Journey toward \((--)-\text{Maoecrystal V}\)

A thesis presented

by

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Dedication

This thesis is dedicated to the love of my life,

my muse, my femme fatale,

my darling wife Egle
Acknowledgements

Phil

First of all, I would like to say thank you, Phil, for guiding me through my entire journey like a shining beacon of hope. Without you, Phil, I would definitely hit some pretty hard and sharp rocks. Thank you for your precious knowledge, your wise advices about life and your generous help with everything. What I experienced in this remarkable place called Baran Lab can never be bought. I was absolutely privileged to fight for my life and face my inner demons under your supervision, for that I will never be able to repay you. I wish you best of luck in your quest to perturb the limits of chemistry and may nothing but great things happen to your wonderful family. PSB #1

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Well, my dear friend, what we have experience in the last couple of years can’t simply be expressed by words. I don’t even know where to begin, but one thing for sure, somewhere among that absolute madness, chaos, absurdity and taffy puller, we became really good friends. It has been an absolute pleasure to put it all on the line, explore the darkest corners of reality, touch the abyss and come back laughing with you. I am sure the story of Ruben and Art has just begun.

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for me and I hope we will keep in touch. Let’s meet sometime on the East coast and best of luck in BMS. I am sure you will absolutely demolish everyone there.

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Remember our conversation at Lake Arrowhead 2016. I said what I meant and I meant what I said. You are exceptionally talented and genuinely nice man. Nobody can take away that from you. Sometimes, you can be your worst enemy. Be confident, Ming, the world will be your oyster sooner that you think.

Tony

Tony, dearest of all my friends. What else can I say? I love you man. What a fantastic series of adventures we had and I hope we will never stop. Remember that you got a friend for life in me and I am very eager to see where life brings us. Get it juicy, Bromonium!
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Every time I see a cube I will remember you, Neil. It has been so fun to camp with you and the rest of the dream team. See you on the East coast!

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Matt, I have biggest respect for you and I am so glad that I can call you a friend. You are the braves and manliest man I have ever met. I hope one day I will be at least 1/10th of a man you are.

Hang

It’s been great pleasure to hang out with you, Hang. Hopefully, our pathways will cross many more times during our journeys in this bizarre world. Thanks for you engaging conversations about chemistry and life. I am very proud I can call you a friend. Lets see what future holds for us.

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I am quite sad that I didn’t get to know you better Kyle, I think we would get along very well. I have no clue why we never really spoke that much. Grad school is jungle, got to adopt and live in the moment or the opportunities escape. I am very excited to see your next project as I feel that you are capable of overcoming many chemical obstacles.

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As a fellow immigrant from completely different culture I understand you very well. Don’t be sad, your persistence will triumph, the Taxol will fall and I am going to teleconference my clap to you. The beauty about dead ends is that they teach you how to be resourceful.
Kyle K

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Thank you for your crucial support and unconditional love. Without you, I would never have the strength to finish this journey.

You gave me somethin' I never had
Pulled me down with you
Hit me up with a big hunka love
Hope you can pull me through
I overdosed on you
Crazy but it's true
I overdosed on you
Ain't nothin' I can do
I overdosed on you
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Abbreviations

Å = angstrom

Ac = acetyl

AcOH = acetic acid

AIBN = azobisisobutyronitrile

aq = aqueous

BHT = 3,5-di-tert-butyl-4-hydroxytoluene

Bn = benzyl

BOM = benzyloxymethyl

n-BuLi = n-butyl lithium

t-BuLi = t-butyl lithium

c = concentration

°C = degrees Celsius

DABCO = 1,4-diazabicyclo[2.2.2]octane

DBU = 1,8-diazabicycloundecene-7-ene

DCM = dichloromethane
DMAP = 4-dimethylaminopyridine

DMDO = dimethyldioxirane

DMF = dimethylformamide

DMP = Dess–Martin periodinane

DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone

DMS = dimethyl sulfide

DMSO = dimethyl sulfoxide

Et₂O = diethyl ether

EtOAc = ethyl acetate

g = grams

gem = geminal

h = hours

HMDS = bis(trimethylsilyl)amine

HRMS = high resolution mass spectrometry

Hz = Hertz

IC₅₀ = half maximal inhibitory concentration
IMDA = intramolecular Diels–Alder

Im = imidazole

KHMDS = potassium bis-(trimethylsilyl)amide

KOT-Bu = potassium t-butoxide

LDA = lithium diisopropylamide

LiHMDS = lithium bis-(trimethylsilyl)amide

$m$-CPBA = $m$-chloroperbenzoic acid

MOMCl = methoxymethyl chloride

NMO = 4-methylmorpholine N-oxide

PCC = pyridinium chlorochromate

PhMe = toluene

TsOH = para-toluenesulfonic acid

Pyr = pyridine

TBAF = tetrabutylammonium fluoride

TFA = trifluoroacetic acid
Tf = Triflyl

THF = tetrahydrofuran

TIPS = triisopropylsilyl

TLC = thin layer chromatography

TMS = trimethylsilyl

TMSCN = trimethylsilyl cyanide

TMSI = trimethylsilyl iodide
Abstract

A synthetic journey toward the highly congested ent-kaurane diterpene maoecrystal V is presented. This arduous quest, which lasted for several years, was inspired by a key pinacol shift in the proposed biosynthesis. This thesis describes how determination and persistence lead to the eventual fall of this notorious natural product in our lab. In the end, only eleven steps, that involve several unique and unexpected maneuvers, were required to access (−)-maoecrystal V. Developed synthesis described herein also led to reevaluation of the biological activity of this deceiving molecule.
Chapter 1

Maoecrystal V:
Isolation and Background
1.1 Isolation, Structure and Bioactivity

Maoecrystal V (1), a unique C\textsubscript{19} diterpenoid, was isolated from the leaves of Chinese medicinal herb *Isodon eriocalyx* by Sun and co-workers in 1994 as a part of an ongoing search for anticancer diterpenoid compounds.\textsuperscript{1} Although 5 mg of this novel diterpenoid were obtained from the methanolic extracts of 11.9 kg of dried and powdered leaves (0.000042% overall yield), its structure was so puzzling and peculiar that it was only disclosed in 2004 after an unambiguous structural assignment via single crystal X-ray diffraction. As it can be seen from Figure 1.1, the remarkable molecular architecture of maoecrystal V features an extremely congested pentacyclic framework with a sequence of four contiguous stereocenters (two are vicinal quaternary) within a highly strained, trans-fused, heptasubstituted tetrahydrofuran ring. In addition, maoecrystal V possesses an unusual bicyclo[2.2.2]octane ring system, spirocyclic δ-lactone, trans-fused cyclohexenone and an epimerizable C16 methyl group. In contrast to its biogenic progenitors, *ent*-kaurenes (Figure 1.2), maoecrystal V does not possess the signature bicyclo[3.2.1]octane motif that is a common trait of all *ent*-kauranoids. In fact, its unique

![Figure 1.1 Daunting structure of maoecrystal V](image)
structure shares so little resemblance with natural products of this family that maoecrystal V has been considered by the isolation chemists to be “the most modified naturally occurring ent-kauranoid isolated to date”.¹

![Diagram of ent-kaurene skeleton with numbering](image1) ![Diagram of maoecrystal V (1)](image2)

**Figure 1.2** Comparison of maoecrystal V and the core carbon framework of ent-kaurenes

Maoecrystal V was evaluated for cytotoxicity against five different human cancer cell lines: K562 (leukemia), A549 (lung cancer), BGC-823 (gastric cancer), CNE (throat cancer) and HeLa (cervical cancer).¹ These studies revealed that maoecrystal V possessed potent and selective cytotoxicity against HeLa cell lines with IC₅₀ = 0.02 μg/mL or 60 nM, while being virtually inactive (IC₅₀ = 1.47 × 10⁴ μg/mL or greater) against remaining four cancer cells (Figure 1.3). Compared to cisplatin (IC₅₀ = 0.99 μg/mL or 3.3 μM), a drug commonly utilized as a treatment for cervical cancer, maoecrystal V was found to be 55-fold more potent versus gynecologic cancer cells. Mode of action and cellular target were not identified during this evaluation of biological activity.

<table>
<thead>
<tr>
<th>Test Substance</th>
<th>K562</th>
<th>A549</th>
<th>BGC-823</th>
<th>CNE</th>
<th>HeLa</th>
</tr>
</thead>
<tbody>
<tr>
<td>maoecrystal V</td>
<td>6.43 × 10⁴</td>
<td>2.63 × 10⁵</td>
<td>1.47 × 10⁴</td>
<td>–</td>
<td>0.02</td>
</tr>
<tr>
<td>cisplatin</td>
<td>0.32</td>
<td>1.61</td>
<td>0.25</td>
<td>2.31</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Figure 1.3** Promising bioactivity profile of maoecrystal V
1.2 Biosynthetic Hypothesis

Pathway describing biosynthesis of maoecrystal V from eriocalyxin B (1.3), a major terpene constituent of *Isodon eriocalyx*, was proposed by Han and co-workers. This biosynthetic hypothesis combined with a proposed biosynthesis of the ent-kaurene skeleton is shown in Scheme 1.1. Geranylgeranyl pyrophosphate (1.1) undergoes cyclization mediated by cyclase enzymes ent-copalyl diphosphate synthase and then ent-kaurene synthase to give the ent-kaurene (1.2) tetracyclic core of the eriocalyxin family of natural products. This carbon framework is the heavily oxidized by various cytochrome enzymes to eventually give eriocalyxin B (1.3), along with many other related natural products of varying oxidation patterns. Subsequent enzymatic vicinal cis-diol cleavage affords epi-eriocalyxin A (1.4) that is further enzymatically modified via a sequence of oxidation to carboxylic acid and decarboxylation. This process results in formation of cationic species

Scheme 1.1 Proposed biosynthesis of maoecrystal V
that is readily trapped by water to yield a secondary alcohol 1.6. Next, a skeletal rearrangement of a bicyclo[3.2.1]octane to a bicyclo[2.2.2]octane proceeds presumably via 1,2-shift, which is triggered by a hydride abstraction at C9 that results in the formation of carbocation 1.7. This highly unstable cationic species is readily intercepted by the proximal secondary alcohol, thus forging the central tetrahydrofuran ring of maoecrystal V. The overall sequence results in a highly oxidized nor-C6-diterpene with a daunting architecture that is highly tantalizing for synthetic chemists.

1.3 Previous Synthetic Efforts and Achievements

The combination of striking structural features and exciting bioactivity exhibited by maoecrystal V has attracted immense attention within the synthetic community.4-13 Ever since disclosure of its structure, fourteen progress toward papers have been published by some of the most renowned and prolific scientists in the field, including Nicolaou4, Danishefsky5a,b, Trauner6, Zakarian7 and Baran8. Despite significant efforts from synthetic community the molecule remained elusive for multiple years, thus establishing itself as incredibly challenging target even for modern synthetic chemists. However, no king rules forever, with so much effort directed toward this notorious natural product it was just a matter of time until maoecrystal V would finally succumb to total synthesis. Indeed, Yang and co-workers published first total synthesis of maoecrystal V in 20109, and this was followed by successful syntheses from Danishefsky10, Zakarian11 and Thompson12 Labs. This section will briefly discuss selected approaches13 toward 1 as well as all four successful total syntheses of this remarkable natural product.
The group of Nicolaou/Chen was able to forge the functionalized core of maoecrystal V in 2009 (Scheme 1.2). The synthesis commenced with a decarboxylative Heck coupling between carboxylic acid 1.8 and cyclohexanone to furnish β-aryl enone 1.9. A three step sequence of deprotection, alkylation and E1cB elimination yielded vinyl ether 1.10. Silyl enol ether formation with TBSOTf/Et3N afforded diene 1.11, that was able to undergo intramolecular Diels–Alder reaction (IMDA) to give the desired [2.2.2]bicycle 1.12 after deprotection of TBS group with 1 M aq. HCl. This compound was able to undergo smooth oxidative dearomatization upon exposure to PIFA in MeOH furnishing dienone 1.13 in good yield. Hydrogenation of the latter compound with H2, Pd/C afforded a 1:2 mixture of the undesired aromatized product 1.14 and ketone 1.15, respectively, in a combined 99% yield. Compound 1.14 could be recycled to dienone 1.13 by treating it with
PIFA in MeOH. Unfortunately, it was discovered that ketone \textbf{1.15} possessed undesired stereochemistry at C5 as a result of delivery of hydrogen from the undesired face of the olefin. Next, ester of \textbf{1.15} was hydrolyzed with aq. NaOH to provide crude carboxylic acid that upon exposure to chloroiodomethane and \textit{t}-BuOK generated spirocyclic \(\beta\)-lactone \textbf{1.16} in 42\% yield over two steps. The reaction was accompanied by the formation of undesired exocyclic methylene at C2 presumably via alkylation and subsequent E1cB elimination. In the follow up work, Chen and co-workers were able to successfully access the desired stereochemistry at C5 by utilizing hydroxyl-directed hydrogenation of C5–C10 olefin of \textbf{1.17} to arrive at the advanced intermediate \textbf{1.18} (Scheme 1.3).\textsuperscript{13d} This compound was elaborated to diketone \textbf{1.19} in four more steps and only needed installation of spirolactone to access the entire penta cyclic framework of maoecrystal V.

![Scheme 1.3 Efforts toward maoecrystal V by Chen and co-workers](image-url)

Trauner and co-workers have published an interesting approach toward maoecrystal V in 2010 that doesn’t rely on an IMDA as the key step (Scheme 1.4).\textsuperscript{6} Instead, their strategy was to build the bicycle[2.2.2]octane motif first, followed by central tetrahydrofuran ring and then spirocyclic lactone formation. Thus, leaving the formation of cyclohexanone ring till the very last stage of the synthesis. It was mentioned that this approach was shaped by the necessity to maneuver in a sterically hindered environment. The synthesis commenced by subjecting ketone \textbf{1.20} (prepared in two steps from
cyclohexenone) to ozonolysis/ozonide reduction with dimethylsulfide to yield the corresponding aldehyde 1.21. Treatment of this compound with aq. HCl and subsequent protection of the alcohol with TBSCI/Imidazole resulted in formation of [2.2.2]bicycle 1.22 in 41% yield as 7:1 mixture of diastereoisomers favoring the desired one. Next, cyanation with Nagata’s reagent (Et₂AlCN) resulted not only in the formation of cyanohydrin but also effected transesterification to furnish the lactone 1.23 in 84% yield. Unfortunately, the cyanide attacked exclusively from the undesired face as was determined by X-ray crystallographic analysis. The authors then decided to utilize the nitrile as a protecting group and were able to elaborate 1.23 into aldehyde 1.24 in four steps. Efforts to achieve prenylation of 1.24 were fruitless presumably due to severe steric hindrance surrounding that aldehyde. Other attempts to access compound 1.25 were unsuccessful as well.

![Scheme 1.4 Non-IMDA approach to maoecrystal V by Trauner group](image)

In the second generation approach Trauner and co-workers were able to achieve nucleophilic attack of deprotonated TMS-acetylene into the ketone of 1.22 to afford alkyne 1.26 as a single desired diastereoisomer (Scheme 1.5). Treatment with NaH caused transesterification and subsequent hydrogenation in the presence of Lindlar catalyst.
resulted in the formation of olefin 1.27. Next, double hydroxymethylation was attempted by intercepting enolate of 1.27 with formaldehyde, however, the major product was monohydroxymethylated 1.28. Installation of a second hydroxymethylene unit was achieved in three more steps via a sequence of oxidation with DMP, reduction with NaBH₄ and then trapping the enolate with formaldehyde to provide diol 1.29. Subsequent ozonolysis/ozonide reduction with dimethyl sulfide furnished advanced intermediate 1.30 that has multiple functional group handles to install the last ring of maoecrystal V.

Scheme 1.5 Synthesis of advanced tetracyclic intermediate 1.30 by Trauner and co-workers

A remarkable approach that utilized Rh-catalyzed C–H activation to forge the central tetrahydrofuran ring of maoecrystal V has been attempted by Sorensen and co-workers.¹⁴ Even though this work hasn’t been published yet, it was a major part of Michael J. Smith’s PhD dissertation in the Sorensen Lab that described an exceptionally elegant approach toward maoecrystal V. This synthetic endeavor began by utilizing commercially available (+)-limonene oxide (1.31) as the source of chirality (Scheme 1.6). It was transformed into allylic carbonate 1.32 by rupturing the C–O bond of the epoxide
with LDA in Et₂O and then trapping the free alcohol with EtOCOCl. Next, Pd-catalyzed Tsuji–Trost reaction between 1.32 and TMSCN afforded nitrile 1.33 in 90% yield. Hydroboration of 1.33 with thexylborane followed by subsequent treatment with UHP and then classic Swern oxidation furnished keto aldehyde 1.34 as a single diastereoisomer in 86% overall yield. Acid mediated aldol reaction gave a mixture of desired [2.2.2]bicycle 1.36 and undesired diastereoisomer 1.35 in an ca. 2.5:1 ratio favoring the desired product. The undesired 1.35 could be further recycled by refluxing it in PhMe with 6 M aq. HCl for several days. This practical sequence was able to provide gram quantities of [2.2.2]bicycle 1.36 in just six steps from (+)-limonene oxide. The protected diazo compound 1.39 was accessed by first protecting the ketone of 1.36 as a ketal after the exposure to trimethylsilyl protected diol 1.37 in the presence of TMSOTf, followed by a diazo-transfer reaction of the lithium enolate with 1.38 at –100 ºC (Scheme 1.7). This sequence could be run on up to 10 g scale, thus setting the stage for the key C–H activation step. This key step was achieved by treating 1.39 with 0.5 mol% of Rh₂(S-BTPCP)₄ in PhCF₃ to provide 1.40 as a desired stereoisomer in 70% yield on a gram scale. This unusual Rh catalyst was developed

Scheme 1.6 Synthesis of the key building block 1.36 by Sorensen and co-workers
by the group of Davies and it was crucial for obtaining high yield and correct diastereoselectivity at C5. Lactone opening with MeNHOMe and subsequent TES protection of the secondary alcohol gave amide 1.41 in 57% yield over 2 steps. Introduction of C7 was achieved via Lewis acid mediated cyanation with TMSCN to afford nitrile 1.42 as a single desired diastereoisomer in 65% yield. Protection of the alcohol as a bulky silyl ether was crucial for obtaining desired stereoselectivity as cyanation of lactone 1.40 gave exclusively the undesired diastereoisomer. Three steps required to obtain keto aldehyde 1.43 which upon refluxing with TsOH in PhMe formed enone 1.44 thus forging the fourth ring of maoecrystal V in the process. At this stage only installation of C20 hydroxymethylene unit and oxidation of the secondary remained to achieve synthesis of

**Scheme 1.7** Synthesis of advanced intermediate 1.45 by Sorensen and co-workers

1. TMSOTf, 2. LiHMDS, 1.38, –110 °C (70%, 2 steps)
2. 0.5 mol% Rh₂(S-BTPCP)₄ PhCF₃
3. i-PrMgBr, MeNHOMe
4. TESOTf, 2,6-lutidine (57%)
5. BF₃·OEt₂, TMSCN
6. Base, ICH₂Cl or CH₂O

R = TES
maoecrystal V. However, hydroxymethylation or alkylation of 1.44 and carboxylic acid derivative 1.45 to provide pentacyclic structure 1.46 proved to be insurmountable challenge despite exhaustive efforts. The strategy of this approach was exceptionally elegant, if the installation of the last carbon would have been successful, it would have resulted in an absolutely phenomenal synthesis of 1.

Due to its formidable complexity, it is no surprise that maoecrystal V was a sought after molecule in our lab as well. The first generation strategy relied on the sequence of Wessely oxidative dearomatization followed by venerable Diels–Alder to forge the signature [2.2.2]bicycle of maoecrystal V (Scheme 1.8). This synthetic endeavor began with Barton arylation of β-keto aldehyde 1.47 (made in 3 steps from cyclohexane-1,3-

dione) with Ar$_3$BiCl$_2$ to furnish 1.48 in 67% yield and 7:3 dr, thus installing the first quaternary stereocenter of 1. Selective reduction of the aldehyde, introduction of acrylate as a dienophile and MOM deprotection gave compound 1.49 in 32% overall yield. Wessely oxidative dearomatization with Pb(OAc)$_4$ afforded diene 1.50 as an inconsequential
mixture of diastereomeric acetates at C16. Heating 1.50 in the microwave at 165 °C resulted in smooth IMDA to furnish [2.2.2]bicycle 1.51 in 69–79% yield. Reduction with H₂, Pd/C followed by deacetoxylation with SmI₂ gave advanced intermediate 1.52 – a complete carbon skeleton of maocystal V. Only formation of central tetrahydrofuran ring by stitching C5 and C8 through the oxygen was needed to forge the entire pentacyclic framework of 1. Unfortunately, α-oxidation of C8 proceeded with undesired diastereoselectivity. Overall, a fantastic approach that rapidly builds complexity and if it wasn’t for some unfortunate and controversial events, without a doubt, this would have been extraordinary synthesis of maocystal V.¹⁵

The first total synthesis of 1 was achieved by the group of Yang in 2010 (Scheme 1.9).⁹ Along with a previously published progress toward paper in 2009¹³a, it caused a lot of controversy in our lab as one of the people on this paper, Dr. Chuang-chuang Li, had been a postdoctoral fellow in our laboratory and discussed synthetic efforts of Paul Krawczuk (graduate student at that time) and his colleague Dr. Niklas Schöne. The synthetic strategy of Yang’s total synthesis closely mirrors those discussed above.¹⁵ Controversy aside, the synthesis began with formation of β-keto ester 1.55 from ketone 1.54, which is claimed to commercially available even though it is only sold by exotic suppliers and costs more than $1100 per gram. The authors actually make it in five steps from 1.53 as mentioned in supporting information.¹⁶ The next step is arylation of 1.55 with organolead species 1.56 that proceeds in 88% yield to afford ketone 1.57. After three more steps that include reduction of both carbonyl groups and esterification, 1.58 is converted to diazo compound and then treated with catalytic amounts of Rh₂(OAc)₄ that mediates formation of cyclic ether 1.59. Formation of exocyclic methylene was achieved by treating
Scheme 1.9 First total synthesis of maoecrystal V by Yang and co-workers

1.59 with paraformaldehyde under basic conditions, subsequent deprotection of MOM group with TFA provided 1.60 oxidative in 86% yield over two steps. Wessely oxidative dearomatization was accomplished with Pb(OAc)$_4$ and subsequent heating at 145 ºC resulted in IMDA reaction to furnish undesired endo product 1.61 in 50% yield as a 2.3:1 mixture of diastereoisomers at C16 and desired exo product 1.62 in 36% yield as a single stereoisomer at C16. This sequence had built the entire pentacyclic framework of
maoecrystal V as only functional group manipulations were needed to finish the synthesis. Installation of C1 oxygen was achieved via allylic bromination with NBS, followed by generation of allyl radical with Bu$_3$SnH and trapping it with TEMPO, subsequent cleavage of N–O bond afforded 1.63 in 57% overall yield. Deacetoxylation with SmI$_2$ and hydrogenation of olefin in the presence Lindlar catalyst resulted in formation of 1.64, which possessed undesired stereochemistry at C16. Oxidation of secondary alcohol with DMP and epimerization of C16 methyl under basic conditions in PhMe at 100 ºC afforded a 1:1 mixture of maoecrystal V and epi-maoecrystal V. Thus, finishing the first total synthesis of this notorious natural product.

The group of Yang was also able to render their synthesis enantioselective in 2015 (Scheme 1.10). Starting from primary alcohol 1.65 they utilized venerable Sharpless epoxidation to obtain epoxide 1.66 in 92% yield and impressive 99% ee. Subsequent oxidation with DMP and treatment with organolithium species generated from 1.67 via metal halogen exchange provided 1.68 in 83% yield over two steps as an inconsequential mixture of diastereoisomers. Semipinacol rearrangement was triggered upon exposure to

### Scheme 1.10 Development of enantioselective synthesis of 1 by Yang and co-workers
Et₂AlCl that after the in situ reduction with LiAlH₄ provided 1.70 in 50% and 80–87% ee. The authors attribute some loss of enantioselectivity due to formation of carbocationic species during the semipinacol rearrangement step. Three more steps were needed to transform 1.70 into 1.71 intercepting their racemic route and thus rendering synthesis asymmetric.

After publication of first and second generation approaches toward maoecrystal V the group of legendary Danishefsky finally achieved the total synthesis of this daunting target in 2012 (Scheme 1.11).¹⁰ Similarly to the group of Yang, their approach relied on

Scheme 1.11 Total synthesis of maoecrystal V by Danishefsky and co-workers
IMDA to forge [2.2.2]bicycle of 1. The synthesis commenced by combining ester 1.72 and enone 1.73 and then preparing IMDA precursor 1.74 in five steps. Heating 1.74 in a sealed tube at 165 °C and then treating it in situ with TBAF resulted in formation of [2.2.2]bicycle 1.75 in 62% yield. The installation of C8 oxygen was accomplished via a sequence of nucleophilic epoxidation with H2O2/NaOH, MgI2 mediated opening of epoxide and then radical dehalogenation with Bu3SnH to provide alcohol 1.76 in 48% yield over three steps. Epoxidation of this compound and subsequent exposure to acidic conditions resulted in formation of pentacyclic structure 1.77 with central tetrahydrofuran ring intact albeit with exclusively undesired stereochemistry at C5. Despite this unfortunate outcome, Danishefsky and co-workers developed a chemical sequence that successfully inverted the stereochemistry at C5. After ten steps cyclic acetate 1.78 was deprotected with K2CO3 in MeOH to unmask secondary alcohol that presumably directed epoxidation of the enol ether upon treatment with DMDO, followed by exposure to BF3•OEt2 that mediated epoxide opening and stereospecific 1,2-hydride shift that furnished ketone 1.79 with correct stereochemistry at C5. Next, ketone was converted to exocyclic olefin with Lombardo reagent, followed by subsequent Simmons–Smith cyclopropanation with CH2I2 and Zn/Ag to give cyclopropane 1.80 in 75% overall yield. Interestingly, this transformation also resulted in insertion of carbene into C–H bond thus transforming MOM group into MOE. After four steps that included hydrogenation of cyclopropane to reveal gem-dimethyl moiety of ketone 1.81, the latter compound was transformed to enone 1.82 by utilizing Pd-mediated Saegusa oxidation. Treatment with TFDO resulted in epoxidation of the olefin to give a 1:1 mixture of diastereomeric epoxides 1.83 in a combined 90% yield. The epoxides
were separated chromatographically and the desired diastereoisomer was subjected to Lewis acid mediated 1,2-hydride shift to furnish racemic maoecrystal V in 82% yield.

Zakarian and co-workers accomplished an impressive total synthesis of maoecrystal V relying on early stage C–H functionalization and IMDA (Scheme 1.12).\textsuperscript{11}

\[
\begin{align*}
\text{TsNHNH}_2, \text{DBU} & \quad (82\%) \\
\text{LDA, THF} & \quad \text{then Et}_2\text{Zn, BOMCl} \\
& \quad (76\%, 9:1 \text{ dr}) \\
\end{align*}
\]

\[
\begin{align*}
\text{TMS}_3\text{SiH}, \text{AIBN, 80 }^\circ\text{C} & \quad (55\%) \\
\text{LiHMDS, MeI} & \quad \text{THF, } -40^\circ\text{C} \\
& \quad (90\%, 7:1) \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 1.12 Total synthesis of maoecrystal V by Zakarian and co-workers}
\end{align*}
\]

\(\alpha\)-Keto ester \textbf{1.84} (prepared in two steps from sesamol) was transformed into diazo compound \textbf{1.85} and in process setting up the stage for the essential C–H functionalization step. This was achieved by treatment of \textbf{1.85} with catalytic \(\text{Rh}_2(\text{OAc})_4\) to give benzo[...]

18
1.86 in high yield and excellent dr. Hydroxymethylation of 1.86 was achieved via intermediacy of zincate enolate that was intercepted by BOMCl to afford 1.87 in 75% yield and 9:1 dr. Four steps were required to convert 1.87 into diene 1.88 that underwent IMDA upon refluxing in PhMe to furnish bicyclo[2.2.2]octane 1.89 in almost quantitative yield. A sequence of four steps transformed 1.89 into selenocarbonate 1.90 that upon exposure to TMS$_3$SiH/AIBN formed acyl radical that underwent 6-exo-trig cyclization to furnish lactone 1.91 in 55% yield. Several functional group manipulations gave 1.92 which was methylated with LiHMDS/MeI to provide 1.93 in 90% yield and 7:1 dr. Only three more steps were required to obtain 1.94 that in the presence of second generation Hoveyda-Grubbs catalyst and subsequent oxidation with DMP furnished racemic maocryystal V.

A productive collaboration between Davies and Zakarian groups rendered the above synthesis enantioselective by identifying an appropriate auxiliary for the enantiodetermining C–H functionalization step.$^{18}$ As it can be seen in Scheme 1.13, a chiral auxiliary derived from pyrrolidine amide of mandelic acid resulted in C–H functionalization of 1.95 to provide 1.96 that after methanolysis gave 1.86, thus intercepting the previously established route to maocryystal V. Unfortunately, approach utilizing chiral ligands was abandoned due to inferior diastereoselectivities and yields.

Scheme 1.13 Enantiodetermining C–H functionalization en route to (−)-maocryystal V
An elegant enantioselective total synthesis of maoecrystal V was accomplished by Thomson and co-workers that employed intermolecular Diels–Alder reaction to forge the bicyclo[2.2.2]octane motif as well as intramolecular Heck reaction to install the first quaternary stereocenter of 1 (Scheme 1.14). This route commenced with commercially available enone 1.97 was subjected to Baylis-Hillman reaction and Sharpless asymmetric epoxidation to produce epoxide 1.98 in 53% yield and 94% ee. Formation of allylic alcohol
was accomplished via four step sequence of benzylation with 1.99 in the presence of TfOH, followed by reductive fragmentation of the epoxide. After TES protection of the secondary alcohol, the stage was set for crucial spirocyclization via Heck reaction which proceeded to give desired spirolactone 1.102 in 53% yield along with undesired minor product 1.101 formed in 13% yield. Oxidative dearomatization was accomplished by treating 1.101 with PIDA, this was also accompanied by formation of tetrahydrofuran ring to give dienone 1.103 in nearly quantitative yield. Selective conjugate reduction of the less hindered double bond with Stryker’s catalyst and PhSiH$_3$, followed by formation of diene 1.104 that participated in an intermolecular Diels–Alder reaction upon exposure to nitroethylene resulted in formation of 1.105 in 55% yield over two steps. Late stage functional group manipulation provided 1.106 that was readily transformed into compound 1.107 that required only selective oxidation of cyclic ether into lactone to furnish maocystal V. This was achieved by subjecting 1.107 to CrO$_3$ in AcOH to provide 1 as a minor product in 28% yield along with regioisomeric 1.108 as a major product in 47% yield. Overall, a fantastic synthesis that featured many incredible transformations.

In summary, maocystal V received an incredible amount of attention from the synthetic community that resulted in a great amount of beautiful chemistry developed. It is interesting to note, that majority of groups decided to utilize Diel–Alder transform to forge the bicyclo[2.2.2]octane ring system which is in striking contrast to biosynthetic hypothesis. In the end, the daunting complexity that embodies the exotic structure of maocystal V proved to be no match for modern synthetic chemists as four spectacular total syntheses have been accomplished, thus highlighting the determination, bravery and ingenuity of scientists in this field.
1.4 References


13. For other studies toward maoecrystal V that have not been discussed here, see:


Chapter 2

Strategy and Start of the Journey
2.1 Inspiration from Biosynthetic Hypothesis

As it was mentioned in Chapter 1, most of the studies toward papers and all the successful syntheses of maoecrystal V utilized Diels–Alder as the key step either in inter- or intramolecular fashion to forge the signature bicyclo[2.2.2]octane of 1 (Figure 2.1). In addition, many groups recognized that phenol can serve as a diene precursor that can be conveniently unmasked via oxidative dearomatization. Overall, this strategy is highly efficient as it creates multiple stereocenters and ring systems in a single step. However, is interesting to note that nobody attempted to disconnect a highly strategic C9–C10 bond (highlighted in red) that would effectively break the molecule in half.

![Figure 2.1 Strategic disconnections that resulted in successful syntheses maoecrystal V](image)

In striking contrast, the biosynthetic route to this system is proposed to arise via an unusual pinacol-type shift of cation 2.1 that is derived from epi-eriocalyxin A (1.4) (Figure 2.2). This sequence would be incredibly difficult to replicate in the flask mainly due to the stability of the resulting carbocation 1.7, where the positive charge is located right next to electron withdrawing ester group. This brings into question whenever
existence of such species is even feasible, especially under ambient conditions. However, a vast majority of natural products isolated from *Isodon eriocalyx* contained the [3.2.1]bicycle, in contrast, maoecrystal V and Z did not possess such structural motif (Figure 2.3). While maoecrystal Z did not have bicyclic ring system whatsoever,

**Scheme 2.3** Natural products isolated from *Isodon eriocalyx*
presumably due to rupturing of C8–C15 carbon bond during the biosynthesis, it is still mostly likely derived from a [3.2.1]bicycle containing natural product or intermediate. Only maoecrystal V possessed this highly unusual motif for ent-kauranoid. As a result, it is reasonable to assume that 1, indeed, arose via some sort of rearrangement of a [3.2.1]bicycle to a [2.2.2]bicycle during its biosynthesis. Intuitively it simply made sense to us. Consequently, it was reasoned that a route to maoecrystal V loosely patterned off of this theme might efficiently access the C9 bridgehead quaternary center of the [2.2.2] bicycle and allow for a convergent fragment assembly at the C9/C10 juncture (Figure 2.4).

![Diagram](image)

**Figure 2.4** Inspiration from biosynthetic hypothesis

### 2.2 Retrosynthetic analysis and overall strategy

Our retrosynthetic analysis began with removal of reactive enone moiety and sensitive methyl ketone to avoid potential problems of epimerization at C16 during the synthesis, thus arriving at structure 2.2 (Scheme 2.1). The central tetrahydrofuran ring was envisioned to arise from reductive cyclization between ketone and tertiary alcohol of 2.3. Next, it was expected that 2.3 could be made by a simple lactonization featuring nucleophilic attack of
alkoxide into the cyanide, thus arriving at cyanohydrin 2.4. Then removal of essentially a molecule of formaldehyde to give 2.5, followed by removal of cyanide to obtain diketone 2.6. When making maoecrystal V it is important to realize that it is a constant uphill battle against steric hindrance, consequently, all electrophiles and nucleophiles must be as small as possible to overcome unfavorable steric interactions. Previously mentioned reagents fit that category perfectly. The most strategic bond to disconnect is highlighted in red because it would break the molecule in half, into two pieces of similar size. However, there are no ways how to execute this disconnection directly, as to the best of our knowledge, there are no methods that would achieve C–C bond formation at the bridgehead in an intermolecular fashion. This is where inspiration from the biosynthetic hypothesis steps in: by employing a pinacol transform, that would presumably proceed through intermediacy of 2.7 with a methoxy group as a driving force, we end up with a tertiary alcohol 2.8. This is highly

Scheme 2.1 First generation retrosynthetic analysis of maoecrystal V
simplifying because 2.8 is much easier to make via either a classic aldol reaction between two ketones 2.9 (known compound)\textsuperscript{4} and 2.10 or a Grignard addition into 2.10. Although, there were definitely some issues with this retrosynthetic analysis, especially in terms of stereocontrol, it was short and convergent, the potential benefits were significant, and so we decided to go for this “high risk, high reward” strategy. However, in order to execute this plan, access to bicycle[3.2.1]octanone 2.10 had to be developed. That proved to be far from trivial on its own.

2.3 Start of the Journey: Synthesis of bicycle[3.2.1]octanone 2.10

Initial approaches toward ketone 2.10 are summarized in Scheme 2.2. At first, it was envisioned that 2.10 could be prepared via pinacol coupling, but only reduction of aldehyde or both carbonyl was observed without any traces of cyclized product. Next, intramolecular Barbier coupling was investigated that also failed to deliver even traces of [3.2.1]bicycle as only dehalogenation was observed. Since cyclization to give the bicyclo[3.2.1]octane motif was so challenging, it was reasoned that it might be more prudent to use a reaction that has already been known to generate a [3.2.1]bicycle. Au-

![Scheme 2.2 Initial attempts to prepare key building block 2.10](image-url)
catalyzed Conia-ene cyclization developed by Toste\(^5\) seemed particularly powerful in this regard, as it was also utilized for this purpose and proved to be highly efficient in the context of total synthesis of platencin by Nicolaou.\(^6\) As a result, ketone 2.10 was slightly modified in order to take advantage of this powerful method, thus giving rise to the new target 2.11 (Scheme 2.3). This synthetic endeavor began by TIPS protecting pent-4-yn-1-ol, followed by oxidation with DMP to provide aldehyde 2.13 in 82% over two steps. Next, Robinson annulation between aldehyde 2.13 and methyl vinyl ketone in the presence of TMS\(_2\)NH and then subsequent treatment with TBAF provided enone 2.14 in 31% yield. Exposure of 2.14 to catalytic Mn(dpm)\(_3\) in \(i\)-PrOH under 1 atm of O\(_2\) gas furnished alcohol 2.15 in 69% yield as a 1.2:1 mixture of inconsequential diastereoisomers. Strangely, all

Scheme 2.3 Au-catalyzed Conia-ene approach
Attempts to methylate (MeI, Ag₂O/Me₃OBF₄, proton sponge) the secondary alcohol of 2.15 to obtain ether 2.16 turned out to be fruitless (with or without alkyne protection) for unknown reasons. As a result, it was decided to protect alcohol as TMS ether in situ during silyl enol ether formation, which resulted in formation of inseparable mixture of isomers that upon treatment with Au(I) catalyst and Ag(I) co-catalyst did not, unfortunately, afford the corresponding cyclized product 2.17 despite significant efforts to optimize this reaction. Attempts to achieve this transformation via Pd-catalyzed Conia-ene cyclization were unsuccessful as well.

Next, it was decided to target 2.11 once again, but this time access it by activating electrophilic carbonyl with a potent Lewis acid in the presence of a milder nucleophile such as allyl silane. Intramolecular Sakurai reaction perfectly fit these requirements as it is known as a robust method to forge polycyclic structures with great efficiency. In order to access the precursor, cyclohexanone was oxidized in the presence of Pb(OAc)₄ in refluxing
PhMe to give acetoxy enone 2.18 in about 60% yield (Scheme 2.4). This was followed by CuI-catalyzed conjugate addition of Grignard reagent 2.19 in THF at 0 °C to provide silane 2.20 in 65% yield as a 2:1 mixture of inconsequential diastereoisomers. The stage was set to evaluate the propensity to undergo intramolecular Sakurai reaction. Unfortunately, when silane 2.20 was subjected to a myriad of different Lewis acids, the result would always be the undesired protodesilylation to afford ketone 2.21 in essentially quantitative yields, without even a trace of cyclization. Why was such a cyclization so difficult to achieve? While on the first sight it seemed to be favored 5-exo-trig cyclization according to Baldwin rules, upon closer inspection, it turned out to possess identical orbital alignment as 5-enolendo-exo-trig (see inset graphic, Scheme 2.4), thus making it disfavored by Baldwin rules. Consequently, it was reasoned that Sakurai reaction was most likely slower than competing protodesilylation that was presumably mediated by adventitious acid.

![Scheme 2.5 Successful synthesis of racemic bicyclo[3.2.1]octanone 2.10](image)

Fortunately, it was known in the literature that EtAlCl₂ is not only a potent Lewis acid, but also great Bronsted acid scavenger. It reacts with acids with the formation of
Al(III) salts and evolution of ethane gas. To our delight, it was found that EtAlCl$_2$ in PhMe at 0 ºC was able to mediate a clean intramolecular Sakurai reaction to furnish [3.2.1]bicycle 2.22 in 77% yield (Scheme 2.5). It is interesting to note that acetate protecting group was also crucial for the success of this reaction as benzyl or silyl ethers and free alcohol failed to react productively even in the presence of EtAlCl$_2$. This could be explained by the additional inductive effect of the acetate that further activates the electrophilic carbonyl. In addition, with trifluoroacetate as a protecting group the Sakurai reaction was much faster and higher yielding but this functionality was not compatible with further chemistry downstream. Next, methylation of tertiary alcohol was achieved with NaH in DMF with Me$_2$SO$_4$ as a methylating agent and subsequent one-pot addition of aq. LiOH mediated removal of the acetate group that served its purpose to provide secondary alcohol 2.23. While the latter compound could be isolated and purified it was more practical, especially on scale, to run the Parikh–Doering oxidation on a crude alcohol. Thus, oxidation of 2.23 under these conditions furnished the desired racemic bicyclo[3.2.1]octanone 2.10 in 81% yield over two steps. It was crucial to prestir DMSO and Pyr•SO$_3$ prior to adding alcohol 2.23 to the reaction mixture in order to obtain high yield of the product. Although, the synthesis described in Scheme 2.5 was able to provide gram quantities of key building block 2.10, it provided it as a racemic mixture. Thus, in order to render the synthesis of maocrystal V asymmetric, a modified sequence was developed that began with a highly enantioselective conjugate addition of an allyl silane 2.19$^{10}$ to cyclohexenone to deliver 2.24 in 80% isolated yield (99% ee). Among the many ligands explored, the TADDOL-
derived phosphine-phosphite L1 designed by Schmalz was singularly successful. The use of CuI•0.75DMS was also critical to minimize dimerization of the Grignard reagent. A profound solvent effect was also observed with a mixture of PhMe/MeTHF being essential to obtain consistently high yield and enantioselectivity on 20-gram scale. The seemingly simple α-acetoxylation of ketone 2.24 turned out to be remarkably difficult to execute in a scalable way. Rubottom oxidation was unsuccessful due to competitive oxidation of electron rich allyl silane moiety. Oxidants such as MoOPH, Pb(OAc)4 and Mn(OAc)3 gave complex mixtures, while Tomkinson's reagent13 and similar enamine chemistry suffered from poor regioselectivity. Gratifyingly, deprotonation of 2.24 with LiTMP followed by sequential treatment with Davis oxaziridine14 and Ac2O in a mixture of THF/DMF gave the desired α-acetoxylated product 2.20 in 64% yield as an inconsequential mixture of diastereoisomers (2:1) on a 30 g scale. This reaction, when run properly and diligently, would give moderate to good yield of the product 2.20 with the range of 55–70% yield depending on the scale. However, it is still quite finicky and a

Scheme 2.6 Enantioselective synthesis of bicyclo[3.2.1]octane 2.10

\[
\begin{align*}
\text{Scheme 2.6 Enantioselective synthesis of bicyclo[3.2.1]octane 2.10} \\
\end{align*}
\]
difficult reaction to execute to this date and sometimes for unknown reasons would produce strange by-products thus reducing the overall yield of 2.20 down to ca. 30% yield. Despite this, the entire five step sequence was quite efficient and scalable enough to afford 7 g of enantioenriched ketone 2.10 in just a single pass. With ample quantities of this building block secured, the stage was finally set for the key addition/pinacol rearrangement sequence.

2.4 References

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2.5 Experimental Section for Chapter 2.

**General Experimental.** All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry acetonitrile (MeCN), dichloromethane (DCM), diethyl ether (Et₂O), tetrahydrofuran (THF), toluene (PhMe) and triethylamine (Et₃N) were obtained by passing the 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 (¹H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an acidic solution of vanillin and heat, or KMnO₄ and heat as developing agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm), flash alumina chromatography was performed using Brockman Grade 1 aluminum oxide (activated, basic, 58 Å, 60 mesh powder. NMR spectra were recorded on Bruker DRX-600 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (CDCl₃ ¹H NMR = 7.26 ppm, ¹³C NMR = 77.16 ppm; C₅D₆ ¹H NMR = 7.16 ppm, ¹³C NMR = 128.06 ppm, C₅D₅N ¹H NMR = 8.71, 7.57, 7.19 ppm, ¹³C NMR = 149.91, 135.56, 123.54). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.
Compound 2.13:

This compound was made via slightly modified literature.\textsuperscript{15} To a solution of 4-pentyn-1-ol (1.0 mL, 0.90 g, 10.8 mmol, 1.0 equiv) in THF (20 mL) was added ethylmagnesium chloride (2.1M THF, 10.8 mL, 22.6 mmol, 2.1 equiv) over 30 min at room temperature. The mixture was refluxed for 12 h resulting in a cloudy white solution. The reaction was cooled to room temperature and a solution of triisopropylchlorosilane (2.30 mL, 2.1 g, 10.8 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) was added over a 15 min period. The mixture was refluxed for 6 h. The reaction was cooled to room temperature, poured into 10% aq. HCl, extracted with Et\textsubscript{2}O, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated to a brown oil that was used in the next step without further purification.

To a solution of Dess-Martin periodinane (4.50 g, 10.6 mmol, 1.05 equiv) in DCM (35 mL) was added a solution of crude 5-triisopropylsilanyl-pent-4-yn-1-ol (assumed 2.4 g, 10.1 mmol, 1.0 equiv) in DCM (10 mL) followed by the addition of water (0.19 mL, 10.6 mmol, 1.05 equiv). The reaction was stirred at room temperature for 30 min, poured into a 1:1 solution of aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} and aq. NaHCO\textsubscript{3}, and extracted with Et\textsubscript{2}O. The combined organic layers were washed with a solution of aq. NaHCO\textsubscript{3} and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated to an oil. The crude product was purified by silica gel flash chromatography (10→20% Et\textsubscript{2}O in hexanes) to provide aldehyde 2.13 (2.1 g, 82% yield). The spectroscopic data was identical to the one reported in the literature.\textsuperscript{15}
Compound 2.14:

Round-bottom flask was charged with aldehyde 2.13 (1 equiv), methyl vinyl ketone (1.5 equiv), TMS₂NH (1.5 equiv) and MeCN (c = 0.1 M). The obtained reaction mixture was refluxed for 12 h, followed by addition of TBAF (1 M in THF, 5 equiv) and stirred at room temperature for 5 h. The reaction mixture was then quenched with aq. NaHCO₃, extracted with Et₂O and concentrated to a brown oil under reduced pressure. The crude product was purified by silica gel flash chromatography (5→15% Et₂O in hexanes) to provide enone 2.14 in 31% yield.

Data for compound 2.14:

Physical state: yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 6.93 (ddd, J = 10.2, 2.5, 1.6 Hz, 1H), 6.04 (ddd, J = 10.2, 2.6, 0.9 Hz, 1H), 2.67 (dqt, J = 11.9, 4.6, 2.4 Hz, 1H), 2.54 – 2.49 (m, 1H), 2.44 – 2.34 (m, 3H), 2.24 – 2.15 (m, 1H), 2.06 (td, J = 2.7, 0.4 Hz, 1H), 1.84 (tdd, J = 13.1, 10.0, 4.5 Hz, 1H).
Compound 2.15:

Round-bottom flask was charged with enone 2.14, Mn(dpm)₃ (5 mol%) and i-PrOH (c = 0.2 M). Oxygen was bubbled through the solution for 5 h as it was stirring at room temperature. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (10→20% EtOAc in hexanes) to afford 2.15 in 69% yield as an inconsequential 1.2:1 mixture of diastereoisomers.

Data for compound 2.15:

**Physical state:** colorless oil.

**¹H NMR** (500 MHz, CDCl₃): δ 4.34 (ddd, J = 11.0, 6.7, 2.9 Hz, 1H), 4.30 – 4.23 (m, 1H), 3.66 (d, J = 3.5 Hz, 1H), 3.51 (d, J = 3.4 Hz, 1H), 2.72 – 2.50 (m, 8H), 2.34 (ddd, J = 6.2, 3.6, 2.7 Hz, 6H), 2.25 (dddt, J = 27.2, 11.9, 6.1, 2.9 Hz, 2H), 2.13 – 2.09 (m, 1H), 2.08 – 1.97 (m, 1H), 1.83 (ddd, J = 13.5, 11.7, 5.2 Hz, 1H), 1.64 – 1.54 (m, 1H).

**¹³C NMR** (126 MHz, CDCl₃): δ 211.02, 202.49, 82.21, 81.72, 74.19, 71.77, 70.54, 70.42, 41.71, 39.26, 38.10, 35.30, 34.39, 32.63, 32.33, 30.07, 24.74, 21.91.
Compound 2.18:

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

This compound was made via slightly modified literature.\textsuperscript{16} To a stirred solution of cyclohexeneone (30.6 g, 300.0 mmol) in toluene (800 mL) was added Pb(OAc)$_4$ (280.0 g, 600.0 mmol, 2.0 equiv). The mixture was then heated to reflux for 12 h, and cooled to room temperature. The resulting mixture was diluted with Et$_2$O, washed with 1 M aq. HCl, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10→20% EtOAc in hexanes) to afford 2.18 (27.7 g, 60% yield). The spectroscopic data was identical to the one reported in the literature.\textsuperscript{16}
Compound ($\pm$)-2.24:

Racemic 2.24 was as required in order to analyze the enantioselectivity of the asymmetric Cu-catalyzed conjugate addition described above, acting as the racemic mixture control sample with which to calibrate the chiral HPLC experiment.

A flame-dried round-bottom flask was equipped with stir bar was charged with CuI (9.5 mg, 0.05 mmol, 0.05 eq.) and 5 mL of THF under Ar. The resulting suspension was stirred for 30 min at 0 °C. Grignard reagent was prepared from (2-bromoallyl)trimethylsilane\(^{16}\) (483 mg, 2.5 mmol, 2.5 eq.) and Mg turnings (170 mg, 7 mmol, 7 eq.) in the same manner as above, with exception of using THF (3 mL) instead of MeTHF. The Grignard reagent in THF was transferred to a flask containing CuI via cannula. The obtained orange solution was stirred for 10 min at 0 °C. Cyclohexenone (96 mg, 1 mmol, 1 eq.) dissolved in THF (1 mL) was added dropwise over a period of 30 min. The reaction mixture was then stirred for 1 h at 0 °C, then quenched with aq. sat. NH\(_4\)Cl (10 mL) and diluted with Et\(_2\)O (10 mL). The layers were separated and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). Combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (3% Et\(_2\)O in hexanes) to give racemic 2.24 (159 mg, 76% yield) as pale yellow liquid.
Compound (+)-2.24:

A flame-dried 2 L round-bottom flask equipped with a stir bar was charged with CuI•0.75DMS (302 mg, 1.28 mmol, 0.6 mol%) and ligand L1 (1.42 g, 1.70 mmol, 0.8 mol%) under Ar. Toluene (650 mL) was added to this flask and the obtained mixture was stirred until all of the CuI•0.75DMS was dissolved (ca. 1h). Separate 2 L round-bottom flask was charged with Mg turnings (38.8 g, 1.60 mol, 7.50 eq.), flame-dried and back-filled with Ar. MeTHF (650 mL) was added to this flask followed by 1,2-dibromoethane (3.0 mL, 36 mmol, 0.16 eq.). After bubbling has ceased (2-bromoallyl)trimethylsilane (103.2 g, 532 mmol, 2.50 eq.) was added dropwise to the Mg turnings via syringe pump over 2 h maintaining gentle reflux. The bronze-green solution of Grignard reagent was allowed to cool to room temperature and then stirred for 30 min. The flask containing CuI•0.75DMS and ligand L1 in toluene was cooled to −78 °C and charged with freshly distilled cyclohexenone (20.5 g, 213 mmol, 1.00 eq.), followed by the dropwise addition of Grignard reagent in MeTHF via syringe pump over 4 h. The reaction mixture was then stirred for 40 min at −78°C and quenched by transferring it via cannula to a 3 L round-bottom flask containing toluene (450 mL), AcOH (49 mL) and Et3N (60 mL) that was maintained at 40 °C using large water bath. The quenched reaction mixture was allowed to reach room temperature, stirred for 30 min and then sat. aq. NH4Cl (500 mL) was added. The layers were separated and the aqueous phase was extracted with hexanes (3 x 250 mL). Combined organic layers were dried over Na2SO4 and concentrated.
under reduced pressure. The crude product was purified by distillation (1 mbar, 65–70 ºC) to provide ketone 2.24 (35.65 g, 80% yield).

**Notes:** Commercial grade CuI•0.75DMS gave inferior yields and enantioselectivities. Consequently, it must be made fresh following the House protocol.  

Typical quench with MeOH/NH₄Cl worked well on up to 5 g scale. However, on larger scales (especially >10 g) it was inefficient and resulted in significant quantities of aldol products, diminishing the overall yield of 2.24. Therefore, the reverse quench that is described above was developed to avoid this problem.

**Physical state:** pale yellow liquid.

**TLC:** R<sub>f</sub> = 0.53 (10% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>): δ 4.64 (d, J = 1.1 Hz, 1H), 4.62 (s, 1H), 2.47 (ddt, J = 13.6, 3.9, 2.0 Hz, 1H), 2.41–2.34 (m, 1H), 2.33–2.23 (m, 2H), 2.22–2.14 (m, 1H), 2.08 (dddd, J = 13.4, 7.5, 6.5, 3.6 Hz, 1H), 2.02–1.94 (m, 1H), 1.64 (ddtt, J = 13.1, 12.0, 4.7, 3.2 Hz, 1H), 1.54 (s, 2H), 1.54–1.52 (m, 1H), 0.02 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>): δ 211.78, 149.94, 106.61, 47.28, 45.87, 41.42, 30.63, 25.83, 25.32, −1.21.

**HRMS** (ESI-TOF): Calcd for C₁₂H₂₃SiO [M+H]<sup>+</sup>: 211.1513, found 211.1513.

**Optical Rotation:** [α]<sup>23</sup><sub>D</sub> = +18.0º (c 1.0, CHCl<sub>3</sub>).
Method for determining the enantioselectivity of the asymmetric conjugate addition, using (±)-2.24 and (+)-2.24:

Column: Chiralcel® OZ-3

Dimensions: 4.6 × 250 mm

Eluent: hexanes:IPA = 99.5:0.5

Flow rate: 1mL/min

We thank Dr. Dragos Gherase from Blackmond lab for developing the method and assisting with chiral HPLC.

Chromatogram and the report of (±)-2.24 on a chiral column, showing ~0% ee.
Chromatogram and the report of (+)-2.24 on a chiral column, showing ~99% ee.
**Method A (racemic):**

A flame-dried 1 L round-bottom flask equipped with a stir bar was charged with CuI (324 mg, 1.7 mmol, 5.0 mol%) and THF (200 mL) under Ar. Separate 1 L round-bottom flask was charged with Mg turnings (5.81 g, 238 mmol, 7.50 eq.), flame-dried and back-filled with Ar. THF (250 mL) was added to this flask followed by 1,2-dibromoethane (0.5 mL). After bubbling has ceased (2-bromoallyl)trimethylsilane\textsuperscript{10} (13.1 g, 68 mmol, 2.00 eq.) was added dropwise to the Mg turnings via syringe pump over 2 h maintaining gentle reflux. The bronze solution of Grignard reagent was allowed to cool to room temperature and then stirred for 30 min. The flask containing suspension of CuI in THF was cooled to 0 °C and Grignard reagent in THF was transferred via cannula into it over 30 min. The bright orange homogenous solution was then stirred for 10 min at 0 °C and charged with enone 2.18 (5.2 g, 34 mmol, 1.00 eq.) dissolved in THF (20 mL). The reaction mixture was stirred at 0 °C for 1 h and then quenched with sat. aq. NH\textsubscript{4}Cl (300 mL). The layers were separated and the aqueous phase was extracted with hexanes (3 x 250 mL). Combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (5→15% Et\textsubscript{2}O in hexanes) to provide α-acetoxy ketone 2.20 (5.92 g, 65% yield) as ca. 1:1 mixture of inconsequential diastereomers.

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**Compound 2.20:**

![Diagram of compounds 2.20, 2.20a, and 2.20b]
Method B (enantioselective):

A flame-dried 1 L round-bottom flask equipped with a stir bar was charged with freshly distilled 2,2,6,6-tetramethylpiperidine (26.9 mL, 158 mmol, 1.10 eq.) and THF (280 mL) under Ar. BuLi (58.8 mL of 2.5 M soln in hexanes, 147 mmol, 1.02 eq.) was added dropwise at 0 °C and the obtained orange solution was stirred for 30 min at 0 °C. The acquired LiTMP solution was then cooled to −78 °C and ketone 7 (30.23 g, 144 mmol, 1.0 eq.), diluted with THF (15 mL), was added dropwise via syringe pump over 40 min. The reaction mixture was then stirred for 1 h at −78 °C. A separate flame-dried 2 L round-bottom flask equipped with a stir bar was charged with Davis oxaziridine (48.8 g, 187 mmol, 1.30 eq.), THF (700 mL), DMPU (350 mL, freshly distilled from CaH$_2$) and then cooled to −78 °C. The enolate solution was transferred to the Davis oxaziridine solution via short cannula under positive pressure of Ar over 30 min and then stirred for 30 min at −78 °C. Freshly distilled Ac$_2$O (16.3 mL, 173 mmol, 1.20 eq.) was added to the reaction mixture and it was allowed to reach 0 °C and stirred for 1 h at this temperature. The reaction mixture was quenched by sequential addition of AcOH (6.3 mL), thiourea (5.5 g) and H$_2$O (40 mL) and then stirred for 40 min at room temperature. The reaction mixture was diluted with 10 wt.% aq. LiCl (600 mL) and extracted with Et$_2$O (3 x 600 mL). Combined organic phases were washed with 10 wt.% aq. LiCl (3 x 500 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (5→15% Et$_2$O in hexanes) to provide α-acetoxy ketone 2.20 (24.61 g, 64% yield) as 2:1 mixture of inconsequential diastereomers. In practice, diastereomers were always combined and submitted to the next reaction as a mixture (viscous yellow oil). However, for spectroscopic identification they were characterized individually.
Notes: Addition of thiourea during work-up was necessary to prevent oxidation of TMP to TEMPO by unreacted Davis oxaziridine (was not observed at –78 °C or 0 °C but proceeded slowly at room temperature). Substantial amounts of TEMPO would form otherwise, significantly complicating purification of the product.

Regioselectivity in deprotonation of 2.24 would range from 5.5:1 to 7:1 depending on the scale, as a result, regioisomer of 2.20 was formed in approx. 10–15% yield as a by-product.

Data for compound 2.20a (major):

Physical state: white solid.

TLC: Rf = 0.57 (20% EtOAc in hexanes).

$^1$H NMR (600 MHz, CDCl$_3$): δ 5.19 (dd, $J$ = 12.3, 6.6 Hz, 1H), 4.68 (s, 1H), 4.63 (s, 1H), 2.58 (dt, $J$ = 13.2, 3.1 Hz, 1H), 2.37 (td, $J$ = 13.3, 0.9 Hz, 1H), 2.31 (ddt, $J$ = 12.2, 6.4, 3.1 Hz, 1H), 2.16–2.15 (s, 3H), 2.14–2.07 (m, 2H), 1.78–1.65 (m, 2H), 1.54 (s, 2H), 0.00 (s, 9H).

$^{13}$C NMR (151 MHz, CDCl$_3$) : δ 204.05, 170.20, 148.99, 106.82, 76.45, 46.57, 46.03, 31.68, 29.67, 25.81, 20.89, –1.20.

HRMS (ESI-TOF): Calcd for C$_{14}$H$_{25}$SiO$_3$ [M+H]$^+$: 269.1567, found 269.1566.

Optical Rotation: $[\alpha]_{D}^{23} = +57.7^\circ$ (c 1.00, CHCl$_3$).
X-ray crystal structure of Bz derivative of 2.20a (major).

Stereochemical assignment was based on X-ray of benzoyl (Bz) derivative of 2.20a. This also confirmed absolute stereochemistry, for more information see attached CIF file.
Data for compound **2.20b (minor):**

**Physical state:** yellow oil.

**TLC:** Rf = 0.50 (20% EtOAc in hexanes).

**$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$ 5.11 (t, $J$ = 7.9 Hz, 1H), 4.72 (d, $J$ = 2.8 Hz, 1H), 4.61 (d, $J$ = 3.0 Hz, 1H), 2.69 (ddd, $J$ = 14.2, 3.9, 2.0 Hz, 1H), 2.60 (m, 1H), 2.54 (ddd, $J$ = 14.2, 6.1, 1.1 Hz, 1H), 2.15 (s, 3H), 2.04–1.91 (m, 4H), 1.57 (d, $J$ = 13.8 Hz, 1H), 1.46 (d, $J$ = 13.8 Hz, 1H), 0.01 (s, 9H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$) : $\delta$ 205.05, 170.20, 148.06, 110.02, 76.45, 44.12, 43.14, 28.00, 26.07, 25.89, 20.95, −1.20.

**HRMS** (ESI-TOF): Calcd for C$_{14}$H$_{25}$SiO$_3$ [M+H]$^+$: 269.1567, found 269.1567.

**Optical Rotation:** $[\alpha]_{D}^{23} = -5.1^{\circ}$ (c 1.00, CHCl$_3$).
Compound 2.22:

A flame-dried 1 L round-bottom flask equipped with a stir bar was charged with 2-acetoxy ketone 2.20 (21.0 g, 2:1 mixture of diastereomers, 78.4 mmol, 1.00 eq.) and toluene (390 mL) under Ar. The reaction mixture was cooled to 0 ºC and EtAlCl₂ (157 mL of 1 M soln in hexanes, 157 mmol, 2.00 eq.) was added dropwise and obtained orange solution was stirred for 1 h at 0 ºC. The reaction mixture was quenched with sat. aq. NaHCO₃ (200 mL), followed by sat. aq. Rochelle’s salt (200 mL) and then it was allowed to reach room temperature and stirred for 2 h. The layers were separated and the aqueous phase was extracted with Et₂O (3 x 200 mL). Combined organic phases were dried over Na₂SO₄ and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (20→30% EtOAc in hexanes) to give alcohol 2.22 (11.83 g, 77% yield) as a ca. 2:1 mixture of inconsequential diastereomers. Compound 2.22 was submitted to the next reaction as a mixture of diastereomers (viscous yellow oil). For spectroscopic identification diastereomers (2.22a – major, 2.22b – minor) were characterized individually.
Data for compound 2.22a (major):

**Physical state:** viscous yellow oil.

**TLC:** Rf = 0.20 (25% EtOAc in hexanes).

**1H NMR** (600 MHz, CDCl₃): δ 4.94 (dt, J = 3.9, 1.9 Hz, 1H), 4.87 (t, J = 2.6 Hz, 1H), 4.85 (bs, 1H), 2.74 (t, J = 4.7 Hz, 1H), 2.45 (dt, J = 17.1, 2.7 Hz, 1H), 2.42 (bs, 1H), 2.39 (dq, J = 17.1, 2.1 Hz, 1H), 2.12 (s, 3H), 1.94 (dd, J = 10.8, 2.1 Hz, 1H), 1.79 (dddd, J = 15.3, 13.3, 6.1, 4.0 Hz, 1H), 1.73 (dq, J = 6.0, 1.8 Hz, 1H), 1.71 (ddt, J = 7.2, 3.6, 1.8 Hz, 1H), 1.60 (tdd, J = 13.0, 5.6, 2.2 Hz, 1H), 1.42 (dddt, J = 12.6, 6.3, 4.2, 2.0 Hz, 1H).

**13C NMR** (151 MHz, CDCl₃): δ 171.90, 151.02, 106.74, 79.47, 77.65, 43.18, 42.83, 39.70, 29.14, 25.41, 21.57.

**HRMS** (ESI-TOF): Calcd for C₁₁H₁₇O₃ [M+H]+: 197.1172, found 197.1173.

**Optical Rotation:** [α]D²³ = −52.4° (c 1.00, CHCl₃).

Data for compound 2.22b (minor):

**Physical state:** viscous yellow oil

**TLC:** Rf = 0.20 (25% EtOAc in hexanes).

**1H NMR** (600 MHz, CDCl₃): δ 4.89 (t, J = 7.4 Hz, 1H), 4.84 (s, 2H), 2.72 (s, 1H), 2.69 (s, 1H), 2.30 (s, 1H), 2.25 (d, J = 16.3 Hz, 1H), 2.10 (s, 3H), 2.04–1.98 (m, 2H), 1.59–1.54 (m, 4H).

**13C NMR** (151 MHz, CDCl₃): δ 171.84, 151.57, 106.24, 79.11, 78.11, 44.03, 42.60, 39.36, 31.75, 25.97, 21.47.

**HRMS** (ESI-TOF): Calcd for C₁₁H₁₇O₃ [M+H]+: 197.1172, found 197.1172.

**Optical Rotation:** [α]D²³ = −26.2° (c 1.00, CHCl₃).
**Compound 2.23:**

A flame-dried 500 mL three-neck round-bottom flask equipped with a stir bar was charged with alcohol **2.22** (10.8 g, 2:1 mixture of diastereomers, 55.1 mmol, 1.00 eq.), tetrabutylamonium iodide (20.3 g, 55.0 mmol, 1.00 eq.), Me$_2$SO$_4$ (15.6 mL, 165 mmol, 3.00 eq.) and DMF (86 mL) under Ar. NaH (2.64 g of 60% dispersion in mineral oil, 66.1 mmol, 1.2 eq.) was added portionwise and the reaction mixture was left stirring at room temperature for 2 h. LiOH•H$_2$O (19.7 g, 468 mmol, 8.50 eq.) dissolved in H$_2$O (95 mL) was added dropwise at 0 ºC and the reaction mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with sat. aq. NH$_4$Cl (100 mL) and diluted with Et$_2$O (200 mL). The layers were separated and the aqueous phase was extracted with Et$_2$O (3 x 200 mL). Combined organic extracts were washed with 10 wt% aq. LiCl (2 x 100 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was submitted to the next reaction without further purification. A small sample was purified by silica gel flash chromatography (0→20% Et$_2$O in hexanes) for characterization purposes.

**Notes:** Bu$_4$NI was necessary for achieving complete methylation of tertiary alcohol on a gram-scale. In the absence of it, only ~20% conversion was observed on >100 mg scale.
Data for compound **2.23a (major)**:

**Physical state:** white solid.

**TLC:** Rf = 0.24 (20% EtOAc in hexanes).

$^1$H NMR (600 MHz, CDCl$_3$): δ 4.89 (ddt, $J = 3.0$, 2.1, 1.0 Hz, 1H), 4.86 (qt, $J = 1.7$, 0.9 Hz, 1H), 3.97 (dt, $J = 4.0$, 1.9 Hz, 1H), 3.27 (s, 3H), 2.69-2.68 (m, 1H), 2.48 (dt, $J = 16.6$, 2.7 Hz, 1H), 2.29 (s, 1H), 2.23–2.19 (m, 1H), 1.90 (dd, $J = 10.6$, 2.4 Hz, 1H), 1.76–1.63 (m, 4H), 1.41–1.37 (m, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 151.29, 106.90, 85.35, 70.82, 50.56, 42.69, 36.91, 35.42, 29.43, 25.96.

**HRMS (ESI-TOF):** Calcd for C$_{10}$H$_{17}$O$_2$ [M+H]$^+$: 169.1223, found 169.1223.

**Optical Rotation:** [α]$^2$$_D$ = $–4.8^\circ$ (c 1.00, CHCl$_3$).

Data for compound **2.23b (minor)**:

**Physical state:** viscous colorless oil.

**TLC:** Rf = 0.24 (20% EtOAc in hexanes).

$^1$H NMR (600 MHz, CDCl$_3$): δ 4.84–4.83 (m, 2H), 3.87 (ddd, $J = 10.0$, 6.0, 1.8 Hz, 1H), 3.28 (s, 3H), 2.68 (s, 1H), 2.57 (dq, $J = 16.9$, 2.1, 0.9 Hz, 1H), 2.48 (s, 1H), 2.26 (dq, $J = 16.9$, 2.5 Hz, 1H), 2.04–1.92 (m, 2H), 1.54 (ddd, $J = 10.8$, 6.6, 4.4, 2.1 Hz, 1H), 1.49 (ddd, $J = 12.6$, 4.8, 2.3 Hz, 1H), 1.46–1.38 (m, 1H), 1.34 (dd, $J = 10.8$, 2.3 Hz, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 151.45, 106.06, 84.74, 77.16, 71.88, 50.39, 42.58, 37.98, 34.31, 31.73, 27.44.

**HRMS (ESI-TOF):** Calcd for C$_{10}$H$_{17}$O$_2$ [M+H]$^+$: 169.1223, found 169.1223.

**Optical Rotation:** [α]$^2$$_D$ = $–19.1^\circ$ (c 1.00, CHCl$_3$).
Compound 2.10:

A flame-dried 500 mL round-bottom flask equipped with a stir bar was charged with crude 2.23 (assumed 55.1 mmol, 2:1 mixture of diastereomers, 1.0 eq.), Et₃N (65.0 mL, 468 mmol, 8.50 eq.) and DCM (55 mL) under Ar. Pyr•SO₃ (30.72 g, 193 mmol, 3.50 eq.) and DMSO (60 mL) were prestirred in a separate round-bottom flask under Ar for 30 min at room temperature. This mixture was transferred to the solution containing crude alcohol 2.23 at 0 ºC via cannula under a positive pressure of Ar. The reaction mixture was stirred for 2 h at 0 ºC and then for 14 h at room temperature. The reaction mixture was quenched by the addition of 10 wt% aq. NaS₂O₃ (300 mL) at 0 ºC and diluted with Et₂O (200 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 150 mL). Combined organic extracts were washed with brine (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (0→15% EtOAc in hexanes) to give ketone 2.10 (7.42 g, 81% yield over 2 steps) as a colorless liquid.

Notes: Prestirring Pyr•SO₃ and DMSO was crucial to obtain high yield in oxidation step. Sequential addition consistently resulted in significantly lower yields.
Data for compound 2.10:

**Physical state:** colorless liquid.

**TLC:** Rf = 0.39 (20% EtOAc in hexanes).

**$^1$H NMR** (600 MHz, CDCl$_3$): $\delta$ 5.07 (t, $J = 2.6$ Hz, 1H), 5.02 (bs, 1H), 3.43 (s, 3H), 2.98 (bs, 1H), 2.66 (m, 2H), 2.43–2.40 (m, 2H), 2.19 (ddd, $J = 11.4, 5.3, 2.9$ Hz, 1H), 1.89–1.87 (m, 1H), 1.88–1.84 (m, 1H), 1.81–1.75 (m, 1H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$): $\delta$ 210.24, 149.68, 108.44, 88.58, 54.29, 42.50, 42.16, 41.06, 36.40, 33.48.

**HRMS** (ESI-TOF): Calcd for C$_{10}$H$_{13}$O$_2$ [M+H]$^+$: 167.1067, found 167.1067.

**Optical Rotation:** $[\alpha]_D^{23} = -85.1^\circ$ (c 1.00, CHCl$_3$).
Chapter 2 Appendix

NMR Spectra
Compound 2.14

$^1$H NMR (400 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

Compound 2.15 (1:2:1 dr)
Compound 2.15 (1.2:1 dpm)

$^{13}$C NMR (126 MHz, CDCl$_3$)
OAc

Compound 2.18

1H NMR (400 MHz, CDCl3)

1H NMR (400 MHz, CDCl3) Compound 2.18

\begin{align*}
0.0 & 0.5 & 1.0 & 1.5 & 2.0 & 2.5 & 3.0 & 3.5 & 4.0 & 4.5 & 5.0 & 5.5 & 6.0 & 6.5 & 7.0 & 7.5 & 8.0 \\
0.0 & 0.5 & 1.0 & 1.5 & 2.0 & 2.5 & 3.0 & 3.5 & 4.0 & 4.5 & 5.0 & 5.5 & 6.0 & 6.5 & 7.0 & 7.5 & 8.0 \\
\end{align*}
O
TMS

\text{Compound 2.24}

\text{H NMR (600 MHz, CDCl}_3)
$^{13}$C NMR (151 MHz, CDCl$_3$)

Compound 2.24

1.27
-25.82
-147.5
106.1
-148.1
-217.8

TMS
$^1$H NMR (600 MHz, CDCl$_3$)
Compound 2,2,2-OMe (major)

$^{13}$C NMR (151 MHz, CDCl$_3$)

1.20
2.38
3.18
46.63
76.41
106.80
148.99
170.20

TMS
$^1$H NMR (600 MHz, CDCl$_3$) Compound 2.20b (minor)
$^{13}$C NMR (151 MHz, CDCl$_3$)
OH

AcO

Compound 2.22a (major)

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

Compound 2.22a (major)
Compound 2.22b (minor)

$^1H$ NMR (600 MHz, CDCl$_3$)
$\text{Compound 222b (minor)}$

$\text{^13C NMR (151 MHz, CDCl}_3\text{)}$

---

Diagram of a molecule with chemical shifts indicated on the plot.
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 2.32a (major)

HO

OME
$\text{Compound 2.23a (major)}$

$^{13}C$ NMR (151 MHz, CDCl$_3$)
Compound 2.23b (minor)

$^1$H NMR (600 MHz, CDCl$_3$)

Minor (2.23b)

HO

OME
$\text{Compound } 2.23b$ (minor) 

$^{13}C$ NMR (151 MHz, CDCl$_3$)

Diagram: 
- 76.72 ppm
- 71.88 ppm
- 50.39 ppm
- 38.88 ppm
- 37.88 ppm
- 7.54 ppm
- 151.46 ppm
OMe

H NMR (600 MHz, CDCl₃)

Compound 2.10
\[ 13C \text{NMR (151 MHz, CDCl}_3) \]

- 210.24
- 149.68
- 108.44
- 88.58
- 54.29
- 42.50
- 42.16
- 41.06
- 36.40
- 33.48
Chapter 3

Pinacol Rearrangement and Cyanation Saga
3.1 Initial struggle with addition/pinacol rearrangement sequence

With the route to the key building block 2.10 finally secured it was time to combine it with the second fragment that would eventually become the cyclohexanone ring of maocystal V. However, this proved to be challenging as upon exposure of 2.10 to a myriad of different enolates and their equivalents, only starting material would be recovered (Scheme 3.1). The difficulty to undergo such aldol reaction could be explained by the presence of quaternary carbons next to both carbonyls of the two ketones. Unexpectedly, the last ditch effort, samarium (II) diiodide mediated Reformatsky reaction,\(^1\) actually was able to couple 2.10 with a model system bromoketone 3.1 to furnish tertiary

Scheme 3.1 Initial attempts to develop addition/pinacol rearrangement sequence
alcohol \textbf{3.2} in 85\% yield as a single diastereoisomer at C9 (relative stereochemistry unknown). This particular ketone was chosen as model system because it was much easier to prepare than the dimethyl analogue as it was not volatile and was much easier to purify and handle. Interestingly, performing this reaction on the real system with bromoketone \textbf{3.3} resulted in formation of \textbf{3.4} with a significant drop in yield (~24\%, stereochemistry at C9 unknown). This was mainly due to difficulty to push the reaction to completion as it appeared that \textbf{3.3} was reacting with itself during the course of the reaction, presumably at the olefin as cyclohexanone derivatives not possessing the alkene participated in this reaction without any issues. This reaction that proceeds through the formation of a rather exotic samarium enolate\textsuperscript{1} was the only condition that was able to combine these two particular fragments and with exquisite stereoselectivity.

Despite rather low yield in the Reformatsky reaction, the amount of \textbf{3.4} obtained was sufficient to evaluate the heart of this project – pinacol rearrangement. However, upon subjecting \textbf{3.4} to various Lewis and/or Bronsted acids would always result in retro-aldol reaction to give back starting materials with occasional double bond isomerization on both fragments (Scheme 3.1). Protecting the tertiary alcohol to prevent retro-aldol would not solve this problem as the outcome would be: no reaction at all, deprotection followed by retro-aldol or elimination/double bond isomerization. It was clear that this pesky retro-aldol issue needed to be addressed.
It was reasoned that by introducing the double bond and performing addition of an organometallic reagent in to ketone 2.10, the propensity to undergo retro aldol would be significantly minimized as the resulting carbanion would be orthogonal to the $\pi^*$ of the carbonyl, consequently, it would be poor leaving group as it can’t delocalize the negative charge anymore. Thus, ketal protected iodoenone 3.5 derived in two steps from commercially available 4,4-dimethylcyclohexenone was subjected to Li/I exchange with $t$-BuLi and the resulting organolithium species was treated with ketone 2.10 (Scheme 3.2).

Scheme 3.2 First success with addition/pinacol rearrangement sequence

Unfortunately, no addition would occur, presumably due to sterics as there is a fully substituted tetrahedral carbon next to the reactive site. In order to minimize unfavorable steric interactions, the carbonyl group of coupling partner was protected as the silyl enol ether to give 3.6 that would now have a planar carbon next to the nucleophilic site, that after transforming it to organolithium reagent would add to ketone 2.10 resulting in 1:2 mixture of diastereoisomers 3.7 and 3.8, respectively, in 70% combined yield. At this point it was not clear how consequential stereochemistry at C9 was but it turned out to be
important as subjecting 3.7 to the acidic condition in hot PhMe gave furnished the desired [2.2.2]bicycle 3.9 in 67% yield. While submitting 3.8 to the same conditions resulted in formation of undesired [3.2.1]bicycle 3.10 in 65% yield. Thus, it seems that the mechanism of this particular pinacol rearrangement is concerted as the bond anti-periplanar to the leaving group migrates exclusively. If it would proceed through carbocation, which was hoped for at the onset of this project, the stereochemistry would be inconsequential. Although, this sequence would only provide ~15% yield of 3.10 from ketone 2.10, it was enough to test the subsequent steps. It was reasoned that perhaps this step could be later optimized toward the desired diastereoisomer, once the route toward maocryystal V would be established. Unfortunately, all efforts to install a hydroxymethylene unit or a cyanide into 3.9 were met with bitter failure. Attempts to functionalize enone moiety of 3.9 via conjugate addition were also fruitless as it appeared that 3.9 is a remarkably inert molecule. Perhaps the fact that it is shielded from all the sides by bulky gem-dimethyl and bicyclo[2.2.2]octane moieties. Even though this particular approach reached a demoralizing dead end, at least it was a proof of principle that the [2.2.2]bicycle could, indeed, be accessed via pinacol rearrangement.

3.2 Successful addition/pinacol rearrangement sequence

By taking into account all the lessons learned with the approach described earlier, it was reasoned that maybe moving the gem-dimethyl group as far away from the olefin of the enone as possible would decrease steric effects and open up new opportunities for the functionalization of pinacol rearrangement product. Thus, retrosynthesis was modified accordingly to accommodate these modifications (Scheme 3.3). As a result, the coupling
partner would be some sort of protected version of known iodoenone 3.11 that was easily accessible in four steps from methyl cyclohexanone.\(^2\) Organometallic reagents generated from 3.12 did not participate in 1,2-addition into carbonyl of 2.10 presumably due to steric hindrance as tetrahedral carbon of the ketal most likely block the nucleophilic site (Scheme 3.4). Surprisingly, organometallic reagents generated from silyl enol ether, that has a planar carbon next to the nucleophilic site, 3.13 did not add into 2.10 as well. While this trick solved the issue of sterics previously, it was not as successful in this case. At this point, mainly out of desperation, unprotected 3.11 was examined in this difficult reaction even though it would mean generating an organometallic reagent right next to the ketone in the same molecule, which at that time was questionable at best. However, it was reasoned that maybe negative charge density on the \(\alpha\)-carbon would repel nucleophiles and prevent self-condensation, while non-coordinating PhMe as a solvent would promote aggregation,

Scheme 3.3 Modified retrosynthesis of maoecrystal V
thus stabilizing this rather bizarre species. Remarkably, treating 3.11 with \( i\text{-MgCl}\cdot\text{LiCl} \) followed by addition of ketone 2.10 resulted in formation of adduct 3.14 in 92% yield as a

![Scheme 3.4 Attempts to promote addition of 3.11 into 2.10](image)

1.5:1 mixture of diastereoisomers. It is interesting to note that both \( i\text{-PrMgCl}\cdot\text{LiCl} \) and PhMe were important in this reaction. Other organomagnesium and organolithium reagents resulted in much lower yields or no reaction at all, while use of more coordinating solvents such as THF, resulted in poor conversion due to consumption of 3.11 by self-condensation. With the newly obtained adduct 3.14 it was time to revisit the key pinacol rearrangement.

The diastereoisomers were separated and the relative configuration was determined by crystallographic X-ray analysis of the minor 3.14b diastereoisomer. By the principle of exclusion, the major diastereoisomer 3.14a had axial alcohol as shown Scheme 3.5. To our delight, treatment of major diastereoisomer with TsOH in PhMe at 75 °C resulted in smooth pinacol rearrangement to give exclusively [2.2.2]bicycle 3.15 (confirmed by X-ray) in 70% yield. Surprisingly, minor diastereoisomer 3.14b under same conditions furnished
undesired rearrangement product [3.2.1]bicycle 3.16 (confirmed by X-ray) in 52% yield along with the desired product 3.15 in 15% yield. Attempts to optimize the diastereoselectivity of the addition toward 3.14a or pinacol rearrangement to obtain more

\[
\begin{align*}
\text{i-PrMgCl-LiCl} & \quad \text{PhMe, } -78 \degree C \\
\text{PhMe, } 75 \degree C & \quad (70\%) \\
\text{TsOH, PhMe, } 75 \degree C & \quad (15\%) \\
\text{TsOH, PhMe, } 75 \degree C & \quad (52\%)
\end{align*}
\]

\[
\begin{align*}
\text{X-ray} & \quad \equiv \quad \text{X-ray} \\
\text{X-ray} & \quad \equiv \quad \text{X-ray}
\end{align*}
\]

Scheme 3.5 Successful addition/pinacol rearrangement sequence maecrystal V

3.15 were fruitless. It is interesting to note, that with free alcohol instead of the methoxy group at the bridgehead of 3.14 the pinacol rearrangement would give no product at all, only decomposition was observed in that particular case. This highlights how narrow the window of opportunity is for the synthesis of this treacherous natural product. Since both addition and pinacol rearrangement were run in PhMe, a much more convenient one-pot protocol was developed, where the tertiary alcohol was not isolated, but treated with aq. TsOH in situ and then heated at 85 °C to afford the desired 3.14 in 45% yield from 2.20. While the yield of this sequence was quite modest, it proved to be quite scalable as 5 g of 3.15 could be produced in a single pass.
So what is going on in the pinacol rearrangement? Why a mixture of products is formed in the case of minor diastereoisomer 3.14b? We believe that two mechanism operate simultaneously in this case: concerted and stepwise (Scheme 3.6). Concerted mechanism seems to be the dominant one, where the bond anti-periplanar to the leaving group migrates preferentially. In the case of minor diastereoisomer 3.14b it gives undesired [3.2.1]bicycle 3.16. However, stepwise mechanism that proceeds via carbocation also operates to minor extent. In the newly formed carbocation the C–C bond of the two carbon bridge has a better overlap with empty p-orbital than C–C bond of one carbon bridge that has poorer allignment. This results in the formation of desired [2.2.2]bicycle 3.15 in 15% yield as well. In the case of the major diastereoisomer 3.14a both mechanisms are indistinguishable as they result in the same product 3.15. However, alternative mechanism that proceeds through exo olefin isomerization, followed by anchimeric assistance by the

Scheme 3.6 Proposed mechanistic rationale for pinacol rearrangement step
newly formed internal double bond in the dehydration step is also possible. To date, it is unknown whenever the alkene isomerization happens before or after the pinacol rearrangement. With ample quantities of \textbf{3.15} finally secured, it was time to install the last two carbons of maocrystal V, which turned out to be easier said than done.

\subsection*{3.3 Hydroxymethylation/Cyanation Saga}

At this stage, the synthesis was only six steps long and installation of only two carbons was needed to forge complete carbon framework of maocrystal V. This was the point where difficult but so far successful journey toward \textbf{1} would turn into an absolute stereochemical nightmare that would haunt us for over a year. The incorporation of the first carbon via chemo- and stereoselective cyanation was achieved by subjecting \textbf{3.15} to TMSCN in the presence of TMSOTf to give cyanohydrin \textbf{3.17} in 80\% as a single desired diastereoisomer (Scheme 3.7). Unfortunately, subsequent installation of the last C20 carbon via hydroxymethylation or alkylation was unsuccessful despite enormous efforts.

\textbf{Scheme 3.7} Attempts to install the last C20 carbon of maocrystal V
Various bases, electrophiles (CH₂O, ICH₂Br, MOMCl, BOMCl) and protecting groups were evaluated in this challenging transformation without success. It seems that C10 carbon is just too hindered as it is shielded from all the sides by gem-dimethyl, cyanide and [2.2.2]bicycle. It was reasoned that rendering this event intramolecular by tethering electrophile to the oxygen of cyanohydrin would result in successful alkylation of C10 (Scheme 3.8). Unfortunately, no reaction would occur even under relatively harsh conditions. Utilizing similar logic, hydrolysis of the cyanide moiety was attempted in order to tether electrophiles to the carboxylic acid group in a similar manner Chen/Nicolaou did in their approach toward 1.⁵ Surprisingly, such hydrolysis was not achieved under basic or acidic conditions. Parkins catalyst⁶ was able to deliver amide 3.19 in 40% yield but no further elaboration of this compound was achieved.

![Scheme 3.8](image)

**Scheme 3.8** Attempts to manipulate cyanide to direct alkylation at C10

Since hydroxymethylation was not possible to achieve after introduction of the cyanide, it was reasoned, that the order of these transformation can be switched by doing hydroxymethylation of 3.15 first, followed by cyanation. This, however, brought a whole new set of issues as now we would need to achieve a stereo-, regio- and chemoselective
hydroxymethylation of much more hindered C5 ketone in the presence of much more accessible one at C8. Protection of C8 ketone as a ketal would not solve this issue as it would create a fully substituted tetrahedral carbon resulting in the same steric environment as with cyanohydrin 3.17. However, in attempt to see if functionalization of C10 is possible at all, unprotected 3.15 was subjected to hydroxylation condition (Scheme 3.9). Surprisingly, hydroxymethylation turned out to be innately chemoselective as not even a trace of hydroxymethylation at C14 was detected. The real challenge of this transformation turned out to be regioselectivity as the C2 functionalized 3.21 was the major product formed in 74% yield as a single diastereoisomer (unknown stereochemistry at C2). The desired product 3.20 was formed in messily 13% yield as a 1:1 mixture of diastereoisomers. Exhaustive screening of different enolates, electrophiles, additives and co-solvents turned
out to be fruitless. Attempts to eliminate the possibility of C2 hydroxymethylation by performing conjugate addition with TMSLi resulted in the formation of 3.22 in 63% yield as a single desired diastereoisomer (confirmed by X-ray). However, this compound turned out to be inert presumably due to steric as further elaboration was unsuccessful. The epoxidation of the double bond of the [2.2.2]bicycle was performed with DMDO to give 3.23, in hope, that it would result in some sort of change in reactivity. This compound, when submitted to hydroxymethylation conditions would form interesting but synthetically useless [3.2.1.0]tricycle 3.24 (confirmed by X-ray). At this point, the decision to optimize the hydroxymethylation of 3.15 was made that resulted in an exhaustive study exploring every conceivable variable that was driven purely by an unhealthy obsession to make maocryystal V. Inspired by our previous encounter with samarium enolate, we decided to evaluate lanthanide salts as additives in this reaction. Emerging from this study was the remarkable finding that the addition of LaCl₃·2LiCl to the extended sodium enolate of 3.15, followed by quenching with freshly prepared formaldehyde gas led to the desired adduct 3.20a (confirmed by X-ray) and undesired epimer 3.20b (confirmed by X-ray) in 84% yield as a 2:1 diastereomeric mixture favoring 3.20a (Scheme 3.10). Complete chemoselectivity was achieved because the more accessible C8 ketone did not enolize under these conditions presumably due to: (1) due to poor alignment of C–H bond with π* orbital of C8 carbonyl the acidity of the adjacent hydrogens on [2.2.2]bicycle is much lower compared to cyclohexanone for example; (2) increasing angle strain introduced onto the bicyclic system upon C-8/14 enolate generation; (3) destabilizing non-bonding interactions between π-systems (see inset graphic, Scheme 3.10). It is important to note, that addition of LaCl₃·2LiCl resulted in complete switch in regioselectivity since only a trace (ca. 2%)
of 3.21 was observed in this reaction. While the diastereoselectivity was modest, the
diastereoisomers could be separated and after some experimentation this reaction could be
run on 3 g scale. With seemingly insurmountable challenge of selective
hydroxymethylation finally solved, it was time to incorporate the last carbon via cyanation.

![Diagram of 3.15 cyanation](attachment:image.png)

**Scheme 3.10** Successful stereo-, regio- and chemoselective hydroxymethylation of 3.15

It was expected that there would be no problem with the stereocontrol during
cyanation of 3.20a based on the results obtained with cyanation of substrate 3.15, where it
proceeded exclusively form the desired face (Scheme 3.7). Unfortunately, with the
hydroxymethylene unit intact the stereoselectivity completely switched to give exclusively
the undesired diastereoisomer 3.25 (confirmed by X-ray, Scheme 3.11). A variety of
conditions were examined but this was always the outcome, except for a handful of cases.
Unusual iodine catalyzed cyanation\(^8\) gave product 3.26 in 53% yield (confirmed by X-ray)
which possessed the correct stereochemistry but undesired chemoselectivity as the cyanide attacked the more hindered bis-neopentyl ketone instead. Interestingly, Cu(I) triflate with TMSCN mediated formation of cyclic enol ether 3.27 in 22% yield with the rest of mass balance being mainly starting material 3.20a. This result is quite interesting because it in agreement with our hypothesis that two internal olefins in a [2.2.2]bicycle induce too much strain on the rigid, non-flexible framework of the bicycle. As a result, in order to relieve this strain one double bond migrates into an exocyclic position in order to accommodate the newly formed enol ether. The only example where cyanide attacked from the desired face was under Zn(OTf)$_2$/TMSCN conditions to furnish 3.28 in 89% yield. Unfortunately, it was also accompanied with the formation of undesired tetrahydrofuran ring. Attempts to

Scheme 3.11 The cyanation saga
rupture this ring with BBr₃ or TMSI were fruitless so the compound 3.28 turned out to be synthetic dead end despite having the desired stereochemistry.

![Scheme 3.12 Attemps to block the undesired face of approach](image)

Since reagent type control was unsuccessful in obtaining the desired stereocontrol, it was reasoned that perhaps substrate type control should solve this problem. Thus, 3.20a was epoxidized with DMDO to give diepoxide 3.29 that had oxygen atom right above the carbonyl (Scheme 3.12). Nucleophiles had to go through that oxygen atom in order to attack from the undesired face which seemed highly unlikely at that time. Surprisingly, subjecting 3.29 to ZnI₂/TMSCN conditions afforded compound 3.30 (confirmed by X-ray) in 51% yield where the cyanide still attacked from the undesired face. Attempts to perform dihydroxylation of the olefin with OsO₄/NMO to block the undesired face with bulkier functionality turned out unsuccessful as only starting material was recovered. Other nucleophiles, such as vinyl lithium, furanyl lithium, deprotonated 1,3-dithianes were investigated as well but with no success. It seemed that we reached a dead end and the situation was absolutely dire as maocystal V was completely out of reach, mocking us and laughing at our best efforts.
3.4 Modified strategy

Looking back at all our negative results, one particularly stood out: Zn(OTf)₂/TMSCN mediated cyanation of 3.20a mentioned in Scheme 3.11. The only example that gave us the correct stereoselectivity. It proceeds presumably via formation of five-member ring oxonium that gets trapped with TMSCN. Based on this, it was reasoned that maybe premaking the correct tetrahydrofuran ring and then performing the cyanation would result in the same stereochemical outcome (Scheme 3.13). Upon exploring a molecular model of such an oxonium, it was noticed that it possessed a distinct C-shape with the convex face being the desired. Thus, the synthetic route was modified accordingly.

However, this modified strategy had several new issues. Now selective reduction of more hindered C5 ketone in the presence of more sterically accessible C8 ketone. Initial efforts to selectively protect C8 ketone as a ketal were unsuccessful as only mixtures of mono- and bis-protected products would form (Scheme 3.14). Interestingly, Zn(OTf)₂ proved to be an outlier once again and mediated selective protection of a more hindered C5 ketone to give 3.31 in 81% yield. At this point it was clear that Zn(OTf)₂ was particularly unique reagent for this system as it always provided unexpected outcomes. Eventually this problem was solved by taking advantage of the alcohol moiety and

![Scheme 3.13 Modified approach premaking the THF ring before cyanation](image-url)
developing an intramolecular protecting strategy, where $3.20a$ was treated with TFA in mixture of MeOH/HC(OMe)$_3$ to afford $3.32$ in nearly quantitative yield. This ketal was quite sensitive so it was much more convenient to use it without purification after evaporating solvent. After treatment with a myriad of various reducing agents the undesired diastereoisomer $3.33$ would be formed either exclusively or predominately. It was evident that the stereochemical nightmare was never going to end, however, we thought that maybe we can perturb this reactivity via addition of Lewis acids. We had one particular Lewis acid in mind – Zn(OTf)$_2$, the reagent that generated strange and unexpected outcomes whenever utilized throughout this synthesis. Miraculously, treatment of crude $3.32$ (confirmed by X-ray) after evaporation of solvent with DCM and stoichiometric Zn(OTf)$_2$, followed by dropwise addition of 4M LiBH$_4$ solution in THF resulted in formation of $3.34$ (confirmed by X-ray) as a 3:1 mixture of epimers favouring the desired one in 83%.

Scheme 3.14 Stereoselective reduction of C5 ketone
combined yield. Once again, we barely managed to stay afloat in this perfect storm of obstacles that surrounded us and simply refused to let us go. To date, it is still unclear how Zn(OTf)$_2$ is able to switch the stereoselectivity of this reaction. Based on experimental observations, we believe that it simply coordinates to the C5 ketone and sits in the least hindered quadrant, thus blocking the undesired face of approach, while small reducing agent such as LiBH$_4$ is able to approach from the opposite face.

Next, it was time to say goodbye to our good friend the five-member ring ketal that served us so well, and treatment with TsOH in wet THF accomplished such task (Scheme 3.15). Upon removal of solvent, the diol 3.35 would equilibrate into a mixture of various ketals that was difficult to handle, consequently, it was protected as a dinitrobenzoyl (DNB)

![Scheme 3.15 Synthesis of the entire skeleton of maoecrystal V](image)

in one-pot without isolation to afford 3.36 in 86% yield. The DNB group was fortuitously
chosen in order to render intermediates crystalline for stereochemical assignment but was later realized to be essential (use of a Bz ester was unsuccessful). Formation of the strained THF ring of 1 could be accomplished using a 6:1 ratio of CH(OMe)\textsubscript{3}:MeOH with methanesulfonic acid. The intermediate ketal 3.37 was directly exposed to ZnI\textsubscript{2} and TMSCN, smoothly incorporating the C7 carbon (as a single diastereoisomer) which after saponification in the same flask delivered 3.40 (confirmed by X-ray) in 82\% overall yield. The cyanide attacked exclusively from the desired face so our decision to premake the tetrahydrofuran ring payed off as we successfully forged the entire architecture of maoecrystal V. After a lengthy and unforgiving clash, we finally felt that the tide of the battle had slowly shifted in our favour as installation of only two oxygens was required to finish this cursed molecule. The stereochemical nightmare that haunted us for over a year was finally over. However, we anticipated that maoecrystal V would not go down without a final last stand.
3.5 References


3.6 Experimental Section for Chapter 3.

**General Experimental.** All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry acetonitrile (MeCN), dichloromethane (DCM), diethyl ether (Et$_2$O), tetrahydrofuran (THF), toluene (PhMe) and triethylamine (Et$_3$N) were obtained by passing the 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 (¹H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an acidic solution of vanillin and heat, or KMnO$_4$ and heat as developing agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm), flash alumina chromatography was performed using Brockmann Grade 1 aluminum oxide (activated, basic, 58 Å, 60 mesh powder. NMR spectra were recorded on Bruker DRX-600 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (CDCl$_3$ ¹H NMR = 7.26 ppm, ¹³C NMR = 77.16 ppm; C$_6$D$_6$ ¹H NMR = 7.16 ppm, ¹³C NMR = 128.06 ppm, C$_5$D$_5$N ¹H NMR = 8.71, 7.57, 7.19 ppm, ¹³C NMR = 149.91, 135.56, 123.54). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.
Compound 3.2:

Test tube equipped with stir bar was charged with ketone 2.20 (1.0 eq.), bromoketone 3.1 (1.5 eq.) and THF (c = 0.2 M) under Ar atmosphere and cooled to \(-78 ^\circ C\). Next, SmI\(_2\) (0.06 M in THF, 3.5 eq.) was added dropwise via syringe pump over 30 min. The reaction mixture was then stirred for 30 min at \(-78 ^\circ C\) and quenched at that temperature with aq. NH\(_4\)Cl, warmed to room temperature, extracted with Et\(_2\)O and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (10→20% EtOAc in hexanes) to afford compound 3.2 in 85% yield.

**Physical state:** white solid

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.24 – 7.03 (m, 10H), 5.42 (s, 1H), 4.79 (dt, \(J = 2.6, 1.5\) Hz, 1H), 4.71 (d, \(J = 2.2\) Hz, 1H), 3.33 (s, 3H), 3.21 (dd, \(J = 13.1, 5.9\) Hz, 1H), 3.13 – 2.95 (m, 4H), 2.68 (s, 1H), 2.57 (d, \(J = 13.9\) Hz, 1H), 2.46 – 2.36 (m, 3H), 2.30 – 2.21 (m, 1H), 1.94 – 1.78 (m, 2H), 1.75 – 1.56 (m, 4H), 1.36 – 1.23 (m, 2H).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 220.51, 152.84, 138.51, 136.91, 131.25, 130.91, 130.65, 128.23, 128.14, 127.93, 126.78, 126.48, 126.12, 104.53, 88.21, 79.97, 55.55, 51.96, 50.55, 43.05, 42.90, 42.28, 40.54, 39.91, 39.18, 35.36, 34.61, 33.72, 29.85, 29.33, 29.13, 25.84, 20.77.
Compound 3.3:

Test tube equipped with stir bar was charged with 2,2-dimethylyclohex-3-en-1-one (1 eq., prepared in five steps according to *Chem. Asian J.* **2015**, *10*, 903) and THF (c = 0.1 M) under Ar atmosphere and cooled to −78 °C. Next, LiHMDS (1.0 M soln in THF, 1.2 eq.) was added dropwise and the resulting yellow solution was stirred for 45 min at −78 °C, followed by addition of freshly recrystallized NBS (1.5 eq.). The reaction mixture was the stirred for 30 min, then allowed to reach room temperature and stirred for additional 30 min. The reaction mixture was quenched with sat. aq. NH₄Cl and Na₂S₂O₃, extracted with Et₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (5% Et₂O in hexanes) to afford compound **3.3** in 73% yield.

**Physical state:** yellow oil

**¹H NMR** (400 MHz, CDCl₃): δ 5.71–5.54 (m, 2H), 4.90 (dd, J = 9.7, 6.6 Hz, 1H), 3.09–2.99 (m, 1H), 2.88–2.78 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H).
**Compound 3.4:**

Test tube equipped with stir bar was charged with ketone 2.20 (1.0 eq.), bromoketone 3.3 (10 eq.) and THF (c = 0.2 M) under Ar atmosphere and cooled to –78 ºC. Next, SmI₂ (0.06 M in THF, 25 eq.) was added dropwise via syringe pump over 30 min. The reaction mixture was then stirred for 30 min at –78 ºC and quenched at that temperature with aq. NH₄Cl, warmed to room temperature, extracted with Et₂O and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (10→20% EtOAc in hexanes) to afford compound 3.4 in 24% yield.

**Physical state:** thin white film

$$^{1}H \text{ NMR (400 MHz, CDCl}_3): \delta \ 6.01 \ (d, J = 2.1 \ Hz, 1H), \ 5.98 \ – \ 5.90 \ (m, 2H), \ 4.80 \ (ddt, J = 3.2, 2.2, 1.1 \ Hz, 1H), \ 4.73 \ (d, J = 2.3 \ Hz, 1H), \ 3.16 \ (s, 3H), \ 2.87 \ – \ 2.86 \ (m, 1H), \ 2.66 \ (s, 1H), \ 2.46 \ (dd, J = 16.3, 2.7 \ Hz, 1H), \ 2.30 \ (dt, J = 17.6, 2.8 \ Hz, 1H), \ 2.22 \ (dd, J = 10.3, 2.8 Hz, 1H), \ 2.00 \ (dd, J = 16.2, 6.5 \ Hz, 1H), \ 1.94 \ – \ 1.82 \ (m, 2H), \ 1.70 \ (ddd, J = 10.5, 5.5, 1.9 Hz, 1H), \ 1.48 \ (dt, J = 12.2, 2.5 \ Hz, 1H), \ 1.40 \ – \ 1.34 \ (m, 1H), \ 1.17 \ (s, 3H), 1.07 \ (s, 3H).$$

$$^{13}C \text{ NMR (151 MHz, CDCl}_3): \delta \ 218.97, \ 152.67, 128.05, 126.82, 104.89, 88.59, 83.20, 52.84, 50.91, 44.35, 43.09, 37.25, 37.19, 35.52, 32.51, 29.25, 27.21, 24.70.$$
**Compound 3.7 and 3.8:**

![Compound 3.7](image1.png) ![Compound 3.8](image2.png)

Test tube equipped with stir bar was charged with silyl enol ether 3.6 (1.5 eq.) and THF (c = 0.2 M) under Ar atmosphere and cooled to –78 °C. Next, t-BuLi (1.6 M in pentane, 3.0 eq.) was added dropwise and the reaction mixture was then stirred for 30 min at –78 °C. Ketone 2.20 (1.0 eq.), dissolved in minimal amount of THF, was then added dropwise and the resulting reaction mixture was stirred for 1 h at –78 °C and 30 min at room temperature. The reaction mixture was then quenched with aq. HCl (1 M), extracted with Et₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (5→20% EtOAc in hexanes) to afford compound 3.7 in 23% yield and compound 3.8 in 46% yield.

Data for compound 3.7:

**Physical state:** colorless oil

**1H NMR** (600 MHz, CDCl₃): δ 6.50 (s, 1H), 6.48 (d, J = 1.8 Hz, 1H), 4.85 (ddt, J = 3.2, 2.2, 1.0 Hz, 1H), 4.80 (t, J = 1.8 Hz, 1H), 3.22 (s, 3H), 2.70 (d, J = 5.1 Hz, 1H), 2.59 (dt, J = 16.1, 7.5 Hz, 1H), 2.44 – 2.26 (m, 3H), 2.18 (dq, J = 17.3, 2.3 Hz, 1H), 1.87 – 1.80 (m, 3H), 1.74 (ddd, J = 10.4, 5.5, 1.9 Hz, 1H), 1.59 – 1.47 (m, 1H), 1.38 (ddp, J = 9.1, 4.2, 2.0 Hz, 1H), 1.21 (s, 3H), 1.15 (s, 3H).

**13C NMR** (151 MHz, CDCl₃): ¹³C NMR (126 MHz, DMSO) δ 204.37, 154.80, 152.55, 135.40, 105.47, 88.66, 81.13, 52.00, 43.03, 38.05, 36.22, 35.70, 34.48, 33.59, 31.26, 29.15, 28.71, 27.98.
Data for compound 3.8:

**Physical state:** colorless oil

**$^1H$ NMR** (600 MHz, CDCl$_3$): $\delta$ 6.62 (s, 1H), 6.47 (d, $J = 1.0$ Hz, 1H), 4.85 (dt, $J = 4.1$, 2.2, 1.1 Hz, 2H), 3.23 (s, 3H), 3.02 – 2.89 (m, 1H), 2.71 (s, 1H), 2.64 (dt, $J = 15.7$, 7.5 Hz, 1H), 2.47 – 2.34 (m, 2H), 1.95 – 1.78 (m, 3H), 1.67 – 1.54 (m, 3H), 1.35 (dd, $J = 11.5$, 2.4 Hz, 1H), 1.23 (s, 3H), 1.15 (s, 3H).

**$^{13}C$ NMR** (151 MHz, CDCl$_3$): $\delta$ 204.01, 154.87, 152.40, 136.81, 105.84, 88.32, 81.70, 52.20, 42.69, 36.93, 36.11, 35.89, 33.69, 33.63, 33.60, 28.61, 28.11.
**Compound 3.9:**

![Compound 3.9]

Test tube equipped with stir bar was charged with compound 3.7 (1.5 eq.), TsOH (0.3 eq.) and PhMe (c = 0.1 M) under Ar atmosphere. The obtained reaction mixture was then stirred vigorously for 1.5 h at 70 ºC. The reaction mixture was allowed to reach room temperature, then quenched with aq. NaHCO$_3$, extracted with Et$_2$O, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (20% EtOAc in hexanes) to afford compound 3.9 in 67% yield.

**Physical state:** white solid

$^1$H NMR (600 MHz, CDCl$_3$): δ 6.61 (t, J = 4.1 Hz, 1H), 5.54 (t, J = 1.8 Hz, 1H), 2.69 (hept, J = 2.6 Hz, 1H), 2.49 (dddd, J = 19.5, 7.4, 5.5, 3.9 Hz, 1H), 2.44 – 2.37 (m, 1H), 2.24 (dt, J = 18.0, 2.7 Hz, 1H), 2.05 (dd, J = 17.8, 2.6 Hz, 1H), 1.93 – 1.86 (m, 2H), 1.84 (d, J = 1.7 Hz, 3H), 1.73 – 1.67 (m, 1H), 1.65 – 1.54 (m, 3H), 1.18 (s, 3H), 1.11 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 211.71, 202.70, 143.35, 141.61, 137.74, 126.24, 54.62, 41.71, 41.14, 37.66, 36.05, 28.18, 24.39, 24.26, 24.19, 23.55, 20.22.
**Compound 3.10:**

![Compound 3.10](image)

Test tube equipped with stir bar was charged with compound **3.8** (1.5 eq.), TsOH (0.3 eq.) and PhMe (c = 0.1 M) under Ar atmosphere. The obtained reaction mixture was then stirred vigorously for 1.5 h at 70 °C. The reaction mixture was allowed to reach room temperature, then quenched with aq. NaHCO₃, extracted with Et₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (20% EtOAc in hexanes) to afford compound **3.10** in 65% yield.

**Physical state:** white solid

**¹H NMR** (600 MHz, CDCl₃): δ 6.70 (t, J = 4.1 Hz, 1H), 5.78 – 5.60 (m, 1H), 2.76 – 2.65 (m, 1H), 2.59 (dd, J = 11.2, 2.2 Hz, 1H), 2.49 (dddd, J = 19.4, 7.1, 5.5, 3.9 Hz, 1H), 2.39 (dddd, J = 19.4, 6.4, 5.5, 4.2 Hz, 1H), 2.15 (ddd, J = 13.1, 10.9, 3.9 Hz, 1H), 2.09 – 2.02 (m, 1H), 2.00 (d, J = 1.4 Hz, 3H), 1.87 (dt, J = 13.6, 6.0 Hz, 1H), 1.81 (ddd, J = 13.3, 7.1, 5.5 Hz, 1H), 1.72 (dddd, J = 13.2, 9.0, 4.8, 1.7 Hz, 1H), 1.67 – 1.56 (m, 1H), 1.42 (dd, J = 11.2, 4.3 Hz, 1H), 1.14 (s, 3H), 1.11 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ 203.27, 201.36, 168.69, 142.84, 139.41, 123.86, 58.82, 44.33, 43.06, 41.77, 36.01, 29.70, 29.68, 24.45, 24.18, 23.52, 23.10.
**Compound 3.11:**

Compound 3.11 was prepared *via* a modified literature procedure. A flame-dried 2 L two-neck round-bottom flask equipped with stir bar and reflux condenser was charged with NaH (36.3 g of 60% dispersion in mineral oil, 0.91 mol, 1.1 eq.) and THF (800 mL) under Ar. 2-methylcyclohexan-1-one (100 mL, 0.82 mol, 1.0 eq.) was added and the reaction mixture was refluxed for 1.5 h. HMDS (25.8 mL, 0.12 mol, 0.15 eq.) was added and the solution was refluxed for another 15 min. The reaction mixture was cooled to 0 °C and MeI (68.5 mL, 0.90 mol, 1.1 eq.) was added dropwise (CAUTION! Highly exothermic). After addition was complete, the reaction mixture was allowed to reach room temperature and then it was stirred for 3 h. The solvent was removed under reduced pressure (40 ºC, 210 mbar) and Et₂O (300 mL) was added to precipitate NaI which was removed by filtration. The reaction mixture was concentrated under reduced pressure (40 ºC, 210 mbar) and the obtained crude product was purified by distillation (62-64 ºC, 19 mbar) to afford 2,2-dimethylcyclohexanone (82 g, 79% yield) as a colorless liquid. The spectroscopic data was identical to the one reported in the literature.

A flame-dried 2 L round-bottom flask equipped with a stir bar was charged with 2,2-dimethylcyclohexanone (82 g, 0.65 mol, 1.0 eq.), CHCl₃ (813 mL) and then cooled to 0°C. Br₂ (33.4 mL, 0.65 mol, 1.0 eq.) in CHCl₃ (66.8 mL) was added dropwise over 1 h at 0 °C. The reaction mixture was stirred for 1 h at 0°C and then quenched with sat. aq. Na₂S₂O₃ (300 mL). The layers were separated and the aqueous phase was extracted with DCM (2 x 200 mL). Combined organic phases were washed with sat. aq. NaHCO₃ (300 mL), dried
over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was recrystallized from Et$_2$O/hexane to $\alpha$-bromo-dimethylcyclohexanone (93.2 g, 70% yield) as a white solid. The spectroscopic data was identical to the one reported in the literature$^5$.

A flame-dried 2 L round-bottom flask equipped with a stir bar was charged with $\alpha$-bromo-dimethylcyclohexanone (93 g, 0.45 mol, 1.0 eq.), DMF (670 mL) and MgO (23.6 g, 0.59 mol, 1.3 eq.) under Ar. The reaction mixture was stirred vigorously at 140 °C for 3 h. The reaction mixture was then allowed to cool to room temperature, filtered and Et$_2$O (1 L) was added. The organic phase was washed with brine (3 x 300 mL), sat. aq. NaHCO$_3$ (300 mL), then dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by distillation to afford dimethylcyclohexenone (27.4 g, 49% yield) as a colorless liquid. The spectroscopic data was identical to the one reported in the literature$^5$.

A flame-dried 1 L round-bottom flask equipped with a stir bar was charged with dimethylcyclohexenone (27.4 g, 0.22 mol, 1.0 eq.), pyridine (220 mL) and CCl$_4$ (220 mL). Iodine (112 g, 0.44 mol, 2.0 eq.), dissolved in pyridine:CCl$_4$ (1:1) (440 mL), was added slowly to the reaction mixture and then stirred for 12 h at room temperature. The reaction mixture was then quenched with sat. aq. Na$_2$S$_2$O$_3$ (300 mL) and diluted with Et$_2$O (400 mL). Layers were separated and organic phase was washed with 4 M aq. HCl (4 x 400 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Crude product was purified by distillation (75 °C, 1 mbar) to afford 3.11 (41 g, 75% yield) as a viscous orange oil. The spectroscopic data was identical to the one reported in the literature$^5$. 

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Compounds 3.14a, 3.14b, 3.15 and 3.16:

A flame-dried 1 L round-bottom flask equipped with a stir bar was charged with α-iodo enone 3.11 (16.4 g, 65.7 mmol, 1.50 eq.), toluene (400 mL) under Ar and then cooled to −78 °C. i-PrMgCl•LiCl (50.5 mL of 1.3 M soln in THF, 65.7 mmol, 1.5 eq.) was added dropwise and the reaction mixture was stirred for 10 min at −78 °C. Ketone 2.20 (7.27 g, 43.8 mmol, 1.00 eq.) in toluene (20 mL), was added dropwise and the obtained solution was stirred for 1 h at −78°C. The reaction mixture was allowed to reach 0 ºC and aq. TsOH (81.4 mL of 3.5 M soln in H₂O, 285 mmol, 6.50 eq.) was added. The biphasic mixture was stirred vigorously for 16 h at 85 °C. The reaction mixture was allowed to cool to room temperature and then it was quenched with sat. aq. NaHCO₃ (200 mL) at 0 ºC and diluted with Et₂O (100 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 200 mL). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (0→20% EtOAc in hexanes) to afford 3.15 (5.07 g, 45% yield) as a yellow viscous oil and 3.16 (2.47 g, 22%) as a white solid.
Data for compound 3.15:

**Physical state:** yellow viscous oil that occasionally solidifies to a white solid.

**TLC:** Rf = 0.35 (20% EtOAc in hexanes).

**$^1$H NMR** (600 MHz, CDCl₃): $\delta$ 6.61 (t, $J = 4.1$ Hz, 1H), 5.53 (s, 1H), 2.69 (sextet, $J = 2.6$ Hz, 1H), 2.48 (dddd, $J = 19.5$, 7.4, 5.5, 4.0 Hz, 1H), 2.41 (dtd, $J = 19.5$, 5.8, 4.3 Hz, 1H), 2.23 (dt, $J = 17.9$, 2.6 Hz, 1H), 2.05 (dd, $J = 17.9$, 2.6 Hz, 1H), 1.91–1.82 (m, 3H), 1.84 (d, $J = 1.7$ Hz, 3H), 1.72–1.68 (m, 1H), 1.60–1.59 (m, 2H), 1.17 (s, 3H), 1.11 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl₃): $\delta$ 211.66, 202.68, 143.32, 141.61, 137.76, 126.25, 54.64, 41.72, 41.15, 37.68, 36.07, 28.20, 24.40, 24.27, 24.21, 23.56, 20.22.

**HRMS (ESI-TOF):** Calcd for C₁₇H₂₅O₂ [M+H]$^+$: 259.1692, found 259.1692.

**Optical Rotation:** $[\alpha]_{D}^{23} = +46.2^\circ$ (c 1.00, CHCl₃).
X-ray crystal structure of 3.15. For more information, see attached CIF file.
Data for compound 3.16:

**Physical state:** white solid.

**TLC:** Rf = 0.20 (20% EtOAc in hexanes).

**$^1$H NMR** (600 MHz, CDCl$_3$): $\delta$ 6.70 (t, $J$ = 4.1 Hz, 1H), 5.72 (s, 1H), 2.69 (dd, $J$ = 6.2, 4.4 Hz, 1H), 2.59 (d, $J$ = 11.1 Hz, 1H), 2.49 (dddd, $J$ = 19.4, 7.1, 5.5, 4.0 Hz, 1H), 2.39 (ddddd, $J$ = 19.5, 6.4, 5.5, 4.2 Hz, 1H), 2.15 (ddd, $J$ = 13.1, 10.9, 3.9 Hz, 1H), 2.05 (ddddd, $J$ = 12.3, 10.9, 6.3, 4.7 Hz, 1H), 2.00 (d, $J$ = 1.3 Hz, 2H), 1.87 (dt, $J$ = 13.6, 6.0 Hz, 1H), 1.81 (ddd, $J$ = 13.3, 7.3, 5.7 Hz, 1H), 1.72 (ddddd, $J$ = 13.3, 9.0, 4.6, 1.7 Hz, 1H), 1.63 (ddddd, $J$ = 12.4, 9.0, 3.7, 2.1 Hz, 1H), 1.14 (s, 3H), 1.11 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$): $\delta$ 203.26, 201.33, 168.64, 142.81, 139.44, 123.88, 58.84, 44.34, 43.07, 41.78, 36.03, 29.72, 29.70, 24.46, 24.19, 23.52, 23.09.

**HRMS** (ESI-TOF): Calcd for C$_{17}$H$_{23}$O$_2$ [M+H]$^+$: 259.1692, found 259.1692.

**Optical Rotation:** $[\alpha]^{23}_D = +81.3^\circ$ (c 1.00, CHCl$_3$).
X-ray crystal structure of 3.16. For more information, see attached CIF file.
Data for compound **3.14a (major)**:

Compound **3.14a** was isolated for characterization purposes by taking an aliquot from the reaction mixture and quenching it with sat. aq. NH₄Cl, followed by standard work up and purification by PTLC (20% Et₂O in hexanes).

**Physical state:** colorless oil.

**TLC:** Rᵣ = 0.60 (20% EtOAc in hexanes).

**¹H NMR** (600 MHz, CDCl₃): δ 6.71 (t, J = 3.8 Hz, 1H), 6.66 (d, J = 1.7 Hz, 1H), 4.84 (ddt, J = 3.0, 2.0, 1.0 Hz, 1H), 4.79 (bs, 1H), 3.19 (s, 3H), 2.69 (t, J = 4.9 Hz, 1H), 2.48 (dddd, J = 19.7, 8.6, 5.8, 3.7 Hz, 1H), 2.38 (ddt, J = 19.7, 5.8, 4.5 Hz, 1H), 2.34 (dt, J = 12.4, 2.5 Hz, 1H), 2.31 (t, J = 2.9 Hz, 1H), 2.2–2.18 (m, 1H), 1.87–1.74 (m, 5H), 1.56–1.53 (m, 1H), 1.41–1.37 (m, 1H), 1.13 (s, 3H), 1.08 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ 210.03, 152.73, 142.67, 136.80, 105.43, 88.65, 81.49, 51.38, 42.95, 42.66, 37.42, 36.23, 34.22, 31.28, 29.25, 24.50, 23.99, 23.43.


**Optical Rotation:** [α]ᵢ²³ = +27.3° (c 1.00, CHCl₃).
Data for compound **3.14b (minor)**:

Compound **3.14b** was isolated for characterization purposes by taking an aliquot from the reaction mixture and quenching it with aq. sat. NH₄Cl, followed by standard work up and purification by PTLC (20% Et₂O in hexanes).

**Physical state:** white solid.

**TLC:** $R_f = 0.52$ (20% EtOAc in hexanes).

$^1$H NMR (600 MHz, CDCl₃): δ 6.83 (s, 1H), 6.67–6.66 (m, 1H), 4.85 (ddt, $J = 4.2, 2.1, 1.0$ Hz, 2H), 3.17 (s, 3H), 2.92 (dddt, $J = 17.3, 3.2, 2.2, 1.1$ Hz, 1H), 2.71–2.70 (m, 1H), 2.51 (dddd, $J = 19.6, 9.5, 5.8, 3.6$ Hz, 1H), 2.42 (dt, $J = 17.2, 2.7$ Hz, 1H), 2.39–2.34 (m, 1H), 1.94–1.91 (m, 1H), 1.90–1.85 (m, 2H), 1.78 (dddd, $J = 13.7, 5.7, 3.6, 1.1$ Hz, 1H), 1.66–1.57 (m, 3H), 1.36 (dd, $J = 11.4, 2.4$ Hz, 1H), 1.16 (s, 3H), 1.08 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl₃) δ 209.59, 152.54, 142.66, 138.21, 105.82, 88.38, 82.02, 51.28, 42.64, 36.59, 36.10, 33.63, 33.53, 33.06, 24.55, 23.47, 23.41.


**Optical Rotation:** $[\alpha]_D^{23} = −61.9^\circ$ (c 1.00, CHCl₃).
X-ray crystal structure of 3.14b (minor). For more information, see attached CIF file.
Compound 3.17:

A flame-dried 25 mL round-bottom flask equipped with stir bar was charged with ketone 3.15 (500 mg, 1.94 mmol, 1.0 eq.) and TMSCN (1.0 mL, 12.7 mmol, 6.5 eq.) under Ar. Next, TMSOTf (0.35 mL, 1.94 mmol, 1.0 eq.) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. aq. NaHCO₃ (5 mL), extracted with Et₂O (3 x 5 mL), dried over Na₂SO₄, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (30% EtOAc in hexanes) to afford cyanohydrin 3.17 (442 mg, 80% yield).

Notes: A TMS-protected version of cyanohydrin 3.17 could be isolated in identical yield by quenching the reaction mixture with 10 eq. of Et₃N, followed by sat. aq. NaHCO₃.

Physical state: white solid.

¹H NMR (600 MHz, CDCl₃): δ 7.03 (t, J = 4.0 Hz, 1H), 6.59 (s, 1H), 5.29 (s, 1H), 2.59–2.56 (m, 2H), 2.19 (dd, J = 13.8, 1.9Hz, 1H), 2.11 (t, J = 8.9 Hz, 1H), 1.98 (dt, J = 13.9, 7.3 Hz, 1H), 1.86–1.84 (m, 2H), 1.83 (d, J = 1.3 Hz, 3H), 1.65 (td, J = 9.0, 1.8 Hz, 1H), 1.28–1.25 (m, 3H), 1.18 (s, 3H), 1.16 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 209.49, 150.14, 143.40, 138.54, 122.30, 121.28, 75.85, 48.73, 44.00, 42.50, 35.73, 35.04, 27.90, 25.50, 24.27, 24.18, 23.45, 20.36.
X-ray crystal structure of 3.17 (without TMS). For more information, see attached CIF file.
Compound 3.19:

A flame-dried 25 mL round-bottom flask equipped with stir bar was charged with cyanohydrin 3.17 (1.0 eq.) and 1:1 EtOH:H₂O solvent mixture (c = 0.1 M). Next, Parkins catalyst (0.05 eq.) was added and the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was quenched with sat. aq. NaHCO₃, extracted with Et₂O, dried over Na₂SO₄, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (50% EtOAc in hexanes) to afford amide 3.17 (40% yield). The remaining mass balance mainly consisted of starting material 3.15.

Physical state: white solid.

¹H NMR (600 MHz, CDCl₃): δ 6.96 (s, 1H), 6.91 (t, J = 4.1 Hz, 1H), 6.25 (s, 1H), 5.60 (s, 1H), 5.49 (s, 1H), 2.69 (ddd, J = 12.4, 9.3, 3.6 Hz, 1H), 2.52 (s, 1H), 2.46 (ddt, J = 17.6, 9.3, 4.9, Hz, 2H), 2.17 (dd, J = 13.0, 1.7 Hz, 1H), 1.84 (d, J = 1.4 Hz, 3H), 1.82 (dd, J = 6.7, 5.5 Hz, 2H), 1.73 (dt, J = 11.8, 6.0, 3.4 Hz, 1H), 1.51 (dt, J = 13.1, 3.4 Hz, 1H), 1.25–1.21 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H).
X-ray crystal structure of 3.19. For more information, see attached CIF file.
Compound 3.21:

A flame-dried test tube equipped with a stir bar was charged with ketone 3.15 (33.0 mg, 0.127 mmol, 1.00 eq.), THF (0.6 mL) and DMPU (0.3 mL, freshly distilled from CaH$_2$) under Ar and then cooled to $-45 \, ^\circ$C (m-xylene/dry ice bath). NaHMDS (0.165 mL of 1 M soln in THF, 0.165 mmol, 1.30 eq.) was added dropwise and the obtained solution was stirred for 1 h 30 min at $-45 \, ^\circ$C. A separate flame-dried 25 mL two-neck round-bottom flask was charged with paraformaldehyde (38.1 mg, 1.27 mmol, 10.0 eq.) and heated to 140 $^\circ$C. The generated formaldehyde gas was directly bubbled through the enolate solution using PTFE tubing and positive pressure of Ar. After all of the paraformaldehyde has been transferred, the reaction mixture was stirred vigorously for 30 min at $-45 \, ^\circ$C. The reaction mixture was quenched with sat. aq. NH$_4$Cl (1.0 mL), sat. aq. NaHSO$_3$ (1.0 mL) and diluted with Et$_2$O (1.0 mL). The layers were separated and the aqueous phase was extracted with Et$_2$O (3 x 1.0 mL). Combined organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (10$\rightarrow$30% EtOAc in hexanes) to afford compound 3.21 (27 mg, 74% yield) and compound 3.20 (5 mg, 13% yield) as a 1:1 mixture of diastereoisomers.

Physical state: white solid.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.98 (s, 1H), 6.65 (d, $J = 2.0 \, Hz$, 1H), 5.46 (s, 1H), 3.73 (dd, $J = 10.3$, 6.0 Hz, 1H), 3.64 (dd, $J = 10.3$, 7.2 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.71 (q, $J = 2.7 \, Hz$, 1H), 2.27 (s, 2H), 2.24 (t, $J = 2.7 \, Hz$, 1H), 2.07 (dd, $J = 17.9$, 2.5 Hz, 1H), 1.95
1H NMR (600 MHz, CDCl₃): δ 5.60 (s, 1H), 3.36 (d, J = 11.1 Hz, 1H), 2.64 (q, J = 2.6 Hz, 1H), 2.23–2.17 (m, 1H), 2.10–2.07 (m, 2H), 1.90 (dt, J = 13.3, 4.2 Hz, 1H), 1.86–1.77 (m, 4H), 1.83 (d, J = 1.6 Hz, 3H), 1.62–1.68 (m, 2H), 1.29 (s, 3H), 1.09–1.04 (m, 1H), 1.04 (s, 3H), 0.74 (s, 9H).

13C NMR (151 MHz, CDCl₃): δ 217.93, 211.03, 145.53, 124.13, 54.95, 48.82, 46.26, 44.56, 39.33, 37.22, 32.80, 25.74, 25.35, 24.66, 24.31, 23.81, 20.23, 0.261.
X-ray crystal structure of 3.22. For more information, see attached CIF file.
**Compound 3.24:**

A flame-dried test tube equipped with stir bar was charged with epoxide 3.23 (1.0 eq.), THF and DMPU (c = 0.1 M) under atmosphere of Ar. Next, NaHMDS (1 M soln. in THF, 1.5 eq.) was added dropwise at –45 °C and the reaction mixture was stirred for 1 h at –78 °C. Paraformaldehyde gas (10 eq.), obtained by heating solid paraformaldehyde at 160 °C, was passed through the reaction mixture at –45 °C via small cannula under positive pressure of Ar. The reaction mixture was quenched with sat. aq. NH₄Cl, extracted with Et₂O, dried over Na₂SO₄, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (25% EtOAc in hexanes) to afford compound 3.24 (40% yield).

**Physical state:** white solid.

**¹H NMR** (600 MHz, CDCl₃): δ 6.63 (t, J = 4.1 Hz, 1H), 4.57 (s, 1H), 2.73 (s, 1H), 2.47 (ddddd, J = 19.7, 7.5, 5.6, 3.9 Hz, 1H), 2.41 (q, J = 4.4 Hz, 1H), 2.39–2.35 (m, 2H), 2.31–2.25 (m, 1H), 2.15–2.09 (m, 1H), 1.97 (d, J = 2.3 Hz, 1H), 1.93 (dq, J = 10.7, 3.5 Hz, 1H), 1.87–1.78 (m, 3H), 1.52–1.47 (m, 1H), 1.42 (s, 3H), 1.15 (s, 3H), 1.08 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ 210.16, 203.65, 147.14, 135.83, 75.77, 60.54, 54.31, 41.84, 40.13, 35.90, 35.84, 28.17, 24.47, 24.10, 17.99, 17.14.
X-ray crystal structure of 3.24. For more information, see attached CIF file.
Compounds 3.20a and 3.20b:

A flame-dried 1 L three-neck round-bottom flask equipped with a stir bar was charged with ketone 3.15 (3.28 g, 12.7 mmol, 1.00 eq.), THF (65 mL) and DMPU (25 mL, freshly distilled from CaH₂) under Ar and then cooled to −45 °C (m-xylene/dry ice bath). NaHMDS (16.5 mL of 1 M soln in THF, 16.5 mmol, 1.30 eq.) was added dropwise and the obtained solution was stirred for 1 h 30 min at −45 °C. LaCl₃•2LiCl (21.2 mL of 0.6 M soln in THF, 12.7 mmol, 1.00 eq.) was added dropwise, followed by DMPU (66 mL) and the reaction mixture was stirred for 20 min at −45 °C. A separate flame-dried 50 mL two-neck round-bottom flask was charged with paraformaldehyde (3.81 g, 127 mmol, 10.0 eq.) and heated to 140 °C. The generated formaldehyde gas was directly bubbled through the enolate solution using PTFE tubing and positive pressure of Ar. After all of the paraformaldehyde has been transferred (ca. 40 min), the reaction mixture was stirred vigorously for 30 min at −45 °C. The reaction mixture was quenched with sat. aq. NH₄Cl (200 mL), sat. aq. NaHSO₃ (50 mL) and diluted with Et₂O (150 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 150 mL). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by a preparative HPLC (column: Agilent Prep-C18, eluent: 5→50% MeCN in H₂O, flow rate: 60 mL/min, \( t_R(3.20b) = 21.4 \text{ min}, \ t_R(3.20a) = 22.9 \text{ min} \)) to afford 3.20a (2.05 g, 56% yield) as a white solid and the undesired diastereomer 3.20b (1.02 g, 28% yield) as a white solid.
Notes: Cracking paraformaldehyde at 140 °C was necessary to avoid clogging of the tubing on a larger scale (>0.5 g), since CH₂O gas was generated in a slower and more controlled rate compared to 160 °C (commonly employed temperature).

Data for compound 3.20a:

Physical state: white solid.

TLC: Rf = 0.22 (25% EtOAc in hexanes).

¹H NMR (600 MHz, CDCl₃): δ 6.03 (ddd, J = 10.4, 6.1, 2.5 Hz, 1H), 6.00–5.94 (m, 2H), 3.92 (d, J = 10.6 Hz, 1H), 3.82 (d, J = 10.6 Hz, 1H), 2.62 (dq, J = 5.1, 2.6 Hz, 1H), 2.59–2.55 (m, 1H), 2.38–2.37 (m, 1H), 2.13 (dd, J = 17.0, 6.0 Hz, 1H), 2.07–2.03 (m, 1H), 1.98 (dd, J = 18.3, 2.4 Hz, 1H), 1.85 (d, J = 1.7 Hz, 3H), 1.69–1.64 (m, 1H), 1.56–1.50 (m, 1H), 1.23 (s, 3H), 1.12 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 219.00, 211.88, 145.52, 129.60, 128.06, 121.58, 66.45, 44.50, 41.38, 38.97, 36.72, 27.41, 27.29, 26.09, 25.32, 20.76.


Optical Rotation: [α]D²³ = +141° (c 1.00, DCM).
X-ray crystal structure of 3.20a. For more information, see attached CIF file.
Data for compound **3.20b**:

**Physical state:** white solid.

**TLC:** Rf = 0.22 (25% EtOAc in hexanes).

**$^1$H NMR** (600 MHz, CDCl$_3$): δ 6.23 (s, 1H), 6.04 (ddd, $J$ = 10.4, 6.3, 2.4 Hz, 1H), 5.64 (dd, $J$ = 10.4, 2.9 Hz, 1H), 4.00 (dd, $J$ = 11.0, 6.4 Hz, 1H), 3.73 (dd, $J$ = 11.0, 3.3 Hz, 1H), 2.72 (dt, $J$ = 17.0, 2.8 Hz, 1H), 2.60 (dq, $J$ = 5.1, 2.7 Hz, 1H), 2.20 (br s, 1H), 2.13 (dd, $J$ = 16.9, 6.3 Hz, 1H), 2.04 (dt, $J$ = 18.1, 3.2 Hz, 1H), 1.98 (dd, $J$ = 18.1, 2.0 Hz, 1H), 1.88 (ddd, $J$ = 13.2, 10.5, 5.7 Hz, 1H), 1.84 (d, $J$ = 1.6 Hz, 3H), 1.78–1.70 (m, 2H), 1.52 (tdt, $J$ = 11.6, 5.4, 2.8 Hz, 1H), 1.24 (s, 3H), 1.13 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$) : δ 219.04, 210.25, 146.21, 129.97, 127.41, 121.66, 66.98, 62.90, 52.82, 44.48, 39.39, 38.98, 36.46, 27.12, 26.20, 25.57, 24.53, 20.79.

**HRMS** (ESI-TOF): Calcd for C$_{18}$H$_{25}$O$_3$ [M+H]$^+$: 289.1798, found 289.1800.

**Optical Rotation:** $[\alpha]_D^{23} = +57.3^\circ$ (c 1.00, DCM).
X-ray crystal structure of 3.20b. For more information, see attached CIF file.
Compound 3.25:

A flame-dried test tube equipped with stir bar was charged with ketone 3.20a (1.0 eq.) and TMSCN (7.0 eq.) under Ar. Next, TMSOTf (1.0 eq.) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with Et₃N, followed by sat. aq. NaHCO₃, extracted with Et₂O, dried over Na₂SO₄, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (20% Et₂O in hexanes) to afford compound 3.25 (86% yield).

Physical state: white solid.

¹H NMR (600 MHz, CDCl₃): δ 6.07 (dd, J = 10.5, 3.1 Hz, 1H), 5.97 (s, 1H), 5.88 (ddd, J = 10.5, 6.4, 1.8 Hz, 1H), 3.87 (d, J = 10.1 Hz, 1H), 3.54 (d, J = 10.1 Hz, 1H), 2.58 (d, J = 17.7 Hz, 1H), 2.44–2.41 (m, 1H), 2.17 (ddd, J = 13.2, 5.4, 2.6 Hz, 1H), 2.13 (dt, J = 9.8, 3.1 Hz, 1H), 1.90–1.86 (m, 1H), 1.85 (d, J = 1.6 Hz, 3H), 1.67 (tdd, J = 10.3, 3.3, 1.9 Hz, 1H), 1.59 (d, J = 13.2 Hz, 1H), 1.57–1.52 (m, 1H), 1.33–1.26 (m, 1H), 1.13 (s, 3H), 0.97 (s, 3H), 0.24 (s, 9H), 0.10 (s, 9H).

¹³C NMR (151 MHz, CDCl₃): δ 142.36, 129.78, 127.21, 125.13, 123.79, 116.40, 86.62, 64.32, 53.38, 53.34, 39.42, 38.72, 36.99, 35.50, 29.57, 24.84, 24.75, 21.35, 20.75, 2.89, 0.40.
X-ray crystal structure of 3.25. For more information, see attached CIF file.
Compound 3.26:

A flame-dried test tube equipped with stir bar was charged with ketone 3.20a (1.0 eq.) and TMSCN (7.0 eq.) under Ar. Next, iodine (0.3 eq.) was added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. aq. NaHCO₃, followed by sat. aq. Na₂S₂O₃, then extracted with Et₂O, dried over Na₂SO₄, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (10% Et₂O in hexanes) to afford compound 3.26 (53% yield).

Physical state: white solid.

¹H NMR (600 MHz, CDCl₃): δ 6.03 (quint, J = 4.7 Hz, 1H), 5.76–5.70 (m, 2H), 4.21 (d, J = 9.1 Hz, 1H), 3.84 (d, J = 9.1 Hz, 1H), 2.40–2.38 (m, 1H), 2.09–2.02 (m, 2H), 1.75–1.73 (m, 2H), 1.72 (d, J = 1.6 Hz, 3H), 1.65–1.60 (m, 1H), 1.58 (d, J = 12.7 Hz, 1H), 1.21–1.17 (m, 1H), 1.12 (s, 3H), 1.04 (s, 3H), 0.39 (s, 9H), 0.11 (s, 9H).

¹³C NMR (151 MHz, CDCl₃): δ 143.85, 131.23, 125.93, 124.20, 123.57, 116.53, 86.78, 65.02, 53.45, 53.21, 39.43, 38.74, 36.86, 35.52, 29.35, 24.95, 24.73, 21.74, 19.81, 2.91, –1.03.
X-ray crystal structure of 3.26. For more information, see attached CIF file.
Compound 3.27:

A flame-dried test tube equipped with stir bar was charged with ketone 3.20a (1.0 eq.) and TMSCN (7.0 eq.) under Ar. Next, CuOTf (0.5 eq.) was added and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was quenched with sat. aq. NaHCO₃, extracted with Et₂O, dried over Na₂SO₄, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (5% Et₂O in hexanes) to afford compound 3.27 (22% yield).

**Physical state:** colorless oil.

**¹H NMR** (600 MHz, CDCl₃): δ 5.90 (tdd, J = 9.2, 5.4, 3.7 Hz, 1H), 5.78 (m, 1H), 5.59 (m, 1H), 4.74 (s, 1H), 4.59 (s, 1H), 4.17 (d, J = 8.8 Hz, 1H), 3.82 (d, J = 8.8 Hz, 1H), 2.90 (t, J = 5.8 Hz, 1H), 2.41 (dt, J = 17.2, 2.6 Hz, 1H), 2.27–2.23 (m, 1H), 2.14 (ddd, J = 16.4, 8.8, 3.9 Hz, 1H), 2.02–1.96 (m, 1H), 1.94 (dd, J = 9.8, 4.7 Hz, 1H), 1.88–1.83 (m, 2H), 1.47–1.38 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ 214.23, 155.74, 151.34, 130.82, 125.60, 119.91, 108.35, 89.29, 76.84, 59.02, 44.03, 42.10, 39.73, 38.78, 36.70, 29.77, 25.701, 24.97.
**Compound 3.28:**

A flame-dried test tube equipped with stir bar was charged with ketone 3.20a (1.0 eq.) and TMSCN (7.0 eq.) under Ar. Next, Zn(OTf)$_2$ (0.5 eq.) was added and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with sat. aq. NaHCO$_3$, extracted with Et$_2$O, dried over Na$_2$SO$_4$, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (10% Et$_2$O in hexanes) to afford compound 3.28 (89% yield).

**Physical state:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.32 (d, $J = 10.0$ Hz, 1H), 6.07 (dt, $J = 9.7$, 4.8 Hz, 1H), 5.38 (s, 1H), 4.72 (d, $J = 9.5$ Hz, 1H), 3.89 (d, $J = 9.5$ Hz, 1H), 2.50–2.46 (m, 1H), 2.42–2.33 (m, 3H), 2.27 (dd, $J = 16.8$, 4.9 Hz, 1H), 1.80 (d, $J = 1.5$ Hz, 3H), 1.74–1.69 (m, 3H), 1.46–1.38 (m, 3H), 1.17 (s, 3H), 1.15 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 214.39, 144.66, 130.91, 128.83, 123.47, 122.89, 82.95, 80.38, 58.94, 56.88, 43.52, 42.57, 39.07, 35.10, 29.86, 25.18, 21.08, 20.03.
X-ray crystal structure of C1–C2 epoxide (for crystallinity) of 3.28. For more information, see attached CIF file.
Compound 3.30:

A flame-dried test tube equipped with stir bar was charged with bisepoxide 3.29 (1.0 eq.) and TMSCN (7.0 eq.) under Ar. Next, ZnI$_2$ (0.5 eq.) was added and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with sat. aq. NaHCO$_3$, extracted with Et$_2$O, dried over Na$_2$SO$_4$, concentrated under reduced pressure. Obtained crude product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford compound 3.30 (51% yield).

Physical state: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 4.73 (d, $J$ = 9.5 Hz, 1H), 4.05 (d, $J$ = 7.9 Hz, 1H), 3.93 (ddd, $J$ = 12.8, 8.0, 3.7 Hz, 1H), 3.35 (s, 1H), 2.41 (ddd, $J$ = 14.6, 4.3, 2.8 Hz, 1H), 2.12–2.09 (m, 2H), 1.66–1.67 (m, 3H), 1.48–1.41 (m, 3H), 1.40 (s, 3H), 1.23–1.12 (m, 4H), 1.09 (s, 6H), 0.17 (s, 9H), 0.15 (s, 9H).
X-ray crystal structure of 3.30. For more information, see attached CIF file.
Compounds 3.32, 3.33 and 3.34:

A flame-dried 250 mL round-bottom flask equipped with a stir bar was charged with compound 3.20a (1.94 g, 6.74 mmol, 1.00 eq.), MeOH (6 mL), HC(OMe)_3 (28 mL) and TFA (0.26 mL, 3.37 mmol, 0.50 eq.) under Ar. The reaction mixture was stirred for 3 h at 60 ºC, then diluted with toluene (50 mL) and concentrated under reduced pressure. The reaction mixture was azeotroped with toluene (2 x 50 mL) and then redissolved in DCM (67 mL) under Ar. Zn(OTf)_2 (4.90 g, 13.5 mmol, 2.00 eq.) was added and the obtained heterogeneous mixture was stirred vigorously for 10 min at room temperature. LiBH_4 (14.3 mL of 4 M soln in THF, 57.3 mmol, 8.50 eq.) was added dropwise via syringe pump over 2 h. After addition of LiBH_4 was complete, the obtained colorless homogeneous solution was stirred for 48 h at room temperature. The reaction mixture was cooled to 0 ºC and quenched with MeOH (10 mL), followed by pH = 7.4 aq. phosphate buffer (1 M, 100 mL) and then it was stirred vigorously for 1 h at room temperature. The layers were separated and the aqueous phase was extracted with DCM (3 x 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (0→20% Et_2O in hexanes with 2% Et_3N) to afford alcohol 3.34 (1.27 g, 62% yield) and epimer 3.33 (0.425 g, 21% yield).
Data for compound **3.34**:

**Physical state:** white crystalline solid.

**TLC:** Rf = 0.17 (10% Et<sub>2</sub>O in hexanes).

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6**): δ 6.51 (t, J = 1.7 Hz, 1H), 6.43 (dd, J = 10.3, 3.0 Hz, 1H), 5.46 (ddd, J = 10.4, 6.2, 1.9 Hz, 1H), 4.80 (d, J = 8.7 Hz, 1H), 3.76 (d, J = 3.2 Hz, 1H), 3.50 (d, J = 8.7 Hz, 1H), 3.08 (s, 3H), 2.35 (ddd, J = 11.3, 9.1, 1.9 Hz, 1H), 2.19 (tq, J = 3.7, 1.7 Hz, 1H), 1.85–1.78 (m, 2H), 1.71 (d, J = 1.7 Hz, 3H), 1.70–1.65 (m, 1H), 1.57–1.51 (m, 2H), 1.43 (d, J = 3.7 Hz, 1H), 1.25 (ddddd, J = 12.5, 9.3, 4.3, 2.2 Hz, 1H), 0.96 (td, J = 11.3, 6.2 Hz, 1H), 0.85 (s, 3H), 0.79 (s, 3H).

**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6**): δ 142.49, 135.88, 128.71, 122.42, 111.03, 77.00, 72.79, 57.39, 50.41, 47.38, 39.17, 37.29, 36.71, 35.56, 28.03, 25.76, 21.62, 20.19, 19.69.

**HRMS (ESI-TOF):** Calcd for C<sub>19</sub>H<sub>29</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 305.2111, found 305.2112.

**Optical Rotation:** [α]<sub>D</sub><sup>23</sup> = –24° (c 0.64, DCM).
X-ray crystal structure of 3.34. For more information, see attached CIF file.
Data for compound 3.33:

**Physical state:** white crystalline solid.

**TLC:** Rf = 0.37 (10% Et₂O in hexanes).

**1H NMR** (600 MHz, C₆D₆): δ 6.66 (ddt, J = 10.7, 3.1, 1.5 Hz, 1H), 6.23 (t, J = 1.9 Hz, 1H), 5.61 (ddd, J = 10.6, 5.6, 2.0 Hz, 1H), 4.02 (d, J = 9.0 Hz, 1H), 3.66 (d, J = 9.0 Hz, 1H), 3.61 (dd, J = 6.7, 1.8 Hz, 1H), 3.11 (s, 3H), 2.41 (t, 1H), 2.19 (dh, J = 3.9, 1.8 Hz, 1H), 2.10 (dt, J = 17.5, 2.5 Hz, 1H), 1.77 (dd, J = 12.2, 3.6 Hz, 1H), 1.70 (s, 3H), 1.65 (dddd, J = 10.0, 8.2, 5.2, 1.4 Hz, 1H), 1.53 (dt, J = 12.2, 2.2 Hz, 1H), 1.47–1.39 (m, 2H), 1.36–1.23 (m, 2H), 1.02 (s, 3H), 0.66 (s, 3H).

**13C NMR** (151 MHz, CDCl₃): δ 143.08, 131.98, 127.48, 124.59, 112.05, 80.31, 77.88, 56.87, 50.37, 47.78, 38.00, 37.19, 34.82, 34.50, 28.40, 26.46, 25.11, 22.68, 20.16.


**Optical Rotation:** [α]$_D^{23}$ = +11.4° (c 1.00, DCM).
X-ray crystal structure of 3.33. For more information, see attached CIF file.
Data for compound **3.32**:

Crude **3.32** was sufficiently pure to be fully characterized without any further purification.

**Physical state:** colorless oil.

**TLC:** $R_f = 0.51$ (10% EtOAc in hexanes).

$^1$H NMR (600 MHz, C$_6$D$_6$): $\delta$ 6.22 (dt, $J = 10.2$, 1.6 Hz, 1H), 5.87 (t, $J = 1.9$ Hz, 1H), 5.62 (dt, $J = 10.1$, 4.4 Hz, 1H), 5.01 (d, $J = 8.4$ Hz, 1H), 3.56 (d, $J = 8.4$ Hz, 1H), 3.03 (s, 3H), 2.47 (t, $J = 9.1$ Hz, 1H), 2.24–2.08 (m, 1H), 1.99 (ddd, $J = 17.0$, 4.5, 1.6 Hz, 1H), 1.87 (ddd, $J = 16.9$, 4.2, 1.6 Hz, 1H), 1.72 (dd, $J = 12.3$, 3.7 Hz, 1H), 1.62–1.57 (m, 1H), 1.54 (d, $J = 1.9$ Hz, 3H), 1.48 (dt, $J = 12.3$, 2.1 Hz, 1H), 1.28–1.15 (m, 2H), 1.12 (s, 3H), 1.08 (s, 3H).

$^{13}$C NMR (151 MHz, C$_6$D$_6$): $\delta$ 214.81, 142.43, 135.12, 127.73, 125.15, 113.54, 79.45, 59.08, 58.19, 47.72, 43.61, 39.32, 37.04, 36.83, 27.35, 26.04, 24.85, 22.20, 19.96.


**Optical Rotation:** $[\alpha]_D^{23} = -16^\circ$ (c 0.70, DCM).
Compound 3.36:

A 100 mL round-bottom flask equipped with a stir bar was charged with alcohol 3.34 (1.17 g, 3.85 mmol, 1.00 eq.), THF (15 mL), H₂O (0.14 mL, 7.7 mmol, 2.0 eq.) and p-TsOH·H₂O (37 mg, 0.193 mmol, 0.050 eq.). The reaction mixture was stirred at room temperature until full conversion was observed by TLC (ca. 2 h), then cooled to 0 ºC and charged with Et₃N (2.70 mL, 19.3 mmol, 5.0 eq.), DMAP (94 mg, 0.77 mmol, 0.20 eq.) and 3,5-dinitrobenzoyl chloride (3.11 g, 13.5 mmol, 3.50 eq.) dissolved in DCM (6 mL). The reaction mixture was stirred vigorously for 12 h at room temperature. The reaction mixture was cooled to 0 ºC and quenched with sat. aq. NaHCO₃ (20 mL) and diluted with Et₂O (20 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (15→25% Et₂O in hexanes) to afford 3.36 (1.62 g, 86% yield).

Physical state: white foam.

TLC: Rf = 0.21 (20% Et₂O in hexanes).

¹H NMR (600 MHz, CDCl₃): δ 9.19 (s, 1H), 9.09 (s, 2H), 5.97 (br s, 1H), 5.59 (d, J = 10.2 Hz, 1H), 5.41 (s, 1H), 5.37 (s, 1H), 4.85 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 3.72 (s, 1H), 2.70 (s, 1H), 2.27 (s, 2H), 2.10–1.83 (m, 4H), 1.96 (s, 2H), 1.87 (s, 3H), 1.61 (br s, 1H), 1.12 (s, 3H), 1.07 (s, 3H).
$^{13}$C NMR (151 MHz, CDCl$_3$) : $\delta$ 216.44, 162.30, 148.78, 147.91, 134.21, 131.02, 129.63, 127.98, 122.34, 121.31, 78.11, 66.70, 60.76, 47.46, 42.02, 39.69, 36.70, 35.27, 29.9, 26.22, 23.88, 20.65, 20.57.

HRMS (ESI-TOF): Calcd for C$_{25}$H$_{29}$N$_2$O$_8$ [M+H]$^+$: 485.1918, found 485.1918.

Optical Rotation: $[\alpha]_D^{23} = +18^\circ$ (c 0.52, DCM).
Compounds 3.37, 3.38, 3.39 and 3.40:

A flame-dried test tube equipped with a stir bar was charged with 3.36 (399 mg, 0.82 mmol, 1.00 eq.) and a 1:6 mixture of MeOH:HC(OMe)_3 (4.1 mL) under Ar. MsOH (5 x 27 L, 5 x 0.41 mmol, 5 x 0.50 eq.) was added in four portions (0.5 eq. every 4 h) and the reaction mixture was stirred for 20 h at 55 ºC. Next, Et₃N (0.5 mL) was added and the reaction mixture was stirred for 2 h at room temperature, then concentrated under reduced pressure and azeotroped with toluene (3 x 6 mL). TMSCN (0.51 mL, 4.1 mmol, 5.0 eq.) and ZnI₂ (79 mg, 0.25 mmol, 0.30 eq.) were added under Ar. The obtained reaction mixture was stirred neat at room temperature for 1 h and then THF (4 mL) and aq. LiOH (3.3 mL of 3 M soln in H₂O, 9.9 mmol, 12 eq.) were added sequentially. The reaction mixture was stirred vigorously for 3 h at room temperature, then cooled to 0 ºC and aq. HCl (2.7 mL of 6 M soln in H₂O, 16.2 mmol, 20 eq.) was added dropwise. The reaction mixture was stirred for 1 h at 65 ºC, then cooled to 0 ºC, quenched by transferring it to a 100 mL Erlenmeyer flask containing cold pH = 7.4 aq. phosphate buffer (1 M, 15 mL), followed by dilution with Et₂O (15 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0→20% Et₂O in hexanes) to afford 3.40 (203 mg, 82% yield).
Notes: It was found that MsOH was consumed under the reaction conditions:

\[
\text{MsOH} + \text{HC(OMe)}_3 \rightarrow \text{MsOMe} + \text{HCO}_2\text{Me}
\]

The esterification of MsOH proceeded at a rate faster than ketal 15 formation, hence, the reaction would stall once all MsOH was consumed. Adding MsOH in batches (0.5 eq. every 4 h) pushed the reaction to completion.

Although Et₃N is not a necessary reaction component, it is added to quench MsOMe, thus minimizing exposure to this carcinogen.

Data for compound 3.40:

Physical state: white crystalline solid.

TLC: \( R_f = 0.56 \) (20% EtOAc in hexanes).

\(^1\)H NMR (600 MHz, CDCl₃): \( \delta \) 5.85 (ddd, \( J = 9.8, 4.3, 3.3 \) Hz, 1H), 5.64 (dt, \( J = 9.8, 2.3 \) Hz, 1H), 5.49 (t, \( J = 1.7 \) Hz, 1H), 4.49 (d, \( J = 12.1 \) Hz, 1H), 4.13 (dd, \( J = 12.2, 1.8 \) Hz, 1H), 4.03 (d, \( J = 1.7 \) Hz, 1H), 2.82 (dd, \( J = 13.7, 3.5 \) Hz, 1H), 2.46 (tq, \( J = 3.7, 1.8 \) Hz, 1H), 2.31 (ddd, \( J = 19.1, 3.3, 2.4 \) Hz, 1H), 2.16 (ddd, \( J = 19.1, 4.2, 2.1 \) Hz, 1H), 1.83 (d, \( J = 1.5 \) Hz, 3H), 1.74 (ddd, \( J = 11.9, 9.3, 2.4 \) Hz, 1H), 1.54 (dddd, \( J = 12.6, 9.5, 5.3, 1.8 \) Hz, 1H), 1.48 (dt, \( J = 13.6, 2.4 \) Hz, 1H), 1.39 (dd, \( J = 12.0, 5.2 \) Hz, 1H), 1.32 (tdt, \( J = 11.7, 3.9, 2.5 \) Hz, 1H), 1.21 (s, 3H), 1.11 (s, 3H).

\(^{13}\)C NMR (151 MHz, CDCl₃): \( \delta \) 171.82, 145.07, 133.99, 122.97, 122.57, 91.29, 86.75, 69.60, 48.90, 45.83, 42.10, 36.01, 33.33, 32.78, 23.00, 22.63, 22.03, 19.95.


Optical Rotation: \([\alpha]_D^{23} = -41^\circ\) (c 0.46, MeOH).
X-ray crystal structure of 3.40. For more information, see attached CIF file.
Data for compound 3.37:

After evaporation of solvent a small amount of crude 3.37 was filtered through a short plug of silica (eluent: 20% Et₂O in hexanes with 1% Et₃N) to obtain pure sample for characterization purposes.

**Physical state:** colorless oil.

**TLC:** $R_f = 0.68$ (20% EtOAc in hexanes).

**¹H NMR** (600 MHz, C₆D₆): $\delta$ 8.75 (d, 1H), 8.60–8.29 (m, 1H), 6.19 (ddd, $J = 9.6, 3.1, 1.4$ Hz, 1H), 5.79 (t, $J = 1.6$ Hz, 1H), 5.60 (ddd, $J = 9.6, 5.3, 2.6$ Hz, 1H), 5.54 (d, $J = 10.0$ Hz, 1H), 5.03 (d, $J = 10.0$ Hz, 1H), 4.13 (s, 1H), 3.25 (s, 3H), 2.65 (q, $J = 10.9, 9.1, 1.9$ Hz, 1H), 2.21 (dt, $J = 18.9$, 2.8 Hz, 1H), 2.18 (dq, $J = 4.1, 1.9$ Hz, 1H), 2.00–1.92 (m, 2H), 1.79 (ddddd, $J = 12.4$, 8.9, 5.9, 1.5 Hz, 1H), 1.64 (d, $J = 1.7$ Hz, 3H), 1.53–1.46 (m, 2H), 1.33 (dddt, $J = 12.9$, 11.0, 4.0, 1.9 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H).

**¹³C NMR** (151 MHz, C₆D₆): $\delta$ 162.48, 148.30, 145.39, 133.69, 130.80, 129.83, 128.66, 126.57, 121.81, 112.30, 93.26, 69.79, 54.90, 49.09, 48.07, 41.51, 39.97, 37.17, 34.01, 32.39, 26.25, 24.34, 22.63, 19.83.


**Optical Rotation:** $[\alpha]_D^{23} = -21^\circ$ (c 0.36, DCM).
Data for compound 3.38:

Compound 3.38 was isolated for characterization purposes by taking an aliquot from the reaction mixture and quenching it with aq. sat. NaHCO₃, followed by standard work up and purification by PTLC (30% Et₂O in hexanes).

**Physical state:** white foam.

**TLC:** Rᵣ = 0.45 (20% EtOAc in hexanes).

**¹H NMR** (600 MHz, CDCl₃): \( \delta 9.23 \) (t, \( J = 2.2 \) Hz, 1H), 9.12 (d, \( J = 2.2 \) Hz, 2H), 6.09 (ddd, \( J = 9.7, 2.9, 1.5 \) Hz, 1H), 5.77 (ddd, \( J = 9.8, 5.1, 2.8 \) Hz, 1H), 5.53 (s, 1H), 5.29 (d, \( J = 11.3 \) Hz, 1H), 5.04 (d, \( J = 11.3 \) Hz, 1H), 2.64 (dd, \( J = 13.1, 4.3 \) Hz, 1H), 2.56–2.52 (m, 2H), 2.42 (dt, \( J = 19.0, 2.8 \) Hz, 1H), 2.24 (ddd, \( J = 19.0, 5.1, 1.6 \) Hz, 1H), 1.91 (ddddd, \( J = 13.0, 9.0, 6.1, 1.6 \) Hz, 1H), 1.87 (d, \( J = 1.6 \) Hz, 3H), 1.73–1.65 (m, 2H), 1.48 (dddd, \( J = 13.5, 11.3, 4.2, 2.1 \) Hz, 1H), 1.24 (s, 3H), 1.12 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃) : \( \delta 162.14, 148.86, 146.10, 133.93, 130.84, 129.49, 128.60, 124.31, 123.40, 122.55, 94.03, 81.35, 67.88, 53.79, 49.89, 46.20, 41.68, 35.55, 33.62, 32.10, 28.10, 24.01, 21.75, 19.71.


**Optical Rotation:** \([\alpha]_{D}^{23} = +30.7^\circ\) (c 0.43, DCM).
Data for compound 3.39:

Compound 3.39 was isolated for characterization purposes by taking an aliquot from the reaction mixture and quenching it with aq. sat. NaHCO₃, followed by standard work up and purification by PTLC (30% EtOAc in hexanes).

Data for compound 3.39:

**Physical state:** white crystalline solid.

**TLC:** R₉ = 0.26 (20% EtOAc in hexanes).

**¹H NMR** (600 MHz, CDCl₃): δ 5.81 (dt, J = 9.8, 3.7 Hz, 1H), 5.63 (dt, J = 9.7, 2.3 Hz, 1H), 5.50 (t, J = 1.8 Hz, 1H), 4.29 (d, J = 11.7 Hz, 1H), 4.04 (dd, J = 11.8, 1.7 Hz, 1H), 3.99 (d, J = 1.6 Hz, 1H), 3.05 (d, J = 13.4 Hz, 1H), 2.45 (tt, J = 3.9, 1.9 Hz, 1H), 2.30 (dt, J = 19.0, 2.9 Hz, 1H), 2.15 (ddd, J = 19.1, 4.2, 2.0 Hz, 1H), 1.83 (d, J = 1.7 Hz, 3H), 1.76 (t, J = 9.8 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.50 (dt, J = 13.4, 2.2 Hz, 1H), 1.30 (tdd, J = 13.7, 11.8, 7.2 Hz, 2H), 1.21 (s, 3H), 1.12 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ 169.36, 144.97, 133.40, 123.34, 123.32, 90.87, 85.80, 69.33, 48.88, 45.95, 42.25, 36.94, 36.36, 33.42, 32.93, 22.98, 21.73, 19.95.


**Optical Rotation:** [α]D²³ = −22° (c 0.1, MeOH).
Chapter 3 Appendix

NMR Spectra
\textbf{(updd) \textsuperscript{1}H NMR} (600 MHz, CDCl\textsubscript{3})
$^{13}$C NMR (151 MHz, CDCl$_3$)

Compound 3.2

![Chemical Structure Image]
$\text{H NMR (400 MHz, CDCl}_3)$

Compound 3.3

\[
\begin{array}{c}
\text{H} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]
1H NMR (600 MHz, CDCl3)
$^{13}C$ NMR (121 MHz, CDCl$_3$)

Compound 3.4
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 37

H (ppm)

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0

Me

HO

OME
$^{13}$C NMR (121 MHz, CDCl$_3$)

Compound 3.7
Compound 3.8

$^1$H MRI (600 MHz, CDCl₃)

$\delta$ 3.8
$^{13}C$ NMR (121 MHz, CDCl₃)

Compound 3.8

H(p)Me

OMe

HO
$^{13}$C NMR (121 MHz, CDCl₃)
Compound 3.10

$^1$H NMR (600 MHz, CDCl$_3$)

(peak (ppm))
$^1$H NMR (500 MHz, CDCl$_3$)

Me

Me

Compound 3.10

$^{13}$C NMR (121 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 3.14a
Compound 3.14

$^{13}$C NMR (151 MHz, CDCl$_3$)

- 210.03
- 152.73
- 142.67
- 136.80
- 105.43
- 88.65
- 81.49
- 51.38
- 42.95
- 42.86
- 37.42
- 36.23
- 34.22
- 31.28
- 29.25
- 24.50
- 23.99
- 23.43
$\text{Compound 3.1 4b}$

$\text{H NMR (600 MHz, CDCl}_3)$
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 3.15
$^1$H NMR (400 MHz, CDCl$_3$)
$\text{Me}$

$\text{Me}$

$\text{Me}$

$\text{O}$

$\text{Me}$

$\text{Me}$

$\text{Me}$

$\text{O}$

$\text{H NMR (600 MHz, CDCl}_3)$

$\delta$ NMR (600 MHz, CDCl$_3$)
Compound 3.16

$^{13}C$ NMR (151 MHz, CDCl$_3$)
\textbf{\textit{H} NMR (600 MHz, CDCl$_3$)  \\
Compound 3.17}
13C NMR (121 MHz, CDCl3)

Compound 3.17
$^{1}H$ NMR (600 MHz, CDCl$_3$)
\( ^1H (ppm) \)

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) \]

Compound 3.22

\[ \text{MeO} \]

\[ \text{TMS} \]
$^{13}$C NMR (121 MHz, CDCl$_3$)

Compound 3.22
Compound 3.24

$^1$H NMR (600 MHz, CDCl$_3$)
\[ \text{Compound 3.24} \]

$^{13}$C NMR (121 MHz, CDCl$_3$)

\[ \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{HO} \]
Compound 3.25

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (121 MHz, CDCl$_3$)

Compound 3.25
Compound 3.26

$^1$H NMR (600 MHz, CDCl₃)
^{1}H NMR (600 MHz, CDCl$_3$)

Compound 3.25

Me
TMS
NC
Me
Me

\( \text{(ppm)} \)
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 3.27

Me

Me
Compound 3,27

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 3.28
$^1\text{H} \text{NMR}$ (600 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 3.30
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 3.20a
$^{13}\text{C} \text{ NMR (151 MHz, CDCl}_3\text{)}$
$^1$H NMR (600 MHz, CDCl$_3$)

Compound 3.20b
$^{13}C$ NMR (151 MHz, CDCl$_3$)

Compound 3.20b
\[ ^1H \text{ NMR (600 MHz, CDCl}_3) \]

Compound 3.21

\[ (ppm) \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) \]
$\text{Compound 3.21}$

$^{13}C\text{NMR (151 MHz, CDCl}_3)$
Compound 3.32

$^{1}H$ NMR (600 MHz, CD$_6$D)

The diagram shows the NMR spectrum of Compound 3.32, with peaks at various ppm values.
$^{13}$C NMR (151 MHz, CD$_6$D$_6$)

Compound 3.32

\[
\begin{align*}
\text{OMe} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
\[ \text{Compound 3.33} \]

\[ \text{H NMR (600 MHz, C}_{6}\text{D}_{6}) \]
$^{13}$C NMR (151 MHz, CD$_6$D$_6$)

Compound 3.33

[Chemical structure image]
Compound 3.34

$^{1}H$ NMR (600 MHz, C$_6$D$_6$)
Compound 3.34

$^{13}$C NMR (151 MHz, CD$_6$)

- 142.49
- 135.88
- 128.71
- 122.42
- 111.03
- 77.00
- 72.79
- 57.39
- 50.41
- 47.38
- 38.17
- 37.29
- 36.71
- 35.56
- 28.03
- 25.76
- 21.62
- 20.19
- 19.69
Compound 3.36

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CD$_6$D)$^d$

Compound 3.37

DNBO

OMe

OMe

Me

Me

Me

Me

Me

Me
$^{13}$C NMR (151 MHz, CD$_6$D$_6$)

- 162.48
- 148.30
- 145.39
- 133.69
- 130.80
- 129.83
- 128.67
- 126.57
- 121.81
- 112.30
- 93.26
- 69.79
- 54.90
- 49.09
- 48.06
- 41.50
- 39.96
- 37.16
- 34.01
- 32.39
- 26.25
- 24.34
- 22.63
- 19.82
$\text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3$)
$^{13}C$ NMR (151 MHz, CDCl$_3$)

Compound 3.38

DNBO

CN

Me

Me

Me

Me
Compound 3.39

$^1$H NMR (600 MHz, CDCl$_3$)

- 3.48 ppm
- 5.38 ppm

Diagram of compound with structural representation.
\[ \text{Compound: } 3.39 \text{ ppm (151 MHz, CDCl}_3) \]

13C NMR (151 MHz, CDCl₃)
Compound 3.40

$^{1}H$ NMR (600 MHz, CDCl$_3$)
Compound 3.40

$^{13}$C NMR (151 MHz, CDCl$_3$)

O
O
Me
Me
Chapter 4

Completion of Total Synthesis of
(−)-Maoecrystal V
4.1 Completion of the synthesis

With the route to 3.40 established through resilience and determination, all the major challenges posed by the intricate molecular structure of maocrystal V had been conquered. Only transformation of two olefins into an enone and a ketone remained. It was reasoned that executing these transformations in a simultaneous manner would the most efficient way to accomplish such a task. Thus, lactone 3.40 was subjected to DMDO in acetone that resulted in clean diepoxidation to furnish 3.41a (major, confirmed by X-ray) and 3.41b (minor, confirmed by X-ray) as a 2:1 mixture of inconsequential diastereoisomers in essentially quantitative yield (Scheme 4.1). Both diepoxides were synthetically useful because the stereochemistry of the disubstituted epoxide

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

Scheme 4.1 Diepoxidation of 3.40 and subsequent epoxide manipulations
didn’t matter since it is going to be destroyed during the eventual transformation into an enone of maoecrystal V. Fortunately, the stereochemistry of trisubstituted epoxide on the [2.2.2]bicycle was the desired one for the subsequent planned transformation. It was envisioned that the trisubstituted epoxide upon treatment with Lewis acid would undergo stereospecific 1,2-hydride shift to form a methyl ketone. At the same time, the disubstituted epoxide would be ruptured to give halohydrin that could be potentially elaborated into the enone moiety. After a lot of experimentation, it was discovered that BiCl₃ was able to mediate such transformations simultaneously. In the case of the major diastereoisomer 3.41a, the desired halohydrin 3.42 was formed in essentially quantitative yield and correct regioselectivity of epoxide opening. Methyl ketone on the [2.2.2]bicycle was also formed exclusively as the desired stereoisomer suggesting that 1,2-hydride shift proceeded with complete inversion as expected. Unfortunately, in the case of minor diepoxide 3.41b resulted in inseparable 3:1 mixture of regioisomers 3.43 and 3.44 in a combined 93% yield favoring the undesired halohydrin 3.43. At this point optimization of this reaction was put on hold in order to investigate whenever it is possible to transform halohydrin into the enone moiety, thus completing the synthesis of maoecrystal V. If this approach would prove to be viable, then efforts to obtain exclusively the desired halohydrin from 3.41b would commence.

Chlorohydrin 3.42 was oxidized with PCC to provide α-chloroketone 3.45 in a modest but serviceable 43% yield. Only elimination of a chloride separated us from the victory, a transformation that seemed quite trivial (Scheme 4.2). Surprisingly, this chloride turned out to be remarkably resilient as a myriad of basic conditions, even with additives as such as Ag(I) salts, proved to be incapable of eliminating it. Only epimerization of C16 methyl group was achieved under harsher conditions but not even a trace of maoecrystal V was observed. Attempts to perform nucleophilic substitution with sulfur or selenium nucleophiles, in order to take advantage of
classical syn-type eliminations of sulfoxides and selenoxides, were fruitless presumably to steric hindrance surrounding that C2 carbon. The difficulty to undergo E2 type elimination can be explained by the lack of antiperiplanar hydrogen in 3.45. Consequently, a syn-type elimination was necessary to establish the enone moiety of maoecrystal V. Inspired by Saegusa oxidation\(^2\), it was reasoned that perhaps Pd(0) could oxidatively insert into C–Cl bond and then undergo a syn \(\beta\)-hydride elimination to install the enone moiety and eliminate HPd(II)Cl that can regenerate Pd(0) after subsequent reductive elimination of HCl with the assistance of base. Oxidation of 3.42 with Dess–Martin periodinane resulted in almost quantitative yield of 3.45, a significant improvement over the conditions with PCC (Scheme 4.3). Next, treatment of \(\alpha\)-chloroketone 3.45 with catalytic amount of Pd(PPh\(_3\))\(_4\) in the presence of Et\(_3\)N in MeCN at 85 °C resulted in formation of maoecrystal V. At long last this cursed molecule had finally fallen in our lab. However, our joy and celebration was short-lived as it turned out that the last reaction was quite irreproducible. While during the several initial runs it gave maoecrystal V in 90% yield with only traces of other

![Scheme 4.2 Attempts to form enone of maoecrystal V via elimination](image-url)
by-products, during subsequent runs on slightly larger scale it resulted in greatly diminished yield due to significant formation, up to 46% yield, of compound **3.46**. This saturated version of maoecrystal V was latter dubbed dihydro-maoecrystal V and was formed presumably via isomerization of C2-bound Pd(II) species into Pd(II)-enolate that upon aqueous work up afforded **3.46**. It is unclear why this reaction was so finicky and irreproducible, attempts to utilize freshly purchased, purified or even made in-house Pd(PPh₃)₄ did not solve this issue. Efforts to optimize this reaction by utilizing other Pd catalysts, ligands, solvents and bases resulted in increased amount of **3.46** formed with almost no maoecrystal V. Surprisingly, Pd(PPh₃)₄ was best by far at mediating this reaction, while MeCN was the most optimal solvent for this transformation. In addition, the reaction mixture was very difficult to purify as it was highly challenging to separate maoecrystal V from dihydro-maoecrystal V (**3.46**) and PPh₃. Furthermore, on some occasion epimerization of C16 methyl group was observed during the course of the reaction making this reaction even more impractical. Even though an overall victory was achieved that day as maoecrystal V has been conquered, it was bittersweet triumph since the sequence of last steps was

**Scheme 4.3** Syn elimination via Pd insertion into C–Cl bond

mediating this reaction, while MeCN was the most optimal solvent for this transformation. In addition, the reaction mixture was very difficult to purify as it was highly challenging to separate maoecrystal V from dihydro-maoecrystal V (**3.46**) and PPh₃. Furthermore, on some occasion epimerization of C16 methyl group was observed during the course of the reaction making this reaction even more impractical. Even though an overall victory was achieved that day as maoecrystal V has been conquered, it was bittersweet triumph since the sequence of last steps was
low yielding and impractical. In the end, a proof of principle was obtained and decision to streamline the end game was made.

4.2 Improvement of the end game

The optimization of the end game began with epoxide rearrangement/opening step as currently it would only utilize only two thirds of the material since diepoxide 3.41b would give regioisomeric mixture of chlorohydrins 3.43 and 3.44. First of all, a closer look at this reaction was required to understand why diepoxide 3.41b misbehaved in this reaction. According to Fürst–Plattner rule, epoxides prefer to undergo diaxial opening because it leads to a chair transition state, opposed to diequatorial opening that leads to a twist boat transition state that is significantly higher in energy and thus disfavored.\(^3\) In the case of major diastereoisomer 3.41b, the carbon that leads to diaxial opening via axial attack of a nucleophile is also least hindered as it is further away from

![Figure 4.1 Axial vs equatorial attack in the context of epoxides 3.41a and 3.41b](image)
quaternary carbon stereocenter of spirolactone (Figure 4.1). In this case steric and diaxial opening preferences matched, as a result, only one regioisomer 3.42 is obtained which is the desired one. In the case of minor diastereoisomer 3.41b, the carbon that leads to diaxial opening is also more hindered as it is right next to a quaternary carbon. Hence, steric effects and preference to undergo diaxial opening are mismatched and a mixture of products 3.43 and 3.44 is obtained. In the case of chloride anion, the preference to undergo diaxial opening is more prevalent and overcomes the steric hindrance. Consequently, major product of this reaction was undesired regioisomer 3.43. Perhaps this can be used to our advantage, utilizing a bulkier nucleophile, such as iodide anion, would result in more unfavorable steric interaction and thus make equatorial attack a lower energy pathway. To our delight, after evaluation of multiple Lewis acids it was found that 5 mol% of InI₃ and stoichiometric MgI₂ afforded exclusively the desired iodohydrins 3.47a and 3.47b from both epoxides in almost quantitative yield (Scheme 4.4). Not even a trace of undesired regioisomer was detected in both cases. These conditions also cleanly mediated stereospecific 1,2-hydride shift as expected. As it can be seen from the X-ray crystal structure of 3.47b we were able to promote diequatorial opening of the epoxide by utilizing steric to our advantage. It is interesting to note

**Scheme 4.4** High-yielding regioselective opening of both epoxides
that InI$_3$ is able to promote epoxide rearrangement but doesn’t open the disubstituted epoxide (even with stoichiometric quantities), while MgI$_2$, on the other hand, transforms disubstituted epoxides into iodohydrin but is not capable of promoting the rearrangement. When used in combination they were able to accomplish both tasks with impressive efficiency. Both diepoxides were now synthetically useful and no longer needed to be chromatographically separated. What is more, both iodohydrins could be oxidized to $\alpha$-iodoketone in one-pot by a simple addition of DMP. During such oxidation with commercial bottle of DMP, a trace amount (1-3%) of maoecrystal V would form along with $\alpha$-iodoketone and no epimerization or dihydro-maoecrystal V was detected (Figure 4.2). However, freshly made DMP would not promote such transformation. It was only that one particular bottle of commercial DMP. What was in that bottle? Most likely some impurity

**Figure 4.2** maoecrystal V is formed during oxidation with commercial DMP
mediated such a transformation quite cleanly. Since DMP is made from IBX, which is made from 2-iodobenzoic acid and Oxone®, perhaps commercial DMP was contaminated with a little bit of Oxone® and that mediated this reaction. Since oxidative elimination of iodide to form enone with \( m \)-CPBA was known\(^4\), and although it didn’t work in our hands, we decided to evaluate Oxone® as a reagent potentially capable of promoting such a transformation. Amazingly, adding aqueous

![Chemical structures](image)

**Scheme 4.5** Successful synthesis of (−)-maoecrystal V

buffered solution of Oxone® to the DMP reaction mixture and stirring it overnight furnished maoecrystal V in high yield and purity. The final optimized end game is depicted in Scheme 4.5, where maoecrystal V is converted in a one-pot sequence from lactone 3.40. Subjecting the latter compound to DMDO in acetone and then evaporating volatiles, followed by exposure to catalytic InI₃ and stoichiometric MgI₂ in MeCN furnished iodohydrins 3.47 as an inconsequential mixture
of diastereoisomers. Next, simple addition of solid DMP to the same flask gave α-iodoketone 3.48 as essentially a single diastereoisomer. This can be explained by epimerization of highly acidic C2 hydrogen of α-iodoketone to the thermodynamically more preferred configuration (most likely equatorial) during the course of the reaction. After oxidation was complete according to TLC analysis, aqueous buffered solution of Oxone® was added dropwise to the reaction mixture and left stirring overnight. This would gradually oxidize the iodine atom to a putative iodoso species 3.49, that would spontaneously eliminate providing maoecrystal V as a single compound in 76% overall yield. No epimerization or other by-products were detected in the crude reaction mixture. Structure and absolute configuration of the product obtained was confirmed without a shadow of a doubt by X-ray crystallographic analysis. Using this route about 80 mg of (–)-maoecrystal V were made that allowed detailed evaluation of its biological activity.

The primary goal of this study was to demonstrate that the notorious difficulties surrounding the exotic architecture of 1 could be solved by total synthesis in a practical way. This was eventually accomplished by employing a strategy not wedded to Diels−Alder type disconnections but rather a desire to maximize convergency and minimize concession steps. Some of the memorable lessons from this concise synthesis (73% ideal) include: (1) short access to ketone 2.20 via a highly enantioselective conjugate addition and anti-Baldwin cyclization; (2) convergent coupling of fragments 2.20 and 3.11 with concomitant pinacol shift and olefin isomerization to establish the [2.2.2] bicycle; (3) the first use of a lanthanide Lewis acid to control the regio- and stereochemical course of an aldol reaction with an extended enolate; (4) Zn(OTf)2-assisted reversal of the stereoselectivity of a bis-neopentyl ketone reduction; (5) an efficient cascade sequence to install key oxidations and unsaturation.
4.3 Reevaluation of biological activity

In the original isolation paper maoecrystal V was reported to have an exciting bioactivity profile with potent and selective cytotoxicity against HeLa cell lines. Once a route to maoecrystal V was finally developed and over 80 mg of it produced, the next stage was to explore its biological activity more thoroughly since both mode of action and cellular target were unknown. It was screened against 32 different cell lines (including HeLa) across four different laboratories and showed little to no activity in any of them, suggesting that the originally exciting findings were either due to a flawed assay or impure V (Figure 4.3). Maoecrystal V was evaluated for antibacterial activity as well but it possessed no useful activity against bacteria. These results call into question the initial exuberance over this natural product that resulted in so much effort and hard work from the synthetic community.

Figure 4.3 maoecrystal V was found inactive against HeLa cell lines

![HeLa viability graph](image)
In the end, persistence, determination and obsession to make this notorious natural product has triumphed as maoeocrystal V has been finally slain in our lab. Even though, the road to this demonic molecule was treacherous, debilitating and at times an absolutely crippling experience, the precious lessons learned from this endeavor are absolutely immeasurable. At long last, the journey to (−)-maoeocrystal V, turned a wild roller-coaster ride of emotions, has finally come to an end. “It is good to have an end to journey toward; but it is the journey that matters, in the end.”

4.4 References

4.5 Experimental Section for Chapter 4.

General Experimental. All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry acetonitrile (MeCN), dichloromethane (DCM), diethyl ether (Et₂O), tetrahydrofuran (THF), toluene (PhMe) and triethylamine (Et₃N) were obtained by passing the 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 (¹H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an acidic solution of vanillin and heat, or KMnO₄ and heat as developing agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm), flash alumina chromatography was performed using Brockmann Grade 1 aluminum oxide (activated, basic, 58 Å, 60 mesh powder). NMR spectra were recorded on Bruker DRX-600 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (CDCl₃ ¹H NMR = 7.26 ppm, ¹³C NMR = 77.16 ppm; C₆D₆ ¹H NMR = 7.16 ppm, ¹³C NMR = 128.06 ppm, C₅D₅N ¹H NMR = 8.71, 7.57, 7.19 ppm, ¹³C NMR = 149.91, 135.56, 123.54). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.
Compounds 3.41a and 3.41b:

A flame-dried 25 mL round-bottom flask equipped with stir bar was charged with 3.40 (6.5 mg, 0.022 mmol, 1.0 eq.) and freshly prepared DMDO (0.66 mL of 0.1 M soln in acetone, 0.066 mmol, 3.0 eq.). The reaction mixture was stirred for 12 h at room temperature, then additional DMDO (6.6 mL of 0.1M soln in acetone, 0.66 mmol, 3.0 eq.) was added and the reaction mixture was stirred for another 12 h at room temperature. The reaction mixture was concentrated under reduced pressure, azeotroped with toluene (2 x 1 mL). The crude product was purified by silica gel flash chromatography (20%→30% EtOAc in hexanes) to afford compound 3.41a (xx mg, xx % yield) and compound 3.41b (xx mg, xx % yield)

Data for compound 3.41a:

Physical state: white solid.

TLC: Rf = 0.22 (30% EtOAc in hexanes).

$^1$H NMR (600 MHz, CDCl$_3$): δ 4.49 (d, $J = 11.9$ Hz, 1H), 4.40 (d, $J = 1.9$ Hz, 1H), 4.17 (dd, $J = 11.9$, 1.9 Hz, 1H), 3.45 (s, 1H), 3.15 (d, $J = 4.0$ Hz, 1H), 3.13 (dt, $J = 4.1$, 2.0 Hz, 1H), 2.88 (dd, $J = 14.4$, 4.0 Hz, 1H), 2.20 (ddd, $J = 16.6$, 2.0, 0.5 Hz, 1H), 2.11-2.09 (m, 1H), 2.08 (dd, $J = 16.6$, 2.1 Hz, 1H), 2.03 (ddd, $J = 12.6$, 11.4, 5.5 Hz, 1H), 1.70-1.64 (m, 1H), 1.62 (dt, $J = 14.5$, 2.3 Hz, 1H), 1.45 (s, 3H), 1.30 (ddddd, $J = 12.7$, 11.3, 2.6, 1.4 Hz, 1H), 1.21-1.16 (m, 1H), 1.15 (s, 3H), 1.13 (s, 3H).
$^{13}$C NMR (151 MHz, CDCl$_3$) : δ 170.12, 86.17, 85.56, 68.35, 60.65, 56.25, 51.48, 51.28, 47.15, 45.36, 38.33, 34.59, 34.19, 32.96, 30.76, 24.46, 20.73, 19.68, 18.50.

HRMS (ESI-TOF): Calcd for C$_{19}$H$_{25}$O$_5$ [M+H]$^+$: 333.1696, found 333.1697.

Optical Rotation: $[\alpha]_D^{23} = -58^\circ$ (c 0.53, DCM).
X-ray crystal structure of $3.41a$. For more information, see attached CIF file.
Data for compound 3.41b:

**Physical state:** white solid.

**TLC:** R\textsubscript{f} = 0.27 (30% EtOAc in hexanes).

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): \(\delta\) 4.66 (d, \(J = 12.8\) Hz, 1H), 4.22 (dd, \(J = 12.8, 1.7\) Hz, 1H), 3.88 (d, \(J = 1.3\) Hz, 1H), 3.41 (d, \(J = 3.6\) Hz, 1H), 3.20 (s, 1H), 3.17 (ddd, \(J = 4.4, 3.7, 1.5\) Hz, 1H), 2.95 (dd, \(J = 14.4, 4.1\) Hz, 1H), 2.15 (dd, \(J = 16.3, 1.4\) Hz, 1H), 2.13 (m, 1H), 2.05 (ddd, \(J = 12.8, 11.3, 5.6\) Hz, 1H), 1.90 (dd, \(J = 16.3, 4.4\) Hz, 1H), 1.70–1.65 (m, 1H), 1.64 (dt, \(J = 14.3, 2.2\) Hz, 1H), 1.48 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H).

\textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}): \(\delta\) 170.28, 90.97, 85.83, 68.03, 60.93, 56.96, 52.34, 51.17, 47.51, 42.77, 39.01, 34.13, 33.32, 31.37, 30.82, 22.05, 20.69, 20.11, 18.59.

**HRMS** (ESI-TOF): Calcd for C\textsubscript{19}H\textsubscript{25}O\textsubscript{5} [M+H]\textsuperscript{+}: 333.1696, found 333.1696.

**Optical Rotation:** \([\alpha]\)\textsubscript{D}\textsuperscript{23} = –107° (\(c 0.45,\) DCM).
X-ray crystal structure of \textbf{3.41b}. For more information, see attached CIF file.
**Compound 3.42:**

A test tube equipped with stir bar was charged with 3.41 (6.5 mg, 0.022 mmol, 1.0 eq.), DCM (1 mL) and BiCl₃ (14 mg, 0.044 mmol, 2.0 equiv). The reaction mixture was stirred for 12 h at room temperature, then it was filtered through a silica plug, which was rinsed with 1:1 mixture of Et₂O:Hexanes. The crude product was purified by silica gel flash chromatography (20%→30% EtOAc in hexanes) to afford compound 3.42 (7.5 mg, 94 % yield).

Data for compound 3.42:

**Physical state:** white solid.

**TLC:** $R_f = 0.34$ (30% EtOAc in hexanes).

$^{1}H$ NMR (600 MHz, CDCl₃): δ 4.49 (d, $J = 12.4$ Hz, 1H), 4.36 (s, 1H), 4.27 (d, $J = 12.5$ Hz, 1H), 4.19 (td, $J = 11.2$, 9.4, 3.4 Hz, 1H), 3.27 (dd, $J = 14.5$, 4.9 Hz, 1H), 3.16 (dd, $J = 12.4$, 9.5 Hz, 1H), 2.44 (d, $J = 8.0$ Hz, 1H), 2.15 (s, 1H), 2.11 – 2.01 (m, 2H), 1.92 (q, $J = 13.9$ Hz, 3H), 1.66 (d, $J = 12.6$ Hz, 1H), 1.27 (d, $J = 7.7$ Hz, 3H), 1.11 (s, 3H), 1.08 (s, 3H).

$^{13}C$ NMR (151 MHz, CDCl₃): δ 220.95, 168.89, 85.21, 84.97, 78.77, 71.02, 60.38, 58.60, 49.96, 49.65, 46.49, 35.20, 33.43, 32.27, 32.25, 31.57, 22.99, 18.63, 17.92, 16.02.

Compound 3.45:

A test tube equipped with stir bar was charged with 3.42 (5.0 mg, 0.014 mmol, 1.0 eq.), DCM (1 mL) and Dess–Martin periodinane (18 mg, 0.042 mmol, 3.0 eq.). The reaction mixture stirred vigorously at room temperature for 12 h. Et₂O (2 mL) was added to the reaction mixture and it was filtered through a short silica plug that was washed with 30% Et₂O in Hexanes to afford pure 3.45 (4.5 mg, 90% yield).

Data for compound 3.45:

**Physical state:** white waxy solid.

**TLC:** Rᵣ = 0.52 (30% EtOAc in hexanes).

**¹H NMR** (600 MHz, CDCl₃): δ 4.94 (dd, J = 14.2, 5.2 Hz, 1H), 4.72 (d, J = 12.2 Hz, 1H), 4.45 (s, 1H), 4.25 (d, J = 12.2 Hz, 1H), 3.15 (dd, J = 14.7, 4.6 Hz, 1H), 2.37 (d, J = 7.9 Hz, 1H), 2.29 (dd, J = 14.4, 5.2 Hz, 1H), 2.22 (t, J = 14.3 Hz, 1H), 2.16 (s, 1H), 2.09 (t, J = 12.4 Hz, 1H), 2.05 – 1.91 (m, 2H), 1.70 (d, J = 14.7 Hz, 1H), 1.25 (s, 3H), 1.22 (d, J = 7.5 Hz, 3H), 1.20 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ 213.21, 199.10, 168.46, 85.05, 69.42, 59.49, 59.28, 53.68, 48.12, 46.54, 34.73, 34.06, 32.99, 31.62, 22.98, 18.87, 18.13, 15.03.

Compound 3.47a, 3.47b, 3.48 and (−)-maoecrystal V (1):

A flame-dried 25 mL round-bottom flask equipped with stir bar was charged with 3.40 (65 mg, 0.22 mmol, 1.0 eq.) and freshly prepared DMDO (6.6 mL of 0.1 M soln in acetone, 0.66 mmol, 3.0 eq.). The reaction mixture was stirred for 12 h at room temperature, then additional DMDO (6.6 mL of 0.1M soln in acetone, 0.66 mmol, 3.0 eq.) was added and the reaction mixture was stirred for another 12 h at room temperature. The reaction mixture was concentrated under reduced pressure, azeotroped with toluene (2 x 10 mL) and redissolved in MeCN (4.0 mL) under Ar. InI₃ (5.5 mg, 0.011 mmol, 0.05 eq.) was added and the obtained reaction mixture was stirred at room temperature for 1 h. MgI₂ (74 mg, 0.26 mmol, 1.2 eq.) was added and obtained homogeneous yellow reaction mixture was stirred for 4 h at room temperature. Dess–Martin periodinane (280 mg, 0.66 mmol, 3.0 eq.) was added at 0 ºC and the reaction mixture was stirred vigorously at room temperature for 12 h. Next, pH = 7.4 aq. phosphate buffer (1 M, 4.0 mL), aq. sat. Rochelle’s solution (0.3 mL), Bu₄NHSO₄ (7.5 mg, 0.022 mmol, 0.10 eq.), K₂CO₃ (182 mg, 1.32 mmol, 6.0 eq.), and Oxone® (676 mg, 2.2 mmol, 10.0 eq.), dissolved in H₂O (2 mL), were added sequentially to the reaction mixture at 0 ºC and it was stirred vigorously for 12 h at room temperature. The reaction mixture was quenched with sat. aq. Na₂S₂O₃ (5 mL) and then diluted with Et₂O (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (25% EtOAc in hexanes) to afford (−)-maoecrystal V (1) (54 mg, 76% yield) as a white solid.
Notes: Diepoxidation of 3.40 with DMDO yields 3.41 as 2:1 mixture of inconsequential diastereomers (verified by X-ray).

Oxidation of iodohydrin 3.47 (2:1 mixture of inconsequential diastereomers) with DMP results in oxidation of C-1 alcohol and subsequent epimerization at C-2 to afford 3.48 as ~15:1 mixture of iodo epimers. Oxidizing diastereomerically pure 347a (major) and 3.47b (minor) under the same reaction conditions gave 3.48 in the same ~15:1 ratio of iodo epimers.

Interesting to note, that myriad of attempts to achieve E2 type elimination of HI in 3.48 under basic conditions were met with complete failure. However, about 2–4% of maecrystal V (1) was formed as a by-product during oxidation when commercial DMP was used. The hypothesis that it might have been contaminated with small amount of Oxone® lead to the development of this reaction.
Data for compound **3.47a (major)**:

Compound **3.47a (major)** was isolated for characterization purposes by taking an aliquot from the reaction mixture and quenching it with aq. sat. NaHCO₃ and aq. sat. Rochelle’s salt, followed by standard work up and purification by PTLC (35% Et₂O in hexanes).

**Physical state:** white solid.

**TLC:** \( R_f = 0.45 \) (20% EtOAc in hexanes).

\(^1\text{H NMR}\) (600 MHz, CDCl₃): \( \delta \) 4.50 (d, \( J = 12.5 \) Hz, 1H), 4.41 (ddd, \( J = 13.7, 10.2, 3.3 \) Hz, 1H), 4.36 (d, \( J = 1.8 \) Hz, 1H), 4.32 (d, \( J = 12.5 \) Hz, 1H), 4.23 (dd, \( J = 12.5, 1.9 \) Hz, 1H), 3.32 (dd, \( J = 12.5, 10.2 \) Hz, 1H), 3.26 (dd, \( J = 14.5, 4.9 \) Hz, 1H), 2.45 (q, \( J = 7.4 \) Hz, 1H), 2.33 (dd, \( J = 14.5, 3.4 \) Hz, 1H), 2.22 (t, \( J = 14.2 \) Hz, 1H), 2.14 (s, 1H), 2.07 (t, \( J = 11.4 \) Hz, 1H), 1.96–1.83 (m, 2H), 1.65 (dt, \( J = 16.7, 8.3 \) Hz, 1H), 1.26 (d, \( J = 7.4 \) Hz, 3H), 1.10 (s, 3H), 1.07 (s, 3H).

\(^{13}\text{C NMR}\) (151 MHz, CDCl₃): \( \delta \) 221.01, 168.89, 84.80, 84.62, 80.38, 70.97, 58.92, 49.63, 49.55, 49.22, 35.35, 35.17, 32.30, 31.48, 30.51, 22.92, 18.64, 17.93, 16.01.

**HRMS** (ESI-TOF): Calcd for C₁₉H₂₆IO₅ \([M+H]^+\): 461.0819, found 461.0821.

**Optical Rotation:** \( [\alpha]_D^{23} = +26^o \) (c 0.50, DCM).
Data for compound 3.47b (minor):

Compound 3.47b (minor) was isolated for characterization purposes by taking an aliquot from the reaction mixture and quenching it with aq. sat. NaHCO₃ and aq. sat. Rochelle’s salt, followed by standard work up and purification by PTLC (35% Et₂O in hexanes).

Physical state: white solid.

TLC: Rᵣ = 0.40 (20% EtOAc in hexanes).

¹H NMR (600 MHz, CDCl₃): δ 5.40 (dd, J = 10.8, 3.3 Hz, 1H), 4.76 (d, J = 12.9 Hz, 1H), 4.63 (d, J = 12.9 Hz, 1H), 4.35–4.29 (m, 1H), 4.00 (d, J = 1.6 Hz, 1H), 3.23 (dd, J = 14.4, 4.9 Hz, 1H), 2.40 (d, J = 3.4 Hz, 1H), 2.34–2.29 (m, 2H), 2.11–2.05 (m, 3H), 1.90 (t, J = 12.4 Hz, 1H), 1.87–1.79 (m, 1H), 1.63 (q, J = 14.3 Hz, 2H), 1.24 (d, J = 7.4 Hz, 3H), 1.14 (s, 3H), 1.03 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 216.13, 169.60, 88.15, 83.99, 74.41, 66.66, 55.47, 49.75, 48.47, 37.56, 35.24, 35.06, 32.39, 31.67, 19.86, 19.13, 18.27, 15.66.


Optical Rotation: [α]D³³ = −23° (c 0.21, DCM).
X-ray crystal structure of 3.47b. For more information, see attached CIF file
Data for compound 3.48:

Compound 3.48 was isolated for characterization purposes by taking an aliquot from the reaction mixture and filtering it through a short plug of silica (eluent: 25% Et$_2$O hexanes), followed by concentration under reduced pressure and purification by PTLC (40% Et$_2$O in hexanes).

**Physical state:** white solid.

**TLC:** $R_f = 0.55$ (30% EtOAc in hexanes).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.38 (dd, $J = 14.6$, 5.3 Hz, 1H), 4.71 (d, $J = 12.1$ Hz, 1H), 4.47 (d, $J = 1.8$ Hz, 1H), 4.22 (dd, $J = 12.1$, 1.8 Hz, 1H), 3.15 (dd, $J = 14.7$, 4.7 Hz, 1H), 2.53 (dd, $J = 14.6$, 5.3 Hz, 1H), 2.46 (t, $J = 14.6$ Hz, 1H), 2.35 (dd, $J = 138.2$, 7.0 Hz, 1H), 2.15 (s, 1H), 2.11–2.05 (m, 1H), 2.04–1.92 (m, 2H), 1.69 (dt, $J = 14.7$, 2.1 Hz, 1H), 1.63 (q, $J = 12.3$, 11.4 Hz, 1H), 1.23 (s, 3H), 1.21 (d, $J = 7.4$ Hz, 3H), 1.18 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) : $\delta$ 212.99, 199.71, 168.52, 85.35, 84.87, 69.08, 59.25, 52.25, 49.89, 48.11, 35.65, 34.71, 32.98, 31.57, 29.60, 22.98, 18.76, 18.12, 15.06.

**HRMS (ESI-TOF):** Calcd for C$_{19}$H$_{24}$IO$_5$ [M+H]$^+$: 459.0663, found 459.0669.

**Optical Rotation:** $[\alpha]_D^{23} = -61^\circ$ (c 0.42, DCM).
Data for (–)-maoeocrystal V (1):

**Physical state:** white solid

**TLC:** Rf = 0.33 (30% EtOAc in hexanes).

**H NMR** (600 MHz, CDCl$_3$): δ 6.66 (d, $J = 10.1$ Hz, 1H), 5.95 (d, $J = 10.2$ Hz, 1H), 4.63 (d, $J = 12.2$ Hz, 1H), 4.43 (d, $J = 1.6$ Hz, 1H), 4.13 (dd, $J = 12.2$, 1.7 Hz, 1H), 3.18 (dd, $J = 14.6$, 4.7 Hz, 1H), 2.34 (q, $J = 7.4$ Hz, 1H), 2.17–2.13 (m, 1H), 2.13–2.04 (m, 2H), 2.01–1.93 (m, 1H), 1.69 (dt, $J = 14.6$, 2.1 Hz, 1H), 1.65–1.60 (m, 2H), 1.29 (s, 3H), 1.25 (d, $J = 7.5$ Hz, 3H), 1.22 (s, 3H).

**H NMR** (600 MHz, C$_5$D$_5$N): δ 6.54 (d, $J = 10.1$ Hz, 1H), 5.99 (d, $J = 10.1$ Hz, 1H), 4.73 (d, $J = 12.3$ Hz, 1H), 4.66 (d, $J = 1.6$ Hz, 1H), 4.32 (dd, $J = 12.3$, 1.7 Hz, 1H), 3.28 (dd, $J = 14.4$, 4.7 Hz, 1H), 2.31 (q, $J = 7.6$ Hz, 1H), 2.20–2.09 (m, 2H), 1.91–1.86 (m, 1H), 1.78 (d, $J = 14.8$ Hz, 1H), 1.76–1.71 (m, 1H), 1.52–1.44 (m, 1H), 1.22 (s, 3H), 1.09 (d, $J = 7.5$ Hz, 3H), 1.06 (s, 3H).

**C NMR** (151 MHz, CDCl$_3$) : δ 211.64, 194.95, 169.18, 156.83, 127.17, 85.03, 84.23, 69.34, 56.69, 52.03, 48.38, 38.39, 34.68, 32.76, 30.74, 18.69, 18.66, 18.13, 15.28.

**C NMR** (151 MHz, C$_5$D$_5$N) : δ 211.75, 194.77, 169.52, 156.72, 127.26, 85.52, 84.67, 69.54, 56.97, 52.43, 48.37, 38.36, 34.89, 32.95, 30.48, 18.71, 18.39, 18.29, 15.05.

**HRMS** (ESI-TOF): Calcd for C$_{19}$H$_{23}$O$_5$ [M+H]$^+$: 331.1540, found 331.1542.

**Optical Rotation:** $[\alpha]_D^{23} = -98.2^\circ$ (c 1.00, MeOH).
X-ray crystal structure of (−)-maoeystal V (1). For more information, see page 243.
Experimental Summary for X-ray Analysis of (–)-Maoecrystal V

The single crystal X-ray diffraction studies were carried out on a Bruker Pt 135 CCD diffractometer equipped with Cu K$_\alpha$ radiation (1.54178 Å). Crystals of the subject compound were used as received (grown from Acetone). A 0.25 x 0.020 x 0.020 mm piece of a colorless needle was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\phi$ and $\varpi$ scans. Crystal-to-detector distance was 45 mm and exposure time was 45 and 90 seconds per frame (depending on 2theta) using a scan width of 1.5$^\circ$. Data collection was 100.0% complete to 67.679$^\circ$ in $\theta$. A total of 12068 reflections were collected covering the indices, $-18 \leq h \leq 18$, $-14 \leq k \leq 18$, $-7 \leq l \leq 7$. 3290 reflections were found to be symmetry independent, with a $R_{int}$ of 0.0634. Indexing and unit cell refinement indicated a Primitive, Trigonal lattice. The space group was found to be $P3_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized below.

Notes: Model in agreement with proposed structure.

Absolute structure parameter 0.08(17) Conclusive

Solvent squeezed 40el per unit cell
Crystal data and structure refinement for Baran584_sq.

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Max. and min. transmission 0.7533 and 0.6037
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 3290 / 1 / 220
Goodness-of-fit on F^2 1.034
Final R indices [I>2sigma(I)] R1 = 0.0387, wR2 = 0.0816
R indices (all data) R1 = 0.0496, wR2 = 0.0853
Absolute structure parameter 0.08(17)
Extinction coefficient n/a
Largest diff. peak and hole 0.361 and -0.182 eÅ^-3
Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\text{Å}^2 \times 10^3)\) for Baran584_sq. \(U(\text{eq})\) is defined as one third of the trace of the orthogonalized \(U_{ij}\) tensor.

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Anisotropic displacement parameters (Å$^2 \times 10^3$) for Baran584_sq. The anisotropic displacement factor exponent takes the form: 

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<td>4.66 (s, 1H)</td>
<td>4.66 (d, (J = 1.6) Hz, 1H)</td>
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<td>7</td>
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<tr>
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<td>10</td>
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<tr>
<td>11</td>
<td>2.14 (m, 2H)</td>
<td>2.20–2.09 (m, 2H)</td>
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<td>12</td>
<td>1.48 (m, 1H)</td>
<td>1.52–1.44 (m, 1H)</td>
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<tr>
<td>13</td>
<td>1.73 (m, 1H)</td>
<td>1.76–1.71 (m, 1H)</td>
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<td>14</td>
<td>1.88 (m, 1H)</td>
<td>1.94–1.89 (m, 1H)</td>
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<td>15</td>
<td>3.28 (dd, (J = 14.1, 4.8) Hz, 1H)</td>
<td>3.28 (dd, (J = 14.4, 4.7) Hz, 1H)</td>
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<td>2.31 (m, 1H)</td>
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<td>1.09 (d, (J = 7.5) Hz, 3H)</td>
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<td>1.04 (s, 3H)</td>
<td>1.06 (s, 3H)</td>
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<td>1.21 (s, 3H)</td>
<td>1.22 (s, 3H)</td>
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<td>4.73 (d, (J = 12.3) Hz, 1H)</td>
<td>4.73 (d, (J = 12.3) Hz, 1H)</td>
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<tr>
<td>20</td>
<td>4.32 (d, (J = 12.3) Hz, 1H)</td>
<td>4.32 (dd, (J = 12.3, 1.7) Hz, 1H)</td>
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(−)-Maoecrystal V $^{13}$C spectra comparison:

![Diagram of (-)-maoecrystal V (1)]

<table>
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<tr>
<th>Position</th>
<th>$^{13}$C NMR (δ) Natural Sample (100 MHz, C$_5$D$_3$N)</th>
<th>$^{13}$C NMR (δ) Synthetic Sample (151 MHz, C$_5$D$_3$N)</th>
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<td>56.97</td>
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<td>10</td>
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<td>52.43</td>
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<td>18.7</td>
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<td>18.39</td>
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<tr>
<td>20</td>
<td>69.5</td>
<td>69.54</td>
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</table>
Evaluation of Biological Activity.

Data from ProQinase.

Test samples:

Synthetic (-)-maocystal V (1) was dissolved in 100% DMSO at a concentration of 1 mM. MMAE and DM-1 were purchased as powders and dissolved in 100% DMSO at a concentration of 10 mM. Dilutions (1:5) were performed in 100% DMSO. The reference compound Actinomycin D was provided by ProQinase.

Cell culture of tumor cells:

Cells were cultured in RPMI-1640 containing 10% FCS and Penicillin/Streptomycin (A431, BXPC3, HCT-15, HL-60, NCI-H292, OVCAR-3), RPMI-1640 containing 20% FCS, 10ng/ml GM-CSF and Penicillin/Streptomycin (M07e), MEM containing 10% FCS and Penicillin/Streptomycin (A427), McCoys 5a containing 10% FCS and Penicillin/Streptomycin (SK.BR-3) or DMEM containing 10% FCS and Penicillin/Streptomycin (all remaining cells). For the assays, cells were seeded in 150 µL medium on a 96-well cell culture plate and incubated at 37 °C overnight before the compounds were added.

Application of a compound:

Samples were prepared as predilution in medium which was 16-fold concentrated to the final assay concentration. A day after cell seeding, 10 µL of prediluted compound was added to the cells (1:16 dilution). Treatment of cells with 0.1% DMSO and Staurosporine (1.0E–05 M) served as high control (100% viability) and low control (0% viability), respectively.
Alamar blue assay:

Measurement of the impact of a compound on cell viability was performed as follows: Cells 2.500 cell/well (A549, NCI-H292, HeLa, U2OS), 10.000 cells/well (A427, NCI-N87, HL-60, ZR-75-1), 15.000 cells/well (C33a), 30.000 cells/well (M07e) or 5.000 cells/well (all remaining cells) were seeded in the inner wells of 96-well-plates in 150 µL complete medium. A day after cell seeding, the test compound was added to the medium to reach the final concentration and incubated for 72 h at 37 °C at 5% or 10% CO₂ dependent on the medium. Subsequently 15 µL Alamar Blue reagent was added and fluorescence at 590 nm was measured after 3–5 h incubation at 37 °C, 5% CO₂ using a fluorometer.

Evaluation of raw data:

Raw data were converted into percent cell viability relative to the high control (0.1% DMSO) and low control (1E–05 M Staurosporine), which were set to 100% and 0%, respectively. IC₅₀ calculation was performed using GraphPad Prism software with a variable slope sigmoidal response fitting model using 0% cell growth as bottom constraint and 100% cell growth as top constraint. When compound does not induce a complete inhibition of cell growth in different cell lines the IC₅₀s were calculated additionally without bottom constraint. Doing so the curve is not forced to go through 0% which allows a more significant fitting of the curve and the calculation of a more reliable IC₅₀ in those cases where the cell growth is not completely inhibited by the compound.
Example for IC\textsubscript{50} curves calculated with and without bottom constraint.

**Results:**

Titrati\on curves are provided below.
Data from Stemcentrx.

<table>
<thead>
<tr>
<th>Cancer Cell Line</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>Naive 293T</td>
<td>&gt;10 µM</td>
</tr>
<tr>
<td>MES SA</td>
<td>&gt;10 µM</td>
</tr>
<tr>
<td>MES DX</td>
<td>&gt;10 µM</td>
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<tr>
<td>HCT</td>
<td>&gt;10 µM</td>
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</table>

Data from Charles River.

<table>
<thead>
<tr>
<th>Cancer Cell Line</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt;</th>
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<tr>
<td>BT474</td>
<td>&gt;10 µM</td>
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</table>

Data from Calibr.

<table>
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<tr>
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<tr>
<td>HepG2</td>
<td>15.02</td>
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</tbody>
</table>
Chapter 4 Appendix

NMR Spectra
$\text{HO}$

$\text{Cl}$

$\text{Me}$

Compound 3.42

$\text{H NMR}$ (600 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

**Compound 3.45**
$^{1}H$ NMR (600 MHz, CDCl$_3$)

Compound 3.41a
$^{13}$C NMR (151 MHz, CDCl₃)

Compound 3.41a
$\text{H} N\text{MR (600 MHz, CDCl}_3\}$

Compound 3.41b
Compound 3.41b

$^{13}$C NMR (151 MHz, CDCl$_3$)

- 170.44
- 91.13
- 85.99
- 68.19
- 61.08
- 57.13
- 52.49
- 51.32
- 47.68
- 42.94
- 39.18
- 34.30
- 33.49
- 31.53
- 30.98
- 22.21
- 20.86
- 20.28
- 18.75
Compound 3478

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)

Compound 3.47a
Compound 3.47b

$\text{1H NMR (600 MHz, CDCl}_3\text{)}$
$^{13}$C NMR (151 MHz, CDCl$_3$)

- 216.13
- 169.60
- 88.15
- 83.99
- 74.41
- 66.66
- 55.47
- 49.75
- 48.47
- 37.56
- 35.24
- 35.06
- 32.39
- 31.67
- 19.86
- 19.13
- 18.27
- 15.66

Compound 3.47b
Compound 3.48

$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl₃)

Compound 3.48
(-)-maeacrystal V(1)

1H NMR (600 MHz, CDCl₃)
$^{1}H$ NMR (600 MHz, CD$_3$N)

(-)-maeocystin V (1)
\begin{align*}
\delta_{13C}^{(\text{ppm})} & \quad \text{NMR (151 MHz, C\textsubscript{5}D\textsubscript{5}N)} \\
\end{align*}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{13C_NMR.png}
\end{figure}