.78 (s, 1 H), 1.47 (s, 3 H), 1.41 – 1.34 (m, 1 H), 1.16 – 1.05 (m, 1 H), 0.81 (s, 3 H);

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 210.1, 168.9, 160.0, 144.7, 117.6, 116.2, 75.2, 68.8, 65.3, 64.6, 57.5, 49.3, 49.2 (2 C), 46.9, 39.4, 36.5, 34.2, 32.1, 32.0, 22.2, 21.0, 19.6, 14.9.

**Compound 1.92**: Bromocyclopropane **1.80** (1.5 g, 2.6 mmol) was dissolved in dry THF (128 ml, 0.02 M) under Ar and freshly distilled DMPU (14.3 ml) was added. The solution was bubbled with Ar for 30 min, after which SmI$_2$ (65 ml, 6.5 mmol, 0.1 M in THF, 2.5 equiv) was quickly added. After 10 min, the reaction was cooled to $\sim$78°C and a 0.12 M solution of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) in CH$_2$Cl$_2$ (43.3 ml, 5.2 mmol, 2 equiv) was added. The reaction mixture was kept at $\sim$78°C over 1 h, at which point it was quenched with sat. aq. NaHCO$_3$ solution (100 ml). The aqueous layer was extracted four times with EtOAc (4 × 150 mL) and the combined organic portions were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Chromatography on silica (1:3 EtOAc:hexanes) furnished **1.92** as a white foam. $R_f = 0.46$ (1:1 EtOAc:hexanes); IR (neat) $\nu_{\max}$ = 2959, 1686, 1426, 1176, 1120, 1034, 882, 846 cm$^{-1}$; $^1$H NMR (600 MHz, C$_6$D$_6$) $\delta$ 7.78 (s, 1 H), 7.00 (s, 1 H), 5.47 (s, 1 H), 4.76 (bs, 1 H), 4.13 (d, J = 3.0 Hz, 1 H), 4.05 (t, J = 3.3 Hz, 1 H), 3.60 (d, J = 13.8 Hz, 1 H), 3.39 – 3.32 (m, 2 H), 3.25 – 3.17 (m, 2 H), 2.96 – 2.92 (m, 1 H), 2.38 – 2.33 (m, 1 H), 2.28 (d, J = 13.2 Hz, 1 H), 2.06 (dd, J = 13.2, 2.4 Hz, 1 H), 1.90 – 1.84 (m, 1 H), 1.82 – 1.77 (m, 1 H), 1.63 – 1.60 (m, 2 H), 1.49 – 1.54 (m, 3 H), 1.42 – 1.36 (m, 1 H), 0.95 – 0.92 (m, 1 H), 0.75 (s, 3 H), $-0.11$ (s, 9 H).
H; $^{13}$C NMR (150 MHz, C$_6$D$_6$) $\delta$ 199.2, 157.6, 141.1, 125.2, 117.7, 96.4, 79.6, 77.1, 68.6, 65.3, 64.6, 63.9, 47.6, 45.8, 43.8, 43.2, 33.8, 33.4 (2 C), 25.3, 22.4, 14.9, –0.3; HRMS (ESI-TOF) calcd for C$_{26}$H$_{36}$BrNO$_7$Si [M+H]$^+$: 582.1517; found: 582.1521.

**Compound 1.76:1.92** was dissolved in dry DMF (26 ml, 0.1 M) and to this solution were added LiBr (4.5 g, 52 mmol, 20 equiv) and Li$_2$CO$_3$ (3.8 mg, 52 mmol, 20 equiv). The reaction mixture was stirred at 60 °C for 1 h, at which point it was diluted with Et$_2$O (400 mL), washed with sat. aq. NaHCO$_3$ (100 mL) and H$_2$O (4 × 100 mL), dried with MgSO$_4$, filtered, and concentrated in vacuo. Chromatography on silica (1:2 EtOAc:hexanes) afforded dienone 1.76 (845 mg, 65%) as a white solid. $R_f = 0.26$ (1:1 EtOAc:hexanes); [$\alpha$]$_D$ = –10.2° (c 0.93, CH$_2$Cl$_2$), IR (neat) $\nu_{\text{max}}$ = 2953, 1678, 1426, 1253, 1128, 1081, 1038, 878, 846 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.22 (s, 1 H), 6.50 (s, 1 H), 5.90 (s, 1H), 4.58 (s, 1 H), 4.28 (dd, $J = 4.2$, 1.8 Hz, 1 H), 4.10 (t, $J = 3.6$ Hz, 1 H), 3.96 – 3.92 (m, 2 H), 3.89 – 3.83 (m, 2 H), 3.14 (dd, $J = 15.0$, 7.5 Hz, 1 H), 2.64 (d, $J = 16.2$ Hz, 1 H), 2.50 (dd, $J = 14.7$, 11.1 Hz, 1 H), 2.35 (d, $J = 16.8$ Hz, 1 H), 2.36 – 2.29 (m, 1 H), 2.15 – 2.06 (m, 2 H), 2.03 – 1.91 (m, 4 H), 1.67 – 1.56 (m, 2 H), 0.90 (s, 3 H), 0.15 (s, 9 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 197.4, 163.5, 157.6, 135.5, 129.1, 119.9, 117.5, 96.9, 80.7, 77.6, 66.8, 65.5, 46.6, 48.0 (2 C), 47.0, 46.1, 38.5, 34.0, 33.3, 25.3, 22.3, 14.9, 0.1; HRMS (ESI-TOF) calcd for C$_{26}$H$_{35}$NO$_7$Si [M+H]$^+$: 502.2255; found: 502.2273.

**Compound 1.23**: A freshly prepared solution of AlH$_3$ (34.2 mL, 17.1 mmol, 6 equiv, 0.5 M in THF) was added to dienone 1.76 (1.46 g, 2.85 mmol) in THF (28.5 mL, 0.1 M) at ambient temperature. After stirring vigorously for 1 h, methanol (28.5 mL) was added dropwise, followed by K$_2$CO$_3$ (1.97 g, 14.3 mmol, 5 equiv). This suspension was then stirred for 12 h, at which point it was diluted with CH$_2$Cl$_2$ (100 mL) and sat. aq. sodium
potassium tartrate (100 mL). The organic phase was removed and the aqueous layer extracted three more times with CH₂Cl₂ (3 × 100 mL). Drying over Na₂SO₄, filtration, concentration in vacuo, and yielded 1.23 (1.0 g, 85%, 1:1 inseparable mixture of diastereomers) as a white foam.

**Compound 1.23** (mixture of diastereomers):

\[ R_f = 0.47 \ (2:8 \ NEt₃: \ EtOAc) \]

\[ [\alpha]_D = +74.7^\circ \ (c = 1.6, \ CH₂Cl₂) \]

HRMS (m/z): calcd for C₂₃H₃₆N₆O₆ [M+H]⁺, 422.2537; found, 422.2551;

IR (film) \( \nu_{max} = 3368, 2942, 2878, 1699, 1458, 1303, 1096, 965, 734 \) cm⁻¹;

Diastereomer 1.23-1

\(^1\)H NMR (600 MHz, CD₃OD) \( \delta \)

6.19 (s, 1 H), 4.29 – 4.26 (m, 2 H), 4.12 – 4.10 (m, 1 H),
3.95 – 3.90 (m, 4 H), 2.86 – 2.80 (m, 1 H), 2.49 (s, 6 H), 2.37 – 2.10 (m, 4 H), 2.05 – 1.61 (m, 6 H), 1.57 – 1.36 (m, 3 H), 0.96 (s, 3 H);

\(^{13}\)C NMR (150 MHz, CD₃OD) \( \delta \)

147.4, 140.8, 132.4, 129.9, 119.8, 83.4, 74.7, 71.7, 71.4, 66.8, 66.3, 65.6, 49.7, 48.9, 43.2, 42.9, 41.3, 39.0, 35.9, 35.2, 25.5, 23.7, 15.0;

Diastereomer 1.23-2

\(^1\)H NMR (600 MHz, CD₃OD) \( \delta \)

6.03 (s, 1 H), 4.25 – 4.19 (m, 2 H), 4.09 – 4.07 (m, 1 H),
3.99 – 3.80 (m, 4 H), 2.63 – 2.57 (m, 1 H), 2.47 (s, 6 H), 2.31 – 2.09 (m, 4 H), 2.07 – 1.61 (m, 6 H), 1.57 – 1.36 (m, 4 H), 0.81 (s, 3 H);

\(^{13}\)C NMR (150 MHz, CD₃OD) \( \delta \)

145.7, 141.1, 130.6, 129.8, 119.7, 83.1, 74.6, 71.5, 71.3, 66.7, 66.4, 65.6, 48.8, 45.2, 43.3, 42.9, 41.4, 40.6, 36.2, 35.5, 25.5, 23.7, 16.1.

**Cortistatinone (1.22)**: To a solution of 1.23 (1.02 g, 2.42 mmol) in MeCN (484 mL, 0.005 M) was added BiCl₃ (1.52 g, 4.84 mmol, 2 equiv) and the reaction was warmed to
40 °C for 2 h. Then, additional BiCl₃ (762 mg, 2.42 mmol, 1 equiv) was added to the reaction mixture at 40 °C for 30 min. Then, H₂O (150 mL) and BiCl₃ (1.52 g, 4.84 mmol, 2 equiv) was added to the reaction mixture at 40 °C. After 4 h, sat. aq. NaHCO₃ (300 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 × 500 mL). The combined organic portions were washed sat. aq. NaCl (500 mL), dried over Na₂SO₄ and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (silica gel, MeOH:CH₂Cl₂:Et₃N 90:10:1) furnishing compound 1.22 (642 mg, 73%) as a white foam. Rₚ = 0.17 (20% MeOH:EtOAc); [α]_D = +148.0° (c 0.60, CH₂Cl₂); IR (neat) ν_max = 3393, 2933, 2356, 1734, 1456, 1072, 1018, 1002 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.25 (d, J = 1.9 Hz, 1 H), 5.44 (dd, J = 4.7, 2.7 Hz, 1 H), 4.16 (d, J = 10.9 Hz, 1 H), 3.42 (t, J = 9.8, Hz, 1 H), 2.76 (bt, J = 10.3 Hz, 1 H), 2.56 – 2.49 (m, 2 H), 2.44 (s, 6 H), 2.37 (dd, J = 12.7, 5.8 Hz, 1 H), 2.27 – 2.18 (m, 4 H), 2.15 – 2.10 (m, 1 H), 1.97 (dd, J = 12.4, 3.1 Hz, 1 H), 1.91 – 1.79 (m, 3 H), 1.72 – 1.67 (m, 1 H), 0.91 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ 220.3, 139.9, 139.4, 120.9, 119.5, 81.6, 79.4, 73.9, 73.0, 62.3, 47.8, 47.1, 40.0 (2C), 39.7, 35.9, 33.9, 31.4, 29.4, 18.8, 16.9; HRMS (ESI-TOF) calcd for C₂₁H₂₉NO₄ [M+H]⁺: 360.2169; found: 360.2174.

**Compound 1.101**: To a solution of cortistatinone (1.22) (200 mg, 0.56 mmol) in absolute EtOH (9.3 mL, 0.06 M) were added hydrazine monohydrate (0.28 mL, 5.6 mmol, 10 equiv) and Et₃N (0.78 mL, 5.6 mmol, 10 equiv). The reaction was immersed in a preheated oil bath at 50 °C for 6 h, after which the reaction was allowed to cool and the solvent removed in vacuo. The residue so obtained was dissolved in THF (9.3 mL, 0.06 M), and Et₃N (0.23 mL, 1.68 mmol, 3 equiv) was added. A stock solution of I₂ (283 mg, 1.12 mmol, 2 equiv) in THF (2.83 mL) was prepared and added dropwise to the reaction.
mixture; addition was halted when the iodine was not decolorized after 30 sec. The reaction was then diluted with EtOAc (50 mL) and washed with sat. aq. Na$_2$S$_2$O$_3$ (50 mL). The aqueous layer was extracted four times with EtOAc (4 × 50 mL). The combined organic portions were washed with sat. aq. NaCl (10 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo to furnish vinyl iodide which was carried forward directly without purification. The residue from the previous reaction (yield assumed to be quantitative) was dissolved in DMSO (9.3 mL, 0.06 M). To this solution was added 7-trimethylstannylisoquinoline (164 mg, 0.56 mmol, 1 equiv), CuCl (554 mg, 5.6 mmol, 10 equiv), LiCl (235 mg, 5.6 mmol, 10 equiv) and Pd(PPh$_3$)$_4$ (323 mg, 0.28 mmol, 0.5 equiv). The reaction was degassed by bubbling argon through the solution for 10 min. It was then immersed in a preheated oil bath at 60°C for 1 h. The reaction was then diluted with EtOAc (25 mL) and washed with 5% aq. NH$_4$OH. The aqueous layer was extracted four times (4 × 25 ml) with EtOAc. The combined organic portions were washed wth sat. aq. NaCl (25 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue so obtained was purified by (silica, NH$_3$ deactivation; 10% MeOH : CH$_2$Cl$_2$) furnishing vinylisoquinoline 1.101 (145 mg, 55% from cortistatine 1.22) as a yellow foam. $^1$H NMR (CDCl$_3$, 600 MHz): 9.22 (bs, 1 H), 8.48 (bs, 1 H), 7.92 (s, 1 H), 7.79 (dd, $J = 8.6$, 1.6 Hz, 1 H), 7.75 (d, $J = 8.6$ Hz, 1 H), 7.61 (d, $J = 5.5$ Hz, 1 H), 6.29 (d, $J = 1.9$ Hz, 1 H), 6.24 (as, 1 H), 5.57 – 5.52 (m, 1 H), 4.13 (d, $J = 9.0$ Hz, 1 H), 3.37 (at, $J = 3.37$, 1 H), 2.75 (dd, $J = 11.2$, 6.9 Hz, 1 H), 2.61 (dd, $J = 9.0$ Hz, 5.8 Hz, 1 H), 2.56 – 2.48 (m, 3 H), 2.47 – 2.38 (m, 2 H), 2.35 (s, 6 H), 2.23 (t, $J = 10.1$ Hz, 1 H), 2.05 – 1.96 (m, 2 H), 1.96 – 1.87 (m, 1 H), 1.76 – 1.68 (m, 1 H), 1.15 (s, 3 H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 152.5, 150.4, 142.8, 140.0, 139.4, 135.3, 134.8, 134.3, 130.0, 128.4, 126.4, 123.9, 121.8,
120.2, 119.4, 81.2, 79.3, 74.1, 73.5, 62.3, 53.3, 47.7, 40.0 (2 C), 39.6, 38.2, 31.0, 29.3, 28.6, 19.3; HRMS (ESI-TOF) calcd for C_{30}H_{34}N_2O_3 [M+H]^+: 471.2642; found: 471.2656.

(+)-Cortistatin A (1.11): For this procedure, Raney nickel (1.0 g) was washed with H_2O (3 × 5 mL), sat. aq. Rochelle’s salt (3 × 5 mL), H_2O (5 × 5 mL), MeOH (3 × 5 mL), and H_2O again (3 × 5 mL, all supernatants were removed with pipette) after which it was stored under H_2O (10 mL). To 1.101 (10 mg, 63 µmol) in i-PrOH (3 mL) and H_2O (0.3 mL), was added the washed Raney nickel (100 mg, 10 wt. equiv, which includes water). The heterogeneous reaction was warmed to 60 °C while stirring vigorously for 30 min, at which point the reaction had progressed to approximately 50% conversion, as judged by LCMS. Removal of the supernatant, followed by washing of the Raney nickel catalyst with 1:1 MeOH:EtOAc (20 mL), and concentration of the combined filtrates yielded a colorless residue, which was purified by HPLC (Eclipse XDB-C8 column, 9.4 mm × 25 cm; gradient = 1%→30% MeCN:H_2O over 30 min), yielding recovered 1.101 (5 mg) and (+)-cortistatin A (2.3 mg, 50% conversion, 50% brsm) as a white solid. [α]_D = +31.4 (c 0.035, MeOH) [lit: [α]_D = +30.1 (c 0.56, MeOH)]; ^1H NMR (CDCl_3, 600 MHz): 9.22 (1 H), 8.49 (d, J = 5.3 Hz, 1 H), 7.79 (s, 1 H), 7.76 (d, J = 8.3 Hz, 1 H), 7.63 (d, J = 5.3 Hz, 1 H), 7.59 (d, J = 8.5 Hz, 1 H), 6.25 (d, J = 1.6 Hz, 1 H), 5.44 (d, J = 3.0 Hz, 1 H), 4.09 (d, J = 9.5 Hz, 1 H), 3.33 (t, J = 9.8 Hz, 1 H), 3.15 (t, J = 9.9 Hz, 1 H), 2.51 (dd, J = 11.3, 8.6, 1 H), 2.46 – 2.42 (m, 1 H), 2.39 – 2.33 (m, 2 H), 2.30 (s, 6 H), 2.28 – 2.26 (m, 2 H), 2.23 – 2.16 (m, 2 H), 2.07 – 2.01 (m, 1 H), 1.97 (dd, J = 17.4, 5.2 Hz, 1 H), 1.93 (dd, J = 13.3, 3.3 Hz, 1 H), 1.90 – 1.83 (m, 2 H), 1.78 (ddd, 12.9, 8.7, 8.2 Hz, 1 H), H_2O peak covers proton at 1.66 (1 H), 0.54 (s, 3 H); ^13C NMR (150 MHz, CDCl_3) δ 152.3, 142.5, 140.0, 139.7, 139.5, 134.7, 132.0, 128.5, 126.3, 125.8, 121.5, 120.1, 119.5, 81.9, 79.5,
74.1, 73.7, 62.2, 56.9, 51.6, 44.8, 40.1 (2 C), 40.0, 39.7, 30.6, 29.1, 26.4, 20.5, 15.2; for NMR data comparisons, see Tables 1 and 2 (*vide infra*); HRMS (ESI-TOF) calcd for C$_{30}$H$_{36}$N$_2$O$_3$ [M+H]$^+$: 473.2799; found: 473.2807.

**Table 1.** $^1$H NMR data comparison between synthetic (+)-cortistatin A (I) and natural (+)-cortistatin A. *Calculated as center of observed multiplet.

<table>
<thead>
<tr>
<th></th>
<th>Synthetic 1 (CDCl$_3$, 600 MHz)</th>
<th>Natural 1 (CDCl$_3$, 600 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.54</td>
<td>0.54</td>
<td>0.54</td>
</tr>
<tr>
<td>H$_2$O peak</td>
<td>1.66</td>
<td>1.66</td>
</tr>
<tr>
<td>1.78</td>
<td>1.78</td>
<td>1.78</td>
</tr>
<tr>
<td>1.84'</td>
<td>1.84</td>
<td>1.84</td>
</tr>
<tr>
<td>1.88'</td>
<td>1.89</td>
<td>1.89</td>
</tr>
<tr>
<td>1.93</td>
<td>1.93</td>
<td>1.93</td>
</tr>
<tr>
<td>1.97'</td>
<td>1.97</td>
<td>1.97</td>
</tr>
<tr>
<td>2.04'</td>
<td>2.05</td>
<td>2.05</td>
</tr>
<tr>
<td>2.17'</td>
<td>2.19</td>
<td>2.19</td>
</tr>
<tr>
<td>2.22'</td>
<td>2.21</td>
<td>2.21</td>
</tr>
<tr>
<td>2.27'</td>
<td>2.28</td>
<td>2.28</td>
</tr>
<tr>
<td>2.30</td>
<td>2.30</td>
<td>2.30</td>
</tr>
<tr>
<td>2.35'</td>
<td>2.35</td>
<td>2.35</td>
</tr>
<tr>
<td>2.38'</td>
<td>2.38</td>
<td>2.38</td>
</tr>
<tr>
<td>2.44'</td>
<td>2.43</td>
<td>2.43</td>
</tr>
<tr>
<td>2.51</td>
<td>2.51</td>
<td>2.51</td>
</tr>
<tr>
<td>3.15</td>
<td>3.15</td>
<td>3.15</td>
</tr>
<tr>
<td>3.33</td>
<td>3.33</td>
<td>3.33</td>
</tr>
<tr>
<td>4.09</td>
<td>4.09</td>
<td>4.09</td>
</tr>
<tr>
<td>5.44</td>
<td>5.44</td>
<td>5.44</td>
</tr>
<tr>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
</tr>
<tr>
<td>7.59</td>
<td>7.59</td>
<td>7.59</td>
</tr>
<tr>
<td>7.63</td>
<td>7.63</td>
<td>7.63</td>
</tr>
<tr>
<td>7.76</td>
<td>7.76</td>
<td>7.76</td>
</tr>
<tr>
<td>7.79</td>
<td>7.78</td>
<td>7.78</td>
</tr>
<tr>
<td>8.49</td>
<td>8.49</td>
<td>8.49</td>
</tr>
<tr>
<td>9.22</td>
<td>9.22</td>
<td>9.22</td>
</tr>
</tbody>
</table>
Table 2. $^{13}$C NMR data comparison between synthetic (+)-cortistatin A (I) and natural (+)-cortistatin A.

<table>
<thead>
<tr>
<th></th>
<th>Synthetic 1</th>
<th>Natural 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(CDCl$_3$, 150 MHz)</td>
<td>(CDCl$_3$, 150 MHz)</td>
</tr>
<tr>
<td>15.2</td>
<td>15.2</td>
<td>15.2</td>
</tr>
<tr>
<td>20.5</td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>26.4</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>29.1</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>30.6</td>
<td>30.5</td>
<td></td>
</tr>
<tr>
<td>39.7</td>
<td>39.7</td>
<td></td>
</tr>
<tr>
<td>40.0</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>40.1</td>
<td>40.1</td>
<td></td>
</tr>
<tr>
<td>44.8</td>
<td>44.8</td>
<td></td>
</tr>
<tr>
<td>51.6</td>
<td>51.6</td>
<td></td>
</tr>
<tr>
<td>56.9</td>
<td>56.9</td>
<td></td>
</tr>
<tr>
<td>62.2</td>
<td>62.2</td>
<td></td>
</tr>
<tr>
<td>73.7</td>
<td>73.7</td>
<td></td>
</tr>
<tr>
<td>74.1</td>
<td>74.1</td>
<td></td>
</tr>
<tr>
<td>79.5</td>
<td>79.5</td>
<td></td>
</tr>
<tr>
<td>81.9</td>
<td>81.9</td>
<td></td>
</tr>
<tr>
<td>119.5</td>
<td>119.5</td>
<td></td>
</tr>
<tr>
<td>120.1</td>
<td>120.1</td>
<td></td>
</tr>
<tr>
<td>121.5</td>
<td>121.5</td>
<td></td>
</tr>
<tr>
<td>125.8</td>
<td>125.8</td>
<td></td>
</tr>
<tr>
<td>126.3</td>
<td>126.3</td>
<td></td>
</tr>
<tr>
<td>128.5</td>
<td>128.5</td>
<td></td>
</tr>
<tr>
<td>132.0</td>
<td>132.0</td>
<td></td>
</tr>
<tr>
<td>134.7</td>
<td>134.7</td>
<td></td>
</tr>
<tr>
<td>139.5</td>
<td>139.5</td>
<td></td>
</tr>
<tr>
<td>139.7</td>
<td>139.8</td>
<td></td>
</tr>
<tr>
<td>140.0</td>
<td>140.0</td>
<td></td>
</tr>
<tr>
<td>142.5</td>
<td>142.5</td>
<td></td>
</tr>
<tr>
<td>152.3</td>
<td>152.3</td>
<td></td>
</tr>
</tbody>
</table>

**Compound 1.30:** To a solution of compound 1.29 (95 mg, 0.25 mmol) in DMF (2.5 mL, 0.1 M) at ambient temperature was added sodium azide (82 mg, 1.25 mmol, 5 equiv). The
reaction was allowed to stir at ambient temperature for 14 h, after which it was diluted with 35 mL of EtOAc. The resulting mixture was washed twice with H₂O and sat. aq. NaCl and dried over MgSO₄. The solvent was removed \textit{in vacuo} and the crude material purified by silica gel flash chromatography (3:1 hexanes:EtOAc) to afford compound \textbf{1.30} (91 mg, 94 %, 9:1 mixture of diastereomers) as a white solid.

\( R_f = 0.38 \) (3:1 hexanes:EtOAc)

\[ [\alpha]_D = 167^\circ \ \text{(c = 0.1, CHCl}_3) \]

m.p. = 185–189 °C

HRMS (\( m/z \)): calcd for C₂₁H₂₈N₃O₄ [M+H]⁺, 386.2074; found, 386.2076;

IR (film) \( \nu_{\max} = 2971, 2941, 2884, 2097, 1703, 1669, 1458, 1438, 1383, 1313, 1208, 1174, 1104, 1053, 1040 \ \text{cm}^{-1}; \)

\(^1\text{H NMR} (600 \ \text{MHz, CDCl}_3) \delta 5.17 – 5.13 \ (m, 1 \ H), 3.95 – 3.87 \ (m, 4 \ H), 3.85 – 3.78 \ (m, 2 \ H), 3.56 – 3.52 \ (m, 1 \ H), 2.70 \ (d, J = 12.4, 1 \ H), 2.31 – 2.24 \ (m, 2 \ H), 2.21 – 2.15 \ (m, 1 \ H), 2.11 – 1.99 \ (m, 3 \ H), 1.95 – 1.78 \ (m, 4 \ H), 1.39 – 1.34 \ (m, 1 \ H), 1.32 \ (s, 3 \ H), 1.19 – 1.11 \ (m, 1 \ H), 0.84 \ (s, 3 \ H); \)

\(^{13}\text{C NMR} (150 \ \text{MHz, CDCl}_3) \delta 210.7, 144.5, 117.5, 113.5, 65.4, 64.6, 57.9, 57.7, 55.3, 55.1, 49.7, 49.2, 48.6, 37.4, 37.0, 34.1, 32.1, 31.7, 22.2, 17.8, 14.9. \)

\textbf{Compound 1.36: \( i \).} To a solution of compound \textbf{1.29} (95 mg, 0.25 mmol) in acetone (2.5 mL, 0.1 M) were added K₂CO₃ (69 mg, 0.5 mmol, 2 equiv) and thiophenol (39 µL, 0.38 mmol, 1.5 equiv). The resulting mixture was heated to 65 °C for 15 h. After cooling to ambient temperature, the solvent was removed \textit{in vacuo}. The obtained residue was taken up in H₂O and extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed with sat. aq. NaCl and dried over MgSO₄. The solvent was
removed *in vacuo* and the crude material purified by silica gel flash chromatography (3:1 hexanes:EtOAc) to afford sulfide (102 mg, 96 %, 9:1 mixture of diastereomers) as a white solid.

*ii.* A solution of compound sulfide (100 mg, 0.22 mmol) in CH$_2$Cl$_2$ (2.2 mL, 0.1 M) was cooled to 0 °C. *m*-CPBA (60 mg, purity 70 %, 0.24 mmol, 1.1 equiv) was added and the reaction was stirred for at 0 °C. After 1 h the mixture was poured onto 10 % aqueous Na$_2$S$_2$O$_3$ and the resulting biphasic mixture was extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed with sat. aq. NaHCO$_3$ (30 mL), sat. aq. NaCl (30 mL) and dried over MgSO$_4$. The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (3:1 hexanes:EtOAc) to afford a mixture of diastereomers **1.36** (98 mg, 94 %) as a white foam (data reported for major diastereomer only).

$R_f = 0.21$ (1:1 EtOAc:hexanes)

$\left[\alpha\right]_D^0 = +118.5^\circ$ (c = 0.2, CH$_2$Cl$_2$)

HRMS (m/z): calcd for C$_{27}$H$_{33}$O$_5$S [M+H]$^+$, 469.2043; found, 469.2034;

IR (film) $\nu_{\text{max}} =$ 2973, 2938, 2880, 1703, 1443, 1313, 1171, 1103, 1044, 1019, 753, 690 cm$^{-1}$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.83 – 7.80 (m, 2 H), 7.56 – 7.53 (m, 3 H), 5.67 – 5.64 (m, 1 H), 3.96 – 3.87 (m, 3 H), 3.86 – 3.77 (m, 3 H), 3.52 (dd, $J = 5.9$, 2.9 Hz, 1 H), 2.77 – 2.72 (m, 1 H), 2.70 (d, $J = 12.4$, 1 H), 2.32 – 2.22 (m, 2 H), 2.12 – 1.98 (m, 3 H), 1.94 – 1.74 (m, 4 H), 1.39 – 1.33 (m, 1 H), 1.32 (s, 3 H), 1.23 – 1.12 (m, 1 H), 0.84 (s, 3 H);
\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 210.7, 144.7, 142.0, 131.7, 129.2 (2 C), 125.0 (2 C), 117.5, 110.0, 65.4, 64.6, 64.5, 58.8, 57.8, 49.9, 49.5, 49.2, 48.6, 37.4, 37.0, 34.1, 32.0, 31.9, 22.1, 17.8, 15.0.

**Compound 1.38:** *i.* A solution of compound 1.27 (200 mg, 0.55 mmol) in CH\(_2\)Cl\(_2\) (5.5 mL, 0.1 M) was cooled to 0 °C. \(m\)-CPBA (190 mg, purity 70 %, 0.24 mmol, 1.4 equiv) was added and the reaction was stirred for at 0 °C. After 1 h the mixture was poured onto 10 % aqueous Na\(_2\)S\(_2\)O\(_3\) (30 mL) and the resulting biphasic mixture was extracted three times with EtOAc (3 x 25 mL). The combined organic portions were washed with sat. aq. NaHCO\(_3\) (30 mL), sat. aq. NaCl (30 mL), dried over MgSO\(_4\) and the volatiles removed *in vacuo* to yield the crude *bis*-epoxide.

*ii.* The aforementioned crude *bis*-epoxide was dissolved in CH\(_2\)Cl\(_2\) (11 mL, 0.05 M). DMP (168 mg, 0.61 mmol, 1.1 equiv) was added and the mixture stirred for 2 h at ambient temperature. Then the mixture was poured onto 10 % aq. Na\(_2\)S\(_2\)O\(_3\) (10 mL) and the resulting biphasic mixture was extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed with sat. aq. NaHCO\(_3\) (10 mL), sat. aq. NaCl (10 mL), dried over MgSO\(_4\) and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (hexanes:EtOAc 2:1) furnishing compound 1.38 (185 mg, 90 % over two steps) as a white foam.

\[ R_f = 0.41 \text{ (1:1 EtOAc:hexanes)} \]

\[ [\alpha]_D = + 59^\circ \ (c = 0.1, \text{ CH}_2\text{Cl}_2) \]

HRMS (m/z): calcd for C\(_{21}\)H\(_{27}\)O\(_6\) [M+H]\(^+\), 375.1802; found, 375.1800;

IR (film) \(\nu_{\text{max}} = 2944, 2878, 1702, 1173, 1105, 1033, 922, 771 \text{ cm}^{-1};\)

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 4.26 (d, \(J = 4.3 \text{ Hz}, 1 \text{ H}\), 3.98 – 3.90 (m, 2 H), 3.87 – 3.79
(m, 2 H), 3.36 (dd, J = 4.3, 2.5 Hz, 1 H), 3.25 (d, J = 2.5 Hz, 1 H), 2.86 (d, J = 11.4 Hz, 1 H), 2.79 (d, J = 12.1 Hz, 1 H), 2.26 – 2.18 (m, 2 H), 2.13 (d, J = 12.1 Hz, 1 H), 2.05 (ddd, J = 15.0, 11.8, 3.5 Hz, 1 H), 1.99 – 1.92 (m, 2 H), 1.89 – 1.81 (m, 2 H), 1.57 (ddd, J = 15.0, 11.8, 3.5 Hz, 1 H), 1.41 – 1.32 (m, 4 H), 1.04 – 0.99 (m, 1 H), 0.863 (s, 3 H);

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 210.5, 200.4, 117.3, 73.8, 65.4, 64.6, 64.3, 63.1, 56.6, 55.8, 49.6, 49.5, 48.6, 36.7, 36.7, 34.2, 30.6, 28.6, 22.1, 17.0, 15.0.

**Compound 1.45:** Compound 1.34 (250 mg, 0.56 mmol) was dissolved in 5.6 mL anhydrous benzene (0.1 M) and the temperature adjusted to 20 ºC (waterbath). Burgess reagent (148 mg, 0.62 mmol, 1.1 equiv) was added and the reaction stirred at 20 ºC for 30 min. The reaction was diluted with EtOAc (20 mL) and washed with sat. aq. NaHCO$_3$. The aqueous phase was extracted two times with EtOAc (2 x 25 mL). The combined organic portions were washed sat. aq. NaCl (20 mL), dried over MgSO$_4$ and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) furnishing compound 1.45 (206 mg, 86 %) as a white foam.

$R_f = 0.35$ (1:1 EtOAc:hexanes)

$[\alpha]_D = + 159 ^\circ$ (c = 0.1, CH$_2$Cl$_2$)

HRMS (m/z): calcd for C$_{24}$H$_{32}$NO$_6$ [M+H]$^+$, 430.2224; found, 430.2224;

IR (film) $\nu_{max} = 2948, 2140, 1748, 1702, 1372, 1220, 1052, 1033, 772$ cm$^{-1}$;

$^1$H NMR (600 MHz, CDCl$_3$) δ 5.38 (d, J = 3.5 Hz, 1 H), 5.24 (dd, J = 5.4, 3.6 Hz, 1 H), 4.35 (t, J = 5.6 Hz, 1 H), 4.07 (dd, J = 6.4, 3.4 Hz, 1 H), 3.96 – 3.88 (m, 2 H), 3.89 – 3.77 (m, 2 H), 2.72 – 2.68 (m, 2 H), 2.64 (d, J = 11.3 Hz, 1 H), 2.35 – 2.26 (m, 1 H), 2.19 – 2.15 (m, 1 H), 2.13 – 2.00 (m, 6 H), 1.96 – 1.87 (m, 3 H), 1.85 – 1.79 (m, 1 H), 1.40 – 1.32 (m, 4 H), 1.26 – 1.18 (m, 1 H), 0.82 (s, 3 H);
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.06 (s, 1 H), 5.13 – 5.07 (m, 1 H), 4.55 – 4.51 (m, 1 H), 4.30 – 4.20 (m, 2 H), 3.96 – 3.88 (m, 2 H), 3.86 – 3.78 (m, 2 H), 2.91 (d, $J = 11.3$ Hz, 1 H), 2.71 (d, $J = 12.5$ Hz, 1 H), 2.22 – 2.11 (m, 2 H), 2.07 (s, 3 H), 2.05 – 1.98 (m, 2 H), 1.96 – 1.85 (m, 2 H), 1.87 – 1.78 (m, 3 H), 1.69 – 1.50 (m, 4 H), 1.46 – 1.38 (m, 1 H), 1.37 – 1.30 (m, 1 H), 1.19 (s, 3 H), 0.78 (s, 3 H);

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 213.1, 169.5, 156.6, 146.4, 117.5, 71.7, 71.5, 65.4, 64.6, 57.4, 50.3, 49.5, 49.4, 48.8, 41.4, 36.9, 34.2, 31.9, 31.8, 22.2, 20.9, 19.3, 15.0.

**Compound 1.52:** To a solution of compound 1.34 (112 mg, 0.25 mmol) in THF (5.0 mL, 0.05 M) was added Co(acac)$_2$ (12.8 mg, 50 µmol, 0.2 equiv). The reaction mixture was saturated with O$_2$ by bubbling O$_2$ through the stirred solution for 30 min. Then freshly distilled PhSiH$_3$ (0.14 mL, 1.0 mmol, 4 equiv) was added over 5 min. Stirring was continued under an static O$_2$-atmosphere (no bubbling) for 12 h. The reaction was then diluted with EtOAc (25 mL), washed with 1 M aq. HCl (10 mL), sat. aq. NaHCO$_3$ (10 mL), H$_2$O (10 mL), and sat. aq. NaCl (10 mL), dried over MgSO$_4$, and concentrated in vacuo. The residue so obtained was purified by flash column chromatography (CH$_2$Cl$_2$:acetone 3:1) furnishing 1.52 (99 mg, 85%) as a white foam.

$R_f = 0.21$ (90:10:2 CH$_2$Cl$_2$:MeOH:Et$_3$N)

[$\alpha$]$_D$ = −19 ° (c = 0.1, CH$_2$Cl$_2$)

HRMS (m/z): calcld for C$_{24}$H$_{36}$N$_2$O$_8$ [M+H]$^+$, 466.2435; found, 466.2432;

IR (film) $\nu_{\text{max}}$ = 3388, 2942, 2879, 1735, 1702, 1665, 1503, 1432, 1382, 1239, 1239, 1175, 1112, 1050, 771 cm$^{-1}$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.06 (s, 1 H), 5.13 – 5.07 (m, 1 H), 4.55 – 4.51 (m, 1 H), 4.30 – 4.20 (m, 2 H), 3.96 – 3.88 (m, 2 H), 3.86 – 3.78 (m, 2 H), 2.91 (d, $J = 11.3$ Hz, 1 H), 2.71 (d, $J = 12.5$ Hz, 1 H), 2.22 – 2.11 (m, 2 H), 2.07 (s, 3 H), 2.05 – 1.98 (m, 2 H), 1.96 – 1.85 (m, 2 H), 1.87 – 1.78 (m, 3 H), 1.69 – 1.50 (m, 4 H), 1.46 – 1.38 (m, 1 H), 1.37 – 1.30 (m, 1 H), 1.19 (s, 3 H), 0.78 (s, 3 H);

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 212.2, 170.3, 160.7, 117.7, 75.6, 75.4, 73.4, 65.4, 64.6, 52.0, 49.7, 49.5, 49.0, 44.9, 41.4, 35.9, 35.6, 34.2, 33.8, 25.3, 22.1, 21.3, 16.2, 15.0.

**Compound 1.73:** A freshly prepared solution of AlH$_3$ (2.2 mL, 1.1 mmol, 5 equiv, 0.5 M
in THF) was added to 1.72 (51 mg, 0.11 mmol) in THF (1.1 mL, 0.1 M) at ambient temperature. After stirring vigorously for 1 h, methanol (0.6 mL) was added dropwise, followed by K$_2$CO$_3$ (60 mg, 0.44 mmol, 4 equiv). This suspension was then stirred for 12 h. Then, the reaction mixture was diluted with CH$_2$Cl$_2$ (30 mL) and sat. aq. sodium potassium tartrate (10 mL). The organic phase was removed and the aqueous layer extracted two more times with CH$_2$Cl$_2$ (30 mL). Drying over MgSO$_4$, filtration, concentration in vacuo, and chromatography on silica (100:10:1 MeOH:CH$_2$Cl$_2$:NH$_3$H$_2$O) yielded 73 (34 mg, 74%) as white foam.

$R_f = 0.41$ (90:10:2 CH$_2$Cl$_2$:MeOH: NH$_3$H$_2$O)

$[\alpha]_D = +34^\circ$ (c = 0.5, CH$_2$Cl$_2$)

HRMS (m/z): calcd for C$_{23}$H$_{38}$NO$_6$ [M+H]$^+$, 424.2694; found 424.2696;

IR (film) $\nu_{\text{max}} = 3398, 2936, 2875, 2783, 1456, 1165, 1100, 1054, 1038, 967, 897 \text{ cm}^{-1}$;

$^1$H NMR (600 MHz, CD$_3$OD) $\delta$ 4.27 – 4.25 (m, 1 H), 3.87 – 3.75 (m, 5 H), 3.47 – 3.43 (m, 1 H), 2.90 – 2.85 (m, 1 H), 2.50 (s, 6 H), 2.18 – 2.03 (m, 3 H), 1.98 – 1.89 (m, 2 H), 1.82 – 1.65 (m, 3 H), 1.56 – 1.40 (m, 5 H), 1.32 – 1.24 (m, 1 H), 1.07 (s, 3 H), 0.88 (d, $J = 5.6$ Hz, 1 H), 0.74 (d, $J = 5.6$ Hz, 1 H);

$^{13}$C NMR (150 MHz, CD$_3$OD) $\delta$ 120.8, 81.0, 73.6, 73.2, 72.9, 66.1, 65.6, 65.3, 64.4, 49.3, 46.9, 42.2, 38.1, 35.6, 34.9, 34.7, 34.6, 32.9, 31.9, 24.1, 21.3, 20.2, 17.2.

**Compound 1.75:** Cyclopropane 1.72 (50 mg, 0.1 mmol) was dissolved in CH$_3$CN (2 mL, 0.05 M) under Ar and freshly distilled DMPU (0.22 mL) was added. The solution was bubbled with Ar for 10 min, after which SmI$_2$ (3.0 mL, 0.3 mmol, 3.0 equiv, 0.1 M in THF) was quickly added. After stirring for 10 min at ambient temperature sat. aq. NH$_4$Cl (10 mL) was added and the biphasic mixture extracted three times with EtOAc ($3 \times 15$
mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over MgSO₄ and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) furnishing compound 1.75 (42 mg, 84 %) as a white foam (data report for major diastereomer only).

*Rf* = 0.41 (1:1 EtOAc:hexanes)

[α]D = +27 ° (c = 0.2, CH2Cl2)

HRMS (*m/z*): calcd for C26H₄₀NO₇Si [M+H]+, 506.2568; found, 506.2580;

IR (film) *ν*max = 3360, 2952, 2884, 1711, 1679, 1431, 1319, 1254, 1124, 1030, 1004, 876, 844, 757 cm⁻¹;

¹H NMR (600 MHz, CDCl₃) δ 8.18 (s, 1 H), 5.78 (s, 1 H), 4.50 (s, 1 H), 4.05 – 3.75 (m, 4 H), 2.74 – 2.60 (m, 2 H), 2.26 (d, *J* = 13.6, 1 H), 2.17 – 1.95 (m, 6 H), 1.94 – 1.80 (m, 4 H), 1.76 – 1.65 (m, 2 H), 1.54 – 1.21 (m, 5 H), 0.79 (s, 3 H), 0.19 (s, 9 H);

¹³C NMR (150 MHz, CDCl₃) δ 211.5, 176.6, 157.5, 117.6, 96.9, 77.5, 66.7, 65.9, 65.4, 64.5, 59.5, 49.4, 48.5, 47.5, 47.0, 43.9, 41.0, 33.7, 29.7, 27.5, 25.0, 22.5, 15.2, - 0.1 (3 C).

**Compound 1.89:** *i.* compound 1.80 (25 mg, 42 µmol) was dissolved in THF (0.4 M LiCl in THF solution, 2.1 ml) under Ar. The solution was bubbled with Ar for 10 min, after which SmI₂ (1.3 mL, 0.13 mmol, 2.5 equiv, 0.1 M in THF) was quickly added. After stirring for 5 min at ambient temperature, sat. aq. NaHCO₃ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over MgSO₄ and the volatiles removed in vacuo. The compound 1.88 was used in crude form for the next reaction directly.

*ii.* 1.88 was was dissolved in MeOH (2.1 ml) and NaBH₄ (1.6 mg, 44 µmol, 1.05 equiv)
was added. After stirring for 5 min at ambient temperature, sat. aq. NaHCO₃ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl, dried over MgSO₄ and the volatiles removed in vacuo. The residue was then dissolved in CH₂Cl₂ (2.1 ml) and pyridine (10 µL, 0.126 mmol, 3 equiv) was added. At 0 ºC, SOCl₂ (5 µL, 63 µmol, 1.5 equiv) was added into reaction mixture and then warmed up to ambient temperature for 30 min. Sat. aq. NaHCO₃ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over MgSO₄ and the volatiles removed in vacuo.

**iii.** A freshly prepared solution of AlH₃ (0.42 mL, 0.2 mmol, 5 equiv, 0.5 M in THF) was added to abovementioned residue in THF (2.1 mL) at ambient temperature. After stirring vigorously for 30 min, the reaction mixture was diluted with CH₂Cl₂ (25 mL) and sat. aq. sodium potassium tartrate (10 mL). The organic phase was removed and the aqueous layer extracted two more times with CH₂Cl₂ (10 mL). Drying over MgSO₄, filtration, concentration in vacuo, and chromatography on silica (100:10:1 MeOH:CH₂Cl₂:NH₄OH) yielded 1.89 (4 mg, 23% overall yield) as a white foam.

\[ R_f = 0.35 \text{ (MeOH:CH}_2\text{Cl}_2:\text{NH}_4\text{OH = 100:10:1)} \]

\[ [\alpha]_D = +1.6^\circ \text{ (c = 0.12, CH}_2\text{Cl}_2) \]

HRMS (m/z): calcd for C₂₃H₃₆NO₅ [M+H]⁺, 406.2588; found, 406.2599;

IR (film) \( \nu_{\text{max}} = 3367, 2890, 1458, 1174, 1101, 1038, 1027, 951 \text{ cm}^{-1}; \)

\(^1\text{H NMR (600 MHz, CDCl}_3\) \( \delta = 6.18 \text{ (s, 1 H), 5.85 \text{ (t, } J = 2.5 \text{ Hz, 1 H), 4.32 \text{ (brs, 1 H), 4.16 } (d, J = 3.7 \text{ Hz, 1 H)\), 3.97} - 3.80 \text{ (m, 5 H), 2.63 \text{ (bs, 1H), 2.57 \text{ (s, 6 H), 2.52} - 2.42 \text{ (m, 2 H), 2.14} - 2.03 \text{ (m, 2 H), 2.02} - 1.90 \text{ (m, 3 H), 1.88} - 1.76 \text{ (m, 3 H), 1.75} - 1.62 \text{ (m, 3 H)})}\)

73
(m, 4 H), 1.38 – 1.25 (m, 2 H), 0.84 (s, 3 H);

^{13}C\text{ NMR (150 MHz, CDCl}_3\text{) }\delta\text{ 137.8, 136.4, 135.9, 132.9, 118.7, 81.6, 73.2, 68.8, 66.4, 65.2, 64.5, 46.1, 44.4, 44.0, 43.4, 35.2, 33.6, 33.0, 29.7, 24.3, 23.3, 14.9.}

**Compound 1.91:** Compound 1.80 (25 mg, 42 \mu mol) was dissolved in THF (2.1 mL, 0.02 M) under Ar and freshly distilled DMPU (0.23 mL) was added. The solution was bubbled with Ar for 10 min, after which SmI\textsubscript{2} (1.3 mL, 0.13 mmol, 2.5 equiv, 0.1 M in THF) was quickly added. After stirring for 5 min at ambient temperature, the reaction mixture was bubbled with O\textsubscript{2} for 5 min. Then, sat. aq. NaHCO\textsubscript{3} (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over MgSO\textsubscript{4} and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (hexanes:EtOAc 1:1) furnishing compound 1.91 (16 mg, 72%) as a white foam.

\[R_f = 0.25\text{ (1:1 EtOAc:hexanes)}\]

\[[\alpha]_D = + 6.2^\circ (c = 1.07, \text{CH}_2\text{Cl}_2)\]

HRMS (\textit{m}/\textit{z}): calcd for \textit{C}_{26}\textit{H}_{38}\textit{N}=8\textit{Si [M+H]}^+, 542.2181; found, 542.2187;

IR (film) \nu_{\text{max}} = 3462, 1685, 1316, 1087, 999, 686 \text{ cm}^{-1};

m.p. = 165–168 °C

\(^1\text{H NMR (600 MHz, CDCl}_3\text{) }\delta\text{ 8.19 (s, 1 H), 6.64 (d, }J = 2.7 \text{ Hz, 1 H), 5.77 (s, 1 H), 4.37 (s, 1 H), 4.18 – 4.15 (m, 1 H), 4.01 – 3.80 (m, 4 H), 3.57 (s, 1 H), 3.10 – 3.05 (m, 1 H), 2.64 – 2.59 (m, 1 H), 2.41 – 2.26 (m, 2 H), 2.21 – 2.09 (m, 3 H), 2.06 – 1.86 (m, 4 H), 1.79 – 1.52 (m, 3 H), 1.45 – 1.35 (m, 1 H), 0.89 (s, 3 H), 0.13 (s, 9 H);}

\(^{13}C\text{ NMR (150 MHz, CDCl}_3\text{) }\delta\text{ 199.5, 157.5, 138.4, 118.0, 95.6, 79.7, 70.1, 67.7, 66.5, 64.6, 64.5, 48.4, 46.7, 46.5, 46.1, 39.5, 39.3, 33.7, 33.3, 28.1, 24.0, 21.0, 15.5, - 0.4 (3 C).}
**Compound 1.95: i.** 1.24 (250 mg, 0.6 mmol) was dissolved in actone and water (4:1, 5.8 mL, 0.1 M) and heated at 80 °C with pyridinium p-toluenesulfonate (PPTS, 145 mg, 0.6 mmol, 1 equiv). After 30 min, the reaction was cooled to ambient temperature and sat. aq. NaHCO$_3$ (20 mL) was added three times with EtOAc (3 × 20 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over Na$_2$SO$_4$ and the volatiles removed in vacuo. The resulting foam is sufficiently pure for the next step.

**ii.** To a solution of the abovementioned residue from previous reaction (234 mg, 0.6 mol) in absolute EtOH (10 mL, 0.06 M) were added hydrazine monohydrate (583 µL, 12 mmol, 20 equiv) and Et$_3$N (3.2 mL, 24 mmol, 40 equiv). The reaction was immersed in a preheated oil bath at 50 °C for 2 h, after which the reaction was allowed to cool and the solvent removed in vacuo. The residue so obtained was dissolved in THF (10 mL, 0.06 M), and Et$_3$N (251 µL, 1.8 mmol, 3 equiv) was added. A stock solution of I$_2$ (305 mg, 1.2 mmol, 2 equiv) in THF (2 mL) was prepared and added dropwise to the reaction mixture; addition was halted when the iodine was not decolorized after 30 sec. The reaction was then diluted with EtOAc (15 mL) and washed with sat. aq. Na$_2$S$_2$O$_3$ (15 mL). The aqueous layer was extracted four times with EtOAc (4 × 10 mL). The combined organic portions were washed with sat. aq. NaCl (10 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue so obtained was purified by flash column chromatography (3:7 EtOAc:hexanes) furnishing compound **1.95** (228 mg, 70%) as a white foam.

$R_f = 0.53$ (1:4 hexanes: EtOAc)

$[\alpha]_D = +34.1^\circ$ (c = 0.8, CH$_2$Cl$_2$)

HRMS ($m/z$): calcd for C$_{21}$H$_{27}$INO$_5$ [M+H]$^+$, 500.0928; found, 500.0941;

IR (film) $\nu_{\text{max}} = 3391, 2927, 1667, 1577, 1328, 1264, 1107, 987, 889, 670$ cm$^{-1}$;
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16 (s, 1 H), 6.22 – 6.19 (m, 1 H), 5.77 (s, 1 H), 4.89 – 4.86 (m, 1 H), 4.59 (s, 1 H), 4.25 – 4.21 (m, 1 H), 3.16 (d, $J = 11.0$, 1 H), 2.42 – 2.25 (m, 4 H), 2.14 – 2.00 (m, 2 H), 1.77 – 1.49 (m, 4 H), 1.39 (s, 3 H), 1.25 – 1.14 (m, 1 H), 0.95 – 0.86 (m, 2 H), 0.69 (s, 3 H);

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 210.2, 157.4, 138.3, 107.9, 96.2, 74.7, 68.7, 55.0, 54.9, 53.3, 53.2, 46.8, 42.8, 39.5, 36.6, 34.3, 31.8, 29.6, 25.0, 16.9, 14.9.

**Compound 1.96:** i. **1.95** (110 mg, 0.22 mmol) was dissolved in DMF (3.7 mL, 0.06 M). To this solution was added 7-trimethylstannylisoquinoline **1.105** (65 mg, 0.22 mmol, 1 equiv), CuCl (218 mg, 2.2 mmol, 10 equiv), LiCl (93 mg, 2.2 mmol, 10 equiv) and Pd(PPh$_3$)$_4$ (127 mg, 0.11 mol, 0.5 equiv). The reaction was degassed by bubbling argon through the solution for 10 min. It was then immersed in a preheated oil bath at 60°C for 1 h. The reaction was then diluted with CH$_2$Cl$_2$ (15 mL) and washed with 5% aq. NH$_4$OH. The aqueous layer was extracted four times (4 × 50 ml) with CH$_2$Cl$_2$. The combined organic portions were washed with sat. aq. NaCl (15 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (3:7 EtOAc:hexanes) furnishing vinylisoquinoline (55 mg, 53%).

ii. The abovementioned vinylisoquinoline (5 mg, 10 µmol) was dissolved in EtOAc and MeOH (0.5 mL, 1:1 EtOAc:MeOH, 0.02 M). To this solution was added 10% Pd/C (16.5 mg, 15 µmol, 1.5 equiv), and bubbling H$_2$ through the stirred solution for 10 min. Then stirring was continued under an static H$_2$-atmosphere for 2 h. The reaction mixture was filter through the silica pad, then purified by PTLC (EtOAc:hexanes 4:1) which afforded **1.96** (1.4 mg, 28%) as a clear oil.

$R_f = 0.29$ (EtOAc)
\[ \alpha \]_D = -3^\circ \ (c = 0.1, \text{CH}_2\text{Cl}_2) \\

HRMS (\textit{m}/\textit{z}): \text{calcd for } C_{30}H_{35}N_2O_5 [\text{M+H}]^+, 503.2546; \text{found, 503.2535; }

IR (film) \nu_{\text{max}} = 2922, 2852, 1739, 1684, 1456, 1376, 1259, 1049, 797, 718 \text{ cm}^{-1};

^1\text{H NMR (600 MHz, CDCl}_3) \delta 9.24 (\text{bs, 1 H}), 8.52 (\text{bs, 1 H}), 8.18 (\text{s, 1 H}), 7.79 – 7.72 (m, 2 H), 7.71 – 7.59 (m, 1 H), 7.49 (d, \text{J} = 8.6 \text{ Hz}, 1 \text{ H}), 5.80 (\text{s, 1 H}), 4.78 (d, \text{J} = 2.6 \text{ Hz}, 1 \text{ H}), 4.60 (\text{s, 1 H}), 4.24 (\text{s, 1 H}), 3.32 (d, \text{J} = 11.2 \text{ Hz}, 1 \text{ H}), 3.17 (t, \text{J} = 9.7 \text{ Hz}, 1 \text{ H}), 2.56 – 2.42 (m, 2 \text{ H}), 2.41 – 2.30 (m, 3 \text{ H}), 2.25 – 2.16 (m, 3 \text{ H}), 2.16 – 2.08 (m, 2 \text{ H}), 2.08 – 1.94 (m, 2 \text{ H}), 1.74 – 1.59 (m, 3 \text{ H}), 1.37 (s, 3 \text{ H}), 0.46 (s, 3 \text{ H});

^13\text{C NMR (150 MHz, CDCl}_3) 210.8, 157.3, 152.2, 142.5, 138.9, 134.8, 131.8, 126.2, 126.1, 125.9, 120.2, 96.3, 77.4, 74.7, 68.7, 55.9, 55.4, 54.5, 53.4, 48.2, 46.8, 39.2, 35.6, 31.9, 29.7, 29.6, 26.4, 25.6, 24.0, 13.9.

**Compound 1.98: 1.80** (50 mg, 86 \text{ \mu mol}) was dissolved in actone and water (4:1, 0.86 mL, 0.1 M) and heated at 80 \text{ °C} with pyridinium \textit{p}-toluenesulfonate (PPTS, 16 mg, 86 \text{ \mu mol, 1 equiv}). After 30 min, the reaction was cooled to ambient temperature and sat. aq. NaHCO\textsubscript{3} (20 mL) was added three times with EtOAc (3 \times 20 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and the volatiles removed \textit{in vacuo}. To a solution of the residue in absolute EtOH (1.4 mL, 0.06 M) were added hydrazine monohydrate (83 \text{ \mu L, 1.7 mmol, 20 equiv}) and Et\textsubscript{3}N (480 \text{ \mu L, 3.4 mmol, 40 equiv}). The reaction was immersed in a preheated oil bath at 50 \text{ °C} for 2 h, after which the reaction was allowed to cool and the solvent removed \textit{in vacuo}. The residue so obtained was dissolved in THF (1.4 mL, 0.06 M), and Et\textsubscript{3}N (36 \text{ \mu L, 258 mmol, 3 equiv}) was added. A stock solution of I\textsubscript{2} (44 mg, 172 \text{ \mu mol, 2 equiv}) in THF (0.14 mL) was prepared and added dropwise to the reaction mixture; addition was halted when the
iodine was not decolorized after 30 sec. The reaction was then diluted with EtOAc (5 mL) and washed with sat. aq. Na$_2$S$_2$O$_3$ (5 mL). The aqueous layer was extracted four times with EtOAc (4 × 10 mL). The combined organic portions were washed with sat. aq. NaCl (10 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue so obtained was purified by flash column chromatography furnishing compound 1.98 (EtOAc:hexanes 3:7).

$R_f = 0.69$ (1:4 hexanes: EtOAc)

$[\alpha]_D = +39.5^\circ$ (c = 1.2, CH$_2$Cl$_2$)

HRMS (m/z): calcd for C$_{21}$H$_{24}$BrIN$_5$ [M+H]$^+$, 575.9877; found, 575.9893;

IR (film) $\nu_{max} =$ 3407, 3051, 1672, 1583, 1328, 1304, 1108, 1066, 873, 827, 766, 678 cm$^{-1}$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.21 (s, 1 H), 6.17 (bs, 1 H), 5.85 (s, 1 H), 5.44 (d, $J = 3.7$ Hz, 1 H), 4.71 (bs, 1 H), 4.29 (t, $J = 3.4$ Hz, 1H), 3.47 (s, 1 H), 2.56 – 2.32 (m, 3 H), 2.22 – 2.13 (m, 2 H), 2.10 – 2.03 (m, 1 H), 1.92 – 1.82 (m, 1 H), 1.73 – 1.51 (m, 3 H), 1.50 – 1.43 (s, 3 H), 1.39 – 1.20 (m, 2 H), 0.94 (s, 3H);

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 204.7, 157.6, 137.7, 137.6, 107.4, 96.5, 91.0, 72.3, 69.1, 67.2, 54.6, 52.6, 49.2, 45.7, 40.0, 39.7 37.2, 35.0, 32.9, 31.9, 21.2, 18.0.

**Compound 1.99**: The abovementioned 1.98 was dissolved in DMF (1.43 mL, 0.06 M). To this solution was added 7-trimethylstannylisoquinoline 1.105 (25 mg, 86 µmol, 1 equiv), CuCl (85 mg, 860 µmol, 10 equiv), LiCl (36 mg, 860 µmol, 10 equiv) and Pd(PPh$_3$)$_4$ (50 mg, 43 µmol, 0.5 equiv). The reaction was degassed by bubbling argon through the solution for 10 min. It was then immersed in a preheated oil bath at 60°C for 1 h. The reaction was then diluted with EtOAc (5 mL) and washed with 5% aq. NH$_4$OH.
The aqueous layer was extracted four times (4 × 5 ml) with EtOAc. The combined organic portions were washed with sat. aq. NaCl (5 mL), dried over MgSO4, filtered, and concentrated in vacuo. The residue so obtained was purified by PTLC (MeOH : CH2Cl2 9:1) furnishing 1.99 (8 mg, 16% from 1.80) as a yellow foam.

\[ R_f = 0.32 \text{ (EtOAc)} \]

\[ [\alpha]_D^\circ = +10.2^\circ (c = 0.4, \text{CH}_2\text{Cl}_2) \]

HRMS (m/z): calcd for C30H30BrN2O5 [M+H]^+ 577.1332; found, 577.1314;

IR (film) \( \nu_{\text{max}} = 3335, 2927, 2853, 1679, 1443, 1110, 1038, 936 \text{ cm}^{-1} \);

\(^1\)H NMR (600 MHz, CDCl3) \( \delta \): 9.25 (s, 1 H), 8.51-8.50 (m, 1 H), 8.22 (s, 1 H), 7.88 (s, 1 H), 7.77 (s, 2 H), 7.63 (d, \( J = 5.6 \text{ Hz} \), 1H), 6.96 (s, 1 H), 6.30 – 6.21 (m, 1 H), 5.78 (s, 1 H), 5.48 (d, \( J = 3.9 \text{ Hz} \), 1H), 4.74 (s, 1 H), 4.30 (s, 1 H), 3.55 (s, 1 H), 3.13 (d, \( J = 17.5 \text{ Hz} \), 1H), 2.81 – 2.74 (m, 2 H), 2.64 – 2.57 (m, 1 H), 2.58 – 2.46 (m, 1 H), 2.43 – 2.27 (m, 2 H), 2.09 – 2.01 (m, 2 H), 1.90 – 1.71 (m, 2 H), 1.65 – 1.52 (m, 2 H), 1.38 (s, 3 H);

\(^{13}\)C NMR (150 MHz, CDCl3) \( \delta \): 205.5, 157.6, 152.6, 150.3, 142.9, 135.0, 134.3, 129.7, 128.8, 128.6, 126.7, 123.8, 120.2, 96.5, 72.5, 69.4, 67.3, 55.2, 54.1, 46.3, 40.1, 39.2, 36.9, 33.0, 29.9, 29.7, 29.6, 22.7, 21.3, 19.2.

**Compound 1.103: 1.102** (10 g, 75 mmol) was dissolved in CH2Cl2 (150 mL, 0.5 M). NBS (15 g, 82.5 mmol, 1.1 equiv) was slowly added and the reaction mixture was stirred for 30 min at ambient temperature. To this mixture 30 % NaOH (50 ml, 5 equiv) was added and the resulting biphasic mixture was stirred vigorously for 1 h. The organic layer was washed H2O (200 ml) and 1 M HCl (200 mL). The acid extracts were basified to pH = 10 with 1 M NaOH (220 mL) and extracted with CH2Cl2 (2 × 400 mL). The
organic portions was washed with sat. aq. NaCl (500 mL), dried over MgSO₄ and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (CH₂Cl₂:MeOH 15:1) furnishing compound dihydroisoquinoline (9 g, 92 %) as a colorless oil.²

ii. KNO₃ (10.5 g, 103 mmol, 1.5 equiv) was dissolved in H₂SO₄ (95-98%, 69 mL, 1 M). To this mixture dihydroisoquinoline (9 g, 69 mmol) was added at 0 °C and slowly warmed up to ambient temperature over 2 h. It was then immersed in a preheated oil bath at 60 °C for 4 h, after which the mixture was basified to pH = 10 with 3 M NaOH (500 mL) and extracted three times with CH₂Cl₂ (3 × 500 mL). The organic portions was washed with sat. aq. NaCl (500 mL), dried over MgSO₄ and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (1:1 EtOAc:Hexanes) furnishing compound 7-nitro-3,4-dihydroisoquinoline (8.8 g, 72 %) as a colorless oil.

iii. A mixture of 7-nitro-3,4-dihydroisoquinoline (8.8 g, 50 mmol) and MnO₂ (30 g, 350 mmol, 7 equiv) in toluene (250 ml, 0.2 M) was heated to reflux for 2 h. The reaction was allowed to cool, filtered through Celite® and concentrated in vacuo. Purification of the crude residue by flash column chromatography (2:1 EtOAc:Hexanes) yielded 1.103 (7.9 g, 91 %) as a yellow solid.

Rₛ = 0.64 (EtOAc)

HRMS (m/z): calcd for C₉H₇N₂O₂ [M+H]⁺, 175.0502; found, 175.0499;

IR (film) νₘₐₓ = 3074, 1666, 1629, 1582, 1135, 850, 803, 733 cm⁻¹;
m.p. = 67–68 °C

¹H NMR (500 MHz, CDCl₃) δ 9.48 (s, 1 H), 8.94 (d, J = 2.0 Hz, 1 H), 8.75 (s, 1 H), 8.46 (dd, J = 9.0, 2.2 Hz, 1 H), 7.99 (d, J = 9.0 Hz, 1 H), 7.78 (d, J = 5.5 Hz, 1 H);
\( ^{13} \text{C NMR (125 MHz, CDCl}_3 \) \( \delta 154.2, 146.5, 138.1, 128.5 \) (2 C), 124.4 (2 C), 123.7 (2 C).

**Compound 1.104**: 1.103 (7.9 g, 46 mmol) was dissolved in MeOH (460 mL, 0.1 M). To this solution was added 10% Pd/C (790 mg, 10 wt%), and \( \text{H}_2 \) was bubbled through the stirred solution for 1 h. Stirring was continued under a static \( \text{H}_2 \)-atmosphere for 2 h. The reaction mixture was filtered through the silica pad and concentrated *in vacuo*. This residue is sufficiently pure for the next step.

ii. The abovementioned residue was dissolved in \( \text{H}_2\text{O} \) (11.5 mL, 0.25 M) and HBr (48%, 11.5 mL, 0.25 M). To this mixture aq. 2.5 M NaNO\(_3\) solution (20 mL, 50.6 mmol, 1.1 equiv) was added at 0 °C. After addition, this mixture was cannulated to a solution of CuBr (7.9 g, 55.2 mmol, 1.2 equiv) in HBr (48%, 11.5 mL) which was preheated at 75 °C. After cannulation, the mixture was cooled to ambient temperature and stirred for 12 h. The mixture was basified with 3 M NaOH (500 mL) to pH = 10 and extracted with CH\(_2\)Cl\(_2\) three times (3 \( \times \) 500 mL). The organic portion was washed with sat. aq. NaCl (700 mL), dried over MgSO\(_4\) and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (EtOAc:hexanes 1:1) furnishing compound 1.104 (6.0 g, 63 % over 2 steps) as a white solid.\(^3\)

\( R_f = 0.69 \) (1:1 hexanes: EtOAc)

HRMS (m/z): calcd for C\(_9\)H\(_7\)BrN [M+H]\(^+\), 207.9756; found, 207.9763;

IR (film) \( \nu_{\text{max}} = 3407, 1661, 1572, 878, 835, 741, 674 \) cm\(^{-1}\);

m.p. = 174–178 °C

\(^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta 9.15 \) (s, 1 H), 8.54 (d, \( J = 5.2 \) Hz, 1 H), 8.08 (s, 1 H), 7.75 – 7.70 (m, 1 H), 7.66 (d, \( J = 8.7 \) Hz, 1 H), 7.59 (d, \( J = 5.4 \) Hz, 1 H);

\(^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta 151.3, 143.4, 134.1, 133.7, 129.6, 128.1 \) (2 C), 120.8,
**120.1.**

**Compound 1.105:** To a solution of 1.104 (1.8 g, 8.6 mmol) in PhH (17 ml, 0.5 M) was added LiCl (2.2 g, 51.6 mmol, 6 equiv), Pd(PPh₃)₄ (993 mg, 0.86 mmol, 0.1 equiv) and hexamethylditin (3.0 g, 9.0 mmol, 1.05 equiv). The solution was bubbled with Ar in a sonicator for 10 min. The reaction was then warmed to 105 °C. After 1 h, the reaction was diluted by EtOAc (100 ml), filterd through Celite® and rinsed with two portions of EtOAc (2 x 50 mL). The organic portion was washed with sat. aq. NaHCO₃ (100 ml) and brine (100 ml), dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica (1:2 Et₂O:hexanes) afforded 1.104 (2.2 g, 88%) as a white solid. \( R_f = 0.33 \) (1:1 Et₂O:hexanes); IR (neat) \( \nu_{\text{max}} \) = 3041, 2982, 2909, 1616, 1374, 1336, 1063, 1028, 847, 775, 760, 734 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 9.24 (s, 1 H), 8.50 (d, 1 H, \( J = 5.7 \) Hz), 7.78 (dd, \( J = 17.0, 8.0 \) Hz, 2 H), 7.61 (d, \( J = 5.7 \) Hz, 1 H), 0.38 (t, \( J = 26.6 \) Hz, 9 H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 152.3, 142.9, 142.2, 136.8, 135.6, 128.3, 125.4, 120.3, –9.4; HRMS (ESI-TOF) calcd for C₁₂H₁₅NSn [M+H]⁺: 294.0299; found: 294.0301.

**General Procedure A for synthesizing tertiary alcohol:** ArBr (3 equiv) was dissolved in Et₂O (0.63 M) and cooled to –78 °C. n-BuLi (2.5 M, 3.0 equiv) was added dropwise. After 40 minutes, the mixture was warmed up to room temperature and cannulated into a toluene solution of O-TBS-estrone\(^4\) (0.1 M, 1.0 equiv) at room temperature and stirred at that temperature for 40 minutes. The reaction was then quenched with sat. aq. NaHCO₃. The aqueous layer was extracted with EtOAc (3 times). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica.\(^5\)
Alcohol 1.110a: Prepared from O-TBS-estrone (50 mg, 0.129 mmol) according to general procedure A. Purification by flash chromatography (1:2 hexanes:CH₂Cl₂) afforded alcohol 1.110a (39 mg, 0.084 mmol, 65%) as a white solid (mp 156-159°C): Rₐ = 0.53 (1:4 pentanes:CH₂Cl₂); [α]D²₀ = +46.8° (c = 0.95, CH₂Cl₂); IR (neat) ν_{max} = 3459, 2929, 1495, 1252 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.51 (d, J = 7.7 Hz, 2 H), 7.36 (dd, J = 13.0, 6.1 Hz, 1 H), 7.09 (d, J = 8.5 Hz, 1 H), 6.65 (d, J = 8.4 Hz, 1 H), 6.63 (s, J = 2.6 Hz, 1 H), 2.96 – 2.84 (m, 2 H), 2.54 (ddd, J = 14.5, 9.7, 5.0 Hz, 1 H), 2.26 (dd, J = 13.1, 4.3 Hz, 1H), 2.22 – 2.12 (m, 1 H), 2.05 – 1.98 (m, 3 H), 1.98 – 1.91 (m, 1 H), 1.77 – 1.69 (m, 2 H), 1.61 – 1.46 (m, 3 H), 1.43 – 1.32 (m, 1 H), 1.19 (s, 3 H), 1.07 (s, 9 H), 0.71 (dt, J = 12.9 , 4.0 Hz, 1H), 0.19 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 153.4, 146.1, 137.8, 133.2, 127.5 (2 C), 127.4 (2 C), 127.0, 126.1, 120.0, 117.2, 86.1, 48.3, 47.1, 43.5, 39.6, 38.8, 33.8, 29.8, 27.6, 26.4, 25.9 (3 C), 24.3, 18.3, 15.0, -4.2 (2 C); HRMS (ESI-TOF) calcd for C₃₀H₄₃O₂Si [M+H]⁺: 463.3027; found: 463.3020.

Alcohol 1.110b: Prepared from O-TBS-estrone (48 mg, 0.125 mmol) according to general procedure A. Purification by flash chromatography (1:2 hexanes:CH₂Cl₂) afforded alcohol 1.110b (35 mg, 0.070 mmol, 56%) as a white solid (mp 120-123°C): Rₐ = 0.36 (1:5 hexanes:CH₂Cl₂); [α]D²₀ = +38.2° (c = 0.45, CH₂Cl₂); IR (neat) ν_{max} = 3476, 2931, 1496, 1253 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.30 (d, J = 8.2 Hz, 2 H), 7.00 (d, J = 8.5 Hz, 1 H), 6.56 (dd, J = 8.4 , 2.6 Hz, 1 H), 6.53 (d, J = 2.5, 1 H), 2.86 – 2.74 (m, 2 H), 2.42 (ddd, J = 14.6, 9.8, 5.1 Hz, 1 H), 2.36 (s, 3 H), 2.17 – 2.08 (m, 2 H), 1.93 – 1.83 (m, 4 H), 1.66 – 1.57 (m, 2 H), 1.51 – 1.35 (m, 3 H), 1.33 – 1.24 (m, 1 H), 1.09 (s, 3 H), 0.97 (s, 9 H), 0.65 (dt, J = 12.9 , 4.1 Hz, 1H), 0.18 (s, 6 H);
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 153.3, 143.2, 137.9, 136.5, 133.3, 128.2 (2 C), 127.4 (2 C), 126.2, 120.0, 117.2, 86.0, 48.3, 47.1, 43.5, 39.6, 38.8, 33.8, 29.8, 27.6, 26.4, 25.9 (3 C), 24.2, 21.1, 18.3, 14.9, -4.2 (2 C); HRMS (ESI-TOF) calcd for C$_{31}$H$_{44}$O$_2$SiNa $[M+Na]^{+}$: 499.3003; found: 499.2988.

**Alcohol 1.110c:** Prepared from O-TBS-estrone (49 mg, 0.127 mmol) according to general procedure A. Purification by flash chromatography (1:2 hexanes:CH$_2$Cl$_2$) afforded alcohol **1.110c** (25 mg, 0.051 mmol, 40%) as a white foam: $R_f = 0.30$ (1:5 hexanes:CH$_2$Cl$_2$); $[\alpha]^D_{20} = +38.2^\circ$ (c = 0.3, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}}$ = 3463, 2928, 1607, 1497, 1251 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 (d, $J = 8.5$ Hz, 2 H), 7.01 (d, $J = 8.4$ Hz, 1 H), 6.89 (d, $J = 8.7$ Hz, 2 H), 6.57 (dd, $J = 8.4$, 2.3 Hz, 1 H), 6.54 (d, $J = 2.0$ Hz, 1 H), 3.83 (s, 3 H), 2.87 – 2.75 (m, 2 H), 2.41 (ddd, $J = 14.4$, 9.7, 4.9 Hz, 1 H), 2.18 – 2.10 (m, 2 H), 1.93 - 1.83 (m, 4 H), 1.66 – 1.57 (m, 2 H), 1.51 – 1.21 (m, 4 H), 1.09 (s, 3 H), 0.98 (s, 9 H), 0.67 (dt, $J = 12.9$, 4.0 Hz, 1H), 0.19 (s, 6 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.3, 153.3, 138.2, 137.9, 133.2, 128.6 (2 C), 126.1, 120.0, 117.2, 112.8 (2 C), 85.8, 55.4, 48.3, 47.0, 43.5, 39.6, 38.8, 33.7, 29.8, 27.6, 26.4, 25.8 (3 C), 24.2, 18.3, 14.9, -4.3 (2 C); HRMS (ESI-TOF) calcd for C$_{31}$H$_{45}$O$_3$Si $[M+H]^+$: 493.3132; found: 493.3130.

**Alcohol 1.110d:** Prepared from O-TBS-estrone (50 mg, 0.131 mmol) according to general procedure A. Purification by flash chromatography (2:3 hexanes:EtOAc) afforded alcohol **1.110d** (34 mg, 0.073 mmol, 56%) as a white foam: $R_f = 0.3$ (1:2 hexanes:EtOAc); $[\alpha]^D_{20} = +39.0^\circ$ (c = 0.41, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}}$ = 3237, 2929, 1496, 1252 cm$^{-1}$; $^1$H NMR(400 MHz, CDCl$_3$) $\delta$ 8.56 (s, 1 H), 8.41 (d, $J = 3.8$ Hz, 1 H), 7.79 (d, $J = 7.9$ Hz 1 H), 7.27 – 7.25 (m, 1 H), 7.02 (d, $J = 8.4$ Hz, 1 H), 6.59 (dd, $J = 8.4$, 2.5 Hz, 1 H), 6.55 (d, $J = 2.4$, 1 H), 3.65 – 3.35 (b, 1 H), 2.89 – 2.76 (m, 2 H), 2.39 (ddd, $J =$...
14.5, 9.6, 5.1 Hz, 1 H), 2.23 – 2.11 (m, 2 H), 1.93 – 1.83 (m, 3 H), 1.72 – 1.63 (m, 2 H), 1.55 – 1.39 (m, 2 H), 1.36 – 1.24 (m, 2 H), 1.13 (s, 3 H), 0.99 (s, 9 H), 0.56 (dt, J = 12.7, 3.9 Hz, 1H), 0.20 (s, 6 H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 153.3, 148.5, 147.74, 141.8, 137.7, 135.4, 132.9, 126.1, 122.4, 120.0, 117.2, 84.6, 48.3, 47.2, 43.4, 39.5, 38.5, 33.5, 29.7, 27.5, 26.2, 25.8 (3 C), 24.1, 18.2, 14.8, -4.3 (2 C); HRMS (ESI-TOF) calcd for C\textsubscript{29}H\textsubscript{42}NO\textsubscript{2}Si [M+H]\textsuperscript{+}: 464.2979; found: 464.2984.

**Alcohol 1.110g:** Prepared from O-TBS-estrone (202 mg, 0.527 mmol) according to general procedure A. Purification by flash chromatography (1:2 hexanes:CH\textsubscript{2}Cl\textsubscript{2}) afforded alcohol 1.110g (190 mg, 0.358 mmol, 68%) as a white foam: R\textsubscript{f} = 0.6 (1:4 pentanes:CH\textsubscript{2}Cl\textsubscript{2}); [α]\textsubscript{D}\textsubscript{20} = +40.2° (c = 0.51, CH\textsubscript{2}Cl\textsubscript{2}); IR (neat) ν\textsubscript{max} = 3443, 2927, 1496, 1328 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.60 (d, J = 8.5 Hz, 2 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.00 (d, J = 8.4 Hz, 1 H), 6.57 (dd, J = 8.4, 2.2 Hz, 1 H), 6.54 (s, 1 H), 2.88 – 2.75 (m, 2 H), 2.44 (ddd, J = 14.3, 9.6, 4.9 Hz, 1 H), 2.21 – 2.10 (m, 2 H), 1.96 – 1.83 (m, 4 H), 1.73 – 1.59 (m, 2 H), 1.55 – 1.20 (m, 4 H), 1.11 (s, 3 H), 0.98 (s, 9 H), 0.55 (dt, J = 12.7, 3.7 Hz, 1H), 0.19 (s, 6 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 153.4, 150.1, 137.7, 132.9, 129.1 (q, J\textsubscript{CF} = 32.2 Hz), 127.85 (2 C), 124.4 (q, J\textsubscript{CF} = 271.8 Hz), 124.3 (q, J\textsubscript{CF} = 3.57 Hz, 2 C), 126.1, 120.0, 117.2, 86.1, 48.4, 47.3, 43.4, 39.6, 38.9, 33.6, 29.7, 27.5, 26.2, 25.8 (3 C), 24.2, 18.3, 14.9, -4.3 (2 C); HRMS (ESI-TOF) calcd for C\textsubscript{31}H\textsubscript{42}F\textsubscript{3}O\textsubscript{2}Si [M+H]\textsuperscript{+}: 531.2901; found: 531.2905.

**Alcohol 1.110f:** 4-FC\textsubscript{6}H\textsubscript{4}I (0.78 mmol, 173 mg, 90 µl, 1.1 equiv) was dissolved in toluene (8.1 mL, 0.96 M) and cooled to −78 °C, after which n-BuLi (2.27 M, 0.78 mmol, 378 µl, 1.1 equiv) was added dropwise. After 40 minutes, the ArLi solution was warmed up to room temperature and cannulated into O-TBS-estrone (300 mg, 0.781 mmol, 1
equiv) in toluene (3.9 mL, 0.2 M) and the mixture was stirred for 30 minutes. The reaction was then quenched with sat. aq. NaHCO$_3$ (10 mL). The aqueous layer was extracted with EtOAc (20 mL × 4). The combined organics were dried over MgSO$_4$, filtered, and concentrated in vacuo. Chromatography on silica (6% EtOAc in hexanes) afforded alcohol 1.110f (263.5 mg, 0.549 mmol, 70%) as a white solid (mp 155-159°C): $R_f = 0.32$ (1:4 hexanes:CH$_2$Cl$_2$); $[\alpha]_{D20}^0 = +55.1^\circ$ (c = 1.45, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}}$ = 3462, 2928, 1605, 1496, 1252 cm$^{-1}$; $^1$H NMR(400 MHz, CDCl$_3$) $\delta$ 7.37 (dd, $J = 7.5, 5.2$ Hz, 2 H), 7.08 – 7.00 (m, 3 H), 6.57 (d, $J = 8.5$ Hz, 1 H), 6.54 (s, 1 H), 2.86 – 2.75 (m, 2 H), 2.44 (ddd, $J = 14.5, 9.7, 5.0$ Hz, 1 H), 2.17 – 2.10 (m, 2 H), 1.92 – 1.83 (m, 4 H), 1.67 – 1.58 (m, 2 H), 1.51 – 1.38 (m, 2 H), 1.35 – 1.25 (m, 2 H), 1.09 (s, 3 H), 0.98 (s, 9 H), 0.60 (dt, $J = 12.8, 3.8$ Hz, 1H), 0.18 (s, 6 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.6 (d, $J_{CF} = 245.3$ Hz), 154.1, 142.5 (d, $J_{CF} = 3.0$ Hz), 138.6, 133.8, 129.9 (d, $J_{CF} = 7.7$ Hz, 2 C), 126.9, 120.7, 118.0, 114.9 (d, $J_{CF} = 21.0$ Hz, 2 C), 86.6, 49.0, 47.8, 44.3, 40.3, 39.7, 34.4, 30.5, 28.3, 27.1, 26.6 (3 C), 24.9, 19.1, 15.6, -4.3 (2 C); HRMS (ESI-TOF) calcd for C$_{30}$H$_{42}$FO$_2$Si [M+H]$^+$: 481.2932; found: 481.2944.

**Alcohol 1.110e:** To a THF solution of 7-bromoisoquinoline (40 mg, 0.193 mmol, 1 mL, 0.19 M, 3 equiv) was added n-BuLi (88 µL, 2.3 M, 0.19 mmol, 3 equiv) dropwise at –78 °C. After 40 minutes, TMEDA (88 µL, 0.58 mmol, 9 equiv) was added and the mixture was stirred at –78 °C for 10 minutes. A THF solution of O-TBS-estrone (25 mg, 0.065 mmol, 1 equiv, 0.3 mL, 0.22 M) was added and the reaction mixture was stirred for 40 minutes at –78 °C. The reaction was quenched with sat. aq. NaHCO$_3$ (10 mL). The aqueous layer was extracted with EtOAc (20 mL × 4). The combined organics were dried over MgSO$_4$, filtered, and concentrated in vacuo. Chromatography on silica (30% EtOAc
in hexanes) afforded alcohol 1.110e (25 mg, 0.049 mmol, 74%) as a yellow solid (mp 183-185°C): $R_f = 0.31$ (1:1 EtOAc:CH$_2$Cl$_2$); $[\alpha]^D_{20} = +16.9^\circ$ (c = 0.54, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}} = 3210, 1496, 1285, 1251, 837 \text{ cm}^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.28 (s, 1 H), 8.51 (d, $J = 4.8$ Hz, 1 H), 7.88 (d, $J = 7.8$ Hz, 2 H), 7.79 (d, $J = 8.9$ Hz, 1 H), 7.65 (d, $J = 5.6$ Hz, 1 H), 6.95 (d, $J = 8.3$ Hz, 1 H), 6.55 – 6.50 (m, 2 H), 2.73 – 2.87 (m, 2 H), 2.59 (ddd, $J = 14.8$, 9.8, 5.1 Hz, 1 H), 2.25 (ddd, $J = 17.1$, 12.5, 4.4 Hz, 1 H), 2.10 – 2.00 (m, 2 H), 1.96 – 1.91 (m, 1 H), 1.79 (td, $J = 11.2$, 4.0 Hz, 1 H), 1.75 – 1.65 (m, 2 H), 1.55 – 1.45 (m, 1 H), 1.47 – 1.32 (m, 1 H), 1.33 – 1.22 (m, 2 H), 1.15 (s, 3 H), 0.95 (s, 9 H), 0.57 (td, $J = 12.8$, 4.1 Hz, 1 H), 0.16 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 153.2, 152.8, 145.2, 142.9, 137.6, 134.6, 132.8, 130.8, 127.9, 125.9, 125.3, 125.2, 120.0, 119.8, 117.0, 86.1, 48.3, 47.4, 43.3, 39.5, 38.9, 33.7, 29.6, 27.4, 26.1, 25.7 (3 C), 24.2, 18.1, 14.8, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{33}$H$_{44}$NO$_2$Si [M+H]$^+$: 514.3136; found: 514.3140.

**Alcohol 1.112**: O-TBS-estrone (30 mg, 0.078 mmol, 1 equiv) was dissolved in toluene (0.78 mL, 0.1 M). n-BuLi (2.5 M, 0.23 mL, 3 equiv) was added dropwise at room temperature and stirred for 40 minutes. The reaction was then quenched with sat. aq. NaHCO$_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were dried over MgSO$_4$, filtered, and concentrated in vacuo. Chromatography on silica (10% EtOAc in hexanes) afforded alcohol 1.112 (22.5 mg, 0.051 mmol, 65 %) as a white solid (mp 85-89°C): $R_f = 0.30$ (1:4 hexanes:CH$_2$Cl$_2$); $[\alpha]^D_{20} = +26.9^\circ$ (c = 0.84, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}} = 3443, 2930, 1605, 1496, 1286, 1252, 954 \text{ cm}^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.12 (d, $J = 8.5$ Hz, 1 H), 6.61 (dd, $J = 8.4$, 2.5 Hz, 1 H), 7.08 – 7.00 (m, 3 H), 6.55 (d, $J = 2.4$ Hz, 1 H), 2.86 – 2.75 (m, 2 H), 2.34 –
2.26 (m, 1 H), 2.18 – 2.13 (m, 1 H), 2.05 – 1.99 (m, 1 H), 1.90 – 1.85 (m, 1 H), 1.66 – 1.51 (m, 6 H), 1.51 – 1.49 (m, 4 H), 1.43 – 1.23 (m, 6 H), 0.98 (s, 9 H), 0.95 (t, J = 7.1 Hz, 3H), 0.91 (s, 3 H), 0.19 (s, 6 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.3, 137.9, 133.1, 126.1, 126.1, 119.9, 117.1, 83.5, 49.5, 46.7, 43.9, 39.6, 36.5, 34.4, 31.6, 29.7, 27.6, 26.3, 25.9, 25.7 (3 C), 23.6, 23.4, 18.2, 14.4, 14.3, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{28}$H$_{47}$O$_2$Si [M+H]$^+$: 443.3340; found: 443.3324.

**General Procedure B to synthesize styrene 1.108:** Vinyl triflate$^2$ (1.0 equiv), ArB(OH)$_2$ (1.3 equiv) and Pd(dppf)Cl$_2$ (10 mmol%) were dissolved in DME (0.1 M) and 2 M NaOH (1.3 equiv) was added. The solution was degassed for 10 minutes by bubbling with Ar under sonication. The reaction was then immersed in an oil bath preheated to 80°C for 1 hour. The reaction was allowed to cool to ambient temperature, diluted with EtOAc, and washed with sat. aq. NaHCO$_3$. The aqueous layer was extracted with EtOAc (3 times). The combined organic portions were washed with sat. aq. NaCl, dried over MgSO$_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica. (Note: vinyl triflate was prepared according to ref. 4 and 90% yield from O-TBS-Estrone)

**Stryrene 1.108a:** Prepared from vinyl triflate (48 mg, 0.093 mmol) according to general procedure B. Purification by flash chromatography (15:1 hexanes:CH$_2$Cl$_2$) afforded stryrene 1.108a (34 mg, 0.076 mmol, 82%) as a white solid (mp 108-111°C): $R_f = 0.27$ (9:1 hexanes:CH$_2$Cl$_2$); $[α]_{D}^{20} = +29.7°$ (c = 0.4, CH$_2$Cl$_2$); IR (neat) $ν_{max} = 2932, 1495, 1258 \text{ cm}^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41 (dd, $J$ = 8.3, 1.3 Hz, 2H), 7.33 – 7.28 (m, 2 H), 7.25 – 7.21 (m, 1 H), 7.12 (d, $J$ = 8.4 Hz, 1 H), 6.62 (dd, $J$ = 8.4, 2.6 Hz, 1 H), 6.58 (d, $J$ = 2.6 Hz, 1 H), 5.94 (dd, $J$ = 3.2, 1.8 Hz, 1 H), 2.94 – 2.80 (m, 2 H), 2.38 – 2.27 (m,
3 H), 2.20 (dd, J = 8.5, 2.3 Hz, 1H), 2.12 (ddd, J = 15.5, 11.4, 1.7 Hz, 1H), 1.98 – 1.92 (m, 1H), 1.80 (dt, J = 11.3, 6.5 Hz, 1H), 1.72 – 1.61 (m, 3H), 1.52 – 1.41 (m, 1H), 1.07 (s, 3H), 0.98 (s, 9H), 0.19 (s, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 155.1, 153.5, 138.0, 137.5, 133.5, 128.3 (2C), 127.4, 126.9, 126.8 (2C), 126.0, 120.1, 117.2, 57.0, 47.7, 44.3, 37.4, 35.7, 31.5, 29.7, 27.9, 26.7, 25.9 (3C), 18.3, 16.9, -4.2 (2C); HRMS (ESI-TOF) calcd for C\textsubscript{30}H\textsubscript{41}OSi [M+H]\textsuperscript{+}: 445.2921; found: 445.2903.

**Styrene 1.108b**: Prepared from vinyl triflate (49 mg, 0.095 mmol) according to general procedure B. Purification by flash chromatography (15:1 hexanes:CH\textsubscript{2}Cl\textsubscript{2}) afforded styrene \textbf{1.108b} (37 mg, 0.081 mmol, 85%) as a white solid (mp 103-107°C): R\textsubscript{f} = 0.31(10% CH\textsubscript{2}Cl\textsubscript{2} in hexanes); [α]\textsubscript{D}\textsuperscript{20} = +24.2° (c = 0.75, CH\textsubscript{2}Cl\textsubscript{2}); IR (neat) \nu\textsubscript{max} = 2931, 1738, 1494, 1251 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.32 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.0 Hz, 3H), 6.63 (dd, J = 8.4, 2.6 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 5.91 (dd, J = 3.2, 1.7 Hz, 1H), 2.95 – 2.81 (m, 2H), 2.40 (s, 1H), 2.36 (s, 3H), 2.34 – 2.28 (m, 2H), 2.21 (dd, J = 8.4, 2.4 Hz, 1H), 2.11 (ddd, J = 15.4, 11.3, 1.6 Hz, 1H), 1.99 – 1.93 (m, 1H), 1.79 (dt, J = 11.3, 6.4 Hz, 1H), 1.73 – 1.62 (m, 3H), 1.54 – 1.42 (m, 1H), 1.07 (s, 3H), 1.00 (s, 9H), 0.21 (s, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 154.8, 153.3, 136.8, 134.4, 128.8 (2H), 126.6 (2H), 126.3, 125.8, 120.0, 117.2, 56.8, 47.5, 44.2, 37.3, 35.3, 31.3, 29.6, 27.8, 26.6, 25.7 (3H), 21.1, 18.2, 16.7, -4.4 (2H); HRMS (ESI-TOF) calcd for C\textsubscript{31}H\textsubscript{43}OSi [M+H]\textsuperscript{+}: 459.3078; found: 459.3087.

**Styrene 1.108c**: Prepared from vinyl triflate (51 mg, 0.099 mmol) according to general procedure B. Purification by flash chromatography (15:1 hexanes:CH\textsubscript{2}Cl\textsubscript{2}) afforded styrene \textbf{1.108c} (38 mg, 0.080 mmol, 81%) as a white solid (mp 96-101°C): R\textsubscript{f} = 0.28 (4:1 hexanes:CH\textsubscript{2}Cl\textsubscript{2}); [α]\textsubscript{D}\textsuperscript{20} = +25.8° (c = 0.31, CH\textsubscript{2}Cl\textsubscript{2}); IR (neat) \nu\textsubscript{max} = 2928, 1497, 1251
H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.32 (d, J = 8.8 Hz, 2 H), 7.13 (d, J = 8.4 Hz, 1 H), 6.86 (d, J = 8.8 Hz, 2 H), 6.62 (dd, J = 8.4, 2.6 Hz, 1 H), 6.58 (d, J = 2.5 Hz, 1 H), 5.85 (dd, J = 3.1, 1.7 Hz, 1 H), 3.82 (s, 3 H), 2.95 – 2.81 (m, 2 H), 2.39 – 2.27 (m, 3 H), 2.19 (dd, J = 8.5, 2.3 Hz, 1 H), 2.10 (ddd, J = 15.4, 11.3, 1.6 Hz, 1 H), 1.98 – 1.92 (m, 1 H), 1.78 (dt, J = 11.3, 6.5 Hz, 1 H), 1.72 – 1.61 (m, 3 H), 1.47 (ddd, J = 24.1, 11.7, 6.8 Hz, 1 H), 1.05 (s, 3 H), 0.99 (s, 9 H), 0.20 (s, 6 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 158.5, 154.4, 153.3, 137.9, 133.3, 129.9, 127.8 (2 C), 125.8, 125.4, 120.0, 117.1, 113.5 (2 C), 56.8, 55.2, 47.5, 44.2, 37.3, 35.6, 31.2, 29.6, 27.8, 26.6, 25.7 (3 C), 18.2, 16.7, -4.4 (2 C); HRMS (ESI-TOF) calcd for C\textsubscript{31}H\textsubscript{43}O\textsubscript{2}Si [M+H]\textsuperscript{+}: 475.3027; found: 475.3010.

Styrene 1.108d: Prepared from vinyl triflate (49 mg, 0.094 mmol) according to general procedure B. Purification by flash chromatography (2:1 EtOAc:hexanes) afforded styrene 1.108d (26 mg, 0.058 mmol, 62%) as a white foam: R\textsubscript{f} = 0.5 (1:1 hexanes:EtOAc); [α]\textsuperscript{D}\textsubscript{20} = +24.1° (c = 0.85, CH\textsubscript{2}Cl\textsubscript{2}); IR (neat) ν\textsubscript{max} = 2930, 1496, 1380, 1253, 1188 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.66 (s, 1 H), 8.48 (s, 1 H), 7.71(d, J = 7.88 Hz, 1 H), 7.71 – 7.69 (m, 1 H), 7.12 (d, J = 8.42 Hz, 1 H), 6.62 (dd, J = 8.4, 2.6 Hz, 1 H), 6.58 (d, J = 2.6 Hz, 1 H), 6.03 (dd, J = 3.2, 1.8 Hz, 1 H), 2.94 – 2.82 (m, 2 H), 2.39 – 2.27 (m, 3 H), 2.18 – 2.10 (m, 2 H), 1.98 – 1.92 (m, 1 H), 1.81 (dt, J = 11.5, 6.5 Hz, 1 H), 1.72 – 1.60 (m, 3 H), 1.48 (ddd, J = 17.7, 11.8, 6.0 Hz, 1 H), 1.05 (s, 3 H), 0.98 (s, 9 H), 0.20 (s, 6 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 153.5, 151.7, 147.3, 147.2, 137.9, 133.2, 129.6, 126.9, 125.9, 123.6, 120.1, 117.3, 113.5, 56.9, 47.9, 44.2, 37.3, 35.6, 31.7, 29.6, 27.9, 26.6, 25.9 (3 C), 18.3, 16.9, -4.2 (2 C); HRMS (ESI-TOF) calcd for C\textsubscript{29}H\textsubscript{40}NOSi [M+H]\textsuperscript{+}: 446.2874; found: 446.2863.
**General procedure C to synthesize styrene 1.108:** To a solution of alcohol (1.0 equiv) in benzene (0.03 M) was added Methyl N-(triethylammoniumsulphonyl)carbamate (5.0 equiv). The reaction was then immersed in a preheated oil bath at 50°C. After 2 hours, the reaction was allowed to cool to ambient temperature and diluted with EtOAc. The reaction was washed with H₂O and sat. aq. NaCl, dried over MgSO₄, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on silica.

**Styrene 1.108f:** Prepared from alcohol 1.110f (117 mg, 0.243 mmol) according to general procedure C. Purification by flash chromatography (1:6 CH₂Cl₂:hexanes) afforded styrene 1.108f (92 mg, 0.197 mmol, 81%) as a white solid (mp 140–144°C): Rₐf = 0.33 (1:6 CH₂Cl₂:hexanes); [α]²⁰ D = +32.5° (c = 0.54, CH₂Cl₂); IR (neat) ν max = 2930, 1497, 1255 cm⁻¹;¹H NMR (400 MHz, CDCl₃) δ 7.39 (dd, J = 8.7, 5.5 Hz, 2 H), 7.17 (d, J = 8.4 Hz, 1 H), 7.03 (t, J = 8.8 Hz, 2 H), 6.68 (dd, J = 8.4, 2.5 Hz, 1 H), 6.63 (d, J = 2.2 Hz, 1 H), 5.92 (dd, J = 2.8, 1.5 Hz, 1 H), 2.99 – 2.85 (m, 2 H), 2.42 – 2.31 (m, 3 H), 2.19 – 2.11 (m, 2 H), 2.05 – 1.97 (m, 1 H), 1.82 (dt, J = 11.3, 6.5 Hz, 1 H), 1.76 – 1.66 (m, 3 H), 1.51 (dq, J = 12.2, 11.8, 6.8 Hz, 1 H), 1.05 (s, 3 H), 1.04 (s, 9 H), 0.25 (s, 6 H);¹³C NMR (100 MHz, CDCl₃) δ 162.1 (d, J CF = 245.7 Hz) 154.2, 153.5, 138.0, 133.5 (d, J CF = 3.3 Hz), 128.4 (d, J CF = 7.7 Hz, 2 C), 127.1, 126.0, 120.2, 117.3, 115.1 (d, J CF = 21.1 Hz, 2 C), 57.0, 47.8, 44.3, 37.5, 35.7, 31.4, 29.7, 27.9, 26.7, 25.9 (3 C), 18.3, 16.8, -4.2 (2 C) ; HRMS (ESI-TOF) calcd for C₃₀H₄₁FOSi [M+H]+: 463.2872; found: 463.2835.

**Styrene 1.108g:** Prepared from alcohol 1.110g (100 mg, 0.188 mmol) according to general procedure C. Purification by flash chromatography (1:5 CH₂Cl₂:hexanes) afforded styrene 1.108g (82 mg, 0.160 mmol, 85%) as a white solid (mp 75-81°C): Rₐf = 0.32 (1:6 CH₂Cl₂:hexanes); [α]²⁰ D = +18.8° (c = 0.67, CH₂Cl₂); IR (neat) ν max = 2930,
1497, 1325, 1125 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, J = 26.4, 8.3 Hz, 4 H), 7.18 (d, J = 8.4 Hz, 1 H), 6.69 (dd, J = 8.4, 2.6 Hz, 1 H), 6.65 (d, J = 2.4 Hz, 1 H), 6.09 (dd, J = 3.1, 1.7 Hz, 1 H), 3.00 – 2.81 (m, 2 H), 2.46 – 2.32 (m, 3 H), 2.32 – 2.26 (m, 2 H), 2.05 – 1.98 (m, 1 H), 1.85 (dt, J = 11.4, 6.5 Hz, 1 H), 1.78 – 1.65 (m, 3 H), 1.56 – 1.43 (m, 1 H), 1.13 (s, 3 H), 1.05 (s, 9 H), 0.26 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 154.0, 153.5, 141.0, 137.9, 133.2, 129.5, 128.7 (q, J_CF = 32.3 Hz), 126.9, 126.5 (q, J_CF = 32.3 Hz), 125.9, 125.1 (q, J_CF = 3.7 Hz, 2 C), 121.7 (q, J_CF = 269.7 Hz), 120.1, 117.3, 56.9, 47.8, 44.2, 37.3, 35.5, 31.6, 29.6, 27.8, 26.6, 25.8 (3 C), 18.2, 16.9, -4.3 (2 C) ;


**Stryene 1.108e**: To a solution of vinyl triflate (134 mg, 0.26 mmol, 1.0 equiv) in DMSO (2.6 mL, 0.1 M) was added 7-trimethylstannylisoquinoline (152 mg, 0.52 mmol, 2.0 equiv), CuCl (254 mg, 2.6 mmol, 10 equiv), LiCl (110 mg, 2.6 mmol, 10 equiv) and Pd(PPh₃)₄ (300 mg, 0.26 mmol, 0.1 equiv). The solution was bubbled with Ar under sonication for 10 minutes. The reaction was then immersed in a preheated oil bath at 60°C. After 2 hours, the reaction was allowed to cool to ambient temperature and diluted with EtOAc (10 mL) and washed with 5% NH₄OH (10 mL). The aqueous layer was extracted with EtOAc (10 mL × 4). The combined organic portions were washed with sat. aq. NaCl (20 mL), dired over MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica (1:4 EtOAc:hexanes) afforded Styrene 1.108e (103 mg, 0.208 mmol, 79%) as a white foam: R_f = 0.35 (1:3 EtOAc:hexanes); [α]D²₀ = +22.5° (c = 0.08, CH₂Cl₂); IR (neat) ν_max = 2925, 2854, 1604, 1496, 1250, 954, 840, 781 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.23 (s, 1 H), 8.48 (d, J = 5.6 Hz, 1 H), 7.95 (s, 1 H), 7.77 (dd, J = 15.8, 8.5 Hz, 2 H), 7.62 (d, J = 5.5 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 1 H), 6.63 (dd, J = 8.1,
2.0 Hz, 1H), 6.59 (s, 1 H), 6.15 (d, J = 1.2 Hz, 1 H), 2.95 – 2.81 (m, 2 H), 2.43 – 2.35 (m, 1 H), 2.03 – 1.94 (m, 1 H), 1.86 (ddd, J = 17.9, 11.4, 6.5 Hz, 1 H), 1.78 – 1.66 (m, 2 H), 1.53 – 1.46 (m, 1 H), 1.40 – 1.28 (m, 2 H), 1.15 (s, 3 H), 0.98 (s, 9 H), 0.88 (t, J = 6.8 Hz, 1 H), 0.20 (s, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 154.1, 153.3, 152.6, 142.7, 137.8, 136.2, 134.7, 133.1, 130.2, 129.1, 128.8, 126.2, 125.8, 123.8, 124.0, 120.2, 120.0, 117.0, 56.9, 47.8, 44.1, 37.2, 35.6, 31.5, 27.7, 26.5, 25.7 (3 C), 18.2, 16.8, 1.0, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{33}$H$_{42}$NO$_2$Si [M+H]$^+$: 496.3030; found: 496.3036.

**General Procedure for the Standardization of Raney Nickel (Ra-Ni):** Raney® 2800 Nickel (ca. 1 g of a 1g/mL slurry in H$_2$O, pH = 9, Sigma-Aldrich) was placed in a vial. The water was removed by pipette, and the Ra-Ni was washed by 5 seconds of shaking, followed by removal of the supernatant: first H$_2$O (2 x 2 mL), then sat. aq. Rochelle’s salt (2 x 2 mL), then H$_2$O (10 x 2 mL). After all washes, the Ra-Ni aqueous solution (pH = 7) was stored under H$_2$O (1 mL).

**General Procedure D for hydrogenation:** To a solution of styrene in i-PrOH/toluene (9:1, 0.01 M), was added the suspension of Ra-Ni prepared above (the Ra-Ni suspension was removed by 5.75’ pipette from the thick bottom layer of the vial; 1 drop suspension per 0.1 mL solution). The reaction flask was immersed in an oil bath preheated to 60 °C and stirred vigorously for 120 minutes. After cooling to ambient temperature, the reaction mixture was passed through Celite, the Ra-Ni washed by CH$_2$Cl$_2$, and the combined filtrates were concentrated in vacuo. The product was purified by flash column chromatography.

**1.109a:** Prepared from Styrene 1.108a (15 mg, 0.033 mmol) according to general procedure D. Purification by flash chromatography (15:1 hexanes:CH$_2$Cl$_2$) afforded
1.109a (14.3 mg, 0.032 mmol, 97%) as a white solid (mp 110-113°C): $R_f = 0.60$ (1:3 CH$_2$Cl$_2$:hexanes); $[\alpha]^{D}_{20} = +3.1^\circ$ (c = 0.48, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}}$ = 2925, 1495, 1253 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31 – 7.19 (m, 5 H), 7.11 (d, $J = 8.5$ Hz, 1 H), 6.60 (dd, $J = 8.5$, 2.5 Hz, 1 H), 6.55 (d, $J = 2.5$ Hz, 1 H), 2.85 – 2.82 (m, 3 H), 2.78 (t, $J = 10.0$ Hz, 1 H), 2.28 – 2.24 (m, 2 H), 2.19 – 2.12 (m, 1 H), 2.05 – 1.87 (m, 3 H), 1.72 – 1.70 (m, 1 H), 1.48 – 1.42 (m, 6 H), 0.98 (s, 9 H), 0.51 (s, 3 H), 0.18 (s, 6 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 153.2, 138.0, 137.9, 135.4, 133.4, 128.6 (2 C), 128.4 (2 C), 126.1, 119.9, 117.1, 56.8, 55.3, 44.4, 44.1, 39.2, 37.8, 29.7, 26.33, 26.29, 25.7 (3 C), 24.2, 21.0, 18.2, 12.8, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{30}$H$_{43}$OSi [M+H]$^+$: 447.3078; found: 447.3078.

1.109b: Prepared from Styrene 1.108b (17 mg, 0.037 mmol) according to general procedure D. Purification by flash chromatography (15:1 hexanes:CH$_2$Cl$_2$) afforded 1.109b (16.7 mg, 0.036 mmol, 98%) as a white solid (mp 108-112°C): $R_f = 0.60$ (1:3 CH$_2$Cl$_2$:hexanes); $[\alpha]^{D}_{20} = +5.1^\circ$ (c = 0.82, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}}$ = 2930, 1497, 1254 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.14 – 7.10 (m, 5 H), 6.60 (dd, $J = 8.5$, 2.5 Hz, 1 H), 6.55 (d, $J = 2.5$ Hz, 1 H), 2.87 – 2.78 (m, 3 H), 2.74 (t, $J = 10.0$ Hz, 1 H), 2.33 (s, 3 H), 2.27 – 2.24 (m, 2 H), 2.14 – 2.09 (m, 1 H), 2.05 – 1.86 (m, 3 H), 1.71 – 1.69 (m, 1 H), 1.46 – 1.40 (m, 6 H), 0.98 (s, 9 H), 0.51 (s, 3 H), 0.19 (s, 6 H); $^{13}$C NMR $\delta$ 153.2, 138.0, 137.9, 135.4, 133.4, 128.6 (2 C), 128.4 (2 C), 126.1, 119.9, 117.1, 56.8, 55.3, 44.4, 44.1, 39.2, 37.8, 29.7, 26.33, 26.29, 25.7 (3 C), 24.2, 21.0, 18.2, 12.8, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{30}$H$_{43}$OSi[M+H]$^+$: 461.3234; found: 461.3236.

1.109c: Prepared from Styrene 1.108c (15 mg, 0.031 mmol) according to general procedure D. Purification by flash chromatography (15:1 hexanes:CH$_2$Cl$_2$) afforded 1.109c (14.0 mg, 0.029 mmol, 93%) as a white solid (mp 110-113°C): $R_f = 0.26$ (1:3 CH$_2$Cl$_2$:hexanes); $[\alpha]^{D}_{20} = +3.1^\circ$ (c = 0.48, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}}$ = 2925, 1495, 1253 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31 – 7.19 (m, 5 H), 7.11 (d, $J = 8.5$ Hz, 1 H), 6.60 (dd, $J = 8.5$, 2.5 Hz, 1 H), 6.55 (d, $J = 2.5$ Hz, 1 H), 2.85 – 2.82 (m, 3 H), 2.78 (t, $J = 10.0$ Hz, 1 H), 2.28 – 2.24 (m, 2 H), 2.19 – 2.12 (m, 1 H), 2.05 – 1.87 (m, 3 H), 1.72 – 1.70 (m, 1 H), 1.48 – 1.42 (m, 6 H), 0.98 (s, 9 H), 0.51 (s, 3 H), 0.18 (s, 6 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 153.2, 138.0, 137.9, 135.4, 133.4, 128.6 (2 C), 128.4 (2 C), 126.1, 119.9, 117.1, 56.8, 55.3, 44.4, 44.1, 39.2, 37.8, 29.7, 26.33, 26.29, 25.7 (3 C), 24.2, 21.0, 18.2, 12.8, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{30}$H$_{43}$OSi[M+H]$^+$: 487.3078; found: 487.3078.
CH$_2$Cl$_2$:hexanes); $[\alpha]^{D}_{20} = +1.8^\circ$ (c = 0.33, CH$_2$Cl$_2$); IR (neat) $\nu_{max} = 2924, 1258$ cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.16 (d, $J = 9.0$ Hz, 2 H), 7.10 (d, $J = 8.5$ Hz, 1 H), 6.84 (d, $J = 9.0$ Hz, 2 H), 6.59 (dd, $J = 8.5$, 2.5 Hz, 1 H), 6.51 (d, $J = 2.5$ Hz, 1 H), 2.86 – 2.78 (m, 2 H), 2.72 (t, $J = 9.5$ Hz, 1 H), 2.29 – 2.23 (m, 2 H), 2.12 – 1.85 (m, 4 H), 1.70 – 1.67 (m, 1 H), 1.43 – 1.40 (m, 6 H), 0.98 (s, 9 H), 0.50 (s, 3 H), 0.18 (s, 6 H); $^{13}$C NMR $\delta$ 157.9, 153.2, 137.9, 133.3, 133.1, 129.5 (2 C), 126.1, 119.9, 117.1, 113.1 (2 C), 56.3, 55.2, 44.4, 44.1, 39.2, 37.7, 29.74, 29.71, 27.8, 26.3, 26.3, 25.7 (3 C), 24.2, 21.0, 18.2, 12.7, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{31}$H$_{45}$O$_2$Si [M+H]$^+$: 477.3183; found: 477.3193.

$\bf{1.109d}$: Prepared from Styrene $\bf{1.108d}$ (6.3 mg, 0.014 mmol) according to general procedure D. Purification by flash chromatography (2:1 hexanes:EtOAc) afforded $\bf{1.109d}$ (4.5 mg, 0.010 mmol, 72%) as a white solid (mp 168-170°C): $R_f = 0.15$ (1:3 EtOAc:hexanes); $[\alpha]^{D}_{20} = +2.1^\circ$ (c = 0.52, CH$_2$Cl$_2$); IR (neat) $\nu_{max} = 2930, 1495, 1258$ cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.49 (brs, 1 H), 7.56 (d, $J = 7.5$ Hz, 1 H), 7.23 (brs, 1 H), 7.10 (d, $J = 8.5$ Hz, 1 H), 6.60 (dd, $J = 8.5$, 2.5Hz, 1 H), 6.56 (d, $J = 2.5$ Hz, 1 H), 2.86 – 2.80 (m, 2 H), 2.78 (t, $J = 9.5$ Hz, 1 H), 2.30 – 2.24 (m, 2 H), 2.15 – 1.92 (m, 4 H), 1.70 – 1.60 (m, 1 H), 1.43 – 1.40 (m, 6 H), 0.97 (s, 9H), 0.53 (s, 3 H), 0.18 (s, 6 H); $^{13}$C NMR $\delta$ 153.3, 150.3, 147.5, 137.8, 135.7, 133.0, 126.1, 119.9, 117.0, 55.3, 54.6, 44.7, 44.0, 39.2, 37.5, 29.7 (2 C), 27.8, 26.2, 25.9, 25.7 (3 C), 24.2, 18.2, 12.8, 1.0, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{29}$H$_{42}$NOSi [M+H]$^+$: 448.3030; found: 448.3034.

$\bf{1.109f}$: Prepared from Styrene $\bf{1.109f}$ (10 mg, 0.022 mmol) according to general procedure D. Purification by flash chromatography (15:1 hexanes:CH$_2$Cl$_2$) afforded $\bf{1.109f}$ (9.3 mg, 0.020 mmol, 93%) as a white solid (mp 117-121°C): $R_f = 0.60$ (1:3 CH$_2$Cl$_2$:hexanes); $[\alpha]^{D}_{20} = +1.6^\circ$ (c = 0.37, CH$_2$Cl$_2$); IR (neat) $\nu_{max} = 2928, 1508, 1253$ cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.46 (d, $J = 9.5$ Hz, 2 H), 7.57 (d, $J = 8.5$ Hz, 1 H), 7.22 (t, $J = 9.5$ Hz, 1 H), 6.60 (dd, $J = 9.5$, 2.5 Hz, 1 H), 6.56 (d, $J = 2.5$ Hz, 1 H), 2.86 – 2.80 (m, 2 H), 2.78 (t, $J = 9.5$ Hz, 1 H), 2.30 – 2.24 (m, 2 H), 2.15 – 1.92 (m, 4 H), 1.70 – 1.60 (m, 1 H), 1.43 – 1.40 (m, 6 H), 0.97 (s, 9H), 0.53 (s, 3 H), 0.18 (s, 6 H); $^{13}$C NMR $\delta$ 153.3, 150.3, 147.5, 137.8, 135.7, 133.0, 126.1, 119.9, 117.0, 55.3, 54.6, 44.7, 44.0, 39.2, 37.5, 29.7 (2 C), 27.8, 26.2, 25.9, 25.7 (3 C), 24.2, 18.2, 12.8, 1.0, -4.4 (2 C); HRMS (ESI-TOF) calcd for C$_{29}$H$_{42}$NOSi [M+H]$^+$: 448.3030; found: 448.3034.
1H NMR (400 MHz, CDCl₃) δ 7.20 (d, J = 8.8 Hz, 1 H), 7.19 (d, J = 8.8 Hz, 1 H), 7.11 (d, J = 8.4 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 1 H), 6.61 (dd, J = 8.4, 2.4 Hz, 1 H), 6.57 (d, J = 2.4 Hz, 1 H), 2.86 – 2.82 (m, 2 H), 2.75 (t, J = 10.0 Hz, 1 H), 2.40 – 2.30 (m, 2 H), 2.10 – 1.89 (m, 4 H), 1.67 (dd, J = 8.4, 2.4 Hz, 1 H), 1.45 – 1.42 (m, 6 H), 0.98 (s, 9 H), 0.50 (s, 3 H), 0.19 (s, 6 H); 13C NMR (125 MHz, CDCl₃) δ 161.5 (d, J_CF = 242.1 Hz), 153.3, 137.9, 136.7 (d, J_CF = 3.1 Hz), 133.2, 129.9 (d, J_CF = 7.5 Hz, 2 C), 126.1, 119.9, 117.1, 114.4 (d, J_CF = 20.6 Hz, 2 C), 56.4, 55.2, 44.4, 44.1, 39.2, 37.7, 29.7, 27.8, 26.5, 26.3, 25.7 (3 C), 24.2, 18.2, 18.2, -4.4 (2 C); HRMS (ESI-TOF) calcd for C₃₀H₄₂OFSi [M+H]^+: 465.2983; found: 465.2972.

1.109g: Prepared from Styrene 1.108g (17 mg, 0.030 mmol) according to general procedure D. Purification by flash chromatography (15:1 hexanes:CH₂Cl₂) afforded 1.109g (15.0 mg, 0.029 mmol, 96%) as a white solid (mp 129-131°C): Rₚ = 0.65 (1:3 CH₂Cl₂:hexanes); [α]D²₀ = +5.1° (c = 0.71, CH₂Cl₂); IR (neat) νmax = 2930, 1497, 1327, 1123 cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.54 (d, J = 8.3 Hz, 2 H), 7.35 (d, J = 8.3 Hz, 2 H), 7.11 (d, J = 8.5 Hz, 1 H), 6.61 (dd, J = 8.5, 2.5 Hz, 1 H), 6.56 (d, J = 2.5 Hz, 1 H), 2.86 – 2.82 (m, 3 H), 2.30 – 2.25 (m, 2 H), 2.18 – 2.12 (m, 1 H), 2.08 – 2.00 (m, 1 H), 1.95 – 1.90 (m, 2 H), 1.71 – 1.68 (m, 1 H), 1.54 – 1.40 (m, 6 H), 0.98 (s, 9 H), 0.51 (s, 3 H), 0.19 (s, 6 H); 13C NMR (125 MHz, CDCl₃) δ 153.3, 145.4, 137.8, 133.1, 128.9 (2 C), 128.3 (q, J_CF = 32.2 Hz), 124.6 (q, J_CF = 3.8 Hz, 2C), 121.7 (q, J_CF = 394.1 Hz), 120.0, 117.1, 57.0, 55.4, 44.9, 44.0, 39.2, 37.7, 29.7, 26.3, 26.2, 25.7 (3 C), 24.2, 18.2, 12.8, -4.4 (2 C); HRMS (ESI-TOF) calcd for C₃₁H₄₂OFSi [M+H]^+: 515.2951; found: 515.2959.

1.109a-d₂: Prepared from Styrene 1.108a (13 mg, 0.029 mmol) according to general procedure D, except Ra-Ni was washed with D₂O and isopropanol-d₈ and toluene-d₈
were used as solvent. Purification by flash chromatography (15:1 hexanes:CH₂Cl₂) afforded 1.109a-d₂ (12.3 mg, 0.027 mmol, 95%) as a white solid (mp 135-138°C): \( R_f = 0.60 \) (1:3 CH₂Cl₂:hexanes); \([\alpha]^{D}_{20} = +3.1^\circ \) (c = 0.19, CH₂Cl₂); IR (neat) \( \nu_{\max} = 2925, 1495, 1253 \text{ cm}^{-1} \); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 7.31 - 7.19 \) (m, 5 H), 7.11 (d, \( J = 8.5 \text{ Hz} \), 1 H), 6.60 (dd, \( J = 2.5, 8.5 \text{ Hz} \), 1 H), 6.55 (d, \( J = 2.5 \text{ Hz} \), 1 H), 2.85 – 2.82 (m, 2 H), 2.78 (t, \( J = 10.0 \text{ Hz} \), 1 H), 2.28 – 2.24 (m, 2 H), 2.19 – 2.12 (m, 1 H), 2.05 – 1.87 (m, 2 H), 1.72 – 1.70 (m, 1 H), 1.48 – 1.42 (m, 6 H), 0.98 (s, 9 H), 0.51 (s, 3 H), 0.18 (s, 6 H); \(^{13}\)C NMR (150 MHz, CDCl₃) \( \delta 153.2, 141.1, 137.9, 133.3, 128.7 \) (2 C), 127.7 (2 C), 126.1, 126.0, 119.9, 57.1 (t, \( J_{CD} = 26.0 \text{ Hz} \)), 55.3, 44.6, 44.1, 39.2, 37.7, 29.8, 29.7, 27.9, 26.3, 25.7 (3 C), 24.2, 23.7 (t, \( J_{CD} = 26.6 \text{ Hz} \)), 18.2, 12.8, -4.4 (2 C); HRMS (ESI-T0F) calcd for C₃₀H₄₀D₂OSi [M+H]⁺: 449.3201; found: 449.3191.

**General procedure E for deoxygenation:** To a solution of alcohol in toluene (0.01 M), was added the suspension of Ra-Ni prepared above (the Ra-Ni suspension was removed by 5.75’ pipette from the thick bottom layer of the vial; 1 drop suspension per 0.1 mL solution). The reaction flask was immersed in an oil bath preheated to 110°C and stirred vigorously for 5 hours. After cooling to ambient temperature, the reaction mixture was passed through Celite, the Ra-Ni washed by CH₂Cl₂, and the combined filtrates were concentrated in vacuo. The product was purified by flash column chromatography.

1.111a: Prepared from alcohol 1.110a (36 mg, 0.081 mmol) according to general procedure E. Purification by flash chromatography (5:1 hexanes:CH₂Cl₂) afforded 1.111a and 1.109a (dr = 6.6:1) as an inseperable mixture (35.0 mg, 0.080 mmol, 98%) (white solid) (mp 113-118°C): \( R_f = 0.60 \) (1:3 CH₂Cl₂:hexanes); \([\alpha]^{D}_{20} = +41.7^\circ \) (c = 0.93, CH₂Cl₂); IR (neat) \( \nu_{\max} = 2930, 1496, 1255 \text{ cm}^{-1} \); \(^1\)H NMR (500 MHz, CDCl₃)
δ 7.31– 7.19 (m, 3 H), 7.14 – 7.11 (m, 2 H), 7.01 (d, J = 8.0 Hz, 1 H), 6.56 (dd, J = 8.5, 2.5 Hz, 1 H), 6.54 (d, J = 2.5 Hz, 1 H), 3.00 (dd, J = 9.0, 1.5 Hz, 1 H), 2.88 – 2.76 (m, 2 H), 2.37– 2.24 (m, 1 H), 2.11 – 1.94 (m, 5 H), 1.55 – 1.37 (m, 6 H), 0.99 (s, 3 H), 0.97 (s, 9 H), 0.62 (dt, J = 15.0, 5.0 Hz, 1 H), 0.18 (s, 6 H); 13C NMR (150 MHz, CDCl3) δ 153.1, 145.0, 137.8, 133.3, 128.7 (2 C), 127.6 (2 C), 126.1, 125.6, 119.8, 117.0, 55.8, 48.8, 45.4, 43.4, 39.3, 35.3, 29.8, 28.4, 26.4, 25.7 (3 C), 21.4, 18.2, -4.4 (2 C); HRMS (ESI-TOF) calcd for C30H43OSi [M+H]+: 447.3078; found: 447.3083.

1.111b: Prepared from Alcohol 1.110b (12 mg, 0.026 mmol) according to general procedure E. Purification by flash chromatography (5:1 hexanes:CH2Cl2) afforded 1.111b and 1.109b (dr = 26:1) as an inseperable mixture (10.3 mg, 0.023 mmol, 88%) (colorless oil): Rf = 0.60 (CH2Cl2:hexanes); [α]D20 = +39.6° (c = 1.14, CH2Cl2); IR (neat) νmax = 2928, 1496, 1288, 1256 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 7.10 (d, J = 8.0 Hz, 2 H), 7.03 (d, J = 8.0 Hz, 2 H), 7.02 (d, J = 8.0 Hz, 1 H), 6.56 (dd, J =8.0, 2.5 Hz, 1 H), 6.54 (d, J = 2.5 Hz, 1 H), 2.97 (dd, J = 8.5, 1.5 Hz, 1 H), 2.88 – 2.77 (m, 2 H), 2.34 (s, 3 H), 2.56 – 2.29 (m, 1H), 2.12 – 1.89 (m, 5 H), 1.54 – 1.38 (m, 1 H), 0.98 (s, 3 H), 0.97 (s, 9 H), 0.65 (brdt, 1 H), 0.18 (s, 6 H); 13C NMR (150 MHz, CDCl3) δ 153.1, 145.0, 137.8, 133.3, 128.6 (2 C), 128.3 (2 C), 126.1 (2 C), 119.8, 117.0, 55.3, 48.8, 45.3, 39.3, 35.3, 29.8, 28.5, 28.3, 26.4, 25.7 (3 C), 21.4, 21.0, 18.1, -4.4 (2 C); HRMS (ESI-TOF) calcd for C30H43OSi [M+H]+: 461.3234; found: 461.3231.

1.111c: Prepared from Alcohol 1.111c (19 mg, 0.038 mmol) according to general procedure E. Purification by flash chromatography (5:1 hexanes:CH2Cl2) afforded 1.111c and styrene 1.109c (dr = 4.2:1) as an inseperable mixture (12.0 mg, 0.025 mmol, 68%) (white solid) (mp 78-83°C); [α]D20 = +10.9° (c = 0.42, CH2Cl2); IR (neat) νmax = 2925,
1498, 1252 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.16 (d, \(J = 8.6\) Hz, 2 H), 7.09 – 6.96 (m, 2 H), 6.84 (dd, \(J = 8.4, 6.0\) Hz, 2 H), 6.57 – 6.53 (m, 2 H), 3.80 (s, 3 H), 2.95 (dd, \(J = 8.9, 1.5\) Hz, 1 H), 2.88 – 2.77 (m, 2 H), 2.35 – 2.20 (m, 2 H), 2.11 – 2.06 (m, 1 H), 2.02 – 1.85 (m, 3 H), 1.69 – 1.37 (m, 6 H), 0.98 (s, 3 H), 0.97 (s, 9 H), 0.65 (dt, \(J = 13.6, 13.3, 4.1\) Hz 1 H), 0.18 (s, 6 H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 157.6, 153.1, 137.8, 137.1, 133.3, 129.5 (2 C), 126.1, 119.8, 113.0 (2 C), 55.1, 54.8, 48.7, 45.3, 39.3, 35.3, 29.8, 28.6, 28.3, 25.7 (3 C), 24.2, 21.3, 18.1, 12.7, -4.4 (2 C); HRMS (ESI-TOF) calcd for C\(_{31}\)H\(_{44}\)O\(_2\)Si [M+H]\(^+\): 477.3183; found: 477.3181.

1.111d: Prepared Alcohol 1.110d (12 mg, 0.025 mmol) according to general procedure E. Purification by flash chromatography (3:1 hexanes:EtOAc) afforded 1.111d and 1.109d (dr = 13:1) as an inseperable mixture (8.4 mg, 0.019 mmol, 72%) (white solid) (mp 82-84°C): \(R_f\) = 0.15 (3:1 hexanes: EtOAc); [\(\alpha\)]\(^D\)\(\text{20}\) = +34.5° (c = 0.55, CH\(_2\)Cl\(_2\)); IR (neat) \(\nu\)\(_{\text{max}}\) = 2931, 1498, 1220 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.43 (brd, 2 H), 7.44 (brd, 1 H), 7.24 (brt, 1 H), 7.00 (d, \(J = 8.5\) Hz, 1 H), 6.56 (dd, \(J = 8.5, 2.0\) Hz, 1 H), 6.53 (d, \(J = 2.0\) Hz, 1 H), 3.00 (dd, \(J = 8.5, 1.5\) Hz, 1 H), 2.87 – 2.76 (m, 2 H), 2.41 – 2.33 (m, 1 H), 2.13 – 1.88 (m, 5 H), 1.57 – 1.37 (m, 6 H), 1.01 (s, 3 H), 0.96 (s, 9 H), 0.59 (brdt, 1 H), 0.17 (s, 6 H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 153.2, 150.2, 147.2, 137.7, 135.8, 133.0, 126.0, 119.8, 117.1, 53.2, 49.0, 45.5, 43.4, 39.3, 35.2, 29.7, 28.2, 28.1, 26.3, 25.7 (3 C), 25.6, 21.2, 18.2, -4.4 (2 C); HRMS (ESI-TOF) calcd for C\(_{29}\)H\(_{42}\)NOSi [M+H]\(^+\): 448.3030; found: 448.3028.

1.111a-d\(_4\): Prepared from Alcohol 1.110a (18 mg, 0.039 mmol) according to general procedure E, except Ra-Ni was washed with D\(_2\)O and toluene-d\(_8\) was used as solvent. Purification by flash chromatography (5:1 hexanes:CH\(_2\)Cl\(_2\)) afforded 1.111a-d\(_4\) and
1.111a (dr = 10:1) as an inseperable mixture (white solid) (17.0 mg, 0.037 mmol, 96%) (mp 110-115°C): \( R_f = 0.60 \) (1:3 \( \text{CH}_2\text{Cl}_2 \):hexanes); \([\alpha]^{D}_{20} = +43.4^\circ \) (c = 1.63, \( \text{CH}_2\text{Cl}_2 \)); IR (neat) \( \nu_{\text{max}} = 2930, 1496, 1255 \) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 7.14 \) (s, 2 H), 7.02 (d, \( J = 8.0 \) Hz, 1 H), 6.57 (dd, \( J = 8.5, 2.5 \) Hz, 1 H), 6.54 (d, \( J = 2.5 \) Hz, 1 H), 2.88 – 2.77 (m, 2 H), 2.36 – 2.34 (m, 1 H), 2.11 – 1.94 (m, 5 H), 1.55 – 1.37 (m, 6 H), 1.00 (s, 3 H), 0.98 (s, 9 H), 0.63 (dt, \( J = 15.0, 5.0 \) Hz, 1 H), 0.19 (s, 6 H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta = 153.1, 145.0, 137.8, 133.3, 128.7, 127.5 \) (t, \( J_{CD} = 32.0 \) Hz, 2 C), 126.1 (2 C), 125.4 (t, \( J_{CD} = 24.3 \) Hz), 119.8, 117.0, 55.3 (t, \( J_{CD} = 26.6 \) Hz), 48.9, 45.3, 43.4, 39.3, 35.3, 29.8, 28.4, 26.4, 25.7 (3 C), 21. 4, 18.2, -4.4 (2 C); HRMS (ESI-TOF) calcd for C\(_{30}\)H\(_{39}\)D\(_4\)OSi \([\text{M+H}]^+\): 451.3325; found: 451.3320.

1.111a-d\(_3\): Prepared from 1.111a (14 mg, 0.031 mmol) according to general procedure E, except Ra-Ni was washed with D\(_2\)O and toluene-\(d_8\) was used as solvent. Purification by preparative TLC (10:1 hexanes:CH\(_2\)Cl\(_2\)) afforded 1.111a-d\(_3\) (dr = 10:1) and its diastereoisomer as an inseperable mixture (10 mg, 0.023 mmol, 75%) (white foam): \( R_f = 0.60 \) (1:3 CH\(_2\)Cl\(_2\):hexanes); \([\alpha]^{D}_{20} = +45.8^\circ \) (c = 0.31, CH\(_2\)Cl\(_2\)); IR (neat) \( \nu_{\text{max}} = 2930, 1496, 1255 cm^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 7.14 \) (s, 2 H), 7.02 (d, \( J = 8.0 \) Hz, 1 H), 6.57 (dd, \( J = 8.5, 2.5 \) Hz, 1 H), 6.54 (d, \( J = 2.5 \) Hz, 1 H), 3.00 (dd, \( J = 9.0, 1.5 \) Hz, 1 H), 2.88 – 2.77 (m, 2 H), 2.36 – 2.34 (m, 1 H), 2.11 – 1.94 (m, 5 H), 1.55 – 1.37 (m, 6 H), 1.00 (s, 3 H), 0.98 (s, 9 H), 0.63 (dt, \( J = 15.0, 5.0 \) Hz, 1 H), 0.19 (s, 6 H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta = 153.1, 145.0, 137.8, 133.3, 128.7, 127.5 \) (t, \( J_{CD} = 32.0 \) Hz, 2 C), 126.1 (2 C), 125.4 (t, \( J_{CD} = 24.3 \) Hz), 119.8, 117.0, 55.3, 48.9, 45.3, 43.4, 39.3, 35.3, 29.8, 28.4, 26.4, 25.7 (3 C), 21. 4, 18.2, -4.4 (2 C); HRMS (ESI-TOF) calcd for C\(_{30}\)H\(_{40}\)D\(_3\)OSi \([\text{M+H}]^+\): 450.3263; found: 450.3251.
17-epi-cortistatin A (1.106): To cortistatinone (5 mg, 0.014 mmol, 1.0 equiv) in CH₂Cl₂ (1.4 mL, 0.001 M) was added TMSimidazole (5.8 mg, 6.1 µl, 0.042 mmol, 3.0 equiv). After 5 hours, the reaction mixture was diluted with CH₂Cl₂ (10 mL) and washed with by sat. aq. NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 × 10 mL) and these portions were added to the organic layer, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography (EtOAc) and then dissolved into THF (28 µl, 0.5 M) (solution A). To 7-bromoisoquinoline (8.6 mg, 0.042 mmol, 3.0 equiv) in THF (0.21 mL, 0.2 M) was added n-BuLi (17 µL, 2.5 M, 0.042 mmol, 3.0 equiv) dropwise at -78 °C. After 40 minutes, TMEDA was added (19 µL, 0.13 mmol, 9.0 equiv). After 10 minutes, solution A was added into the reaction mixture. After another 10 minutes, the reaction was quenched with sat. aq. NaHCO₃ (10 mL). The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organics were dried with MgSO₄, filtered, and concentrated in vacuo. The residue was dissolved in 1% EtOH in toluene (2.8 ml, 0.005 M) and Ra-Ni (prepared by procedure above, 28 drops) was added. The reaction was immersed in an oil bath preheated to 110°C and stirred vigorously for 30 minutes, at which point the reaction had progressed to approximately 70% conversion, as judged by LCMS. Removal of the supernatant, followed by washing of the Raney nickel catalyst with 1:1 MeOH:EtOAc (10 mL), and concentration of the combined filtrates produced a residue that was stirred in 10% aq. AcOH (1 mL) for 10 mintues and concentrated in vacuo. The residue was then purified by HPLC, yielding 17-epi-cortistatin A (4) (1.1 mg, 0.002 mmol, 16%) as a colorless oil and cortistatin A (1) (0.3 mg, 0.0006 mmol, 5%) as a white solid. 17-epi-cortistatin A (1.106): [α]D20 = +45.5° (c = 0.068, CD3OD); IR (neat) νmax = 3355, 3039, 1679, 1295, 1202, 897, 887 cm⁻¹;
\(^1\)HNMR (600 MHz, CDCl\(_3\)) \(\delta\) 9.27 (s, 1 H), 8.32 (d, \(J = 6.0\) Hz, 1 H), 7.95 – 7.85 (m, 3 H), 7.69 (d, \(J = 8.1\) Hz, 1 H), 6.01 (d, \(J = 2.4\) Hz, 1 H), 5.15 (dd, \(J = 5.1, 2.5\) Hz, 1 H), 3.9 (d, \(J = 9.0\) Hz, 1 H), 3.36 (t, \(J = 9.8\) Hz, 1 H), 3.28 – 3.25 (m, 1 H), 3.12 (t, \(J = 7.2\) Hz, 1 H), 2.84 (s, 3 H), 2.69 (s, 3 H), 2.50 – 2.44 (m, 1 H), 2.40 – 2.31 (m, 2 H), 2.11 – 2.03 (m, 3 H), 1.95 – 1.88 (m, 3 H), 1.75 – 1.64 (m, 3 H), 1.04 (s, 3 H);

HRMS (ESI-MS) calcd for C\(_{30}\)H\(_{36}\)N\(_2\)O\(_3\) [M + H]\(^+\) 473.2799, found 473.2786.

**Compound 1.114: 1.101** (4 mg, 5.7 \(\mu\)mol) and **117** (4 mg, 12 \(\mu\)mol) were dissolved in CH\(_2\)Cl\(_2\):DMSO 10:1 (0.55 mL, 0.01 M). To this solution added EDC (2.6 mg, 17 \(\mu\)mol, 3 equiv) and DMAP (1 mg, 9 \(\mu\)mol, 1.5 equiv). The reaction mixture was stirred at room temperature for 12 h, at which point it was quenched with sat. aq. NaHCO\(_3\) (5 mL). The aqueous layer was extracted with EtOAc (4 \(\times\) 5 mL). The combined organics were dried with MgSO\(_4\), filtered, and concentrated in vacuo. The residue was then purified by HPLC, yielding **1.114a** (1.2 mg, 25%) and **1.114b** (1.7 mg, 25%) as a colorless oil.

**1.114a:** \(^1\)H NMR (600 MHz, MeOD) \(\delta\) 8.43 (brs, 1H), 8.35 – 8.31 (m, 1H), 8.19 – 8.16 (m, 1H), 6.56 (brs, 1H), 6.29 (brs, 1H), 5.63 (s, 1H), 5.13 – 5.09 (m, 1H), 4.52 – 4.48 (m, 1H), 4.35 – 4.31 (m, 1H), 4.28 – 4.27 (m, 1H), 3.86 – 3.76 (m, 1H), 3.45 (s, 3H), 3.21 (s, 3H), 3.07 – 2.98 (m, 1H), 2.95 (d, \(J = 12.8\) Hz, 1H), 2.90 – 2.82 (m, 5H), 2.73 – 2.70 (m, 6H), 2.64 – 2.47 (m, 8H), 2.38 (s, 3H), 2.23 – 2.17 (m, 6H), 1.96 – 1.90 (m, 6H), 1.47 – 1.40 (m, 5H), 1.27 (s, 3H).

**1.114b:** \(^1\)H NMR (600 MHz, MeOD) \(\delta\) 8.45 (s, 1H), 8.34 (d, \(J = 8.7\) Hz, 1H), 8.20 (d, \(J = 8.8\) Hz, 1H), 6.57 (brs, 1H), 5.84 (s, 1H), 5.62 (brs, 1H), 5.49 – 5.45 (m, 1H), 4.51 – 4.49 (m, 1H), 4.32 – 4.29 (m, 1H), 3.90 – 3.84 (m, 1H), 3.47 – 3.43 (m, 2H), 3.25 – 3.19 (m, 4H), 3.00 (s, 3H), 2.97 – 2.92 (m, 1H), 2.84 (s, 3H), 2.79 – 2.66 (m, 2H), 2.64 – 2.42 (m,
6H), 2.33 – 2.15 (m, 6H), 1.91 – 1.57 (m, 9H), 1.50 – 1.29 (m, 7H), 1.26 (s, 3H).

**General Procedure for Suzuki Coupling:** Vinyl iodide (1.0 equiv), ArB(OH)$_2$ (2 equiv) and Pd$_2$(dba)$_3$ (20 mmol%), Ruphos (0.8 equiv), and K$_3$PO$_4$ (3 equiv) were dissolved in n-BuOH:H$_2$O 5:1 (0.5 M). The solution was degassed for 10 minutes by bubbling with Ar under sonication. The reaction was then immersed in an oil bath preheated to 60°C for 36 hour. The reaction was allowed to cool to ambient temperature, diluted with EtOAc, and washed with sat. aq. NaHCO$_3$. The aqueous layer was extracted with EtOAc (3 times). The combined organic portions were washed with sat. aq. NaCl, dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on silica.

**Compound 1.115b:** (3.0 mg, 22%) $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 9.17 (brs, 1H), 9.03 (d, $J$ = 8.1 Hz, 1H), 8.27 (d, $J$ = 8.5 Hz, 2H), 8.17 (d, $J$ = 8.8 Hz, 1H), 8.07 – 7.91 (m, 1H), 6.74 (s, 1H), 6.35 (s, 1H), 5.64 (s, 1H), 4.14 (d, $J$ = 8.1 Hz, 1H), 3.60 – 3.57 (m, 1H), 3.03 (s, 3H), 2.89 (s, 3H), 2.86 – 2.77 (m, 2H), 2.72 – 2.21 (m, 7H), 2.22 – 2.00 (m, 3H), 1.98 – 1.82 (m, 1H), 1.33 (s, 3H). IR (neat) $\nu_{\text{max}}$ = 3321, 1646, 1442, 1108, 1128, 1015, 948, 868 cm$^{-1}$; HRMS (ESI-MS) calcd for C$_{30}$H$_{34}$N$_2$O$_3$ [M + H]$^+$ 471.2642, found 471.2642.

**Compound 1.115c:** (2.2 mg, 22%) $^1$H NMR (600 MHz, CD$_3$OD) $\delta$ 8.78 (s, 1H), 8.37 (d, $J$ = 7.5 Hz, 2H), 8.11 – 7.86 (m, 3H), 7.67 – 7.43 (m, 1H), 6.33 (s, 1H), 6.24 (s, 1H), 5.55 (s, 1H), 4.05 (s, 1H), 3.65 (s, 1H), 3.59 – 3.39 (m, 2H), 2.86 (s, 6H), 2.66 – 2.59 (m, 2H), 2.58 – 2.40 (m, 3H), 2.38 – 2.13 (m, 3H), 2.08 – 1.74 (m, 6H), 1.19 (s, 3H). IR (neat) $\nu_{\text{max}}$ = 3303, 1736, 1550, 1101, 1018, 1001, 967, 832, 707 cm$^{-1}$; HRMS (ESI-MS) calcd for C$_{30}$H$_{34}$N$_2$O$_3$ [M + H]$^+$ 471.2642, found 471.2628.
**Compound 1.116:** To a solution of 1.22 (5 mg, 14 µmol) in MeOH (0.28 mL, 0.005 M) added NH₄OAC (53 mg, 700 µmol, 50 equiv) and stirred at room temperature for 1 h. Then, NaBH₃CN (8.8 mg, 140 µmol 10 equiv) were added and stirred for 12 h, at which point it was quenched with sat. aq. NaHCO₃ (5 mL). The aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organics were dried with MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by preparative TLC (100:10:1 MeOH:CH₂Cl₂:NH₃H₂O) yielded 116 (3.2 mg, 65%) as white foam. ¹H NMR (600 MHz, CDCl₃) δ 6.25 (s, 1H), 5.46 (s, 1H), 4.09 (d, J = 8.9 Hz, 1H), 3.32 (t, J = 9.8 Hz, 1H), 2.92 (t, J = 9.4 Hz, 1H), 2.40 – 2.36 (m, 2H), 2.29 (s, 6H), 2.25 – 2.06 (m, 5H), 2.08 – 1.75 (m, 8H), 0.89 (t, J = 7.0 Hz, 1H), 0.70 (s, 3H).

**Compound 115d:** 1.116 (3 mg, 8.3 µmol) and 2-nicotinic acid (1 mg, 8.3 µmol) were dissolved in CH₂Cl₂ (0.42 mL, 0.002 M). To this solution added EDC (2.6 mg, 17 µmol, 2 equiv), i-Pr₂EtN (14 µL, 83 µmmol, 10 equiv) and HOBT (2.2 mg, 17 µmol, 2 equiv). The reaction mixture was stirred at room temperature for 2 h, at which point it was quenched with sat. aq. NaHCO₃ (5 mL). The aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organics were dried with MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by HPLC, yielding 1.115d (3.1 mg, 54%) as a colorless oil.

115d: ¹H NMR (600 MHz, MeOD) δ 9.13 (s, 1H), 8.86 (s, 1H), 8.55 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 6.24 (d, J = 2.2 Hz, 1H), 5.48 (d, J = 2.7 Hz, 1H), 4.36 (t, J = 9.4 Hz, 1H), 4.04 (d, J = 9.1 Hz, 1H), 3.66 – 3.47 (m, 1H), 3.44 – 3.33 (m, 2H), 2.95 (s, 3H), 2.82 (s, 3H), 2.48 – 2.29 (m, 3H), 2.23 – 1.97 (m, 3H), 1.97 – 1.68 (m, 4H), 0.87 (s, 3H). ¹³C NMR (150 MHz, MeOD) δ 139.8, 139.2, 121.7, 119.8, 82.0, 78.6, 72.5, 72.2, 63.2, 59.9,
IR (neat) ν max = 3331, 1656, 1449, 1201, 1138, 1015 cm⁻¹; HRMS (ESI-MS) calcd for C27H36N3O4 [M + H]⁺ 466.2700, found 466.2698.

Reference:


1.9 Appendix to Chapter 1: Spectra
Formamide Rotamer
Formamide Rotamer
X-ray Crystal Structure
X-ray Crystal Structure
X-ray Crystal Structure
X-ray Crystal Structure
X-ray Crystal Structure
X-ray Crystal Structure
TBSO

X-ray Crystal Structure
Chapter 2

Total Synthesis of Vinigrol
2.1 Introduction

Vinigrol (2.1), a novel diterpenoid, was isolated from the fungal strain *Virgaria nigra* F-5408 in 1987 by Ando and coworkers.\(^1\) Initially identified from a fungus with antihypertensive properties,\(^2\) it was later discovered that 2.1 possesses a broad scope of interesting biological activities, such as being a Ca\(^{2+}\) channel agonist,\(^2\) TNF (tumor necrosis factor) antagonist,\(^3\) an anti-HIV\(^4\) agent, and an anti-inflammation agent.\(^5\)

Initial IR, MS, \(^1\)H and \(^13\)C NMR evidence failed to lead to the elucidation of the exact structure of vinigrol. Therefore, the structure of its derivative 2.2, synthesized via Jones oxidation of 2.1 (Scheme 2.1), was identified by X-ray analysis.\(^1\) Further determination of the configuration of C4 by NMR data and CD spectra provided the structure of vinigrol (2.1),\(^1\) which possesses a unique tricyclic core containing a cis-fused \([4.4.0]\) system bridged by an eight-membered ring with eight contiguous stereocenters.

**Scheme 2.1. Structure of vinigrol (2.1)**

**A. Vinigrol (2.1) and its structure determination**

**B. Illustrations of vinigrol (2.1)**

- Unprecedented 1,5-butanonaphthalene skeleton
- Eight contiguous stereocenters
- Bicycle[5.3.1]undecane
- *Taxol-like* skeleton
The biogenesis of vinigrol has been proposed by Corey and Goodman based on the known biosyntheses of artennium B and pseudopterosin. It was postulated that the cis-decalin portion of the molecule could be derived from an enzymatically-assisted cyclization of geranylgeranyl pyrophosphate (2.3) as shown in Scheme 2.2. Thus, polyolefin 2.3 is hypothesized to convert to 2.5 via a hydride shift/cyclization/elimination sequence. Subsequent oxidation of 2.5 can lead to phenol 2.6. From this intermediate, the unique decahydro-1,5-butanonaphthalene framework might be obtained from an oxidative phenolic coupling. Finally, enzymatic oxidations of the carbon skeleton could deliver vinigrol (2.1).

Scheme 2.2. Proposed biogenesis of vinigrol by Corey and Goodman

From a chemical standpoint, vinigrol contains an unprecedented decahydro-1,5-butanonaphthalene ring system with eight contiguous stereocenters, rendering this diterpenoid a formidable challenge for organic synthesis. Over the past two decades, numerous efforts towards its total synthesis have been reported, including studies from...
the Paquette, Corey, Barriault, Hanna, Mehta, Matsuda, Fallis and Njardarson groups. Some of the representative approaches to the total synthesis vinigrol (2.1) from the abovementioned research groups, focusing on their key transformations or disconnections, are listed below. Several reviews on this topic have recently appeared.

One of the early efforts toward the synthesis of vinigrol was reported by Paquette and co-workers, which enlisted the construction of the cis-decalin subunit embedded in vinigrol via a well-studied anionic oxy-Cope reaction (Scheme 2.3). The key intermediate 2.9 was synthesized by the addition of lithiated alkene to ketone 2.8. The anionic oxy-Cope reaction proceeded with KHMDS and 18-crown-6 and afforded cis-decalin 2.10 in 72% yield. Initially, Paquette’s strategy for the formation of the eight-membered ring was based on an intramolecular S\textsubscript{N}2 cyclization of 2.11, which was generated from 2.10 via a number of functional group manipulations. However, all the efforts to form the eight-membered ring met with failure. Although medium-sized ring syntheses such as olefin metathesis, aldol condensation, Barbier-type coupling, McMurry coupling, Ramberg-Bäcklund reaction and ring contraction were studied, none of them generated the desired octalin belt. Indeed, according to the X-ray analysis of 2.11, it was shown that both sidechains possess an equatorial orientation, positioning the desired reaction centers too distant for a productive C–C bond formation. Calculations on the related model 2.13 indicate that 2.13-1 is the more favored conformation over 2.13-2 in the equilibrium, which lacks the proximity for the desired ring closure.
Scheme 2.3. Paquette’s approach to the cis-decalin and studies on constructing decahydro-1,5-butanonaphthalene

A. Synthesis of cis-decalin 2.11

B. Calculations of related model (2.13)

<table>
<thead>
<tr>
<th></th>
<th>2.13-1</th>
<th>2.13-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔE_{strain} (kcal/mol)</td>
<td>15.5</td>
<td>28.2</td>
</tr>
<tr>
<td>ΔH_{f} (kcal/mol)</td>
<td>-92.1</td>
<td>-79.4</td>
</tr>
<tr>
<td>ΔE_{total} (kcal/mol)</td>
<td>25.6</td>
<td>38.3</td>
</tr>
</tbody>
</table>
Corey and coworkers also showed an early interest in the synthesis of vinigrol. Their strategy involved the construction of decahydro-1,5-butanonaphthalene via an intramolecular Diels-Alder reaction followed by a Grob fragmentation (Scheme 2.4). Mukaiyama aldol reaction between 2.17 and 2.18 yielded 2.19. TMS protection followed by TMS enol ether formation led to the key Diels-Alder precursor 2.16. Unfortunately, all attempts to the intramolecular Diels-Alder reaction were proven to be unsuccessful.

**Scheme 2.4.** Corey and Goodman’s intramolecular Diels-Alder approach

A. Retrosynthetic analysis

B. Synthesis of triene 2.16

Hanna’s approach was the first report with successful construction of decahydro-1,5-butanonaphthalene, featuring a key anionic oxy-Cope rearrangement reaction. The approach to their most advanced intermediate is presented in Scheme 2.5. Starting from
1,4-benzoquinone and diene 2.22, a Diels-Alder reaction followed by Luche reduction afforded 2.23. After a few functional group manipulations, oxy-Cope rearrangement precursor 2.24 was synthesized. Under the condition of KH and heat, an anionic oxy-Cope rearrangement occurred smoothly and delivered the key tricycle 2.25. Terminal olefin reduction, ketone reduction and elimination of resulting alcohol led to 2.26. Epoxidation and olefin reduction finally provided the advanced intermediate 2.27. It is important to note that Hanna’s approach marked a milestone in the history of vinigrol synthesis, owing to the fact that they demonstrated the first synthesis of the complete tricyclic core.

**Scheme 2.5.** Hanna’s approach to decahydro-1,5-butanonaphthalene

Barriault’s group also made substantial contributions in the field of vinigrol total synthesis. In 2007, Barriault and coworkers published a concise synthesis of the tricyclic core of vinigrol (Scheme 2.6). Diene 2.29 was synthesized from 2.28 under the effect
of Grubbs II catalyst. Cyanide reduction, Grignard addition, and oxidation provided triene 2.30. Intramolecular Diels-Alder reaction mediated by BF$_3$·Et$_2$O afforded tricycle 2.31 in excellent yield. Their approach features a highly regioselective intramolecular Diels-Alder reaction to construct two rings of the tricyclic vinigrol skeleton simultaneously.

Scheme 2.6. Barriault’s approach to tricyclic core of vinigrol$^8$

![Scheme 2.6](image)

In summary, the intriguing architecture of vinigrol, together with its significant biological activities, render it a challenging synthetic target and considerable efforts have been devoted to the total synthesis of vinigrol. These synthetic challenges have stimulated researchers in our lab to design new and effective strategy to tackle this problem and chemical investigations on this target are discussed in the subsequent section of this chapter.

2.2 Synthetic Strategy

By analyzing the existing approaches, we reached the conclusion that although a number of routes may lead to the formation of the cis-decalin structure embedded in structure 2.32 at the early stage of the synthesis, the subsequent eight-membered ring closure would be problematic as the cis-decalin may adopt a lower energy conformation where the side chains suitable for the octalin belt formation may occupy equatorial
position far away from each other, lacking the proximity to form the bridge. In light of this analysis, we target the construction of tricyclic compound 2.33, which incorporates the octalin belt at the early stage of the synthesis. With 2.33, 2.32 may be generated via cleavage of the C4–C11 bond through Grob fragmentation\(^\text{15}\) (Scheme 2.7). Tetracycle 2.33 could arise from Diels-Alder reaction of triene 2.34. The latter could be obtained from an intermolecular Diels-Alder reaction/organometallic addition sequence.\(^\text{16}\)

**Scheme 2.7. Retrosynthetic analysis**

In 2008, our laboratory reported a concise route to the skeleton of 2.1, utilizing the abovementioned disconnections.\(^\text{15}\) The route commences from an *endo*-selective intermolecular Diels-Alder reaction of diene 2.36 and 2.37 to produce bicyclic ketone 2.38 (Scheme 2.8). Triflation of 2.38, Stille coupling and reduction of the ester provided 2.39 in 78% yield over 3 steps. DMP oxidation of the alcohol, Grignard addition to the resulting aldehyde, intramolecular Diels-Alder reaction and TBS group removal delivered
tetracycle 2.40 in 60% yield over 4 steps. Since the C10 alcohol of 2.40 is not positioned in the desired antiperiplanar geometry required for Grob fragmentation, it was epimerized via a DMP oxidation/reduction sequence followed by mesylation to afforded mesylate 2.41 in 79% overall yield. Treatment of 2.41 with KHMDS caused the Grob fragmentation to take place and subsequent epoxidation produced vinigrol core 2.42.

**Scheme 2.8.** Model studies of synthesis of vinigrol core by Maimone and coworkers\(^{15}\)

2.3 Synthesis of vinigrol skeleton

Based on the preliminary model study, a route to the vinigrol skeleton 2.48 is depicted in Scheme 2.9.\(^{17}\) The C9 methyl group was installed by alkylation (LDA, MeI). Following silyl group removal (TBAF), the adjacent alcohol stereochemistry was established using Evans’ Me\(_4\)NBH(OAc)\(_3\)–mediated\(^{18}\) hydroxyl-directed reduction to deliver 2.44 as a single diastereomer in 72% yield. Non-directed reduction conditions (e.g. DIBAL) afforded mainly the undesired alcohol diastereomer at C11 due to the shielding effect of the C9 methyl group. The correct stereochemistry is critical for
ensuing Grob fragmentation that furnished 2.32 (see Scheme 2.7 for structure) after mesylation and treatment with KHMDS (85% yield over 2 steps). Installation of the C8 methyl and C8a hydroxyl group proved to be a challenging due to their *cis* orientation. The methyl group cannot arise from the simple hydrogenation of an exocyclic olefin because reagents approach from the less hindered (and wrong) diastereoface. In essence, a hypothetical transform to achieve the *cis*-addition of the -CH₃ and -OH groups of *methanol* across an olefin was required. After extensive exploration, the formal equivalent of such a reaction was developed. Thus, exposure of 2.32 to bromonitrile oxide
(generated *in situ* from dibromoformaldehyde and KHCO₃) resulted to the formation of 2.45 in 88% yield on gram-scale with complete control over regio- and positional selectivities. Ketone reduction with DIBAL followed by directed olefin hydrogenation (20% Crabtree’s catalyst, H₂, B(O-iPr)₃) furnished 2.46 in 83% yield. It should be noted that olefin hydrogenation was confounded by the C9 methyl and C12 isopropyl groups flanking the disubstituted olefin on the face in which most hydrogenations would be expected to occur from. In our hands this was the only intermediate and the only set of conditions that succeeded; dozens of hydrogenation conditions on several different intermediates failed.¹⁵b Xanthate formation (NaH, CS₂, MeI) and subsequent Chugaev elimination (180 °C) furnished olefin 2.47 in 85% overall yield. The bromoisoxazole was unveiled to the desired tertiary alcohol 2.48 by the Saegusa deamination sequence:²¹ (1) Reduction with LiAlH₄ and immediate formylation of the crude amine, (2) Dehydration to a primary isonitrile, and (3) Treatment with Bu₃SnH in the presence of AIBN in 56% overall yield. The robustness of this route is
evident from the fact that over 5 grams of 2.48 have been readily prepared and all the steps leading to this key intermediate have been conducted on a gram-scale.

**Scheme 2.9. Approach to vinigrol skeleton 2.48**

Access to large quantities of key intermediates such as 2.48 was critical since, as alluded to above, we encountered a maze of unpredictable failures en route to 2.1, a small sampling of which are shown in Scheme 2.10.\textsuperscript{15b} Thus, alcohol 2.50 was produced from 2.49 via TMS enol ether formation and Mukaiyama aldol reaction. However, the unsaturation on C2–C3 cannot be installed. 1,3-dipolar cycloaddition of bromonitrile oxide to allylic alcohol 2.52 led to 2.53, which was anticipated to undergo elimination of the C2 hydroxyl group to produce 2.54. Unfortunately no formation of 2.54 was observed. Epoxidation of olefin 2.55 delivered 2.56, however, subsequent Et\textsubscript{2}AlCN-mediated epoxide opening met with failure. Further more, oxidation of alcohol 2.58, dehydrogenation of C2–C3 and reduction of C4 ketone produced 2.59. Although the
desired unsaturation of C2–C3 was successfully installed, epimerization of C4 alcohol was proved to be unsuccessful.

Scheme 2.10. Failed routes for the further functionalization

From these results, it appears that the challenge of achieving the total synthesis of vinigrol lies not only in the construction of tricyclic core but also in the manipulation of functional groups presented in the very congested structure. Since the route to the core has been well established in our lab, in order to conquer the total synthesis of vinigrol,
further efforts needed to be focused on the careful placement and manipulation of stericly congested functionalities.

2.4 Synthesis of 2,3-dihydrovinigrol

In 2008, an in-house methodology for directed 1,3-diol synthesis was developed by Dr. Ke Chen and coworkers in our laboratory. In this method, 1,3-diol 2.66 can be synthesized from alcohol 2.61 via (Scheme 2.11): (1) Installation of a carbamate directing group; (2) Bromination of carbamate 2.62; (3) formation of alkyl bromide 2.65 from 2.63 via “N” radical formation, 1,6-hydrogen transfer and recombination with a bromine radical; and 4) hydrolysis of 2.65 to produce 1,3-diol 2.66.

Scheme 2.11. Directed 1,3-diol synthesis by Chen and coworkers

Inspired by this methodology, we designed a route to the natural product via a directed halogenation/elimination sequence (Scheme 2.12). Carbamate formation of triol 2.68 followed by carbamate directed bromination would afford tertiary bromide 2.67. It was then expected that vinigrol could be obtained by elimination of tertiary bromide 2.67.
In essence, we were aiming for the formation of 2,3-dihydrovinigrol (2.68), a starting point for the subsequent dehydrogenation to achieve the desired degree of unsaturation present in the natural product.

Scheme 2.12. Retrosynthetic analysis for directed halogenation strategy

In order to synthesize triol 2.68, diazo chemistry explored by Ganem and coworkers\(^2\) was initially applied (Scheme 2.13). Primary amine 2.69 was synthesized from 1,3-dipolar addition and reduction of the resulting bromoisoxazole. Converting primary amine 2.69 to triol 2.68 by using NaNO\(_2\) in Ac\(_2\)O/AcOH and K\(_2\)CO\(_3\)/MeOH was successful, however, suffering from low yield (Scheme 2.13). Efforts to optimize the reaction by using different nitrites (\(t\)-BuONO, NaNO\(_2\)), nucleophile sources (\(t\)-Bu\(_4\)NOAc, \(t\)-OH) and solvents turned to be fruitless with the best yield of 25%. The major byproduct for this transformation was determined to be ether 2.70, which possibly arose from C8a hydroxyl intramolecular displacement of C16 diazo group. In order to utilize this intermediate, a variety of conditions that would open the ether bridge were explored. However, none of these attempts was successful. Finally, it was found that after acylation of C4 alcohol, C16 could be oxidized to lactone 2.71 using DMDO and subsequent reduction of lactone 2.71 provided triol 2.68.
Scheme 2.13. Synthesis of 2,3-dihydrovinigrol (2.68)

Capitalizing on the observation that the C8a hydroxyl group is prone to cyclize onto the C16 due to the cis-decalin conformation, an improved synthesis of 2,3-dihydrovinigrol (2.68) was formulated (Scheme 2.14). Thus, 1,3-dipolar cycloaddition and Zn–mediated reduction furnished 2.58. Hydrolysis of the nitrile and intramolecular lactonization afforded lactone 2.72. Finally, LAH reduction produced triol 2.68 in 91% yield.

Scheme 2.14. Improved synthesis of 2,3-dihydrovinigrol (2.68)
2.5 Synthesis of vinigrol (2.1)

With a scalable route to triol 2.68 secured, our attention was turned to directed halogenation on C3. Carbamate 2.73 was formed using CF₃CH₂NCO in 85% yield. Treatment of 2.73 with AcOBr afforded brominated carbamate 2.74. Unfortunately, radical reaction of 2.74 only led to the decomposition.

Scheme 2.15. Failed directed halogenation

It was rationalized that the cause for the decomposition arose from the unprotected secondary alcohol. Therefore, alcohol 2.73 was protected with TMS group and acetate group respectively and subsequently brominated to afford 2.74 and 2.75 (Scheme 2.16). Under radical conditions, the undesired olefins 2.79 and 2.80 were observed. This transformation most likely proceeds via initial N-centered radical formation under the reaction conditions, subsequent isopropyl radical formation via remote hydride transfer, recombination with a bromine radical and subsequent elimination to produce 2.79 and 2.80. This experimental result suggested that the C13 hydrogen, rather than the C3 hydrogen, was more favored to be abstracted to form a stable isopropyl radical under the reaction conditions. This observation strongly suggested that while holding the potential, the proposed radical dehydrogenation approach might not feasible to produce the natural product on current system.
**Scheme 2.16.** Directed halogenation and elimination led to undesired olefin

Since installation of the C4 alcohol was feasible, the challenge of completing the synthesis of vinigrol rested on the dehydration of C2–C3 and installation of the C16 primary alcohol in the presence of a pre-existing oxidized skeleton. A number of proposals in hopes of completing the synthesis of vinigrol from the key intermediate 2.48 are outlined in Scheme 2.17. For instance: 1) vinyl iodide$^{24}$ 2.81 could be synthesized from ketone 2.84 and carbonylation followed by reduction could afford vinigrol; 2) olefination of ketone 2.84 should produce olefin 2.82 and singlet O2-ene reaction$^{25}$ would deliver vinigrol; 3) tosyl hydrazone formation of 2.84 could produce 2.83 and a Shapiro reaction$^{26}$ with formaldehyde could also yield vinigrol. Toward this end, we decided to target hydroxy ketone 2.84, which we speculated as an essential intermediate en route to the natural product.
While dihydroxylation of olefin 2.48 proceeded smoothly and provided diol 2.85 in 95% yield, the challenge in synthesizing ketone 2.84 was the selective oxidation of the C3 alcohol in the presence of the C4 alcohol. It is obvious that the C3 alcohol is less hindered than the C4 alcohol because it is adjacent to a methylene (C2) while the C4 alcohol is next a quaternary center (C4a). Initial attempts in selective oxidation did not proceed well. For instance, Dess-Martin periodinane and IBX oxidations only led to decomposition of the starting material. After extensive experimentation, it was finally found that with one equivalent of NaOCl and catalytic amount of TEMPO,27 diol 2.85 was selectively oxidized to hydroxy ketone 2.84. Obviously, being able to successfully prepare 2.84 was encouraging since the further transformations of a ketone to an allylic alcohol seemed feasible. With 2.84 in hand, attention was directed to installation of the allylic alcohol. Hydrazone 2.86 was synthesized from 2.84, however, treatment of 2.86
with I₂ and base failed to furnish the desired vinyl iodide 2.81. It was then expected that ketone 2.84 would undergo olefination to furnish olefin 2.82. However, 2.82 was not observed under a variety of olefination conditions, such as Wittig olefination and Tebbe olefination.

Scheme 2.18. Synthesis of the key hydroxy ketone 2.84 and attempts to install the allylic alcohol

A. Synthesis of the key hydroxy ketone

Eventually, the total synthesis of vinigrol (2.1) was completed via a hydrazone formation/Shapiro reaction sequence (Scheme 2.19). Tosyl hydrazone 2.83 was synthesized from hydroxyl ketone 2.84 to test the Shapiro reaction. To our delight, the
natural product was synthesized in one step from 2.83 by treatment with an excess of n-BuLi and quenching the resulting trianion species 2.88 with paraformaldehyde. The spectral characteristics of natural and synthetic vinigrol are identical to those reported in the literature. In order to achieve a better yield for this final transformation, optimizations were executed as shown in the table below. Based on the literature\textsuperscript{28} reported that a major problem of using the tosyl (4-methylphenylsulfonyl) group in the Shapiro reaction is the competitive deprotonation of an ortho-position on the aromatic ring, the trisyl (2,4,6-triisopropylphenylsulfonyl) group was investigated. To our delight, the yield of Shapiro reaction was greatly improved by using trisyl hydrazone 2.87 (synthesized from 2.84). In addition, various bases (n-BuLi, s-BuLi and t-BuLi), additives (LiCl, DMPU, HMPU and TMEDA) and solvents (THF, hexanes and TMEDA) were also screened. It was determined that the combination of n-BuLi/TMEDA/THF provided the optimal yield (49\%).

**Scheme 2.19. Synthesis of vinigrol (2.1)**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Base</th>
<th>Additives</th>
<th>solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.83</td>
<td>n-BuLi</td>
<td>N/A</td>
<td>THF</td>
<td>8%</td>
</tr>
<tr>
<td>2.84</td>
<td>n-BuLi</td>
<td>N/A</td>
<td>THF</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>n-BuLi</td>
<td>LiCl</td>
<td>THF</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>n-BuLi</td>
<td>TMEDA</td>
<td>THF</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>n-BuLi</td>
<td>TMEDA</td>
<td>hexanes</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>n-BuLi</td>
<td>DMPU</td>
<td>THF</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>n-BuLi</td>
<td>HMPA</td>
<td>THF</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>n-BuLi</td>
<td>N/A</td>
<td>TMEDA</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>s-BuLi</td>
<td>TMEDA</td>
<td>THF</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>n-BuLi</td>
<td>TMEDA</td>
<td>THF</td>
<td>0%</td>
</tr>
</tbody>
</table>
2.6 Conclusion and distribution of credit

In conclusion, the venerable challenge posed by vinigrol (2.1) has been addressed by a 23 step route in 3% overall yield from commercially available materials. Aside from a minimal use of protecting group chemistry, nearly complete stereocontrol over all eight stereocenters, and the scalability of the route, notable aspects include: (1) simple formation of the decahydro-1,5-butanonaphthalene ring system by way of inter- and intramolecular Diels-Alder reactions followed by Grob fragmentation, (2) highly selective functionalization of 2.32 via an unusual dipolar cycloaddition, and (3) a Shapiro reaction that takes place via trianion intermediate 2.88.

The vinigrol core synthesis was originally designed by Dr. Phil. Baran and Dr. Tom Maimone, who was a graduate student in our lab. Dr. Tom Maimone carried out most of work on synthesis of vinigrol skeleton and studies toward the total synthesis of vinigrol. Florina Voica, a current graduate student in our lab, contributed her technical assistance to the early model study. Dr. Shinji Ashida, a postdoctoral associate, performed the optimization of the Crabtree hydrogenation and discovery of the second cycloaddition. I joined the project at the time when Tom Maimone was writing his thesis. I continued to study the total synthesis single-handedly, designed a number of plausible routes, and strived to transform the functional groups presenting in the very congested molecule. I designed and optimized a highly improved route to the synthesis of 2,3-dihydrvinigrol (2.68), and attempted dehydrogenation of dihydronigrol to the natural product. Ultimately, I designed the route to the key hydroxy ketone, conducted the final Shapiro reaction and finished the total synthesis of vinigrol.
2.7 References


(5) Keane, J. T. PCT Int. Appl. WO 2001000229, **2001**.


2.8: Experimental section

**General procedures.** All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (CH$_2$Cl$_2$), benzene, toluene, methanol (MeOH), acetonitrile, 1,2-dimethoxyethane (DME), $N,N$-dimethylformamide (DMF), and triethylamine (Et$_3$N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO$_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl$_3$ @ 7.26 ppm $^1$H NMR, 77.0 ppm $^{13}$C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin
Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.

**Compound 2.68 and Compound 2.70:** Amine 2.69 (10 mg, 0.031 mmol, 1 equiv) was dissolved in THF (0.6 mL, 0.05 M) and cooled to 0°C. t-BuNO₂ (74 µL, 0.62 mmol, 20 equiv) was added and the solution warmed up to room temperature and stirred for 12 h. The reaction was partitioned between NaHCO₃ (5.0 mL) and DCM (2.0 mL) and the aqueous layer extracted with DCM (5 × 2.0 ml). The combined organic layers were washed with saturated aqueous NaHCO₃ (3 × 10 ml), brine (10 ml), and dried (MgSO₄). The solvent was removed *in vacuo* and the crude material purified by preparative thin-layer chromatography (developed with Et₂O) to yield compound 2.68 (2.5 mg, 25%) and 2.70 (4.7 mg, 50%):

**Compound 2.68:** a white crystalline solid: m.p.: 164 –172 °C (EtOAc); TLC (pure Et₂O): \( R_f = 0.6 \); \(^1\)H NMR (600 MHz, CDCl₃) \( \delta \): 4.20 (bs, 1 H), 4.07 (s, 1 H), 3.87 (dd, \( J = 12.0, 4.2 \) Hz, 1 H), 3.72 (dd, \( J = 12.1, 4.3 \) Hz, 1 H), 2.30 – 2.27 (m, 1 H), 2.17 – 2.16 (m, 1 H), 2.15 – 2.11 (m, 1 H), 2.09 – 2.04 (m, 2 H), 1.96 – 1.94 (m, 1 H), 1.67 – 1.42 (m, 8 H), 1.33 – 1.25 (m, 5 H), 0.98 (d, \( J = 6.6 \) Hz, 3 H), 0.96 – 0.92 (m, 6 H), 0.84 (d, \( J = 6.8 \) Hz, 3 H); \(^1^3\)C NMR (150 MHz, CDCl₃) \( \delta \): 77.7, 75.3, 67.0, 50.2, 40.2, 38.9, 36.3, 34.4, 32.7, 31.9, 30.9, 29.7, 29.4, 25.5, 22.7, 22.3, 21.6, 18.9, 14.1, 13.3; IR (film) \( \nu_{\text{max}} \): 3366, 2955, 2927, 2872, 1459, 1375, 1260, 1160, 949, 907, 734 cm\(^{-1}\); HRMS (m/z): [M+Na]\(^+\) calcd. for C\(_{20}\)H\(_{36}\)O\(_3\)Na, 347.2556; found, 347.2554.

**Compound 2.70:** a white solid; TLC (pure Et₂O): \( R_f = 0.6 \); \(^1\)H NMR (600 MHz, CDCl₃) \( \delta \): 4.28 (d, \( J = 8.9 \) Hz, 1H), 4.16 – 3.93 (m, 1H), 3.83 – 3.58 (m, 1H), 2.43 – 2.16 (m, 1H), 2.01 – 1.86 (m, 3H), 1.80 – 1.71 (m, 3H), 1.73 – 1.60 (m, 3H), 1.57 – 1.36 (m, 7H), 1.26
− 1.20 (m, 3H), 1.03 (d, J = 4.7 Hz, 3H), 0.90 (d, J = 4.7 Hz, 3H), 0.85 (d, J = 4.9 Hz, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 77.0, 71.7, 63.2, 52.6, 39.3, 39.0, 37.3, 36.5, 35.7, 32.6, 30.9, 30.7, 30.5, 27.4, 26.8, 24.3, 22.59, 23.6, 21.4, 15.7. IR (film) $\nu_{\text{max}}$ 3433, 2945, 1633, 1465, 1233, 1145, 1066, 944, 722 cm$^{-1}$; HRMS (m/z): [M+H]$^+$ calcd. for C$_{20}$H$_{35}$O$_2$, 307.2631; found, 307.2645.

**Compound 2.72:** Nitrile 2.58 (23 mg, 0.072 mmol) was dissolved in MeOH (1.4 mL, 0.05 M) and 3M HCl (1.4 mL) was added and the solution was stirred for 1 h. The reaction mixture was concentrated in vacuo and the crude material purified by chromatography (developed with Et$_2$O) to yield the compound 2.72 (17 mg, 72%) as a white solid: TLC (2:1 EtOAc: hexanes): $R_f$ = 0.6; $^1$H NMR (600 MHz, CDCl$_3$) δ 4.49 (d, J = 5.5 Hz, 1H), 2.79 (s, 1H), 2.20–2.10 (m, 3H), 2.00 (d, J = 5.9 Hz, 4H), 1.79–2.10 (m, 4H), 1.50–1.45 (m, 6H), 1.33–1.25 (m, 1H), 1.06 (d, J = 6.9 Hz, 6H), 0.93 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 175.7, 90.4, 71.5, 53.5, 53.4, 46.5, 38.3, 37.6, 35.1, 34.2, 33.5, 33.4, 33.3, 30.3, 29.7, 28.0, 24.1, 22.3, 20.9, 16.3. IR (film) $\nu_{\text{max}}$ 3427, 2925, 1733, 1465, 1366, 1230, 1157, 1062, 1018, 940, 734 cm$^{-1}$; HRMS (m/z): [M+H]$^+$ calcd. for C$_{20}$H$_{33}$O$_3$, 321.2424; found, 321.2420.

**Compound 2.73:** Triol 2.68 (6.5 mg, 0.020 mmol) was dissolved in DCM (0.1 mL, 0.2 M) and CF$_3$CH$_2$NCO$^1$ (250 µL, 0.12M, 1.5 equiv) was added. The reaction solution was stirred for 2 h. The reaction mixture was concentrated in vacuo and the crude material purified by chromatography (3:1 Et$_2$O:hexanes) to yield the compound 2.73 (7.5 mg, 84%) as a white solid: TLC (1:1 EtOAc: hexanes): $R_f$ = 0.5; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.08 (brs, 1H), 4.35–4.20 (m, 1H), 4.04 (dt, J = 39.5, 19.8 Hz, 1H), 3.90–3.73 (m, 3H), 3.62 (d, J = 7.8 Hz, 1H), 2.59 (brs, 1H), 2.28–2.20 (m, 1H), 2.21–2.03 (m, 2H),
1.94 – 1.88 (m, 2H), 1.81 – 1.69 (m, 3H), 1.68 – 1.40 (m, 5H), 1.35 – 1.24 (m, 5H), 1.01 (d, J = 6.6 Hz, 3H), 0.99 – 0.97 (m, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). IR (film) ν_{max} 3323, 2944, 2832, 2047, 1654, 1449, 1415, 1113, 1021 cm^{-1}; HRMS (m/z): [M+Na]^+ calcd. for C_{23}H_{38}F_{3}NO_{4}Na, 472.2645; found, 472.2644.

**Compound 2.74:** i. Carbamate 2.73 (5.5 mg, 11 µmol) was dissolved in DCM (0.55 mL, 0.02 M). Ac_{2}O (4 µL, 33 µmol, 3.0 equiv), Et_{3}N (10 µL, 0.066 mmol, 6.0 equiv), and DMAP (ca. 0.3 mg, 3 µmol, 0.3 equiv) was added. The reaction solution was stirred for 2 h, at which point it was diluted with CH_{2}Cl_{2} (4 mL), washed with sat. aq. NaHCO_{3} (5 mL) and H_{2}O (5 mL), dried with MgSO_{4}, filtered, and concentrated in vacuo. The crude material purified by preparative thin-layer chromatography (developed with Et_{2}O) as a white solid.

ii. The abovementioned acetate was dissolved in DCM (0.22 mL, 0.05 M) and AcOBr (147 µL, 0.09M, 1.2 equiv) was added. The reaction mixture was stirred for 10 min, at which point it was concentrated in vacuo and the crude material (it is not stable and must be used for the next reaction in 30 min) is 95% pure by ^{1}H NMR:TLC (1:1 EtOAc: hexanes): R_{f} = 0.7; ^{1}H NMR (500 MHz, CDCl_{3}) δ 5.30 (d, J = 3.2 Hz, 1H), 4.19 (dd, J = 16.4, 8.2 Hz, 2H), 4.13 – 4.06 (m, 2H), 2.74 (brs, 1H), 2.07 (s, 3H), 2.05 – 2.00 (m, 3H), 1.94 (s, 1H), 1.88 – 1.75 (m, 3H), 1.72 – 1.39 (m, 6H), 1.37 – 1.28 (m, 5H), 1.00 (dd, J = 6.6, 4.4 Hz, 6H), 0.95 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H).

**Compound 2.79:** Carbamate 2.74 (5 mg, 0.023 mmol) was dissolved in CCl_{4} (0.1 mL, 0.23 M). The reaction solution was stirred under light (100 W, sunlump) for 10 min, at which point it was concentrated in vacuo and the crude material was purified by preparative thin-layer chromatography (developed with Et_{2}O) as a white waxy solid. ^{1}H
NMR (600 MHz, CDCl$_3$) $\delta$ 5.28 (d, $J = 3.9$ Hz, 1H), 5.00 (s, 1H), 4.83 (s, 1H), 4.71 (s, 1H), 4.02 (dt, $J = 19.1$, 9.9 Hz, 3H), 3.85 – 3.75 (m, 3H), 2.69 (d, $J = 15.2$ Hz, 1H), 2.28 – 2.12 (m, 3H), 2.06 (s, 3H), 2.00 (dd, $J = 21.7$, 14.9 Hz, 2H), 1.83 – 1.61 (m, 4H), 1.50 – 1.33 (m, 9H), 0.94 (d, $J = 6.6$ Hz, 4H), 0.86 (d, $J = 6.9$ Hz, 4H). IR (film) $\nu_{\text{max}}$ 2953, 2924, 2854, 1735, 1466, 1389, 1366, 1231, 1157, 1018 cm$^{-1}$; HRMS ($m/z$): [M+Na]$^+$ calcd. for C$_{25}$H$_{38}$F$_3$NO$_5$Na, 512.2594; found, 512.2591.

**Compound 2.84**: Olefin 2.48 (59 mg, 0.21 mmol, 1 equiv.) was dissolved in Acetone:H$_2$O = 3:1 (4 mL), OsO$_4$ (218 $\mu$L, 0.02 mmol, 0.1 equiv.) and NMO (32 mg, 0.27 mmol, 1.3 equiv.) were added. The reaction mixture was stirred for 12 hours at room temperature and then quenched at this temperature by the dropwise addition of saturated aqueous NaHCO$_3$ (25 mL). The reaction mixture was partitioned between saturated aqueous Na$_2$S$_2$O$_3$ (10 mL) and DCM (15 mL), and the aqueous layer extracted with DCM (10 mL, 2X). The combined organic layers were washed with H$_2$O (20 mL), brine (20 mL) and dried (MgSO$_4$). Volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et$_2$O) to afford triol (61 mg, 95%) as a colorless solid.

The aforementioned triol (45 mg, 0.145 mmol, 1 equiv.) was dissolved in DCM (5 mL) followed by the addition of 5% aqueous NaHCO$_3$ (2.0 mL), KBr (1.7 mg, 0.014 mmol, 0.10 equiv.) and TEMPO (2.2 mg, 0.014, 0.10 equiv.). The biphasic mixture was cooled to 0 $^\circ$C and bleach (commercial bleach solution, 6% NaOCl, 0.27 mL, 0.22 mmol, 1.5 equiv.) was added dropwise to the rapidly stirring mixture. The reaction mixture was stirred for 1.5 hours at 0 $^\circ$C and then partitioned between saturated aqueous Na$_2$S$_2$O$_3$ (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (10 mL, 2X) and
the combined organic layers were washed with brine (25 mL) and dried (MgSO$_4$). Volatiles were removed in vacuo and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et$_2$O) to afford to yield ketone 2.84 (37 mg, 85%) as a white foam: TLC (EtOAc:hexanes, 1:1 v/v): $R_f$ = 0.5; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.35 (d, $J$ = 3.9 Hz, 1 H), 3.86 (bs, 1 H), 2.75 (dd, $J$ = 17.7, 9.8 Hz, 1 H), 2.44 (d, $J$ = 9.6 Hz, 1 H), 2.22 (d, $J$ = 17.8 Hz, 1 H), 2.15 (bs, 1 H), 1.96 (s, 2 H), 1.73 – 1.66 (m, 4 H), 1.67 – 1.60 (m, 2 H), 1.57 – 1.41 (m, 4 H), 1.45 – 1.34 (m, 2 H), 1.00 (d, $J$ = 4.3 Hz, 3 H), 0.94 (d, $J$ = 6.4 Hz, 3 H), 0.86 (d, $J$ = 6.6 Hz, 6 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 213.9, 76.6, 73.4, 58.6, 42.4, 40.5, 38.7, 37.5, 36.1, 35.4, 31.6, 31.5, 29.0, 25.5, 24.7, 24.0, 21.5, 20.4, 14.2; IR (film) $\nu_{max}$ 3438, 2955, 1711, 1465, 1374, 1235, 1099, 941 cm$^{-1}$; HRMS (m/z): [M+Na]$^+$ calcd. for C$_{19}$H$_{32}$NaO$_3$, 331.2244; found, 331.2245.

**Compound 2.83**: Ketone 2.84 (22 mg, 0.071 mmol, 1 equiv.) was dissolved in CH$_2$Cl$_2$ (0.7 mL, 0.1 M) and 4-methylbenzenesulfonyl hydrazide (66 mg, 0.36 mmol, 5 equiv.) was added. The reaction mixture was stirred for 5 hours at room temperature. Volatiles were removed in vacuo and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et$_2$O) to afford hydrazone 2.83 as inseperable mixture of Z- and E- isomers (31 mg, 93%) as a white foam: TLC (EtOAc:hexanes, 1:1 v/v): $R_f$ = 0.7; Both Z and E isomers of 2.83 are observed, here reported the major isomer: $^1$H NMR (600 MHz, CD$_3$OD) $\delta$ 7.84 (d, $J$ = 7.5 Hz, 2H), 7.38 (d, $J$ = 7.8 Hz, 2H), 4.24 (s, 1H), 2.68 (dd, $J$ = 16.9, 7.3 Hz, 1H), 2.44 (s, 3H), 2.40 – 2.29 (m, 4H), 2.21 – 2.06 (m, 3H), 1.94 – 1.59 (m, 4H), 1.54 – 1.50 (m, 3H), 1.49 – 1.25 (m, 5H), 0.97 – 0.95 (m, 6H), 0.90 (d, $J$ = 5.8 Hz, 3H), 0.86 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (151 MHz, D$_2$O) $\delta$ 176.6, 143.7, 129.1, 127.7, 125.7, 76.2, 73.1, 53.2, 47.8, 47.3, 41.8, 40.6, 36.7, 34.8, 32.0, 31.4, 29.2, 25.3,
24.7, 23.2, 22.2, 20.9, 20.1, 13.4. IR (film) $\nu_{\text{max}}$ 3478, 3172, 2881, 1604, 1454, 1416, 1343, 1163, 1037, 954, 845, 732 cm$^{-1}$; HRMS ($m/z$): [M+H]$^+$ calcd. for C$_{26}$H$_{41}$N$_2$O$_4$S, 477.2781; found, 477.2790.

**Compound 2.87:** Ketone 2.84 (35 mg, 0.11 mmol, 1 equiv.) was dissolved in CH$_2$Cl$_2$ (1 mL) and 2,4,6-Triisopropylbenzenesulfonyl hydrazide (68 mg, 0.22 mmol, 2 equiv.) was added. The reaction mixture was stirred for 5 hours at room temperature. Volatiles were removed in vacuo and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et$_2$O) to afford hydrazone 11 as inseperable mixture of Z- and E- isomers (32 mg, 96%) as a white foam: TLC (EtOAc:hexanes, 1:1 v/v): $R_f$ = 0.7; Both Z and E isomers of 11 are observed, here reported the major isomer: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.60 (brs, 1 H), 7.15 (s, 2 H), 4.34 (brs, 1 H), 4.27 (brs, 2 H), 2.91 – 2.76 (m, 1 H), 2.39 – 2.32 (m, 1 H), 2.10 – 1.88 (m, 4 H), 1.61 – 1.45 (m, 4 H), 1.45 – 1.34 (m, 7 H), 1.27 – 1.22 (m, 21 H), 0.93 – 0.88 (m, 12 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 160.2, 153.3, 151.5, 131.0, 123.7, 71.2, 55.4, 40.2, 39.9, 37.1, 35.3, 29.9, 29.7, 28.9, 25.5, 24.8, 24.0, 23.6, 23.1, 21.7, 20.6, 14.3; IR (film) $\nu_{\text{max}}$ 3484, 3173, 2957, 2871, 1600, 1462, 1426, 1383, 1320, 1164, 1153, 1037, 940, 882, 732 cm$^{-1}$; HRMS ($m/z$): [M+H]$^+$ calcd. for C$_{34}$H$_{56}$N$_2$O$_4$S, 589.4033; found, 589.4037.

**Compound 2.1:** To a flame dried tube was added hydrazone 2.87 (25.0 mg, 0.043 mmol, 1.0 equiv.) and THF:TMEDA = 1:2 (2.1 mL) under Argon. The solution was cooled to – 78 °C and n-BuLi (2.49 M in Hexanes, 72 µL, 0.17 mmol, 4.0 equiv.) was added dropwise. The mixture was stirred for 1 hour at –78 °C, warmed to 0 °C and stirred for 20 minutes, then room temperature and stirred for 10 minutes, finally cooled back to 0 °C and stirred for 5 minutes. Paraformaldehyde (39 mg, 1.29 mmol, 30 equiv., in 0.1 mL
THF) was added dropwise at 0 °C and the solution stirred for 5 minutes at 0 °C. The mixture was then slowly warmed to room temperature and stirring continued for 20 minutes at this temperature. The reaction was partitioned between saturated aqueous NH₄Cl (5 mL) and DCM (5 mL) and the aqueous layer extracted with DCM (5 mL, 2X). The combined organic layers were washed with 1 N HCl (10 mL, 2X), brine (10 mL), dried (MgSO₄), and the volatiles removed in vacuo. The crude material was purified by PTLC (pure Et₂O) to afford vinigrol 2.1 (7.5 mg, 53%) as a colorless film: TLC (pure Et₂O): Rₛ = 0.6; ¹H NMR (600 MHz, CDCl₃) δ 5.83 (d, J = 5.5 Hz, 1 H), 4.30 (AB q, J = 12.0 Hz, 2 H), 4.20 (s, 1 H), 3.40 (bs, 1 H), 2.65 (bs, 1 H), 2.30 (d, J = 5.4 Hz, 1 H), 2.25 (d, J = 3.7 Hz, 1 H), 2.15 – 2.09 (m, 1 H), 1.99 – 1.93 (m, 2 H), 1.80 – 1.70 (m, 5 H), 1.65 – 1.50 (m, 4 H), 1.40 – 1.05 (m, 6 H), 1.00 – 0.95 (m, 9 H), 0.90 (d, J = 6.8 Hz, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ 136.5, 128.4, 127.8, 75.5, 72.8, 67.9, 51.1, 45.5, 44.2, 40.2, 35.8, 34.5, 33.0, 29.6, 28.9, 28.6, 27.2, 24.8, 21.5, 20.5, 15.3; IR (film) νₘₐₓ 3393, 2955, 2928, 2851, 1469, 1385, 1262, 1138, 1109, 966, 904 cm⁻¹; HRMS (m/z): [M+H]+ calcd. for C₂₀H₃₄NaO₃, 345.2400; found, 345.2407.
Table 1. $^1$H NMR data comparison between synthetic vinigrol (2.1), natural vinigrol (natural sample provided by Astellas Pharma Inc. (Japan)) and natural vinigrol reported data$^1$.

<table>
<thead>
<tr>
<th>Synthetic Vinigrol (1) $^1$H NMR (CDCl₃, 600 MHz)</th>
<th>Natural Vinigrol $^1$H NMR (CDCl₃, 600 MHz, sample provided by Astellas Pharma Inc.)</th>
<th>Natural Vinigrol $^1$H NMR (CDCl₃, 400 MHz, reported by ref. 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta$, multiplicity, coupling constant (Hz)</td>
<td>$\delta$, multiplicity, coupling constant (Hz)</td>
<td>$\delta$, multiplicity, coupling constant (Hz)</td>
</tr>
<tr>
<td>5.83, d, 5.5</td>
<td>5.83, d, 5.5</td>
<td>5.81, d, 5.6</td>
</tr>
<tr>
<td>4.30, AB q, 12.0</td>
<td>4.30, AB q, 12.0</td>
<td>4.25, AB q, 12.0</td>
</tr>
<tr>
<td>4.20, s</td>
<td>4.19, bs</td>
<td>4.20, s</td>
</tr>
<tr>
<td>3.40, bs</td>
<td>3.40, bs</td>
<td>–</td>
</tr>
<tr>
<td>2.65, bs</td>
<td>2.65, bs</td>
<td>–</td>
</tr>
<tr>
<td>2.30, d, 5.4</td>
<td>2.30, d, 5.4</td>
<td>2.32, d, 5.6</td>
</tr>
<tr>
<td>2.25, d, 3.7</td>
<td>2.25, d, 3.7</td>
<td>2.23, d, 3.6</td>
</tr>
<tr>
<td>2.15 - 2.09, m</td>
<td>2.15 - 2.09, m</td>
<td>2.12, m</td>
</tr>
<tr>
<td>1.99 - 1.93, m</td>
<td>1.99 - 1.93, m</td>
<td>1.96, m</td>
</tr>
<tr>
<td>1.80 - 1.70, m</td>
<td>1.80 - 1.70, m</td>
<td>1.8 - 1.5, m</td>
</tr>
<tr>
<td>1.65 - 1.50, m</td>
<td>1.65 - 1.50, m</td>
<td>–</td>
</tr>
<tr>
<td>1.40 - 1.05, m</td>
<td>1.40 - 1.05, m</td>
<td>1.4 - 1.0, m</td>
</tr>
<tr>
<td>1.00 - 0.95, m</td>
<td>1.00 - 0.95, m</td>
<td>1.0 - 0.8, m</td>
</tr>
<tr>
<td>0.9, d, 8.8</td>
<td>0.9, d, 6.8</td>
<td>–</td>
</tr>
</tbody>
</table>
Table 2. $^1$C NMR data comparison between synthetic vinigrol (2.1), natural vinigrol (natural sample provided by Astellas Pharma Inc. (Japan)) and natural vinigrol reported data$^1$.

<table>
<thead>
<tr>
<th>Synthetic Vinigrol (1) $^{13}$C NMR (CDCl$_3$, 150 MHz) (δ)</th>
<th>Natural Vinigrol (1) $^{13}$C NMR (CDCl$_3$, 150 MHz, sample provided by Astellas Pharma Inc.) (δ)</th>
<th>Natural Vinigrol (1) $^{13}$C NMR (CDCl$_3$, 100 MHz, reported by ref. 1) (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>136.5</td>
<td>136.4</td>
<td>136.5</td>
</tr>
<tr>
<td>128.4</td>
<td>128.5</td>
<td>128.5</td>
</tr>
<tr>
<td>75.5</td>
<td>75.5</td>
<td>75.5</td>
</tr>
<tr>
<td>72.8</td>
<td>72.8</td>
<td>72.7</td>
</tr>
<tr>
<td>67.9</td>
<td>67.9</td>
<td>67.6</td>
</tr>
<tr>
<td>51.1</td>
<td>51.1</td>
<td>51.3</td>
</tr>
<tr>
<td>45.5</td>
<td>45.3</td>
<td>45.1</td>
</tr>
<tr>
<td>44.2</td>
<td>44.2</td>
<td>44.3</td>
</tr>
<tr>
<td>40.2</td>
<td>40.2</td>
<td>40.3</td>
</tr>
<tr>
<td>35.8</td>
<td>35.8</td>
<td>35.9</td>
</tr>
<tr>
<td>34.5</td>
<td>34.5</td>
<td>34.6</td>
</tr>
<tr>
<td>33.0</td>
<td>33.0</td>
<td>33.1</td>
</tr>
<tr>
<td>29.6</td>
<td>29.6</td>
<td>29.7</td>
</tr>
<tr>
<td>28.9</td>
<td>28.9</td>
<td>28.9</td>
</tr>
<tr>
<td>28.6</td>
<td>28.6</td>
<td>28.6</td>
</tr>
<tr>
<td>27.2</td>
<td>27.2</td>
<td>27.3</td>
</tr>
<tr>
<td>24.8</td>
<td>24.8</td>
<td>24.8</td>
</tr>
<tr>
<td>21.5</td>
<td>21.5</td>
<td>21.5</td>
</tr>
<tr>
<td>20.5</td>
<td>20.5</td>
<td>20.6</td>
</tr>
<tr>
<td>15.3</td>
<td>15.3</td>
<td>15.5</td>
</tr>
</tbody>
</table>
Reference:

2.9 Appendix to Chapter 2: Spectra
X-ray Crystal Structure
Chapter 3

Study Towards the Total Synthesis of Maoecrystal V
3.1 Introduction

Maoecrystal V (3.1), a novel diterpenoid, was isolated from the leaves of a Chinese medicinal herb, *Isodon eriocalyx*, in 1994 by Sun and coworkers.\(^1\) Although its NMR and MS spectra data have been established since isolation, the structure of maoecrystal V was not elucidated until 2004 after obtaining a suitable single crystal for X-ray crystallographic analysis. Structurally, maoecrystal V possesses a unique 6,7-seco-6-nor-15(8→9)-abeo-5,8-epoxy-ent-kaurane, featured with a highly congested pentacyclic ring system with seven stereocenters, three of which are quaternary ring junctions and it is considered as the most modified naturally occurring *ent*-kauranoid isolated so far.\(^2\)

Maoecrystal V (3.1) exhibits significant cytotoxicity against HeLa cell (IC\(_{50} = 0.02\) ug/mL, *cis*-platin: IC\(_{50} = 0.99\) ug/mL) while it shows almost noncytotoxicity toward other human tumor cell lines (K562, A549, BGC-823) in the same bioassay, indicating it has highly selective cytotoxicity towards cervical cancer cells.\(^1\)

**Scheme 3.1.** Structure of maoecrystal V (3.1)
The structural evolution among *ent*-kaurane diterpenoids was proposed based on an *in vivo* biosynthesis study from a commonly occurring 7,20-epoxy-*ent*-kaurane (3.5). Cleavage of the C6–C7 bond in 3.5 leads to 3.6. Subsequent C8–C15 bond cleavage and condensation provides the skeleton of maoecrystal Z (3.7). When 3.5 is further oxidized to carboxylic acid 3.8 (the skeleton of maoecrystal N and O), subsequent decarboxylation and rearrangement would result in the formation of the maoecrystal V skeleton (3.10). Although these enzymatically-catalyzed biotransformations are intriguing, it is neither practical nor feasible to adopt such transformations efficiently in a synthetic design, at least with today’s technology.

Scheme 3.2. Origins of maoecrystals

A. Other maoecrystals from the family

B. Proposed biogenesis of maoecrystals
Due to its unique architecture as well as its interesting biological activity, maoecrystal V (3.1) has received significant attention from the synthetic community since its discovery. Several research groups have reported progress towards the synthesis of maoecrystal V (3.1). At the end of 2010, Yang and coworkers published the first total synthesis.

### 3.2 Synthetic Strategy

Our laboratory embarked on the total synthesis of maoecrystal V in 2005, anticipating a concise and elegant approach towards its construction. Our initial strategy was outlined in Scheme 3.3. The key feature of the route includes the formation of a bicyclic ring system via an intramolecular Diels-Alder (IMDA) reaction of a diene/acrylate conjugate 3.12. The latter could be generated from dearomatization of the phenol 3.13 and subsequent acylation. It was envisioned that 3.13 could arise from arylation of 3.14.

**Scheme 3.3. Initial retrosynthetic analysis**

Following this retrosynthetic analysis, a concise route to the skeleton of 3.1 was reported from our laboratory in 2009 (Scheme 3.4). The synthesis commences with Barton arylation of β-keto aldehyde 3.16 and following aldehyde reduction furnished alcohol 3.17. Acylation of alcohol 3.17, methoxymethyl ether group removal and
Pb(OAc)$_4$ mediated dearomatization$^{10}$ of the resulting phenol afforded Diels-Alder reaction$^{11}$ precursor 3.18, which provided bicycle 3.19 in 79% yield upon heating at 165 °C for 1.5 h. Subsequent hydrogenation of the olefin and SmI$_2$ mediated acetate removal$^{12}$ delivered 3.20, whose structure contains the complete carbon skeleton of maoecrystal V. Further attempts towards oxygenation of C8 by Rubottom oxidation$^{13}$, unfortunately, only led to C8 hydroxy epimer 3.21.

**Scheme 3.4.** Synthesis of the carbon skeleton of maoecrystal V by Krawczuk and coworkers$^7$

3.3 Attempts to install the THF ring

Now that the essential carbon skeleton of maoecrystal V was successfully constructed, the focus of future efforts shifted to the formation of the THF ring and installation of A ring functionalities. Since undesired *epi*-C8 hydroxy 3.21 was obtained from intermediate 3.20 (Scheme 3.4), which only carries C3 OTBS group on the A-ring, it was envisioned that the stereoselectivity of C8 oxidation could be altered and the
correct facial selectivity might be achieved in presence of A-ring functionalities. To test this hypothesis, the requisite A ring enone was installed (Scheme 3.5). In a similar fashion (vide supra), acylation, methoxymethyl ether group deprotection and Pd(OAc)$_4$ mediated dearomatization led to 3.23. Subsequent Diels-Alder reaction occurred smoothly and SmI$_2$-mediated acetate removal afforded the correct C16 isomer 3.24-1 as a minor diastereomer. Although SeO$_2$ mediated allylic oxidation$^{14}$ successfully delivered a mixture of enone 3.25 (32%) and allylic alcohol 3.27 (45%), initial attempts to selectively reduce C11-C12 olefin in the presence of A ring olefin met with enormous difficulties. Due to the fact that the bicyclic olefin is more hindered than A ring olefin (C2–C3), under a number of hydrogenation conditions C2–C3 olefin was preferentially reduced. It was thus rationalized that it might be more logical to construct the A ring olefin after reduction of the C11–C12 olefin (Scheme 3.5B). As such, 3.19 was converted into ketone 3.28 via the following sequence: (1) C11–C12 olefin reduction, (2) TBS deprotection and (3) Dess-Martin periodinane oxidation. Subsequently, tosyl hydrazone formation and Shapiro reaction installed the C2–C3 olefin. With this substrate, SmI$_2$-mediated acetate removal afforded the correct C16 isomer 3.29 as major diastereomer, which was subjected to SeO$_2$-mediated allylic oxidation to afford the desired enone 3.26. Since A ring and bicycle functionalities have been successfully installed, all that remained was to introduce THF ring. Thus, a set of experiments was investigated in order to install the C8 alcohol with the correct stereochemistry (Scheme 3.5C). Unfortunately, Rubottom oxidation$^{13}$ of 3.25, 3.26 and 3.27 were unsuccessful, while oxidation of 3.29 only led to the formation of $epi$-C8 hydroxyl 3.31.
Scheme 3.5. Installation of A-ring enone and attempts to oxygenate C8

A. Attempts to selectively reduce C11-C12 olefin

Since A ring functionalization has been proven to be feasible, in essence, all that was left to complete the synthesis was to correct the stereochemistry of the C8 alcohol.
As such, a retro-aldol/aldol strategy\textsuperscript{15} was investigated to epimerize the C8 alcohol (Scheme 3.6). It was expected that the C8 alcohol would undergo retro-aldol reaction to generate macrocycle 3.22. Due to the ring strain of the macrocycle, subsequent aldol reaction would immediately close the bicycle and form the THF ketal ring. Further reduction of the C5 ketal would produce the desired THF ring.

Scheme 3.6. Proposed retro-aldol/aldol strategy to epimerize C8 alcohol

Acidic conditions were introduced initially for this strategy.\textsuperscript{15f} While most acids ($p$-TsOH, TFA, H\textsubscript{2}SO\textsubscript{4}) only led to decomposition, two unexpected intermediates 3.35 and 3.36 were observed under the condition of MeOH and HCl at 50 °C. The possible reaction pathway for the formation of 3.35 and 3.36 is depicted in Scheme 3.7: retro-aldol reaction might produce $\alpha$-keto ester 3.32; C8 ketone tautomerized to enol 3.37 and subsequent condensation could lead to the formation of 3.35. From the same intermediate 3.32, deformylation and cyclodehydration produced 3.36. The formation of 3.35 and 3.36 indicated that our proposed the retro-aldol reaction did occur as planned, however under the experimental conditions, enol 3.37 favored to cyclize to the C5 ketone over the desired aldol reaction.
Scheme 3.7. Acid mediated retro-aldol reaction

As an alternative to acid-mediated retro-aldol/aldol reaction, we turned our attention to the use of amines, a well-documented reagent in retro-aldol/aldol reaction.\textsuperscript{15a, 15d, 15e} Unfortunately, treatment of 3.21 with pyrrolidine only produced 3.40, possibly generated from the retro-aldol reaction followed by lactone opening (Scheme 3.8). It was anticipated that 3.40 could further undergo aldol reaction to close the bicycle and form the THF ring. However, only the formation of dihydrofuran 3.42 was observed.

Thus far, all efforts to epimerize the C8 alcohol have met with failure to produce the desired result. While retro-aldol reaction appeared to occur readily, the aldol reaction of the resulting macrocycle 3.32 encountered tremendous difficulties. Owing to the ring strain and sensitive function groups, macrocycle 3.32 was prone to perform undesired
enol (3.37, Scheme 3.7) cyclization or lactone (3.40, Scheme 3.8) opening. Therefore, we discontinued further studies towards the epimerization of the C8 hydroxyl group.

**Scheme 3.8.** Retro-aldol reaction by using amine

3.4 Attempts to synthesize the key diol 3.44

Given the fact that late stage installation of THF ring met with failure, installation of the THF ring at an earlier stage of the synthesis was pursued next. To obtain the core structure of maoecrystal V, an efficient Diels-Alder reaction, which would lead to the formation of THF ring and bicycle simultaneously, was proposed as shown in Scheme 3.9. In order to obtain the key precursor 3.43, acylation and etherification were postulated to form the required seven-membered lactone from diol 3.44. Due to the fact that the C5
alcohol and the C20 adopt cis-orientation on the cyclohexane which is embedded in the natural product, it was believed that diol 3.44 could provide a key foundation for the THF ring synthesis, which may possibly solve the remaining problem towards the total synthesis of maoecrystal V. While this synthetic route bears a resemblance to Yang and coworkers’ work reported in late 2010, it is worth mentioning that our lab has considered this disconnection immediately after I joined this project and has been pursuing this approach independently since the beginning of 2010.

**Scheme 3.9.** Retrosynthetic analysis led to diol 3.44

For the first foray to synthesize diol 3.44, a straightforward reduction of C5 ketone of our early stage intermediate 3.22 was pursued. Unfortunately it only led to the formation of the undesired diastereomer 3.45 under a number of reduction conditions. Therefore, an alternative synthesis of diol 3.44 was required.

**Scheme 3.10.** Reduction of C5 ketone
Inspired by the generation of quaternary carbon centers via a semi-pinacol rearrangement reported by Snap,\textsuperscript{16} it was rationalized that the key diol 3.44 could be produced from the epoxy-alcohol via a semi-pinacol rearrangement (Scheme 3.11A). To test this proposal, epoxy alcohol 3.49 was synthesized from enone 3.48 via the following sequence shown in Scheme 3.11B: (1) Baylis-Hillman reaction to install the primary alcohol;\textsuperscript{17} (2) Aryl lithium addition to the ketone; and (3) \( m \)-CPBA mediated epoxidation. In order to achieve the key semi-pinacol rearrangement, a variety of Lewis acids (TiCl\(_4\), Sc(OTf)\(_3\), BF\(_3\)Et\(_2\)O, BBr\(_3\), TMSOTf) were examined, however no desired product was generated. In these cases, only decomposition was observed. It was postulated that the cause of the decomposition might derive from the unprotected primary alcohol and tertiary alcohol. Thus, the formation of 3.50 was performed using \( t \)-Bu\(_2\)Si(OTf)\(_2\). When 3.50 was subjected to BF\(_3\)·Et\(_2\)O followed by treatment with HF·Py, it was initially concluded that 3.44 was successfully synthesized because all the NMR spectra (\(^1\)H-NMR, \(^13\)C-NMR, HMQC, HMBC, COSY, ROSEY) and mass spectrometry data favorably suggested the formation of structure 3.44. However, the actual product was later revealed to be 3.51, which was elucidated by X-ray crystallography of its derivative 3.52. A possible explanation for the formation of 3.51 could be a sequential tandem ring expansion/contraction reaction sequence. It is proposed that under the mediation of BF\(_3\)·Et\(_2\)O, instead of the desired epoxide opening, the benzylic tertiary alcohol at C1 was preferentially activated due to its superior ionizability, which led to the formation of oxonium species 3.53 and the subsequent cyclized acetal 3.54. With HF·Py, fluoride ion
is likely to attack the silicon center causing the production of aldehyde 3.55. Further intramolecular aldol condensation would ultimately lead to the formation of 3.51.

**Scheme 3.11. Semi-pinacol strategy to synthesize diol 3.44**

A. Semi-pinacol strategy to synthesize diol 3.44

B. Semi-pinacol rearrangement led to 3.51

Since we initially misassigned the structure of 3.44, while focusing on obtaining a high quality crystal of 3.52, 3.51 was taken further in the synthesis as shown in Scheme 3.12. Acylation and diazo group formation produced 3.56. Initial Rh$_2$(OAc)$_4$ mediated O–
H insertion\textsuperscript{18} of 3.56 was unsuccessful, instead, the carbene species inserted into the C1 ketone and generated an undesired epoxide.\textsuperscript{19} To prevent such an event, protection of the ketone by formation of cyanohydrin was evaluated.\textsuperscript{20} However, treatment of 3.56 with Et\textsubscript{2}AlCN provided 3.58 via a retroaldol-ketal formation sequence. Rh-mediated O–H insertion occurred smoothly on 3.58 to afford cyclic ketal 3.59. Horner-Wadsworth-Emmons olefination\textsuperscript{21} of 3.59 produced 3.60, whose structure was confirmed by X-ray analysis. Subsequent deprotection, dearomatization and intramolecular Diels-Alder reaction furnished 3.61, whose structure was also verified by X-ray analysis.

**Scheme 3.12.** Synthesis sequence on unexpected substrate 3.51
While we were pursuing the abovementioned semi-pinacol approach, Yang’s lab published the first total synthesis of maoecrystal V. In their synthesis, a similar Diels-Alder disconnection was presented, however, suffering from low facial selectivity. It was proposed that the Diels-Alder reaction of our substrate might produce a better selectivity due to the ketone moiety on C1 which can potentially block the rotation of diene (Scheme 3.9). In essence, what we need is diol 3.44 with C5 and C10 in cis-orientation on the ring. As 1,3-dipolar cycloaddition to a suitable cyclohexene ideally meets such requirement, an alternative approach to diol 3.44 via a 1,3-dipolar cycloaddition-reduction sequence was evaluated as shown in Scheme 3.13. While efforts towards the direct cycloaddition of bromonitrile oxide to enone 3.63 failed to produce the desired product, a stepwise route was carried out instead. Treatment of enone 3.49 and dibromoformaldoxime with Na2CO3 furnished cycloadduct 3.63. While initial arylation of 3.63 with Ar2IBF4 failed, after extensive experimentation, it was eventually discovered that arylation took place under the condition of LDA and Ar3BiCl2 to produce 3.62. It was envisioned that the reduction of 3.62 would produce diol 3.44 which might hold the key to a stereocontrolled total synthesis of maoecrystal V. This route is current under investigation.
3.5 Conclusion and distribution of credit

In conclusion, the A ring enone functionality has been successfully installed on the skeleton of maoecystal V. Numerous endeavors to construct the THF ring of maoecystal V, such as oxygenations of C8 and retro-aldol/aldol strategy, were carried out. However, such efforts failed to install the requisite THF ring. Further attempts, including direct reduction, semi-pinacol rearrangement and 1,3-cycloaddition, to synthesize diol 3.44 were pursued. While direct reduction of 3.22 gave the wrong
diastereomer 3.45 and semi-pinacol strategies produced a undesired product 3.51, the 1,3-cycloaddition strategy successfully furnished cycloadduct 3.62, which might lead to the preparation of the key diol 3.44.

Maoecrystal V skeleton synthesis was originally designed by Dr. Phil. Baran, Paul Krawczuk, a current graduate student in our lab, and Dr. Niklas Schöne, a former postdoctoral associate. Paul and Niklas carried out the synthesis of maecrystal V skeleton. I joined the project at the end of 2009 after they published their initial approach to maecrystal V skeleton. I have designed a number of plausible routes, and strived to transform the functional groups present in this highly sensitive and congested molecule. I have discovered the method to functionalize A ring and studied oxidations of C8 on advanced A-ring intermediates. I proposed the retro-aldol/aldol strategy (Scheme 3.7), semi-pinacol rearrangement approach (scheme 3.11) and identified all the unexpected products. Lastly, I have proposed the 1,3-cycloaddition reaction route and managed to synthesize cycloadduct 3.62.
3.6 References


B.; Finet, J. P.; Motherwell, W. B.; Papoula, M. T. B.; Stanforth, S. P. J. Chem. Soc.,
Perkin Trans. 1 1985, 2667-2675. (c) Barton, D. H. R.; Finet, J. P.; Giannotti, C.; Halley,

(10) (a) Wessely, F.; Sinwel, F. Monatsh. Chem. 1950, 81, 1055-1070. (b) Yates, P.;
Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.;

(11) (a) Barnes-Seeman, D.; Corey, E. J. Org. Lett. 1999, 1, 1503-1504. For review: (b)


(14) (a) Corey, E. J.; Schaefer, J. P. J. Am. Chem. Soc. 1960, 82, 917-929. (b) Umbreit,
Lett. 2007, 9, 1825-1828.

(15) (a) Xu, K.; Lalic, G.; Sheehan, S. M.; Shair, M. D. Angew. Chem., Int. Ed. 2005, 44,
2259-2261. (b) Wang, J.; Cole, K. P.; Wei, L.-L.; Zehnder, L. R.; Hsung, R. P.
Lett. 2008, 49, 6202-6204. For base-mediated retro-aldol-aldol reaction: (d) Flock, A. M.;
Li, J.; Cheng, J.-P. Chem. Eur. J. 2010, 16, 4457-4461. For acid-mediated retro-aldol-


3.7: Experimental section

**General procedures.** All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (CH$_2$Cl$_2$), benzene, toluene, methanol (MeOH), acetonitrile, 1,2-dimethoxyethane (DME), N,N-dimethylformamide (DMF), and triethylamine (Et$_3$N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO$_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl$_3$ @ 7.26 ppm $^1$H NMR, 77.0 ppm $^{13}$C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded
on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.

**Compound 3.23:** i. To a stirred solution of compound 3.22 (401 mg, 1.3 mmol), DMAP (51 mg, 390 µmol, 0.3 equiv) and i-Pr₂EtN (1.3 mL, 7.7 mmol, 6 equiv) in CH₂Cl₂ (13 mL, 0.1 M) at −78 ºC was added acryloyl chloride (318 µL, 3.9 mmol, 3 equiv) dropwise down the wall of the reaction vessel. The reaction mixture was then stirred for 10 min until complete conversion was detected by TLC. Then MeOH (154 µL, 3.9 mmol) was added dropwise down the glass wall to quench excess acid chloride. The reaction mixture was warmed to rt and chromatography with 3:1 hexanes:EtOAc furnished acrylate (335 mg, 72%) as a colorless oil.

ii. To a solution of the abovementioned acrylate (335 mg, 0.94 mmol) in CH₂Cl₂ (9.4 mL) was added Amberlyst 15 (335 mg). After 2 h, the reaction mixture was filtered through a plug of silica gel, which was then washed with CH₂Cl₂. Silica gel chromatography with 3:1 hexanes:EtOAc furnished phenol (250 g, 85%) as a white foam.

iii. To a stirred solution of abovementioned phenol (250 mg, 0.8 mmol) in AcOH (16 mL 0.05 M) was added Pb(OAc)₄ (537 mg, 1.2 mmol) quickly at room temperature. After stirring for 2 h, complete conversion was detected by TLC. The reaction mixture was diluted with EtOAc (50 mL) and H₂O (50 mL) was added and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated. Silica gel chromatography with 3:1 hexanes/EtOAc furnished 3.23 (204 mg, 68%) as two isomers. For the major isomer: 1H NMR (400 MHz, CDCl₃) δ 6.84 (dd,
$J = 8.9, 5.0 \text{ Hz, 1H}$, 6.34 – 6.30 (m, 1H), 6.27 – 6.16 (m, 2H), 6.11 – 6.05 (m, 1H), 5.80 – 5.77 (m, 1H), 5.63 – 5.55 (m, 2H), 4.48 – 4.40 (m, 2H), 2.87 (dt, $J = 17.9, 2.3 \text{ Hz, 1H}$), 2.25 – 2.12 (m, 1H), 2.03 (s, 3H), 1.39 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H).

**Compound 3.24**: To a sealed pretreated vial, equipped with a magnetic stir bar, was added 3.23 (95 mg, 250 µmol) and BHT (28 mg, 125 µmol). The vial was capped and evacuated on high vacuum followed by backfilling with argon. To the vial was then added $o$-DCB (5 mL, 0.05 M) and it was heated to 170 °C for 3.5 h. The reaction mixture was directly loaded on a silica gel column. The column was eluted with hexanes until the BHT was eluted (as evidenced by TLC), and the eluent was switched to 70:30 hexanes/EtOAc. Furnishing bicycle (80 mg, 85%) as a white foam.

ii. The abovementioned compound (73 mg, 0.20 mmol), in MeOH (2 mL) and THF (2 mL) was degassed by bubbling argon through the solution for 15 min and with sonication. To this solution was added a solution of commercially purchased SmI$_2$ (6 mL, 0.1 M in THF, 0.6 mmol, 3 equiv) at room temperature until the blue color of the SmI$_2$ solution persisted. Sat. aq. NaHCO$_3$ (4 mL) solution was added to the reaction mixture with shaking. The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried with Na$_2$SO$_4$ and concentrated. Silica gel chromatography with 4:1 hexanes:EtOAc furnished 3.24 (60 mg, 78%) as a mixture of diastereomers (5:1) as a white powder. **3.24-1**: $^1$H NMR (400 MHz, CDCl$_3$) δ 6.64 (dt, $J = 17.2, 8.6 \text{ Hz, 1H}$), 5.94 (d, $J = 7.1 \text{ Hz, 1H}$), 5.76 – 5.65 (m, 2H), 4.60 (t, $J = 16.4 \text{ Hz, 1H}$), 4.39 – 4.28 (m, 1H), 4.24 – 4.10 (m, 1H), 3.03 – 2.93 (m, 1H), 2.85 (dt, $J = 15.1, 6.7 \text{ Hz, 1H}$), 2.37 – 2.24 (m, 2H), 2.16 (dt, $J = 12.0, 6.0 \text{ Hz, 1H}$), 2.04 (ddd, $J = 13.0, 6.1, 2.8 \text{ Hz, 1H}$), 1.31 (s, 3H), 1.24 (s, 3H), 1.07 (d, $J = 7.1 \text{ Hz, 3H}$). IR (film) $\nu_{\text{max}}$ 2926,
Compound 3.25 and Compound 3.27: To a sealed vial was added 3.24 (9 mg, 28 μmol) and SeO₂ (9 mg, 85 μmol). To the vial was then added 1,4-dioxane (2.8 mL, 0.01 M) and it was heated at 110 °C for 12 h. The reaction mixture was then cooled down to room temperature. Sat. aq. NaHCO₃ (2 mL) and aq. Na₂S₂O₃ solution was added to the reaction mixture with shaking. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were dried with Na₂SO₄ and concentrated. Silica gel chromatography with 4:1 hexanes:EtOAc furnished 3.25 (2.8 mg, 32%) and 3.27 (3.9 mg, 45%).

3.25: ¹H NMR (600 MHz, CDCl₃) δ 6.91 (d, J = 10.4 Hz, 1H), 6.54 – 6.49 (m, 1H), 6.40 (d, J = 8.3 Hz, 1H), 6.19 (dd, J = 10.4, 5.8 Hz, 1H), 4.62 (d, J = 12.2 Hz, 1H), 4.47 (d, J = 12.2 Hz, 1H), 4.21 (dd, J = 9.7, 4.6 Hz, 1H), 2.86 (brs, 1H), 2.17 – 2.03 (m, 2H), 1.47 (s, 3H), 1.33 (s, 3H), 1.05 (d, J = 7.1 Hz, 3H). IR (film) νmax 2924, 1720, 1473, 1264, 1224, 1159, 1029, 733, 702 cm⁻¹; HRMS (m/z): [M+H]⁺ calcd. for C₁₉H₂₃O₄, 315.1591; found, 315.1604.

3.27: ¹H NMR (500 MHz, CDCl₃) δ 6.83 (d, J = 8.3 Hz, 1H), 6.63 – 6.51 (m, 1H), 5.75 (dd, J = 10.4, 2.2 Hz, 1H), 5.65 (dd, J = 10.5, 1.8 Hz, 1H), 5.02 (s, 1H), 4.80 (d, J = 12.4 Hz, 1H), 4.26 (d, J = 12.4 Hz, 1H), 4.14 (dd, J = 9.4, 4.2 Hz, 1H), 2.86 (s, 1H), 2.39 (dt, J = 13.1, 3.8 Hz, 1H), 2.25 – 2.12 (m, 2H), 1.88 (d, J = 5.5 Hz, 1H), 1.31 (s, 3H), 1.22 (s, 3H), 1.11 (d, J = 7.0 Hz, 3H). IR (film) νmax 3475, 2928, 1714, 1466, 1109, 1025, 720 cm⁻¹; HRMS (m/z): [M+H]⁺ calcd. for C₁₉H₂₄O₆, 331.1540; found, 331.1555.

Compound 3.28: i. To a stirred solution of 3.19 (125 mg, 247 μmol) in EtOAc (12 mL) and Pd/C (25 mg, 10% Pd, dry) was bubbled H₂ for 1 h until complete conversion was
detected by TLC. N₂ was then bubbled through the solution to purge out any residual H₂. The solution was filtered through a pad of Celite® and concentrated to give a colorless foam (340 mg, 97%).

ii. The abovementioned foam (207 mg, 0.41 mmol) was dissolved in MeOH (8.2 mL, 0.05 M) and con. HCl (3 M, 1.5 mL) was added and the solution was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo and the crude material purified by chromatography (2:1 hexanes:EtOAc) to yield a foam (140 mg, 87%).

iii. The aforementioned foam (140 mg, 0.36 mmol) was dissolved in CH₂Cl₂ (7.2 mL, 0.05 M). DMP (257 mg, 0.40 mmol, 1.1 equiv) was added and the mixture stirred for 2 h at ambient temperature. Then the mixture was poured onto 10 % aq. Na₂S₂O₃ (30 mL) and the resulting biphasic mixture was extracted three times with EtOAc (3 x 25 mL). The combined organic portions were washed with sat. aq. NaHCO₃ (30 mL), sat. aq. NaCl (30 mL), dried over MgSO₄ and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (hexanes:EtOAc 2:1) furnishing compound 3.28 (161 mg, 87 %) as a white foam. 3.28: ¹H NMR (400 MHz, CDCl₃) δ 4.62 (d, J = 12.3 Hz, 1H), 4.18 – 4.13 (m, 2H), 4.01 (ddd, J = 10.9, 4.1, 2.2 Hz, 1H), 2.73 (t, J = 2.9 Hz, 1H), 2.70 – 2.59 (m, 2H), 2.52 – 2.33 (m, 3H), 2.08 (s, 3H), 2.03 – 1.87 (m, 2H), 1.93 – 1.70 (m, 2H), 1.55 (s, 3H), 1.51 (s, 3H), 1.29 (s, 3H).

**Compound 3.29:** Ketone 3.28 (20 mg, 0.052 mmol, 1 equiv.) was dissolved in CH₂Cl₂ (0.5 mL, 0.1 M) and 4-methylbenzenesulfonyl hydrazide (18 mg, 0.062 mmol, 1.2 equiv.) was added. The reaction mixture was stirred for 5 hours at room temperature. Volatiles were removed in vacuo and the crude material purified by silica gel flash
chromatography (1:1 hexanes:EtOAc) to afford hydrazone as a white foam (31 mg, 95%).

ii. The abovementioned (30 mg, 0.047 mmol, 1 equiv.) was dissolved in toluene (4.7 mL, 0.01 M) and NaH (60% in mineral oil, 56 mg, 1.42 mmol, 30 equiv.) was added. The reaction mixture was immersed into preheated 110°C oil bath and stirred for 5 min, then cooled down to room temperature. The reaction mixture was poured into to 3 M HCl (25 ml) at 0°C. The resulting biphasic mixture was extracted three times with EtOAc (3 x 25 mL). The combined organic portions were washed with sat. aq. NaHCO₃ (30 mL), sat. aq. NaCl (30 mL), dried over MgSO₄ and the volatiles removed in vacuo. The residue so obtained was purified by flash column chromatography (hexanes:EtOAc 2:1) furnishing a white foam (16 mg, 92%).

iii. The abovementioned compound (13 mg, 0.035 mmol), in MeOH (0.5 mL) and THF (0.5 mL) was degassed by bubbling argon through the solution for 15 min and with sonicaton. To this solution was added a solution of commercially purchased SmI₂ (1.1 mL, 0.1 M in THF, 0.11 mmol, 3 equiv) at rt until the blue color of the SmI₂ solution persisted. Saturated aq. NaHCO₃ (4 mL) solution was added to the reaction mixture with shaking. The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried with Na₂SO₄ and concentrated. Silica gel chromatography with 4:1 hexanes:EtOAc furnished 3.29 (9 mg, 78%) as a mixture of diastereomers (6:1) as a white powder. 3.29: ¹H NMR (400 MHz, CDCl₃) δ 5.88 – 5.44 (m, 2H), 4.64 – 4.42 (m, 1H), 4.27 – 3.98 (m, 3H), 3.06 (d, J = 17.0 Hz, 1H), 2.50 – 2.07 (m, 3H), 2.02 – 1.91 (m, 3H), 1.82 – 1.43 (m, 2H), 1.27 (s, 3H), 1.20 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H). IR (film) νmax 2926, 2344, 2146, 1721, 1458, 1274, 1141, 1079, 713 cm⁻¹; HRMS (m/z):
[M+H]$^+$ calcd. for C$_{19}$H$_{25}$O$_4$, 317.1747; found, 317.1739.

**Compound 3.31:** Compound 3.29 (3 mg, 8.9 µmol, 1 equiv) was dissolved in DCM (0.2 mL, 0.045 M) and cooled to 0°C. Et$_3$N (10 µL, 71 µmol, 8 equiv) and TBSOTf (14 µL, 53 µmol, 6 equiv) was added and the solution warmed up to room temperature and stirred for 2 h. The reaction mixture was filtered through a pad of silica and washed with DCM (5 mL). The solvent was removed *in vacuo* and the crude material was dissolved in DCM (2 mL). At 0°C, m-CPBA (2.3 mg, 13 µmol, 1.5 equiv) was added and the reaction mixture was stirred for 10 min at 0 °C, at which point saturated aq. NaHCO$_3$ (2 mL) and aq. Na$_2$S$_2$O$_3$ (2 mL) solution was added to the reaction mixture with shaking. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic phases were dried with Na$_2$SO$_4$ and concentrated. The crude mixture was purified by preparative thin-layer chromatography (2:1 hexanes:EtOAc) to yield compound 3.31 (1.3 mg, 43%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.68 – 5.62 (m, 2H), 4.85 (d, $J = 11.1$ Hz, 1H), 4.39 (d, $J = 11.1$ Hz, 1H), 2.62 (d, $J = 17.4$ Hz, 1H), 2.51 (dd, $J = 19.9$, 11.3 Hz, 1H), 2.28 (s, 1H), 2.18 (d, $J = 5.9$ Hz, 1H), 2.09 (dd, $J = 17.5$, 4.8 Hz, 1H), 2.03 – 1.92 (m, 2H), 1.92 – 1.85 (m, 1H), 1.39 – 1.33 (m, 1H), 1.26 (s, 3H), 1.21 (d, $J = 5.8$ Hz, 3H), 1.20 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 214.4, 213.4, 171.7, 135.5, 120.4, 73.2, 67.8, 58.5, 57.6, 49.3, 48.8, 44.5, 41.7, 32.1, 27.9, 27.6, 22.1, 19.5, 15.5. IR (film) $\nu_{\max}$ 3423, 2927, 1751, 1709, 1467, 1371, 1238, 1195, 1146, 1085, 1071, 1020, 973, 800, 724 cm$^{-1}$; HRMS ($m/z$): [M+H]$^+$ calcd. for C$_{19}$H$_{25}$O$_5$, 333.1696; found, 333.1705.

**Compound 3.35 and Compound 3.36:** Compound 3.21 (7 mg, 15 µmol) was dissolved in MeOH (1.5 mL, 0.01 M) and con. HCl (0.15 mL) was added and the solution was stirred at 50°C for 12 h. The reaction mixture was concentrated *in vacuo* and the crude
material purified by preparative thin-layer chromatography (2:1 hexanes:EtOAc) to yield compound 3.35 (3 mg, 53%) and 3.36 (2 mg, 39%).

3.35: $^1H$ NMR (600 MHz, CDCl$_3$) $\delta$ 5.87 (d, $J = 6.7$ Hz, 1H), 4.31 (d, $J = 8.7$ Hz, 1H), 3.86 (d, $J = 8.9$ Hz, 1H), 3.79 (s, 3H), 3.57 – 3.51 (m, 1H), 2.72 (dd, $J = 11.7$, 5.8 Hz, 1H), 2.59 – 2.53 (m, 1H), 2.50 (d, $J = 3.1$ Hz, 1H), 2.04 (d, $J = 7.5$ Hz, 1H), 2.00 – 1.94 (m, 1H), 1.94 – 1.85 (m, 1H), 1.79 (dd, $J = 10.2$, 3.9 Hz, 1H), 1.77 – 1.72 (m, 1H), 1.50 – 1.37 (m, 4H), 1.19 (s, 3H), 1.01 (s, 3H), 0.98 (d, $J = 6.8$ Hz, 3H). $^{13}C$ NMR (150 MHz, CDCl$_3$) $\delta$ 213.1, 162.3, 143.5, 110.4, 109.0, 76.1, 75.9, 54.4, 54.3, 52.1, 51.7, 37.4, 36.4, 31.8, 26.9, 26.6, 22.3, 19.0, 18.1, 12.3.

3.36: $^1H$ NMR (600 MHz, CDCl$_3$) $\delta$ 3.90 (s, 3H), 3.75 (d, $J = 8.9$ Hz, 1H), 3.05 (dd, $J = 18.0$, 4.9 Hz, 1H), 2.90 – 2.80 (m, 1H), 2.61 – 2.48 (m, 1H), 2.48 – 2.24 (m, 4H), 2.14 (d, $J = 6.3$ Hz, 1H), 1.94 – 1.86 (m, 3H), 1.54 – 1.44 (m, 1H), 1.31 (s, 3H), 1.27 (d, $J = 6.9$ Hz, 3H), 1.23 (s, 3H), 1.09 (dd, $J = 7.0$, 3.3 Hz, 1H). $^{13}C$ NMR (150 MHz, CDCl$_3$) $\delta$ 193.8, 161.6, 153.7, 151.8, 115.1, 113.7, 76.3, 53.0, 43.0, 37.7, 36.7, 34.2, 27.6, 26.6, 25.6, 21.4, 18.8, 17.9, 17.5; IR (film) $\nu_{max}$ 3445, 2932, 1732, 1440, 1381, 1264, 1052, 735 cm$^{-1}$; HRMS (m/z): [M+H]$^+$ calcd. for C$_{19}$H$_{26}$O$_5$, 335.1853; found, 335.1856.

**Compound 3.40:** Compound 3.21 (7 mg, 15 µmol) was dissolved in toluene (1.5 mL, 0.01 M) and pyrrolidine (15 µL, 11 µmol, 10 equiv) was added and the solution was stirred at 70°C for 12 h. The reaction mixture was concentrated in vacuo and the crude material purified by preparative thin-layer chromatography (2:1 hexanes:EtOAc) to yield compound 3.40 (4.6 mg, 56%). $^1H$ NMR (600 MHz, CDCl$_3$) $\delta$ 4.13 (dd, $J = 9.7$, 4.8 Hz, 1H), 3.71 (d, $J = 11.4$ Hz, 1H), 3.65 (t, $J = 6.8$ Hz, 2H), 3.54 (t, $J = 6.9$ Hz, 2H), 3.50 (dd, $J = 13.7$, 5.5 Hz, 1H), 3.37 (t, $J = 11.1$ Hz, 1H), 3.09 (dd, $J = 17.9$, 3.6 Hz, 1H),
2.88 (dd, $J = 17.9$, 8.2 Hz, 1H), 2.21 (dd, $J = 19.2$, 8.3 Hz, 3H), 2.08 – 1.87 (m, 4H), 1.84 – 1.62 (m, 4H), 1.51 – 1.40 (m, 2H), 1.30 (s, 3H), 1.10 (s, 3H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 222.0, 210.9, 199.5, 162.2, 74.8, 64.0, 55.3, 51.5, 49.9, 49.8, 47.4, 46.6, 43.9, 40.7, 31.5, 27.4, 26.5, 25.9, 25.8, 24.8, 24.0, 23.5, 21.4, 18.0, 11.9, -4.0, -4.8; IR (film) $\nu_{\text{max}}$ 3326, 2944, 2832, 1449, 1414, 1114, 1021 cm$^{-1}$; HRMS (m/z): [M+Na]$^+$ calcd. for C$_{29}$H$_{49}$NO$_6$SiNa, 558.3221; found, 558.3224.

**Compound 3.42:** Compound 3.40 (3 mg, 5 $\mu$mol) was dissolved in DCM (0.5 mL, 0.01 M) and Sc(OTf)$_3$ (8 mg, 15 $\mu$mol, 3 equiv) was added and the solution was stirred at room temperature for 1 min. The reaction mixture was concentrated *in vacuo* and the crude material purified by preparative thin-layer chromatography (2:1 hexanes:EtOAc) to yield compound 3.42 (4.6 mg, 56%). The reaction mixture was filtered through a pad of silica and washed with EtOAc (5 mL). The organic solvent was concentrated *in vacuo* and the crude material purified by preparative thin-layer chromatography (1:1 hexanes:EtOAc) to yield compound 3.42 (2 mg, 74%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.25 (d, $J = 8.6$ Hz, 1H), 3.97 (d, $J = 8.6$ Hz, 1H), 3.65 – 3.63 (m, 2H), 3.56 – 3.39 (m, 2H), 2.90 (dd, $J = 17.5$, 5.9 Hz, 1H), 2.77 (dd, $J = 17.6$, 7.5 Hz, 1H), 2.10 (s, 1H), 2.06 – 1.91 (m, 4H), 1.90 – 1.66 (m, 5H), 1.44 – 1.30 (m, 1H), 1.13 (d, $J = 6.9$ Hz, 3H), 1.10 (s, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 214.3, 200.3, 162.7, 155.0, 109.7, 77.5, 76.2, 60.9, 52.0, 47.4, 46.5, 42.7, 35.6, 33.8, 28.1, 27.1, 26.4 (3C), 25.8, 25.5, 23.6, 22.3, 18.4, 18.3, 18.0, 17.5, -4.1, -5.0. IR (film) $\nu_{\text{max}}$ 3312, 2945, 2832, 1760, 1709, 1667, 1449, 1253, 1109, 1022, 837 cm$^{-1}$. 
**Compound 3.45:** Compound 3.22 (10 mg, 33 µmol) was dissolved in MeOH (0.5 mL, 0.01 M) and NaBH₄ (1.2 mg, 33 µmol, 3 equiv) was added and the solution was stirred at room temperature for 5 min. The reaction mixture was concentrated *in vacuo*, dissolved in EtOAc (10 mL) and washed with H₂O (5 ml). The organic portion was concentrated *in vacuo* and the crude material purified by chromatography (1:1 hexanes:EtOAc) to yield compound 3.45 (9.6 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ 7.18 – 7.07 (m, 2H), 6.99 (t, J = 7.7 Hz, 1H), 5.69 – 5.62 (m, 1H), 5.31 (dd, J = 9.9, 2.5 Hz, 1H), 5.16 (d, J = 5.3 Hz, 1H), 5.07 (d, J = 5.3 Hz, 1H), 4.69 (d, J = 8.4 Hz, 1H), 4.24 (d, J = 7.8 Hz, 1H), 4.04 (d, J = 9.1 Hz, 1H), 3.93 (d, J = 8.4 Hz, 1H), 3.66 (s, 3H), 2.79 (dd, J = 17.8, 5.2 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.33 (s, 3H), 1.83 (brs, 1H), 1.03 (s, 3H), 0.25 (s, 3H); IR (film) νₘₐₓ 3322, 2944, 2832, 1655, 1449, 1413, 1113, 1021 cm⁻¹.

**Compound 3.49:** i. Enone 3.48 (13.3 g, 107 mol) was dissolved in H₂O (107 mL, 1 M) Sodium dodecyl sulfate (2.85g, 10.6 mol, 0.1 equiv) and DMAP (17 g, 107 mol, 1 equiv) was added and the solution was stirred at room temperature for 15 min. To the reaction mixture, formalin (37% aq solution, 107 mL, 1 M) was added and stirred for 45 min. Brine (200 ml) was added and the aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic phases were dried with MgSO₄ and concentrated. The crude mixture was purified by chromatography (2:1 hexanes:EtOAc, Rₜ = 0.4) to yield alcohol (13.3 mg, 80%).

ii. To a flame dried flask was added 1-bromo-2-methoxy-3-methylbenzene (15 g, 0.075 mol, 2.0 equiv) and Et₂O (150 mL, 0.5 M) under Argon. The solution was cooled to −78 °C and n-BuLi (2.5 M in Hexanes, 30 mL, 0.075 mmol, 2 equiv) was added dropwise. The mixture was stirred for 30 min at −78 °C, warmed to 0 °C and stirred for 30 minutes.
The abovementioned alcohol (5.8 g, 0.038 mol, 1 equiv) was dissolved in Et₂O (50 mL) and the solution was cannulated into ArLi solution at 0 °C. The mixture was stirred at 0 °C for 1 h, at which point the reaction was quenched by saturated aqueous NH₄Cl (100 mL) and EtOAc (100 mL) and the aqueous layer extracted with EtOAc (2 X 200 mL). The combined organic layers were washed with H₂O (300 mL), brine (300 mL), dried (MgSO₄), and the volatiles removed in vacuo. The crude material was purified by chromatography (2:1 hexanes:EtOAc, Rf = 0.4) to yield alcohol (8.5 g, 77%).

iii. The abovementioned alcohol (6.8 g, 23 mmol) was dissolved in DCM (115 mL, 0.2 M). At 0°C, m-CPBA (7.9 mg, 46 mmol, 2 equiv) was added and the reaction mixture was kept at 0 °C for 30 min, then warmed up to room temperature and stirred for 12 h. Saturated aq. NaHCO₃ (100 mL) and aq. Na₂S₂O₃ (100 mL) solution was added to the reaction mixture. The aqueous phase was extracted with CH₂Cl₂ (2 x 200 mL). The combined organic phases were dried with MgSO₄ and concentrated. The crude mixture was purified by chromatography (3:1 hexanes:EtOAc) to yield compound 3.49 (6.4 g, 95%).

**1H NMR (500 MHz, CDCl₃)** δ 7.14 – 7.11 (m, 2H), 7.00 (t, J = 7.6 Hz, 1H), 3.87 (s, 3H), 3.45 (dt, J = 31.7, 15.8 Hz, 1H), 3.26 (s, 1H), 2.33 (s, 3H), 2.30 (d, J = 2.9 Hz, 1H), 1.14 (d, J = 17.7 Hz, 6H).

**13C NMR (125 MHz, CDCl₃)** δ 132.02, 123.52, 61.35, 60.79, 34.77, 21.43, 14.59. IR (film) νmax 3324, 2979, 2944, 2885, 2831, 1448, 1416, 1114, 1022 cm⁻¹; HRMS (m/z): [M+H]⁺ calcd. for C₁₇H₂₅O₄, 293.1747; found, 293.1745.

**Compound 3.50:** Compound 3.49 (3.9 g, 13.3 mmol, 1 equiv) was dissolved in DCM (26 mL, 0.5 M) and 2,6-lutidine (9.8 mL, 66.5 mol, 5 equiv) was added. The solution was cooled to -78°C and t-Bu₂Si(OTf)₂ (4.3 mL, 14.6 mol, 1.1 equiv) was added. Then, the solution warmed up to room temperature and stirred for 2 h. Saturated aq. NaHCO₃
(100 mL) was added to the reaction mixture. The aqueous phase was extracted with CH₂Cl₂ (2 x 200 mL). The combined organic phases were dried with MgSO₄ and concentrated. The crude mixture was purified by chromatography (20:1 hexanes:EtOAc) to yield compound 3.50 (3.9 g, 67%). ¹H NMR (600 MHz, CDCl₃) δ 7.13 (d, J = 7.4 Hz, 1H), 6.98 – 6.96 (m, 1H), 6.91 (t, J = 7.6 Hz, 1H), 4.86 (d, J = 11.6 Hz, 1H), 3.85 (s, 3H), 3.49 (d, J = 7.3 Hz, 1H), 2.96 (d, J = 1.5 Hz, 1H), 2.32 (s, 3H), 2.31 – 2.24 (m, 4H), 1.12 (s, 3H), 1.06 (s, 18H), 0.70 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 158.3, 136.3, 132.9, 131.3, 129.2, 126.3, 121.9, 79.7, 70.8, 69.0, 68.9, 64.5, 60.9, 34.6, 27.6 (6 C), 27.5, 27.0, 22.1, 21.1, 20.2, 17.2. IR (film) νmax 3321, 2944, 2833, 1655, 1449, 1413, 1114, 1021 cm⁻¹.

**Compound 3.51:** Compound 3.50 (2.5 g, 5.9 mmol, 1 equiv) was dissolved in DCM (59 mL, 0.1 M) and fresh distilled BF₃·Et₂O (2.2 mL, 17.7 mol, 3 equiv) was added slowly at 0°C. The reaction mixture was stirred for 20 min, at which point saturated aq. NaHCO₃ (50 mL) was added to the reaction mixture. The aqueous phase was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic phases were dried with MgSO₄ and concentrated. The crude mixture was dissolved in THF (59 mL, 0.1 M) and HF·Py (1 mL, 29.5 mol, 5 equiv) was added slowly at 0°C. After 20 min, the reaction mixture was quenched by 1 N HCl (30 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were dried with MgSO₄ and concentrated. The crude mixture was was purified by chromatography (5:1 hexanes:EtOAc) to yield compound 3.51 (465 mg, 27%). ¹H NMR (600 MHz, CDCl₃) δ 7.19 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.07 – 7.03 (m, 1H), 4.34 (d, J = 10.1 Hz, 1H), 4.13 (dd, J = 17.8, 4.5 Hz, 1H), 3.95 (dd, J = 17.8, 4.9 Hz, 1H), 3.80 (d, J = 10.1 Hz, 1H), 3.74 (s, 3H), 2.93 (t, J =
4.9 Hz, 1H), 2.30 (s, 3H), 2.29 – 2.24 (m, 1H), 2.19 – 2.14 (m, 1H), 1.76 – 1.65 (m, 2H), 1.07 (s, 3H), 1.01 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 213.3, 155.8, 137.2, 131.3, 131.2, 124.4, 124.0, 91.1, 65.8, 61.2, 58.5, 42.9, 37.4, 34.3, 28.4, 21.2, 17.1. IR (film) νmax 3322, 2944, 2832, 1655, 1449, 1413, 1113, 1021 cm⁻¹; HRMS (m/z): [M+H]⁺ calcd. for C17H25O4, 293.1747; found, 293.1748.

**Compound 3.52:** compound 3.51 (5.6 mg, 0.019 mmol) was dissolved in DCM (0.5 mL, 0.04 M), DMAP (2.6 mg, 0.02 mmol, 1 equiv) and 4-bromobenzoylchloride (4 mg, 0.02 mmol, 1 equiv) was added. The reaction solution was stirred for 10 min, at which point it was diluted with CH₂Cl₂ (4 mL), washed with sat. aq. NaHCO₃ (5 mL) and H₂O (5 mL), dried with MgSO₄, filtered, and concentrated in vacuo. The crude material purified by preparative thin-layer chromatography (1:1 hexanes:EtOAc) as a white solid (6.3 mg, 85%). 1H NMR (400 MHz, CDCl₃) δ 7.77 – 7.73 (m, 2H), 7.56 – 7.51 (m, 2H), 7.30 (dd, J = 7.7, 1.6 Hz, 1H), 7.14 – 7.11 (m, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.86 (d, J = 16.3 Hz, 1H), 4.68 (d, J = 16.3 Hz, 1H), 4.55 (d, J = 11.3 Hz, 1H), 3.85 (d, J = 11.2 Hz, 1H), 3.78 (s, 3H), 2.62 – 2.60 (m, 1H), 2.33 (s, 3H), 2.12 – 2.04 (m, 1H), 1.75 – 1.67 (m, 1H), 1.71 – 1.60 (m, 1H), 1.09 (s, 3H), 0.98 (s, 3H).

**Compound 3.56:** compound 3.51 (37 mg, 0.13 mmol) was dissolved in CH₂Cl₂ (1.3 mL, 0.1 M), diethyl phosphonoacetic acid (49 mg, 0.25 mmol, 2 equiv), EDC (48 mg, 0.25 mmol, 2 equiv), and DMAP (1.6 mg, 0.012 mmol, 0.1 equiv) was added. The reaction solution was stirred at room temperature for 10 min, at which point it was diluted with CH₂Cl₂ (4 mL), washed with sat. aq. NaHCO₃ (5 mL) and H₂O (5 mL), dried with MgSO₄, filtered, and concentrated in vacuo. The crude material purified by chromatography (1:1 hexanes:EtOAc) as a white solid (30 mg, 50%).
ii. The abovementioned ester (30 mg, 0.064 mmol) was dissolved in MeCN (0.64 mL, 0.1 M), p-ABSA (20 mg, 0.08 mmol, 1.2 equiv) was added. At 0 °C, DBU (10 μL, 0.07 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 30 min, at which point it was diluted with CH₂Cl₂ (10 mL), washed with sat. aq. NH₄Cl (5 mL), dried with MgSO₄, filtered, and concentrated in vacuo. The crude material purified by chromatography (1:1 hexanes:EtOAc) Compound 3.56 as a white solid (15 mg, 47%).

³¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 6.5 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 4.70 (d, J = 16.3 Hz, 1H), 4.53 (d, J = 16.3 Hz, 1H), 4.34 (d, J = 11.3 Hz, 1H), 4.28 – 4.13 (m, 6H), 3.86 (d, J = 11.3 Hz, 1H), 3.74 (s, 3H), 2.66 – 2.60 (m, 1H), 2.31 (s, 3H), 2.06 – 1.98 (m, 1H), 1.81 – 1.72 (m, 1H), 1.68 – 1.62 (m, 1H), 1.36 (t, J = 7.1 Hz, 4H), 1.08 (s, 3H), 0.94 (s, 3H).

**Compound 3.58**: Compound 3.56 (4.5 mg, 9 μmol) was dissolved in toluene (0.45 mL, 0.02 M) and Et₂AlCN (1 M in toluene, 18 μL, 18 μmol, 2 equiv) was added at 0 °C. The reaction was stirred at 0 °C for 2 h, at which point it was quenched with sat. aq. sodium potassium tartrate (5 mL). The aqueous layer extracted two more times with CH₂Cl₂ (5 mL). Drying over MgSO₄, filtration, concentration in vacuo, and the crude material purified by preparative thin-layer chromatography (1:1 hexanes:EtOAc) 3.58 as a white solid (2.6 mg, 58%).

**Compound 3.59**: To a solution of compound 3.58 (10 mg, 19 μmol) in anhydrous benzene (6 mL) in a sealed tube was added rhodium(II) acetate dimer (1 mg, 1.9 μmol). The mixture was immediately immersed in a preheated oil bath (130 °C) and stirred for 2h. After cooling the solvent was removed under vacuum, and the residue was purified
by preparative thin-layer chromatography (1:1 hexanes:EtOAc) **3.59** as a white solid (5.3 mg, 56%).

**Compound 3.60:** To a solution of compound **3.59** (5 mg, 10 µmol) in THF (0.5 mL, 0.05 M) was added DBU (1 M in THF, 20 µL, 20 µmol, 2 equiv) at 0 °C, after stirring at this temperature for 30 min, paraformaldehyde (in 100 mg/mL THF suspension, 0.1 mL, 30 equiv) was added and the mixture was stirred for 20 min at 0 °C. The reaction was quenched with sat. aq. NH₄Cl (3 mL). The aqueous layer extracted two more times with CH₂Cl₂ (5 mL). Drying over MgSO₄, filtration, concentration in vacuo, and the crude material purified by preparative thin-layer chromatography (1:1 hexanes:EtOAc) **3.60** as a white solid (3.2 mg, 61%).

**Compound 3.61:** i. To a solution of compound **3.60** (4 mg, 11 µmol) in THF (0.44 mL, 0.025 M) was added BBr₃ (1 M in DCM, 55 µL, 55 µmol, 5 equiv) at -78 °C, after stirring at this temperature for 30 min, the mixture was warmed up to room temperature and kept at this temperature for 1 h. The reaction was quenched with sat. aq. NaHCO₃ (3 mL). The aqueous layer extracted two more times with CH₂Cl₂ (5 mL). Drying over MgSO₄, filtration, concentration in vacuo, and the crude material purified by preparative thin-layer chromatography (1:1 hexanes:EtOAc) **3.60** as a white solid (3 mg, 75%).

ii. To a stirred solution of phenol (3 mg, 8 µmol) in AcOH (0.4 mL, 0.02 M) was added Pb(OAc)₄ (17 mg, 40 µmol, 5 equiv) quickly at room temperature. After stirring for 2 h, complete conversion was detected by TLC. The reaction mixture was diluted with EtOAc (5 mL) and H₂O (5 mL) was added and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated. The crude
material purified by preparative thin-layer chromatography (1:1 hexanes:EtOAc) dienone as a white solid.

iii. To a sealed pretreated vial, equipped with a magnetic stir bar, was added the abovementioned dienone (95 mg, 250 µmol) and BHT (28 mg, 125 µmol). The vial was capped and evacuated on high vacuum followed by backfilling with argon. To the vial was then added o-DCB (5 mL, 0.05 M) and it was heated to 140 °C for 12 h. The reaction mixture was directly loaded on a silica gel column. The column was eluted with hexanes until the BHT was eluted (as evidenced by TLC), and the eluent was switched to 70:30 hexanes/EtOAc. Furnishing 3.61 (2 mg, 60%) as a white foam. 

$^1$H NMR (600 MHz, CDCl$_3$) δ 6.64 – 6.61 (m, 1H), 6.04 (d, J = 7.3 Hz, 1H), 5.58 (s, 1H), 4.40 (d, J = 10.1 Hz, 1H), 4.10 – 4.06 (m, 2H), 2.93 – 2.85 (m, 2H), 2.45 (dd, J = 14.3, 4.4 Hz, 1H), 2.17 (s, 3H), 2.06 – 2.00 (m, 2H), 1.89 – 1.83 (m, 2H), 1.60 (s, 3H), 1.56 (s, 3H), 1.19 (d, J = 8.9 Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 205.6, 176.6, 170.07, 166.4, 138.8, 127.9, 124.6, 116.9, 114.7, 105.7, 86.8, 82.63, 76.2, 69.7, 62.7, 44.6, 44.5, 40.0, 39.8, 34.8, 27.3, 24.1, 22.8, 22.1, 21.7, 17.4. IR (film) ν$_{max}$ 3322, 2944, 2832, 1655, 1449, 1413, 1113, 1021 cm$^{-1}$; HRMS ($m/z$): [M+H]$^+$ calcd. for C$_{21}$H$_{26}$NO$_7$, 416.1704; found, 416.1701.

**Compound 3.63:** To a solution of compound 3.49 (500 mg, 4.0 mmol) in toluene (20 mL, 0.2 M) was added dibromoformaldoxime (800 mg, 4.0 mmol, 1 equiv) and Na$_2$CO$_3$ (1.3 g, 12 mmol, 3 equiv). The mixture was immediately immersed in a preheated oil bath (110 ºC) and stirred for 1h. After cooling, aq. Na$_2$S$_2$O$_3$ (100 mL) solution was added to the reaction mixture. The aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic phases were dried with MgSO$_4$ and concentrated. The crude
mixture was purified by chromatography (3:1 hexanes:EtOAc) to yield compound 3.63 (441 mg, 45%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.61 (dd, $J = 10.2$, 1.9 Hz, 1H), 3.87 (d, $J = 10.2$ Hz, 1H), 2.65 – 2.61 (m, 1H), 2.49 – 2.42 (m, 1H), 2.17 – 2.10 (m, 1H), 2.08 – 2.03 (m, 1H), 1.16 (s, 3H), 1.05 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 202.8, 135.7, 90.5, 61.9, 34.9, 32.6, 29.6, 25.5, 24.5. IR (film) $\nu_{\text{max}}$ 3325, 2943, 2832, 2520, 2227, 2046, 1655, 1449, 1413, 1114, 1021 cm$^{-1}$; HRMS ($m/z$): [M+H]$^+$ calcd. for C$_9$H$_{13}$BrNO$_2$, 246.0124; found, 246.0124.

**Compound 3.64:** i. To a flame dried flask was added 1-bromo-2-methoxy-3-methylbenzene (5 g, 0.025 mol, 1.0 equiv.) and Et$_2$O (50 mL, 0.5 M) under Argon. The solution was cooled to −78 °C and $n$-BuLi (2.5 M in Hexanes, 10 mL, 0.025 mmol, 1 equiv) was added dropwise. The mixture was stirred for 30 min at −78 °C, warmed to 0 °C and stirred for 30 minutes. BiCl$_3$ (2.6 g, 8.3 mmol, 0.33 equiv.) was added into the reaction mixture quickly (50 mL). The mixture was warmed up to room temperature and stirred at this temperature for 1 h, at which point the reaction was quenched by saturated aqueous NH$_4$Cl (100 mL) and EtOAc (100 mL) and the aqueous layer extracted with EtOAc (2 X 200 mL). The combined organic layers were washed with H$_2$O (300 mL), brine (300 mL), dried (MgSO$_4$), and the volatiles removed in vacuo. The crude material was purified by chromatography (2:1 hexanes:EtOAc, Rf = 0.4) to yield triarylbismuth (2.2 g, 47%).

ii. To a solution of triarylbismuth (160 mg, 0.28 mmol) in CH$_2$Cl$_2$ (14 mL, 0.02) at 0 °C was added freshly distilled SO$_2$Cl$_2$ (33 µL, 0.42 mmol, 1.5 equiv). After warming to rt and concentrating, the resulting solid was dried under vacuum to give dichlorotriarylbismuth 3.64 (169 mg, 99%) as a pale yellow solid, which was pure.
enough for further reactions. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.19 – 8.09 (m, 1H), 7.34 – 7.28 (m, 2H), 3.96 (s, 3H), 2.46 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.5, 156.8, 134.8, 131.8, 131.0, 126.1, 62.1, 18.2.

**Compound 3.62:** To a flame dried flask was added 3.63 (51 mg, 0.21 mmol, 1.0 equiv.) and THF (2 mL, 0.1 M) under Argon. The solution was cooled to $-78 \, ^{\circ}C$ and LDA (0.36 M in THF, 583 $\mu$L, 0.21 mmol, 1.0 equiv) was added dropwise. The mixture was stirred for 30 min at $-78 \, ^{\circ}C$, at which point 3.64 (240 mg in 0.5 mL THF, 0.41 mmol, 2 equiv) was slowly added. After addition, it was warmed to 0 $^{\circ}C$ and stirred for 30 minutes. The mixture was warmed up to room temperature and stirred at this temperature for 1 h, at which point the reaction was quenched by saturated aqueous NH$_4$Cl (10 mL) and EtOAc (10 mL) and the aqueous layer extracted with EtOAc (2 X 10 mL). The combined organic layers were washed with H$_2$O (20 mL), brine (20 mL), dried (MgSO$_4$), and the volatiles removed in vacuo. The crude material was purified by chromatography (2:1 hexanes:EtOAc, Rf = 0.4) to yield 3.62 (33 g, 43%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.19 – 7.15 (m, 1H), 7.03 (t, $J$ = 7.7 Hz, 1H), 6.93 (d, $J$ = 7.9 Hz, 1H), 4.53 (s, 1H), 3.60 (s, 3H), 2.86 – 2.75 (m, 1H), 2.59 – 2.46 (m, 1H), 1.96 – 1.89 (m, 1H), 1.87 – 1.78 (m, 1H), 1.08 (s, 3H), 1.01 (s, 3H). IR (film) $\nu_{max}$ 2927, 1714, 1467, 1264, 1148, 1002, 884, 737 cm$^{-1}$; HRMS ($m/z$): [M+H]$^+$ calcd. for C$_{17}$H$_{21}$BrNO$_3$, 366.0699; found, 366.0701.
3.8 Appendix to Chapter 3: Spectra
X-ray Crystal Structure
X-ray Crystal Structure
X-ray Crystal Structure
Appendix: Curriculum Vitae and Selected Publications
Curriculum Vitae
Jun Shi

Appointment: Graduate Student, 5th year
Department of Chemistry
The Scripps Research Institute
10550 North Torrey Pines Road, BCC-169
La Jolla, California 92037
Telephone: (858) 784-7371
Facsimile: (858) 784-7575
Email: shijun@scripps.edu

Date/Place of Birth: 5 October 1984 / Huangshi, Hubei, P. R. China

Citizenship: P. R. China

Education
2006 – present Ph. D candidate in Chemistry
Advisor: Professor P. S. Baran
The Scripps Research Institute, La Jolla, California

2002 - 2006 B.S., Major in Chemistry, GPA 3.8/4.0, Rank: 1st/103
Advisor: Professor Zhongxing Jiang
Wuhan University, Wuhan, P. R. China

Awards
• Roche Symposium: Excellence in Chemistry Award. 2011
• Novartis Graduate Fellowship in Organic Chemistry for Minorities and Women, 2009-2010
• Bristol-Myers Squibb Graduate Fellowship in Organic Synthesis, 2008-2009
• Graduate Student Symposium Talk Awards, The Scripps Research Institute, 2009
• Chemistry Department Award for Seniors, Wuhan University, 2006
• Outstanding Student Fellowship, Wuhan University, 2005
• Yousheng Foundation Fellowship, Wuhan University, 2004
• Outstanding Student Fellowship, Wuhan University, 2003
• Excellent Leadership Award, Wuhan University, 2002

Publications


**Patents**


**Posters and Presentations**


**Research Experience:**

Jul. 2006 - Present

Doctoral Research in Chemical Synthesis
Supervisor: Prof. Phil Baran
Department of Chemistry, The Scripps Research Institute
I. Synthesis of the natural product cortistatin A and analogs
II. Total synthesis of vinigrol
III. Study towards to the total synthesis of Maoecrystal V


Research Assistant in Organic Chemistry
Supervisor: Prof. Zhongxing Jiang
Department of Chemistry, Wuhan University
Practical synthesis of anti-depressant drug Duloxetine.

Teaching Experience

Supervisor: Dr. Phil. S. Baran
Medicinal Chemistry Department, Celegene Corp.,
San Diego

Apr. 2009 - Jun. 2008  Teaching Assistant for Heterocyclic Chemistry (Graduate
Student Course)
Supervisor: Dr. Phil. S. Baran
Department of Chemistry, The Scripps Research Institute

(Graduate Student Course)
Supervisor: Dr. Phil. S. Baran
Department of Chemistry, The Scripps Research Institute

References: Available upon request
Scalable Synthesis of Cortistatin A and Related Structures

Jun Shi, Georg Manolkakes,* Chien-Hung Yeh,* Carlos A. Guerrero, Ryn A. Shenvi, Hiroki Shigeoka, and Phil S. Baran

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

ABSTRACT: Full details are provided for an improved synthesis of cortistatin A and related structures as well as the underlying logic and evolution of strategy. The highly functionalized cortistatin A ring embedded with a key heteroaromatic core was synthesized by a simple and scalable five-step sequence. A chemoselective, tandem retroaliphatic generation of an unsaturated methyl group, a reductive fragmentation/trapping/elimination of a bombyxocyclopropane, and a facile chemoselective etherification reaction afforded the cortistatin A core, dubbed "cortistatine." A selective DIT alkyne reduction with Raney Ni provided cortistatin A. With this scalable and practical route, copious quantities of cortistatine, DIT-cortistatin A (the equivalent direct precursor to cortistatin A), and its related analogs were prepared for further biological studies.

INTRODUCTION

Steroids are beyond "privileged" structures, playing a vital role not only in medicine and biology but also in the origins and development of organic synthesis. In 1915, the first steroid, cholesterol (1), Figure 1), was isolated from galls of the woolly aphid by Chevreul. But the correct chemical structure of cholesterol was not elucidated until 1952. Subsequently, during the 1930s to the 1960s, the discovery of steroids' useful biological activities coupled with the need for cortisone (2) specifically in World War II immensely stimulated the development of chemical syntheses of steroids in both academic and industrial settings. In 1939, the first total synthesis of aldosterone, an essential hormone, was accomplished by Bachman. Meanwhile, the Robinson, * Fieser, * Woodward, * Barbas, * and Jones* groups investigated numerous synthetic methods aimed at the synthesis of steroids, and a number of total syntheses of cortisone (2) were reported. The mechanistic, stereochemical model for steroid biosynthesis proposed by Enders and Bachman,* and related studies on polynuclear aromatics, ultimately led to Johnson's biosynthetic steroid synthesis, including his landmark total synthesis of progesterone (3) in 1971. * Academic inquiry into the synthesis of steroids has thus resulted in an immense body of knowledge in the realms of both fundamental stereochemical and medicinal chemistry.

In parallel to academic endeavors on the synthesis of steroids, the need for commercialization of certain steroid targets steered the pharmaceutical industry toward more efficient and practical approaches to synthesis. Starting from dienone, an abundant ingredient in feed, Marion, * Matta, * Marini, * and Merck achieved the commercialization of progesterone at Syntho by a six-step sequence (known as "Marrin's degradation") in 1946. * In 1964, Saett at Merck accomplished the first semisynthesis of cortisone (2) from bile acid in 36 steps. * In 1951, a group of chemists at Syntex, led by Carl Djerassi, achieved the semisynthesis of cortisone (2) from dienone in a single step. * In the same year, a highly innovative microbial fermentation approach was disclosed by Upjohn to commercialize the 21 hydroxyl position of progesterone (3), which led to the successful commercialization of cortisone (2). * Currently, the most stereospecific methods (Figure 2) are prepared by semisynthesis, including Deltalone (5), anti-inflammatory agent); Flovent (6), antiasthmatic and antiallergic agent), Lasalet (7), cardiovascular agent); Milenoxone (8), a pregnancy termination agent); Testosterone (9), treatment of male hypogonadism); and Meatrex (10), oral contraceptive).

In 2006 and 2007, the Kobayashi group elucidated structures of novel steroidal alkaloids, cortistatins A–J (1.1–2.1, Figure 3), and disclosed their highly selective antiaestrogenic activity. * Angiogenesis, a process that involves the formation of new capillary blood vessels from pre-existing ones, is fundamental and vital to growth, development, and wound healing but also to cancer metastasis. * Currently, a number of angiogenesis inhibitors, including Angiostatin, Vascular Endothelial Growth Factor, and Herceptin are the major nonselective antibody drugs for cancer treatment based on the inhibition of this mechanism. * Therefore, the isolation and study of new small-molecule natural products with highly selective antiaestrogenic activity is of great interest and significance. Interestingly, cortistatin A (11) showed antiproliferative activity against human umbilical vein endothelial cells (HUVECs) at a low concentration with an IC50 = 1.8 nM, while it demonstrated a selectivity index of more than 3000-fold against HUVECs in comparison with SHED-1 (normal human dermal fibroblast), KB-3-1 (EB epidermoid carcinoma cells).

Received: March 7, 2011
Published: May 03, 2011
KS62 (human chronic myelogenous leukemia cells), and Neuro-2A (mouse neuroblastoma cells), indicating that cortistatin A selectively inhibits angiogenesis but has no apparent cytotoxicity toward cancer cells. As such, cortistatin A could be a promising agent not only in cancer biology but also in other angiogenesis-dependent ailments such as muscular degeneration, rheumatoid arthritis, etc. However, to date, studies of cortistatin A have not been published due to its low availability. The significant potential of its antiangiogenic activity and high selectivity suggested that it would involve a unique mechanism of action.14

Structurally, all of the cortistatins possess an unusual 9(3b,19) alko-anhydrostan skeleton with an analogic[3b,1]octene core. The combination of their unique biactivity and near-availability from Nature makes the cortistatins worthy candidates for synthesis. Indeed, marine sponge (Coccidiotoma simplex) derived molecules are so rare and valuable that the isolation chemists have reported efforts toward their total synthesis.15 Not surprisingly, the last 3 years have witnessed dozens of publications on the chemistry of the cortistatins.16-24 Four elegant total syntheses of cortistatin A have emerged from the Nicolau–Chom,16,17,21,22 Myers,23,24 and Higashizumi25 laboratories, and many approaches have been reported.26 Our own efforts were inspired by the rich history of steroid semisynthesis and the desire to procure gram quantities of the cortistatins for biological evaluations.27 Thus, a route was devised beginning from the abundant terrestrially derived steroidal precursor (4), available for $1.25/gram. This full account describes our studies toward an improved synthesis of cortistatin A and related structures as well as the underlying logic and evolution of strategy.

## RESULTS AND DISCUSSION

Retro-synthetic Analysis. Given the tremendous success of steroid semisynthesises to prepare large quantities of biologically valuable compounds, we decided to explore this higher-level substructure search strategy to identify candidate steroid starting materials to install the global search, an initial retrosynthetic excision of the isopropylidene allowed a bidirectional search for molecules of biomimetic inspiration to the D-ring, and for steroid scaffolds that lacked the C17 side chain. Further considerations for the starting material derived from “ideality” criteria, particularly for an overall isotropic (redox-neutral) conversion from commercial steroid to target.28 Since there are few affordable steroids that bear the appropriate methine oxidation state at C17, a strategic sacrifice was made to introduce this modified carbon from the very common C19 methyl. A look-ahead search for appropriate A-ring processes proved more straightforward, since the cortistatin A-ring is in the same oxidation state as a cyclohexene enone, which is a common motif in commercial steroids. Similarly, the C-ring alkyl ether motif corresponded in oxidation state to a C-ring cyclohexane, a substructure that has been made available in commercial steroids.
by microbial oxidation. When these structures are amalgamated into an imaginary steroid, the result bears striking resemblance to
prednisone, with the exception of the pregnane side chain.
Fortunately, there are several methods for oxidative cleavage of this side chain to the corresponding cyclopentane, which
serves as a useful handle for appending the iminosulfone.
Further considerations that bolstered the proposal to begin
an abundant terrestrial steroid include (1) the unique
strategic opportunities that could arise from rendering a semi-
synthesis amenable to the construction of analogues with deep-
seated modification; (2) the occasion to develop new chemical
methods and tactics to achieve such ends; and (3) the economies
of using prednisone, which possesses ca. 70% of the carbon atoms
and the corresponding enantiopure chirality of the cortistatins.
As discussed above, a crucial target structure became the
cortistatin A ketonic core that we termed (+)-cortistatine
(22, Scheme 1). This key structure was anticipated to allow for
straightforward elaboration to the natural product, as well as
divergence to other family members and unnatural analogues. As
part of this plan, numerous exciting challenges had to be
addressed, including control of all four A-ring stereocenters,
oxidation of the unfunctionalized C19 and C8 centers, expansion
of the B-ring, and chemoselective installation of the
iminosulfone side chain.
A-ring Functionalization. Our initial efforts for A-ring
functionalization are depicted in Scheme 2. Starting from predi-
nisone (4), side-chain cleavage and subsequent ketonization led
to the known steroid core 25 in 92% overall yield after
recrystallization.27 Nucleophilic epoxidation of enone 25 gener-
at ed epoxide 26 in 82% yield (70-80 g) under the mediation of
β-BuOOH, a protocol that is operationally superior on a large
scale to a reported dimethylsulfone procedure.28 For our first
forays, a straightforward hydride reduction/activation/displace-
ment sequence was pursued to install the C3 amino group. In the
event, ketone reduction provided α-hydroxy derivative 27 as a
major diastereomer, which upon activation with p-TsCl led to
allylic chloride 28 in 75% yield over two steps. Treatment of 29
with NaN₃ delivered the corresponding allylic azide 30, which
Scheme 2. Initial Efforts To Install the C3 Amino Group on the A-Ring

\[ \text{Reagents and conditions: (a) BH}_3\cdot\text{THF (1.05 equiv), THF, 0 °C, 12 h; NaIO}_4 (0.50 equiv), H_2O, acetone, 0 °C → 33 °C, 3 h; (b) p-TsOH (0.07 equiv), ethylene glycol (25 equiv), toluene, reflux, 1 h, 92% over two steps; (c) tBuOOH (1 equiv), DBU (1.8 equiv), THF, 23 °C, 72 h, 82%; (d) L-selectride (1.5 equiv), THF, 0 °C, 20 min, 95%; (e) p-TsCl (3.0 equiv), DMAP (1.0 equiv), DMF, 35 °C, 1 h, 79%; (f) NaI (6.0 equiv), DMAP, 85 °C, 6 h, 96%; (g) nBuNH}_2 (1 equiv), THF, 23 °C, 16 h, 95%; (h) p-toluene sulfonyl chloride, DBU = 1.8 equiv, nBuLi, 5-dodecyl-1,3,4,5-tetrahydropyridine; DMF = N,N-dimethylformamide.} \]

Scheme 3. Simplified Route to Epoxy Alkenyl Formamide 31

\[ \text{Reagents and conditions: (a) } \text{NH}_3\cdot\text{OH}, \text{NaBH}_4\cdot\text{CN (1.2 equiv), MeOH, THF, 23 °C, 18 h; then HCO}_2\text{H, DMF, 35 °C, } 73\% \text{ (g) scale); (b) } \text{Ti(Oi-Pr)}_4 (2.0 equiv), \text{NH}_3\cdot\text{OH} (4.0 equiv), \text{ClCH}_2\text{Cl} (6.0 equiv), \text{NalBH}_4 (1.0 equiv), 1 h, 23 °C; \text{HCO}_2\text{H (1.1 equiv), } \text{CDMT (1.2 equiv), DMAP (0.3 equiv), NMM (1.1 equiv), CH}_2\text{Cl}_2, 0 °C → 23 °C, 6 h, 95%; CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine, NMM = N-methylmorpholine.} \]

Scheme 4. First Approach To Open Epoxide 31

\[ \text{Reagents and conditions: (a) } \text{TFA (30 °C, 1 h, 97%); (b) } \text{NaBH}_4\cdot\text{CN (1.2 equiv), } \text{Co(acac)}_3 (0.08 equiv), \text{Pd} (0.2 equiv), \text{PhMe}, 90 °C, 24 h, 95%; 70% from TFA; (c) } \text{TFA = trifluoroacetic acid, acac = acetylacetonate.} \]

was subjected to a Staudinger reduction with PPh_3, followed by formylation of the resulting amine, to afford epoxy alkenyl formamide 31 in 39% overall yield.

Capitalizing on the observation that hydride attacks the β-face of ketone 26, a more concise route to epoxy alkenyl formamide 31 was formulated (Scheme 3). Thus, reductive amination of the
Scheme 5. Second Approach To Open Epoxide 31

![Scheme 5 diagram]

*Reagents and conditions: (a) Br₂N, H₂O, 130 °C, 16 h; 34, 64%; 35, 32%; (b) DMAP (0.1 equiv), toluene, reflux, 24 h; 34, 64%; 35, 31%.

Scheme 6. Attempts at Installing the Requisite O-Disposed C5-Tertiary Alcohol

![Scheme 6 diagram]

*Reagents and conditions: (a) PhSH (1.5 equiv), K₂CO₃ (2 equiv), acetone, 65 °C, 15 h, 96%; (b) m-CPBA (1.1 equiv), CH₂Cl₂, 0 °C, 1 h, 94%; (c) m-CPBA (1.4 equiv), CH₂Cl₂, 0 °C, 1 h; (d) DMAP (1.1 equiv), CH₂Cl₂, 23 °C, 2 h, 90% over two steps; (e) Co(acac)₃ (0.2 equiv), PhSH₃ (4 equiv), THF, 0 °C (1 atm), 12 h, 23 °C, 75%; m-CPBA = m-chloroperbenzoic acid, DMAP = N,N-Dimethyl-4-aminopyridine.

C3 ketone moiety of 26 with NH₄OAc and NaBH₄CN furnished the corresponding allylic amine, which was directly formylated, to give formamide 31 in 73% overall yield. After extensive optimization, formamide 31 was obtained in 95% overall yield by using TiCl₃, Ph₃P, NH₃, and NaBH₄ for reductive amination followed by formylation.

With a scalable (>25 g) route to the epoxy allylketone formamide 31 secured, attention was turned to the C1,C2 trans-vinylalcohol formation via epoxide opening. Acid (TFA)-mediated opening of the L2-epoxide was initially attempted, resulting in cyclization to the proximal C1 ketone and then dehydration to form dihydrofuran 32 in 93% yield (Scheme 4). Solvolytic of 32 to the desired trans-diol 33 met with failure. Ultimately, it was found that the epoxide opening could be accomplished with complete positional selectivity using m-BuNOAc as a soluble and highly nucleophilic source of acetate anion in the presence of catalytic Co(acac)₃ as a Lewis acid additive.

While the above-mentioned epoxide-opening reaction provided a decent quantity (hundreds of milligrams) of material for our early-stage studies, the moderate yield for this transformation deterred us from the preparation of alcohol 34 on a gram scale. A number of conditions were subsequently investigated, and alternative epoxide-opening conditions were established (Scheme 5).

By treatment of epoxide 31 with triethylamine and acetic acid, both C2 acetate 34 and C1 acetate 35 were obtained in a 2:1 ratio (34, 64%; 35, 32%). The undesired C1 regioisomer 35 can be recycled using DMAP in refluxing toluene to deliver the same equilibrium mixture (34, 64%; 35, 31%); 34:35 = 2:1).

In parallel to the epoxide-opening studies, installation of the requisite C5 hydroxyl was investigated on several different intermediates (Scheme 6). For instance, displacement of allylic chloride 29 with PhSH under basic media followed by m-CPBA oxidation delivered sulfide 36 in 90% overall yield. It was expected that sulfide 36 would undergo a Malow-Evans
Figure 4. Rationale for the stereoselectivity of the Cs hydration.

Scheme 7. Successful Installation of the Requisite α-Disposed Cs-Tertiary Alcohol

A. First access to install Cs tertiary alcohol

B. Improved installation of Cs tertiary alcohol

Reagents and conditions: (a) Burgess reagent (1.1 equiv), benzene, 20 °C, 30 min, 86%; (b) CuO (1.0 equiv), benzene, 80 °C, 1 h, 63%; (c) Mn(acac)₃ (0.2 equiv), PhSH₂ (4 equiv), O₂ (1 atm), 130 °C, 20 h, 50%; (d) Co(acac)₃ (0.2 equiv), PhSH (4 equiv), O₂ (1 atm), 110 °C, 23 h, 83%.

rearrangement to furnish allylic alcohol. However, it was not observed under a variety of conditions, presumably due to the pseudo-equatorial orientation of the epoxide group which lacks the necessary proximity to Cs for the rearrangement to occur. An alternative approach for the installation of the Cs hydroxyl group was carried out by treating allylic alcohol 27 with m-CPBA followed by Dess–Martin periodinane oxidation to generate a hydroxy ketone 38 (89% yield over two steps). However, the C₄–C₅ epoxide could not be opened to the desired Cs alcohol 29 under a variety of reductive conditions. Finally, Co-catalyzed Mukaiyama hydration of the C₄–C₅ olefin in 31 delivered the undesired β-oriented tertiary alcohol 40 in 75% yield. An X-ray crystallographic analysis of 40 confirmed its stereochemical assignment.

The origin of this selectivity likely arises from the preference of the A-ring to adopt a half-chair conformation (41) with the C3 formamide group in an equatorial rather than an axial position (42, Figure 4A). It was reasoned that a complete reversal of selectivity could arise if a tether was present between the C1 and C3 atoms as shown in Figure 4B. To test this hypothesis, the requisite substrate 48 was synthesized in 54% overall yield by the following sequence (Scheme 7A): (1) dehydration of formamide 34 to isoxazole 45 by using the Burgess reagent and (2) Ccatalyzed cyclization of the C1 hydroxyl onto the isoxazole. When imidate 48 was subjected to Mn(acac)₃, PhSH₂, and O₂, the desired Cs-oxygenated α-isomer 49 was produced in 78% yield. Subsequently, it was found that simply reacting 34 with Co(acac)₃, PhSH₂, and O₂ produced the desired Cs-OH α-isomer 52, which can be rationalized as arising from the greater stability of the desired radical configuration 51 over 50 (Scheme 7B).

After extensive experimentation, Cs-oxygenated orthoamide 24 was synthesized in one pot from intermediate 34 in 65% yield via (1) Mukaiyama hydration of the transenamidated C₄–C₅ olefin, (2) condensation of the formamido-diol with trimethyl orthoformate, and (3) solvolysis of the C2 acetate (Scheme 8). Thus, the final optimized route to the fully functionalized cortistatin A-ring is described in Scheme 8. This simple five-step sequence provides scalable entry to the highly functionalized A-ring steroid.
Scheme 8. A Simple Five-Step Stereoselective Process for Converting the Known Steroid Core 25 into the Fully A-Ring-Functionalized Intermediate 24

Rearrangement and conditions: (a) BuOOH (2 equiv.), DBU (1.8 equiv.), THF, 23 °C, 2h, 82%; (b) Te(OTf)2 (2.0 equiv.), NH3 (4.0 equiv.), CH2Cl2, 6h, 23 °C; NaBH4 (1.0 equiv.), HCO2H, CDMT (1.2 equiv.), DMAP (0.3 equiv.), NMM (1.1 equiv.), CH2Cl2, 0 °C to 23 °C, 6 h, 95%; (c) Et3N (10 equiv.), HOAc (10 equiv.), 130 °C, 16 h, 64%; (d) CO(acac)2 (0.2 equiv.), PPh3H2 (4 equiv.), O2 (1 atm), THF, 23 °C, 20 h; HCl (3 M), (50 equiv.), p-TsOH (6.5 equiv.), 45 °C, 10 h; then Et2CO2H (5 equiv.), MeONa, 12 h; 65%.

Scheme 9. Key Considerations and Historical Context for the B-Ring Expansion

A. Plausible biosynthesis of cortisone

B. Semi-synthesis of the Bucus alkaloids cycloprostanol A (84) via a key C19 methyl activation

C. The key proceeds of transforming 9β,19-cycloandrostenol to 9/15α-bio-epiandrostanol

Intermediate 24. The salient strategic aspect of this work involves the construction of the key "heterocyclic" system expressed in ring A which served three pivotal roles: (1) it reorganized the system for the ensuing B-ring expansion (side infra); (2) it protected three of the four A-ring heterocycles; and (3) in subsequent removal would, in principle, not necessitate additional construction steps since the orthoester and formamide carbons are oxidized forms of the C3 dimethyamino group found in the cortistatins.

B-Ring Expansion. The hallmark seven-membered B-ring of the cortistatins (9β,19)-bio-epiandrostanol, which contains the 6-7-6-5 ring system, presented the exciting challenge of developing a practical and scalable method for B-ring expansion of a "normal" steroid (containing the 6-6-6-5 ring system). The presumed biosynthesis of the cortistatins, initially proposed by the Kobayashi group, was particularly path-pointing to us (Scheme 9A). Inspired by the known biosynthesis of the Bucus alkaloids where both the 9β,19-cyclophane system (84) and the
Scheme 10. Synthesis of Cyclopropane 72 and its B-Ring Expansion

A. Synthesis of a cyclopropylated B-ring

- 379
- 379

B. Ring expansion studies

- 72
- 72
- 72
- 72
- 72

* Reagents and conditions: (a) PhI(OAc)₂ (1 equiv), Br₂ (3 equiv), CH₂Cl₂, light, −10 °C, 5 min; then TMSCl (5 equiv), imidazole (5 equiv), CH₂Cl₂, 0 °C, 10 min, −5 °C, 24 h, 93% (b) HCl (10 equiv), THF, 23 °C, 24 h, 89% (c) AlBr₃ (6.6 M in THF, 6 equiv), THF, 23 °C, 1 h, 95% (d) SiH₄ (1 M in THF, 10 equiv), 1,9-DMPU, MeCN, 23 °C, 10 min, 84% (e) SiH₄ (10 equiv), 1,9-DMPU, MeCN, 23 °C, 10 min, 85% (f) PPh₃ (4 equiv), 60 °C, 30 min, 33 °C, 1 h, 5 (1 M in THF, 30% aqueous solution, 135 equiv), NH₂Cl (4 equiv in aqueous solution), CH₂Cl₂, 23 °C, 30 min, 50% over two steps. DMPU = N,N-dimethylpropyleneurea, TMSCl = trimethylsilyl chloride.

The compounds 379 are naturally occurring, 54 was proposed to be the biogenetic precursor of 55. Based on this information, the Kobayashi group proposed that the carbamazepine family might be generated from 3,5-dimethylaminoethanol (53), a hypothetical metabolite that bears resemblance to related natural products (Scheme 9A).³⁴ Starting from this strong key precursor, cyclopropane formation via C19-methyl activation followed by subsequent ring expansion should produce 55. Hydrosilylation to tris-56 and oxidation would afford the unique THF (5,6-oxide) ring system in 57 and in all other members of the carbamazepine family. This biosynthetic pathway has been a key step in a number of early synthetic studies. For instance, in Martin and coworkers' seminal synthesis of the Baxax alkaloid cyclopropoxine A (64) from lanosteryl (60, Scheme 9B),© the C19 methyl group in 61 was transformed into the allylic iodide 62 via Barton nitrene photolysis and trapping with L. Subsequent ketone formation and cyclopropagation delivered cyclopropane 63 in 60% yield over four steps. In other reports, B-ring expansions of steroids have also been documented (Scheme 9C),© such as in the case of 65 which was smoothly transformed to 379-10(19)-dienen 66 in 82% yield under TFA mediation.© Variations in these conditions have also been used in this type of fragmentation as illustrated with the conversion of 67 to 69 via the cyclopropyl radical 68.© In this context it is known that a synthetic plan for conformation B-ring formation was devised, involving a remote C19 methyl group functionalization/cyclopropagation/ring expansion sequence.

For the first stage of the planned B-ring expansion, a mild method was needed for C19 methyl functionalization. Conveniently, the rigidity imparted by the 'heteroalanine-tanne' A ring forced the C2 hydroxyl and the C19 methyl groups into a pseudo-1,3-diaxial conformation and thus in very close proximity to one another (distance between C2 oxygen and C19 is 2.89 Å based on the X-ray crystal structure of 24). Several potential methods were therefore at our disposal for an alcohol-directed C–H functionalization. The Barton nitrite ester reaction was attempted first, but unfortunately, this chemistry failed to produce the desired result from 24. Subsequently, conditions for the controlled halogenation of C19 were explored. It was found that modification of Sauer's conditions⁸ for remote methyl oxidation using PhI(OAc)₂ and Br₂ effected monobromination of C19 (Scheme 10A). The reaction proceeds by 1,3-formation of ACCBr₃ that most likely leads to formation of an O–Br bond at the C2 hydroxyl, subsequent O–Br bond homolysis, hydrogen atom abstraction, and recombination with bromine radical or Br₂ at C19. The intermediate hydroxy bromide was not isolated due to its rapid closure to a tetrahydropryran, instead, immediate protection of the C19 alcohol as a trimethylsilyl ether and base-induced cyclopropagation afforded cyclopropane 72 in 64% yield over two steps. It should be noted that the use of the well-documented PhI(OAc)₂/Br₂ conditions for monobromination resulted in competitive THF formation, likely due to a much larger coefficient of the σ⁺C–Br orbital.³⁹
Scheme 11. Synthesis of Bromocyclopropane 80

![Chemical Structures](image)

Reagents and conditions: (a) Pd(OAc)$_2$ (5 equiv), Br$_2$ (8 equiv), CH$_2$Cl$_2$, light, $-30^\circ$C; 10 h; then TMSCl (5 equiv), imidazole (5 equiv), CH$_2$Cl$_2$, 0°C, 15 min, 57%; (b) DBU (5 equiv), LiCl (5 equiv), THF, 23°C, 24 h, 65%.

The subsequent B-ring expansion, selected attempts to open cyclopropane 72 are shown in Scheme 10B. AH$_2$-mediated reduction of the orthoquinone moiety provided 73 in 74% yield. Unfortunately, acid-catalyzed fragmentation of cyclopropyl alcohol 73 to diene 74 was unsuccessful. After exhaustive experimentation, cycloprenyl ketone 72 could be efficiently fragmented to give cyclohexyl ketone 75 upon exposure to SnMe$_2$ followed by acidic workup in 84% yield. Alternatively, quenching the reaction with PtSi$_x$Br and subsequent oxidative elimination furnished conjugated diene 77 in 56% yield over two steps. Clearly, the obtention of cyclohexyl ketones 75 and 77 marked a milestone in our studies since they were the first intermediates to bear a seven-membered B-ring. Cycloprenyl ketones 75 and 77 merely required a loss of four or two hydrogens, respectively, in order to arrive at the desired cyclohexyl diene 76. The realization of this crucial dehydrogenation, however, proved challenging; no reaction conditions were identified to perform this transformation chemoselectively on these ketones.

Since dehydrogenation at C10 and C19 following the B-ring expansion proved difficult, establishing the desired oxidation state on C19 prior to B-ring expansion was evaluated. Fortunately, during our studies on the Suits-type monobromination (Scheme 10A), small quantities of bis-brominated material were always isolated. It was reasoned that this geminal dibromide (see 79, Scheme 11) possessed the exact oxidation state required of the C19 carbon atom for its eventual expression in 76. After substantial optimization, 79 was obtained in 53% yield via an iterative, double C–H activation process, while suppressing the attack of the alcohol on the 4$_{1}$,6$_{1}$-orbital of monobromide 81. To the best of our knowledge, this is a rare example of an alcohol-directed, geminal dihalogenation of an unactivated hydrocarbon. The unstable dibromo alcohol 83 was capped with a trimethyldimethyl group to prevent an unwanted intramolecular cyclization. α-Alkylation of the C11 ketone with the proximal dibromomethyl group proceeded with DBU and LiCl to generate the exotic bromocyclopropane 80 as a single diastereomer in 48% yield over two steps, whose configuration was confirmed by X-ray crystallographic analysis.

Now that the desired oxidation state at C19 was obtained, bromocyclopropane 80 was subjected to the SnMe$_2$ reductive fragmentation conditions. Pleasingly, 80 underwent B-ring expansion as anticipated and unconjugated diene 88 was obtained, bearing no bromine atom but rather a C10–C19 alkene (Scheme 12A). This product is presumably formed via radical-induced ring expansion from 85 to 86, extrusion of bromine radical, and quenching of dieneolate 87 with H$_2$O. 40 Reduction of the C11 ketone in 88, elimination of resulting hydroxyl group, and heteroazamantane reduction with AH$_2$ afforded diene 89 in 23% yield over three steps. Thus, the oxidation state deliberately embedded into C19-methyl dibromide 79 was translated smoothly into the olefinic C19-methine of the cortistatin core. In addition, 89 possessed all of the correct A-ring functionalities with the correct stereochemistry and the hallmark C10–C19–C11 diene expressed in the natural product. However, thereafter, all attempts to oxidize the C8 position in order to form the THF ring unfortunately met with failure. In essence, what we hoped to achieve was an isobicyclic reaction (in this case an isomerization) to convert bromocyclopropane 80 into the redox isomeric diene 76 in a single operation. Thus, a set of trapping experiments on the reactive allenium dienolate 87 was investigated as shown (Scheme 12B). Trapping dieneolate 87 with O$_2$ afforded γ-hydroxy enone 91 in 72% yield, whose structure was identified by X-ray crystallographic analysis. Dehydration of 91 turned out to be difficult, and the desired product was not observed. Eventually, it was found that trapping dieneolate 87 with 2,4,6-triethylumbelliferyl 2,5-dienone (TBDCH) delivered the α-disposed allylic C9 bromide 92 with high diastereoselectivity, which could be converted to the cross-conjugated diene 76 on a gram scale under mildly basic conditions (LiBr, Li$_2$CO$_3$). This two-step process took place in 65% overall yield, and the structure of the coveted diene 76 was verified by X-ray crystallographic analysis.

THF Ring Closures. Diene 76 represented a "point of no return" in our path to the cortistatins with carbons 8, 9, 10, and 19 having the correct oxidation state. All that remained in order to complete the core synthesis was a THF ring formation and a chemoselective dimethylation of the heteroazamantane-cloaked A-ring. It was reasoned that the THF ring could be constructed by attack of the C5 tertiary alcohol onto the C8 position by an Sn$_2^{1}$ or Sn$_{2}^{2}$ mechanism. Treatment of diene 76 with AH$_2$ led to a notably clean and precise delivery of five hydroxys to give an intermediate dimethylmino triol. Addition of MeOH to the
reaction mixture served to quench any remaining hydride, and the addition of KHCO₃ removed the TMS group on the C2 alcohol to afford tetralk 23 in 85% yield. Acetylation of tetralk 23 furnished triacetal 93 in 93% yield, which allowed us to test the hypothesis that the biphasic ether in cortistatin A might be formed through selective ionisation. After screening a number of conditions, it was found that MgBr₂·Et₂O and 2,6-di-tert-butylpyridine was an effective combination of reagents to perform the desired cyclization. Subsequent deketalization and saponification delivered cortistatinone (22) in 82% overall yield. Comparison of the 1H NMR data with those of cortistatin A (11) was encouraging, as all of the non-aromatic carbons bore strong resemblance to the natural product spectra.

The three-step sequence from tetralk 23 to cortistatinone (22), while easy to perform, was not efficient in terms of step count and reaction time. Therefore, a direct route from tetralk 23 to cortistatinone (22) was investigated. A variety of acids were screened to effect this transformation (Scheme 13B), upon which it was found that both Lewis and Bronsted acids (for example, HCl, entry 5) were able to produce the desired compound — cortistatinone (22). BCl₃ was identified as the superior reagent to perform the cyclization and deketalization simultaneously in 73% yield. This improvement reduced the operations of the original route by three and enabled the preparation of milligram quantities of cortistatinone (22).

The final optimized route from orthoamide 24 to cortistatinone (22) is shown in Scheme 14. It features a number of gram-scale transformations: (1) a newly invented alcohol-directed alkylation; (2) an isocyanide cascade to access the 9(10,19)αβ-ando-trione skeleton; (3) an olefin-sparing, heteroarylmethane fragmentation to deplete the tethered aminoacid; and (4) a mild Sβ cyclization to close the THF ring. With this robust pathway developed, over 50 g of cortistatinone (22) has been prepared to date.

Isoquinoline installation. In parallel to our efforts to synthesize cortistatinone (22), methods were developed for the introduction of the C17 isoquinoline moiety at earlier stages in our
Scheme 13. THF Ring Closure\(^a\)

\(\begin{align*}
\text{A. Stepwise THF ring closure} \\
\text{B. Direct THF ring closure}
\end{align*}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions(^b)</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OOTf)(_2)</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>IrCl(_3)</td>
<td>56%</td>
</tr>
<tr>
<td>3</td>
<td>NaBr(_2)Et(_2)O</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>BuCl(_2)</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td>HCl</td>
<td>40%</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OOTf)(_2)</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^a\) Reagents and conditions: (a) ASH\(_2\) (93 M in THF, 6 equiv), THF, 25°C, 1 h; then K\(_2\)CO\(_3\) (5 equiv), MeOH, 23°C, 12 h, 85%; (b) Ac\(_2\)O (20 equiv), Et\(_3\)N (40 equiv), DMAP (0.1 equiv), CH\(_2\)Cl\(_2\), 24°C, 3 h, 93%; (c) MgBr\(_2\)Et\(_2\)O (1.1 equiv), 2,6-di(tert-Butyl)pyridine (2.1 equiv), Pd(0), 80°C, 1 h; (d) PPTS (5 equiv), butanol-H\(_2\)O (1:1), 90°C, 2 h; then K\(_2\)CO\(_3\) (10 equiv), 23°C, 5 h, 82% over two steps. PPTS = pyridinium p-toluenesulfonate.

\(^b\) Reagents and conditions: acid (4 equiv), MeCN, 40°C, 2 h; H\(_2\)O, 40°C, 4 h.

Scheme 14. Final Optimized Route to Curtistatitone (22)\(^a\)

\(\begin{align*}
\text{A. Intermediate formation} \\
\text{B. Curtistatitone (22)}
\end{align*}\)

\(^a\) Reagents and conditions: (a) Pd(0)OAc\(_2\) (5 equiv), B\(_2\)O\(_3\) (6 equiv), CH\(_2\)Cl\(_2\) light, −30°C, 10 h then TMSCl (5 equiv), imidazole (5 equiv), CH\(_2\)Cl\(_2\) (0°C, 15 min). (b) DMAP (5 equiv), 1,1′-EDT (5 equiv), THF, 71°C, 7.4 h, 89%. (c) DMSO (1 equiv), THF 71°C, 15 min. (d) DMF (5 equiv), THF 71°C, 15 min then THF/H\(_2\)O (2 equiv), −78°C, 1 h, (d) LiBr (20 equiv). LiCl\(_2\) (20 equiv), DMF 80°C, 1 h, 65% over two steps; (e) ASH\(_2\) (65 M in THF, 4 equiv), THF, 23°C, 1 h, 76% then K\(_2\)CO\(_3\) (5 equiv), MeOH, 23°C, 12 h, 85%. (f) BuCl\(_2\) (5 equiv), MeCN, 40°C, 2.5 h, BuCl\(_2\), 40°C, 5 h, 73%.

The synthesis (Scheme 15) of the fundamental strategic problem with such an approach is that it presents the desired late-stage diversification, and the isoquinoline moiety itself poses incompatibilities with key reactions. For example, intermediate 24 could be transformed to isoquinoline-containing steroid 96 in one overall yield by a sequence employing xenial cleavage, aryl vinyl iodide formation [leading to 95], and Stille coupling\(^c\) with stannane 105S, and stereospecific hydrogenation with Pd/C. Unfortunately, the isoquinoline moiety was incompatible with halogenation conditions.\(^d\) In this vein, bromocyclopentene-isoquinoline conjugate 99 could be prepared in 16% overall yield, but bromocyclopentene was not compatible with hydrogenation conditions. Therefore, the original plan for late-stage isoquinoline installation remained the most logical, and indeed the only viable option.

with two new amines, one tertiary amine, and a sensitive amine adjacent to a THF ring, curtistatitone (22) requires "gentle" chemistry for derivatization. Barton's vinyl iodide preparation (side note) fulfills this requirement, as does the Stille coupling.\(^e\) In the event, this reaction sequence works well to
Scheme 15. Studies on Isoquinoline Installation

A. Attempted side chain installation at early stages of the synthesis

B. Synthesis of cortistan A (11)

*Reagents and conditions: (a) PPTS (1 equiv), 1:4 H<sub>2</sub>O:acetone, 80 °C, 30 min; (b) NH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> (20 equiv), Et<sub>2</sub>NH (40 equiv), EtOH, 50 °C, 2 h, 2 equiv, Br<sub>2</sub>N (3 equiv), THF, 21 °C, 10 min; 70% over two steps; (c) 101 (1 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.5 equiv), CuCl (10 equiv), LiCl (10 equiv), DMP, 60 °C, 1 h, 33%; (d) 106 (1 equiv), 2.1 EtOH:MeOH (1:2), 12 h; 28%; (e) PPTS (1 equiv), 1:4 H<sub>2</sub>O:acetone, 80 °C, 30 min; (f) NH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> (20 equiv), Et<sub>2</sub>NH (40 equiv), EtOH, 50 °C, 2 h; 1 equiv, Br<sub>2</sub>N (5 equiv), THF, 23 °C, 10 min; (g) 105 (1 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.5 equiv), CuCl (10 equiv), LiCl (10 equiv), DMF, 60 °C, 1 h, 55% over two steps; (h) Raney Ni (10 wt equiv), p-C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>, 50 °C, 1 h, 50%, 50-60% bromine. DMSO = dimethyl sulfoxide.

Scheme 16. Scalable Synthesis of 7-Substituted Isoquinoline

*Reagents and conditions: (a) NBS (1.1 equiv), NaOH (39%, 5 equiv), CH<sub>3</sub>Cl<sub>2</sub>, 1.5 h, 92%; (b) KNO<sub>3</sub> (1.5 equiv), H<sub>2</sub>SO<sub>4</sub>, 0 °C → 32 °C, 2 h, 60 °C, 4 h, 72%; (c) MnO<sub>2</sub> (7 equiv), toluene, reflux, 2 h, 91%; (d) Pd/C (10%), H<sub>2</sub> (1 atm), 3 h; (e) Cul (1.2 equiv), NaNO<sub>2</sub> (1.1 equiv), H<sub>2</sub>O, HBr, 0 °C → 75 °C, 30 min; 23 °C, 12 h, 69% over two steps; (f) H<sub>2</sub>P(OB<sub>2</sub>Me)<sub>2</sub> (0.1 equiv), hexamethylditin (105 equiv), LiCl (6 equiv), toluene, 105 °C, 1 h, 88%. NBS = N-bromosuccinimide.

delivered A<sup>16</sup> cortistan A (101) in 5.3% isolated yield (on a scale ranging from 1 to 300 mg). The final conversion of 101 to cortistan A (11) required numerous screens in order to identify a suitably chemoselective reducing agent that could differentiate a styrene-like olefin from an isoquinoline and a diene and do so in the presence of numerous unprotected functionalities. Whereas Sm- and Pd-based agents led to over-reduction (observed by LC/MS, uncharacterized), and Rh-mediated transfer hydrogenation or diimide methods did not work in our hands, Raney Ni led to an excellent conversion to 11, thus completing the synthesis. This reaction was never run beyond a 10 mg scale since it was soon found that 101 is nearly equipotent to 11 in all biological assays tested. In a separate report, we have demonstrated the generality of this reaction and explored its mechanism. In passing, we note that although isoquinolines 101 is commercially available, it is prohibitively expensive (ca. $80/10 mg in 2007 when we started our studies). Furthermore, the existing methods to synthesize 7-bromoisoquinoline by the Pomeranz-Fritsch reaction<sup>17</sup> gives 5-bromoisoquinoline as a byproduct that is difficult to separate. Therefore, a scalable and practical synthesis of 7-bromoisoquinoline was developed, as shown in Scheme 16. Starting from tetrahydroisoquinoline (102), imine formation with NBS/NaOH<sup>15</sup> nitration at the C7 position, and dehydrogenation with MnO<sub>2</sub> furnished 7-nitroisoquinoline (103) in 61% yield over three steps. Subsequent reduction of the nitro group and Sandmeyer reaction afforded the desired 7-bromoisoquinoline (104) in 63% yield over two steps. Lastly, stannylation of 7-bromoisoquinoline (104) delivered 7-trimethylstannylisoquinoline (105) in 88% yield.
CONCLUSION

This full account describing a scalable synthesis of cortisone A and related structures stands as an example of how the judicious choice of strategy can yield new insights into chemical reactivity, even in a field as exhaustively studied as steroid synthesis. Several transformations were developed that were either not feasible or not possible prior to this work: the easily scalable side-chain cleavage protocol; the chemoselective, tandem geminal dialkylolation of an unactivated methyl group; the reductive fragmentation/trapping/elimination of a bromocyclopropane to simultaneously establish both the $\Delta^{10(13)}$ and $\Delta^{12}$-olone as well as the 7-membered B-ring; the facile chemoselective etherification reaction for installation of the oxido bridge; and the remarkably selective $\Delta^{12}$-alkene reduction with Raney Ni. Although our primary motive for pursuing a synthesis of the cortisone A was to uncover new reactivity, develop new strategies, and educate students, we were keenly aware of the societal need for a scalable route due to its extraordinary biological activity. With these factors in mind, a semisynthetic approach was chosen— one that successfully converted one of the most abundant terrestrial-based steroids into one of the ocean’s scarcest steroidal alkaloids ever isolated. The synthesis outlined in this work is amenable, in an academic setting, to the gram-scale production of the cortisone A and has also been successfully outsourced to an industrial setting. It is sufficiently short and flexible for analog synthesis, especially those which vary the aromatic heterocycle at the late stage of the synthesis. Finally, the copious quantities prepared thus far, particularly of cortisone A’s equivalent epoxide 101, have been widely distributed to numerous academic laboratories and pharmaceutical companies. Indeed, extremely promising biological findings enabled by the synthesis have already been made and will be described in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental details, spectra, and X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
pbran@scripps.edu

Author Contributions
*These authors contributed equally to this paper.

ACKNOWLEDGMENT

We thank Dr. C. Moore and Prof. A. Rheingold for X-ray crystallographic measurements, Dr. G. Stierak for mass spectrometric assistance, and Dr. D. H. Huang and Dr. L. Pastorack for NMR assistance. We thank Dr. C. C. Li and Mr. T. Uramachi for preparing NMR samples. We are grateful to Novartis and Bristol-Myers Squibb (predoctoral fellowship to J.S.), the German Academic Exchange Service (DAAD, postdoctoral fellowship to G.M.), the NSC of Taiwan (NSC98-2917-I-007-122, graduate fellowship to C.H.Y.), the Department of Defense (postdoctoral fellowship to R.A.S.), the NIH (predoctoral fellowship to C.A.G.), and the Uehara Memorial Foundation (postdoctoral fellowship to H.S.). Financial support for this work was provided by Amsgen, Bristol-Myers Squibb, Leo Pharma, and the Skaggs Institute for Chemical Biology.

REFERENCES


(28) The Brooks’s–Nooyen formal method was found to be impractical on a large scale, see: Brooks, C. J.; Nooyenreik, J. B. Biochem. J. 1953, 55, 371–370.


(32) Decalin-bridged radicals have been shown to deviate from planar geometry, see: Lloyd, R. V.; Pate, R. V. J. Phys. Chem. 1985, 89, 5379–5381.


(39) Formation of a germinal diolide using Staudinger chemistry has been implicated previously. For an account, see: Hsu, B.; Kalvoda, C. J. Am. Chem. Soc. 1994, 61, 492–505.

(40) It is also possible that 87 was formed via E1, B elimination of the bromide in 86, followed by reaction of the 8-cis conjugated carbon radical with an additional equivalent of SIM. (41) Bartos, D. R.; O’Brian, R. E.; Stenhouse, S. J. Am. Chem. Soc. 1962, 470–478.

(42) Han, X. J.; Strota, B. M.; Corey, E. J. J. Am. Chem. Soc. 1999, 121, 7600–7606.


(47) We are aware of at least two outsourcing companies that have been hired to procure counterfeit using the route published in ref 24.
The total synthesis of the biologically significant antibiotic vinigrol (1) has stood for over two decades as a major unexplored challenge for organic synthesis. The extreme difficulty in preparing this molecule stems from its unprecedented and highly congested decalylidene, 1,2-dihydroxynaphthalene ring system containing eight contiguous stereocenters (shown in four different views in Figure 1A). In this Communication we report a solution to this longstanding problem in complex terpene synthesis.

Last year we reported a short route to the core skeleton of 1 featuring a sequence of classic transformations such as the Diels-Alder and Grob fragmentation, that proved to be capable of delivering structures similar to 2 (Figure 1B), albeit lacking the C-9 methyl group. In accord with the well-documented reluctance of late-stage intermediates to be converted to 1,2,5 seemingly logical routes to 1 from 2 and related intermediates failed in our hands. The final route presented herein was derived from a detailed series of experiments.

The route to 1 commences from 3 (Scheme 1), an intermediate available in docigrams quantities in seven steps from commercially available materials. The C-9 methyl group was installed by allylation (EDA, MeI), and, following silyl group removal (TBAF), the adjacent acetoxy group was converted to an intermediate using Evans’ n-butyl lithium/copper(I) chloride mediated, hydroxy-directed reduction to deliver 4 as a single diastereomer in 72% yield over the three-step sequence. Indirectly, reduction (i.e., DBAL) afforded mainly the undesired alcohol diastereomer at C-11, due to the shielding effect of the C-9 methyl group. The correct stereochemistry was confirmed by the ensuing Grob fragmentation that furnished 2 (see Figure 1B for structure) after mesylation and treatment with KHMD5 (85% yield over two steps).

Installation of the C-8 methyl and C-8a hydroxyl groups proved to be a challenge due to their cis orientation. The required group cannot arise from the simple hydrogenation of an exocyclic olefin because reagents approach the less hindered (and wrong) diastereoface. In essence, a hypothetical transform to achieve the cis-addition of the —CH₂ and —OH groups of methanol across an olefin was required. After extensive exploration, the formal equivalent of such a reaction was developed. Thus, exposure of 2 to bromonitro oxide (generated in situ from dibromomofomaldehyde and VINO₃) resulted in a bipolar cycloaddition, leading to the formation of 5 as a single isomer in 88% yield on a gram scale. This cycloaddition proceeds with complete control over regio- and positional selectivity to produce a single diastereomer of 5 (verified by X-ray crystallography). Ketone reduction with DBAL followed by directed olefin hydrogenation (20% Crabbe’s catalyst, H₂, B(OH)₂) furnished 6 in 83% yield. It should be noted that olefin hydrogenation was confounded by the C-9 methyl and C-12 isopropyl groups flanking the disubstituted olefin on the face from which almost hydrogenations would be expected to occur. In our hands this was the only intermediate and the only set of conditions that succeeded; dozens of hydrogenation conditions on several different intermediates failed.

Xantophyll formation (MAT, Cs₂CO₃, MeI) and subsequent Claisen condensation (180 °C) furnished olefin 7 in 85% overall yield. The

Figure 1. (A) Illustrations of vinigrol (1) and (B) retrosynthetic analysis.

bromonitrooxide was unmasked to the desired tertiary alcohol 9 by the Siegnera-demethylation sequence: (1) reduction with LiAlH₄ and immediate formation of the crude amine; (2) dehydration to a primary isocyanate; and (3) treatment with PhSiH₃ in the presence of AIBN in 56% overall yield. The robustness of this overall route is evident from the fact that over 50 g of 9 has been easily prepared, and all the steps leading to this key intermediate have been conducted on a gram scale.

Access to large quantities of key intermediates such as 9 was critical since, as alluded to above, we encountered a maze of unpredictable failures on enantio 1, 2, a sampling of which are shown in Figure 2. Thus, allylic oxidation of 9 led to 13, which could not be further elaboration functionalized further. Although olefin 9 reacted with bromonitrooxide to furnish 14, its downstream product 15 and related structures could not be consumed to 1. Finally, 13, dihydrovinigrol (16) and derivatives thereof could not be dehydrogenated to 1.

Figure 2. A small sampling of "dead-end" intermediates.

Ultimately, a simple route to 1 from 9 was developed. Thus, debenzylation of 9 with Ce(O₂)₂ and subsequent either of the resulting diol (NaOCl, TEMPO) or led to o-hydroxy ketone 10 in 81% overall yield. A Shapiro reaction via triethylmagnesium took place presumably via the tinonionic species 12 to deliver (±)-1 (spectroscopically identical in all respects to a natural sample of 1, with the exception of optical rotation).

10.1021/ja081944b CCC: 8675 © 2009 American Chemical Society
387


Natural products have always been a successful pool of molecules from which the pharmaceutical industry can find novel medicinal agents. Steroids, in particular, continue to be the subject of medicinal investigations for two reasons: they are "privileged" pharmacophores and their scrutiny for over half a century has resulted in a vast body of knowledge regarding their reactivity. Recently, Kobayashi and co-workers elucidated the structures of cortistatin A-L (Scheme 1). The synthesis of cortistatin A (1) from the sponge *Corticium simplex* reveals how the marine derived steroids exhibit potent anti-angiogenic activity against HUVECs (human umbilical vein endothelial cells) by a possibly unique mechanism. While the Kobayashi research group has already delineated a preliminary structure-activity relationship (SAR) of the family (see Scheme 1), their scarce natural supply renders chemical synthesis as the only means to decipher their medicinal potential. Particularly intriguing is the impact of the isoquinoline moiety on biological activity since its absence significantly lowers activity. Here, we illustrate the critical influence of D-ring configuration on biological activity with the synthesis of 17-α-cortistatin A (2). Specifically, we have found that C-17 stereocchemistry may be removed all together as α-sterocortistatin A (2) retains much of the potency of 1. This line of chemical inquiry has also led to the first useful method for the stereocentred preparation of other α-aryl substituted D-ring steroids.

Several approaches have been reported for the preparation of the core structure of cortistatin[@ref] and two elegant total syntheses of the most potent member of this natural product class, cortistatin A (1), have appeared from the Nicolaou/Chen[@ref] and Sairi research groups.[@ref]

Our own synthetic goal was profoundly affected by the strategic choice to use precision—synthetic corticosteroid produced on multiton scale by microbial oxidations of naturally occurring steroids—as a starting material. Aside from economical considerations, this choice was made with the knowledge that semi-synthetic approaches have enjoyed decades of success in the pharmaceutical industry. Thus, a twelve-step sequence was utilized from this starting point to arrive at cortistatinine (3) in gram quantities[@ref]. The synthesis concluded with a highly chemoselective Raney nickel (Ra-Ni) mediated hydrogenation of α-sterol cortistatin A (3). In order to evaluate the importance of a β-oriented isoquinoline moiety, an estrone-derived model (5, Scheme 2) was employed as a testbed for a strategy that would deliver both systems from a common intermediate.

By analogy to the synthesis of 2, arostin model 5 was converted to the D-ring styrene 6a as depicted in Scheme 2. Regardless of the reducing conditions, the only observed product was the expected β-aryl substituted product 7a: A Ra-Ni mediated reduction led to a 97% yield of isolated 7a. This is not surprising given the fact that an overwhelming majority of macrocyclic, electrocyclic, and radical substitution reactions at C17 occur from the α-face. Attention was therefore turned to an alternative approach that began with tertiary alcohol 8a, derived from addition of PhLi to S. Based on preliminary evidence[@ref] and a report that Ra-Ni reductions of benzylic alcohols occurred with retention of configuration.[@ref]
alcohol 8a was subjected to Ra-Ni in toluene at reflux. A diastereomeric pair of compounds was isolated in a 6:6:1 ratio, the major isomer of which bore the desired α-configuration. The structures of 6a-9a were all verified by X-ray crystallography.

The generality of this reagent system, a synthesis of 17-epi-coristatin A, mechanistic analysis of these reductive processes, and biological evaluation of coristatin analogues are presented below.

As shown in Table 1, both pathways (6 to 7 and 8 to 9) are amenable to the incorporation of electron rich, neutral, and withdrawn arenes, as demonstrated by the successful deoxy-

tabulation and hydrogenation mediated by Ra-Ni.

<table>
<thead>
<tr>
<th>Table 1: Deoxygenation and hydrogenation mediated by Ra-Ni.</th>
<th>Yields and diastereoselectivities</th>
</tr>
</thead>
</table>
| 8a (α): 63%, dr = 11.2:1 | 8b (α): 53%, dr = 20:1  
 8a (β): 57%, dr = 20:1 | 8b (β): 59%, dr = 22:1  
 9a (α): 66%, dr = 20:1 | 9b (α): 53%, dr = 11:1  
 9a (β): 66%, dr = 20:1 | 9b (β): 53%, dr = 11:1 |

The reaction of 6a was conducted in deuterated isopropyl alcohol and toluene (toluene or [D6]toluene gave identical results) with D2O-washed Ra-Ni, affording [D6]7a with deuterium incorporation at C16 and C17. For Ra-Ni mediated deoxygenation, the reaction of 8a employed deuterated toluene with D2O-washed Ra-Ni. Surprisingly, [D6]9a was obtained as the major product in 96% yield. However, 7a and 9a exhibited identical aromatic deuterium substitution when subjected to the same reduction conditions as 8a, demonstrating that this aromatic deuteriation is independent of the deoxygenation process.

The divergence in observed stereochemical outcome between 7 and 9 seemingly excludes the intermediacy of free-radicals in deoxygenation (8 → 9), radical deoxygenation produces β-configuration at C-17). The difference in stereo-selectivity between 6 and 8 can be rationalized based on the facial selectivity of chemo-adsortion to the metal surface as depicted in Scheme 4. Previous studies[8] have demonstrated that a high degree of stereo-electricity can be incurred in Ra-Ni mediated reductions based on steric/electrostatic adsortion.

In the case of 6, adsorption likely occurs most favorably on the relatively flat α-face, away from the angular methyl group (C-18). Hydrogen and/or electrons are then transferred from the metal surface to the preferentially adsorbed face.[9]

In the case of 8, adsorption possibly takes place on the convex face, with interaction occurring between the surface and both the aromatic α-system and the benzylic hydroxyl, followed by hydrogen/deuterium delivery from the metal.
Finally, the mechanistic requirement of an ary1 group at C-17 during deoxygenation is supported by the fact that 17β-hydroxy-17α-(n-butyryl)-estrone (10) was inert to deoxygenation using Ra-Ni. In addition to submitting 10 to the reaction condition, a control experiment was carried out with an equimolar mixture of 10 and 8a premixed in the same reaction vessel and treated with Ra-Ni. While 8a was completely deoxygenated, 10 was quantitatively recovered.

The utility of the present invention is aptly demonstrated by the synthesis of 17-epi-cortistatin (4), as shown in Scheme 5. Thus, protection of the diazadiol motif in cortistatins (3) with TMS-imidazole, followed by treatment with an excess of 7-thiobenzoisquinoline in a THF/TMEDA solvent mixture at -78°C generated an alkylbenzoisquinoline that was deoxygenated with Ra-Ni to deliver 17-epi-cortistatin A (4) in 16% yield over three steps.

This substance proved crucial in testing the substrate scope/specificity of cortistatin A's biological target. The importance of this substrate is clear since the greatest modulation of biological activity in the naturally occurring cortistatins stems from structure variations of the C-17 substituent.****

In an assay to determine activity against HUVECs (carried out by Pfizer Inc.), synthetic cortistatin A exhibited an IC₅₀ value of 2.4 M, which is in good agreement with the reported value (Table 2).*° Remarkably, 2 still retains high potency against HUVECs, with an IC₅₀ of 3.88 M. This result is a significant step forward in the simplification of the overall cortistatin structure from a synthesis standpoint. However, 4 does not exhibit useful levels of activity (>1 µM). This profound difference of biological activity clearly indicates that the C-17 stereochemistry is essential for biological behavior. Modeling studies (shown in Figure 1) suggested

![Figure 1: Superimposed structures of the lowest energy conformation of 1 (red), 2 (magenta), and 4 (green) by schrodinger software oriental dive macromodel.](image)

Table 2: Selective growth inhibition of cortistatins against HUVECs.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>IC₅₀ [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>cortistatin A (7)</td>
<td>2.4 M, 7.2 M</td>
</tr>
<tr>
<td>17α-epi-cortistatin A (6)</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td>17α-epi-cortistatin A (4)</td>
<td>&gt; 1000</td>
</tr>
</tbody>
</table>

*IC₅₀ of synthetic cortistatin A tested by Pfizer Inc. **IC₅₀ of natural cortistatin A tested by Kobayashi group. ° The TBS groups were removed prior to testing. The results of 6a and 7a are from Ref. [6].

![Scheme 5: Synthesis of 17-epi-cortistatin A](image)
Experimental Section

General procedure for the standardization of Raney nickel (Ra-Ni): Raney 2000 Nickel (ca. 1 g of 1 g/L slurry in H2O, pH 9, Sigma-Aldrich) was placed in a vial. The water was removed by pipette, and the Raney Ni was washed with 5 × shaking, followed by removal of the supernatant: 5 ml H2O (5 × 2 ml), then immersed aqueous Rochelle's salt (2 × 2 ml), then 50 ml H2O (1 ml). After all washes, the Ra-Ni aqueous solution (pH 7) was stored under H2O (1 ml).

General procedure for deoxygenation: To a solution of styrene in \( \text{PhOH} \) volume (9:1, 0.04 M) was added an excess of Ra-Ni prepared above (the Ra-Ni suspension was removed by 5.75% pipette from the thick bottom layer of the vial; one drop suspension per 0.1 ml solution). The reaction flask was immersed in an oil bath preheated to 60°C and stirred vigorously for 1.5 min. After cooling to ambient temperature, the reaction mixture was passed through Celite, the Ra-Ni washed with CH2Cl2, and the combined filtrate were concentrated in vacuo. The product was purified by flash column chromatography.

General procedure for hydrogenation: To a solution of alcohol in toluene (0.1 M) was added an excess of Ra-Ni prepared above (the Ra-Ni suspension was removed by 5.75% pipette from the thick bottom layer of the vial; one drop suspension per 0.1 ml solution). The reaction flask was immersed in an oil bath preheated to 100°C and stirred vigorously for 5 h. After cooling to ambient temperature, the reaction mixture was passed through Celite, the Ra-Ni washed with CH2Cl2, and the combined filtrate were concentrated in vacuo. The product was purified by flash column chromatography.

Received: February 27, 2009
Revised: April 5, 2009
Published online: May 11, 2009

Keywords: angiogenesis - asymmetric synthesis - natural products

References:

27. See Supporting Information for detailed experimental procedures and copies of all spectra. CCDC 721528 (a-a), 721538 (74a), 721529 (8a), 721530 (9a), and 721527 (18b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Synthesis of (−)-Cortistatin A

Ryan A. Shervin, Caido A. Guerrero, Jun Shi, Chuang-Chuang Li, and Phil S. Baran
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received March 31, 2008; E-mail: pbaran@scripps.edu

Steroids have historically elicited attention from the chemical sciences owing to their utility in living systems, as well as their intrinsic and diverse beauty.1 The cortistatin family (Figure 1, 1−7 and others),2 a collection of unusual marine 9(10,15)-abroadiastere steroid, is certainly no exception, aside from challenging stereochemistry and an odd bit of chemical groups, the salient feature of these sponge metabolites is, incomparably, their biological activity. Cortistatin A, the most potent member of the small family, inhibits the proliferation of human umbilical vein endothelial cells (HUVECs, IC50 = 1.0 μM), evidently with no general toxicity toward other healthy or cancerous cell lines (IC50 > 200 μM, Figure 1).2 From initial pharmacological studies, binding appears to occur reversibly, but to an unknown target, inhibiting the phosphorylation of an unidentified 110 kDa protein, and implying a pathway that may be unique to known antiangiogenic compounds.3

Compiled by the pharmacological potential of the cortistatins,4,5 together with the unanswered questions surrounding their biological activity,6 our group embarked on a synthesis of cortistatin A (I), aiming for a concise route from inexpensive, commercially available materials and the opportunity to develop new chemistry as the occasion arose. A crucial target structure became the cortistatin A ketonic core, (−)-cortistatinone (R), which was anticipated to allow for straightforward elaboration to the natural product, as well as divergence to other family members. A semisynthetic route to these marine steroids was deemed an acceptable strategy largely due to the economy of using precursors, which at $1.20/g possesses 70% of the carbon atoms and the corresponding, nonstoichiometric selectivity of I.

Preliminary attempts to convert the known steroid core 9 (Scheme 1) to a short two-step sequence (see Supporting Information) and its 92% overall yield after acetylation. The C1, C2 trans-vinylidene diol was targeted through the intermediary of the trans-disposed epoxide 10, which was installed using tert-butyl hydroperoxide instead of the proceedurated, but unstable, dihydroxydihydroxide (DHDO) procedure.7 Reductiveamination of the unatrated ketone proceeded uneventfully, and reducing the ene reaction mixture with ethyl bromide generated transmethyl 11 in good yield. The epoxide, however, proved inaccessible to a number of standard procedures for nucleophilic addition. Under acidic aqueous conditions, the nascent diol underwent facile cyclization onto the C11 ketone, followed by dehydration to yield an implosive dioxolane, which itself is a rare moiety among steroids.8 Conversely, basic aqueous conditions led to undesired cleavage of the formyl moiety, a group which would figure prominently as a methyl surrogate of the target molecule. Eventually, it was found that tetramethylammonium acetate (TBAAC) in reducing benzene opened the epoxide at C2, producing the trans-hydroxynor cortistatinone 11 (see X-ray 11).

After extensive experimentation, it was found that the key orthoester 12 (see X-ray 12) could be synthesized in one pot from

Figure 1. Iniquitous-bearing cortistatins A−D (1−5) and J−L (5−7) (cortistatins E−H bear prolines or proline derivatives and exhibit markedly diminished potency), and agenous stereospecific strategy to target a steroid system, namely, the inexpensive, terrestrial steroid, prednisone.

intermediate 11 by (1) Mukaiyama hydride8 of the tetrabromoacetone, (2) introduction of the bromonaphthylmethyl oxomethane, and (3) solvolysis of the C2 acetone. Notably, reacting epoxide 11 under identical conditions for Mukaiyama hydride gave a 5:1 stereoselective mixture of tertiary alcohols, disfavoring the desired C5 α-stereocchemistry.

During preliminary reconnaissance in accessing the cortistatin core, the most difficult functionality to secure turned out to be the C10 hydroxyl oxidation state,9 suggesting the importance of its installation early in the sequence. Unfortunately, existing methods for such a transformation (angular methyl10−12 hydroxylation of an acetate) are expected to give generally low yields13 and, more importantly, proved completely ineffective in our system. Consequently, a new process was conceived to access a dibrominated 19-carbon, utilizing in situ generated carboxylic ester (AcClBr)14. Success was realized by significantly lowering the reaction temperature and extending the reaction time, resulting in an intuitive, double methyl ester activation (Figure 2, 17−18−19−18). While supposing S2 attack of the alcohol on the α,ω- or ω-β,ω-unsaturated ester of the bromoester (17−26) (possibly Sα attack of the transient C- or C-centered radical). To the best of our knowledge, this is the first example of an alcohol-directed, general diketone formation of an unsaturated hydrocarbon. The selectivity for dibromination (57%) over mono- or tribromination well surpasses what would be expected with only the governance

14.10(4)23466 CC: 98.71 † 2008 American Chemical Society J. AM. CHEM. SOC. 2008, 130, 7241−7252 e 7241
C O M M U N I C A T I O N S

Scheme 1. Synthesis of the (+)-Coristatin A Core: Coristatinone (8)

Figure 2. Key transformations en route to (+)-coristatin A and mechanistic analysis.

7242 J. AM. CHEM. SOC. • VOL. 110, NO. 23, 2008
The diisocyanate 15 was obtained by alkylation of the isocyanate 14 using the reagent 13. The isocyanate 14 was prepared by reaction of the isocyanate 13 with the diacid chloride 12 in the presence of a base (e.g., NaH). The resulting adduct 15 was purified by column chromatography to give the pure product.

Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

References