DESIGN AND SYNTHESIS OF NATURAL PRODUCT ANALOGS OF STEVIOSIDE AND SYNTHETIC ANALOGS OF RETINOIC ACID

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Dedication

I dedicate this dissertation to my son, David Hieu Holth. May you dream big, work hard to achieve greatness, and be a kind gentleman through it all.

Abstract

Part I

Stevioside is a natural product from the *Stevia rebaudiana* Bertoni plant native to South America. It is one of the major steviol glycosides, with rebaudioside A as the other main natural product, isolated from the *Stevia* plant and comprises 5 – 22% by weight from the dried plant leaves. These natural products are commercially sold as natural sweeteners with reports of being 200 to 300 times sweeter than table sugar. Steviol glycosides are made up of a tetracyclic diterpene, also called *ent*-kaurene, core structure attached to varying sugar chains at the A ring carboxyl group or C-ring hydroxyl group; Stevioside contains three glucose molecules while rebaudioside A contains four glucose molecules. The stevioside diterpene serves as novel template for analog development and exploration because there are numerous directions to diversify the different rings, mainly the A, C and D rings, within the molecule. Stevioside undergoes enzymatic or basic hydrolysis to form the steviol acid, which rearranges to the isosteviol acid under acidic conditions via a Wagner-Meerwein methyl shift of the bridging carbon. These two diterpenes were further explored via a diversity-oriented synthetic approach to yield other diterpene scaffolds from which compound libraries were synthesized in order to explore novel chemical space. Testing of the libraries demonstrate initial activity in several biological assays, thus proving that the *ent*-kaurene core scaffold is a viable starting point to elicit biological activity and for therapeutic development.

Part II

Through the efforts by the National Institutes of Health, research is being conducted to develop non-hormonal reversible male contraceptive agents. Current forms of male contraception include a temporary barrier by means of condoms or permanent surgical sterilization. Their unpopularity and the unmet need for something more tolerable have led to the development of non-hormonal male contraceptive agents targeting the retinoic acid receptor alpha (RARα) nuclear receptor. Previous research has shown that RARα disrupts spermatogenesis during mitosis and the administration of RAR agonists to Vitamin A deficient mice, which is similar to RARα gene knockout mice, reversed infertility effects. Given these promising results, we designed and synthesized retinoids for the development of RARα antagonists. Four compounds were produced and assayed for activity in RARα as well as selectivity against RAR beta (RARβ) and RAR gamma (RARγ).

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List of Abbreviations

Ac	Acetyl
AcCl	Acetyl Chloride
Ar	Aryl
Bn	Benzyl ($C_6H_5CH_2$-)
°C	Degrees Celsius
Calcd	Calculated
CYP	Cytochrome P450
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIBALH	Diisobutylaluminum Hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopryidine
DMB	2,4-Dimethoxybenzyl
DMF	Dimethylformamide
DMP	Dess-Martin Periodinate
DMSO	Dimethylsulfoxide
equiv	Equivalent
TEA	Triethylamine
EtOAc	Ethyl Acetate
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
IC_{50}	50% inhibitory concentration
IR	Infrared Radiation
J	Coupling Constant (NMR)
K_d	Dissociation Constant
LCMS or LC/MS	Liquid Chromatography-Mass Spectrometry
LRMS	Low-Resolution Mass Spectrometry
Me	Methyl
MeI	Methyl Iodide
MeOH	Methanol
mp	Melting Point
MTBE	Methyl Tert-Butyl Ether
MS	Molecular Sieves
NMR	Nuclear Magnetic Resonance
PPh_3	Triphenylphosphine
*p*TSOH or pTSA	*p*-Toluenesulfonic acid
py	Pyridine
i-Pr or iPr	Isopropyl
Rf	Ratio to Front
RT or rt	Room or Ambient Temperature
$t_{1/2}$	Half-Life Time
TBAI	Tetrabutyl Ammonium Iodide
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
TMS	Trimethylsilyl

PART I- STEVIOSIDE LIBRARY DEVELOPMENT

Chapter 1. Design and Synthesis of Diterpene Scaffolds from Stevioside

A. Background of Stevioside, Steviol, and Isosteviol

For centuries, the indigenous people of South America have been using the ka'a he'ê plant, meaning "sweet herb," for its sweetening power and potential medicinal aspects.[1, 2] After introduction to European settlers and continued use by both natives and non-natives, the plant has become scientifically known as *Stevia rebaudiana* Bertoni and commonly called "stevia" (Figure I-1).[3] The plant was named by Italian-Swiss botanist Moises Santiago de Bertoni, when he first gained a sample in 1887.[4] He at first named it *Eupatorium rebaudianum* after Paraguayan chemist Ovidio Rebaudi,[5] but then later corrected the genus as *Stevia,* after the Spanish botanist Pedro Jaime Esteve, who first researched the plants in a territory of Paraguay.[6] While the *Stevia* genus contains over 230 species, *S. rebaudiana* has been the only plant observed to contain sweetening agents.[7] Eight natural products isolated from the *S. rebaudiana* Bertoni leaf tissues were identified with sweetening properties: dulcoside A (**I-1**), rebaudiosides A-E (**I-2**:**I-6**),

Figure I-1. *Stevia rebaudiana* Bertoni plant.

steviolbioside (**I-7**), and stevioside (**I-8**) (Figure I-2).[8] The four main sweeteners are rebaudioside A (**I-2**), rebaudioside C (**I-4**), dulcoside A (**I-1**), and stevioside (**I-8**).[9]

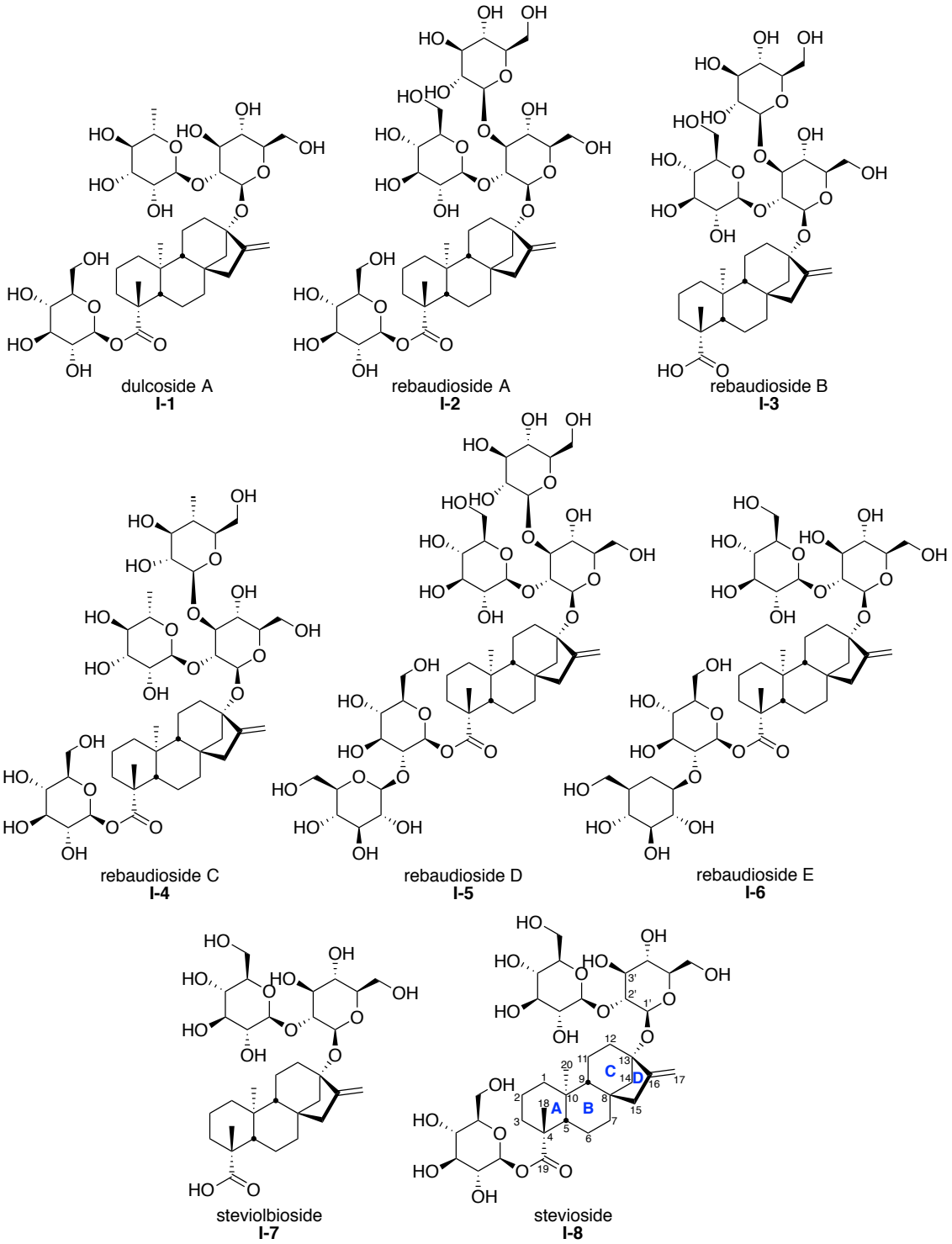
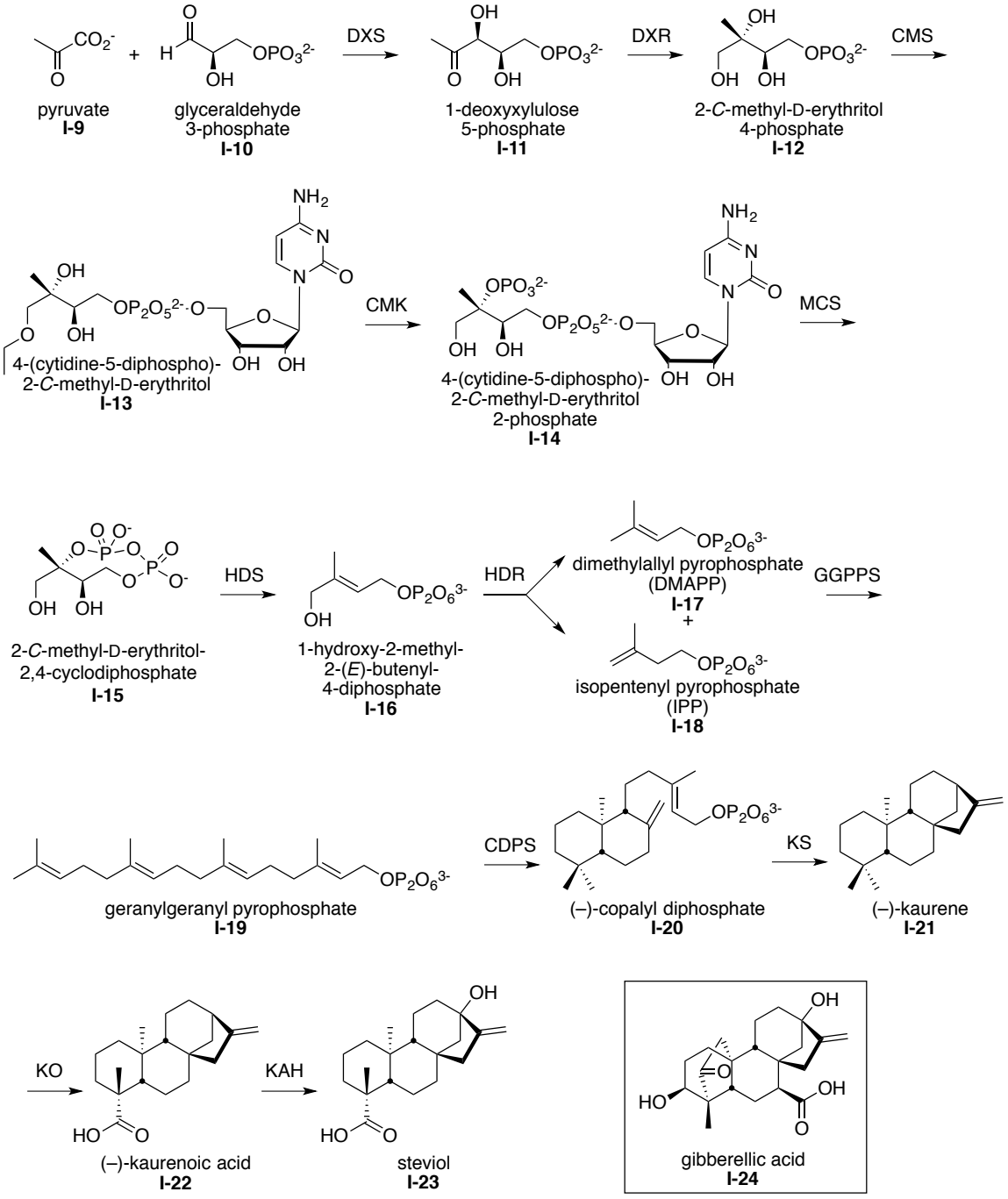


Figure I-2. Stevia sweetening agents.

These compounds are classified as *ent*-kaurene glycosides or steviol glycosides, because they all contain that same kaurenoid precursor. The *ent*-kaurene core is formed by the methylerythritol 4-phosphate (MEP) pathway (Scheme I-1).[10]



Scheme I-1. Biosynthesis of steviol via the MEP pathway**.**

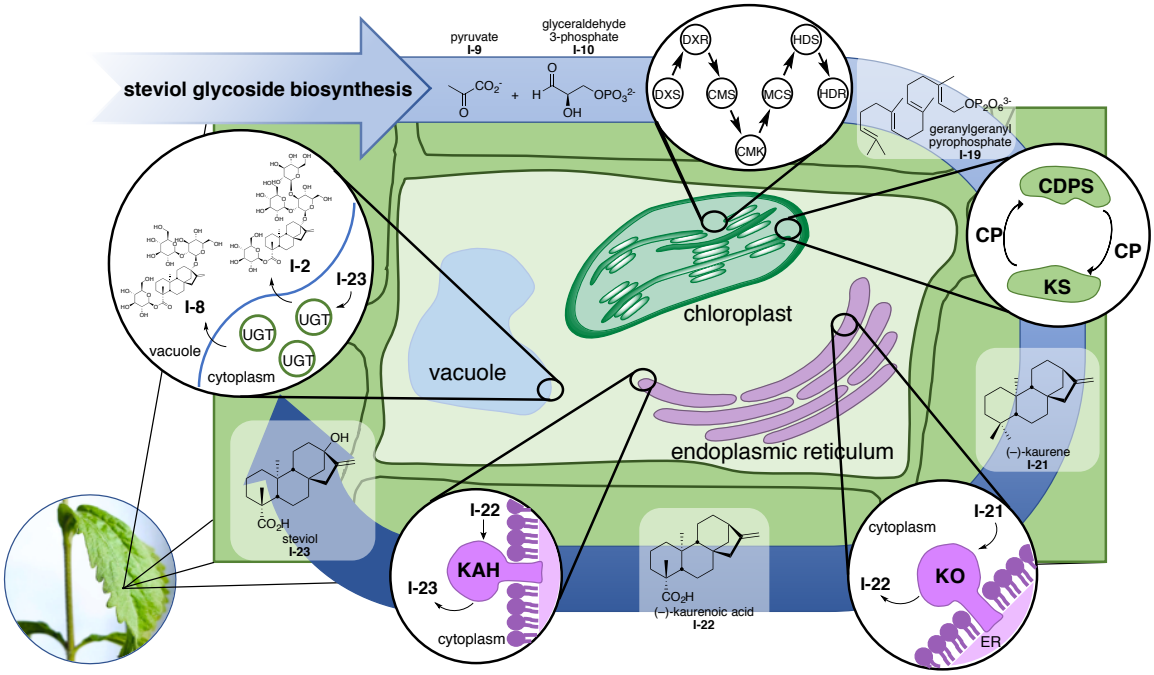
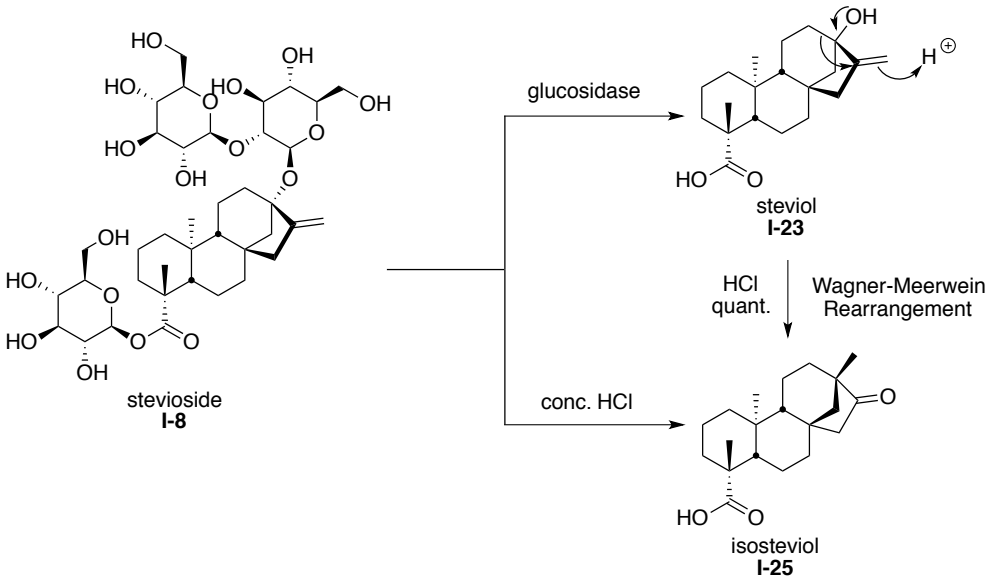


Figure I-3. Biosynthesis of steviol glycoside.[10]

This pathway begins with pyruvate **I-9** and glyceraldehyde 3-phosphate **I-10** in the chloroplasts of the plant cells. From these two common, biosynthetic compounds, deoxyxyulose-5-phosphate (**I-11**, DXP) is generated with the DXP synthase (DXS). DXP can be used for further production of vitamin B1[11] or isoprenoids as with the MEP pathway. With DXP reductase (DXR), the DXP chain is rearranged to form 2-*C*-methyl-D-erythritol 4-phosphate (**I-12**, MEP).[12] From **I-12**, 4-diphosphocytidyl-2-*C*-methyl-D-erythritol synthase (CMS) produces 4-(cytidine-5-diphospho)-2-*C*-methyl-D-erythritol (**I-13**), then 4-diphosphocytidyl-2-*C*-methyl-D-erythritol kinase (CMK) yields 4-(cytidine-5-diphospho)-2-*C*-methyl-D-erythritol-2-phosphate (**I-14**). From there, 2-*C*-methyl-D-erythritol-2,4-cyclodiphosphate (**I-15**) is generated with 4-diphosphocytidyl-2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate synthase (MCS). The next two steps of the synthesis are not well characterized, but essentially, intermediate **I-15** is converted to 1-hydroxy-2-methyl-2-(*E*)-butenyl-4-diphosphate (**I-16**) with 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-

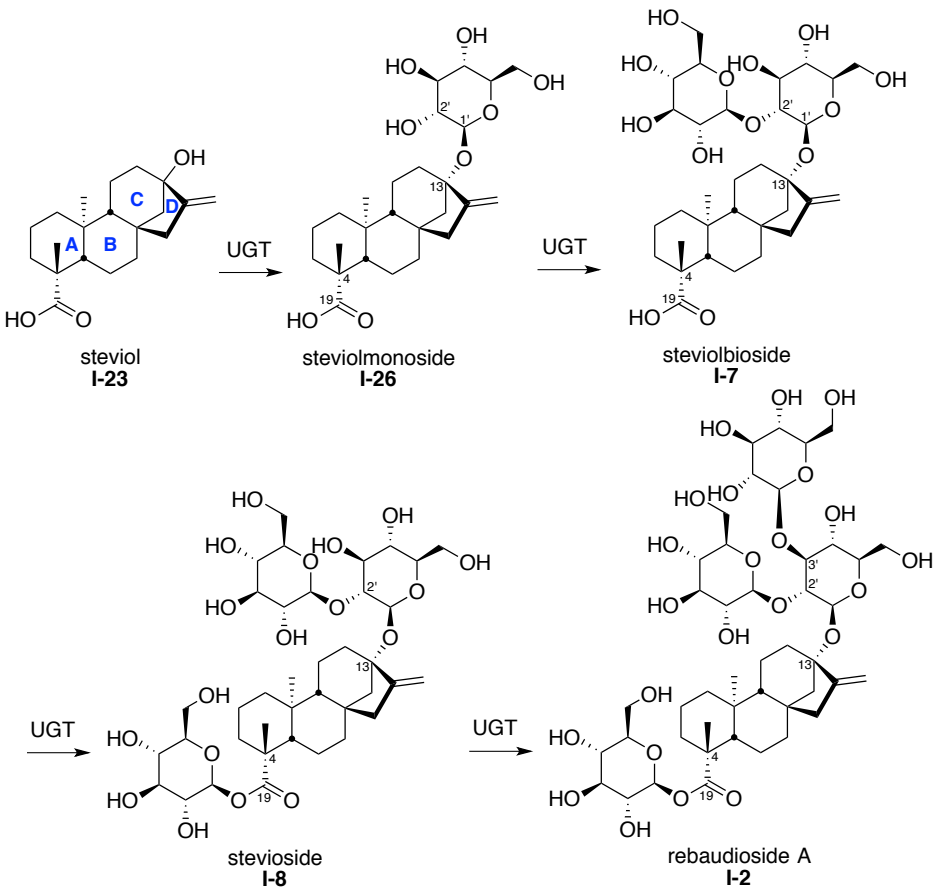
diphosphate synthase (HDS) and then reduced by 1-hydroxy-2-methyl-2(*E*)-butenyl 4-diphosphate reductase (HDR) to provide the MEP pathway products: dimethylallyl pyrophosphate (**I-17**, DMAPP) and its isomer isopentyl pyrophosphate (**I-18**, IPP).[13] DMAPP **I-17** and IPP **I-18** advance to diterpene synthesis starting with the conversion to geranylgeranyl pyrophosphate (**I-19**, GGPP) by GGPP synthase (GGPPS) and three successive condensation steps.[14] Next, copalyl diphosphate (**I-20**, CDP) is made from CDP synthase (CDPS) and then, kaurene synthase produces (–)-kaurene (**I-21**, or *ent*-kaurene) via an ionization dependent cyclization step.[10] Interestingly, GGDP, CDP, and kaurene synthases also play crucial roles in the gibberellic acid biosynthetic pathway and low concentrations of gibberellic acid are found in Stevia plant tissues.[15] However, further research is ongoing to determine the special organization of these enzymes and how they divert the synthesis of steviol glycosides from gibberellic acid (**I-24**, GA).[16]

Next in the steviol glycoside biosynthesis, the kaurene **I-21** is oxidized to kaurenoic acid (**I-22**) by the p450 mono-oxygenase kaurene oxidase (KO). The KO enzyme is also found in the GA biosynthetic pathway and is highly expressed in the same tissues as CDP and kaurene synthases, but the oxidation step has been shown to occur in the endoplasmic reticulum not chloroplasts (Figure I-3).[16] Acid **I-22** is then hydroxylated by kaurenoic acid 13-hydroxylase (KAH) at C-13 to give the steviol diterpene **I-23** (Scheme I-1).[17] The hydroxylation step by KAH is completely separate and different from the GA biosynthetic pathway, marking the divergence of steviol glycoside formation from the gibberellic acid pathway.[18] Additionally, acid treatment of **I-23** will give its isomeric diterpene isosteviol **I-25** via a Wagner-Meerwein rearrangement (Scheme I-2).[19] This alternative structure of steviol **I-23** will be further explored within this chapter.



Scheme I-2. Hydrolysis of stevioside (**I-8**).

Finally, a series of glycosyltransferases append glucose residues onto the aglycone **I-23** to form stevioside (**I-8**).[20] Like with the acid treatment of steviol **I-23**, isosteviol **I-25** can be directly synthesized from **I-8** via acid hydrolysis (Scheme I-2).[19] The first glycosylation occurs at the C-13 hydroxyl of steviol **I-23** to yield steviolmonoside **I-26**,



Scheme I-3. Biosynthesis of stevioside (**I-8**) and rebaudioside A (**I-2**).

followed by another glucose addition to the 13-*O*-glucose at the C-2' of the first glucose on the C-13 end of the steviolmonoside molecule by a UDP-glycosyltransferase (UGT) to give steviolbioside (**I-7**) (Scheme I-3 and Figure I-2). Lastly, the C-19 hydroxyl of the A-ring of **I-7** is glycosylated to generate the desired stevioside (**I-8**). Upon another glycosyl transfer on the C-13 end of **I-8**, rebaudioside A (**I-2**) is produced; stevioside (**I-8**) and rebaudioside A (**I-2**) are the most prominent natural products of the major steviol glycosides isolated from *S. rebaudiana* Bertoni plant. [21] They make up to 20% of the dry leaf weight of the *Stevia* plant.[22]

2. Biological evaluation of stevioside and its metabolites

These diterpene natural products were isolated from the leaves in 1931 and found to be at least 300 times sweeter than sucrose, or table sugar.[23] Specifically, stevioside (**I-8**), which contains one glucose molecule at the C-4 carboxyl end of the A-ring and another two glucose molecules at the C-13 hydroxyl end of the C-ring, has been shown to be 150-250 times sweeter than sucrose.[24] Rebaudioside A (**I-2**), which contains four glucose molecules: one at the C-4 carboxyl end and three at the C-13 hydroxyl end, is 200-300 times more sweet.[24] Due to its sweetness from the steviol glycosides, the stevia plant has become commercially sold as a food additive and non-caloric natural sweetener, after being used as such for centuries by the indigenous Guarani natives in South America.[25] Moreover, the steviol glycosides and their aglycone structures from the stevia plant have been extensively reviewed for their pharmacological effects,[25-31] including glucoregulation for diabetes mellitus treatment,[32] anti-hypertensive activity for blood pressure regulation,[33] anti-tumor effects for cancer therapy,[34] anti-microbial effects,[35] anti-diarrheal or anti-rotavirus capabilities for treatment of gastrointestinal problems,[36] renal function regulation for kidney disease treatment,[37] antiviral activity,[38] antifungal properties,[39] anti-HIV research,[40] hepatoprotective effects,[41] immunomodulatory, and anti-inflammatory effects.[42] Most of these aforementioned studies were performed on mice or rats with ongoing research being conducted for the full effect of stevioside or its metabolites in the human body.[43, 44]

A study of the metabolism of rebaudioside A (**I-2**) and stevioside (**I-8**) from extracts of *S. rebaudiana* plants containing either 85% w/w **I-8** or 90% w/w **I-2** was performed on eleven healthy human subjects and found no levels of either **I-2** or **I-8** in the fecal

analysis.[45] A separate human metabolism study of ten healthy human subjects given 250mg stevioside (**I-8**) capsules for 3 times daily for a period of 3 days did not detect any amounts of stevioside in the blood, urine, or fecal collections examined.[46] Both of these two human studies did find steviol in the stool collections and determined that it was not further degraded. Instead, the human microflora had completely hydrolyzed the steviol glycosides down to the aglycone steviol (**I-23**) metabolite. Moreover, Geuns *et al.* showed that the Caco-2 cell line absorbed steviol but not stevioside.[47] Blood samples taken from the healthy subjects did not identify stevioside (**I-8**), the aglycone steviol (**I-23**), or any other possible steviol metabolites in the blood. Urine analysis from the study by Geuns *et al.* revealed the presence of steviol glucuronide as the major metabolized product.[46] These two studies suggest that stevioside and rebaudioside A are completely metabolized in the colon to steviol, which is then absorbed and glucuronidated in the liver for eventual urine excretion.

Given the increased interest in stevioside (**I-8**) and its metabolites for biological activity evaluation, we determined that this natural product was an excellent source and starting place for our compound library development.

B. Rationale for Developing *ent*-Kaurene Scaffolds

1. Pilot Scale Libraries Initiative

Under the Pilot Scale Libraries Initiative, our goal was to synthesize and submit compounds to become part of the NIH Molecular Libraries Small Molecule Repository (MLSMR) and to be evaluated in the NIH-funded Molecular Libraries Screening Center Network (MLPCN) centers.[48] The MLPCN is a consortium of centers around the United States that perform high throughput screening assays with the library of over 300,000 small

molecules from the MLSMR and the information from these activities are deposited on to the PubChem public database.[49]

Stevioside (**I-8**), a widely used natural sweetener, was chosen for library development for several reasons. First, natural products isolated from plant, marine, and microbial sources are excellent leads for library generation. They are a source of varied molecular structure and continue to be an excellent resource for probing and discovering new therapeutic agents. Therefore, probing biological systems with natural products or natural product-like compounds remains fertile ground to uncover novel lead structures of biomedical significance. Second, carbon skeletons of the complexity of the steviol glycoside natural product cannot be readily accessed via total synthesis. This library project had a unique opportunity to explore the potential of stevioside (**I-8**), which is already produced commercially worldwide through extraction of *Stevia rebaudiana*.[50] The Pilot Scale Libraries project is part of the NIH Molecular Libraries Initiative. The purpose of this work is to synthesize molecules that explore sparsely populated chemical space and then submit them to the MLSMR. The MLSMR is part of the MLPCN and once they are submitted, any screening information will be made available on PubChem, an online database that stores all publicly available structural and biological data, (Scheme I-4).[49]

Scheme I-4. Outline for the PSL.

Unlike many other natural products, stevioside (**I-8**) is readily available in kilogram quantities and can be easily hydrolyzed to provide two scaffolds: steviol (**I-23**) and isosteviol (**I-25**) ideally suited for the development of natural product-derived combinatorial libraries. Library synthesis for these structures is facilitated by the extensive work already published for steviol glycoside chemistry, and chemical transformations that lead to different types of scaffolds are well known.[51-53] Since stevioside (**I-8**), steviol (**I-23**), isosteviol (**I-25**), and related natural products such as gibberellic acid derivatives possess a variety of biological activities, we hypothesized that stevioside-derived libraries could provide promising opportunities to generate hits in screening campaigns.[28, 54-56]

2. Natural Products and Steviol-Related Compounds

Natural products can serve as excellent scaffolds for chemical library development due to their inherent structural diversity and complexity, as compared to synthetic products.[57] In addition, natural products have been shown to occupy areas of chemical space that are generally not well covered by synthetic compounds.[58, 59] Furthermore, natural products, their analogs, and natural product-inspired bioactive compounds have been sources of new drugs over many decades. In a report by Newman *et al.*, over 40% of the 1562 approved drugs from 1981 to 2014 are either natural products, mimic natural products, are derived from natural products, or are synthesized from a natural product (Figure I-4).[60] Therefore, natural products provide a solid platform for the discovery of biologically active small molecules.[61] It has been suggested that because natural products are molded by protein domains, their shape is more likely to be complementary to other protein domains.[62]

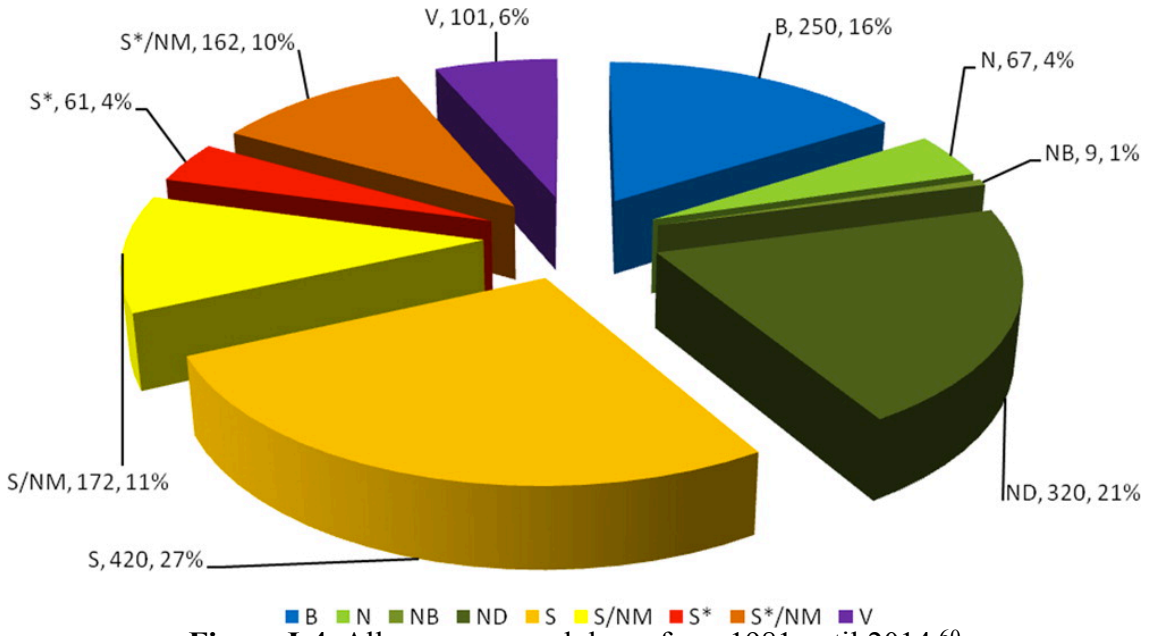


Figure I-4. All new approved drugs from 1981 until 2014.[60]
"B": Biological, usually a large (>50 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host; "N": Natural product, unmodified in structure, though might be semi- or totally synthetic; "NB": Natural product "botanical drug" (in general these have been recently approved); "ND": Derived from a natural product and is usually a semisynthetic modification; "S": Totally synthetic drug, often found by random screening/modification of an existing agent; "S*": Made by total synthesis, but the pharmacophore is/was from a natural product; "V": Vaccine; "NM": Natural product mimic

Additionally, natural products also occupy a large area of chemical space. Chemical space, or multi-dimensional descriptor space, is like a map of the area a molecule occupies. Since it is so vast, chemical space is a region defined by a particular choice of descriptors and limits placed on them. Dobson *et al.* compare the molecular diversity of compounds from combinatorial chemistry, natural products, and drugs (Figure I-5).[63] From the parameters shown, there is still a large amount of "space" or white areas that are not speckled with data.

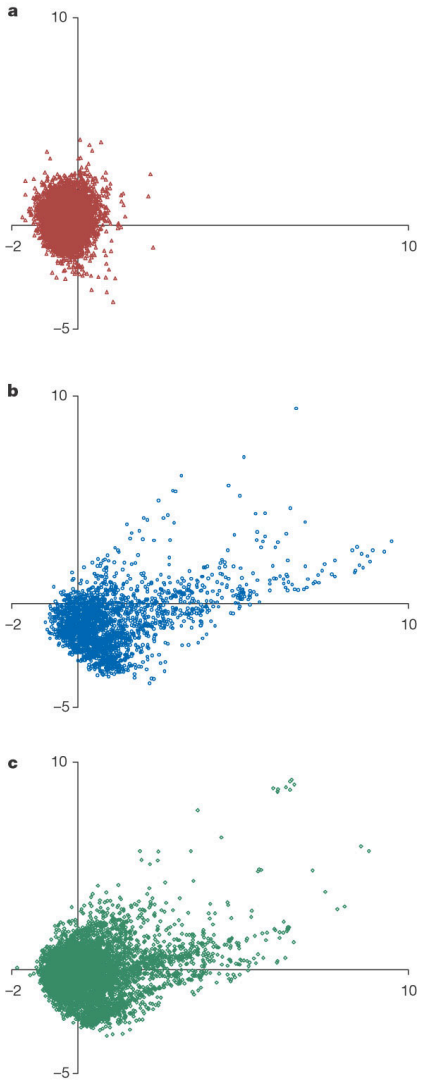


Figure I-5. Chemical space analysis of compounds from a) combinatorial chemistry b) natural products, and c) drugs.[63, 64]

Two major issues associated with the development of high-value information-rich small molecule libraries are achieving skeletal diversity[65-67] and mining areas of biologically relevant chemical space.[64] Because nature can impart chemical diversity in many different areas of chemical space, cheminformatics research for drug discovery aims to chart out these areas and explore their potential.[68] Additionally, Larsson *et al.* introduced ChemGPSNP,[69] a tool for exploring chemical diversity that identifies volumes of chemical space related to particular biological activities and tracks changes in chemical properties

that have been used for natural product drug development.[70, 71] Other more recent cheminformatics tools have been developed to assess chemical space and diversity.[72] With these tools in mind, developing small molecule libraries that are novel and valuable is possible. Stevioside (**I-8**), as mentioned earlier, is easily and readily available and its biosynthetic intermediates could also be used for divergent template development.

Potentially, the steviol glycoside scaffold could provide access to templates representative of the large and diverse family of diterpenes derived from the methylerythritol 4-phosphate pathway[10] and subsequent metabolic processes. Representative diterepenes from this family include platensimycin (**I-27**), and triptolide (**I-28**), labdane (**I-29**) with antibiotic,[73] anticancer,[74] and neuroprotective properties,[75] respectively (Figure I-6).

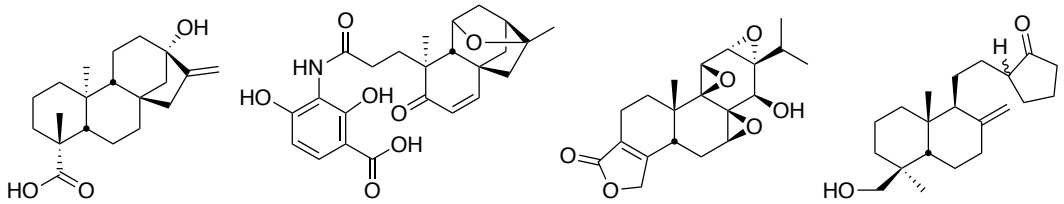


Figure I-6. Structures of steviol-related natural products.

These compounds have attracted much attention from the synthetic community and therefore a large amount of literature has been produced over the last eight decades pertaining to the synthesis[76-81] and structural modification of stevioside[82-84] and structurally-related diterpenes.[85-87] Moreover, studies have revealed that steviol (**I-23**) and isosteviol (**I-25**) have exhibited pharmacological activities;[28] thus, we will unlock their potential by making these molecules as the initial scaffolds for our library.

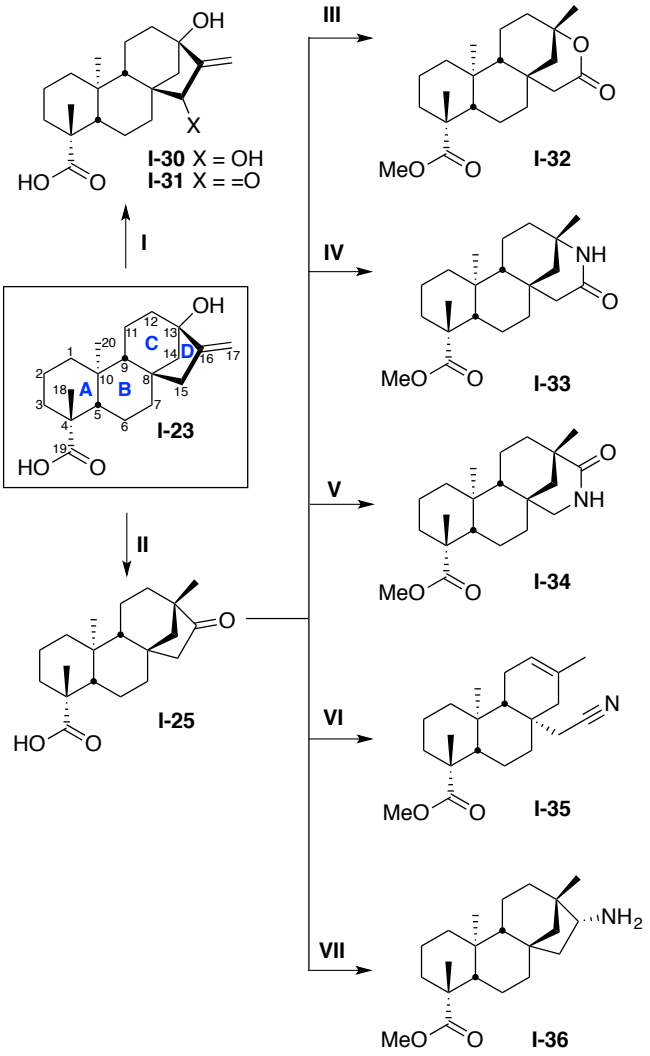
C. Design of Diterpene Scaffolds with Diversity-Oriented Synthesis

1. Background on DOS and its utilities

In order to create functional diverse small-molecule libraries that occupy novel areas of chemical space, a synthetic approach was introduced by Schreiber *et al.* called diversity-oriented synthesis.[88] It is an efficient approach to design and develop multiple small molecules that populate structurally diverse areas of chemical space. "Diversity-oriented synthesis involves the deliberate, simultaneous, and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem."[89] This method provides rapid access to known and previously 'un-tapped' regions of bioactive chemical space to yield complex compound libraries for biological screening.[90] In contrast to target-oriented synthesis (TOS), which focuses on the synthesis of structural analogs in a dense region of chemical space, DOS explores a broad area of chemical space that features compounds with different skeletal and stereochemical moieties.[91] Furthermore, while Fragment-based Drug Design (FBDD) focuses on the synthesis of a small library of compounds or fragments with high structural diversity, DOS is able to achieve a library with both high structural diversity and molecular complexity through a series of parallel reactions.[92] Through DOS, it is possible to create libraries of compounds from a single building block (scaffold) or collections of compounds from structurally similar scaffolds. To generate compounds that are structurally diverse, complex, and have natural product-like properties, we chose to work with stevioside (**I-8**) to provide numerous, different scaffolds from its core skeleton, the *ent*-kaurene.

2. Introduction of Scaffolds

Scheme I-5 illustrates several approaches that can be taken. Path I involves an allylic oxidation of the C-17 methylene of steviol to furnish diol **I-30**, which can be further oxidized to the C-15 ketone analog **I-31**. For path II, the Wagner-Meerwein rearrangement, as discussed above, is achieved with hydrochloric acid to yield isosteviol (**I-25)**. From isosteviol, several different scaffolds can be generated after one or two synthetic steps. Through route III, a Baeyer-Villiger oxidation of isosteviol (**I-25**) produces lactone **I-32**. Formation of an oxime and subsequent Beckmann rearrangement (path IV) yields lactam **I-33**, and photo-Beckman rearrangement leads to the corresponding amide regioisomer **I-34** (path V). As shown for path VI, the Beckman fragmentation product, nitrile **I-35**, can also be obtained with a slight change to reaction conditions. Optimized protocols for isosteviol oxime formation, Beckman rearrangement and Beckmann fragmentation have all been reported by us.[51] In addition to forming novel scaffolds, the functional groups in the molecules can be easily modified for library synthesis.[53] Reductive amination of isosteviol (**I-25**) via route VII yields amine **I-36**.[93, 94] Other obvious modifications involve the carboxylic acid moiety of the A-ring, which can be reduced to the corresponding aldehyde, alcohol, or methyl group. The carboxylic acid can also be converted to an acid chloride or activated ester for amide bond formation, which will be discussed later in this section. Additionally, formation of the acid chloride from the C-4 carboxylic acid and subsequent acyl azide can lead to a Curtius rearrangement toward the formation of a 4-amine analog.[95] The double bond of steviol can be transformed to a hydroxymethyl group or an epoxide, and ozonolysis of the double bond provides the corresponding ketone.[53]

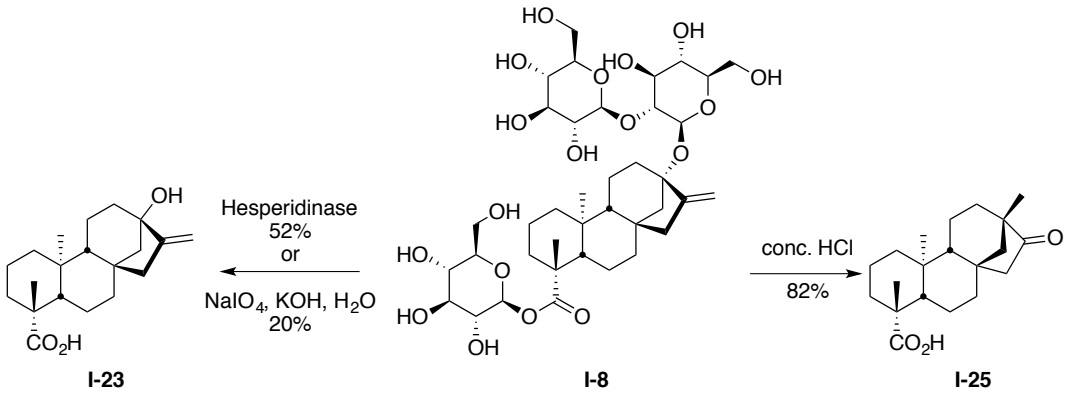


Scheme I-5. DOS approach to the *ent*-kaurene scaffold of steviol (**I-23**) by D-ring modifications.

We focused on steviol (**I-23**) and D-ring modified compounds **I-25**, **I-33**, **I-35**, and **I-36** as the scaffolds for library development. We also describe the synthesis of several pilot scale libraries, their evaluation in multiple high throughput screens and an *in silico* analysis of the chemical and drug-like properties of the compounds prepared in this study.

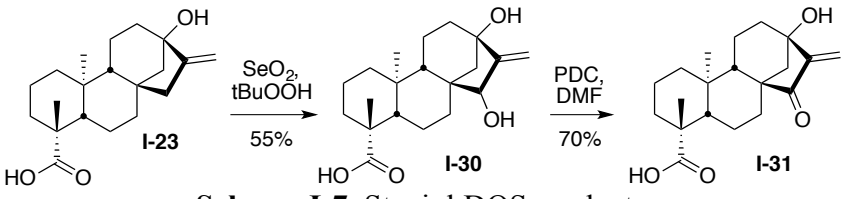
3. Synthesis of DOS Scaffolds

Enzymatic hydrolysis of stevioside under well-known reaction conditions provided steviol (**I-23**) in good yield. Basic hydrolysis also provided steviol (**I-23**) in low yield while acid hydrolysis gave isosteviol (**I-25**) in good yield (Scheme I-6).[21, 96]



Scheme I-6. Hydrolysis of stevioside.

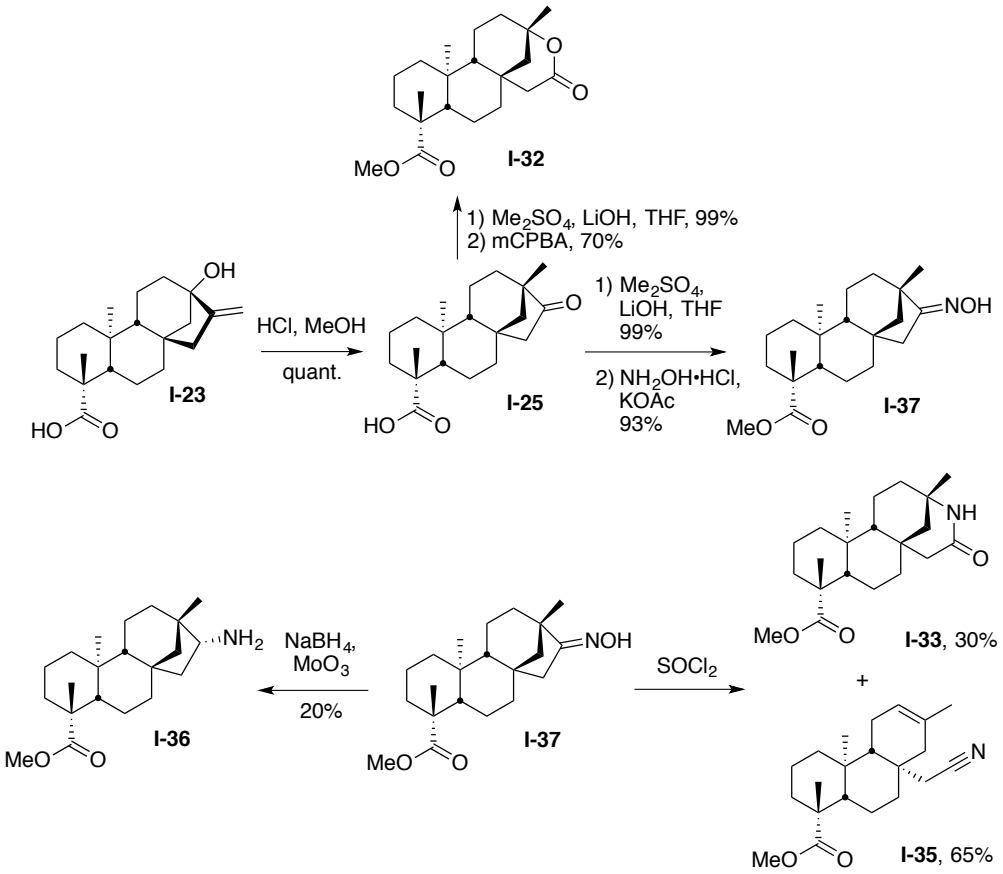
From the steviol scaffold, an allylic oxidation with selenium (IV) dioxide afforded the diol **I-30** in good yield (Scheme I-7).[97] This Riley oxidation step is an excellent way to introduce a hydroxyl moiety into the allylic position of the methylene group.[98] Then, a PDC oxidation of the secondary hydroxyl afforded ketone **I-31**.[99]



Scheme I-7. Steviol DOS products.

When treated with hydrochloric acid, steviol generated the isomerized product, isosteviol (**I-25**), in quantitative yield (Scheme I-8). Isosteviol has a variety of DOS routes

to produce other interesting scaffolds for library development. With *m*CPBA, isosteviol (**I-25**) undergoes a Baeyer-Villiger oxidation to give lactone **I-32** (Scheme 1-8).[100]



Scheme I-8. Synthesis of isosteviol DOS products.

Isosteviol can also be converted to oxime **I-37** with hydroxyl amine under basic conditions in excellent yield. The oxime intermediate can also be reduced with sodium borohydride and molybdenum trioxide to give amine **I-36**.[101] Additionally, treatment of oxime **I-37** with thionyl chloride affords both the Beckmann rearrangement lactam product **I-33** as well as the Beckmann fragmentation nitrile product **I-35**. The freshness of the thionyl chloride can affect the yields of the Beckman reaction products with a significantly decreased lactam **I-**

33 yield if fresh reagent is not used. The chemistry of the Beckmann reaction and its reaction products are described in the next section.[51, 102]

Chapter 2. Exploring the Beckmann Rearrangement Reaction

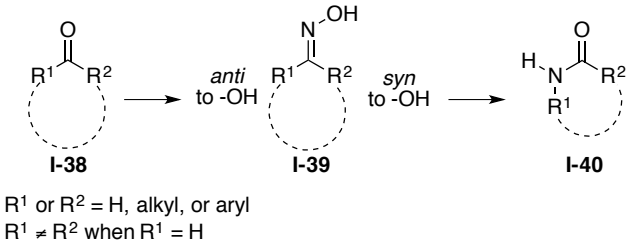
A. Background of the Beckmann Reaction

Since its discovery in 1886 by Ernst Beckmann,[103] the eponymous rearrangement reaction has been a useful tool in organic synthesis to incorporate a nitrogen atom into a molecule. This is typically achieved by a modification of a ketone or aldehyde via oxime formation. The Beckmann rearrangement reaction is an important method to convert oximes in open chain and cyclic systems to the corresponding amides and lactams. Additionally, a Beckmann fragmentation can instead occur during the rearrangement process to form a nitrile group from the initial oxime. The Beckmann reactions have been extensively reviewed because of their versatility and wide synthetic scope.[104-109] Given their utility and significance in synthetic organic chemistry, our group employed this reaction to uncover new steviol and isosteviol scaffolds. This chapter contains sections of a review that we previously published in the book Molecular Rearrangements in Organic Synthesis.[102, 110]

1. Lactam Formation from the Beckmann Rearrangement

The Beckmann rearrangement is the most recognized of the Beckmann reactions and generally describes the conversion of a ketone or aldehyde **I-38** to an oxime **I-39** (Scheme I-9). Oxime **I-39**, under acidic and dehydrating conditions, rearranges to an amide **I-40**. This conversion occurs with the carbon bond *anti* to the oxime hydroxyl group

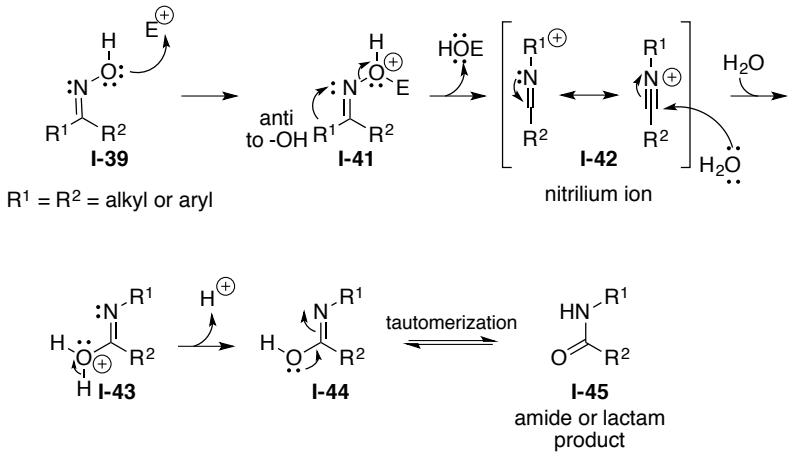
migrating to the nitrogen. Moreover, the Beckmann rearrangement of aldoximes (where R^1 or R^2 = H) produces primary amides via hydrogen migration in a non-stereospecific manner Acyclic ketoximes produce the corresponding secondary amide groups, while cyclic ketoximes yield the lactam moieties (Scheme I-9).



Scheme I-9. General Beckmann rearrangement reaction.

Conventionally, the Beckmann reaction requires a strong acid to initiate the rearrangement reaction; however, there have been reports of milder, greener, and non-acidic conditions for this transformation including: Lewis acids, solid catalysts,[105, 111] ionic liquids,[112] and organocatalysts.[113] Activation of the oxime intermediate **I-39** begins by transforming the *N*-hydroxyl group of the oxime into a better leaving group by reaction with an acid or formation of an ester or an ether. As shown in Scheme I-10, the oxime hydroxyl of **I-39** is converted into a better leaving group with an electrophile, subsequently forming the oxonium intermediate **I-41**. Next in the Beckmann rearrangement, the nitrilium ion **I-42** is formed. This is achieved when the leaving group departs and the substituent situated *anti* to the nitrogen-oxygen (N-O) bond of **I-41** migrates to the nitrogen atom.[106]

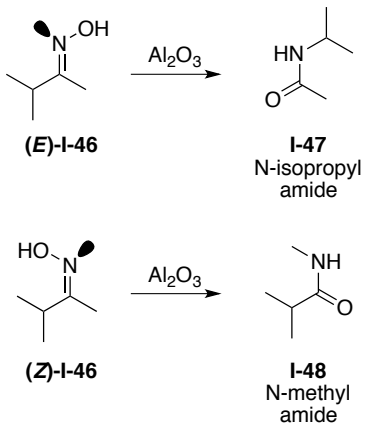
This process maximizes the antiperiplanar electron delocalization of the carbon-carbon (C-C) σ orbital to the antibonding σ* orbital of the N-O bond.[114]



Scheme I-10. Mechanism for Beckmann rearrangement reaction.

Subsequently, the nitrilium ion **I-42** reacts with a nucleophile, such as water, to form intermediate **I-43**. This intermediate is deprotonated to furnish imidic acid **I-44**, which then tautomerizes to yield amide **I-45** (Scheme I-10). In fact, the oxime **I-39** can exist in two different and distinct isomers: the *E* or *anti* isomer and the *Z* or *syn* isomer (Scheme I-11). The (*E*)-isomer **I-46** rearranges to give the *N*-isopropylamide **I-47** upon treatment with aluminum oxide, while the (*Z*)-oxime isomer **I-46** yields the *N*-methylamide **I-48** under

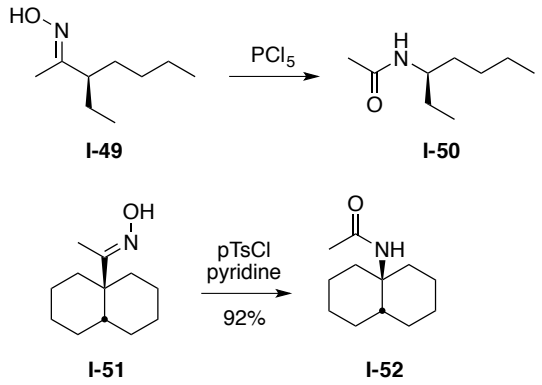
the same normal Beckmann reaction conditions.[115] In some cases, the interconversion of the two distinct isomers takes place. This type of non-stereospecific conversions explains



Scheme I-11. *E*- vs *Z*- oxime isomer.

the different products observed, particularly under acidic conditions and in protic solvents.[116] When both alkyl groups are able to migrate, the more bulky group forms the amide in greater proportion.[105]

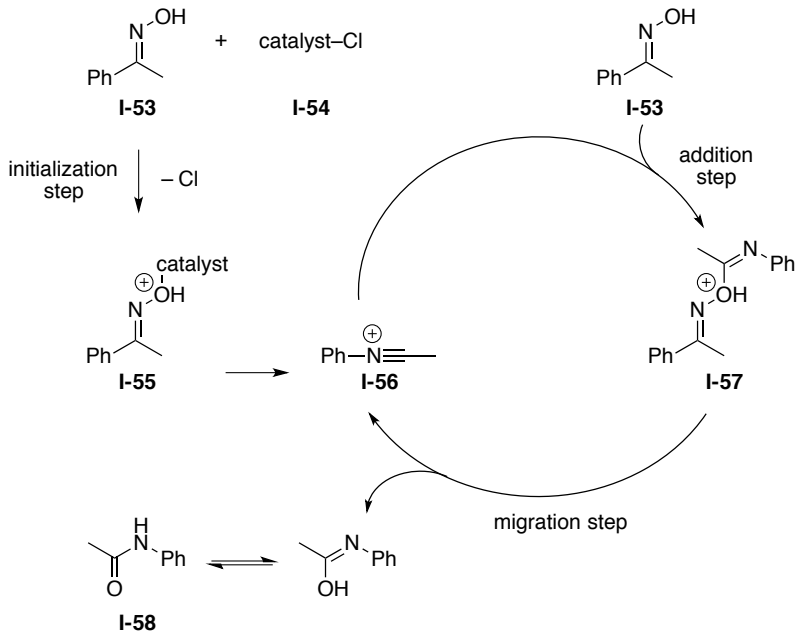
Kenyon *et al.* investigated the stereochemical course of the Beckmann reaction by studying the optically active (*R*,*E*)-3-ethylheptan-2-one oxime **I-49** and its conversion to the corresponding amide **I-50** (Scheme I-12).[117] They treated the dextrorotatory oxime **I-49** with phosphorus pentachloride to afford the dextrorotatory amide product **I-50**.[118] Then, they compared the optical activity of the amide product **I-50** with its corresponding *dl*-amide and determined that the asymmetry of the migrating group was preserved.



Scheme I-12. Examples of retention of stereochemistry during the Beckmann Rearrangement.

Likewise, experiments by Hill *et al.* showed the same retention of stereochemistry of the Beckmann rearrangement on a system with a trisubstituted-stereogenic carbon (Scheme I-12).[119] They treated *cis*-decalin oxime **I-51** with *p*-toluenesulfonic acid chloride in pyridine to produce *cis*-amide **I-52** in very good yield. These examples confirm that the Beckmann rearrangement reaction proceeds in an intramolecular fashion with retention of configuration of the migrating group.[120]

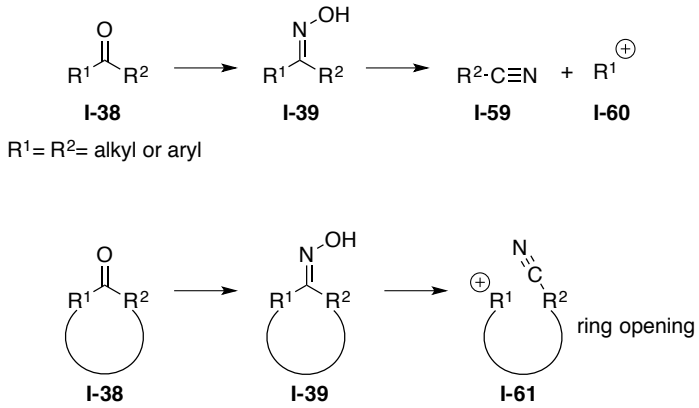
Subsequently, Ericksson and colleagues used DFT calculations to show that in the case of certain organo-mediated Beckmann rearrangements, a self-propagating mechanism is energetically-favored over other mechanisms (Scheme I-13).[121] In their proposal, the chloride reagent **I-54** only initiates the reaction with oxime **I-53** rather than actually catalyzing the reaction.[122] In the initialization step oxime **I-53** reactions with chloride **I-54** to yield oxime complex **I-55**, which then forms nitrilium ion **I-56**. Next, an addition of another oxime **I-53** to nitrilium ion **I-56** forms a dimer-like structure **I-57**. Intermediate **I-57** then undergoes the phenyl migration to produce the rearrangement product **I-58** while simultaneously regenerating the phenyl-nitrilium ion **I-56**.



Scheme I-13. Proposed self-initiation mechanism for Beckmann rearrangement reaction.

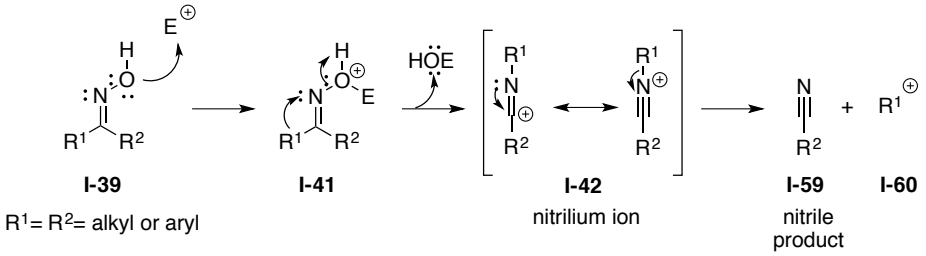
2. Nitrile Formation from the Beckmann Fragmentation

First discovered by Wallach in 1889, the Beckmann reaction can also form a nitrile product instead of the amide by a Beckmann fragmentation reaction. Sometimes called the abnormal or second-order Beckmann rearrangement, or Beckmann fission, this reaction begins like the Beckmann rearrangement reaction with oximes **I-39** derived from linear or cyclic ketones **I-38** (Scheme I-14). The fragmentation occurs when the C-C α bond breaks after shifting to the nitrogen atom, this results in the formation of a nitrile product **I-59** and carbocation intermediate **I-60** (Scheme I-14). In a cyclic system, the fragmentation sequence causes the cyclic oxime ring **I-39** to open and generate the non-cyclic nitrile product **I-61**.



Scheme I-14. Beckmann fragmentation reaction.

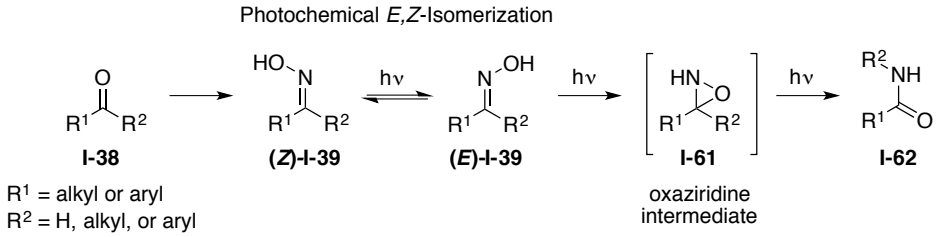
In general, the fragmentation reaction can take place when the hydroxyl group of an oxime is *anti* to a group that can stabilize a positive charge, such as a quaternary carbon or a heteroatom. The process begins with the addition of an electrophile to activate oxime **I-39** (Scheme I-15). From here, the oxonium ion **I-41** is formed and then nitrilium ion **I-42**. Next, **I-42** converts into nitrile **I-59** and carbocation **I-60**. Whether Beckmann rearrangement or fragmentation takes place is wholly dependent on the exact reaction conditions employed, such as using light radiation for promoting the photo-Beckmann rearrangement.



Scheme I-15. Mechanism of Beckmann fragmentation reaction.

3. Photo-Beckmann Rearrangement

In 1963, De Mayo *et al.* observed a different product from the direct irradiation of aldoxime **I-39**.[123] The aldoxime derived from ketone **I-38** forms an oxaziridine intermediate **I-61** before conversion to amide **I-62** (Scheme I-16). This photochemical reaction proceeds through an intramolecular oxygen migration and is commonly considered a photo-Beckmann rearrangement reaction.[124] Ogata and coworkers later determined the exact mechanism for this photochemical reaction through studies with ^{18}O-labeled oximes.[125] Also, the photochemical Beckmann rearrangement is not accompanied by the corresponding alpha-fission to produce nitrile products, like in the Beckmann fragmentation reaction. Instead, the photo-Beckmann reaction is a method to produce the regioisomeric amide product **I-62** (Scheme I-16).

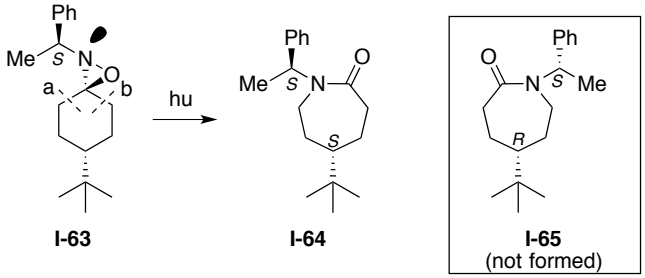


Scheme I-16. Photo-Beckmann reaction.

Traditional acid-catalyzed Beckmann reactions typically show the migration of the carbon bond *anti* to the hydroxyl group of the oxime. Whereas in the photo-Beckmann reaction, stereoelectronic control dictates that the group *anti* to the lone pair of the oxaziridine is the one that migrates to the nitrogen atom. Only empirical evidence of this transformation exists; it suggests that the photo-Beckmann rearrangement reaction involves the photochemical *E,Z*-isomerization of oxime **I-39** (Scheme I-16).[126] The work

of Suginome *et al.* for the photo-Beckmann reaction shows the transformations of the excited singlet *E*- and *Z*-oximes **I-39** into oxaziridine intermediate **I-61** before the molecule is reorganized to the resulting amide **I-62** in a fully concerted manner.

Lattes and coworkers studied oxaziridine **I-63** in which both bonds adjacent to the oxaziridine ring are chemically equivalent which rules out a possible steric influence of neighboring groups (Scheme I-17).[127] X-ray analysis and NMR spectroscopy of **I-63** and its reaction product after irradiation of the oxaziridine, determined the formation of lactam **I-64**. Their work also concluded that the position of the nitrogen lone pair is *anti* to bond "a." Thus, oxaziridine **I-63** generated amide **I-64** by breaking bond "a" and not bond "b" and lactam **I-65** did not form.



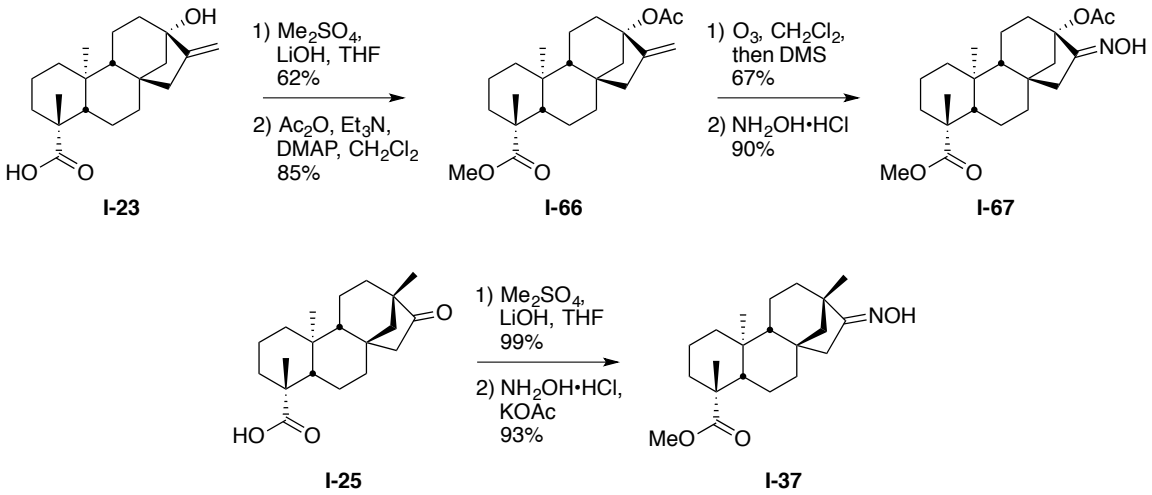
I-63 **I-64** **I-65** (not formed)

Scheme I-17. Mechanism of oxaziridine in photo-Beckmann rearrangement.

The interesting outcomes of the possible Beckmann reactions encouraged us to look into this existing research further when developing scaffolds around steviol and isosteviol. The next section covers our published work with oximes reactions of these aglycones.[51]

B. Oxime Reactions of Steviol and Isosteviol

The following examples show the versatility of the Beckmann reaction in the formation of novel structures by exploring the *ent*-kaurene skeleton of stevioside (**I-8**). Our group initially applied a diversity-oriented approach to synthesize multiple templates from steviol (**I-23**) and isosteviol (**I-25**), but continued to explore various reaction routes from two of those scaffolds: the steviol and isosteviol oximes, **I-67** and **I-37**, respectively (Scheme I-18).[51] To synthesize the steviol oxime, the acid and the hydroxyl moieties were protected to ease the handling of the compounds and the reaction products. First, esterification with dimethyl sulfate followed by acetylation of the C-13 hydroxyl gave intermediate ester **I-66** in good yields for both reactions. Next, ozonolysis of the methylene produced a ketone that was then treated with hydroxylamine to generate the steviol oxime **I-67**. Isosteviol oxime **I-37** was produced by esterification of the C-4 acid followed by oxime formation of the C-16 ketone. From these oximes, multiple scaffolds were prepared from Beckmann rearrangement, Beckmann fragmentation, and photo-Beckmann reactions.

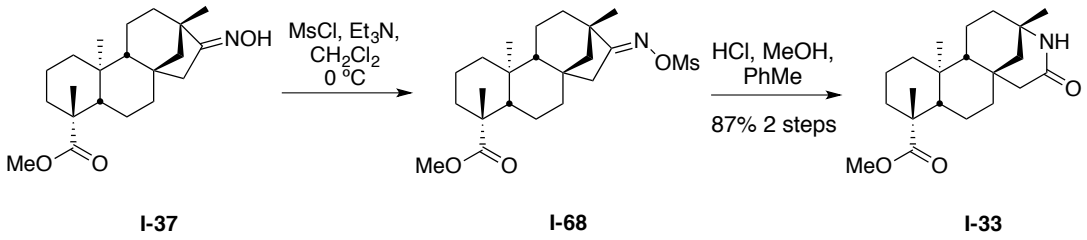


I-23 **I-66** **I-67**

I-25 **I-37**

Scheme I-18. Synthesis of steviol oxime **I-67** and isosteviol oxime **I-37**.

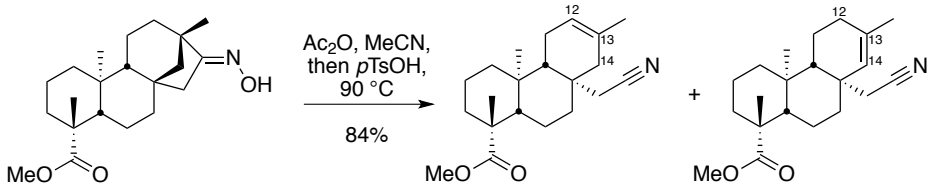
From isosteviol oxime **I-37**, we initially observed the Beckmann rearrangement and fragmentation products (Scheme I-8). When **I-37** was treated with thionyl chloride, an almost 1:2 mixture of the lactam and nitrile products, respectively, was observed. We then tried to change reaction conditions to selectively engender either the Beckmann rearrangement product or the Beckmann fragmentation product in a series of trials (and errors). First, oxime **I-37** was treated with mesyl chloride to produce the mesylated-oxime intermediate **I-68** (Scheme I-23). Then, under acidic conditions made with hydrochloric acid, lactam **I-33**, the Beckmann rearrangement product, was obtained as the sole product, thus shutting out the Beckmann fragmentation pathway.[51] This idea was developed from studying the work of White *et al.* during their morphine synthesis. They formed a brosylated oxime intermediate in acetic acid to provide the desired lactam, whereas the



Scheme I-19. Beckmann rearrangement of oxime **I-37**.

reaction of the corresponding oxime under acidic conditions did not yield any lactam product.[128] Despite being relatively hindered, this amide lends itself well to alkylation and was useful in the development of small-molecule libraries of lactam derivatives, *vida supra*.

Previously, Coates *et al.* reported a Beckmann fragmentation reaction using TsCl in DMF, but this delivered a 2:1 mixture of the alkenes that required a difficult separation.[129] With this problem in mind, we investigated the suitability of this fragmentation pathway for further library production (Scheme I-20). In our hands, a selective Beckmann fragmentation was achieved by reaction of isosteviol oxime **I-37** with acetic anhydride in acetonitrile, followed by treatment with *p*TsOH in acetonitrile at 90 °C. This reaction with *p*-toluenesulfonic acid cleanly delivered the Δ^{12}:Δ^{13} olefinic nitriles **I-35** and **I-69** in an 8:1 ratio, respectively, in 84% yield. Through a single crystallization



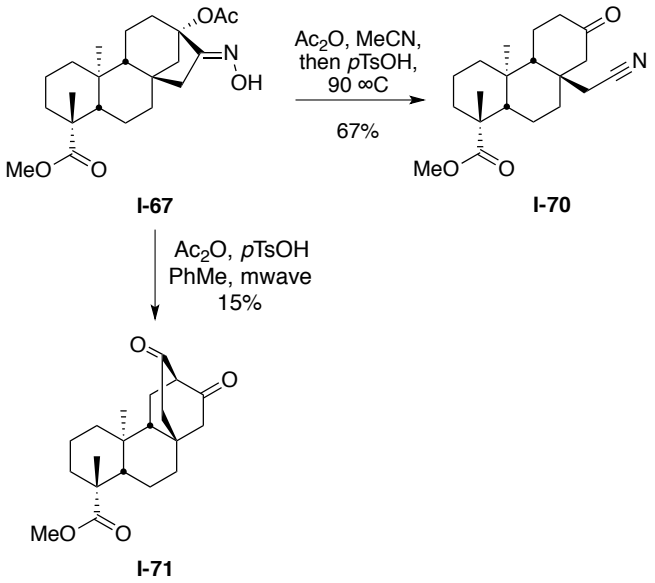
I-37 | **I-35** Δ^{12}, 75% | **I-69** Δ^{13}, 9%

Scheme I-20. Beckmann Fragmentation of isosteviol oxime **I-37**.

with dichloromethane and ethyl acetate, this mixture could be enriched to 20:1 in favor of the Δ^{12}-nitrile product **I-35**. The more robust 2-step procedure perhaps proceeds *via* a tetrahedral intermediate in a similar fashion to that described by White *et al.*, in which the less sterically crowded anti-stereoisomer favors the migration of the bridgehead carbon in the lactam formation.[130] The Beckmann fragmentation reaction is well documented for systems with a quaternary carbon.[131]

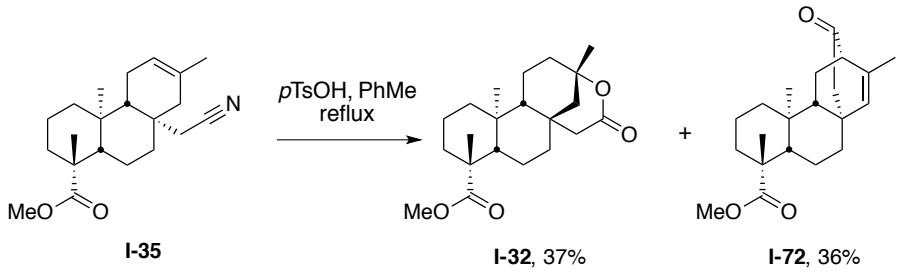
Likewise, we repeated the Beckmann fragmentation reaction with the steviol oxime intermediate **I-67** (Scheme I-21). Upon reaction with acetic anhydride and *p*-toluenesulfonic acid in acetonitrile at 90 °C, the steviol oxime **I-67** exclusively formed

nitrile **I-70**, as expected, in 67% yield. However, when the solvent is changed, the reaction product was completely unexpected. With vigorous heating in toluene, we observed a bicyclo[2.2.2]octane product **I-71**. We determined that the oxime **I-67** undergoes a Thorpe-Ziegler-type cyclization process to afford the octane diketone **I-71**.[51] These experiments suggest that the reaction outcomes are partly determined by the character of the oxime leaving groups. Good leaving groups such as sulfonates promote Beckmann rearrangement pathway, whereas poorer leaving groups such as the acetates promote the Beckmann fragmentation route.



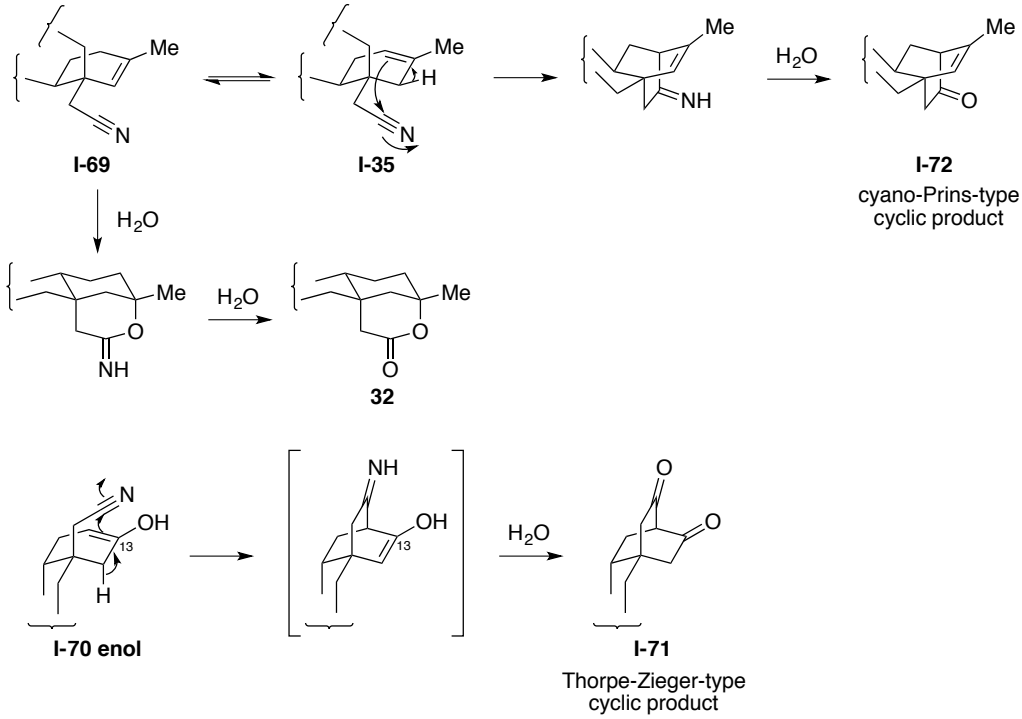
Scheme I-21. Beckmann fragmentation of steviol oxime **I-67**.

Additionally, when the isosteviol oxime **I-37** was subjected to the same reaction conditions as the steviol oxime **I-67** Beckmann fragmentation sequence in an effort to favor the Δ^{12}-nitrile **I-35**, this unexpectedly led to the formation of lactone **I-32** and another bicyclo[2.2.2]octane **I-72** in an almost 1:1 ratio of products in 73% yield (Scheme I-22).



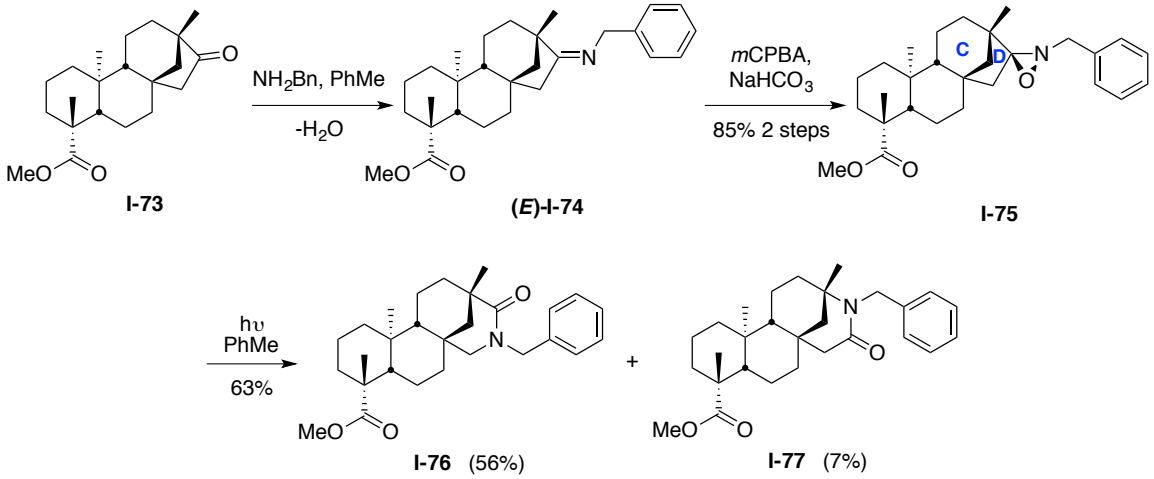
Scheme I-22. Cyclic products from the isosteviol Beckmann fragmentation product **I-35**.

The lactone **I-32** product has been previously observed, *vide supra*, while the cyclic ketone **I-72** product is novel to this work. We conclude that the formation of **I-72** was the result of a cyano-Prins-type cyclization to generate the ketone product.[51] We have proposed the following scheme to show mechanistically how the formations of the cyclic products are possible (Scheme I-23).



Scheme I-23. Proposed mechanisms for the formation of cyclic products.

In our exploration of the Beckmann reaction products of the steviol and isosteviol scaffolds, we also explored the photo-Beckmann rearrangement reaction (Scheme I-24).[132] This work was initially done to verify the isosteviol lactam **I-32** product. We first converted isosteviol **I-25** to its ester **I-73**. From there, the isosteviol ester **I-73** was heated in the presence of benzylamine under dehydrating conditions to afford imine **I-74**.[133] Then, to generate the oxaziridine ring for irradiation, the imine **I-74** was epoxidized with *m*-chloroperoxybenzoic acid to provide oxaziridine **I-75**.



I-73 **(*E*)-I-74** **I-75**

I-76 (56%) **I-77** (7%)

Scheme I-24. Photo-Beckmann of isosteviol ester **I-73**.

Notably, the oxidation occurred exclusively at the *exo* face of the CD-rings. The structure of the oxaziridine was not independently confirmed until we were able to compare the photo-Beckmann lactam product **I-76** with its regioisomeric lactam **I-77** from the photolysis step (Scheme I-24). Equipped with a photochemical immersion well reactor and a 254 nm mercury lamp,[134] we were able to generate a flow reaction and regioselectively deliver the expected photo-Beckmann lactam **I-76** in 56% yield and the minor regioisomer

I-77 in 7% yield. The minor product **I-77** can also be obtained by synthesizing alkylated lactam libraries of amide **I-33**, (*vida infra*, Scheme I-26). For the Beckmann rearrangement, the bond that migrates is the one that is *anti* to the lone pair on nitrogen,[135] however, the outcome of the photo-Beckmann is also stereoelectronically defined. That is to say, the stereoelectronic effect of the oxaziridine ring is able to promote the migration of the N-O bond antiperiplanar to the nitrogen lone pair. Formation of minor regioisomer **I-77** is a result from the *exo*-oxaziridine derived from the other imine isomer, **(*Z*)-I-74** (not shown). As stated earlier, the isolation of the lactam **I-76** helped confirm the assignment of the *E*-imine **I-74**.

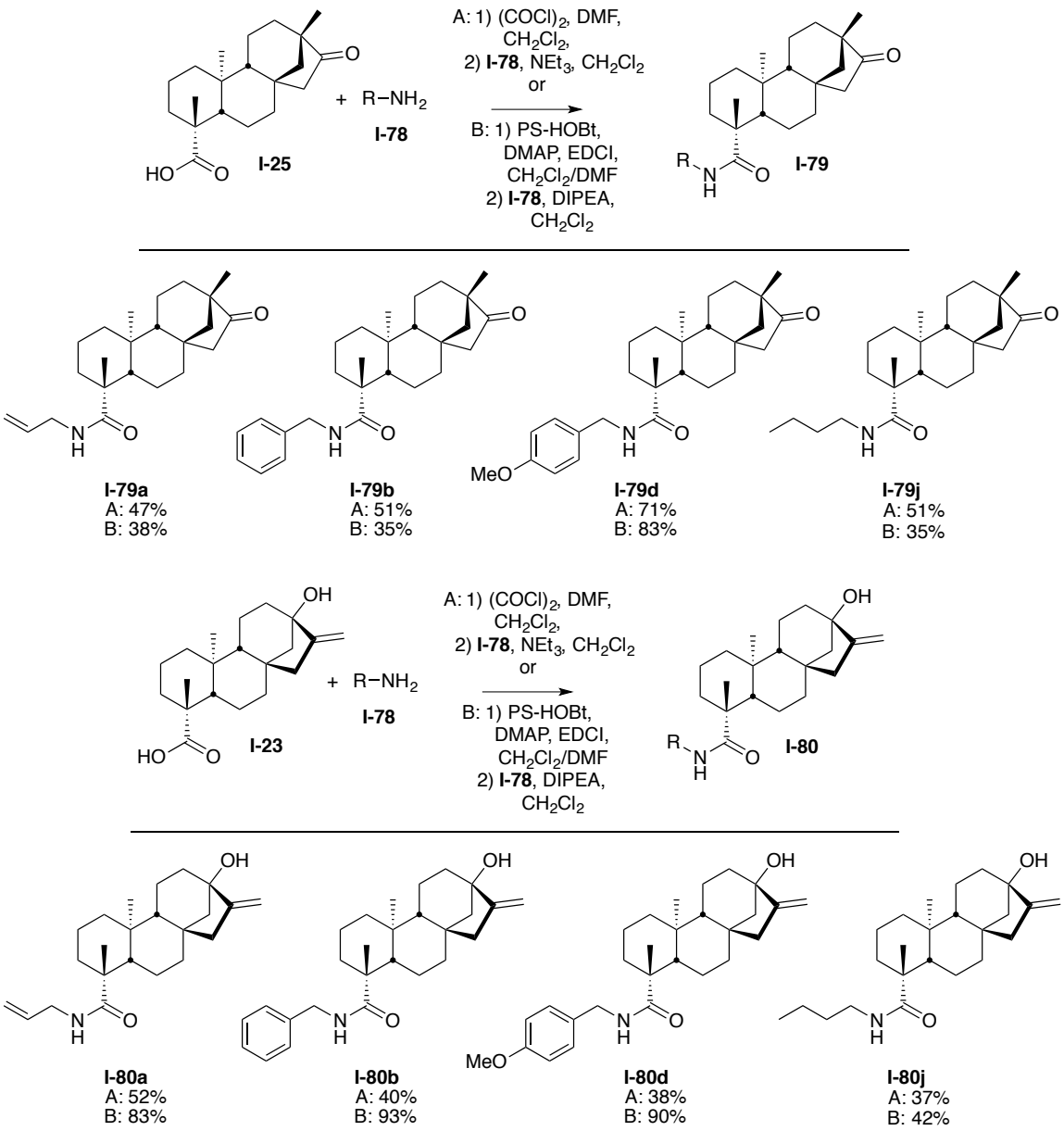
Chapter 3. Design and Synthesis of Small Molecule Libraries from the Stevioside Diterpene Scaffolds

A. Synthesis of Mono-functional Small Molecule Libraries

Steviol and isosteviol serve as scaffolds for library development with reactions aimed at transforming the carboxylic acid moiety of the A-ring in both compounds to amides. Additionally, formation of the oxime intermediate **I-37** from the C-16 ketone of isosteviol was crucial in providing lactam **I-33**, nitrile **I-35**, and amine **I-36** (Scheme I-8). Each of these transformations yielded reaction products that can be further used for library synthesis through amide formation. Another route enlisted explores the D-ring of the *ent*-kaurene core skeleton. D-ring modifications from alkylation of the hydroxyl or amino moieties can further create diverse compounds to explore chemical space.

1. Initial Amide Validation Array

With the steviol aglycones in hand, we set out to prepare a small molecule library using these scaffolds. Validation arrays were set up for the steviol (**I-23**) and isosteviol (**I-25**) molecules for amide bond formation utilizing both solution and solid phase chemistry to provide amides **I-79** and **I-80** (Scheme I-25). These reactions were carried out to compare product yields, ease of work-up, and purity of products. For the solution phase chemistry, steviol (**I-23**) and isosteviol (**I-25**) was converted to the corresponding acid chloride by reaction with oxalyl chloride and then reacted with amines **I-78a**, **b**, **d**, and **j** (Figure I-7) to furnish amides **I-79a**, **b**, **d**, and **j** and **I-80a**, **b**, **d**, and **j**. For the second array, we used polymer-bound 1-hydroxybenzotriazole (HOBt), a reagent that reacts with the acid moiety to form a reactive ester intermediate. Isosteviol was loaded on to the polymer by using the coupling reagent EDCI in the presence of DMAP. The polymer bound activated ester was purified by several washes and then reacted with amines **I-78a**, **b**, **d**, and **j** to form the corresponding amides **I-79a**, **b**, **d**, and **j** and **I-80a**, **b**, **d**, and **j**. Use of the amine as the limiting reagent in this reaction assures high purity of the resulting amide reaction products.



Scheme I-25. Validation array for steviol (**I-23**) and isosteviol (**I-25**) by solution phase (A) and solid phase synthesis (B).

With the solution-phase method we encountered unanticipated problems with solubility during the purification process and NMR analysis showed only 25 to 50 percent conversion of most of the compounds. Eventually, this method was abandoned for an easier solid phase

chemistry approach to obtain multiple compounds in parallel with much easier work up and purification conditions. After careful analysis and comparison of both the solution and solid phase approaches, we decided to carry out a polymer-supported parallel synthesis for the synthesis of our libraries. The resin-bound synthesis approach allowed for a simple filtration to obtain the final products in high purity.

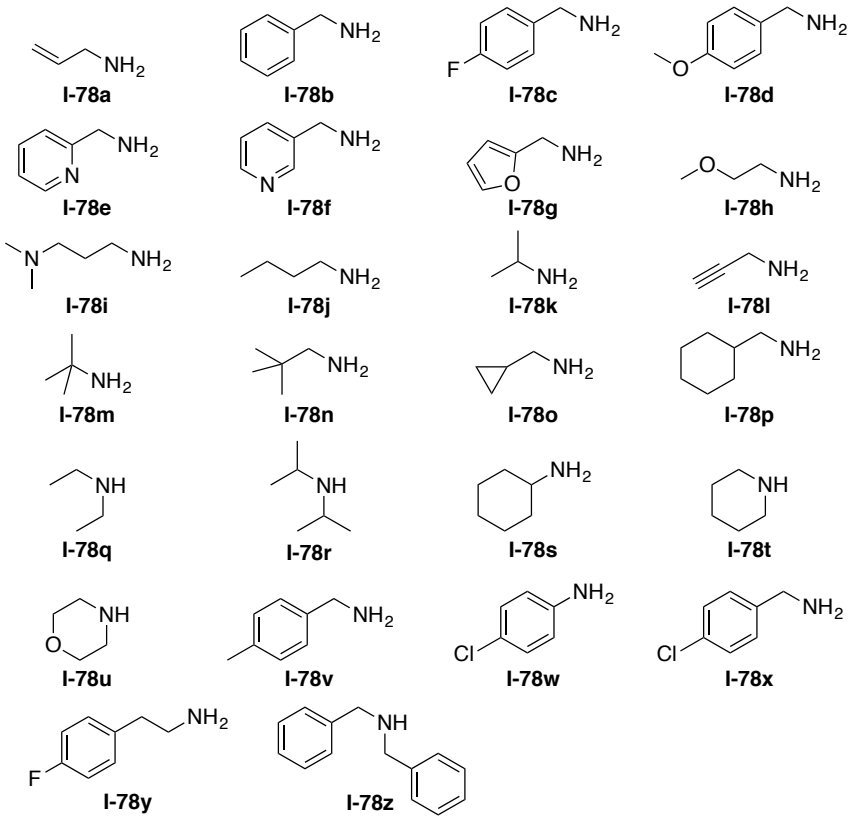
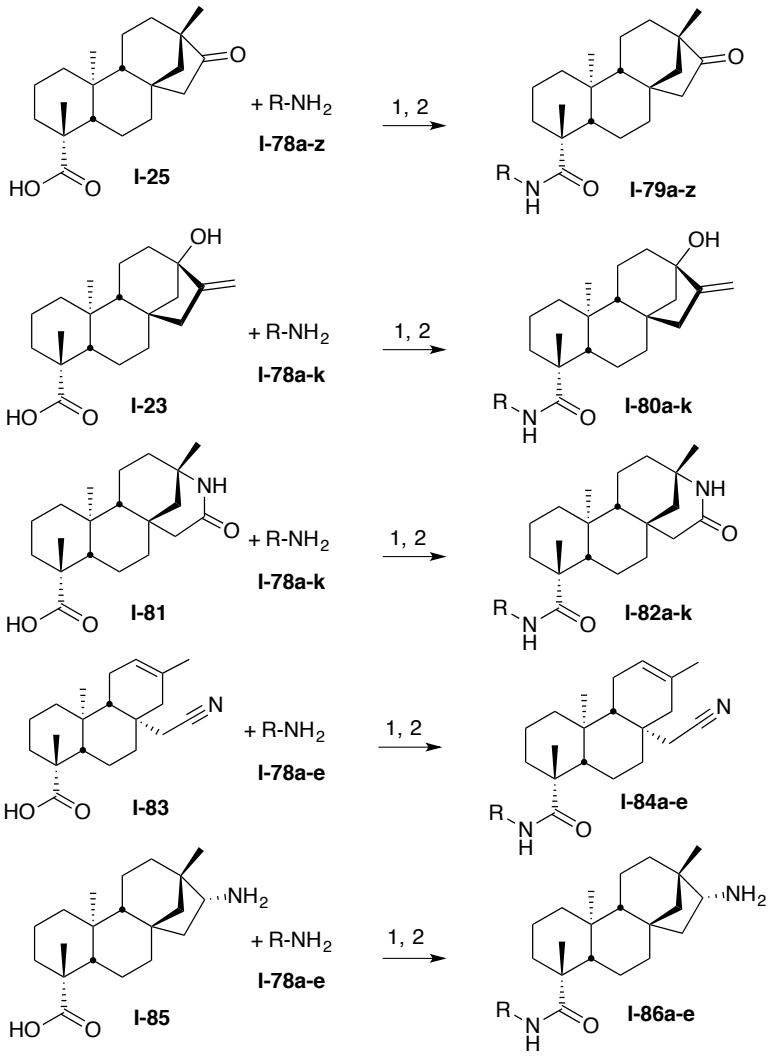


Figure I-7. Amines **I-78a-z** for library synthesis.

2. Amide Libraries

Using parallel solid phase synthesis, we then prepared small libraries from steviol (**I-23**), isosteviol (**I-25**), lactam **I-33**, nitrile **I-35** and amine **I-36** with amines **I-78** (Scheme

I-26). A selection of diverse primary amines was used in the library production (Figure I-7). This work produced almost 60 compounds of diverse amide libraries for evaluation.



Scheme I-26. Amide Libraries **I-79**, **I-80**, **I-82**, **I-84**, and **I-86**.

3. Ether and Amine Libraries

After modifying the carboxylic acid moiety on the A ring, modifications of the C and D rings were explored through alkylation of the hydroxyl group of steviol, reduction

of the ketone of isosteviol, and alkylation of the D-ring lactam (Scheme I-27). A small set of alkyl halides were used for the synthesis of alkylated products (Figure I-8).

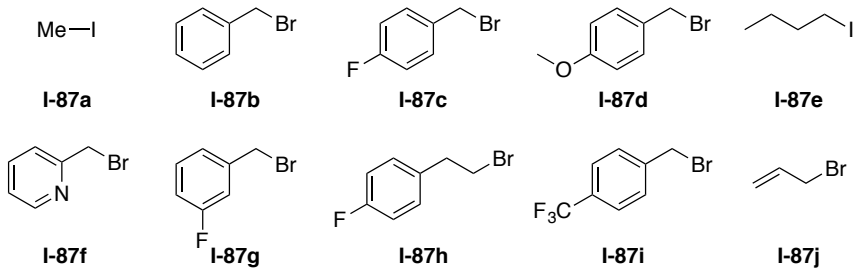
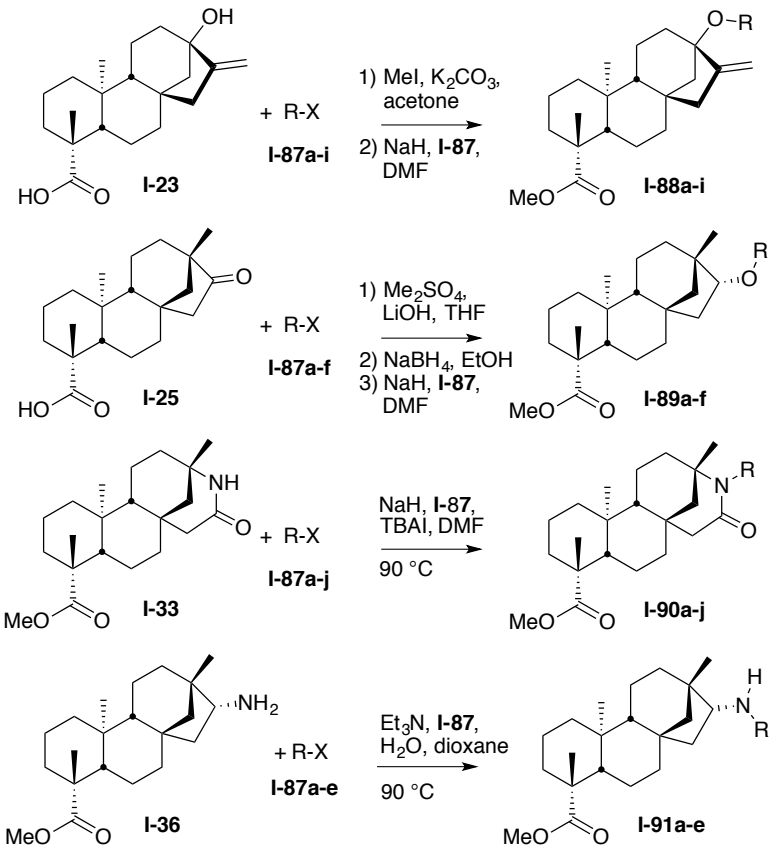


Figure I-8. Alkyl halide compounds for library synthesis.

We first converted the acid functionalities of scaffolds **I-23**, **I-25**, **I-33**, **I-35**, and **I-36** to the corresponding methyl esters. Reacting the hydroxyl group of the steviol methyl ester with alkylating agents **I-87a-i** provided ethers **I-88a-i** (Scheme I-27). The C-16 ketone group of the isosteviol methyl ester was reduced with sodium borohydride to yield the corresponding secondary alcohol, which then was alkylated with **I-87a-f** to provide ethers **I-89a-f**.[136] *N*-Alkylated lactams **I-90a-j** were obtained by reaction of lactam **I-33** with **I-87a-j**, while *N*-alkylated amines **I-91a-e** were generated from reacting amine **I-36** with **I-87a-e**. The alkylation reactions for steviol, isosteviol, and lactam **I-33** were carried out with sodium hydride, because a strong base was necessary to facilitate the removal of the hydroxyl proton for ether formation and amide proton for lactam alkylation. This route created a 30-membered library of *O*- and *N*-alkylated reaction products.



Scheme I-27. Synthesis of ether and amine libraries.

B. Synthesis of Bifunctional Small Molecular Libraries

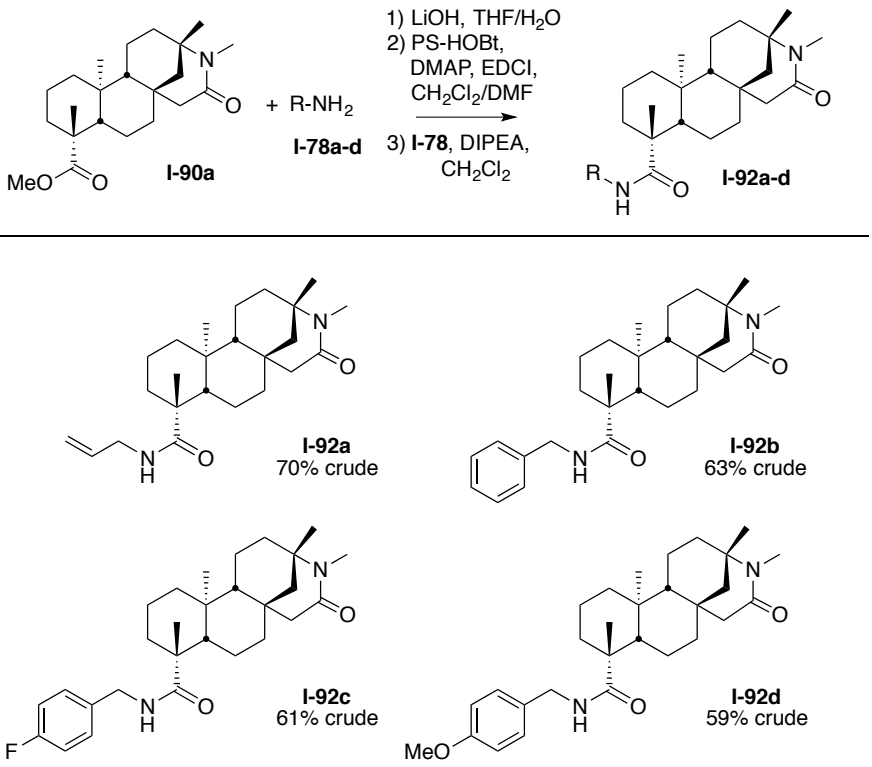
1. Rationale for Bifunctional Libraries

In the drug development and chemical biology disciplines, achieving binding between a target and a small molecule that is generating a biological effect is the starting point that drives further structure-activity exploration. In order to enhance biological activity, often more than one functional group is added to the molecule to form a bi- or multi-functional molecule. A bifunctional molecule can interact either with one protein or with two protein molecules simultaneously. In some instances, a molecule that consists of two protein-binding groups can be connected via a linker.[137] While most linker regions

consist of cleavable groups[138] or drug molecules,[139] there have been molecules with a natural product in the linker region.[140] In the synthesis of our bifunctional libraries, the *ent*-kaurene will essentially serve as the linker with functional groups flanking either end of the scaffold. In addition, drug-like combinatorial libraries can be generated from combinations of "natural product-like" scaffolds and "drug-like" functional groups.[141] As noted by Corson *et al.*, having two functional groups that can potentially bind is better than one, especially in terms of increasing activity.[137] Here, we attempted to expand the potential of biological activity of our compounds by generating bifunctional molecules.

2. Synthesis of Bifunctional Libraries

Bifunctional libraries can be prepared using alkylated products **I-87** through **I-90** and synthesizing their respective amides. Scheme I-28 shows a representative example of one such library: the reaction of *N*-methyl amide analog **I-90a** from previous library synthesis, *vide supra*, with amines **I-78a-d**. First, we hydrolyzed the ester to expose the carboxylic acid for amide production. Then, standard amide formation with polymer-supported chemistry, *vide supra*, generated bifunctional *N*-methyl lactam amides **I-92a-d**.



Scheme I-28. Synthesis of a bifunctional library from amide **I-50a**.

C. Evaluation of Steviol- and Isosteviol-Derived Libraries

1. Biological Activity of Steviol and Isosteviol Library of Analogs

Compounds were then submitted to the NIH Molecular Libraries Small Molecule Repository for biological evaluation.[48] Through PubChem mining, we were able to visualize the activity of our compounds. Table I-1 below provides a listing of compounds that were evaluated in over 50 assays by the Molecular Libraries Screening Center Network so far. Several library members, including previously submitted compounds **I-37**, **I-66**, **I-67**, and **I-93** (Figure I-9) that displayed single digit or double digit micromolar inhibition of target proteins are displayed.

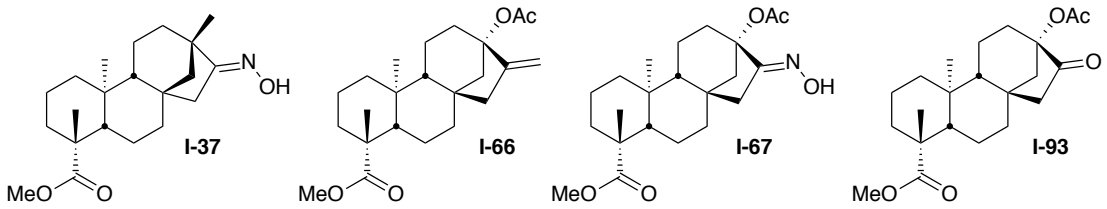
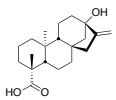
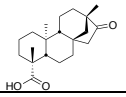
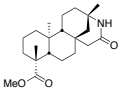
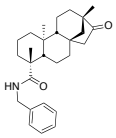


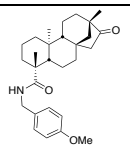
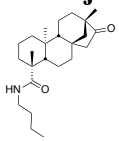
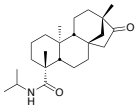
Figure I-9. Other steviol and isosteviol derivatives submitted to the MSLMR.

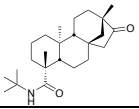
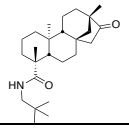
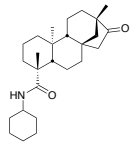
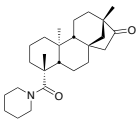
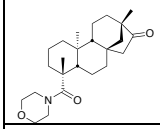
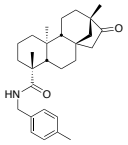
Table I-1 shows current PubChem data on submitted compounds that have been tested by the MLSMR.[142, 143] The compounds were tested in a variety of assays to determine their bioactivity and identified as a chemical probe, active, inactive, inconclusive, or unspecified in the experiments. The table below only displays compounds that were found to be "active" in primary screens or "active" with concentration data in confirmatory assays. Compounds that were found inactive, inconclusive, or unspecified from the bioactivity results, which make up a majority of the available screening data, are not listed. Typically, initial or primary screens were performed first to determine whether or not a compound is active, followed by confirmatory screens to determine the concentration of the compound in the activity screen.

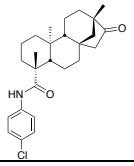
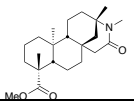
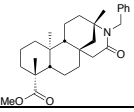
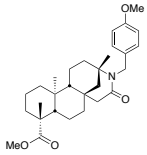
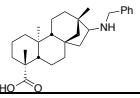
Table I-1. Activity of Steviol and Isosteviol Analogs

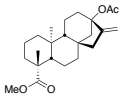
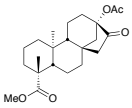
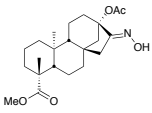
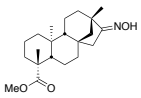
Compound	PubChem ID	Assay ID	BioAssay	Activity (if given)	
				Assay Type	Result or Value (μM)
I-23 	9905087	602438	uHTS identification of modulators of interaction between CendR and NRP-1 using Fluorescence Polarization assay	Primary screen	active
I-25 	42601320	652104	qHTS of TDP-43 inhibitors	Confirmatory screen	IC_{50}[A] 19.953

I-33 	42601318	720706	HTS for bacterial rRNA inhibitors measured in microorganism-based system	Primary screen	active
I-79b 	42601330	540271	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium Falciparum HSP40-mediated toxicity measured in whole organism system	Confirmatory screen	AbsAC[C] 1.427
		686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 18.356
		652041	Cell-based secondary assay to test the inhibitory activity of small molecule on Plasmodium falciparum (HB3 strain) survival in red blood cells measured in cell-based system	Confirmatory screen	AbsAC 21.72
		652047	Cell-based secondary assay to test the inhibitory activity of small molecule on Plasmodium falciparum (3D7 strain) survival in red blood cells measured in cell-based system	Confirmatory screen	AbsAC 30.22
		2825	uHTS Luminescent assay for identification of inhibitors of NALP3 in yeast	Primary screen	active
		435006	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay	Primary screen	active
		504582	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium Falciparum HSP40-mediated toxicity measured in whole organism system	Primary screen	active
I-79d	42601335	624417	qHTS of GLP-1 Receptor Inverse Agonists	Confirmatory screen	EC_{50} 10

		624466	Fluorescence-based cell-based primary HTS assay to identify antagonists of human TAAR1	Primary screen	active
		2825	uHTS Luminescent assay for identification of inhibitors of NALP3 in yeast	Primary screen	active
		504582	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium Falciparum HSP40-mediated toxicity measured in whole organism system	Primary screen	active
I-79j 	42601331	488784	Single concentration confirmation of inhibitors of NALP3 in yeast using Caspase-1-ASC counter screen	Primary screen	active
		2685	qHTS Assay for Lipid Storage Modulators in Drosophila S3 Cells	Confirmatory screen	EC_{50} 0.651
		2825	uHTS Luminescent assay for identification of inhibitors of NALP3 in yeast	Primary screen	active
		463195	uHTS identification of small molecule inhibitors of tim10 yeast via a luminescent assay	Primary screen	active
		435006	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay	Primary screen	active
		488794	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay-retest	Primary screen	active
I-79k 	42601329	2825	uHTS Luminescent assay for identification of inhibitors of NALP3 in yeast	Primary screen	active
		488784	Single concentration confirmation of inhibitors of NALP3 in yeast using Caspase-1-ASC counter screen	Primary screen	active

		488794	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay-retest	Primary screen	active
I-79m 	42601326	2825	uHTS Luminescent assay for identification of inhibitors of NALP3 in yeast	Primary screen	active
I-79n 	42601334	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 23.109
I-79s 	42601327	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 23.109
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 18.356
		602438	uHTS identification of modulators of interactions between CendR and NRP-1 using Fluorescence Polarization assay	Primary screen	active
I-79t 	42601332	602123	Fluorescence polarization-based primary biochemical HTS assay to identify inhibitors of E. coli DNA-binding ATP-dependent protease La (eLon)	Primary screen	active
		624169	Luminescence-based cell-based primary HTS assay to identify agonists of the mouse HTR2A	Primary screen	active
I-79u 	42601333	652048	qHTS of D3 Dopamine Receptor Agonist	Primary screen	active
		652051	qHTS of D3 Dopamine Receptor Potentiators	Primary screen	active
I-79v 	42601336	504582	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium Falciparum HSP40-mediated toxicity measured in whole organism system	Primary screen	active

I-79w 	42601328	602438	uHTS identification of modulators of interactions between CendR and NRP-1 using Fluorescence Polarization assay	Primary screen	active
I-90a 	42601319	-	Inconclusive data in 7 assays and inactive in 417 assays	Primary screen	inactive
I-77/I-90b 	53299290	-	N/A	N/A	N/A
I-90c 	42601337	624132	Shn3: Dual-Go Shn3RL cells measured in cell-based system	Confirmatory screen	AC_{50}^{D} 10.58
		624133	Schnurri-3 Inhibitors: specific inducers of adult bone formation measured in cell-based system	Confirmatory screen	AC_{50} 8.16
		504832	Primary qHTS for delayed death inhibitors of the malarial parasite plastid, 48 hr incubation	Confirmatory screen	IC_{50} 1.651
		504834	Primary qHTS for delayed death inhibitors of the malarial parasite plastid, 96 h incubation	Confirmatory screen	IC_{50} 1.472
		504444	Nrf2 qHTS screen for inhibitors	Confirmatory screen	IC_{50} 14.581
		651820	qHTS assay for inhibitors of Hepatitis C Virus	Confirmatory screen	IC_{50} 12.589
		686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 6.513
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 11.582
		743417	Schnurri-3 Inhibitors: specific inducers of adult bone formation measured in cell-based system	Confirmatory screen	AC_{50} 8.16
I-91b 	42601325	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 20.596

I-66 	42601321	588850	uHTS identification of cystic fibrosis induced NFkB inhibitors in a fluorescence assay	Primary screen	active
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 18.356
		602438	uHTS identification of modulators of interactions between CendR and NRP-1 using Fluorescence Polarization assay	Primary screen	active
I-93 	42601322	686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 20.596
		624466	Fluorescence-based cell-based primary HTS assay to identify antagonists of human TAAR1	Primary screen	active
I-67 	42601323	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 16.360
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50} 16.360
I-37 	42601324	686978	qHTS of inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory screen	EC_{50}^{B} 20.596
		463212	uHTS identification of small molecule inhibitors of tim23-1 yeast via a luminescent assay	Primary screen	active
		463218	Single concentration confirmation of small molecule inhibitors of tim23-1 yeast via a luminescent assay	Primary screen	active

$^{A}IC_{50}$= concentration of an inhibitor required for 50% inhibition of maximum control response; $^{B}EC_{50}$= concentration of an agonist required to produce 50% maximum (effective) response; ^{C}AbsAC= Absolute active concentration with compounds below 10 μM to be considered active hits; $^{D}AC_{50}$= concentration required to elicit a 50% response in an *in vitro* assay

Our small molecule libraries showed activity in numerous assays with a variety of protein targets, including neuropilin-1 (NRP-1), tyrosyl-DNA phosphodiesterase 1

(TDP1), NACHT, Leucine-rich repeat, Pyrin domain-containing-3 (NALP3), hepatitis C virus (HCV), glucagon-like peptide-1 (GLP1), or lipid storage modulators. NRP-1 is a protein receptor for vascular endothelial growth factor; it plays a role in angiogenesis and is being studied for its role in tumor growth progression for anticancer research.[144, 145] The TDP1 enzyme is also investigated for its anticancer development through its mechanism of DNA repair and treatment for spinocerebellar ataxia, which is caused by a TDP1 mutation.[146] Furthermore, many of our compounds showed activity in an assay for NALP3, a protein that is involved in the inflammatory process of the human innate immune system.[147] Primary screens for inhibitors of the NALP3 protein can provide potential starting points for anti-inflammatory therapeutic development.[148] Lactam **I-50c** showed low micromolar activity in a confirmatory inhibitor assay for HCV (Table I-1). Current treatments for HCV infections are costly and poorly accessible, and there is an unmet need to develop a detection method to diagnose those who are infected.[149] Recently, Lin *et al.* created a 33 ureido- and amide-substituted steviol analogs, similar to amide products **I-40a-k** of steviol (**I-23**), to study their inhibitory effects against the Hepatitis B Virus (HBV), which similar to HCV infections can lead to liver cirrhosis and cancer.[95] Their work demonstrates the importance of using natural products and their analogs as sources for therapeutic research as well as implies the potential for isosteviol analogs to be further investigated in HBV drug development. Finally, both GLP1 and lipid storage modulators have been instrumental in diabetes and anti-obesity research.[150, 151] Our compounds showed at least 10 micromolar activity in confirmatory assays for these proteins (Table I-1).

2. Computational Comparison with Commercial Libraries

Additionally, we sought to determine the potential utility of the compounds by measuring parameters beyond the Lipinski's "rule of five."[152] Walters and coworkers previously analyzed over 415,000 molecules reported in the *Journal of Medicinal Chemistry* from 1959 to 2009.[153] In their investigation, they identified eight important properties for all the drugs or drug-like molecules to be molecular weight (MW), cLogP, total polar surface area (TPSA), rotatable bonds, hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), complexity, and fraction of sp^3 carbons (Fsp3). From this information, Hergenrother and coworkers established the importance for compounds to have higher Fsp3 values, from 0 to 1, and lower cLogP values, lower than 5 units, in order to be developed into drugs.[154] The Fsp3 value pertains to the number of sp^3-hybridized carbon atoms in a compound divided by the sum of carbon atoms and this value can indicate lower melting points as well as enhanced aqueous solubility.[155] They calculated four main parameters: Fsp3, cLogP, number of stereocenters, and Tanimoto similarity coefficients of their compounds compared to a 150,000-member ChemBridge collection. In our case, we compared our library to the ChemBridge CombiSet and the Maybridge Diversity Set of compounds, which contain 30,000 and about 54,000 compounds, respectively. We expected this would offer insight in to the diversity of our libraries relative to two commercially-available libraries.

Similarly, our group employed the Pipeline Pilot software to calculate ALogP values,[156] the number of stereocenters, and the Fsp3 ratio.[157] While our compounds have an average cLogP of 4.69, the compounds investigated by Hergenrother *et al.* had an average cLogP of 2.90 (Chart I-1).[154]

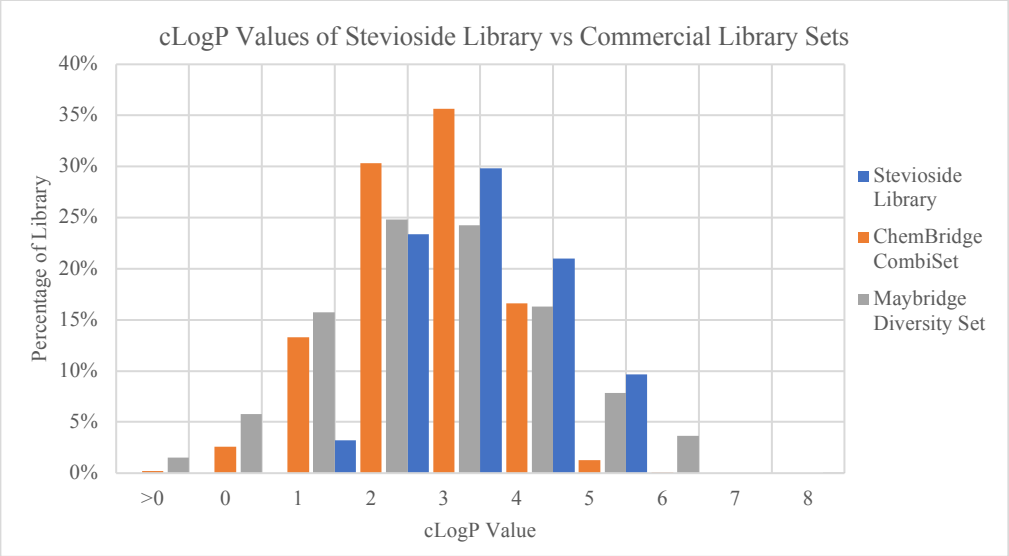


Chart I-1. Comparison of cLogP values.

The ChemBridge and MayBridge library sets that we chose for comparison have an average cLogP value of 3.11 and 3.04, respectively. With such a lipophilic core scaffold, we endeavored to create less lipophilic compounds by adding various substituents and hydrophilic groups that would lower cLogP values. Our Fsp3 calculations yielded an average of 0.79, while the ChemBridge and MayBridge libraries have average Fsp3 values of 0.45 and 0.22, respectively (Chart I-2).

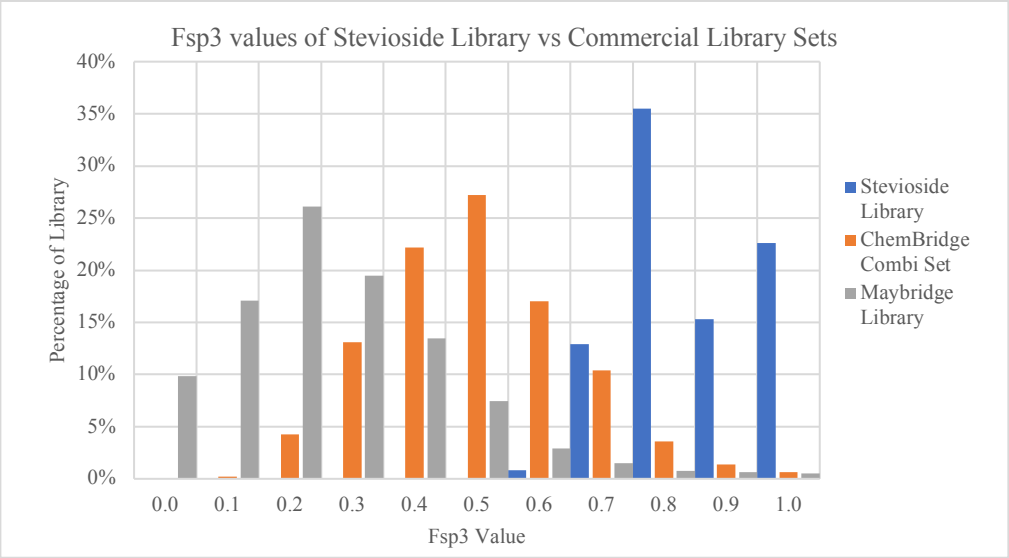


Chart I-2. Comparison of Fsp3 values.

The number of stereocenters in a compound can correlate to its structural complexity; on average, the structures in our compound library contained six stereocenters, while the ChemBridge and Maybridge libraries both have zero averages. Interestingly, Hergenrother's library of compounds had an average of 5.17 stereocenters (Chart I-3).[154] The majority of the compounds in the commercial libraries contain aromatic rings and aryl group substitutions to account for their lack of stereocenters.

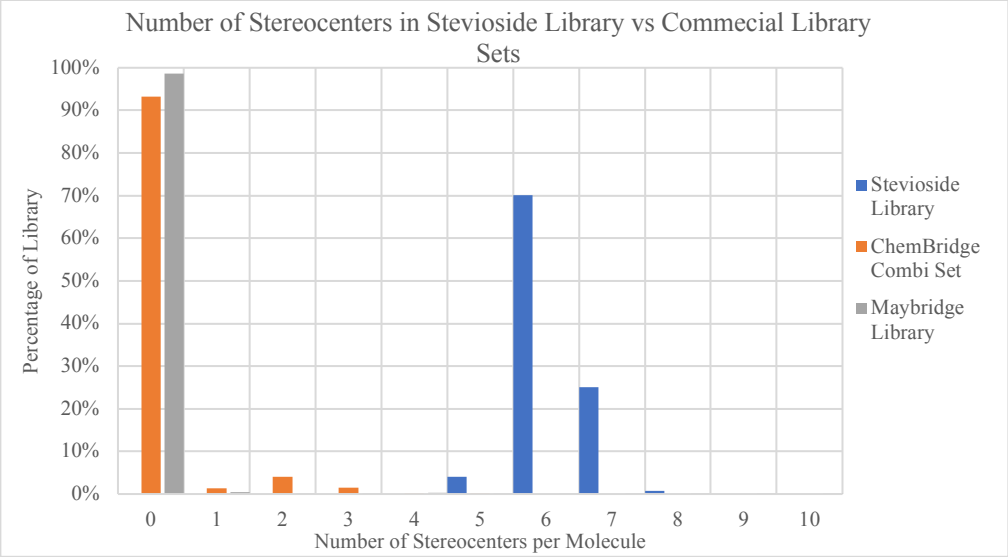


Chart I-3. Comparison of the number stereocenters per molecule.

Our compounds as well as those in the compound library of Hergenrother's group appear to be more structurally complex with a greater number of stereocenters because they are natural product analogs. ChemBridge and Maybridge compound libraries contain compounds with no or few stereocenters. This is perhaps because less complex molecules are relatively easier to synthesize.[158]

Furthermore, similarity coefficients were generated (Tanimoto, ECFP_4) to determine the structural similarity between the compounds in our libraries. These values are graphed in a matrix format in Chart 1 to allow visualization of the pairwise similarity of the compounds. That is an intersection of a column and a row contains the calculated similarity between the compounds in the row and column. Low scores (blue) indicate a relatively high level of difference between the structures, while high scores (red) indicate very similar (0.700< ratio <1.00) or the identical structure (coefficient = 1.00) when a compound is compared to itself. Low (blue) pairwise similarity is desired in a diverse library. The calculated average similarity between compounds in the library was 0.44.

Over half, or 63%, of the complete steviol and isosteviol analog library compounds had similarities below 0.44, represented in Chart 1 as indicated by the blue cells in Chart 1.

Cmpd	24	25	11{1}	10{1}	13{1}	11{5}	10{5}	13{5}	19{2}	17{2}	15{2}	20{3}	20{5}	21{3}	21{5}	22{3}	22{5}	23{1}	26	27	8	5	7	2	1
24	1.000	0.792	0.456	0.406	0.389	0.403	0.346	0.333	0.677	0.329	0.262	0.444	0.463	0.472	0.507	0.438	0.456	0.384	0.737	0.567	0.525	0.576	0.420	0.443	0.525
25	0.792	1.000	0.380	0.455	0.394	0.338	0.405	0.354	0.561	0.333	0.265	0.451	0.470	0.500	0.538	0.444	0.463	0.389	0.750	0.576	0.534	0.614	0.426	0.526	0.435
11{1}	0.456	0.380	1.000	0.695	0.661	0.657	0.440	0.423	0.427	0.425	0.346	0.321	0.329	0.346	0.368	0.333	0.342	0.651	0.378	0.406	0.348	0.391	0.295	0.444	0.691
10{1}	0.406	0.455	0.695	1.000	0.712	0.453	0.631	0.453	0.382	0.437	0.354	0.329	0.338	0.372	0.397	0.342	0.351	0.700	0.370	0.462	0.358	0.424	0.303	0.648	0.444
13{1}	0.389	0.394	0.661	0.712	1.000	0.436	0.453	0.647	0.367	0.419	0.341	0.317	0.325	0.358	0.382	0.329	0.338	0.667	0.355	0.380	0.343	0.644	0.291	0.438	0.424
11{5}	0.403	0.338	0.657	0.453	0.436	1.000	0.721	0.690	0.450	0.487	0.405	0.318	0.294	0.341	0.329	0.345	0.306	0.430	0.337	0.359	0.308	0.346	0.279	0.389	0.594
10{5}	0.346	0.405	0.440	0.631	0.453	0.721	1.000	0.746	0.395	0.507	0.420	0.329	0.305	0.369	0.358	0.357	0.317	0.447	0.333	0.411	0.320	0.378	0.289	0.565	0.375
13{5}	0.333	0.354	0.423	0.453	0.647	0.690	0.746	1.000	0.381	0.487	0.405	0.318	0.294	0.356	0.345	0.345	0.306	0.430	0.321	0.342	0.308	0.567	0.279	0.389	0.360
19{2}	0.677	0.561	0.427	0.382	0.367	0.450	0.395	0.381	1.000	0.434	0.357	0.514	0.432	0.500	0.473	0.468	0.427	0.363	0.529	0.500	0.463	0.507	0.413	0.391	0.463
17{2}	0.329	0.333	0.425	0.437	0.419	0.487	0.507	0.487	0.434	1.000	0.521	0.453	0.411	0.354	0.325	0.507	0.425	0.413	0.316	0.338	0.583	0.342	0.288	0.368	0.357
15{2}	0.262	0.265	0.346	0.354	0.341	0.405	0.420	0.405	0.357	0.521	1.000	0.281	0.241	0.289	0.261	0.322	0.253	0.337	0.253	0.268	0.250	0.272	0.662	0.289	0.282
20{3}	0.444	0.451	0.321	0.329	0.317	0.318	0.329	0.318	0.514	0.453	0.281	1.000	0.656	0.583	0.434	0.712	0.529	0.313	0.427	0.457	0.581	0.464	0.395	0.352	0.342
20{5}	0.463	0.470	0.329	0.338	0.325	0.294	0.305	0.294	0.432	0.411	0.241	0.656	1.000	0.421	0.537	0.529	0.683	0.321	0.443	0.477	0.643	0.484	0.389	0.364	0.353
21{3}	0.472	0.500	0.346	0.372	0.358	0.341	0.369	0.356	0.500	0.354	0.289	0.583	0.421	1.000	0.682	0.575	0.416	0.461	0.453	0.486	0.449	0.515	0.403	0.400	0.370
21{5}	0.507	0.538	0.368	0.397	0.382	0.329	0.358	0.345	0.473	0.325	0.261	0.434	0.537	0.682	1.000	0.429	0.529	0.493	0.486	0.523	0.484	0.556	0.411	0.431	0.397
22{3}	0.438	0.444	0.333	0.342	0.329	0.345	0.357	0.345	0.468	0.507	0.322	0.712	0.529	0.575	0.429	1.000	0.662	0.325	0.421	0.451	0.571	0.457	0.390	0.347	0.338
22{5}	0.456	0.463	0.342	0.351	0.338	0.306	0.317	0.306	0.427	0.425	0.253	0.529	0.683	0.416	0.529	0.662	1.000	0.333	0.437	0.470	0.632	0.477	0.384	0.358	0.348
23{1}	0.384	0.389	0.651	0.700	0.667	0.430	0.447	0.430	0.363	0.413	0.337	0.313	0.321	0.461	0.493	0.325	0.333	1.000	0.351	0.375	0.338	0.400	0.288	0.431	0.418
26	0.737	0.750	0.378	0.370	0.355	0.337	0.333	0.321	0.529	0.316	0.253	0.427	0.443	0.453	0.486	0.421	0.437	0.351	1.000	0.732	0.500	0.548	0.403	0.444	0.431
27	0.567	0.576	0.406	0.462	0.380	0.359	0.411	0.342	0.500	0.338	0.268	0.457	0.477	0.486	0.523	0.451	0.470	0.375	0.732	1.000	0.544	0.596	0.433	0.564	0.467
8	0.525	0.534	0.348	0.358	0.343	0.308	0.320	0.308	0.463	0.583	0.250	0.581	0.643	0.449	0.484	0.571	0.632	0.338	0.500	0.544	1.000	0.554	0.415	0.414	0.400
5	0.576	0.614	0.391	0.424	0.644	0.346	0.378	0.567	0.507	0.342	0.272	0.464	0.484	0.515	0.556	0.457	0.477	0.400	0.548	0.596	0.554	1.000	0.439	0.491	0.450
7	0.420	0.426	0.295	0.303	0.291	0.279	0.289	0.279	0.413	0.288	0.662	0.395	0.389	0.403	0.411	0.390	0.384	0.288	0.403	0.433	0.415	0.439	1.000	0.324	0.314
2	0.443	0.526	0.444	0.648	0.438	0.389	0.565	0.389	0.391	0.368	0.289	0.352	0.364	0.400	0.431	0.347	0.358	0.431	0.444	0.564	0.414	0.491	0.324	1.000	0.640
1	0.525	0.435	0.691	0.444	0.424	0.594	0.375	0.360	0.463	0.357	0.282	0.342	0.353	0.370	0.397	0.338	0.348	0.418	0.431	0.467	0.400	0.450	0.314	0.640	1.000

Chart I-4. A representative chart of the pairwise similarity for the steviol and isosteviol library compounds described herein. Red indicates similarity coefficient of 1.0 (identical) and Blue indicates pairwise structural comparison with similarities less than the average pairwise similarity for the entire library. [a]

[a]A full chart is available in the Appendix A.

D. Concluding Remarks

In conclusion, we have designed and synthesized a number of diverse and novel scaffolds from the stevioside aglycones: steviol **I-23** and isosteviol **I-25**. This research was aimed at eliciting potential biological activity from the modified *ent*-kaurene core given the precedence of natural products exhibiting pharmacological properties that can be used for drug discovery. We have shown different approaches in library development from many different templates as well as explored the synthesis of multiple structures derived from the Beckmann reaction pathways. The submitted compounds from our libraries that have been

tested, demonstrate initial activity in a variety of different assays, thus proving the *ent*-kaurene core scaffold is a viable starting point to elicit biological activity and for therapeutic development.

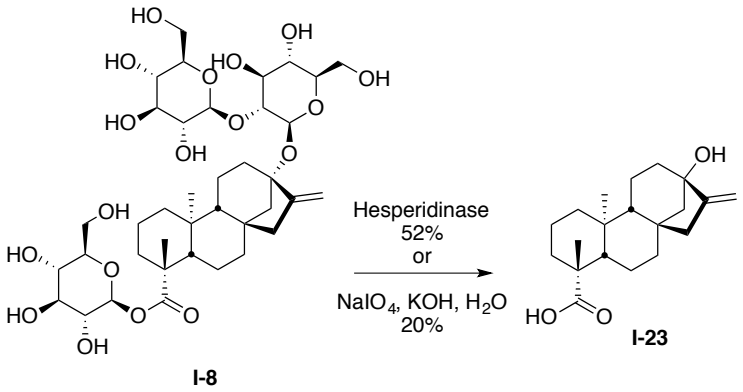
Chapter 4. Experimental Data

A. General Methods

Unless otherwise stated, reactions were carried out open to air with reagent grade solvents without purification. Tetrahydrofuran (THF), toluene, diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2 or DCM) were purified by passage through a bed of activated alumina. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and cerium molybdate stain followed by heating. Infrared spectra (IR) were reported on NaCl or KBr plates using a FT-IR spectrometer. High-resolution mass spectral data were acquired utilizing the electrospray ionization technique. Optical rotations were measured using a polarimeter. ^{1}H NMR spectra were recorded at ambient temperature at 400 MHz and are reported in ppm using a solvent as an internal standard ($CDCl_3$ at 7.26 ppm or CD_3OD at 3.31 ppm). Proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz and are reported in ppm using a solvent as an internal standard ($CDCl_3$ at 77.16 ppm). The data are reported as follows: chemical shift on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Melting points were determined with Electrothermal Digital Mel-Temp 3.0 melting point apparatus. High-resolution mass spectra were recorded with electron-spray

ionization (ESI) or electron ionization (EI) with a Bruker BioTOF II ESI/TOF-MS instrument, while low-resolution mass spectra were recorded with a CombiFlash Rf+ PurIon instrument.

B. DOS Scaffolds

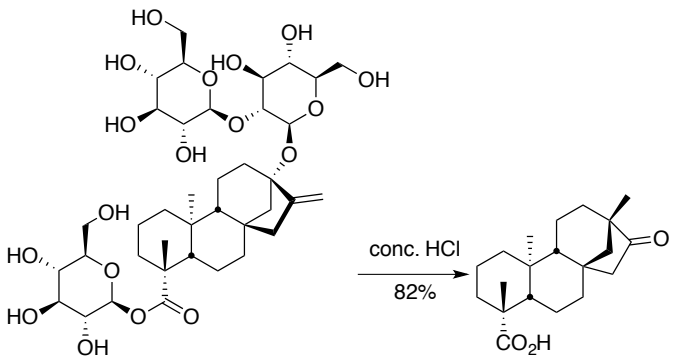


Steviol (I-23).

Enzymatic route: To a 2 L round-bottomed flask containing stevioside (**I-23**) (100 g, 124 mM) in citrate-phosphate buffer (1 L, pH 4) was added hesperidinase enzyme from *Aspergillus niger* (330 g, 100 units).[159] The reaction was allowed to stir at 50 °C for a week, at which time TLC analysis indicated that the starting material was consumed. The precipitate was collected by filtration in a Buchner flask to yield 30 g of crude steviol (**1**) as a colorless powder. The crude compound was then dissolved in ethanol (50 mL) and allowed to crystallize overnight to give steviol (**I-23**, 21 g, 52%).

Non-enzymatic route: To a solution of stevioside (10.0 g, 12.4 mmol) in 200 mL of deionized water was added $NaIO_4$ (7.98 g, 37.3 mmol). The mixture was stirred overnight at 0 °C (Cryocool apparatus). Then, KOH (6.95 g, 124 mmol) was added slowly to the resulting solution, which was subsequently refluxed for another 2 h. The resulting solution

was cooled, acidified with acetic acid to a pH of 3–4, and extracted with EtOAc. The combined extracts were washed with distilled water and brine, dried over MgSO4, and concentrated *in vacuo* to give the crude product, which was then purified by flash chromatography with 25% EtOAc:Hex to give 790 mg of steviol (**I-23**) in 20% yield. mp 203-208 °C (Lit 206-207 ºC);[160] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.83 (d, *J* = 66.2 Hz, 2H), 2.17 – 1.97 (m, 4H), 1.93 – 1.76 (m, 3H), 1.76 – 1.63 (m, 3H), 1.59 – 1.44 (m, 3H), 1.37 (td, *J* = 13.3, 3.9 Hz, 2H), 1.26 – 1.21 (m, 1H), 1.17 (s, 3H), 1.04 – 0.91 (m, 3H), 0.89 (s, 3H), 0.76 (td, *J* = 13.1, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2, 155.7, 103.0, 80.3, 56.8, 53.8, 47.4, 46.9, 43.6, 41.7, 41.2, 40.5, 39.5, 39.3, 37.7, 28.8, 21.8, 20.4, 19.0, 15.4. HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{30}O_3Na$ 341.2087, found 341.2080; $[\alpha]_D^{23}$ –63.8º (*c* 1.00, $CHCl_3$).

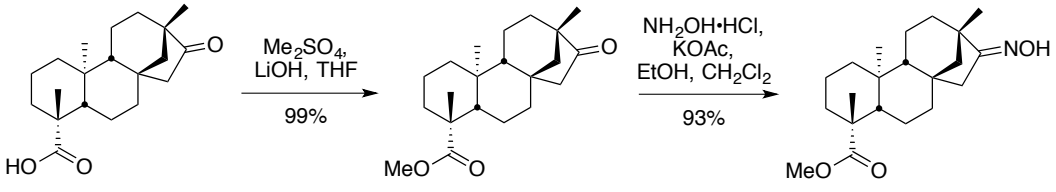


I-8 **I-25**

Isosteviol (I-25).

To a 3L 3-necked round-bottomed flask, mounted on a heating mantle, was added stevioside (**I-8**) (201 g, 250.0 mmol) and MeOH (1 L) at ambient temperature. Upon dissolution of the stevioside, concentrated HCl (75 mL) was added carefully. A reflux condenser was fitted to the flask and the temperature slowly increased until reflux. After 2

h the heating mantle was turned off and the reaction allowed to cool to room temperature overnight. The methanolic solution was then poured with care into a 5 L Erlenmeyer flask (fitted with a mechanical stirrer) of stirring water (3 L). After stirring for 30 minutes, the precipitate was collected by filtration in a 200 mm diameter Buchner flask. The flask was left under vacuum overnight to dry the precipitate to yield 75 g of crude isosteviol as an off-white powder. The crude compound was then dissolved in ethanol (400 mL) and allowed to crystallized overnight to give isosteviol (**I-6**) as colorless crystals (65 g, 82 %): R_f = 0.6 (Hex:EtOAc 2:1); mp 230-232 °C (Lit 230-231 ºC);[161] ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.66 (br s, 1 H), 2.63 (dd, *J* = 18.7, 3.7 Hz, 1H), 2.14 (d, *J* = 13.3 Hz, 1H), 1.87 (dd, *J* = 13.9, 1.9 Hz, 1H), 1.81 (d, *J* = 18.7 Hz, 2H), 1.73 (d, *J* = 12.9 Hz, 2H), 1.65 (ddd, *J* = 26.4, 14.2, 5.0 Hz, 3H), 1.55 (dd, *J* = 11.6, 2.5 Hz, 1H), 1.34-1.51 (m, 4H), 1.24 (s, 3H), 1.18 (ddd, *J* = 14.0, 12.1, 4.7 Hz, 3H), 0.98-1.06 (m, 1H), 0.97 (s, 3H), 0.90 (td, *J* = 13.2, 13.1, 4.1 Hz, 1H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 222.8, 183.9, 57.0, 54.7, 54.3, 48.7, 48.4, 43.7, 41.4, 39.7, 39.5, 38.2, 37.6, 37.3, 28.9, 21.6, 20.3, 19.8, 18.8, 13.3; IR (film) 2957, 1736, 1693, 1455, 1108 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{30}O_3Na$ 341.2087, found 341.2080; $[\alpha]_D^{23}$ –89.1º (*c* 1.00, $CHCl_3$).



I-25 **I-73** **I-37**

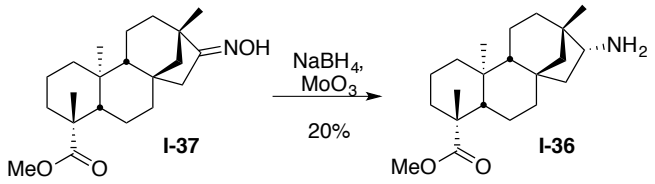
(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-Methyl 4,9,11b-Trimethyl-8-oxotetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (**I-73**).

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*,*E*)-Methyl 8-(Hydroxyimino)-4,9,11b-trimethyl-tetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (**I-37**).

To a flame-dried 500 mL round-bottomed flask was added isosteviol (**I-25**, 20 g, 63 mmol) and dry THF (120 mL). Upon dissolution, $LiOH•H_2O$ (2.9 g, 68 mmol) was added and the reaction stirred for 1 h at room temperature under an atmosphere of nitrogen. Me_2SO_4 (6.5 mL, 69 mmol) was slowly added, then a reflux condenser was fitted to the flask and the temperature was raised to 80 °C for 18 h. The colorless precipitate was then recovered through filtration. The cake was washed repeatedly with Et_2O and then concentrated *in vacuo* to furnish methyl ester **I-73** (18.3 g, 88%). The reaction was quenched with 10% NaOH and then washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent under reduced pressure afforded an additional 2.2 g (11%) of ester **I-73**: R_f = 0.3 (Hex:EtOAc 9:1); mp 200-202 ºC (Lit 202-203 ºC)[1]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H), 2.62 (dd, *J* = 18.6, 3.8 Hz, 1H), 2.18 (d, *J* = 13.3 Hz, 1H), 1.89 (dd, *J* = 13.6, 2.9 Hz, 1H), 1.74-1.85 (m, 2H), 1.57-1.74 (m, 5H), 1.52 (ddd, *J* = 17.8, 12.5, 3.3 Hz, 2H), 1.33-1.45 (m, 3H), 1.19-1.30 (m, 2H), 1.19 (s, 3H), 1.10-1.16 (m, 1H), 0.99-1.06 (m, 1H), 0.97 (s, 3H), 0.92 (dd, *J* = 13.2, 4.2 Hz, 1H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 222.4, 177.8, 57.0, 54.7, 54.3, 51.2, 48.7, 48.5, 48.4, 43.8, 41.5, 39.8, 39.4, 37.9, 37.3, 28.8, 21.7, 20.3, 19.9, 18.9, 13.2; IR (film) 2952, 1744, 1720, 1452, 1240, 1175, 1153 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{32}O_3Na$ 355.2244; found 355.2234; $[\alpha]_D^{23}$ –82.2 (*c* 1.00, $CHCl_3$); reported $[\alpha]_D^{25}$ –69.0º (*c* 1.02, $CHCl_3$).

To a 1 L round-bottomed flask was added **I-73** (18 g, 55 mmol), EtOH (250 mL), CH_2Cl_2 (150 mL), $NH_2OH•HCl$ (10.6 g, 165 mmol) and KOAc (16.2 g, 165 mmol). The mixture was heated to 50 °C for 1 h after which time TLC analysis indicated the starting material was consumed. The mixture was then filtered and the solvent was removed under reduced

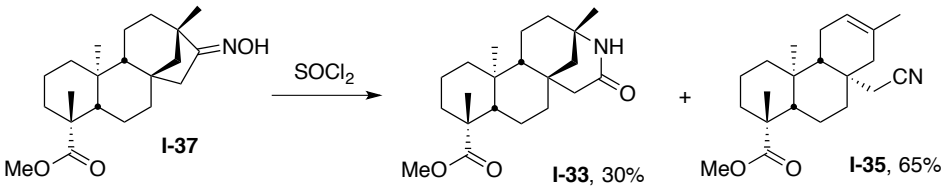
pressure. The colorless residue was taken up in CH_2Cl_2 (200 mL). The organic layer wash then washed with 10% HCl (100 mL), 1M NaOH (100 mL), and brine (100 mL). The aqueous layers were then re-extracted with CH_2Cl_2 (200 mL) and the combined organic layers dried over $MgSO_4$ and filtered. The solvent was then removed under reduced pressure and the residue chromatographed on silica gel (Hex:EtOAc 9:1 → 4:1) to yield oxime **I-37** (18 g, 93%): R_f = 0.2 (Hex:EtOAc 4:1); mp 154-156 ºC (Lit 153-155 ºC);[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (br s, 1H), 3.63 (s, 3H), 2.96 (dd, *J* = 18.6, 3.2 Hz, 1H), 2.17 (d, *J* = 13.5 Hz, 1H), 1.97 (d, *J* = 18.6 Hz, 1H), 1.54-1.89 (m, 8H), 1.38-1.47 (m, 4H), 1.19-1.31 (m, 2H), 1.18 (s, 3H), 1.10 (d, *J* = 3.3 Hz, 3H), 1.07 (t, *J* = 3.3, 3.3 Hz, 1H) 1.00 (td, *J* = 13.5, 13.4, 4.2 Hz, 1H), 0.88 (td, *J* = 13.2, 13.1, 4.2 Hz, 1H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 170.4, 57.1, 56.3, 54.9, 51.2, 43.8, 43.8, 40.9, 40.3, 39.9, 39.5, 38.05, 38.00, 36.8, 28.7, 22.1, 21.7, 20.4, 18.9, 13.1; IR (film) 3292, 2948, 1724, 1453, 1235, 1153, 930, 737 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{33}NO_3Na$ 370.2353; found 370.2338; $[\alpha]_D^{23}$ –57.1º (*c* 1.00, $CHCl_3$).



Methyl (4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-8-Amino-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta [*a*]naphthalene-4-carboxylate (I-36).

To a solution of oxime ester **I-37** (348 mg, 1.00 mmol, 1.0 equiv) in MeOH, cooled to 0 °C (ice bath), was added sodium borohydride (189 mg, 5.00 mmol, 5.0 equiv) then molybdenum (VI) oxide (216 mg, 1.50 mmol, 1.5 equiv). The reaction was stirred at

room temperature overnight. The next day the reaction was filtered, and then the solvent was evaporated. The resulting residue was treated with aqueous KOH (20%) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and then concentrated *in vacuo*. Column chromatography with 5% MeOH/ CH_2Cl_2 provided amine **I-36** in 20% yield. mp 255-258 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 3.60 (s, 3H), 3.12 (dd, *J* = 10.8, 6.6 Hz, 1H), 2.95 – 2.78 (m, 1H), 2.13 (d, *J* = 13.3 Hz, 1H), 1.87 – 1.50 (m, 10H), 1.40 – 1.28 (m, 4H), 1.24 (s, 1H), 1.14 (s, 3H), 1.11 – 1.02 (m, 2H), 1.00 (s, 3H), 0.99 – 0.95 (m, 1H), 0.87 – 0.79 (m, 2H), 0.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 178.2, 59.8, 57.1, 56.2, 55.7, 51.3, 49.8, 43.9, 42.6, 41.3, 41.3, 39.9, 39.2, 38.2, 33.2, 28.9, 24.7, 21.8, 20.3, 18.9, 13.0. HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{36}NO_2$ 334.2746, found 334.2747; $[\alpha]_D^{23}$ –95.3º (*c* 0.468, EtOH).



(3*S*,6a*R*,8a*R*,9*R*,12a*R*,12b*R*)-Methyl 3,12a-Dimethyl-5-oxotetradecahydro-1H-3,6a-methanonaphtho[2,1-d]azocine-9-carboxylate (I-33) and 1*R*,4a*R*,4b*R*,8a*R*,10a*R*)-Methyl 8a-(Cyanomethyl)-4a,7-dimethyl-1,2,3,4,4a,4b,5,8,8a,9,10,10a-dodecahydrophenanthrene-1-carboxylate (I-35).

To a 500 mL flame-dried round-bottomed flask of oxime **I-37** (10.0 g, 28.8 mmol) in chloroform (200 mL), was added thionyl chloride (6.25 mL, 86.3 mmol). The flask was flushed with nitrogen and heated to 60 °C for 10 h until TLC analysis had indicated the consumption of starting material. After reaction cooled to room temperature, the organic

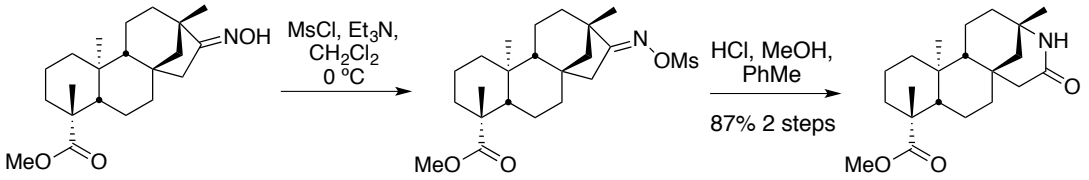
layer was then washed with 1 M NaOH (10 mL) and brine and the aqueous layers were re-extracted with EtOAc (2x20 mL). The combined organic layers were then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was chromatographed on silica gel (Hex:EtOAc 9:1→ CH_2Cl_2:MeOH 9:1) to give nitrile **I-35** (6.23g, 65%) as white needle-like crystals and lactam **I-33** (2.70 g, 27%) as an off-white solid.

I-33: R_f = 0.2 (10% MeOH: CH_2Cl_2); mp 163-165 °C; IR (film) 3193, 1723, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.59 (br s, 1H), 3.62 (s, 3H), 2.91 (dd, *J* = 18.4, 2.2 Hz, 1H), 2.17 (d, *J* = 13.40 Hz, 1H), 1.90 (d, *J* =18.4 Hz, 1H), 1.72-1.89 (m, 4H), 1.58-1.71 (m, 3H), 1.55 (d, *J* = 13.0 Hz, 1H), 1.36-1.50 (m, 3H), 1.28-1.33 (m, 1H), 1.20-1.25 (m, 1H), 1.17 (s, 3H), 1.16 (s, 3H), 1.07 (dd, *J* = 11.4, 3.2 Hz, 1H), 1.00 (td, *J* = 13.5, 13.4, 4.4 Hz, 1H), 0.85 (ddd, *J* = 17.8, 12.9, 3.8 Hz, 2H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 173.6, 57.4, 56.8, 51.8, 51.2, 49.4, 44.2, 43.8, 40.4, 39.9, 39.7, 38.0, 37.8, 35.2, 28.9, 28.5, 19.6, 18.9, 18.8, 13.6; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{33}NO_3Na$ requires 370.2353; found 370.2345; $[\alpha]_D^{23}$ –15.3º (*c* 0.300, $CHCl_3$).

I-35: R_f = 0.5 (Hex:EtOAc 4:1); mp 186-187 ºC; IR (film) 2949, 2242, 1720, 1451, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.36 (d, *J* = 1.7 Hz, 1H), 3.65 (s, 3H), 2.57, 2.42 (dABq, *J* = 16.6, 1.9 Hz, 2H), 2.01-2.19 (m, 4H), 1.93-1.68 (m, 6H), 1.65 (s, 3H), 1.44 (ddd, *J* = 12.8, 4.8, 2.0 Hz, 1H), 1.30 (dd, *J* = 11.8, 5.4 Hz, 1H), 1.19 (s, 3H), 1.12 (dd, *J* = 12.2, 2.3 Hz, 2H), 0.96-1.04 (m, 1H), 0.88 (td, *J* = 13.2, 13.1, 4.2 Hz, 1H), 0.65 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$): δ 177.7, 131.2, 119.8, 119.0, 57.1, 51.7, 51.3, 45.7, 43.7, 39.8, 39.0, 37.8, 37.3, 35.2, 28.6, 23.3, 22.2, 20.0, 19.8, 18.9, 13.3; HRMS (ESI) (*m*/*z*):

[M+Na]$^+$ calcd for $C_{21}H_{31}NO_2Na$ requires 352.2247; found 352.2241; $[\alpha]_D^{23}$ –86.2º (*c* 1.00, $CHCl_3$).

C. Oxime Reaction Compounds

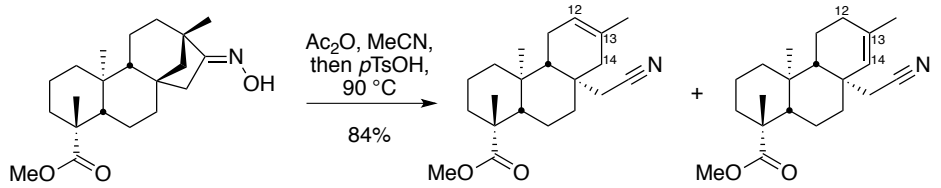


I-37 **I-68** **I-33**

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*,*E*)-Methyl 4,9,11b-Trimethyl-8-(((methylsulfonyl)oxy)imino)tetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (I-68).

To a flame dried 100 mL round-bottomed flask was added oxime (1.00 g, 2.88 mmol) and dichloromethane (40 mL). The flask was cooled to 0 °C (ice bath) then flushed with nitrogen. Triethylamine (5.00 mL) and MsCl (0.450 mL, 5.76 mmol) was added. After 30 min TLC analysis indicated that the starting material was consumed and sat. $NaHCO_3$ (10 mL) was added and the mixture stirred for 10 min. The organic layer was then washed with brine and the aqueous layers re-extracted with CH_2Cl_2 (20 mL). The combined organic layers were then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give mesylate ester **II-68** (1.22 g, 99% crude), which was then carried on without further purification. Then, to another 100 mL flame-dried round-bottomed flask solution of mesylate ester (1.22 g, 2.86 mmol) in MeOH (25 mL) and toluene (5 mL), was added concentrated HCl (416 mg, 11.4 mmol). The mixture was then heated to 60 °C and stirred overnight. The reaction was allowed to cool to room temperature then partitioned

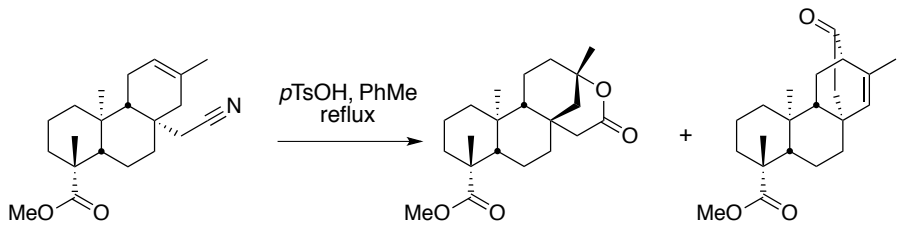
with saturated aqueous bicarbonate and toluene. The organic phase was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield lactam **I-33** (870 mg, 87%).



I-37 **I-35** Δ^{12}, 75% **I-69** Δ^{13}, 9%

(1*R*,4a*S*,4b*R*,8a*R*,10a*S*)-Methyl 8a-(Cyanomethyl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,8,8a,9,10,10a-dodecahydrophenanthrene-1-carboxylate (I-35) and **(1*R*,4a*S*,4b*S*,8a*S*,10a*S*)-Methyl 8a-(Cyanomethyl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydrophenanthrene-1-carboxylate (I-69).**

To a 10 mL flame-dried round-bottomed flask was added oxime **I-37** (10 mg, .029 mmol) and MeCN (5 mL). The flask was then flushed with nitrogen and Ac_2O (6.0 μL, 0.064 mmol) added. After 10 min TLC indicated all the starting material was consumed and *p*TsOH (5.5 mg, 0.032 mmol) was added. The reaction was stirred for 10 min after which time TLC analysis indicated that the reaction was complete. The MeCN was removed under reduced pressure and residue taken up in Et_2O (10 mL) and washed with 10% NaOH, and brine. The aqueous layers were then re-extracted with Et_2O (2x10 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (Hex:EtOAc 9:1→4:1) to yield the nitriles **I-35** and **I-69** (7.9 mg, 84%) as a 8:1 mixture with nitrile **I-35** as the major alkene (7 mg, 75%). Recrystallization with EtOAc:DCM enriched the mixture to 20:1.



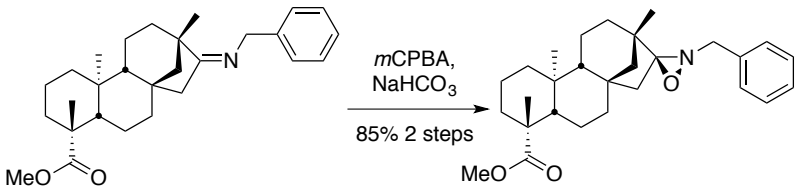
I-35 **I-32**, 37% **I-72**, 36%

(3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-Methyl 3,9,12a-Trimethyl-5-oxotetradecahydro-3,6a-methanonaphtho[2,1-*d*]oxocine-9-carboxylate (I-32) and **(3*S*,4a*S*,4b*S*,8*R*,8a*S*,10a*S*)-Methyl 2,4b,8-Trimethyl-12-oxo-4,4a,4b,5,6,7,8,8a,9,10-decahydro-3*H*-3,10a-ethanophenanthrene-8-carboxylate (I-72).**

To a 50 mL flame-dried round-bottomed flask was added nitrile ester **I-35** (100 mg, 0.30 mmol) in toluene (10 mL). Then *p*TsOH (57 mg, 0.30 mmol) was added. The reaction was heated to 90 °C for 24 h. After the flask was cooled to ambient temperature, the reaction mixture was passed through a silica plug (Hex:EtOAc 9:1). The solvent was then removed under reduced pressure and the residue chromatographed on silica gel (Hex:EtOAc 9:1) to yield both the ketone **I-32** (36 mg, 36%) and lactone **I-72** (39 mg, 37%).

I-32: R_f = 0.1 (Hex:EtOAc 4:1)**;** mp 194-202 °C; IR (film) 2935, 2848, 1732, 1693, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H), 3.07 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.16 (s, 1H), 2.02 (d, *J* = 18.6 Hz, 1H), 1.94-2.00 (m, 1H), 1.67-1.89 (m, 5H), 1.53-1.59 (m, 2H), 1.44 (d, *J* = 8.2 Hz, 1H), 1.36-1.40 (m, 1H), 1.34 (s, 3H), 1.24 (ddd, *J* = 14.3, 9.5, 4.2 Hz, 3H), 1.17 (s, 3H), 1.07 (dd, *J* = 11.8, 2.7 Hz, 1H), 1.00 (d, *J* = 4.4 Hz, 1H), 0.94 (dd, *J* = 12.7, 3.1 Hz, 1H), 0.85 (d, *J* = 4.4 Hz, 1H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.6, 172.6, 80.3, 57.2, 55.8, 51.3, 47.7, 43.7, 43.6, 39.0, 38.7, 38.4, 37.9, 37.8, 34.9, 28.6, 28.3, 19.5, 18.8, 18.6, 13.4; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{33}O_4$ requires 349.2379; found 349.2366 ; $[\alpha]_D^{23}$ –86.0º (*c* 1.03, $CHCl_3$).

I-72: R_f = 0.4 (Hex:EtOAc 4:1)**;** mp 163-165 °C; IR (film) 2947, 2848, 1721, 1466, 1444, 1235, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (t, *J* = 1.46 Hz, 1H), 3.63 (s, 3H), 2.87 (dt, *J* = 3.5, 1.8, 1.8 Hz, 1H), 2.54 (d, *J* = 18.7 Hz, 1H), 2.17 (d, *J* = 14.0 Hz, 1H), 1.99 (dt, *J* = 13.3, 3.2, 3.2 Hz, 1H), 1.86-1.90 (m, 1H), 1.78-1.85 (m, 1H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.70-1.75 (m, 2H), 1.51-1.57 (m, 4H), 1.37-1.44 (m, 1H), 1.25 (ddd, *J* = 11.4, 6.6, 1.7 Hz, 1H), 1.20 (s, 3H), 1.15 (dd, *J* = 12.0, 2.4 Hz, 1H), 1.02 (td, J= 13.5, 13.5, 4.2 Hz, 1H), 0.92 (td, *J* = 13.5, 13.4, 4.3 Hz, 1H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.9, 177.6, 138.4, 135.5, 56.6, 54.4, 51.8, 51.2, 43.6, 42.8, 40.9, 40.3, 38.1, 37.9, 36.8, 28.6, 24.8, 20.2, 19.8, 18.5, 12.5; HRMS (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{31}O_3$ requires 331.2273; found 331.2274; $[\alpha]_D^{23}$ –93.5° (*c* 0.26, $CHCl_3$).

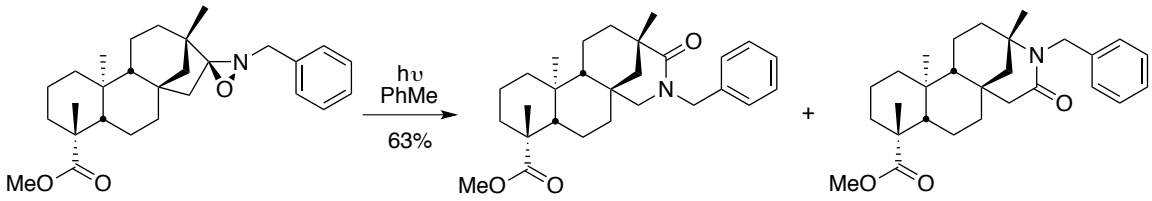


(*E*)-I-74 **I-75**

(3'*S*,4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-Methyl 2'-Benzyl-4,9,11b-trimethyldodecahydro-1*H*-spiro[6a,9-methanocyclohepta[*a*]naphthalene-8,3'-[1,2]oxaziridine]-4-carboxylate (I-75).

To a 100 mL round-bottomed flask was added benzylimine (**I-74**) (1.0 g, 2.35 mmol) in CH_2Cl_2 (50 mL). After cooling to 0 °C *m*CPBA (520 mg, 2.80 mmol) and $NaHCO_3$ (240 mg, 2.80 mmol) were added. The mixture was allowed to stir for 10 min, at which time TLC analysis indicated that the starting material was consumed. The reaction was

quenched with an aqueous solution of NaS_2O_3 (15 mL) then washed with 1M NaOH (100 mL) and brine (100 mL). The aqueous layers were then re-extracted with CH_2Cl_2 (50 mL) and the combined organic layers dried over $MgSO_4$ and filtered. The solvent was then removed under reduced pressure and the residue chromatographed on silica gel (Hex:EtOAc 9:1) to yield benzyl oxaziridine **I-75** (822 mg, 80%): R_f = 0.6 (Hex:EtOAc 2:1); mp 192-198 °C; IR (film) 2949, 2906, 1741, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 7.27-7.35 (m, 2H), 7.18-7.26 (m, 2H), 3.87, 3.75 (ABq, J_{AB} = 13.8 Hz, 2H), 3.59 (s, 3H), 2.54 (dd, *J* = 15.3, 2.6 Hz, 1H), 2.11 (d, *J* = 13.3 Hz, 1H), 1.80 (dd, *J* = 14.9, 3.5 Hz, 1H), 1.50-1.74 (m, 7H), 1.30-1.43 (m, 3H), 1.16 (ddd, *J* = 8.4, 5.4, 2.3 Hz, 1H), 1.12 (s, 3H), 1.08 (d, *J* = 2.4 Hz, 1H), 0.92 (dddd, *J* = 35.9, 18.4, 12.7, 7.8 Hz, 4H), 0.73-0.81 (m, 1H), 0.64 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 136.3, 128.06, 128.05, 127.1, 94.0, 60.9, 56.6, 54.7, 54.2, 50.8, 43.3, 41.0, 40.9, 40.7, 39.4, 37.5, 37.4, 36.1, 35.4, 28.4, 21.3, 19.5, 19.3, 18.5, 12.9; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{28}H_{40}NO_3$ requires 438.3008; found 438.3003; $[\alpha]_D^{23}$ –97.6º (*c* 1.00, $CHCl_3$).



I-75 **I-76** (56%) **I-77** (7%) **(I-90b)**

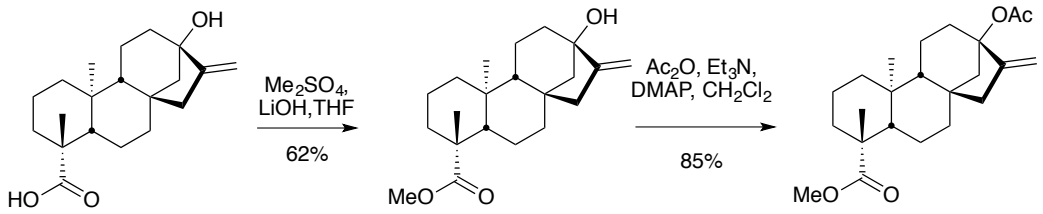
(3*S*,6a*S*,8a*S*,9*R*,12a*S*,12b*S*)-Methyl 5-Benzyl-3,9,12a-trimethyl-4-oxotetradecahydro-1*H*-3,6a-methanonaphtho[2,1-*c*]azocine-9-carboxylate (I-76) and (3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-Methyl 4-Benzyl-3,9,12a-trimethyl-5-oxotetradecahydro-1*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxylate (I-77/I-90b).

To a 25-mL round-bottomed flask was added benzyl oxaziridine **I-75** (110 mg, 0.25 mmol) in toluene (5 mL) and was allowed to stir under an Hg lamp (254 nm) for 1.5 h, at which time TLC analysis indicated the starting material was consumed. The reaction was then chromatographed on silica gel (Hex:EtOAc 4:1) to yield benzyl lactam **I-76** (69 mg, 56%) and benzyl lactam **I-77**/**I-90b** (8 mg, 7%) as a yellowish solid.

I-76: R_f = 0.21 (Hex:EtOAc 4:1); mp 145-151 °C; IR (film) 2947, 2848, 2235, 1723, 1638, 1453, 1233, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 4.35 Hz, 4H), 7.21-7.26 (m, 1H), 5.00, 4.04 (ABq, J_{AB} = 14.0 Hz, 2H), 3.63 (dd, *J* = 12.7, 2.1 Hz, 1H), 3.60 (s, 3H), 2.87 (d, *J* = 12.7 Hz, 1H), 2.11 (d, *J* =13.4 Hz, 1H), 1.99 (dd, *J* = 11.6, 2.4 Hz, 1H), 1.59-1.82 (m, 5H), 1.45-1.59 (m, 3H), 1.34-1.43 (m, 1H), 1.23 (ddd, *J* = 7.7, 9.4, 3.5 Hz, 2H), 1.18 (s, 3H), 1.16 (d, *J* = 3.6 Hz, 1H), 1.13 (s, 3H), 0.93-1.10 (m, 2H), 0.89 (dd, *J* = 12.4, 3.2 Hz, 1H), 0.78 (td, *J* = 13.4, 13.3, 4.3 Hz, 1H), 0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 174.9, 137.6, 128.8, 128.7, 128.4, 127.9, 127.2, 126.9, 57.5, 57.0, 55.5, 51.1. 50.0, 48.9, 43.7, 43.3, 39.7, 39.3, 39.0, 37.7, 34.2, 28.6, 25.3, 20.1, 20.0, 18.8, 12.7; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{28}H_{40}NO_3$ requires 438.3008; found 438.3011; $[\alpha]_D^{23}$ –250.0º (*c* 1.00, $CHCl_3$);

I-77/**I-90b**: R_f = 0.5 (Hex:EtOAc 4:1); mp 209-211 °C; IR (film) 2946, 2848, 1722, 1633, 145, 1399, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.29 (m, 1H), 7.17-7.22 (m, 3H), 5.00, 4.19 (ABq, *J* = 15.8 Hz, 2H), 3.64 (s, 3H), 3.08, 2.19 (dABq, J_{AB}= 18.4, 2.7 Hz, 2 H), 2.15-2.19 (m, 1 H), 1.85-1.95 (m, 1H), 1.74-1.83 (m, 4H), 1.70 (dd, *J* = 13.0, 2.7 Hz, 1H), 1.55-1.58 (m, 3H), 1.42-1.46 (m, 1H), 1.30 (dd, *J* = 13.0, 2.8 Hz, 1H), 1.20-1.25 (m, 2H), 1.17 (s, 3H), 1.12 (s, 3H), 0.96-1.09 (m, 3H), 0.80-0.91 (m, 2H), 0.79 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 177.7, 172.4, 139.8, 128.3, 126.8, 126.5, 57.4, 56.9, 56.5, 51.6, 51.2, 44.6, 44.3, 43.7, 41.1, 39.9, 38.0, 37.8, 37.0, 34.1, 28.5, 28.0, 19.7, 18.8, 18.6, 13.6; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{28}H_{40}NO_3$ requires 438.3008; found 438.3001; $[\alpha]_D^{23}$ –53.5º (*c* 1.00, $CHCl_3$).

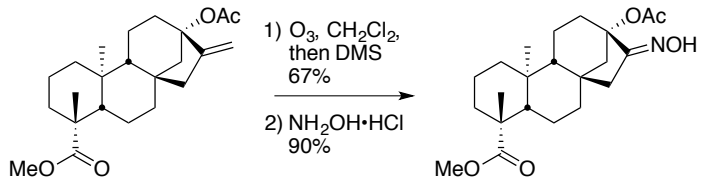


I-23 **I-94** **I-66**

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-Methyl 9-Acetoxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (I-66).

To a solution of steviol (**I-23**, 10 g, 32 mmol) in THF (50 mL) in a 500-mL round-bottomed flask at room temperature was added $LiOH•H_2O$ (1.5g, 34 mmol) The reaction stirred at room temperature for 1 h under nitrogen, then Me_2SO_4 (3.3 mL, 35 mmol) was slowly added, and the reaction vessel was fitted with a reflux condenser. The reaction was refluxed for 18 h at 80 C. Once the reaction cooled to room temperature, the off-white precipitate was collected via filtration to furnish methyl ester **I-94** (7.6 g, 73%). mp 117-118 °C (Lit 113-115 ºC);[160] ^1H NMR (400 MHz, $CDCl_3$): δ 4.92 (d, J = 64.0 Hz, 2H), 3.66 (s, 3H), 2.28 – 2.04 (m, 4H), 1.93 – 1.73 (m, 7H), 1.62 – 1.40 (m, 5H), 1.33 – 1.26 (m, 1H), 1.19 (s, 3H), 1.10 – 0.93 (m, 3H), 0.85 (s, 3H), 0.82 – 0.75 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 156.0, 102.9, 80.3, 56.9, 53.8, 51.2, 47.4, 46.9, 43.8, 41.6, 41.3, 40.7, 39.4, 39.2, 38.0, 28.7, 21.9, 20.4, 19.1, 15.3. HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{32}O_3Na$ 355.2249, found 355.2080; $[\alpha]_D^{23}$ –191.3º (*c* 1.00, $CHCl_3$).

Then, the steviol methyl ester **I-94** (5.0 g, 15.0 mmol) was taken up in dry CH_2Cl_2 (200 mL) and under an atmosphere of nitrogen cooled to 0 °C. Et_3N (28 mL, 200 mmol) and Ac_2O (19 mL, 200 mmol) where added. After 30 min DMAP (200 mg) was added and the ice bath removed and the reaction was allowed to stir for 18 h. The reaction was cooled to 0 °C and H_2O (10 mL) added and the reaction was stirred for 30 minutes. The organic layer was then washed with water (100 mL), 10% HCl (100 mL), 1M NaOH (100 mL) and brine (100 mL). The aqueous layers were then re-extracted with ether (100 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give an oil which was then chromatographed on silica gel (9:1 Hex:EtOAc) to provide the acetoxy methyl ester **I-66** as an oil (4.79 g, 85%): R_f = 0.7 (Hex:EtOAc 4:1); IR (KBr) 2948, 1726, 1447, 1366, 1236, 1149, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.90 (dd, *J* = 2.7, 2.0 Hz, 1H), 4.86 (d, *J* = 0.6 Hz, 1H), 3.63 (s, 3H), 2.57 (dd, *J* = 10.9, 2.6 Hz, 1H), 2.25 (ddd, *J* = 13.2, 4.9, 2.4 Hz, 2H), 2.14-2.20 (m, 1H), 1.98-2.05 (m, 1H), 2.02 (s, 3H), 1.85 (dd, *J* = 9.9, 7.6 Hz, 3H), 1.70-1.78 (m, 3H), 1.63 (dd, *J* = 7.5, 6.0 Hz, 1H), 1.56 (t, *J* = 3.26, 3.26, 1H), 1.44 (ddd, *J* = 15. 0, 11.3, 7.6 Hz, 3H), 1.16 (s, 3H), 1.1 (ddd, *J* = 22.3, 12.6, 5.6 Hz, 3H), 0.86 (s, 3H), 0.80 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 169.9, 152.1, 103.4, 87.6, 556.9, 53.7, 51.2, 46.9, 43.8, 42.6, 42.1, 41.1, 40.7, 39.2 (x2), 38.1, 36.7, 28.7, 21.8, 20.0, 19.1, 15.1; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{34}O_4Na$ requires 397.2347; found 355.2356 $[(M+Na)-Ac]^+$; $[\alpha]_D^{23}$ –55.8º (*c* 1.00, $CHCl_3$).

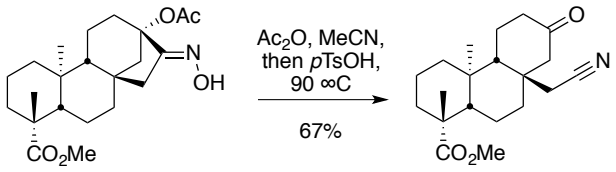


I-66 **I-67**

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*,*E*)-Methyl 9-Acetoxy-8-(hydroxyimino)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (I-67).

To a 50 mL flame-dried round-bottomed flask of acetoxy methyl ester **I-66** (904 mg, 2.4 mmol) in CH_2Cl_2 (30 mL) that was cooled to -78 °C, ozone was bubbled through the solution until the distinctive blue color was maintained for 30 min. The ozone line was then removed and nitrogen was bubbled through the solution until it was clear. Dimethylsulfide (703 mL, 9.6 mmol) was then added and the reaction was allowed to warm to ambient temperature and stir for 18 h. The CH_2Cl_2 was then removed under reduced pressure and residue dissolved in Et_2O (50 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL). The aqueous layers were then re-extract with Et_2O (x2, 50 mL) and the combined organic layers where then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting keto-acetoxy methyl ester was chromatographed on silica gel (25:1→7:1) Hex:EtOAc. From there, a 50 mL round-bottomed flask of the keto-acetoxy methyl ester (437 mg, 1.2 mmol) in dry THF (25 mL) and EtOH (2 mL), was added $NH_2OH•H_2O$ (240 mg, 3.5 mmol) and KOAc (354 g, 3.5 mmol). The mixture was heated to 50 °C for 1 h after which time TLC analysis indicated that the starting material was consumed. The mixture was then filtered and the solvent removed under reduced pressure. The colorless residue was taken up in CH_2Cl_2 (50 mL) and the organic layer was then washed with 10% HCl (10 mL), 1M NaOH (10 mL), and brine (10 mL). The aqueous layers were then re-extracted with CH_2Cl_2 (20 mL) and the combined organic layers dried over

$MgSO_4$ and filtered. The solvent was then removed under reduced pressure and the residue chromatographed on silica gel (Hex:EtOAc 9:1 → 4:1) to give the 13-acetoxy oxime **I-67** (422 mg, 60% over 2 steps) as a colorless solid: R_f = 0.44 (Hex:EtOAc 4:1); mp 178-180 °C; IR (film) 3293, 2946, 1723, 1462, 1446, 1237 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 3.63 (s, 3H), 2.53 (dd, *J* = 11.1, 2.0 Hz, 1H), 2.28 (d, *J* = 2.2 Hz, 1H), 2.17-2.22 (m, 2H), 2.03 (s, 3H), 1.98 (dd, *J* = 11.1, 2.3 Hz, 1H), 1.84 (ddd, *J* = 13.3, 10.7, 6.9 Hz, 5H), 1.66-1.77 (m, 2H), 1.55-1.65 (m, 2H), 1.47 (dd, *J* = 39.3, 15.9 Hz, 2H), 1.17 (s, 3H), 1.03 (ddd, *J* = 20.2, 9.9, 3.2 Hz, 3H), 0.86 (s, 3H), 0.77-0.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 169.7, 163.3, 84.9, 56.6, 53.2, 51.3, 43.7, 42.3, 41.8, 41.7, 40.7, 40.6, 39.2, 37.9, 35.6, 28.6, 21.9, 21.4, 19.5, 18.9, 15.3; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{34}NO_5$ requires 392.2437; found 392.2439; $[\alpha]_D^{23}$ –47.7º (*c* 0.98, $CHCl_3$).

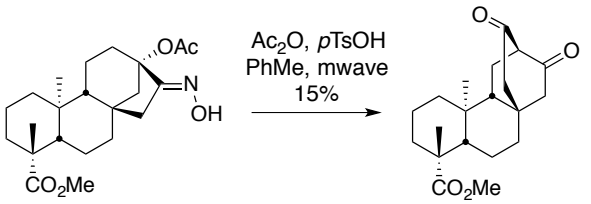


I-67 **I-70**

(1*R*,4a*S*,4b*R*,8a*R*,10a*S*)-Methyl 8a-(Cyanomethyl)-1,4a-dimethyl-7-oxotetradecahydrophenanthrene-1-carboxylate (I-70).

To a 100 mL flame-dried round-bottomed flask containing 13-acetoxy oxime **I-67** (13 g, 39 mmol) and dry acetonitrile (100 mL) flushed with nitrogen, Ac_2O (7.4 mL, 86 mmol) was added. After 10 min TLC indicated that all the starting material was consumed and then *p*TsOH (8 g, 43 mmol) was added. The reaction was heated to reflux for 2 h and then cooled with an ice bath. NaOH (17 g, 390 mmol) dissolved in H_2O (300 mL) was then added and stirred for 5 min. The layers where then partitioned and the aqueous layer was

re-extracted with EtOAc (2x100 mL). The combined organic layers where dried over $MgSO_4$, filtered, and then the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (400 mL) with 3 L of 9:1 Hex:EtOAc to furnish ketone nitrile **I-70** (8.66 g, 67%): R_f = 0.6 (Hex:EtOAc 2:1); mp 136-138 °C; IR (film) 2951, 1759, 1724, 1464, 1447, 1368, 1238, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.96 (d, *J* = 15.5 Hz, 1H), 2.47 (ddd, *J* = 16.8, 12.9, 8.3 Hz, 1H), 2.29-2.39 (m, 2H), 2.13-2.28 (m, 3H), 1.78-2.01 (m, 6H), 1.61-1.76 (m, 3H), 1.53 (d, *J* = 14.4 Hz, 1H), 1.47 (d, *J* = 7.0 Hz, 1H), 1.23 (s, 3H), 1.06 (dd, *J* = 7.4, 4.5 Hz, 2H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.0, 177.6, 117.1, 56.0, 51.4, 48.2, 43.7, 41.2, 39.4, 39.3, 38.3, 37.5, 31.2, 28.6, 20.8, 19.8, 19.1, 16.4; HRMS (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{30}NO_3$ requires 332.2226; found 332.2231; $[\alpha]_D^{23}$ –75.5º (*c* 1.24, $CHCl_3$).



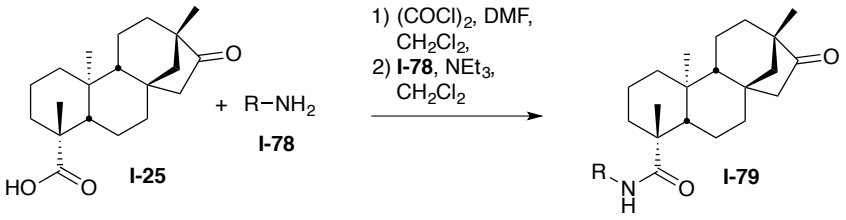
I-67 **I-71**

(3*S*,4a*R*,4b*S*,8*R*,8a*S*,10a*S*)-Methyl 4b,8-Dimethyl-2,12-dioxododecahydro-1*H*-3,10a-ethanophenanthrene-8-carboxylate (I-71).[80]

To a 0.5-2.0 mL microwave vial of 13-acetoxy oxime **I-67** (50 mg, 0.100 mmol) and toluene (1 mL) was added Ac_2O (25 μL, 0.25 mmol). After 10 min, *p*TsOH (23 mg, 0.100 mmol, 1 equiv) was added. The vial was capped and the reaction was heated to 140 °C and stirred for 30 min in the microwave. The reaction mixture was then taken up in EtOAc (35 mL) and washed with 10% NaOH, and brine. The aqueous layers were then re-extracted with EtOAc (2x50 mL) and the combined organic layers were dried over $MgSO_4$, filtered,

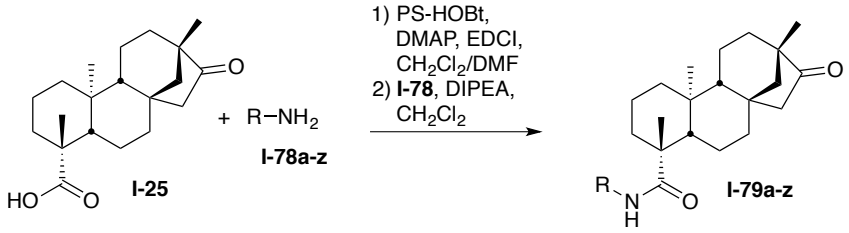
and the solvent removed under reduced pressure. The residue was chromatographed on silica gel (Hex:EtOAc 9:1) to give diketone **I-71** (13 mg, 15 %): R_f = 0.35 (Hex:EtOAc 2:1); mp 238-239 °C; IR (film) 2953, 1743, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.18 (t, *J* = 3.0 Hz, 1H), 2.90 (dd, *J* = 19.7, 3.5 Hz, 1H), 2.26-2.07 (m, 4H), 1.96-1.77 (m, 6H), 1.59-1.35 (m, 4H), 1.21 (s, 3H), 1.15 (dd, *J* = 11.9, 2.8 Hz, 1H), 1.08-1.00 (m, 1H), 0.93 (d, *J* = 4.3 Hz, 1H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 206.9, 177.4, 64.6, 56.4, 55.5, 51.5, 50.5, 46.3, 43.8, 39.6, 38.2, 38.1, 37.9, 37.6, 28.8, 25.5, 19.9, 18.6, 12.4; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{28}O_4Na$ requires 355.1880; found 355.1891; $[\alpha]_D^{23}$ –65.8º (*c* 0.25, $CHCl_3$).

D. Mono- and Bi-functional Library Compounds



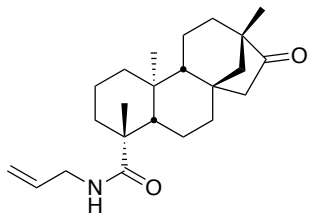
Standard procedure for the solution phase amide bond formation (Scheme I-25). To an oven-dried reaction flask under nitrogen at 0 °C (ice bath), was added DMF (37 μL, 0.47 mmol, 1.5 equiv) in DCM (1.0 mL) followed by oxalyl chloride (41 μL, 0.47 mmol, 1.5 equiv). The ice bath was removed and the mixture was allowed to stir at room temperature for 1 h. Then the reaction flask was cooled to 0 °C (ice bath) and isosteviol (**I-25**, 100 mg, 0.31 mmol) and Et_3N (130 μL, 0.47 mmol, 3 equiv) in DCM (1.0 mL) were added. After stirring for 5 min, allylamine (**I-78a**, 1 mL) was added and the mixture was stirred for 2 h.

Then the mixture was loaded onto a 20-mL silica gel plug in a 70-mL column and eluted with dry THF. The solvent was removed under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL), and methylisocyanate polystyrene resin was added. The mixture was shaken for 20 h and was then loaded onto a 20-mL silica gel plug in a 70-mL column and eluted with ethyl acetate (40 mL). The solvent was removed and the residues was purified using column chromatography with 10% EtOAc:Hex as the eluent to provide the allyl amide product **I-79a** in 47% yield.



Standard procedure for solid phase amide bond formation (Schemes I-25, I-26, and I-28). To a flame-dry reaction vial of isosteviol (**I-25**, 100.0 mg, 0.318 mmol, 1.0 equiv) in CH_2Cl_2/DMF (4:1) was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.67 equiv), 4-dimethylaminopyridine (15.5 mg, 0.127 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resin was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of allylamine (**I-78a**, 15.5 μL, 0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice

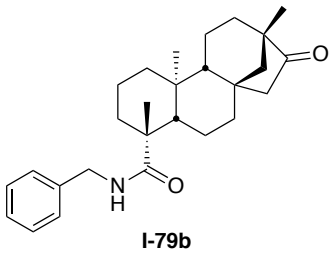
before the solvent was removed under vacuum. Column chromatography with 20% EtOAc:Hex as the eluent gave amide product **I-79a** in 43 mg (38% yield).



I-79a

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Allyl-4,9,11b-trimethyl-8-oxotetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (I-79a).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 – 5.70 (m, 1H), 5.62 (br s, 1H), 5.09 (dd, *J* = 23.1, 13.7 Hz, 2H), 3.79 (t, *J* = 5.1 Hz, 2H), 2.58 (dd, *J* = 18.6, 3.6 Hz, 1H), 2.01 – 1.85 (m, 3H), 1.77 – 1.25 (m, 9H), 1.19 – 1.15 (m, 2H), 1.13 (s, 3H), 1.10 – 1.05 (m, 2H), 0.91 (s, 3H), 0.89 – 0.82 (m, 2H), 0.71 (s, 3H), 0.67 – 0.63 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.6, 176.4, 134.4, 116.6, 57.5, 57.2, 54.7, 54.2, 48.7, 48.4, 43.7, 41.9, 41.7, 40.2, 39.5, 38.1, 37.3, 30.2, 22.2, 20.3, 19.9, 19.2, 13.6;

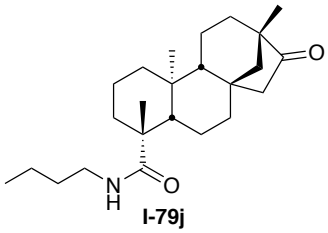


I-79b

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Benzyl-4,9,11b-trimethyl-8-oxotetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (I-79b).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.25 (m, 5H), 5.86 (t, *J* = 4.9 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 2H), 2.62 (dd, *J* = 18.6, 3.6 Hz, 1H), 2.06 – 1.90 (m, 2H), 1.83 – 1.63 (m, 6H), 1.59 – 1.32 (m, 7H), 1.27 – 1.22 (m, 1H), 1.21 (s, 3H), 1.18 – 1.12 (m, 2H), 0.96 (s, 3H), 0.95

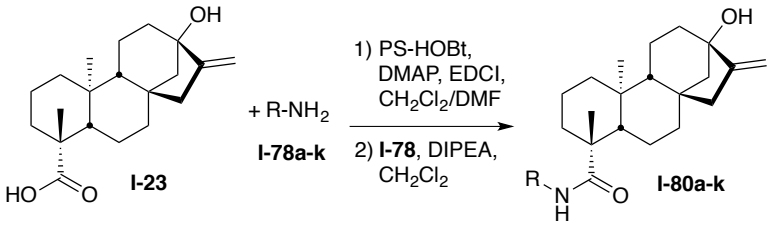
– 0.79 (m, 1H), 0.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.4, 176.4, 138.5, 128.9, 128.7, 128.0, 127.5, 127.5, 57.6, 54.7, 54.3, 48.7, 48.4, 43.7, 41.7, 40.2, 39.5, 38.1, 38.1, 37.3, 30.2, 22.2, 22.2, 20.3, 19.9, 19.2, 13.6; mp 68-69 ºC; LRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{37}NO_2Na$ 430.2824, found 430.4; $[\alpha]_D^{23}$ –44.0º (*c* 1.00, $CHCl_3$).



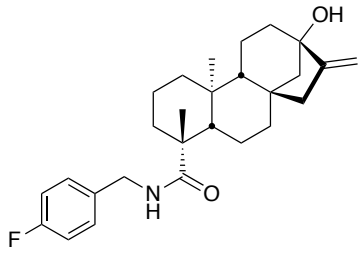
I-79j

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Butyl-4,9,11b-trimethyl-8-oxotetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (I-79j).

oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (s, 1H), 3.21 (dt, *J* = 11.8, 6.7 Hz, 2H), 2.65 (dd, *J* = 18.6, 3.6 Hz, 1H), 2.01 (d, *J* = 14.3 Hz, 1H), 1.95 (d, *J* = 13.3 Hz, 1H), 1.77 (dd, *J* = 19.9, 14.1 Hz, 4H), 1.71 – 1.65 (m, 2H), 1.63 – 1.57 (m, 1H), 1.56 – 1.52 (m, 1H), 1.51 – 1.45 (m, 4H), 1.40 (dd, *J* = 11.8, 3.7 Hz, 1H), 1.37 – 1.30 (m, 3H), 1.25 – 1.18 (m, 2H), 1.17 (s, 3H), 1.16 – 1.09 (m, 2H), 0.97 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 4H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.4, 176.5, 57.6, 54.8, 54.3, 48.7, 48.4, 43.6, 41.8, 40.2, 39.5, 39.2, 38.2, 38.1, 37.3, 31.5, 30.2, 22.3, 20.3, 20.3, 19.9, 19.2, 13.8, 13.5; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{40}NO_2$ 374.2981, found 374.3; $[\alpha]_D^{23}$ –32.2º (*c* 0.500, $CHCl_3$).



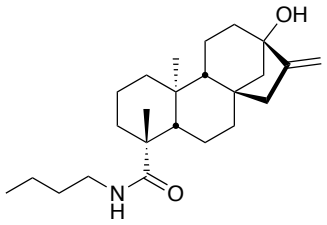
Standard procedure for solid-phase bond formation of steviol amide analogs **I-80a-k** (Scheme I-26). To a solution of steviol (**I-23**, 100 mg, 0.318 mmol, 1.00 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.213 mmol, 0.670 equiv), 4-dimethylaminopyridine (55.4 μL, 0.318 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of 4-flurobenzylamine (**I-78c**, 27.5 mg, 0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography with 20% EtOAc:Hex to furnish the amide **I-80c**.



I-80c

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-(4-Fluorobenzyl)-9-hydroxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (I-80c).

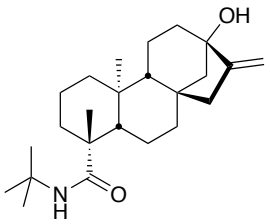
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.70 (dd, *J* = 8.5, 5.7 Hz, 2H), 7.03 (t, *J* = 8.6 Hz, 2H), 4.82 (d, *J* = 67.5 Hz, 2H), 4.69 (s, 2H), 2.13 – 1.93 (m, 4H), 1.88 – 1.63 (m, 6H), 1.58 – 1.22 (m, 5H), 1.20 – 1.16 (m, 1H), 1.11 (s, 3H), 1.08 – 0.97 (m, 3H), 0.88 (d, *J* = 7.9 Hz, 1H), 0.79 (s, 3H), 0.75 (dd, *J* = 12.7, 3.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 160.6, 156.0, 130.1, 129.6, 129.4, 115.6, 115.4, 103.0, 80.2, 64.2, 57.4, 53.7, 47.4, 46.9, 43.8, 42.9, 41.7, 40.9, 39.4, 38.2, 30.1, 23.0, 22.4, 20.4, 19.3, 15.7



I-80j

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Butyl-9-hydroxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (I-80j).

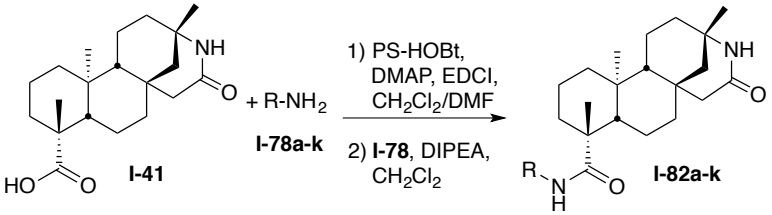
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 5.58 (s, 1H), 4.88 (d, *J* = 68.1 Hz, 2H), 3.20 (dt, *J* = 12.2, 6.8 Hz, 2H), 2.90 (d, *J* = 30.2 Hz, 1H), 2.18 (d, *J* = 17.0 Hz, 1H), 2.14 – 2.09 (m, 1H), 2.07 – 2.00 (m, 2H), 1.89 (dd, *J* = 21.7, 5.2 Hz, 3H), 1.82 – 1.71 (m, 3H), 1.63 – 1.51 (m, 2H), 1.51 – 1.43 (m, 4H), 1.42 – 1.30 (m, 3H), 1.26 (d, *J* = 10.8 Hz, 1H), 1.13 (s, 3H), 1.10 – 0.99 (m, 2H), 0.94 – 0.90 (m, 3H), 0.89 (s, 3H), 0.86 – 0.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 156.1, 102.9, 80.2, 57.3, 53.8, 47.4, 46.9, 43.7, 41.7, 41.6, 41.1, 39.4, 39.3, 39.2, 38.3, 31.5, 30.1, 22.4, 20.5, 20.3, 19.4, 15.6, 13.8; LRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{40}NO_2$ 374.2981, found 374.3; $[\alpha]_D^{23}$ –77.5º (*c* 1.00, $CHCl_3$).



I-80m

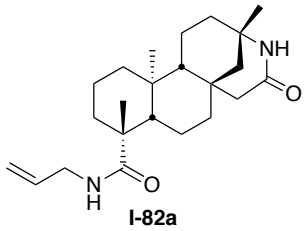
(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-(*tert*-butyl)-9-hydroxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (I-80m).

oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 4.88 (d, *J* = 66.6 Hz, 2H), 2.94 (s, 1H), 2.18 (d, *J* = 19.5 Hz, 1H), 2.10 (d, *J* = 17.2 Hz, 1H), 1.99 (d, *J* = 13.6 Hz, 1H), 1.91 – 1.84 (m, 4H), 1.82 – 1.73 (m, 4H), 1.60 – 1.50 (m, 2H), 1.49 – 1.37 (m, 3H), 1.33 (s, 3H), 1.31 (s, 6H), 1.27 (dd, *J* = 14.7, 3.6 Hz, 1H), 1.12 (s, 3H), 1.08 – 0.98 (m, 2H), 0.95 (s, 3H), 0.82 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.7, 156.1, 102.9, 80.2, 77.4, 77.0, 76.7, 57.2, 53.8, 50.7, 47.4, 46.9, 44.1, 41.7, 41.6, 41.2, 39.5, 39.3, 38.5, 30.2, 28.8, 28.7, 28.7, 22.5, 20.5, 19.3, 15.9; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{40}NO_2$ 374.2981, found 374.3; $[\alpha]_D^{23}$ –102.1° (*c* 0.750, $CHCl_3$).



Standard procedure for solid-phase bond formation of isosteviol lactam (**I-41**) amide analogs **I-82a-k** (Scheme I-26). To a solution of lactam (**I-41**, 100 mg, 0.333 mmol, 1.00 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.223 mmol, 0.670 equiv), 4-

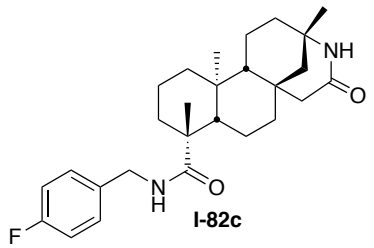
dimethylaminopyridine (58.0 μL, 0.333 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (155 mg, 1.00 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of allylamine (**I-78a**, 29.1 mg, 0.220 mmol, 0.70 equiv) and diisopropylethylamine (58.0 μL, 0.333 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography with 20% EtOAc:Hex to furnish the amide **I-82a**.



I-82a

(3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-*N*-Allyl-3,9,12a-trimethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxamide (I-82a).

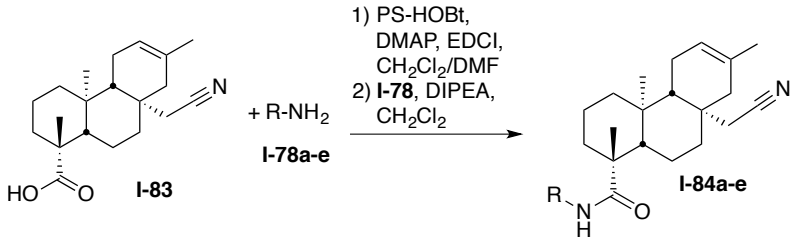
oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 – 5.70 (m, 1H), 5.60 (s, 1H), 5.18 – 5.03 (m, 2H), 3.87 – 3.71 (m, 2H), 2.82 (d, J = 29.2 Hz, 1H), 2.44 (ddd, J = 52.5, 16.6, 2.1 Hz, 1H), 2.14 – 1.62 (m, 8H), 1.52 (s, 6H), 1.49 – 1.16 (m, 4H), 1.13 (s, 3H), 1.13 – 0.99 (m, 3H), 0.84 (dd, J = 13.6, 3.8 Hz, 1H), 0.76 – 0.62 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 134.5, 131.4, 120.0, 116.8, 57.9, 52.0, 45.9, 43.8, 42.1, 40.3, 39.5, 38.1, 37.6, 35.4, 33.2, 30.2, 23.4, 22.4, 20.5, 20.1, 19.4, 14.0; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{36}O_2N_2Na$ 395.2777, found 395.2680; $[\alpha]_D^{23}$ –10.3º (*c* 1.20, $CHCl_3$).



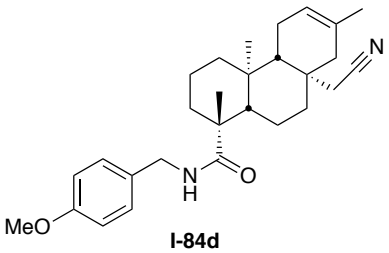
I-82c

(3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-*N*-(4-fluorobenzyl)-3,9,12a-trimethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxamide(I-82c).

oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.29 (m, 1H), 7.25 – 7.22 (m, 1H), 7.03 – 6.97 (m, 2H), 6.51 (t, *J* = 6.0 Hz, 1H), 4.56 (dd, *J* = 15.0, 6.5 Hz, 1H), 4.49 – 4.33 (m, 2H), 2.40 (d, *J* = 12.1 Hz, 1H), 2.31 (d, *J* = 17.8 Hz, 1H), 2.17 (d, *J* = 13.4 Hz, 1H), 1.88 (dd, *J* = 16.9, 2.7 Hz, 4H), 1.78 (d, *J* = 13.2 Hz, 1H), 1.73 – 1.67 (m, 2H), 1.64 – 1.56 (m, 2H), 1.51 – 1.42 (m, 1H), 1.39 (s, 3H), 1.36 – 1.28 (m, 2H), 1.25 (s, 3H), 1.22 – 1.15 (m, 1H), 1.13 –1.04 (m, 2H), 1.02 – 0.93 (m, 2H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.0, 176.1, 171.0, 161.1, 129.5, 129.5, 115.7, 115.5, 77.3, 77.0, 76.7, 59.5, 57.3, 56.6, 51.2, 43.7, 43.6, 42.8, 42.0, 39.8, 38.0, 37.7, 37.5, 35.0, 28.8, 26.1, 19.5, 19.1, 18.9, 13.8; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{38}FN_2O_2$ 441.2339, found 441; $[\alpha]_D^{23}$ 19.2º (*c* 1.00, $CHCl_3$).



Standard procedure for direct amide bond formation from nitrile **I-83** (Scheme I-26). To a flame-dried reaction flask of the nitrile acid **I-83** (1.0 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.67 equiv), 4-dimethylaminopyridine (55.4 μL, 0.318 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of amine **I-78** (0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography with 20% EtOAc:Hex to furnish the amide **I-84**.

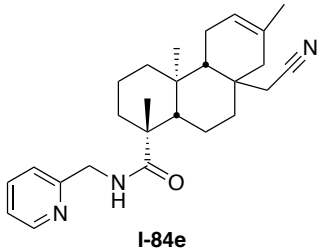


I-84d

(1*R*,4a*S*,4b*R*,8a*R*,10a*S*)-*N*-benzyl-8a-(cyanomethyl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,8,8a,9,10,10a-dodecahydrophenanthrene-1-carboxamide (I-84d).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.69 (s, 1H), 4.36 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 2.98 (dd, *J* = 19.0, 2.5 Hz, 1H), 2.17 (d, *J* = 13.1 Hz, 1H), 2.01 (s, 3H), 2.05 – 1.96 (m, 1H), 1.90 – 1.66 (m, 4H), 1.61 (d, *J* = 13.6 Hz,

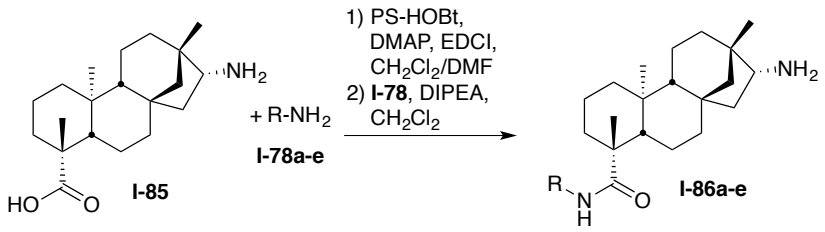
2H), 1.51 – 1.38 (m, 4H), 1.28 (s, 1H), 1.23 (s, 3H), 1.09 (s, 3H), 1.01 (td, *J* = 13.5, 3.8 Hz, 1H), 0.93 – 0.87 (m, 1H), 0.85 (s, 3H^{13}C NMR (125 MHz, $CDCl_3$): δ 183.0, 170.6, 170.0, 159.2, 130.4, 129.4, 129.4, 114.2, 114.2, 77.5, 77.2, 76.8, 57.3, 56.4, 55.5, 55.1, 44.0, 43.7, 43.4, 40.8, 40.1, 39.6, 38.4, 37.2, 29.2, 23.4, 22.3, 21.7, 20.6, 19.1, 13.6; mp 63 – 64 ºC; LRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{38}N_2O_2$ 434.2933, found 457.3; $[\alpha]_D^{23}$ 3.60º (*c* 0.600, $CHCl_3$).



I-84e

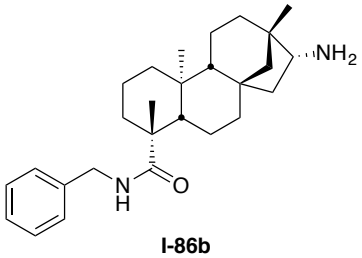
(1*R*,4a*S*,4b*R*,10a*S*)-8a-(cyanomethyl)-1,4a,7-trimethyl-*N*-(pyridin-2-ylmethyl)-1,2,3,4,4a,4b,5,8,8a,9,10,10a-dodecahydrophenanthrene-1-carboxamide (I-84e).

oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 4.5 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.11 (s, 1H), 5.35 (s, 1H), 5.31 (s, 1H), 4.53 (tdd, *J* = 16.5, 11.7, 4.7 Hz, 2H), 2.78 – 2.53 (m, 1H), 2.49 – 2.29 (m, 1H), 2.26 – 2.12 (m, 2H), 2.12 – 1.92 (m, 5H), 1.87 – 1.77 (m, 1H), 1.75 – 1.69 (m, 1H), 1.66 (s, 3H), 1.58 – 1.49 (m, 1H), 1.35 – 1.27 (m, 1H), 1.23 (s, 3H), 1.22 – 1.12 (m, 3H), 0.92 (dt, *J* = 16.0, 8.2 Hz, 1H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ176.6, 156.4, 149.0, 136.7, 131.2, 122.4, 122.3, 119.9, 119.0, 77.4, 77.1, 76.8, 57.7, 51.7, 45.7, 44.4, 43.7, 40.2, 39.4, 37.9, 37.4, 35.3, 29.9, 23.3, 22.2, 20.2, 19.9, 19.1, 13.5; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{35}N_3ONa$ 428.2780, found 428.3; $[\alpha]_D^{23}$ –34.0 º (*c* 1.00, $CHCl_3$).



Standard procedure for direct amide bond formation from amine **I-85** (Scheme I-26).

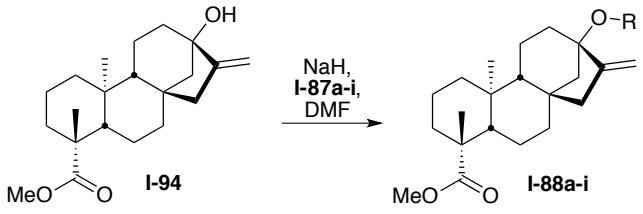
To a flame-dried reaction flask of the amine **I-85** (1.0 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.67 equiv), 4-dimethylaminopyridine (55.4 μL, 0.318 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of amine **I-78** (0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography with 5% MeOH:DCM to furnish the amide **I-86**.



I-86b

(4*R*,4a*S*,6a*R*,8*R*,9*S*,11a*R*,11b*S*)-8-Amino-*N*-benzyl-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (I-86b).

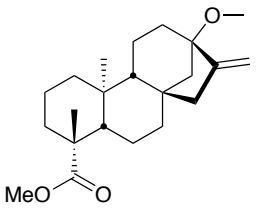
oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.36 (d, *J* = 6.8 Hz, 2H), 7.34 - 7.30 (m, 3H), 4.53 (d, *J* = 6.2 Hz, 2H), 2.18 (d, *J* = 13.9 Hz, 1H), 1.94 – 1.78 (m, 4H), 1.76 - 1.71 (m, 3H), 1.69 – 1.58 (m, 3H), 1.49 – 1.41 (m, 3H), 1.40 – 1.33 (m, 2H), 1.30 – 1.26 (m, 1H), 1.25 (s, 3H), 1.17 – 1.12 (m, 1H), 1.11 – 1.01 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 1H), 0.93 (s, 3H), 0.92 – 0.85 (m, 1H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.3, 159.9, 136.9, 128.8, 128.8, 127.9, 127.9, 57.6, 56.9, 56.0, 55.6, 43.8, 43.6, 42.6, 42.0, 41.3, 40.5, 39.9, 38.2, 37.8, 33.9, 29.0, 24.8, 21.6, 20.7, 18.8, 13.5; LRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{40}N_2O$ 408.3141, found 409; $[\alpha]_D^{23}$ –5.25º (*c* 0.750, $CHCl_3$).



Standard procedure for *O*-alkylation of steviol ester (**I-94**) to form ethers **I-88a-i** (Scheme I-27).

To a solution of steviol ester (100 mg, 0.318 mmol, 1.0 equiv) in DMF (5 mL) in a flame-dry reaction vial was added slowly via cannula a solution of sodium hydride (38.3 mg in 60% dispersion in oil, 0.954 mmol, 3.0 equiv) in dry DMF (5 mL). Then, methyl iodide (90.3 mg, 0.636 mmol, 2.0 equiv) was added to the reaction flask and the mixture was allowed to stir for 2 h at ambient temperature. The reaction was quenched with MTBE and the organic phase was washed successively with water. The aqueous phase was extracted with MTBE and the combined organic layers were dried over $MgSO_4$, filtered, and

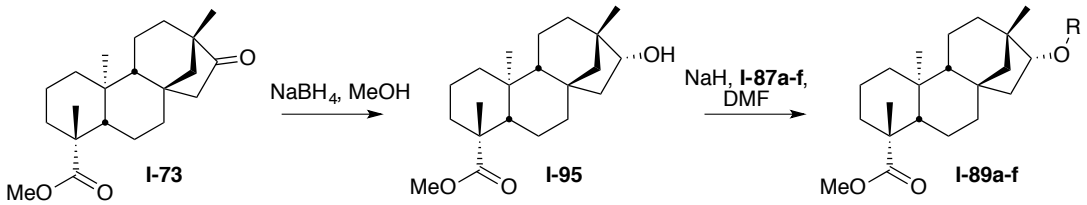
concentrated *in vacuo*. Purification by flash column chromatography with 20% EtOAc:Hex yielded the product.



I-88a

Methyl (4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-9-methoxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (I-88a).

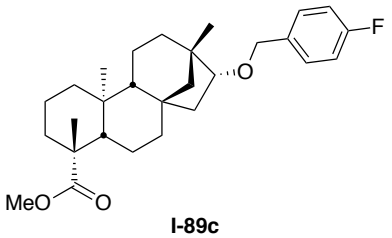
oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (d, *J* = 6.1 Hz, 2H), 3.64 (s, 3H), 3.22 (s, 3H), 2.18 (d, *J* = 13.2 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.89 – 1.80 (m, 4H), 1.79 – 1.71 (m, 3H), 1.69 – 1.58 (m, 1H), 1.57 – 1.49 (m, 2H), 1.48 – 1.40 (m, 3H), 1.17 (s, 3H), 1.07 – 0.94 (m, 3H), 0.82 (s, 3H), 0.85 – 0.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.0, 103.7, 85.2, 77.3, 77.0, 76.7, 57.0, 54.0, 51.2, 50.1, 48.1, 43.8, 41.7, 41.5, 40.7, 40.0, 39.3, 38.8, 38.0, 28.7, 21.9, 20.2, 19.1, 15.3, LRMS (ES) (*m*/*z*): $[M+CH_2O_2]^+$ calcd for $C_{22}H_{34}O_3$ 390.2508, found 390.3; $[\alpha]_D^{23}$ –93.5º (*c* 0.800, $CHCl_3$).



Methyl (4*R*,4a*S*,6a*R*,8*R*,9*S*,11a*R*,11b*S*)-8-Hydroxy-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (I-95).

To a solution of the isosteviol ester (**I-73**, 1.00 g, 3.00 mmol) in 25 mL of MeOH at 0 °C (ice bath), was slowly added $NaBH_4$ (134 mg, 3.55 mmol). The reaction mixture was stirred for 1 h at 0 °C (ice bath), and then solvent was evaporated under reduced pressure. It was then diluted with water and extracted with MTBE. Evaporation of the solvent and purification of the product on a silica gel column using 10% EtOAc:Hex to give hydroxyl ester **I-95** (450 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (dd, J = 10.6, 4.6 Hz, 1H), 3.42 (s, 3H), 1.96 (d, J = 13.4 Hz, 1H), 1.73 (s, 1H), 1.68 – 1.47 (m, 6H), 1.45 – 1.27 (m, 4H), 1.24 – 0.97 (m, 4H), 0.96 (s, 3H), 0.86 – 0.75 (m, 4H), 0.70 (s, 3H), 0.69 – 0.61 (m, 1H), 0.52 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 80.4, 57.1, 55.8, 55.2, 51.1, 43.7, 42.8, 42.0, 42.0, 41.7, 39.9, 38.0, 38.0, 33.7, 28.9, 24.9, 21.7, 20.4, 18.9, 13.1. HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{34}O_3Na$ 357.2406, found 357.2398; $[\alpha]_D^{23}$ –57.1º (*c* 0.833, $CHCl_3$).

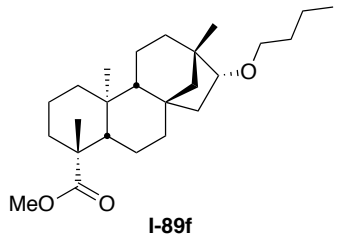
Standard procedure for *O*-alkylation of isosteviol hydroxyl ester (**I-95**) to form ethers **I-89a-f** (Scheme I-27). To a solution of hydroxyl ester (**I-95**, 100 mg, 0.345 mmol, 1.0 equiv) in DMF (5 mL) in a flame-dry reaction vial was added slowly via cannula a solution of sodium hydride (38.3 mg in 60% dispersion in oil, 0.954 mmol, 3.0 equiv) in dry DMF (5 mL). Then, methyl iodide (90.3 mg, 0.636 mmol, 2.0 equiv) was added to the reaction flask and the mixture was allowed to stir for 2 h at ambient temperature. The reaction was quenched with MTBE and the organic phase was washed successively with water. The aqueous phase was extracted with MTBE and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography with 20% EtOAc:Hex yielded the product **I-89**.



I-89c

Methyl (4*R*,4a*S*,6a*R*,8*S*,9*S*,11a*R*,11b*S*)-8-((4-Fluorobenzyl)oxy)-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (I-89c).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.4, 5.7 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 4.45 (dd, 2H), 3.63 (s, 3H), 3.54 (dd, *J* = 10.3, 4.1 Hz, 1H), 2.17 (d, *J* = 13.3 Hz, 1H), 1.96 – 1.79 (m, 4H), 1.76 – 1.62 (m, 3H), 1.59 – 1.53 (m, 2H), 1.50 – 1.36 (m, 3H), 1.33 – 1.24 (m, 2H), 1.17 (s, 3H), 1.06 – 0.96 (m, 4H), 0.93 (s, 3H), 0.91 – 0.83 (m, 1H), 0.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.3, 132.9, 129.0, 128.9, 115.9, 115.2, 115.0, 87.0, 71.3, 57.3, 56.0, 55.5, 51.3, 43.9, 42.4, 42.2, 42.0, 40.3, 40.0, 38.2, 38.1, 34.5, 29.0, 25.6, 21.9, 20.6, 19.1, 13.3; mp 151-152 ºC; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{30}O_3Na$ 465.2883, found 465.2795; $[\alpha]_D^{23}$ –103.7º (*c* 0.655, $CHCl_3$).

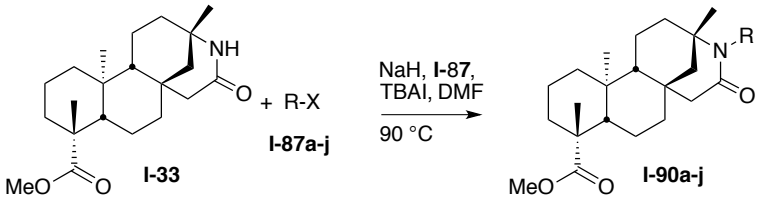


I-89f

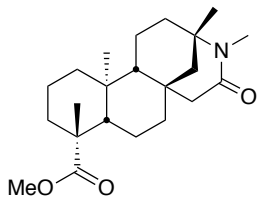
Methyl (4R,4aS,6aR,8R,9S,11aR,11bS)-8-Butoxy-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (I-89f).

oil ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.53 – 3.43 (m, 1H), 3.43 – 3.31 (m, 2H), 2.17 (d, *J* = 13.0 Hz, 1H), 1.89 – 1.84 (m, 2H), 1.83 – 1.77 (m, 3H), 1.72 – 1.66 (m, 2H),

1.64 – 1.56 (m, 3H), 1.51 (dd, J = 12.2, 6.1 Hz, 3H), 1.44 – 1.37 (m, 4H), 1.32 – 1.24 (m, 2H), 1.21 (d, J = 4.7 Hz, 1H), 1.18 (s, 3H), 1.12 – 1.03 (m, 2H), 1.02 – 0.97 (m, 2H), 0.94 (s, 3H), 0.92 – 0.83 (m, 2H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.2, 87.3, 69.9, 57.3, 56.0, 55.5, 51.1, 43.8, 42.2, 42.0, 40.5, 39.9, 38.1, 38.0, 34.4, 32.3, 28.9, 25.6, 21.8, 21.7, 20.4, 19.5, 19.0, 14.0, 13.1; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{42}O_3Na$ 413.3134, found 413.2998; $[\alpha]_D^{23}$ –42.8º (*c* 0.850, $CHCl_3$).



D: Standard procedure for *N*-alkylation of lactam **I-33** (Scheme I-27). To a solution of the lactam (100 mg, 0.347 mmol, 1.0 equiv) in DMF (5 mL) in a flame-dried reaction flask, was added sodium hydride (3.0 equiv, pre-washed with hexanes), alkyl halide **I-87** (5.0 equiv) and a catalytic amount of tetrabutylammonium iodide (TBAI, 10 mol%). The reaction flask was heated to 90 °C, stirred overnight and then the reaction was carefully quenched with water (2 mL). The organic layer was then washed with brine and the aqueous layers were re-extracted with Et_2O (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and the Et_2O was removed under reduced pressure, while a centrifugal evaporator was used to remove the DMF to give alkylated lactam **I-90**. Column chromatography with 5% MeOH:CH_2Cl_2 gave the substituted-lactam products.

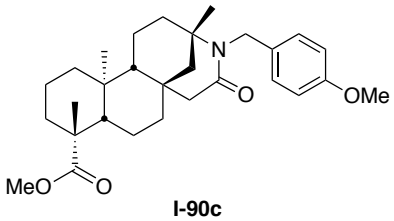


I-90a

(3*S*,8a*S*,9*R*,12a*S*,12b*R*)-Methyl 3,4,9,12a-Tetramethyl-5-oxotetradecahydro-1*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxylate (I-90a).

To a 50 mL flame-dried round-bottomed flask of lactam **I-33** (100 mg, 0.29 mmol) in DMF (15 mL) under nitrogen, was added sodium hydride (35 mg, 0.86 mmol, pre-washed with hexanes), methyl iodide (90 μL, 1.44 mmol) and a catalytic amount of tetrabutylammonium iodide (11 mg, 0.029 mmol). The reaction flask was heated to 90 °C and allowed to stir overnight. At this time TLC analysis indicated the consumption of starting material and the reaction was carefully quenched with water (2 mL). The organic layer was then washed with brine and the aqueous layers were re-extracted with Et_2O (2x15 mL). The combined organic layers were then dried over $MgSO_4$, filtered and the Et_2O was removed under reduced pressure, while a centrifugal evaporator was used to remove the DMF to give methyl alkylated lactam **I-90a** (90 mg, 86%) as an off-white solid. R_f = 0.2 (Hex:EtOAc 4:1); mp 168-172 °C; IR (film) 2926, 1722, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 3H), 2.98 (dd, *J* = 18.3, 2.9 Hz, 1H), 2.84 (s, 3H), 2.16 (d, *J* = 13.3 Hz, 1 H), 2.04 (d, *J* = 18.3 Hz, 1H), 1.83-1.92 (m, 2H), 1.55-1.83 (m, 6H), 1.51 (dt, J= 12.9, 3.2, 3.2 Hz, 1H), 1.40-1.47 (m, 1H), 1.30 (dd, *J* = 12.8, 2.9 Hz, 1H), 1.25 (s, 3H), 1.18-1.23 (m, 1H), 1.16 (s, 3H), 1.11 (dd, *J* = 12.8, 3.8 Hz, 1H), 1.04-1.06 (m, 1H), 1.03-0.95 (m, 1H), 0.86 (d, *J* = 17.65, 2H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 171.9, 57.4, 56.8, 55.3, 51.1, 51.0, 44.3, 43.7, 41.0, 39.9, 38.0, 37.8, 35.7, 33.9, 28.5, 27.4, 26.8,

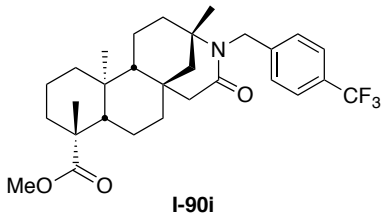
19.7, 18.8, 18.7, 13.5; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{36}NO_3$ 362.2695; found 362.2677; $[\alpha]_D^{23}$ 18.9º (*c* 0.800, $CHCl_3$).



I-90c

Methyl (3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-4-(4-Methoxybenzyl)-3,9,12a-trimethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxylate (I-90c).

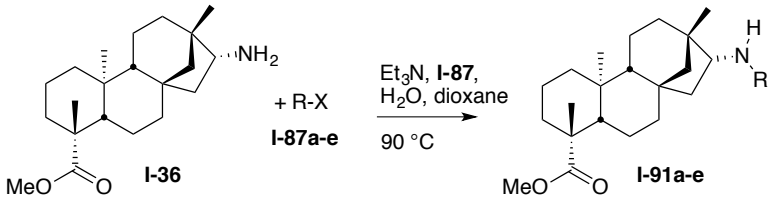
^{1}H NMR (400 MHz, $CDCl_3$): 7.16 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.86 (d, *J* = 15.4 Hz, 1H), 4.20 (d, *J* = 15.5 Hz, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.07 (dd, *J* = 18.4, 2.7 Hz, 1H), 2.16 (d, *J* = 18.2 Hz, 2H), 1.93 – 1.82 (m, 1H), 1.81 – 1.72 (m, 4H), 1.67 (dd, *J* = 13.0, 2.8 Hz, 1H), 1.54 (dd, *J* = 12.9, 3.1 Hz, 2H), 1.48 – 1.39 (m, 1H), 1.31 – 1.19 (m, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.12 – 0.95 (m, 3H), 0.90 – 0.79 (m, 2H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 177.8, 172.3, 158.3, 132.1, 128.3 (2C), 113.7 (2C), 57.5, 56.9, 56.4, 55.2, 51.7, 51.2, 44.3, 44.0, 43.8, 41.2, 40.0, 38.0, 37.8, 37.1, 34.1, 28.6, 28.1, 19.8, 18.9, 18.6, 13.7; mp 151-152 ºC; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{29}H_{42}NO_4$ 468.3036, found 468.3; $[\alpha]_D^{23}$ –15.6º (*c* 1.00, $CHCl_3$).



I-90i

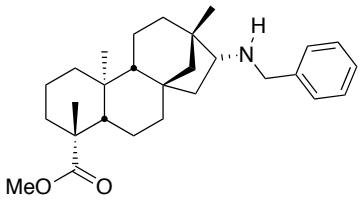
Methyl (3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-3,9,12a-Trimethyl-5-oxo-4-(4-(trifluoromethyl)benzyl)tetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxylate (I-90i).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.08 (d, *J* = 16.2 Hz, 1H), 4.15 (d, *J* = 16.1 Hz, 1H), 3.64 (s, 3H), 3.09 (dd, *J* = 18.2, 2.5 Hz, 1H), 2.23 – 2.15 (m, 2H), 1.91 – 1.75 (m, 5H), 1.71 (dd, *J* = 13.1, 2.5 Hz, 1H), 1.64 – 1.55 (m, 2H), 1.45 (d, *J* = 13.7 Hz, 1H), 1.36 – 1.29 (m, 1H), 1.27 – 1.20 (m, 2H), 1.18 (s, 3H), 1.17 – 1.11 (m, 1H), 1.10 (s, 3H), 1.08 – 0.96 (m, 2H), 0.94 – 0.84 (m, 2H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 172.7, 144.0, 127.1, 127.1, 127.1, 125.6, 125.3, 125.3, 57.4, 56.8, 56.6, 51.5, 51.2, 44.5, 44.2, 43.8, 41.1, 40.0, 38.0, 37.8, 36.9, 34.1, 28.6, 28.0, 19.7, 18.9, 18.6, 13.7; mp 151-152 ºC; LRMS (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{29}H_{38}F_3NO_3$ 505.2814, found 506.4; $[\alpha]_D^{23}$ –-36.6º (*c* 0.905, $CHCl_3$).



Standard procedure for *N*-alkylation of amine **I-36** (Scheme I-27). To a flame-dried reaction flask of the amine **I-36** (100 mg, 0.333 mmol, 1.0 equiv) and trimethylamine (1.5 equiv) in a 1,4-dioxane-water mixed solvent (1:1, 6 mL), the alkyl halide (**I-87**, 1.0 equiv) was added. The reaction flask was heated to 90 °C and allowed to stir for one day. The reaction mixture was quenched with EtOAc and the organic layer was washed with saturated aqueous NH_4Cl. The organic layer was then washed with brine and the aqueous

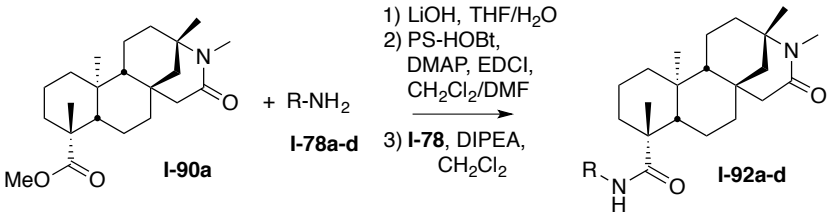
layers were extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude alkylated-amine product **I-91**. Purification was done by column chromatography with 5% MeOH:DCM.



I-91b

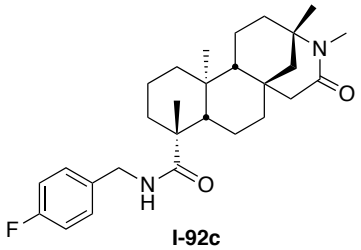
Methyl (4*R*,4a*S*,6a*R*,8*R*,9*S*,11a*R*,11b*S*)-8-(Benzylamino)-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (I-91b).

oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.6 Hz, 4H), 7.29 – 7.25 (m, 1H), 3.80 (q, *J* = 46.0, 13.4, 12.4 Hz, 2H), 3.66 (s, 3H), 3.64 (s, 1H), 2.77 (dd, *J* = 10.6, 5.4 Hz, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 1.86 – 1.80 (m, 2H), 1.74 (d, *J* = 13.5 Hz, 3H), 1.64 – 1.59 (m, 3H), 1.57 – 1.51 (m, 2H), 1.46 – 1.40 (m, 1H), 1.38 – 1.31 (m, 2H), 1.19 (s, 3H), 1.10 – 1.04 (m, 2H), 1.03 – 0.98 (m, 3H), 0.92 (s, 3H), 0.90 – 0.86 (m, 1H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.2, 141.4, 128.3, 128.2, 128.0, 128.0, 126.7, 66.2, 57.3, 57.0, 55.9, 53.2, 51.1, 43.8, 42.4, 41.8, 41.6, 41.2, 40.0, 38.1, 38.1, 34.3, 28.9, 25.6, 21.8, 20.7, 19.0, 13.3; HRMS (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{28}H_{41}NO_2$ 423.3137, found 424.3; $[\alpha]_D^{23}$ –58.5° (*c* 1.00, $CHCl_3$).



Standard procedure for amide bond formation from lactam ester **I-90a** (Scheme I-28).

To a solution of methyl-lactam ester **I-90** (1.00 g, 2.77 mmol) in THF/H_2O (1:1, 10 mL) in a round-bottom flask was added 1M aq. LiOH (5 mL) at room temperature. The reaction was heated to reflux and stirred overnight. Then, it was cooled to room temperature and quenched with 1M aq. HCl to pH 4. The resultant mixture was extracted with EtOAc and the combined organic layers were washed with brined and dried over $MgSO_4$. The acid was carried on without further purification. To a solution of acid (100 mg, 0.302 mmol, 1.0 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.67 equiv), 4-dimethylaminopyridine (21.1 μL, 0.121 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (140 mg, 0.905 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of amine **I-78** (0.211 mmol, 0.70 equiv) and diisopropylethylamine (52.6 μL, 0.302 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography with 20% EtOAc:Hex to furnish the lactam amide **I-92**.



I-92c

(3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-*N*-(4-fluorobenzyl)-3,4,9,12a-tetramethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxamide(I-92c).

oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.23 (m, 2H), 7.03 (t, *J* = 8.5 Hz, 2H), 5.24 (d, *J* = 15.4 Hz, 1H), 4.69 (s, 1H), 4.47 (d, *J* = 15.5 Hz, 1H), 3.66 (s, 3H), 2.21 (d, *J* = 13.8 Hz, 1H), 2.15 (d, *J* = 13.3 Hz, 1H), 1.91 – 1.83 (m, 1H), 1.82 – 1.77 (m, 1H), 1.73 (s, 3H), 1.71 – 1.60 (m, 3H), 1.58 (s, 3H), 1.49 (h, 1H), 1.44 – 1.32 (m, 3H), 1.29 (d, *J* = 6.8 Hz, 2H), 1.26 – 1.21 (m, 1H), 1.19 (s, 3H), 1.08 – 0.94 (m, 4H), 0.90 (dd, *J* = 13.0, 4.1 Hz, 1H), 0.85 – 0.76 (m, 1H); LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{28}H_{40}FN_2O_2$ 455.2996, found 455; $[\alpha]_D^{23}$ –74.3º (*c* 0.450, $CHCl_3$).

PART II- RETINOIC ACID RECEPTOR ALPHA ANTAGONIST DEVELOPMENT FOR MALE CONTRACEPTION

Chapter 5. Design and Synthesis of Retinoids for Non-Hormonal Male Contraceptive Development

A. Contraception Background

Contraception is the prevention of pregnancy with methods that control male or female fertility.[162] The first reports of contraception date back centuries ago with the invention of the condom in 1564.[163] This form of birth control was reliant on the male counterpart of sexual relationships, but much has changed since then in terms of more effective condom development and female contraception.[163] Female birth control most notably began in the 1950s with the introduction of an oral contraception method, also known as "the pill."[164] The birth control pill inhibits ovulation in normal, ovulating women by mimicking gonadal hormones: estrogen and progesterone. The first human trials were in 1956 with Food and Drug Administration (FDA) approval of the first hormonal contraception by 1960.[164, 165]

1. Unintended Pregnancies and Unmet Need for Contraception

Despite significant advances in reproductive services since then, a *Lancet* report in 2013 estimated that around 146 million women worldwide have an unmet need for contraception, or family planning.[166] That is to say, that millions of women, especially in developing nations, lack access to necessary contraceptive methods.

Moreover, that global estimate increases to 225 million women for women who do not use contraception or employ traditional methods, which include withdrawal or

abstinence.[167, 168] Table II-1 below displays all the pregnancies from 2008, including the percent distribution of intended and unintended pregnancies. In that year alone, over 85 million pregnancies were unintended with over ten million of those pregnancies coming from developed regions in the world, like the United States. The Centers for Disease Control and Prevention (CDC) describe an unintended pregnancy as an undesired or mis-timed pregnancy that occurs.[169] Furthermore, of those unintended pregnancies worldwide, 16%, or over 33 million, resulted in undesired births plus the other 25%, or 52 million, pregnancies that ended in abortion or miscarriages.

Table II-1. The number of pregnancies and percent distribution in 2008.[170]

Region	Total # of pregnancies (millions)	% distribution of pregnancies		Unintended pregnancy outcomes (%)		
		Intended	Unintended	Births	Abortions	Miscarriages
World	208.2	59	41	16	20	5
More developed regions	22.8	53	47	15	25	6
Less developed regions	185.4	60	40	16	19	5

We can infer from the number of unintended pregnancies in Table II-1 that there is indeed a large unmet need for families all over the world for modern and effective contraception that will affect millions of women. Compounded by the number of women who experience health problems that prevent them from taking effective contraception,[171] the unmet need has led to more research in both female and male contraception.

2. Current Forms of Male Contraception

Females have a variety of options for contraception, each with potential risks and benefits. Aside from the traditional, and at times unsuccessful, methods of natural family planning or barrier methods, women also can employ hormonal systemic contraception, injectable progestins, long-acting reversible contraception, and permanent sterilization.[165] Male contraceptive research, on the other hand, is underdeveloped, with only two currently available options: condoms or a vasectomy.[172] Condoms provide a temporary barrier to fertilization that is reversible upon removal of its use, while vasectomies, the clamping or cutting of the vas deferens to cause male sterilization, can be permanent.[173] The following chart shows existing contraceptive methods in the developing and developed regions worldwide; the majority of the available methods depend on female fulfillment (Chart II-1).[174]

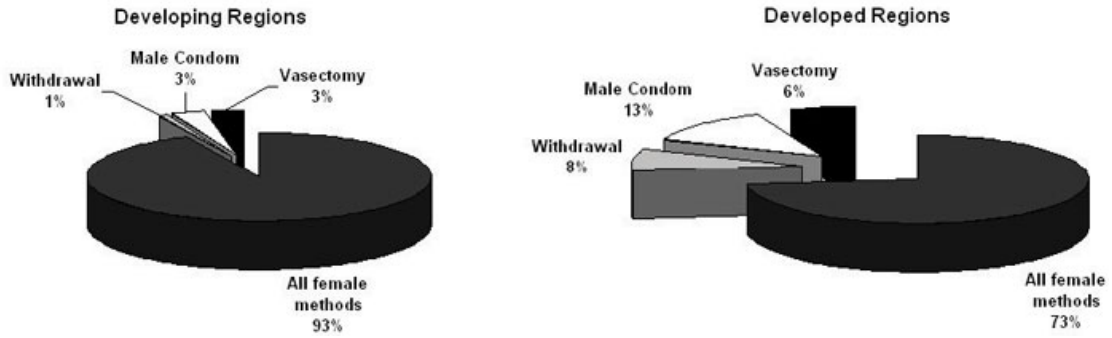


Chart II-1. Existing contraceptive methods in the developing and develop regions in the world.[174]

Several research projects are under way intended on producing other male contraceptive options.[172, 173, 175, 176] Potential male contraceptive methods are classified into categories based on their target of action: hindering the transport of sperm or suppressing spermatogenesis, the maturation of sperm from spermatogonia to spermatozoa.[174] Within

the past decade, the development of a male contraceptive agents that target spermatogenesis is becoming a pharmaceutical option.[172] Understanding spermatogenesis and its mechanism is paramount for male contraceptive development[175] and will be discussed throughout this chapter. As noted by Giwercman *et al.*, spermatogenesis is probably a more vulnerable process than ovulation.[177] Spermatogenesis is the process that generates mature sperm in the testes.[178] This continuous process takes approximately 75 days and produces millions of mature haploid sperm.[173] Figure II-1, illustrates the spermatogenesis process.

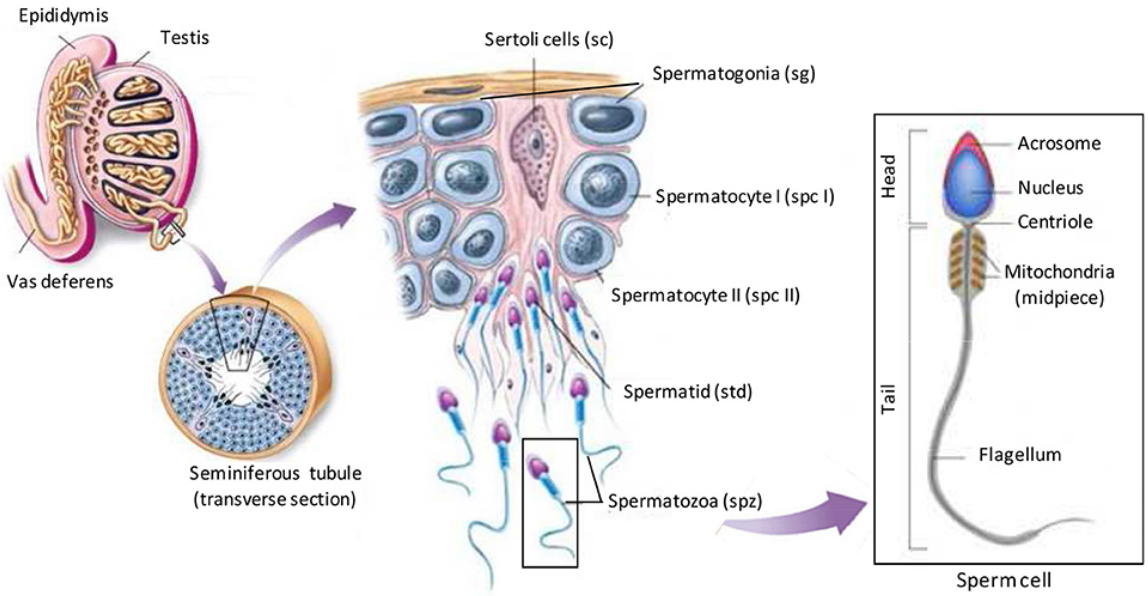


Figure II-1. The process of Spermatogenesis.[179]

Beginning in the seminiferous tubules of the testes, diploid spermatogonia (sg) undergo mitosis to produce diploid primary spermatocytes (spc I). These spermatocytes can continue to divide mitotically or move on to the next step: meiosis I. The spc I migrate toward the lumen to undergo meiosis I and produce haploid secondary spermatocytes (spc II). The spc II continue to meiotically divide through meiosis II to generate haploid

spermatids (std). The spermatids continue to mature into spermatozoa (spz) in the lumen of the seminiferous tubules during spermiogenesis.[179] Spermatozoa, or mature sperm cells, consist of a head, mid-piece, and flagella tail. Research has been done to inhibit spermatogenesis through the exogenesis administration of testosterone derivatives in male hormonal contraceptive development.[180, 181] All these studies show the effects of injecting the androgens subcutaneously, because the oral administration route was not effective.[174] Moreover, aside from the slight pain caused by needle injection, other unwanted side effects of supernatural levels of testosterone include negative cardiovascular effects, mood changes, acne,[182] weight gain,[183] and possible prostrate malignancy.[184] Altogether, these side effects and the type of drug administration have made hormonal contraceptive development unattractive.[174] Herein lies the need for a non-hormonal male contraceptive agent.

3. Areas of Focus for Non-Hormonal Male Contraceptive Development

A non-hormonal male contraceptive approach can be defined as one that does not involve the administration of exogenous hormones or agents that block hormone action or secretion.[185] This approach will be less likely to have the adverse effects from the hormonal treatment. Non-hormonal male contraception is an unmet need and an attractive area for drug development, since this allows men to have power to control their fertility as well as take an active role in family planning. Unfortunately, pharmaceutical interest in the male contraceptive research arena has died down, probably due to the slow research; the burden to provide enough safety, efficacy, and reversibility data; and the assurance of not having deleterious effects to future offspring.[172, 174] As a result, the NIH has taken this global

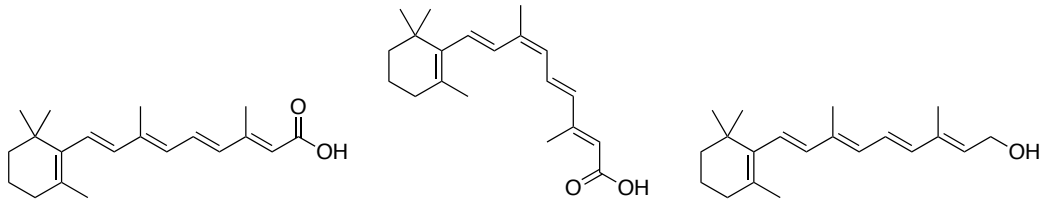
problem as a major financial contributor.[172] Through the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the Male Contraceptive Development Program (MCDP) is an invaluable resource for the future of male birth control.

The MCDP conducts research that can identify mechanisms of sperm maturation regulation and new therapeutic targets.[186] The main areas of research focus on inhibiting spermiogenesis or spermatogenesis, *vide supra*. Our group received funding through the Contraceptive Research Branch to explore multiple areas of potential contraceptive development, such as targeting the sperm-specific Na,K-ATPase alpha 4 (α4), bromodomain testis-specific protein (BRDT), or retinoic acid receptor alpha (RARα). Na,K-ATPase α4 is a specific isoform of a transmembrane protein that is found to control motility and hyperactivation in sperm through active sodium and potassium ion exchange.[187] BRDT is a tissue-restricted protein that is important in spermatogenesis.[188] The RARα target will be discussed in greater detail below.

B. Retinoic Acid Receptor Alpha (RARα)

While the Georg research group focuses on these and other targets for the development of male contraceptive agents, a subset of us (Dr. Rebecca Cuellar, Jillian Kyzer, Dr. Narsihmulu Cheryala, and Trinh Holth) have been investigating RARα nuclear receptor antagonists. Retinoic acid receptors belong to the nuclear receptor family and are composed of three isotypes: RARα, β, and γ.[189] They are involved in many significant biological processes including embryogenesis, reproduction, vision, growth, inflammation, cell differentiation, cell proliferation, and apoptosis.[190] Additionally, this family of nuclear

receptors also includes retinoid X receptors, which also come in three similar isoforms: α, ß, and γ.[191] RARs exist as heterodimers with RXR, forming RAR-RXR complex, which may be responsible for transducing the retinoid signal at the molecular level.[192] RARs are also required for the mediation of the important vitamin A functions during human development.[193] In addition to forming heterodimer complexes with retinoic acid receptors, RXRs can also exist as homodimers.[194] Both RAR and RXR receptors are activated by retinoic acid (RA) in the cells.[195] Retinoic acid receptors can bind to either all-*trans* RA (ATRA) or 9-*cis* RA, while retinoid X receptors, only bind to 9-*cis* RA (Figure II-2).[196, 197]



all-*trans* retinoic acid (ATRA) **II-1** | 9-*cis*-retinoic acid **II-2** | retinol (vitamin A) **II-3**

Figure II-2. Structures of all-*trans* retinoic a, 9-cis RA, and vitamin A.

ATRA (**II-1**) and 9-*cis*-RA (**II-2**) belong to a group of compounds called retinoids: natural or synthetic analogs of retinol (**II-3**), also known as vitamin A (Figure II-2).[198] Retinol (**II-3**) is converted to **II-1** through sequential oxidation steps in the body.[199] While many of the RAR and RXR isoforms are found in spermatocytes and at different developmental stages, RA mediates its effects through the action of the RARα in Sertoli cells, [195] Sertoli cells are located in the seminiferous tubules and aid in spermatogenesis.[200]

1. Implications in Male Contraception

Previous research has shown that a knockout mouse model of RARα exhibited disrupted spermatogenesis and infertility.[201] Additionally, defects in vitamin A-deficient (VAD) wild-type mice were reversed after administration of RAR agonists.[201] While vitamin A-deficiency does occur in humans, not enough information is known regarding the effects on reproductive capabilities.[202] However, there is some evidence of the effect of RA on human male germ cells.[203] Reports reveal that germ cells in fetal human testes cultured with retinoic acid underwent apoptosis after they were stimulated to proliferate.[204] Additionally, retinoic acid also induces an increase in the gene stimulated by *RA gene 8* (*STRA8*) for the expression of RA in the human embryonic ovary and testis and the postnatal testis.[195, 205] While the research is ongoing and these processes are not well understood overall, these reports imply the importance of retinoic acid and vitamin A in spermatogonial differentiation, meiosis, and the cycle of the seminiferous epithelium.

The Wolgemuth group at Columbia University first reported on the connection between vitamin A and retinoic acid in mammalian male sterility.[189, 206] In mouse studies, where the Rara gene is removed ($Rara^{-/-}$), the results showed sterile male mice with specific abnormalities in spermatogenesis, as seen in histological cross sections of the tubules.[207] They also observed that the defects in spermatogenesis were similar to those in vitamin A deficient testes.[208] Chung *et al.* also reported that disruptions in RARα-mediated retinoid signaling in spermatogenesis result in a failure of sperm alignment and release into the seminiferous tubular lumen,[198] which is similar to the effects observed in VAD mice.[189] Of note, RARα is required for spermatogenesis and its absence results in progressive breakdown of the spermatogenesis process.[209] Figure II-3 demonstrates the histological

cross sections (A and B) of a seminiferous tubule in the testes and their illustrations below (C and D) show the effects on spermatogenesis in normal, fertile mice compared to VAD mice.[210]

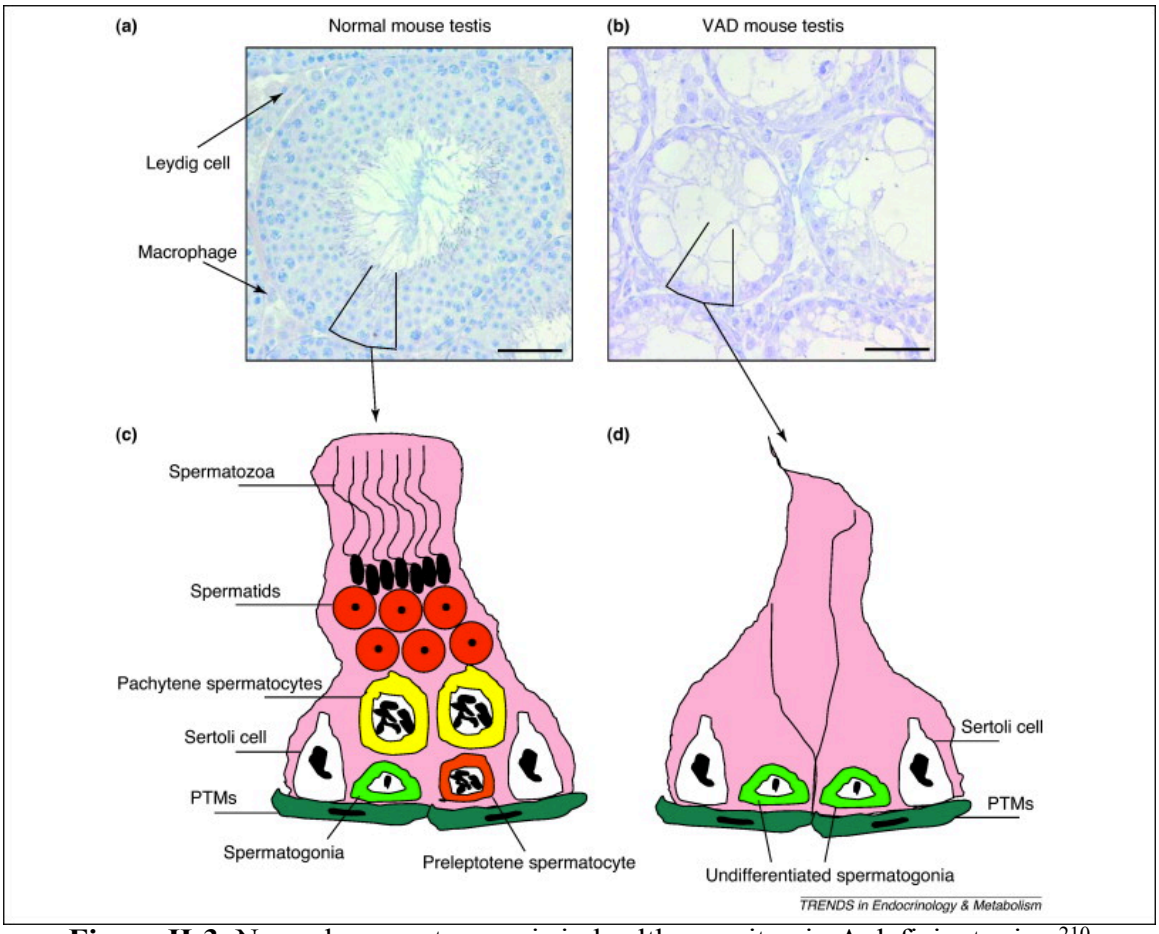
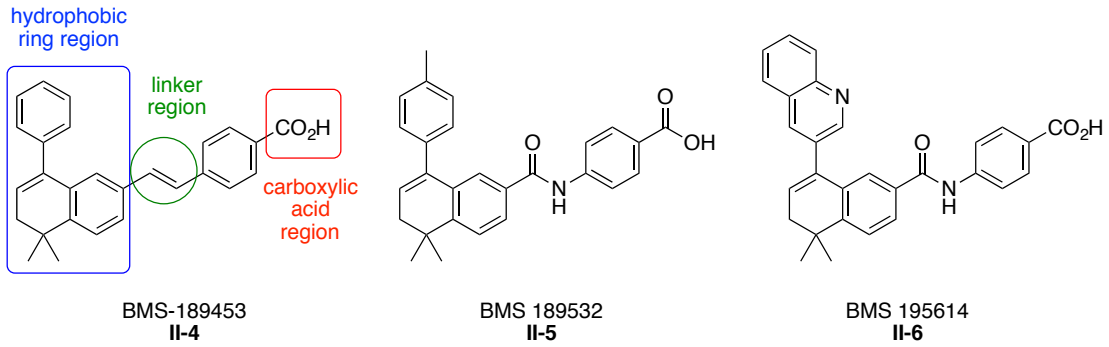


Figure II-3. Normal spermatogenesis in healthy vs vitamin A deficient mice.[210]

Under normal spermatogenic conditions, spermatogonia differentiate into spermatozoa. In between the Sertoli cells, spermatgonia mature to spermatocytes then spermatids before they are released into the lumen for spermiation.[189, 198] In VAD and RARα null mice, the process is completely absent, with no spermatozoa production, which causes the sterility.

2. Previous Agonist and Antagonist Development

The reversibility of sterile effects on mice with abnormalities in vitamin A deficiency or RARα-deficient testes,[206] suggest an opportunity for non-hormonal contraceptive development of specific RARα antagonists. A series of compounds have been developed that block ATRA binding and activation of transcription of RAR target genes by Bristol-Myers Squibb (BMS) (Figure II-4).[211] In the 1980s, BMS 189453 (**II-4**), a non-selective RAR antagonist retinoid, acting on all isoforms (α, ß, and γ), was shown to cause reversible infertility.[212] Retinoids are derivatives of vitamin A and are composed of three general parts: a hydrophobic ring portion, a linker region, and a carboxylic acid end group (Figure II-4). For RARα retinoids, the hydrophobic ring portion imparts antagonism with bulky groups inducing antagonistic effects over less bulky hydrophobic moieties. When a *gem*-dimethyl is in place of the phenyl ring in the hydrophobic region, the molecule exhibits agonistic activity.[213] An amide group in the linker region reveals the greatest RARα selectivity. With an alkene linker, **II-4** is a pan-antagonist, while **II-5** and **II-6** are RARα selective antagonists. Lastly, the carboxylic acid end group is essential for RAR activity.



BMS-189453 **II-4** | BMS 189532 **II-5** | BMS 195614 **II-6**

Figure II-4. BMS compounds.

Interestingly, the BMS compound BMS-189453 was originally tested on animals as a treatment for inflammatory skin diseases. Researchers in the Wolgemuth group at Columbia University reported that when doses for the BMS pan-antagonist were decreased in fertility experiments, the infertility, that was previously observed, had a reversible effect without significant toxicity.[208] Additional studies were performed with other retinoids: BMS-189532 (**II-5**) and BMS-195614 (**II-6**) (Figure II-4).[206] These compounds proved to be RARα-selective antagonists through competition assays with the other RAR isoforms.[206] While both retinoids showed great potential in *in vitro* analyses, they demonstrated poor *in vivo* effects when orally administered to mice.[206] We submitted a sample of both **II-4**, the pan antagonist, and **II-5**, the RARα selective antagonist to Cerep, Inc. for evaluation in a variety of assays including aqueous solubility (in phosphate buffered saline (PBS), pH 7.4), partition coefficient determination (octanol-PBS buffer, pH 7.4), cell permeability (Caco-2 cells), plasma protein binding (mouse), and metabolic stability (mouse liver microsomes), along with the reference compounds used (Table II-2). The partition coefficient (Log D) data shows that **II-4** was less favorable than **II-5**, with a value of 3.25 and 3.84, respectively. Ideally, the higher the Log D value, the more lipophilic

the compound is and the more the drug is absorbed by the cells.[214] Additionally, **II-4** had lower permeability and was considerably less soluble. However, BMS-189453 (**II-4**) did indeed have a more favorable plasma protein binding value. While BMS-189532 (**II-5**) is the more ideal candidate for our project because it is α isoform specific, the compound was ineffective *in vivo*. The Cerep data confirms this knowledge: only 0.8% of **II-5** was not bound to plasma protein and a very small portion of free compound was then metabolized at a much faster rate than the pan-antagonist.

Table II-2. Pharmacology of known RARα antagonist and pan-antagonist.

Assay (conditions)	**II-5**	**II-4**	**Reference compounds**
Aqueous Solubility (PBS, pH 7.4)	136 μM	3.1 μM	diethylstilbestrol, haloperidol, metoprolol tartrate, phenytoin, rifampicin, simvastatin, tamoxifen
Partition Coefficient (Log D, *n*-octanol/PBS, pH 7.4, 1.0×10^{-4} M)	3.84	3.25	diethylstilbestrol, haloperidol, ketoconazole, metoprolol tartrate, phenytoin, rifampicin, simvastatin
Plasma Protein Binding (mouse, CD-1, 1.0×10^{-5} M)	99.2% bound; 99.8% recovery	95.3% bound; 93.3% recovery	acebutolol, quinidine, warfarin
A-B Permeability (TC7, pH 6.5/7.4,1.0×10^{-5} M)	8.3×10^{-6} cm/s; 20% recovery	$<0.7 \times 10^{-6}$ cm/s; 14% recovery	colchicines, labetalol, propanolol, ranitidine
Metabolic Stability (liver microsomes, mouse, CD-1, 1.0×10^{-6} M, 60 min.)	49% parent remaining	79% parent remaining	imipramine, propanolol, terfenadine, verapamil

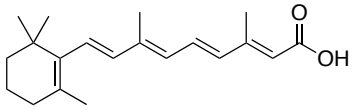
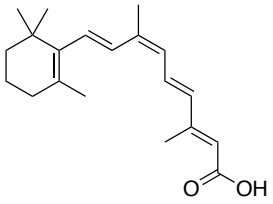
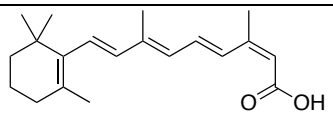
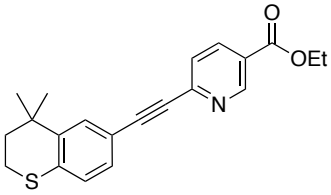
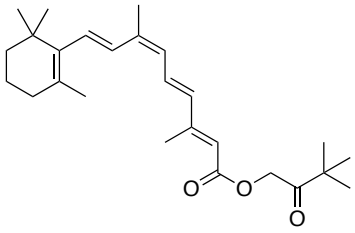
From the results of the biological screening of BMS compounds **II-4** and **II-5** in Table II-2, we determined that the amide linker of **II-5**, the α selective antagonist, has a much larger metabolic liability than the alkene linker of **II-4**, the pan antagonist. We conclude from this data that simultaneously addressing plasma protein binding and metabolic stability should yield compounds that are bioavailable in our later animal models. We determined that the cause of undesired *in vivo* effects was most likely due to poor bioavailability of the compounds and modifications to their structures could circumvent these problems. Given the importance of RARα in sperm maturation and male reproduction, the goal of our research is to develop a reversible, non-hormonal therapeutic agent that targets and blocks RARα. For this, we pursued the BMS retinoids as a starting place for compound development.

C. Design of Retinoids

The retinoids are made up of three general parts: a hydrophobic ring portion, a linker region, and a carboxylic acid end group (Figure II-4). These three general features tolerate a wide range of moieties: quinolone, naphthalene, or chromane heterocycles in the hydrophobic ring portion; an alkene, an amide, or a heterocyclic isostere for the linker region; and benzoic, cyclohexanoic, or naphthoic acid on the end. Table II-3 shows several examples of retinoids that are clinically approved or in clinical testing.[215] Some of these retinoids, including the natural ligands **II-1** and **II-2**, are commercially available as treatments for acne, psoriasis, and various types of cancer. All of these approved drugs contain a similar structure to our target compounds with a hydrophobic region, a linker portion, and a carboxylic end. Additionally, the compounds in Table II-3 all contain a *gem*-

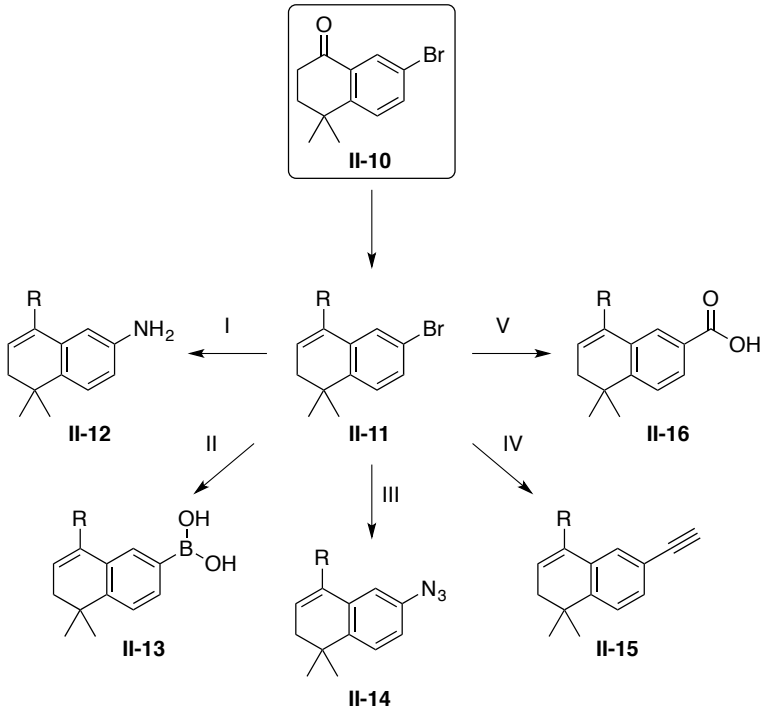
dimethyl group in the hydrophobic ring region, which has been show to promote agonism, *vide supra*.

Table II-3. Commercially available retinoids.

Name (Trade Name)	**Structure**	**Phase: Indication**
ATRA, Tretinoin (Avita)	 **II-1**	Launched: acne, warts Phase II: breast, brain, and renal cancers
9-*cis*-RA, Aliretinoin (Panretin)	 **II-2**	Launched: Karposi's sarcoma
Isotretinoin (Accutane)	 **II-7**	Launched: acne Phase II: T-cell malignancies Phase III: high grade glioma
Tazarotene (Tazorac)	 **II-8**	Launched: acne, psoriasis
Pinacolyl-9-*cis*-retinoate, MDI 301	 **II-9**	Preclinical: acne, cancer, psoriasis

Since we needed to generate compounds that would address our earlier problems with **II-4** and **II-5** yet also be selective for RARα, we sought to develop compounds with

bioisosteres for the amide linker: triazoles, oxadizoles, imidazoles, pyrazoles, oxazoles, and other heterocycles. [216, 217] For the hydrophobic ring region, we initially chose to work with the same naphthalene ring as the BMS compounds because the synthesis was known and modifications at various positions were possible. From bromo-tetralone (**II-10**), a straight forward Grignard reaction followed by elimination provides access to the tetralin core of the hydrophobic ring region (Scheme II-1). The tetralin bromide serves as an excellent DOS template, *vide supra*, because many different reactions with the bromide will provide multiple different linkers for the retinoids.

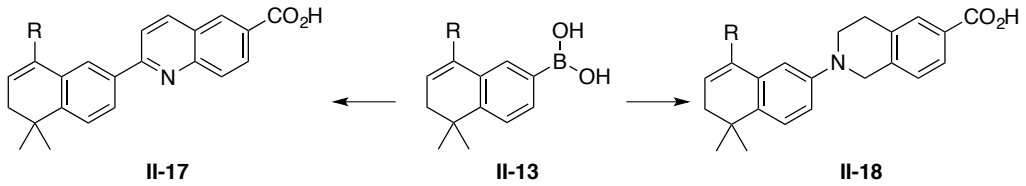


Scheme II-1. Formation of different tetralin linkers.

Path I leads to aniline **II-12** possibly through copper catalysis.[218] Path II pertains the borylation through an organometallic reagent plus a boric ester, followed by acid hydrolysis to yield boronic acid **II-13**.[219] Similarly, **II-14** and **II-15** can be produced

through a lithium-halogen exchange to give the corresponding aldehyde,[220] followed by a sodium azide reaction to give azide **II-14** or Bestmann-Ohira reaction conditions to give alkyne **II-15**.[221] Hydroxycarbonylation can produce an aryl carboxylic acid **II-16** from aryl bromide **II-11**.[222]

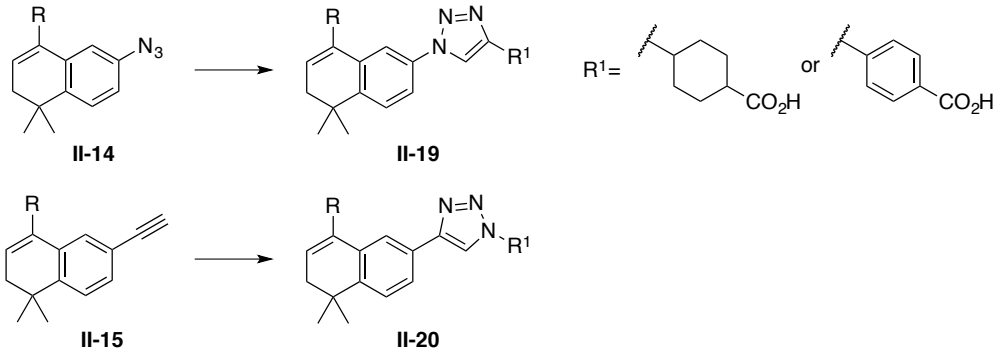
Additionally, from the aryl boronic acid derivative **II-13**, we envisioned synthesizing the quinolone linker analogs (Scheme II-2). While quinolone is not a known bioisostere for the amide group, the robustness of the quinoline and tetrahydroisoquinoline rings could help form tighter or better binding compounds. These heterocycles encompass both the linker and carboxylic acid regions so we wanted to explore their potential in our tetralin series.



II-17 **II-13** **II-18**

Scheme II-2. Quinoline linkers via boronic acid **II-13**.

On the other hand, we are exploring the triazole heterocycle through the synthesis of both aryl azide and aryl alkyne derivatives, **II-14** and **II-15**, respectively, as amide bond bioisosteres. Through click chemistry with the corresponding alkyne or azide, we envision the formation of triazole linker **II-19** or **II-20** (Scheme II-3).



Scheme II-3. Triazole products from azide **II-14** and alkyne **II-15**.

Additionally, my part of this work involves the synthesis of cyclohexanoic acid analogs to understand the behavior of the binding pocket and introduce some rigidity into the retinoids. The DOS approach for the tetralin core is an excellent way to access multiple substituents in the linker region.

D. Computational Modeling of Retinoids

While the synthesis was underway, we also performed *in silico* analysis of our compounds to assess their potential for a structure-based drug design approach of the retinoids. For our investigation, we fortunately had an available crystal structure of a RARα heterodimer (PDB:1dkf) bound with a known BMS antagonist **II-6** (Figure II-5).[223] Using the Schrodinger Molecular Modeling suite, we were able generate a grid for the binding pocket that was established from the bound **II-6**.

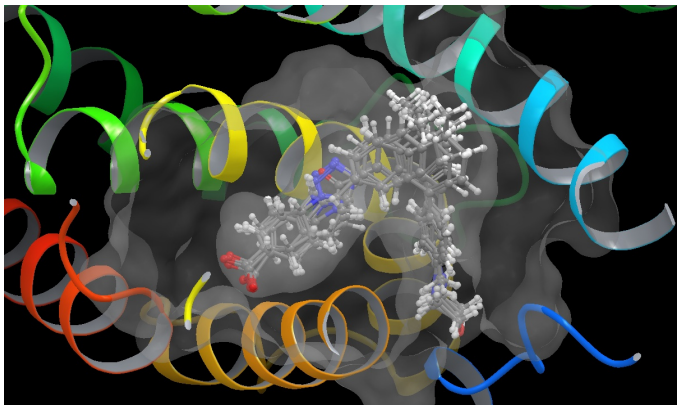
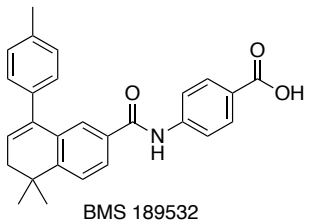
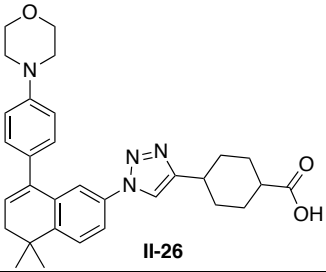
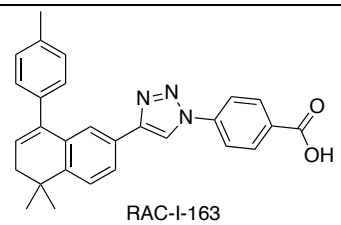
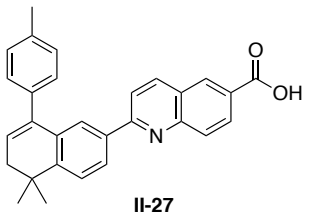
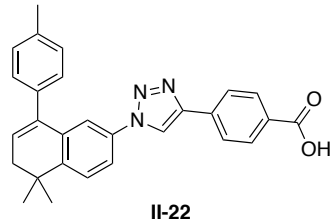
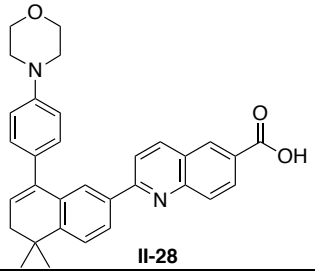
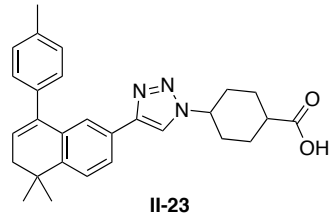
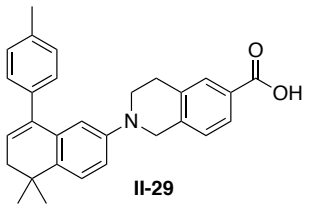
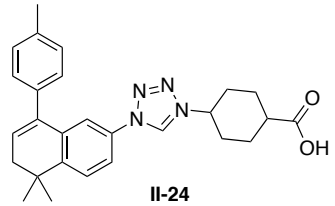
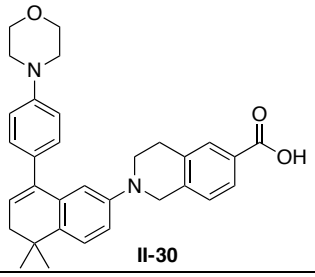
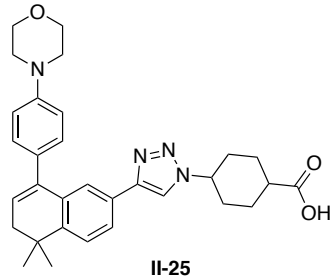


Figure II-5. 1dkf protein structure with proposed docked compounds.

With the Maestro program in the suite, docking scores were calculated for our retinoids bound within the receptor site. Table II-4 shows the lowest docking scores for a sample of our proposed structures; of note, more negative values for docking scores indicate better docking within the grid of the binding pocket. Our scores show that the RAR α selective compound **II-5** did not score as well as our retinoids. Dr. Cuellar from our group has previously synthesized RAC-I-163 (**II-21**) as a triazole analog of **II-5**, as well as its structural isomer (**II-22**). Within the table, there are Dr. Cuellar's triazole analogs with the benzoic acid moiety, cyclohexanoic acid triazole analogs **II-23**-**II-26**, as well as the quinoline linker analogs **II-27**-**II-30** (Table II-4).

Table II-4. Docking scores for proposed retinoids plus **II-5**.

Compound	Docking Score	Compound	Docking Score
 BMS 189532 **II-5**	-14.3615	 **II-26**	-14.6250

 RAC-I-163 **II-21**	-15.3422	 **II-27**	-14.6288
 **II-22**	-15.3401	 **II-28**	-15.4904
 **II-23**	-14.5278	 **II-29**	-14.9819
 **II-24**	-14.8753	 **II-30**	-15.4518
 **II-25**	-14.7372		

With the 1dkf crystal structure, the quinoline moiety of **II-6** computationally displayed an ability to fill the antagonist binding pocket in RARα active site, which suggests that actual binding of our molecules could produce similar results.

From the Maestro program, we were able to calculate the binding energies of the interactions of the retinoids to the amino acids in the binding pocket. Ideally, we want to produce molecules that are more energetically favorable, or -ΔG, as represented as the bars negative from the 0 axis. These purposed retinoids have the most interaction with residues 220 to 280. This analysis is helping in determining which parts of the molecules are interacting with the binding pocket in a positive or negative manner. Future work would be to adjust these parts of the molecule to produce favorably interactions.

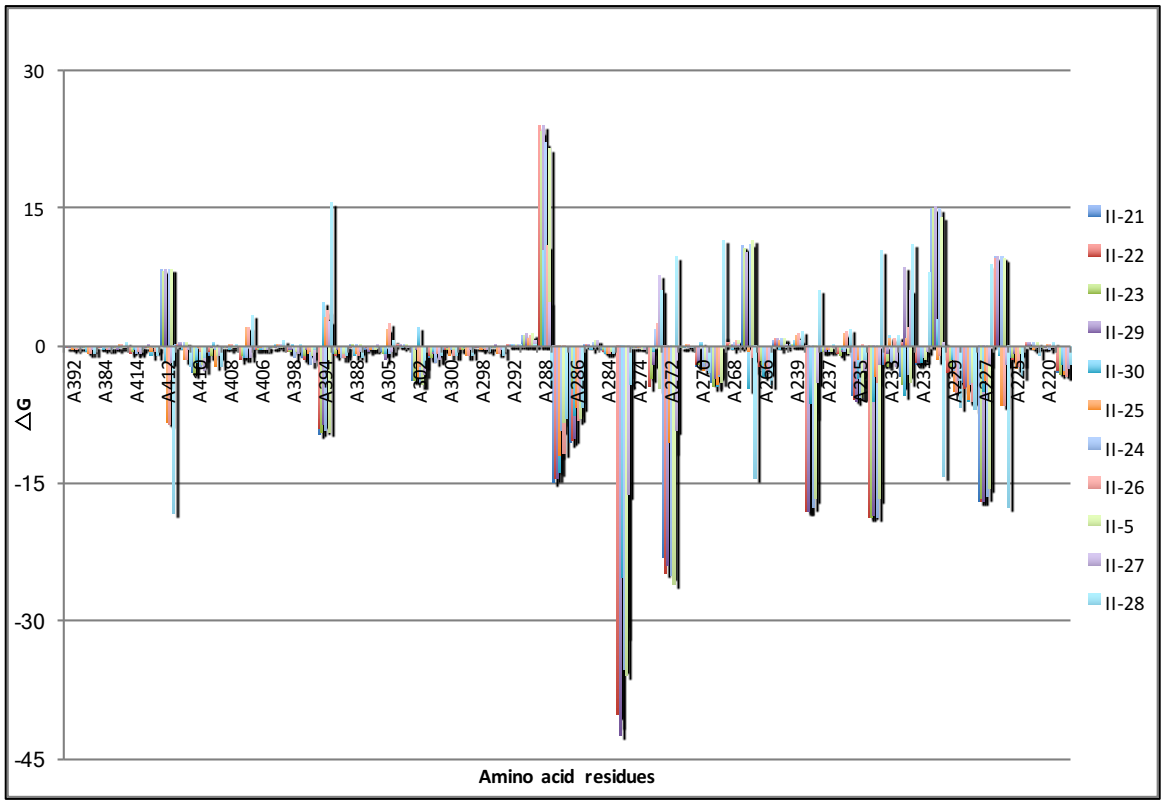


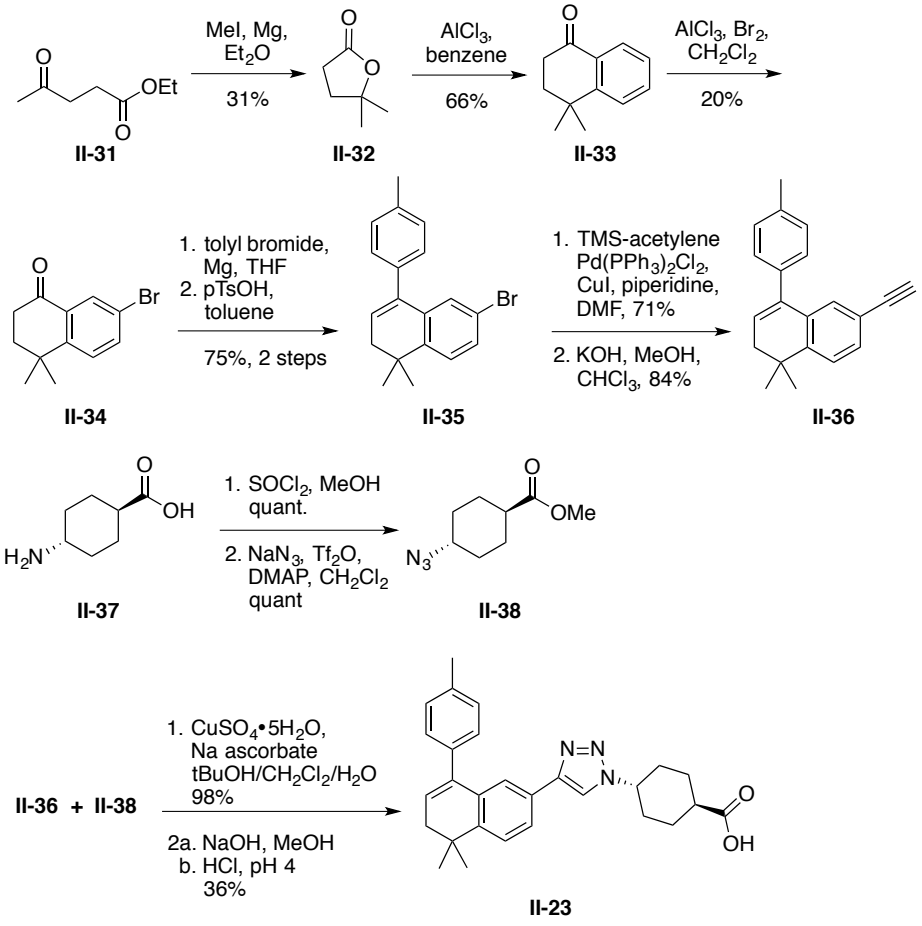
Figure II-6. Binding energies for proposed compounds.

Our computation data suggests that the cyclohexanoic acid moiety could impart some rigidity in the retinoids. Research has been ongoing to produce the BMS triazole analogs as well as a new group of Eisai Research (ER) analogs.

E. Synthesis of Retinoids

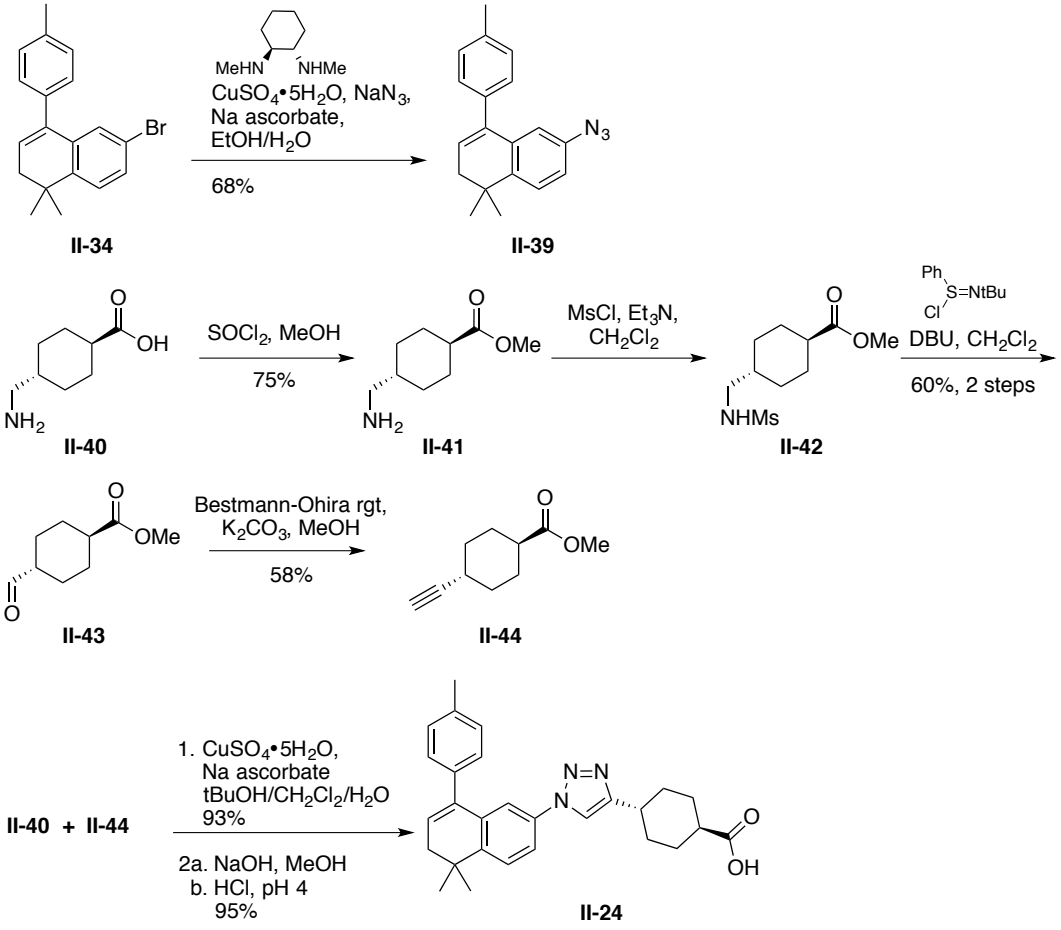
1. BMS Triazole Derivatives

For the RARα retinoid synthesis, my work included the cyclohexanoic acid and quinolone linkers. To start, the 7-bromo tetralone **II-34** was synthesized to serve as a building block for the tetralin core (Scheme II-4). Treatment of ethyl levulinate (**II-31**) with methyl magnesium iodide afforded dimethyl furan **II-32**, which was followed by Friedel–Crafts acylation/intramolecular alkylation of benzene to give tetralone **II-33**.[224] Bromination of **II-33** gave multiple side products (not shown), but the desired **II-34** was isolated in 20% yield. After attempts to optimize the reaction were unsuccessful, we went ahead and bought the commercially available **II-34**.



Scheme II-4. Synthesis of triazole **II-23**.

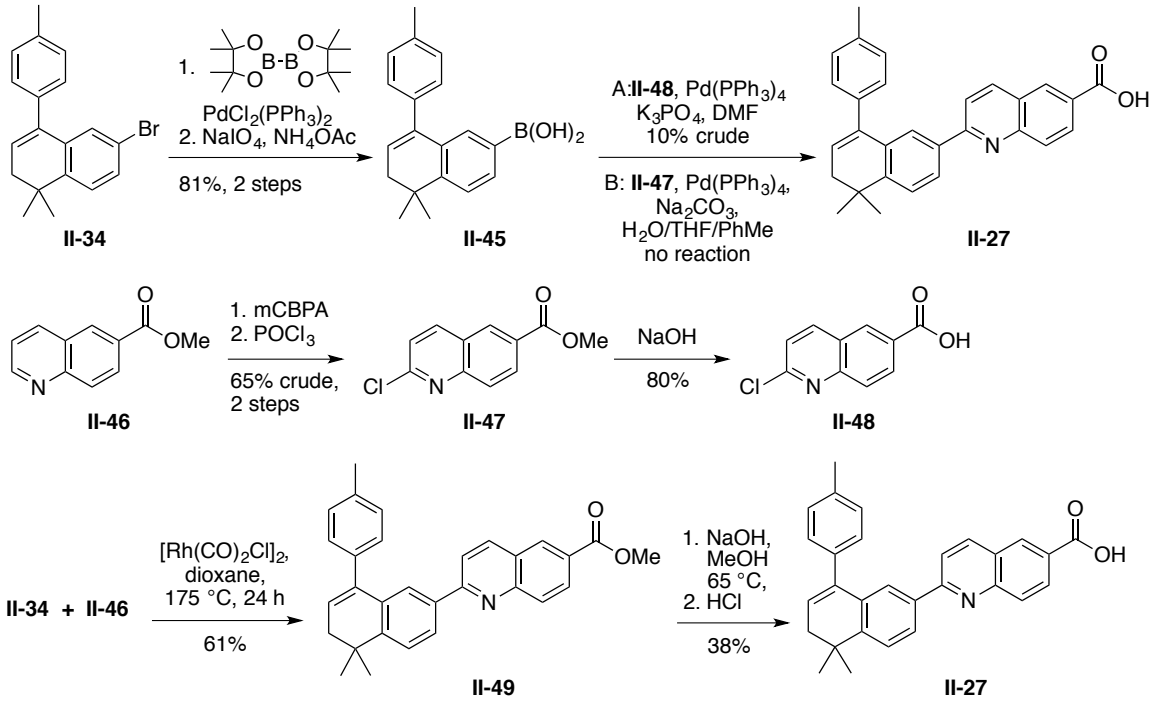
A Grignard reaction with tolyl bromide followed by elimination gave the tolyl bromide **II-35**. Sonogashira coupling with TMS acetylene and silyl deprotection produced alkyne **II-36** (Scheme II-4). The alkyne was then coupled to azide **II-38** with the Huisgen 1,3-cycloaddition reaction, or click chemistry, to give triazole **II-23** after hydrolysis. Azide **II-38** (Scheme II-4) was made by treating trans amino cyclohexanoic acid with thionyl chloride to form the ester in quantitative yield followed by azide formation with sodium azide and triflic anhydride. Triazole **II-23** was carried on to activity screening, *vide infra*.



Scheme II-5. Towards the synthesis of triazole **II-24**.

In addition to the **II-23** triazole, its structural analog **II-24** was produced. Aryl azide **II-39** was synthesized under mild conditions with a chiral diamine ligand.[225] Aryl azide **II-39** then underwent another click reaction with alkyne **II-44** to produce the ester of **II-24**. Hydrolysis of the ester under normal basic conditions followed by crystallization in methylene chloride and hexanes completed the synthesis of **II-24**. To access the alkyne precursor **II-44**, we started with tranexamic acid (**II-40**) and formed its ester **II-41**. Next, the amine was treated with mesyl chloride to give the mesylated amine **II-42**, then it was oxidatively deaminated with N-tert-butylphenylsulfinimidoyl chloride to yield the corresponding aldehyde **II-43**. Lastly, dimethyl (1-diazo-2-oxopropyl) phosphonate, or Bestmann-Ohira reagent, was added under basic conditions to afford the alkyne **II-44** (Scheme II-5).

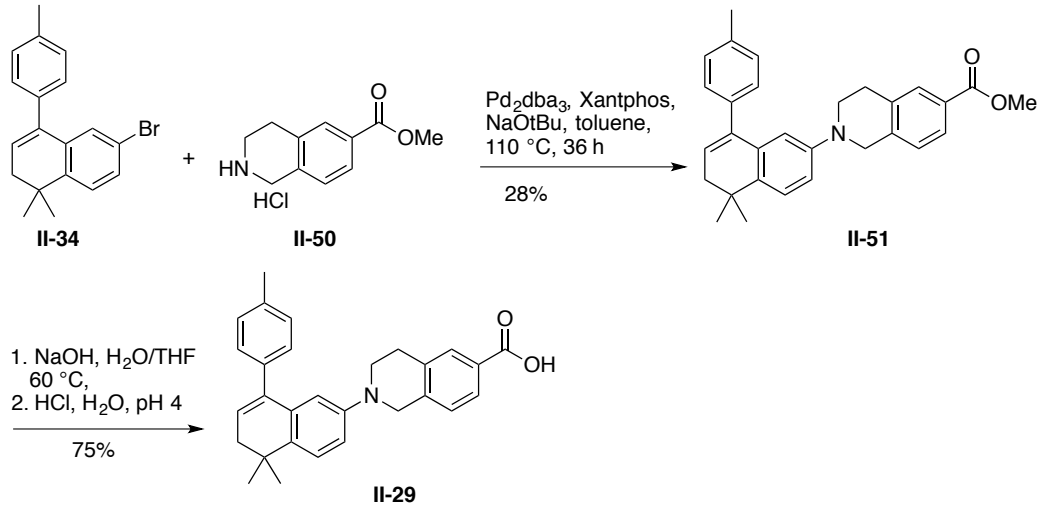
The synthesis of retinoids isoquinoline **II-27** and tetrahydroisoquinoline **II-29** were also performed (Scheme II-6 and II-7). Boronic acid **II-45** was formed from bromide **II-34** with a diboron reagent followed by hydrolysis with sodium periodate. Acid **II-45** was coupled to chloroquinoline **II-47** with a Suzuki coupling protocol.[226] To generate chloroquinoline **II-47**, quinolone **II-46** was treated with *meta*-chloroperoxybenzoic acid followed by phosphoryl chloride.[227] The Suzuki coupling yielded a small amount of **II-27** that was not enough to be biologically tested. We therefore tried coupling with the acid derivative **II-48** to avoid the final saponification step and potentially another low yield (route B, Scheme II-6), but after 24 hours, only starting material was detected.



Scheme II-6. Towards the synthesis of quinoline **II-27**.

Eventually, this route was abandoned when a more simple direct arylation with quinoline using the rhodium catalyst was realized.[228] After optimizing the conditions, we were able to get good yields for both the coupling and saponification steps for the production of **II-27** (Scheme II-6).

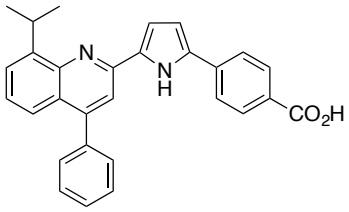
Lastly, synthesis of the quinolone analog **II-29** was completed by catalytic palladium coupling of tetrahydroisoquinoline **II-50** to bromide **II-34** to give the desired ester. Reaction optimization with BINAP did not produce a yield higher than 28% but the product was carried on. Saponification under basic conditions gave quinolone acid **II-29** cleanly without further purification.



Scheme II-7. Synthesis of quinoline analog **II-29**.

2. ER Derivatives

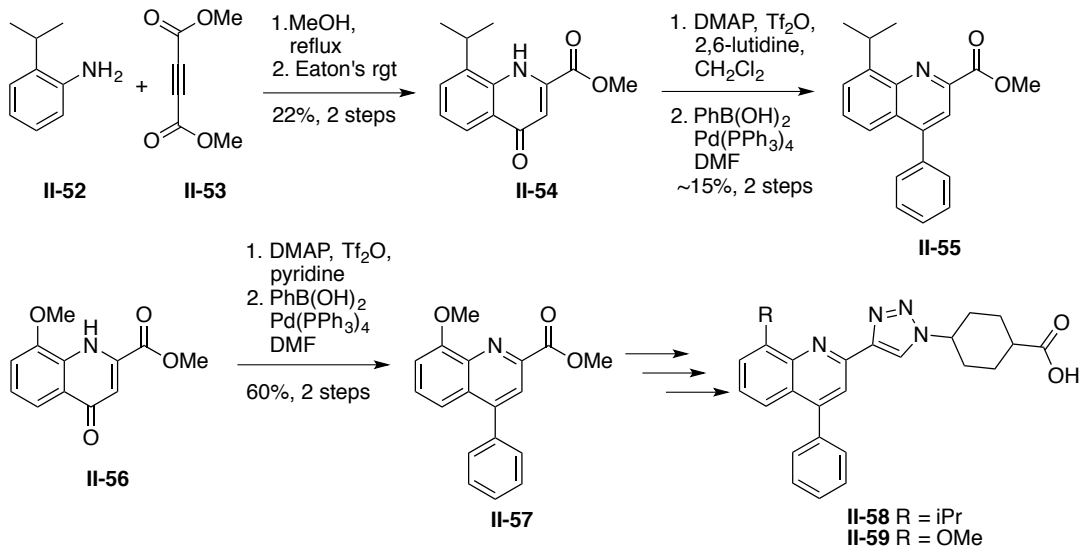
During the synthesis of these BMS-derived retinoids, our group also explored quinoline **II-51** (ER-50891), another α selective compound (Figure II-7).[229] Preliminary results from analogs made in our group showed promise, so a cyclohexanoic acid analog with a triazole linker was attempted.



ER-50891
II-52

Figure II-7. ER-50891 (**II-52**).

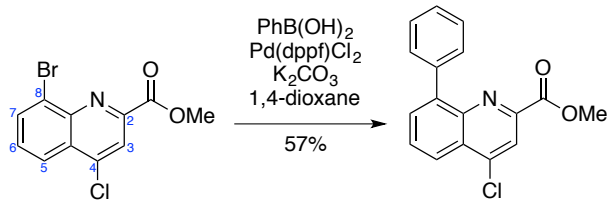
This section covers the brief work I have done towards the synthesis of ER-50891 derived retinoids. I completed the synthesis of the isopropyl and methoxy quinolone analogs **II-54** and **II-57**, respectively, with the aim to convert them to triazole cyclohexanoic acid analogs **II-58** and **II-59** (Scheme II-8).



Scheme II-8. Towards the synthesis of ER analogs.

For the synthesis of isopropyl quinoline **II-55**, isopropyl aniline **II-52** was first treated with butynedioic ester **II-53** followed by Eaton's reagent to generate the quinoline ester **II-54**.[230] This underwent treatment with triflic anhydride and dimethylaminopyridine (DMAP) to yield the triflate intermediate that was then treated with phenyl boronic acid to produce **II-55** in low yield. The triflate intermediate formation followed by the Suzuki reaction was done with methoxy quinoline **II-56** to give ester **II-57** in good yield after two steps. Following the production of the esters **II-55** and **II-57**, the initial goal was to produce retinoids **II-58** and **II-59** with the triazole linker by first reducing the respective ester to its corresponding aldehyde followed by a Seyferth-Gilbert homologation to give the alkyne product that would then be coupled with azide **II-39** (from Scheme II-4) via click chemistry. However, while the syntheses of these triazole analogs were under way, others in our group tested ER analogs with the presence of the triazole linker and found them to

be inactive for RARα. With this in mind, new routes are being explored for different linkers for the ER analogs.



II-60 **II-61**

Scheme II-9. Developing quinoline analogs for hydrophobic pocket exploration.

A new route for quinoline analogs are being explored by our group for selective aryl- or alkylation of the 4- and 8- positions of the quinoline ring (Scheme II-9). The aim of this work is to make different quinoline analogs at the C-4 and C-8 positions to explore the hydrophobic pocket of RARα. With 8-bromo-4-chloroquinoline ester **II-60**, Suzuki coupling with phenylboronic acid using $Pd(dppf)Cl_2$ as the catalyst gave the exclusive bromo-substituted phenyl quinoline **II-61** in good yield. This leaves room to explore further substitution at the chloro- position and saves extra steps from having to form the 8-substituted quinoline exclusively, as in **II-54** or **II-56**.

F. Biological Screening of Retinoids

Once synthesis of the retinoids has been completed, the compounds were subjected to a binding assay and luciferase reporter activity assay.

1. Binding Assay

As a complement to our computational structure-based drug design approach, we have also been able to determine where to make structural modifications on our compounds to maximize binding interactions to their known targets with the help of our collaborators in the Schönbrunn group. They have produced the RARα binding domain with a bacterial over-expression system and have used it in isothermal titration calorimetry (ITC) binding studies and crystallization screens. ITC is the gold standard technique for determining thermodynamic parameters of chemical interactions, especially binding constants. This technique is the only experimental method that simultaneously obtains thermodynamic parameters, which greatly reduces the potential errors introduced from piggybacking calculations. Of note, isothermal titration calorimetry is used for quantifying binding constants, while X-ray co-crystallization is used for qualifying those results from binding. Additionally, X-ray co-crystallization of our compounds will be used to identify possible sites of interest for further modification through structure-activity relationship (SAR) analysis. Furthermore, ITC avoids the use of reporter labels including isotopes, fluorophores, chromophores, to monitor a reaction; thus, it saves time and money.

Generally, ITC involves the titration of a ligand into a solution of protein in a closed system while monitoring the energy consumption or the generation of heat. The change in heat is then used in the Gibbs' free energy equation to determine K_d ($\Delta G = \Delta H - T\Delta S = -RT\ln K_a$ where $K_a = 1/K_d$). The K_d value, or dissociation constant, is a measurement of binding affinity. Binding affinity describes the strength of the interaction between the protein and the ligand. In general, smaller K_d values indicate tighter binding and greater binding affinity.[231]

For the RAR project, both 9-*cis*-retinoic acid (**II-2**) and all-*trans*-retinoic acid (**II-1**) are used as controls, with all tests done in triplicate. Figure II-8 and II-9 shows ITC data for all-*trans*-retinoic acid (**II-1**) and 9-*cis*-retinoic acid (**II-2**) with analysis in both RAR and RXR proteins. As mentioned earlier, **II-1** binds to RAR but not RXR.[197] The K_d value of 0.80 μM for the RAR homodimer is similar to 0.82 μM found for the RAR/RXR heterodimer (Figure II-8). The similar values could account to exclusive binding to just the RAR site.

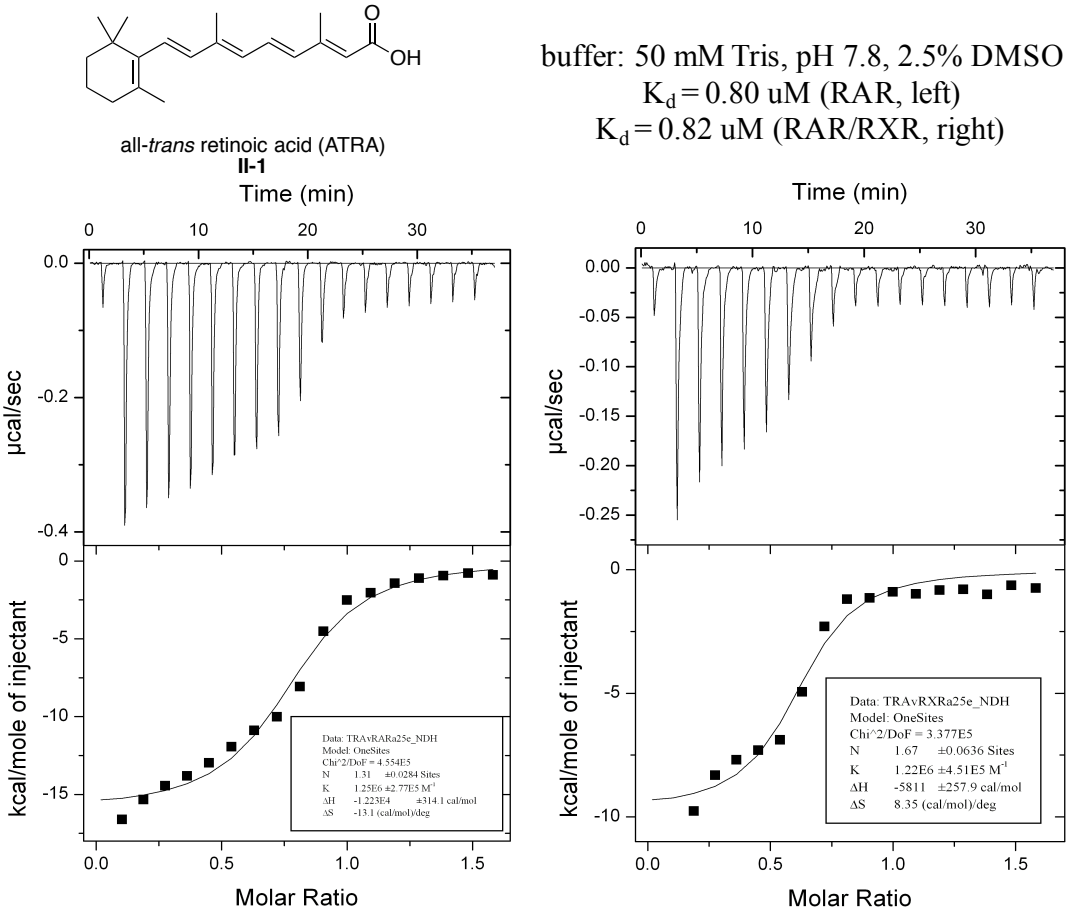


Figure II-8. ITC data for **II-1**.

On the other hand, 9-cis-retinoic acid (**II-2**) binds to both RAR and RXR. ITC binding assays for **II-2** show that binding is lower in RAR by almost two-fold (Figure II-

9). The K_d values for binding to RAR homodimer and RAR/RXR heterodimer are 1.02 μM and 0.63 μM, respectively. Moreover, the natural ligand for RAR is ATRA **II-2** and this data does indicate that RAR has a better affinity for ATRA vs 9-cis-retinoic acid.

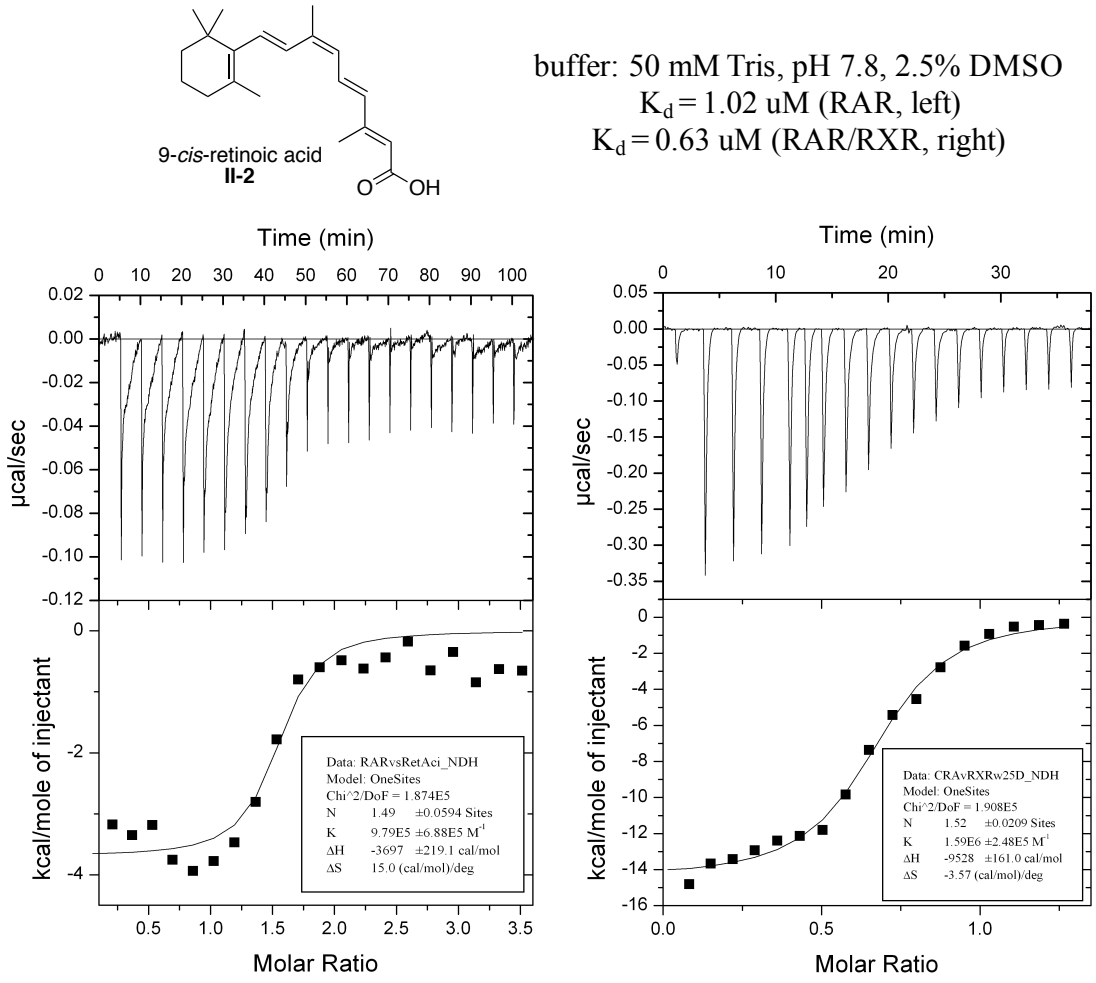
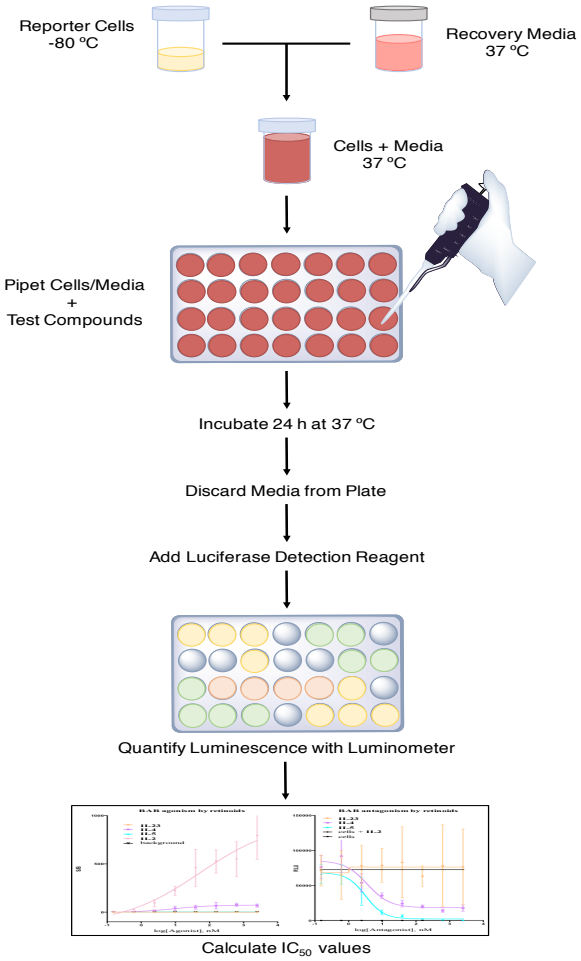


Figure II-9. ITC data for **II-2**.

Many of the compounds in our project have been tested with ITC; my compounds have been submitted for ITC analysis.

2. Luciferase Reporter Activity Assay

We also evaluated our retinoids in a luciferase reporter assay to determine what kind of activity they have in RARα, either agonist or antagonist. Our compounds we also tested in the RARß and RARγ activity assays. We chose to work with INDIGO Biosciences reporter assay kits.[232] These kits are all-inclusive cell-based assay systems with RAR reporter cells, optimized media, a reference agonist, a luciferase detection reagent, and a cell culture-ready assay plate. Their assays utilize proprietary non-human mammalian cells engineered to express human RARα (NR1B1), RARß (NR1B2), and RARγ (NR1B3).[232]



Scheme II-10. General process for INDIGO activity assay.[233]

The RAR reporter cells include the luciferase reporter gene functionally linked to a responsive promoter, which is able to detect small changes in activity through luciferase expression in treated reporter cells. The overall process of the assay is shown in Scheme II-10.[233] First, report cells and the optimized media are mixed and pipetted into the cell plate, along with test compounds and controls. After 24 hours of incubation, the luciferase reagent is added and the plate is allowed to rest for 30 minutes undisturbed. Then, a luminometer is used to quantify the luminescence and the values from this data can be used to calculate the IC_{50} values of the test compounds.

The BMS compounds: **II-23**, **II-24**, **II-27**, and **II-29** were tested for RARα agonism and antagonism with concentrations ranging from 0.31 nM to 5000 nM (Figure II-10).

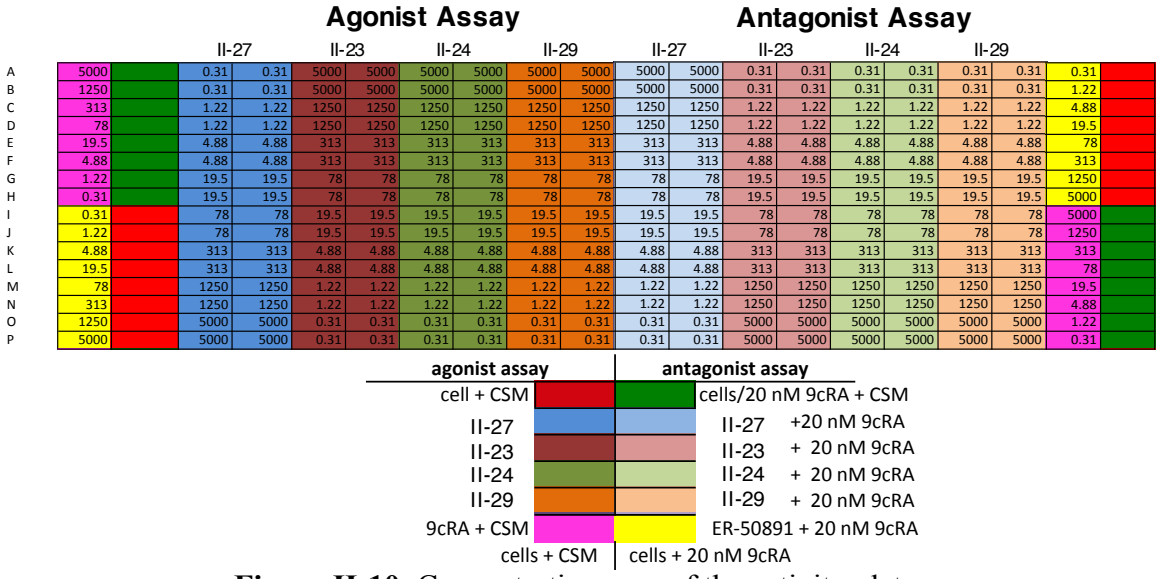


Figure II-10. Concentration map of the activity plate.

From the activity map below, the BMS analogs demonstrated low to no activity in the agonist assay represented by the violet color in the left half of the assay plate (Figure II-11). In the assay plate map, a red color indicates high activity with shades of orange, yellow, green, and blue in between to designate the decreasing levels of activity, respectively.

Compounds **II-23**, **II-24**, and **II-29** did not demonstrate any agonism. However, **II-27** showed slight agonism with 25-fold activity over the background, as compared to the control (9-cis-retinoic acid), which had greater than 750-fold activity at 2500 nM concentration. The antagonist assay showed much more color variation with boxes displaying of yellow and green activity colors (Figure II-11).

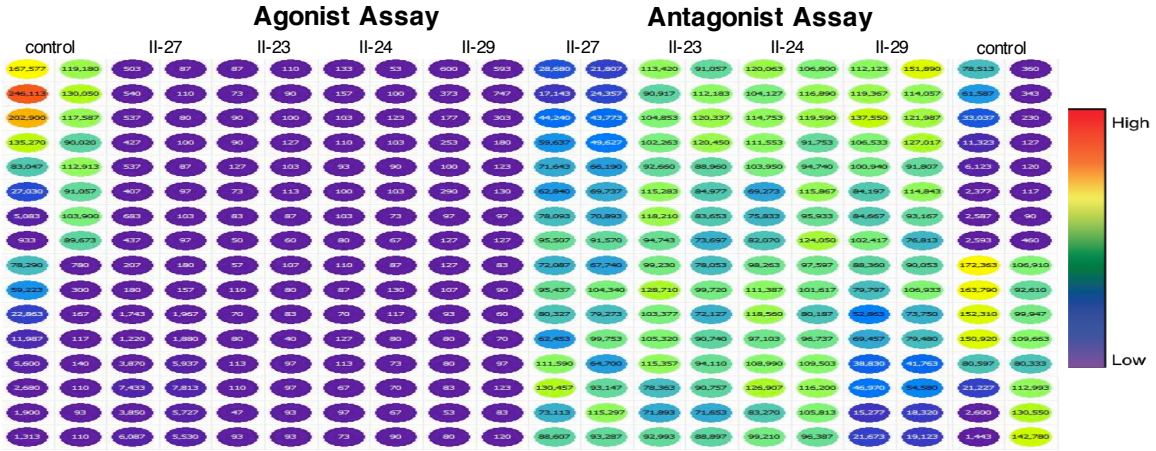


Figure II-11. Map of activity plate assay results of BMS retinoids.

The antagonism activity data was graphed to calculate the IC_{50} values of the tested compounds (Figure II-12). For the antagonist assay analysis, **II-27** and **II-29** showed activity at 321 nm and 341 nm, respectively. Retinoids **II-23** and **II-24** did not exhibit any

antagonism as demonstrated by their non-sigmoidal, flat lines in Figure II-12. The RARβ and RARγ activity assays of these BMS analogs will be performed in the future. There is an immediate need to test all the highly active compounds from the RARα activity assays first.

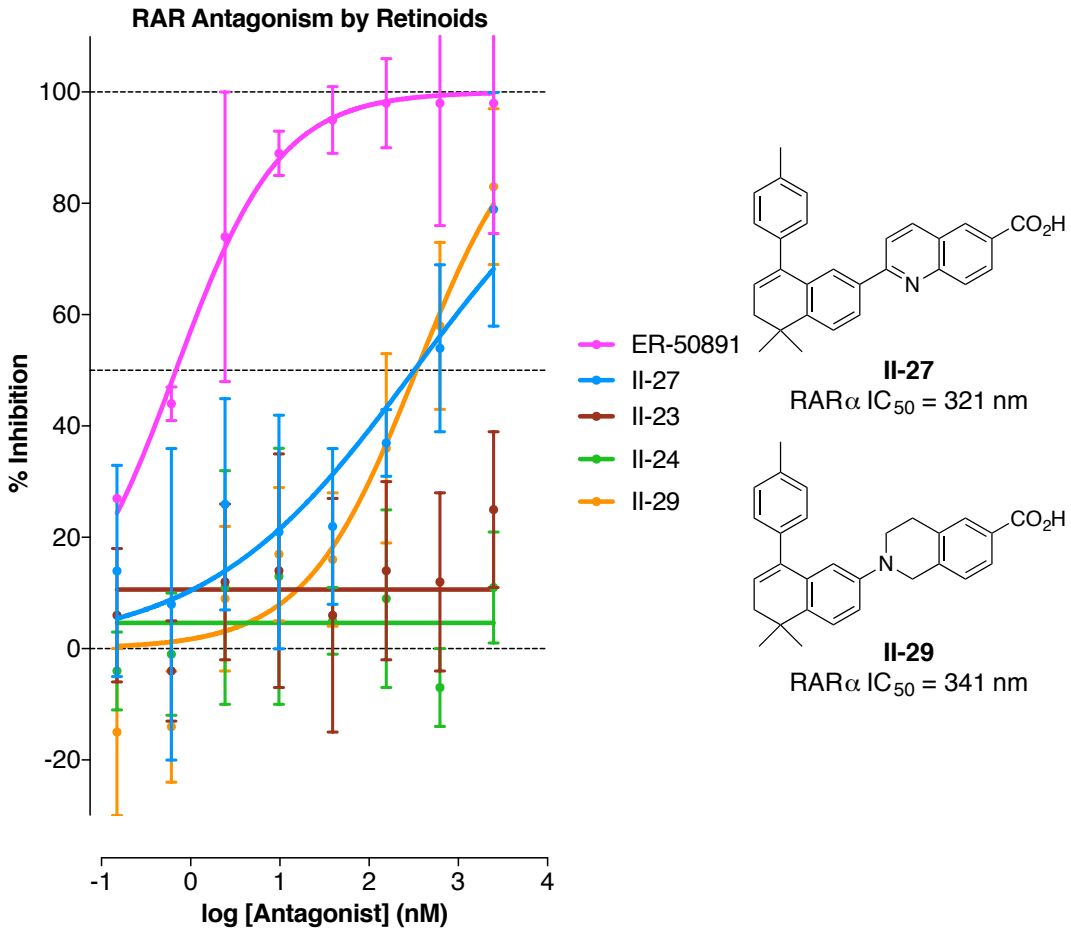


Figure II-12. Antagonistic assay of BMS RAR analogs.

G. Concluding Remarks

Male contraceptive research aims to address the unmet need of finding better alternatives for men and families to prevent pregnancy. While condoms and vasectomies are viable options, the possible ineffectiveness of condoms or the permanency of vasectomies are problematic. Additionally, hormonal contraceptive agents have been researched but have caused unwanted side effects. Our group is investigating non-hormonal male contraceptive agents as a solution to tackle these concerns with the help of the NIH NICHD. Within the Georg research group, a subset of researchers is focused on the discovery of RARα antagonists. This nuclear receptor has been validated as a male contraceptive, non-hormonal drug target. RARα is heavily involved in spermatogenesis since previous reports showed its gene deletion induced sterility in mice.

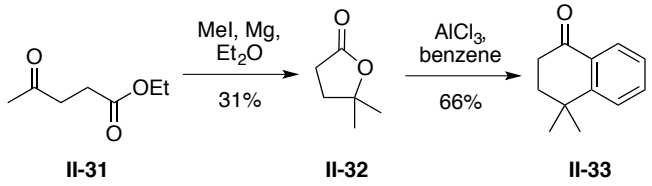
Our work revolves around the design and synthesis of selective, bioavailable RARα antagonists based on retinoids composed of three parts: a hydrophobic ring portion, a linker region, and a carboxylic acid moiety. We used the scaffold of known BMS antagonists (**II-4**, **II-5**, **II-6**) to begin our contraceptive development and the first generation of compounds contained a tetralin core with various aryl substituents in the ring portion, amide bioisosteres in the linker region, and benzoic or cyclohexanoic acids in the carboxylic acid moiety. Our compounds were evaluated using *in silico* analysis with the Schrodinger suite, isothermal titration calorimetry, and a luciferase reporter assay. Evaluation of our first-generation retinoids determined that additional lipophilic substituents in the ring portion and fluoro- groups in the benzoic acid moiety could increase the selectivity. Hence, we are pursuing other ring structures, such as a naphthyl ring scaffold similar to ER-50891(**II-51**), and others, for the discovery of second generation of retinoids.

Once the synthesis of our compounds is complete, they are subjected to biological activity analysis. From the luciferase reporter assay data, my BMS analogs with the cyclohexanoic acid moiety (**II-23** an **II-24**) showed no activity in the agonistic or antagonistic assays. However, the quinoline analogs (**II-27** and **II-29**) showed sub-micromolar activity in the antagonistic assay with **II-27** exhibiting very slight agonism as well.

Chapter 6. Experimental Data

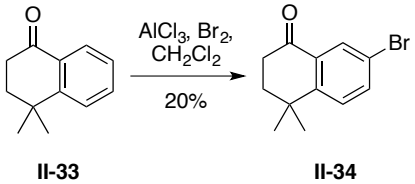
As previous stated in Chapter 4, *vide supra*, unless otherwise indicated, reactions were carried out open to air with reagent grade solvents directly from the bottle. Purified tetrahydrofuran (THF), toluene, diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were purified by passage through a bed of activated alumina in our solvent system. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and cerium molybdate stain followed by heating. Low-resolution mass spectral data were acquired utilizing the electrospray ionization technique. ^1H NMR spectra were recorded at ambient temperature at 400 MHz and are reported in ppm using a solvent as an internal standard ($CDCl_3$ at 7.26 ppm or CD_3OD at 3.31 ppm). Proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz and are reported in ppm using a solvent as an internal standard ($CDCl_3$ at 77.16 ppm). The data are reported as follows: chemical shift on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, dd= doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Melting points were determined with

Electrothermal Digital Mel-Temp 3.0 melting point apparatus. High-resolution mass spectra were recorded with electron-spray ionization (ESI) or electron ionization (EI).



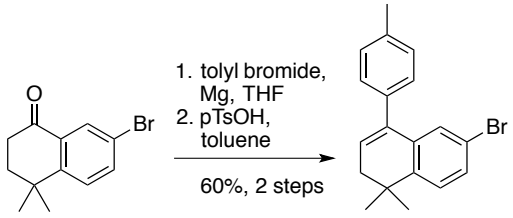
4,4-Dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (II-33).

To a stirring solution of $AlCl_3$ (351 mg, 2.63 mmol) in benzene at 5 ºC (dry ice/benzene bath), was added lactone (100 mg, 0.876 mmol) in benzene dropwise. The mixture was then slowly warmed to 100 ºC and allowed to stir for 3 h. Then an ice-cold solution of 1N HCl quenched the reaction before workup in MTBE with dilute HCl, water, and aqueous $NaHCO_3$, and brine. The combined organic layers then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography with 20% EtOAc/Hex gave UV active product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 7.8, 1.4 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.15 – 7.09 (m, 1H), 2.71 – 2.61 (m, 2H), 1.94 (t, J = 6.6 Hz, 2H), 1.32 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.4, 152.3, 133.9, 128.3, 127.3, 126.3, 125.8, 37.1, 35.1, 33.9, 29.7, 29.7.



7-Bromo-4,4-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (II-34).

To a stirring flask of $AlCl_3$ (1.91 g, 14.3 mmol) in CH_2Cl_2 was added tetralone (1.0 g, 5.74 mmol), dropwise at ambient temperature. Then bromine (1.1 g, 6.90 mmol) was slowly added, and the mixture was allowed to stir for 2 h at ambient temperature. The reaction was then quenched with an ice-cold solution of 6M HCl, followed by extraction with Et_2O. Combined organic layers washed with water, aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. TLC analysis gave several spots and flash column chromatography with 10 % EtOAc/Hex gave a few brominated products. The spectra for the desired 7-bromo tetralone is reported here. mp 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (d, J=3.0 Hz, 1H), 7.60 (dd, J=3.0, 9.0 Hz, 1H), 7.32 (d, J=9.0 Hz, 1H), 2.72 (t, J=6.0 Hz, 2H), 2.01 (t, J=6.0 Hz, 2H), 1.27 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.4, 133.9, 128.3, 127.3, 126.3, 125.8, 37.1, 35.1, 29.7, 29.7; $[M+Na]^+$ calcd for $C_{12}H_{13}OBrNa$ requires 275.0150, found 275.0044.

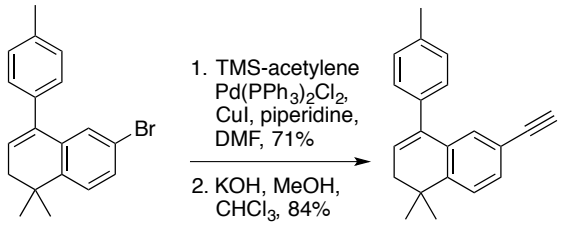


II-34 **II-35**

6-Bromo-1,1-dimethyl-4-(*p*-tolyl)-1,2-dihydronaphthalene (II-35).

To a flask of Mg (24 mg, 2.66 mmol), tolyl bromide (440 mg, 1.3 mmol) and a couple iodine crystals. The flask was heated until bubbles appeared and stirred for 1 h. The reaction is then cooled to 0 ºC (ice bath) and a solution of the bromo tetralone (500mg, 1.97 mmol) in toluene was added. The reaction was allowed to stir overnight at ambient temperature. Then, it was quenched with ammonium chloride, extracted with EtOAc, washed with brine. The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated *in vacuo* before flash column chromatography with 30% EtOAc:Hex to give alcohol intermediate as a yellow oil (74%). Then, to a solution of the alcohol intermediate in toluene (10ml), was added a catalytic amount of pTsOH (1 mol%) and molecular sieves. The reaction was stirred at reflux for 2 h then worked up with water and MTBE, dried over $MgSO_4$, filtered, and concentrated *in vacuo* followed by flash chromatography with 1 to 10% EtOAc: Hex to give tolyl bromide. mp 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, J = 8.2, 2.1 Hz, 1H), 7.28 – 7.23 (m, 5H), 7.20 (d, J = 2.0 Hz, 1H), 6.02 (t, J = 4.7 Hz, 1H), 2.44 (s, 3H), 2.37 (d, J = 4.7 Hz, 2H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 138.5, 137.3, 137.0, 136.2, 130.2, 129.1, 129.1, 128.8, 128.5, 128.2, 127.3, 125.6, 119.8, 38.7, 33.5, 28.0, 28.0, 21.2; $[M]^+$ calcd for $C_{19}H_{19}Br$ requires 326.0670, found 326.0664.

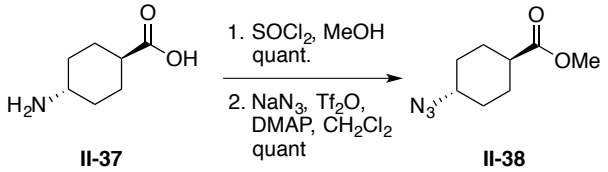


II-35 **II-36**

6-Ethynyl-1,1-dimethyl-4-(*p*-tolyl)-1,2-dihydronaphthalene (II-36).

A flask of bromide (200 mg, 0.61 mmol), TMS-acetylene (78mg, 0.79 mmol), copper iodide (11 mg, 10 mol%), and palladium catalyst (21 mg, 5 mol%) in trimethylamine (2 mL) was stirred overnight at 70ºC. The solvent was then evaporated and the intermediate was purified by column chromatography with 1% EtOAc:Hex to produce 71% product that was carried forward to the desilylation step. The silyl intermediate was then dissolved in a MeOH:$CHCl_3$ (1:1) mixture and 1N KOH was added. The solution stirred overnight at

ambient temperature before work up with DCM. The organic layers were combined, dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. Flash column chromatography with 0 to 1% EtOAc:Hex gave pure tolyl naphthyl alkyne **II-36** in 84% yield. mp 94-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 7.9, 1.5 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.45 – 7.38 (m, 4H), 7.37 (d, J = 1.1 Hz, 1H), 6.17 (t, J = 4.7 Hz, 1H), 3.14 (s, 1H), 2.60 (s, 3H), 2.53 (d, J = 4.7 Hz, 2H), 1.52 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.2, 138.7, 137.5, 136.9, 134.1, 131.2, 129.5, 129.1, 129.1, 128.5, 128.5, 126.7, 123.9, 119.4, 83.9, 76.3, 38.7, 33.7, 28.0, 28.0, 21.2; GCMS (HREI) m/z calcd for $C_{21}H_{20}$ $[M]^+$ requires 272.1565, found 272.1552.

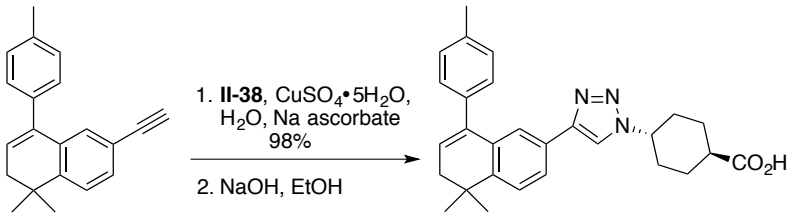


II-37 **II-38**

Methyl (1*r*,4*r*)-4-Azidocyclohexane-1-carboxylate (II-38)

To a solution of acid **II-37** (3.00 g, 20.1 mmol) in MeOH (10 mL) was added thionyl chloride (1.82 mL, 25.1 mmol) at 0 ºC (ice bath). The mixture was allowed to stir overnight at ambient temperature before concentrating *in vacuo*. Then, the residue was washed with hexanes to give the ester salt as a white solid in quantitative yield and carried on without further purification. **II-37** ester: ^{1}H NMR (400 MHz, CD_3OD): δ 3.69 (s, 3H), 3.33 (t, J = 1.2 Hz, 2H), 3.10 (t, J = 11.4 Hz, 1H), 2.37 (tt, J = 12.0, 2.8 Hz, 1H), 2.11 (d, J = 10.1 Hz, 4H), 1.61 – 1.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 52.3, 50.7, 42.8, 30.8, 30.8, 28.0, 28.0. Then, the triflic azide was formed *in situ* by adding to a solution of sodium azide (1.33 g, 20.4 mmol) in 5 mL water at 0 ºC (ice bath), 5 mL DCM followed by Tf_20

(700 μL, 4.14 mmol). The mixture was stirred for 2 h in the ice bath. The DCM phase was separated, and the aqueous phase was extracted with DCM twice. The combined DCM phase was washed with sat. $NaHCO_3$ and water, dried over $MgSO_4$, and set aside. Next, amino ester (172 mg, 1.09 mmol) was dissolved in 5 mL dry DCM and stirred at ambient temperature. To it was added DMAP (585 mg, 4.80 mmol) and then the above-prepared triflic azide in DCM solution was added dropwise. The mixture was stirred for overnight and then concentrated *in vacuo* to give the azide ester **II-38** in quantitative yield as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.26 (tt, J = 20.1, 5.7 Hz, 1H), 2.26 (tt, J = 11.7, 3.0 Hz, 1H), 2.08 – 1.97 (m, 4H), 1.56 – 1.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 59.2, 51.7, 41.8, 30.6, 30.6, 27.1, 27.1.

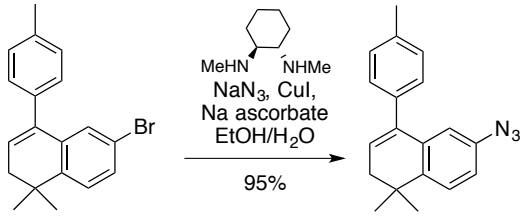


II-36 36% **II-23**

4-(4-(5,5-Dimethyl-8-(*p*-tolyl)-5,6-dihydronaphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)cyclohexane-1-carboxylic acid (II-23).

To a suspension of alkyne **II-36** (50 mg, 0.18 mmol) and azide **II-38** (31 mg, 0.18 mmol) in a solution of H_2O:tBuOH (1:1), was added sodium ascorbate (3.6 mg, 10 mol%) and copper sulfate pentahydrate (1.0 mg, 2 mol%). The mixture was vigorously stirred overnight at ambient temperature. Then the reaction was cooled to -5 ºC (aqueous $NHCl_4$ and ice bath) and a precipitate formed. The precipitate was filtered, washed with ice cold water, collected, and dried *in vacuo* to give triazole ester intermediate. Then, to a round-bottom flask of the triazole ester intermediate (84 mg, 0.18 mmol) in EtOH (2 mL), was added 1M NaOH (1 mL) and the reaction was allowed to stir overnight at ambient

temperature. Then, the mixture was acidified with 1M HCl slowing at 100 μL increments and the product was extracted with EtOAc to give desired triazole acid **II-23**. Further recrystallization in MeOH:DCM to give yellowish crystals. mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 1.6 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.30 – 7.17 (m, 4H), 5.99 (t, J = 4.7 Hz, 1H), 4.47 (tt, J = 11.9, 3.8 Hz, 1H), 3.70 (s, 1H), 2.51 – 2.40 (m, 1H), 2.39 (s, 3H), 2.36 (d, J = 4.7 Hz, 2H), 2.30 – 2.25 (m, 2H), 2.20 (d, J = 13.6 Hz, 2H), 1.92 (qd, J = 12.7, 3.1 Hz, 2H), 1.66 (qd, J = 13.3, 2.8 Hz, 2H), 1.36 (s, 6H), 1.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.5, 147.0, 140.5, 139.2, 138.1, 135.9, 130.3, 130.3, 129.8, 129.8, 129.0, 127.9, 126.2, 125.7, 124.6, 120.0, 60.9, 52.8, 43.1, 40.1, 34.9, 34.9, 33.4, 33.3, 29.0, 29.0, 28.9, 21.9; LRMS (ESI) m/z calcd for $C_{28}H_{32}N_3O_2$ $[M+H]^+$ 442.2, found 442.9.



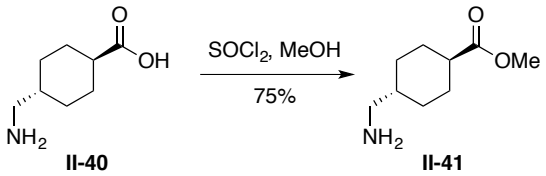
II-35 **II-40**

6-Azido-1,1-dimethyl-4-(*p*-tolyl)-1,2-dihydronaphthalene (II-40).

To a flask of aryl bromide (100 mg, 0.31 mmol) in a solution of EtOH:H_2O (7:3), was added sodium azide (40 mg, 0.61 mmol), sodium ascorbate (3.0 mg, 5.0 mol%), copper iodide (6.0 mg, 5.0 mol%), and diamine ligand (7.0 mg, 15 mol%). The flask was degassed with house nitrogen then stirred under reflux for 6 hours, or until consumption of starting material. The reaction was then cooled to ambient temperature before work up with EtOAc

and brine. The combined organic layers were dried over $MgSO_4$, filtered, and purified over a short silica plug and then concentrated *in vacuo* to give a dark yellow oil.

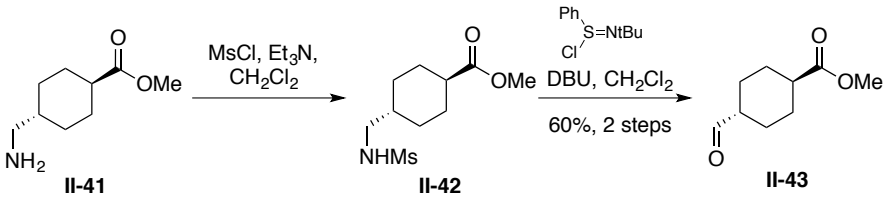
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.2 Hz, 1H), 7.24 – 7.17 (m, 4H), 6.90 (dd, J = 8.2, 2.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.00 (t, J = 4.7 Hz, 1H), 2.40 (s, 3H), 2.34 (d, J = 4.7 Hz, 2H), 1.32 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 138.8, 137.7, 137.5, 137.1, 135.8, 129.2, 129.2, 128.6, 128.6, 127.5, 125.3, 117.7, 117.1, 39.0, 33.6, 28.4, 28.4, 21.3.



II-40 **II-41**

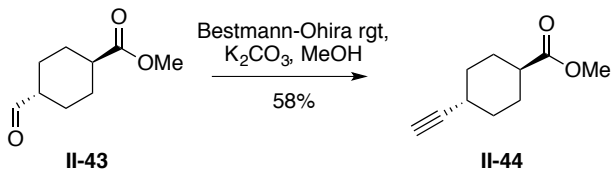
Methyl (1*r*,4*r*)-4-(Aminomethyl)cyclohexane-1-carboxylate (II-41).

To a flask of amino acid (1.00 g, 6.36 mmol) in MeOH (150 mL) was added thionyl chloride (919 µL, 12.7 mmol) slowly at 0 ºC (ice bath) for 10 min. The suspension was allowed to stir at reflux and monitored with TLC. The reaction was then cooled to ambient temperature when TLC indicated consumption of starting material. The solvent was evaporated and the reaction was worked up with EtOAc and concentrated *in vacuo* to give off white crystals. mp 162-164 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 3.68 (s, 3H), 2.81 (d, J = 6.9 Hz, 2H), 2.33 (tt, J = 12.3, 3.5 Hz, 1H), 2.12 – 1.87 (m, 4H), 1.65 (ddp, J = 11.3, 7.2, 3.7 Hz, 1H), 1.47 (qd, J = 13.1, 3.2 Hz, 2H), 1.10 (qd, J = 13.0, 3.2 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ 177.8, 52.4, 46.2, 43.9, 36.7, 30.3, 30.3, 29.3, 29.3; HRMS (ESI) m/z calcd for $C_9H_{17}NO_2$ $[M+H]^+$ requires 172.1338, found 172.1328.



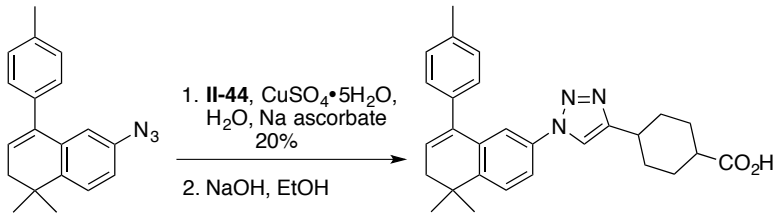
Methyl (1*r*,4*r*)-4-Formylcyclohexane-1-carboxylate (II-43).

To a flask of amine ester **II-41** (1.00 g, 5.84 mmol) in DCM (10 mL) at 0 ºC (ice bath), was added mesyl chloride (452 µL, 5.84 mmol). The mixture was allowed to stir at 0 ºC for 1 h. The reaction was quenched with water, washed with DCM, and then cooled to -78 ºC (dry ice, iPrOH) for the next step without isolation of **II-42**. DBU (1.78 g, 11.68 mmol) was then added to the flask, followed by a solution of the sulfinimidoyl chloride (2.52 g, 11.68 mmol) in DCM. The reaction stirred at -78 ºC for 2 h before warming to ambient temperature and quenching with 1M HCl. Work up was done with Et_2O, then the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography with 5-10% MeOH:DCM gave the desired product in 60% after two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (d, J = 7.0 Hz, 1H), 3.17 (s, 3H), 2.05 (tt, J = 12.3, 3.5 Hz, 1H), 1.88 – 1.80 (m, 2H), 1.74 – 1.67 (m, 2H), 1.49 – 1.37 (m, 1H), 1.29 – 1.17 (m, 2H), 0.87 (qd, J = 13.2, 3.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 175.7, 49.3, 42.5, 31.5, 27.9, 25.0, 23.3, 22.6.



Methyl (1r,4r)-4-Ethynylcyclohexane-1-carboxylate (II-44).

To a suspension of aldehyde **II-43** (500 mg, 2.9 mmol) and K_2CO_3 (1.4 g, 10 mmol) in dry MeOH (10 mL) at ambient temperature, was added the Bestmann-Ohira reagent (790 mg, 4.1 mmol). The reaction stirred for overnight at ambient temperature and monitored with TLC. After consumption of starting material, the solvent was removed and the product was washed with DCM and water. The combined organic layers were washed with brine then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Alkyne **II-44** was obtained by column chromatography with 25% EtOAc: Hex in 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 2.35 – 2.24 (m, 2H), 2.11 – 1.97 (m, 5H), 1.45 (h, J = 11.0, 10.6 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.1, 88.2, 68.2, 51.7, 42.2, 31.8, 31.8, 28.7, 28.1, 28.1.

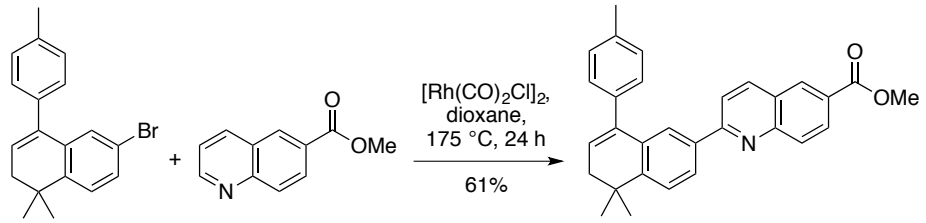


II-40 **II-24**

4-(1-(5,5-Dimethyl-8-(p-tolyl)-5,6-dihydronaphthalen-2-yl)-1H-1,2,3-triazol-4-yl)cyclohexane-1-carboxylic Acid (II-24).

To a suspension of naphthyl azide **II-40** (52 mg, 0.18 mmol) and cyclohexyl alkyne ester **II-44** (30 mg, 0.18 mmol) in a solution of H_2O:tBuOH (1:1), was added sodium ascorbate (3.6 mg, 10 mol%) and copper sulfate pentahydrate (1.0 mg, 2 mol%). The mixture was vigorously stirred overnight at ambient temperature. Then the reaction was cooled to -5 ºC (aqueous $NHCl_4$ and ice bath) and a precipitate formed. The precipitate was filtered, washed with ice cold water, collected, and dried *in vacuo* to give the other triazole ester intermediate. Then, to a round-bottom flask of the other triazole ester intermediate (84 mg,

0.18 mmol) in EtOH (2 mL), was added 1M NaOH (1 mL) and the reaction was allowed to stir overnight at ambient temperature. Then, the mixture was acidified with 1M HCl slowing at 100 µL increments and the product was extracted with EtOAc to give the other desired triazole acid **II-24**. Further recrystallization in MeOH:DCM to give off-white/yellow crystals. mp 235-237 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 7.69 (s, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.22 (q, J = 8.1 Hz, 4H), 6.06 (t, J = 4.7 Hz, 1H), 2.76 (tt, J = 11.2, 3.1 Hz, 1H), 2.43 – 2.40 (m, 2H), 2.39 (s, 3H), 2.33 (ddt, J = 14.7, 6.5, 3.7 Hz, 2H), 2.14 (t, J = 13.7 Hz, 4H), 1.63 – 1.47 (m, 4H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, CD_3OD): δ 179.9, 148.6, 147.6, 139.9, 138.5, 137.0, 133.9, 132.9, 130.5, 130.5, 129.8, 129.8, 129.2, 127.2, 126.6, 121.1, 120.0, 119.5, 44.0, 40.0, 35.9, 35.0, 33.1, 33.1, 30.0, 30.0, 29.2, 22.2; LRMS (ESI) m/z calcd for $C_{28}H_{32}N_3O_2$ $[M+H]^+$ 442.2, found 442.9.

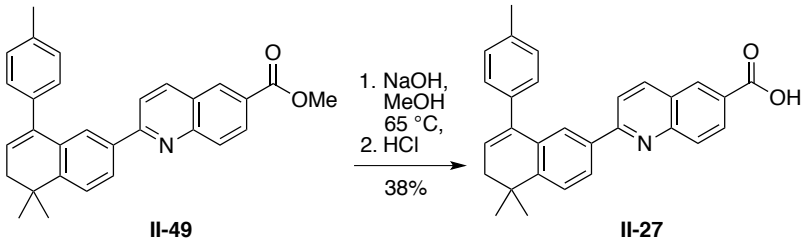


II-34 **II-46** **II-49**

Methyl 2-(5,5-dimethyl-8-(p-tolyl)-5,6-dihydronaphthalen-2-yl)quinoline-6-carboxylate (II-49).

To a sealable microwave vial of tolyl bromide **II-34** (130 mg, 0.400 mmol) and quinoline ester **II-46** (450 mg, 0.2.40 mmol) in dioxane (2 mL) was added the Rh catalyst (8 mg, 5 mol %). The reaction was heated to 175 ºC in an oil bath for 24 h and then allowed to warm temperature. The reaction was sent through a Celite plug and washed with MTBE and then the solvent was removed *in vacuo*. The product was purified by column chromatography

with 1-10% EtOAc:Hex and produced the coupled ester product **II-49** in 61% yield. mp 190-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 1.5 Hz, 1H), 8.27 (dd, J = 8.9, 1.5 Hz, 1H), 8.20 (d, J = 8.6 Hz, 1H), 8.17 – 8.08 (m, 2H), 7.79 (d, J = 1.7 Hz, 1H), 7.64 (dd, J = 72.1, 8.3 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 6.05 (t, J = 4.7 Hz, 1H), 3.99 (s, 3H), 2.42 (s, 3H), 2.39 (d, J = 4.7 Hz, 2H), 1.39 (s, 6H).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 159.6, 150.1, 147.4, 145.9, 139.2, 137.9, 137.8, 136.9, 134.5, 130.6, 129.9, 129.1, 129.1, 129.0, 128.6, 128.6, 127.5, 127.1, 126.7, 126.2, 125.3, 124.6, 119.8, 52.4, 38.9, 33.9, 28.1, 28.1, 21.3; HRMS (ESI) m/z calcd for $C_{30}H_{27}NO_2$ $[M+H]^+$ requires 434.2121, found 434.2132.

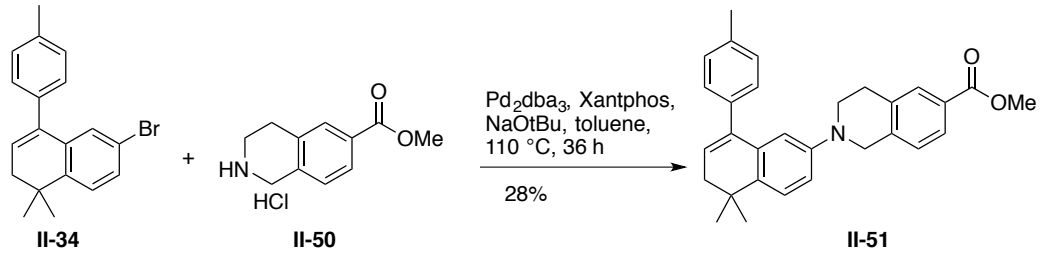


II-49 **II-27**

2-(5,5-Dimethyl-8-(p-tolyl)-5,6-dihydronaphthalen-2-yl)quinoline-6-carboxylic Acid (II-27).

To a flask of quinoline ester II-49 (50 mg, 0.12 mmol) in MeOH (3 mL), was added 1N NaOH (1 mL). The reaction was heated to 65 ºC and stirred for 2 h. Then, the flask was allowed to warm to room temperature and the solvent was removed *in vacuo*. The reaction was diluted with water and acidified to pH 4 with 1N HCl. The product precipitated and was collected via filtration and recrystallized with DCM:MeOH to give desired quinoline acid **II-27** in 38% yield after two steps. mp 268-269 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (d, J = 7.0 Hz, 1H), 3.17 (s, 3H), 2.05 (tt, J = 12.3, 3.5 Hz, 1H), 1.88 – 1.80 (m, 2H),

1.74 – 1.67 (m, 2H), 1.49 – 1.37 (m, 1H), 1.29 – 1.17 (m, 2H), 0.87 (qd, J = 13.2, 3.4 Hz, 2H).^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 51.7, 43.3, 39.5, 28.4, 28.4, 27.1, 27.1; LRMS (ESI) m/z calcd for $C_{29}H_{26}NO_2$ $[M+H]^+$ 420.2, found 420.8.

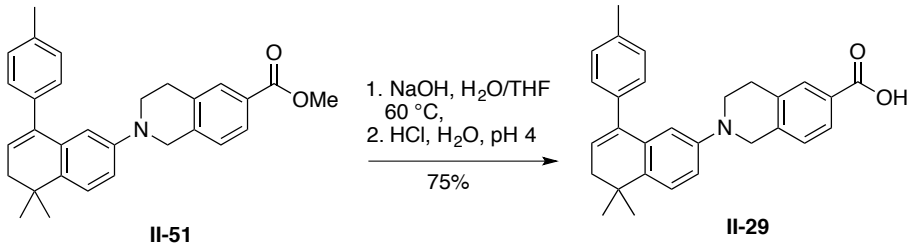


II-34 II-50 II-51

Methyl 2-(5,5-dimethyl-8-(p-tolyl)-5,6-dihydronaphthalen-2-yl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (II-51).

To a two-neck round-bottom flask was added Xantphos (53 mg, 0.092 mmol, 10 mol%) and Pd catalyst (42 mg, 0.046 mmol, 5 mol%) in toluene (2 mL). The reaction was purged with nitrogen for 10-15 min then heated to 110 ºC for 15 min. After it reaction vessel was cooled to ambient temperature, NaOtBu (180 mg, 1.8 mmol) was added followed by the tolyl bromide **II-34** (300 mg, 0.92 mmol), then the quinoline analog **II-50** (350 mg, 1.8 mmol). The reaction was purged again with nitrogen for 10-15 min then heated to 110 ºC and allowed to stir for 36 h. After the flask had cooled to ambient temperature, the reaction was filtered through a Celite plug and the solvent was removed *in vacuo*. Column chromatography with 1% EtOAc:Hex gave the desired coupled ester **II-51** in 38% yield. *Previous attempts with *rac*-BINAP gave less than 20% product after 24 or 48 h. mp 187-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.26 – 7.12 (m, 6H), 7.10 (d, J = 8.4 Hz, 1H), 6.83 (dd, J = 8.4, 2.6 Hz, 1H), 6.70 (d, J = 2.6 Hz, 1H), 5.94 (t, J = 4.7 Hz, 1H), 4.25 (s, 2H), 3.87 (s, 3H), 3.37 (t, J = 5.8 Hz, 2H), 2.91 (t, J = 5.7 Hz, 2H), 2.38 (s, 3H),

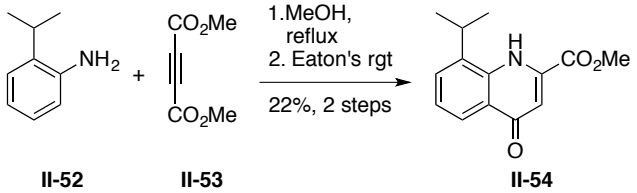
2.28 (d, J = 4.7 Hz, 2H), 1.28 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 148.6, 140.1, 139.6, 138.3, 136.7, 136.7, 135.2, 134.8, 130.0, 129.0, 129.0, 128.7, 128.7, 128.2, 127.1, 126.8, 126.7, 124.7, 114.8, 114.6, 52.1, 51.6, 47.0, 39.3, 33.2, 29.0, 28.5, 28.5, 21.3.



II-51 II-29

2-(5,5-Dimethyl-8-(p-tolyl)-5,6-dihydronaphthalen-2-yl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic Acid (II-29).

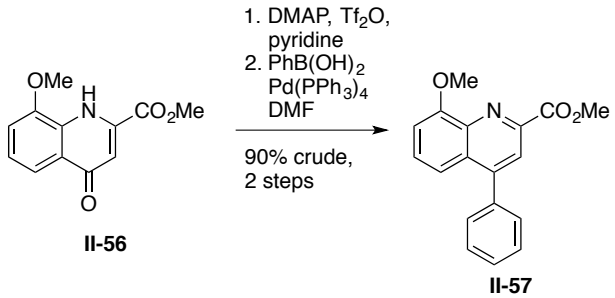
To a flask of quinoline ester **II-51** (50 mg, 0.12 mmol) in THF:H_2O (1:1, 3 mL), was added 1N NaOH (1 mL). The reaction was heated to 60 ºC and stirred for 24 h. Then, the flask was allowed to warm to room temperature and the solvent was removed *in vacuo*. The reaction was diluted with water and acidified to pH 4 with 1N HCl. The product precipitated and was collected via filtration and recrystallized with DCM:MeOH to give desired tetrahydroisoquinoline acid **II-29** in 75% after two steps. mp 243-244 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 7.87 (s, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 4H), 6.97 (d, J = 2.4 Hz, 1H), 6.02 (t, J = 4.6 Hz, 1H), 4.60 (s, 2H), 3.75 (t, J = 6.2 Hz, 2H), 3.19 (d, J = 5.7 Hz, 2H), 2.33 (d, J = 4.7 Hz, 2H), 2.30 (s, 3H), 1.30 (s, 6H). LRMS (ESI) m/z calcd for $C_{29}H_{30}NO_2$ $[M+H]^+$ 424.2, found 424.9.



II-52 II-53 II-54

Methyl 8-isopropyl-4-oxo-1,4-dihydroquinoline-2-carboxylate (II-54).

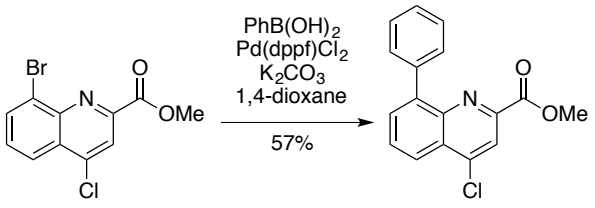
To a flask of aniline (1.0 g, 8.1 mmol) in MeOH (5 mL) at 5 ºC (ice bath), was added dicarboxylate (1.4 g, 9.7 mmol). The reaction stirred for 2 h at ambient temperature. Evaporation of solvent gave a dark yellow solid that was carried on to next step. To a flask of intermediate diester (1.8g, 6.6 mmol), was added Eaton's reagent (7 mL). The reaction was heated to 50 ºC and stirred for 2-3 h, until TLC revealed consumption of starting material. Then, the reaction mixture was cooled to 5 ºC (ice bath) and poured into an ice cold saturated $NaHCO_3$ solution, as precipitate formed. The solid was filtered and washed with water and dried *in vacuo* to give yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.60 (dd, J = 7.4, 0.9 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 1.7 Hz, 1H), 4.07 (s, 3H), 3.30 (p, J = 6.8 Hz, 1H), 1.43 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.0, 163.8, 136.4, 135.6, 135.6, 129.1, 126.7, 124.4, 124.1, 111.2, 53.9, 27.7, 22.7.



II-56 II-57

Methyl 8-methoxy-4-phenylquinoline-2-carboxylate (II-57).

To a flask of quinoline (200 mg, 0.86 mmol) dissolved in dry DCM (5 mL), was added DMAP (41 mg, 0.34 mmol) and 2,6-lutidine (303 µL, 2.6 mmol). Then, the flask was cooled to 0 ºC (ice bath) and triflic anhydride (440 µL, 2.6 mmol) was added dropwise. The reaction was warmed to ambient temperature and allowed to stir overnight. The solvent was then evaporated the next day and the residue was washed with MeOH and concentrated *in vacuo* to give an off-white product. Then, the triflate product (100 mg, 0.27 mmol) was then dissolved in DMF (5 mL) and phenyl boronic acid (50mg, 0.41 mmol), trimethylamine (75 µL, 0.54 mmol) was added. The flask was degassed with house argon, then palladium tetrakis (10 mg, 30 mol%) was added and the reaction stirred for 4 h at reflux. The reaction was extracted with DCM, washed with brine, and dried over $MgSO_4$. After filtration, the product was concentrated *in vacuo* and then purified by flash column chromatography with 30% EtOAc/Hex. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 7.1 Hz, 1H), 8.16 (s, 1H), 7.54-7.52 (m, 4H), 7.36 – 7.29 (m, 2H), 7.14-7.10 (m, 1H), 4.10 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.4, 155.7, 148.7, 138.3, 133.6, 132.1, 129.6, 129.5, 129.5, 128.7, 128.6, 128.5, 128.5, 128.4, 122.0, 117.7, 56.1, 53.1.



II-60 **II-61**

Methyl 4-chloro-8-phenylquinoline-2-carboxylate (II-61)

To a two-neck round-bottom flask was added quinoline **II-60** (500 mg, 1.66 mmol), phenylboronic acid (305 mg, 2.50 mmol, 1.50 equiv), and potassium carbonate (688 mg, 4.98, 3.00 equiv) in 1,4-dioxane (5 mL). The solution was purged with nitrogen for 5-20

min, then $Pd(ddpf)Cl_2$ (136 mg, 0.166 mmol) was added. The reaction was heated to 100 ºC (oil bath) and allowed to stir overnight. After cooling to room temperature, the reaction was diluted with EtOAc and washed with water. The reaction was then filtered and the filtrate was washed again with water and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography with 0 to 10% EtOAc:Hex, gave the 4-phenyl quinoline ester **II-61** in 57% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.25 (m, 2H), 7.92 (d, J = 7.1 Hz, 1H), 7.85 – 7.78 (m, 3H), 7.51 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 7.0 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 147.3, 146.1, 144.1, 142.3, 138.3, 132.0, 131.4, 129.6, 128.9, 128.1, 128.0, 128.0, 123.7, 121.3, 77.5, 53.2; $[M+Na]^+$ calcd for $C_{17}H_{12}ClNO_2Na$ requires 320.0557, found 320.0456.

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APPENDIX A

Full Chart I-4: Pairwise similarity coefficients for **I-23** and **I-25** library compounds

Compound	79m	93	25	54	79k	79q	79t	79u	79z	79r	79s	79n
79m	1.0000	0.4091	0.4839	0.6552	0.7308	0.6364	0.6364	0.6034	0.5645	0.6364	0.7170	0.7547
93	0.4091	1.0000	0.7925	0.3750	0.4091	0.4091	0.4091	0.3913	0.3699	0.4091	0.4030	0.3913
25	0.4839	0.7925	1.0000	0.4412	0.4839	0.4839	0.4839	0.4615	0.4348	0.4839	0.4762	0.4615
54	0.6552	0.3750	0.4412	1.0000	0.6552	0.5738	0.5738	0.5469	0.5606	0.5738	0.6441	0.6230
79k	0.7308	0.4091	0.4839	0.6552	1.0000	0.6364	0.6364	0.6034	0.5645	0.6981	0.7170	0.6909
79q	0.6364	0.4091	0.4839	0.5738	0.6364	1.0000	0.6364	0.6034	0.7321	0.7308	0.6250	0.6316
79t	0.6364	0.4091	0.4839	0.5738	0.6364	0.6364	1.0000	0.8235	0.5645	0.6364	0.6545	0.6034
79u	0.6034	0.3913	0.4615	0.5469	0.6034	0.6034	0.8235	1.0000	0.5385	0.6034	0.5932	0.5738
79z	0.5645	0.3699	0.4348	0.5606	0.5645	0.7321	0.5645	0.5385	1.0000	0.6441	0.5556	0.5625
79r	0.6364	0.4091	0.4839	0.5738	0.6981	0.7308	0.6364	0.6034	0.6441	1.0000	0.6250	0.6034
79s	0.7170	0.4030	0.4762	0.6441	0.7170	0.6250	0.6545	0.5932	0.5556	0.6250	1.0000	0.6786
79n	0.7547	0.3913	0.4615	0.6230	0.6909	0.6316	0.6034	0.5738	0.5625	0.6034	0.6786	1.0000
79x	0.6230	0.3600	0.4225	0.7500	0.6230	0.5714	0.5469	0.5224	0.5821	0.5469	0.6129	0.6721
79o	0.7037	0.3971	0.4688	0.6333	0.7037	0.6429	0.6140	0.5833	0.5714	0.6140	0.6909	0.7593
79v	0.6333	0.3649	0.4286	0.6250	0.6333	0.5806	0.5556	0.5303	0.5909	0.5556	0.6230	0.6833
79l	0.6786	0.3857	0.4545	0.6129	0.6786	0.6207	0.5932	0.5645	0.5538	0.5932	0.6667	0.7321
79y	0.6032	0.3506	0.4110	0.5970	0.6032	0.5538	0.5303	0.5072	0.5652	0.5303	0.5938	0.6508
80a	0.4545	0.4559	0.3803	0.4167	0.4545	0.4118	0.3913	0.3750	0.3733	0.3913	0.4478	0.5000
79a	0.6786	0.4058	0.4545	0.6129	0.6786	0.6207	0.5932	0.5645	0.5538	0.5932	0.6667	0.7321
82a	0.4697	0.3889	0.3944	0.4306	0.4697	0.4265	0.4058	0.3889	0.3867	0.4058	0.4627	0.5152
80a	0.4286	0.4306	0.3600	0.4324	0.4286	0.3889	0.3699	0.3553	0.4861	0.3699	0.4225	0.4714
79b	0.6441	0.3699	0.4348	0.6349	0.6441	0.5902	0.5645	0.5385	0.7049	0.5645	0.6333	0.6949
82b	0.4493	0.3553	0.3784	0.4521	0.4493	0.4085	0.3889	0.3733	0.5070	0.3889	0.4429	0.4928
80c	0.4167	0.4189	0.3506	0.4211	0.4167	0.3784	0.3600	0.3462	0.3974	0.3600	0.4110	0.4583
79c	0.6230	0.3600	0.4225	0.6154	0.6230	0.5714	0.5469	0.5224	0.5821	0.5469	0.6129	0.6721
82c	0.4366	0.3462	0.3684	0.4400	0.4366	0.3973	0.3784	0.3636	0.4156	0.3784	0.4306	0.4789
80d	0.4054	0.4459	0.3766	0.4103	0.4054	0.3684	0.3506	0.3375	0.3875	0.3506	0.4000	0.4459
89d	0.6032	0.3867	0.4507	0.5970	0.6032	0.5538	0.5303	0.5072	0.5652	0.5303	0.5938	0.6508
82d	0.4247	0.3718	0.3947	0.4286	0.4247	0.3867	0.3684	0.3544	0.4051	0.3684	0.4189	0.4658
80e	0.4000	0.4026	0.3375	0.4051	0.4000	0.3636	0.3462	0.3333	0.4000	0.3462	0.3947	0.4400
79e	0.5938	0.3462	0.4054	0.5882	0.5938	0.5455	0.5224	0.5000	0.5797	0.5224	0.5846	0.6406
82e	0.4189	0.3333	0.3544	0.4231	0.4189	0.3816	0.3636	0.3500	0.4177	0.3636	0.4133	0.4595
80f	0.3947	0.3974	0.3333	0.4000	0.3947	0.3590	0.3418	0.3293	0.4125	0.3418	0.3896	0.4342
79f	0.5846	0.3418	0.4000	0.5797	0.5846	0.5373	0.5147	0.4930	0.5942	0.5147	0.5758	0.6308
82f	0.4133	0.3293	0.3500	0.4177	0.4133	0.3766	0.3590	0.3457	0.4304	0.3590	0.4079	0.4533
80k	0.4762	0.4769	0.3971	0.4348	0.6607	0.4091	0.4091	0.3913	0.3699	0.4531	0.4688	0.4545
82k	0.5000	0.3913	0.4179	0.4559	0.6909	0.4308	0.4308	0.4118	0.3889	0.4762	0.4921	0.4769
80g	0.4054	0.4079	0.3418	0.4103	0.4054	0.3684	0.3506	0.3544	0.3875	0.3506	0.4000	0.4459
79g	0.6032	0.3506	0.4110	0.5970	0.6032	0.5538	0.5303	0.5294	0.5652	0.5303	0.5938	0.6508
82g	0.4247	0.3375	0.3590	0.4286	0.4247	0.3867	0.3684	0.3718	0.4051	0.3684	0.4189	0.4658
80h	0.4412	0.4638	0.3889	0.4054	0.4412	0.4203	0.3803	0.3649	0.3636	0.3803	0.4348	0.4853
79h	0.6667	0.4000	0.4697	0.6032	0.6667	0.6379	0.5833	0.5556	0.5455	0.5833	0.6552	0.7193
82h	0.4627	0.3836	0.4085	0.4247	0.4627	0.4412	0.4000	0.3836	0.3816	0.4000	0.4559	0.5075
80i	0.4286	0.4306	0.3600	0.3947	0.4286	0.4085	0.3699	0.3553	0.3718	0.3889	0.4225	0.4714
79i	0.6441	0.3699	0.4348	0.5846	0.6441	0.6167	0.5645	0.5385	0.5522	0.5902	0.6333	0.6949
82i	0.4493	0.3553	0.3784	0.4133	0.4493	0.4286	0.3889	0.3733	0.3896	0.4085	0.4429	0.4928
80j	0.4478	0.4493	0.3750	0.4110	0.4478	0.4265	0.3857	0.3699	0.3684	0.3857	0.4412	0.4925
79j	0.6786	0.3857	0.4545	0.6129	0.6786	0.6491	0.5932	0.5645	0.5538	0.5932	0.6667	0.7321
82j	0.4697	0.3699	0.3944	0.4306	0.4697	0.4478	0.4058	0.3889	0.3867	0.4058	0.4627	0.5152
32	0.4516	0.5763	0.6140	0.4118	0.4516	0.4516	0.4516	0.4531	0.4058	0.4516	0.4444	0.4308
30	0.3333	0.3582	0.3235	0.3056	0.3333	0.3333	0.3333	0.3188	0.3014	0.3333	0.3284	0.3188
88b	0.3649	0.6774	0.5606	0.3718	0.3649	0.3836	0.3649	0.3506	0.4795	0.3649	0.3600	0.3684
88a	0.4286	0.8235	0.6727	0.3913	0.4286	0.4286	0.4286	0.4091	0.3857	0.4286	0.4219	0.4091
88d	0.3553	0.6563	0.5441	0.3625	0.3553	0.3733	0.3553	0.3418	0.3924	0.3553	0.3506	0.3590
88c	0.3553	0.6563	0.5441	0.3625	0.3553	0.3733	0.3553	0.3418	0.3924	0.3553	0.3506	0.3590
88f	0.3418	0.6269	0.5211	0.3494	0.3418	0.3590	0.3418	0.3293	0.3951	0.3418	0.3375	0.3457
88e	0.3803	0.7119	0.5873	0.3506	0.3803	0.4203	0.3803	0.3649	0.3636	0.3803	0.3750	0.3836
88i	0.3590	0.6269	0.5211	0.3494	0.3418	0.3590	0.3418	0.3293	0.3780	0.3418	0.3375	0.3625
88h	0.3462	0.6364	0.5286	0.3537	0.3462	0.3636	0.3462	0.3333	0.3827	0.3462	0.3418	0.3500
88j	0.3375	0.6176	0.5139	0.3452	0.3375	0.3544	0.3375	0.3253	0.4074	0.3375	0.3333	0.3415
79p	0.6786	0.3857	0.4545	0.6129	0.6786	0.6207	0.6207	0.5645	0.5538	0.5932	0.7273	0.7321
89h	0.3205	0.4324	0.4384	0.3293	0.3205	0.3377	0.3205	0.3086	0.3580	0.3205	0.3165	0.3250
89i	0.3333	0.4267	0.4324	0.3253	0.3165	0.3333	0.3165	0.3049	0.3537	0.3165	0.3125	0.3375
89g	0.3125	0.4211	0.4267	0.3214	0.3125	0.3291	0.3125	0.3012	0.3827	0.3125	0.3086	0.3171
86a	0.4030	0.3472	0.3333	0.3699	0.4030	0.3623	0.3429	0.3288	0.3289	0.3429	0.3971	0.4478
86b	0.4000	0.3289	0.3333	0.4054	0.4000	0.3611	0.3425	0.3289	0.4583	0.3425	0.3944	0.4429
86c	0.3889	0.3205	0.3247	0.3947	0.3889	0.3514	0.3333	0.3205	0.3718	0.3333	0.3836	0.4306
86d	0.3784	0.3462	0.3506	0.3846	0.3784	0.3421	0.3247	0.3125	0.3625	0.3247	0.3733	0.4189
86e	0.3733	0.3086	0.3125	0.3797	0.3733	0.3377	0.3205	0.3086	0.3750	0.3205	0.3684	0.4133
84a	0.3289	0.2840	0.2716	0.3210	0.3289	0.2949	0.2785	0.2683	0.2857	0.2785	0.3247	0.3684
84b	0.3205	0.2619	0.2651	0.3293	0.3205	0.2875	0.2716	0.2619	0.3750	0.2716	0.3165	0.3590
84c	0.3125	0.2558	0.2588	0.3214	0.3125	0.2805	0.2651	0.2558	0.3023	0.2651	0.3086	0.3500
84d	0.3049	0.2791	0.2824	0.3140	0.3049	0.2738	0.2588	0.2500	0.2955	0.2588	0.3012	0.3415
84e	0.3012	0.2472	0.2500	0.3103	0.3012	0.2706	0.2558	0.2472	0.3068	0.2558	0.2976	0.3373
89a	0.3810	0.5254	0.5345	0.3478	0.3810	0.3810	0.3810	0.3636	0.3429	0.3810	0.3750	0.3636
89b	0.3378	0.4571	0.4638	0.3462	0.3378	0.3562	0.3378	0.3247	0.4521	0.3378	0.3333	0.3421
89c	0.3289	0.4444	0.4507	0.3375	0.3289	0.3467	0.3289	0.3165	0.3671	0.3289	0.3247	0.3333
89d	0.3289	0.4444	0.4507	0.3375	0.3289	0.3467	0.3289	0.3165	0.3671	0.3289	0.3247	0.3333
89e	0.3380	0.4627	0.4697	0.3117	0.3380	0.3768	0.3380	0.3243	0.3247	0.3380	0.3333	0.3425
89f	0.3165	0.4267	0.4324	0.3253	0.3165	0.3333	0.3165	0.3049	0.3704	0.3165	0.3125	0.3210
90a	0.4444	0.5667	0.6034	0.4058	0.4444	0.4444	0.4677	0.4462	0.4000	0.4444	0.4375	0.4242
90b	0.3836	0.4857	0.5147	0.3896	0.3836	0.4028	0.4028	0.3867	0.5000	0.3836	0.3784	0.3867
90c	0.3733	0.4722	0.5000	0.3797	0.3733	0.3919	0.3919	0.3766	0.4103	0.3733	0.3684	0.3766
90d	0.3733	0.4722	0.5000	0.3797	0.3733	0.3919	0.3919	0.3766	0.4103	0.3733	0.3684	0.3766
90e	0.4000	0.5075	0.5385	0.3684	0.4000	0.4412	0.4203	0.4028	0.3816	0.4000	0.3944	0.4028
90f	0.3590	0.4533	0.4795	0.3659	0.3590	0.3766	0.3766	0.3625	0.4125	0.3590	0.3544	0.3625
90g	0.3544	0.4474	0.4730	0.3614	0.3544	0.3718	0.3718	0.3580	0.4250	0.3544	0.3500	0.3580
90h	0.3636	0.4595	0.4861	0.3704	0.3636	0.3816	0.3816	0.3671	0.4000	0.3636	0.3590	0.3671
90i	0.3766	0.4533	0.4795	0.3659	0.3590	0.3766	0.3766	0.3625	0.3951	0.3590	0.3544	0.3797
91b	0.2118	0.2771	0.2805	0.2247	0.2118	0.2262	0.1977	0.1910	0.2941	0.1977	0.2093	0.2184
91c	0.3421	0.4384	0.4444	0.3500	0.3421	0.3421	0.3247	0.3125	0.3625	0.3247	0.3377	0.3462
91d	0.3421	0.4384	0.4444	0.3500	0.3421	0.3421	0.3247	0.3125	0.3625	0.3247	0.3377	0.3462
91e	0.3521	0.4559	0.4627	0.3247	0.3521	0.3714	0.3333	0.3200	0.3205	0.3333	0.3472	0.3562
91a	0.3906	0.5082	0.5167	0.3571	0.3906	0.3692	0.3692	0.3529	0.3333	0.3692	0.3846	0.3731
92a	0.4627	0.3836	0.3889	0.4247	0.4627	0.4203	0.4203	0.4028	0.3816	0.4000	0.4559	0.5075
92b	0.4429	0.3506	0.3733	0.4459	0.4429	0.4028	0.4028	0.3867	0.5000	0.3836	0.4366	0.4857
92c	0.4306	0.3418	0.3636	0.4342	0.4306	0.3919	0.3919	0.3766	0.4103	0.3733	0.4247	0.4722
92d	0.4189	0.3671	0.3896	0.4231	0.4189	0.3816	0.3816	0.3671	0.4000	0.3636	0.4133	0.4595
67	0.3913	0.7368	0.7500	0.3600	0.3913	0.3913	0.3913	0.3750	0.3553	0.3913	0.3857	0.3750
66	0.4918	0.5667	0.5763	0.4478	0.4918	0.4918	0.4918	0.4688	0.4412	0.4918	0.4839	0.4688
31	0.3538	0.3582	0.3433	0.3239	0.3538	0.3538	0.3538	0.3382	0.3194	0.3538	0.3485	0.3382
90j	0.4000	0.5303	0.5385	0.3684	0.4000	0.4203	0.4203	0.4028	0.3816	0.4000	0.3944	0.4028
36	0.3810	0.5254	0.5345	0.3478	0.3810	0.3810	0.3810	0.3636	0.3429	0.3810	0.3750	0.3636
33	0.4516	0.5763	0.6140	0.4118	0.4516	0.4516	0.4516	0.4308	0.4058	0.4516	0.4444	0.4308
35	0.3014	0.4203	0.4265	0.2949	0.3014	0.3194	0.3014	0.2895	0.3077	0.3014	0.2973	0.3067
25	0.7000	0.4426	0.5263	0.6250	0.7000	0.7000	0.7000	0.6604	0.6140	0.7000	0.6863	0.6604
23	0.4500	0.5254	0.4355	0.4091	0.4500	0.4500	0.4500	0.4286	0.4030	0.4500	0.4426	0.4286

Compound	79x	79o	79v	79l	79y	80a	79a	82a	80a	79b	82b	80c	79c	82c	80d
79m	0.6230	0.7037	0.6333	0.6786	0.6032	0.4545	0.6786	0.4697	0.4286	0.6441	0.4493	0.4167	0.6230	0.4366	0.4054
93	0.3600	0.3971	0.3649	0.3857	0.3506	0.4559	0.4058	0.3889	0.4306	0.3699	0.3553	0.4189	0.3600	0.3462	0.4459
25	0.4225	0.4688	0.4286	0.4545	0.4110	0.3803	0.4545	0.3944	0.3600	0.4348	0.3784	0.3506	0.4225	0.3684	0.3766
54	0.7500	0.6333	0.6250	0.6129	0.5970	0.4167	0.6129	0.4306	0.4324	0.6349	0.4521	0.4211	0.6154	0.4400	0.4103
79k	0.6230	0.7037	0.6333	0.6786	0.6032	0.4545	0.6786	0.4697	0.4286	0.6441	0.4493	0.4167	0.6230	0.4366	0.4054
79q	0.5714	0.6429	0.5806	0.6207	0.5538	0.4118	0.6207	0.4265	0.3889	0.5902	0.4085	0.3784	0.5714	0.3973	0.3684
79t	0.5469	0.6140	0.5556	0.5932	0.5303	0.3913	0.5932	0.4058	0.3699	0.5645	0.3889	0.3600	0.5469	0.3784	0.3506
79u	0.5224	0.5833	0.5303	0.5645	0.5072	0.3750	0.5645	0.3889	0.3553	0.5385	0.3733	0.3462	0.5224	0.3636	0.3375
79z	0.5821	0.5714	0.5909	0.5538	0.5652	0.3733	0.5538	0.3867	0.4861	0.7049	0.5070	0.3974	0.5821	0.4156	0.3875
79r	0.5469	0.6140	0.5556	0.5932	0.5303	0.3913	0.5932	0.4058	0.3699	0.5645	0.3889	0.3600	0.5469	0.3784	0.3506
79s	0.6129	0.6909	0.6230	0.6667	0.5938	0.4478	0.6667	0.4627	0.4225	0.6333	0.4429	0.4110	0.6129	0.4306	0.4000
79n	0.6721	0.7593	0.6833	0.7321	0.6508	0.5000	0.7321	0.5152	0.4714	0.6949	0.4928	0.4583	0.6721	0.4789	0.4459
79x	1.0000	0.6833	0.8448	0.6613	0.6923	0.4583	0.6613	0.4722	0.5797	0.8276	0.6029	0.5857	0.8305	0.6087	0.5694
79o	0.6833	1.0000	0.6949	0.7455	0.6613	0.5077	0.7455	0.5231	0.4783	0.7069	0.5000	0.4648	0.6833	0.4857	0.4521
79v	0.8448	0.6949	1.0000	0.6721	0.7031	0.4648	0.6721	0.4789	0.5882	0.8421	0.6119	0.5942	0.8448	0.6176	0.5775
79l	0.6613	0.7455	0.6721	1.0000	0.6406	0.4925	0.7193	0.5075	0.4648	0.6833	0.4857	0.4521	0.6613	0.4722	0.4400
79y	0.6923	0.6613	0.7031	0.6406	1.0000	0.4459	0.6406	0.4595	0.4800	0.6875	0.5000	0.5915	0.8333	0.6143	0.4744
80a	0.4583	0.5077	0.4648	0.4925	0.4459	1.0000	0.6949	0.6613	0.7097	0.4714	0.4521	0.6875	0.4583	0.4400	0.6667
79a	0.6613	0.7455	0.6721	0.7193	0.6406	0.6949	1.0000	0.7119	0.4857	0.6833	0.4857	0.4722	0.6613	0.4722	0.4595
82a	0.4722	0.5231	0.4789	0.5075	0.4595	0.6613	0.7119	1.0000	0.4658	0.4857	0.6984	0.4533	0.4722	0.6769	0.4416
80a	0.5797	0.4783	0.5882	0.4648	0.4800	0.7097	0.4857	0.4658	1.0000	0.6984	0.6667	0.8361	0.5797	0.5556	0.8095
79b	0.8276	0.7069	0.8421	0.6833	0.6875	0.4714	0.6833	0.4857	0.6984	1.0000	0.7258	0.5797	0.8276	0.6029	0.5634
82b	0.6029	0.5000	0.6119	0.4857	0.5000	0.4521	0.4857	0.6984	0.6667	0.7258	1.0000	0.5556	0.6029	0.8361	0.5405
80c	0.5857	0.4648	0.5942	0.4521	0.5915	0.6875	0.4722	0.4533	0.8361	0.5797	0.5556	1.0000	0.7077	0.6765	0.8125
79c	0.8305	0.6833	0.8448	0.6613	0.8333	0.4583	0.6613	0.4722	0.5797	0.8276	0.6029	0.7077	1.0000	0.7344	0.5694
82c	0.6087	0.4857	0.6176	0.4722	0.6143	0.4400	0.4722	0.6769	0.5556	0.6029	0.8361	0.6765	0.7344	1.0000	0.5467
80d	0.5694	0.4521	0.5775	0.4400	0.4744	0.6667	0.4595	0.4416	0.8095	0.5634	0.5405	0.8125	0.5694	0.5467	1.0000
89d	0.8033	0.6613	0.8167	0.6406	0.6716	0.4459	0.6406	0.4595	0.5634	0.8000	0.5857	0.5694	0.8033	0.5915	0.7164
82d	0.5915	0.4722	0.6000	0.4595	0.4935	0.4286	0.4595	0.6567	0.5405	0.5857	0.8095	0.5467	0.5915	0.8125	0.6857
80e	0.4805	0.4459	0.4868	0.4342	0.4321	0.6567	0.4533	0.4359	0.7692	0.5342	0.5132	0.6957	0.4805	0.4625	0.6761
79e	0.6818	0.6508	0.6923	0.6308	0.6143	0.4400	0.6308	0.4533	0.5342	0.7581	0.5556	0.4805	0.6818	0.5000	0.4684
82e	0.5000	0.4658	0.5067	0.4533	0.4500	0.4231	0.4533	0.6471	0.5132	0.5556	0.7692	0.4625	0.5000	0.6957	0.4512
80f	0.5132	0.4400	0.5200	0.4286	0.4444	0.6471	0.4474	0.4304	0.8125	0.5694	0.5467	0.7353	0.5132	0.4937	0.7143
79f	0.7231	0.6406	0.7344	0.6212	0.6286	0.4342	0.6212	0.4474	0.5694	0.8033	0.5915	0.5132	0.7231	0.5333	0.5000
82f	0.5333	0.4595	0.5405	0.4474	0.4625	0.4177	0.4474	0.6377	0.5467	0.5915	0.8125	0.4937	0.5333	0.7353	0.4815
80k	0.4167	0.4615	0.4225	0.4478	0.4054	0.7069	0.4697	0.4493	0.6613	0.4286	0.4110	0.6406	0.4167	0.4000	0.6212
82k	0.4366	0.4844	0.4429	0.4697	0.4247	0.4348	0.4697	0.6949	0.4110	0.4493	0.6613	0.4000	0.4366	0.6406	0.3896
80g	0.4868	0.4521	0.4933	0.4400	0.4375	0.6667	0.4595	0.4416	0.7538	0.5205	0.5000	0.7059	0.4868	0.4684	0.6857
79g	0.6923	0.6613	0.7031	0.6406	0.6232	0.4459	0.6406	0.4595	0.5205	0.7419	0.5417	0.4868	0.6923	0.5067	0.4744
82g	0.5067	0.4722	0.5135	0.4595	0.4557	0.4286	0.4595	0.6567	0.5000	0.5417	0.7538	0.4684	0.5067	0.7059	0.4568
80h	0.4459	0.4925	0.4521	0.4783	0.4342	0.7333	0.5000	0.4789	0.6875	0.4583	0.4400	0.6667	0.4459	0.4286	0.6716
79h	0.6508	0.7321	0.6613	0.7069	0.6308	0.4853	0.7069	0.5000	0.4583	0.6721	0.4789	0.4459	0.6508	0.4658	0.4533
82h	0.4658	0.5152	0.4722	0.5000	0.4533	0.4648	0.5000	0.7213	0.4400	0.4789	0.6875	0.4286	0.4658	0.6667	0.4359
80i	0.4342	0.4783	0.4400	0.4648	0.4605	0.7097	0.4857	0.4658	0.6667	0.4459	0.4286	0.6471	0.4342	0.4177	0.6286
79i	0.6308	0.7069	0.6406	0.6833	0.6615	0.4714	0.6833	0.4857	0.4459	0.6508	0.4658	0.4342	0.6308	0.4533	0.4231
82i	0.4533	0.5000	0.4595	0.4857	0.4800	0.4521	0.4857	0.6984	0.4286	0.4658	0.6667	0.4177	0.4533	0.6471	0.4074
80j	0.4521	0.5000	0.4583	0.4853	0.4795	0.7458	0.5075	0.4857	0.6984	0.4648	0.4459	0.6769	0.4521	0.4342	0.6567
79j	0.6613	0.7455	0.6721	0.7193	0.6935	0.4925	0.7193	0.5075	0.4648	0.6833	0.4857	0.4521	0.6613	0.4722	0.4400
82j	0.4722	0.5231	0.4789	0.5075	0.5000	0.4714	0.5075	0.7333	0.4459	0.4857	0.6984	0.4342	0.4722	0.6769	0.4231
32	0.3944	0.4375	0.4000	0.4242	0.3836	0.3913	0.4242	0.4058	0.3699	0.4058	0.3889	0.3600	0.3944	0.3784	0.3867
30	0.2933	0.3235	0.2973	0.3143	0.2857	0.4242	0.3333	0.3194	0.4000	0.3014	0.2895	0.3889	0.2933	0.2821	0.3784
88b	0.3924	0.3733	0.3974	0.3636	0.3827	0.4267	0.3816	0.3671	0.5417	0.4795	0.4605	0.4487	0.3924	0.3780	0.4744
88a	0.3750	0.4154	0.3803	0.4030	0.3649	0.4769	0.4242	0.4058	0.4493	0.3857	0.3699	0.4366	0.3750	0.3600	0.4648
88d	0.4000	0.3636	0.4051	0.3544	0.3902	0.4156	0.3718	0.3580	0.4487	0.3924	0.3780	0.4557	0.4000	0.3855	0.5811
88c	0.4000	0.3636	0.4051	0.3544	0.4805	0.4156	0.3718	0.3580	0.4487	0.3924	0.3780	0.5541	0.4933	0.4744	0.4810
88f	0.3529	0.3500	0.3571	0.3415	0.3448	0.4000	0.3580	0.3452	0.4500	0.3951	0.3810	0.4048	0.3529	0.3409	0.4286
88e	0.3544	0.3889	0.3590	0.3784	0.3457	0.4444	0.3973	0.3816	0.4211	0.3636	0.3500	0.4103	0.3544	0.3415	0.4359
88i	0.3855	0.3500	0.3902	0.3415	0.3929	0.4000	0.3580	0.3452	0.4321	0.3780	0.3647	0.4568	0.4024	0.3882	0.4634
88h	0.3902	0.3544	0.3951	0.3457	0.5065	0.4051	0.3625	0.3494	0.4375	0.3827	0.3690	0.5395	0.4805	0.4625	0.4691
88j	0.3647	0.3457	0.3690	0.3373	0.4048	0.3951	0.3537	0.3412	0.4625	0.4074	0.3929	0.4691	0.4146	0.4000	0.4405
79p	0.6613	0.9200	0.6721	0.7193	0.6406	0.4925	0.7193	0.5075	0.4648	0.6833	0.4857	0.4521	0.6613	0.4722	0.4400
89h	0.3659	0.3291	0.3704	0.3210	0.4805	0.3133	0.3210	0.3095	0.3452	0.3580	0.3452	0.4375	0.4545	0.4375	0.3765
89i	0.3614	0.3250	0.3659	0.3171	0.3690	0.3095	0.3171	0.3059	0.3412	0.3537	0.3412	0.3647	0.3780	0.3647	0.3721
89g	0.3412	0.3210	0.3452	0.3133	0.3810	0.3059	0.3133	0.3023	0.3690	0.3827	0.3690	0.3765	0.3902	0.3765	0.3523
86a	0.4110	0.4545	0.4167	0.4412	0.4000	0.6129	0.6333	0.6032	0.4247	0.4225	0.4054	0.4133	0.4110	0.3947	0.4026
86b	0.5507	0.4493	0.5588	0.4366	0.4533	0.4247	0.4366	0.4189	0.6364	0.6667	0.6364	0.5278	0.5507	0.5278	0.5135
86c	0.5571	0.4366	0.5652	0.4247	0.5634	0.4133	0.4247	0.4079	0.5278	0.5507	0.5278	0.6471	0.6769	0.6471	0.5200
86d	0.5417	0.4247	0.5493	0.4133	0.4487	0.4026	0.4133	0.3974	0.5135	0.5352	0.5135	0.5200	0.5417	0.5200	0.6571
86e	0.4545	0.4189	0.4605	0.4079	0.4074	0.3974	0.4079	0.3924	0.4868	0.5068	0.4868	0.4375	0.4545	0.4375	0.4268
84a	0.3580	0.3733	0.3797	0.3816	0.3494	0.5070	0.5217	0.5000	0.3704	0.3671	0.3537	0.3614	0.3580	0.3452	0.3529
84b	0.4545	0.3636	0.4800	0.3718	0.3735	0.3457	0.3544	0.3415	0.5270	0.5493	0.5270	0.4375	0.4545	0.4375	0.4268
84c	0.4615	0.3544	0.4868	0.3625	0.4684	0.3373	0.3457	0.3333	0.4375	0.4545	0.4375	0.5395	0.5616	0.5395	0.4337
84d	0.4500	0.3457	0.4744	0.3537	0.3721	0.3294	0.3373	0.3256	0.4268	0.4430	0.4268	0.4337	0.4500	0.4337	0.5513
84e	0.3765	0.3415	0.3976	0.3494	0.3371	0.3256	0.3333	0.3218	0.4048	0.4198	0.4048	0.3636	0.3765	0.3636	0.3556
89a	0.3333	0.3692	0.3380	0.3582	0.3243	0.3478	0.3582	0.3429	0.3288	0.3429	0.3288	0.3200	0.3333	0.3200	0.3467
89b	0.3671	0.3467	0.3718	0.3377	0.3580	0.3291	0.3377	0.3250	0.4342	0.4521	0.4342	0.3537	0.3671	0.3537	0.3780
89c	0.3750	0.3377	0.3797	0.3291	0.4545	0.3210	0.3291	0.3171	0.3537	0.3671	0.3537	0.4487	0.4667	0.4487	0.3855
89d	0.3750	0.3377	0.3797	0.3291	0.3659	0.3210	0.3291	0.3171	0.3537	0.3671	0.3537	0.3614	0.3750	0.3614	0.4744
89e	0.3165	0.3472	0.3205	0.3378	0.3086	0.3289	0.3378	0.3247	0.3125	0.3247	0.3125	0.3049	0.3165	0.3049	0.3293
89f	0.3294	0.3250	0.3333	0.3171	0.3218	0.3095	0.3171	0.3059	0.3571	0.3704	0.3571	0.3182	0.3294	0.3182	0.3409
90a	0.3889	0.4308	0.3944	0.4179	0.3784	0.3857	0.4179	0.4000	0.3649	0.4000	0.3836	0.3553	0.3889	0.3733	0.3816
90b	0.4103	0.3919	0.4156	0.3816	0.4000	0.3544	0.3816	0.3671	0.4605	0.5000	0.4800	0.3780	0.4103	0.3951	0.4024
90c	0.4177	0.3816	0.4231	0.3718	0.5000	0.3457	0.3718	0.3580	0.3780	0.4103	0.3951	0.4744	0.5135	0.4935	0.4096
90d	0.4177	0.3816	0.4231	0.3718	0.4074	0.3457	0.3718	0.3580	0.3780	0.4103	0.3951	0.3855	0.4177	0.4024	0.5000
90e	0.3718	0.4085	0.3766	0.3973	0.3625	0.3684	0.3973	0.3816	0.3500	0.3816	0.3671	0.3415	0.3718	0.3580	0.3659
90f	0.3690	0.3671	0.3735	0.3580	0.3605	0.3333	0.3580	0.3452	0.3810	0.4125	0.3976	0.3409	0.3690	0.3563	0.3636
90g	0.3810	0.3625	0.3855	0.3537	0.4217	0.3294	0.3537	0.3412	0.3929	0.4250	0.4096	0.4000	0.4321	0.4167	0.3750
90h	0.4074	0.3718	0.4125	0.3625	0.5263	0.3373	0.3625	0.3494	0.3690	0.4000	0.3855	0.4625	0.5000	0.4810	0.4000
90i	0.4024	0.3671	0.4074	0.3580	0.4096	0.3333	0.3580	0.3452	0.3647	0.3951	0.3810	0.3882	0.4198	0.4048	0.3953
91b	0.2727	0.2209	0.2759	0.2159	0.2391	0.2111	0.2159	0.2088	0.3294	0.3415	0.3294	0.2637	0.2727	0.2637	0.2857
91c	0.4231	0.3506	0.4286	0.3418	0.4675	0.3333	0.3418	0.3293	0.4000	0.4156	0.4000	0.5000	0.5205	0.5000	0.4321
91d	0.4231	0.3506	0.4286	0.3418	0.3780	0.3333	0.3418	0.3293	0.4000	0.4156	0.4000	0.4074	0.4231	0.4074	0.5263
91e	0.3291	0.3611	0.3333	0.3514	0.3375	0.3421	0.3514	0.3377	0.3250	0.3377	0.3250	0.3171	0.3291	0.3171	0.3415
91a	0.3425	0.3788	0.3472	0.3676	0.3333	0.3571	0.3676	0.3521	0.3378	0.3521	0.3378	0.3289	0.3425	0.3289	0.3553
92a	0.4658	0.5152	0.4722	0.5000	0.4533	0.6508	0.7000	0.6667	0.4595	0.4789	0.4595	0.4474	0.4658	0.4474	0.4359
92b	0.5942	0.4928	0.6029	0.4789	0.4933	0.4459	0.4789	0.4595	0.6567	0.7143	0.6818	0.5479	0.5942	0.5694	0.5333
92c	0.6000	0.4789	0.6087	0.4658	0.6056	0.4342	0.4658	0.4474	0.5479	0.5942	0.5694	0.6667	0.7231	0.6912	0.5395
92d	0.5833	0.4658	0.5915	0.4533	0.4872	0.4231	0.4533	0.4359	0.5333	0.5775	0.5541	0.5395	0.5833	0.5600	0.6761
67	0.3462	0.3803	0.3506	0.3699	0.3375	0.3784	0.3699	0.3553	0.3590	0.3553	0.3418	0.3500	0.3462	0.3333	0.3750
66	0.4286	0.4762	0.4348	0.4615	0.4167	0.4058	0.4615	0.3803	0.3836	0.4412	0.3649	0.3733	0.4286	0.3553	0.4000
31	0.3108	0.3433	0.3151	0.3333	0.3026	0.4242	0.3529	0.3380	0.4000	0.3194	0.3067	0.3889	0.3108	0.2987	0.3784
90j	0.3718	0.4085	0.3766	0.3973	0.3625	0.4444	0.4783	0.4583	0.3671	0.3816	0.3671	0.3580	0.3718	0.3580	0.3827
36	0.3333	0.3692	0.3380	0.3582	0.3243	0.3478	0.3582	0.3429	0.3288	0.3429	0.3288	0.3200	0.3333	0.3200	0.3467
33	0.3944	0.4375	0.4000	0.4242	0.3836	0.3913	0.4242	0.6441	0.3699	0.4058	0.6129	0.3600	0.3944	0.5938	0.3867
35	0.3000	0.3108	0.3205	0.3200	0.2927	0.2949	0.3026	0.2911	0.2963	0.3077	0.2963	0.2892	0.3000	0.2892	0.3133
25	0.5932	0.6731	0.6034	0.6481	0.5738	0.4444	0.6481	0.4375	0.4179	0.6140	0.4179	0.4058	0.5932	0.4058	0.3944
23	0.3913	0.4355	0.3971	0.4219	0.3803	0.6909	0.4444	0.4242	0.6441	0.4030	0.3857	0.6230	0.3913	0.3750	0.6032

Compound	89d	82d	80e	79e	82e	80f	79f	82f	80k	82k	80g	79g	82g	80h	79h	82h	80i	79i	82i	80j	79j	82j	32	30	88b	88a	88d	88c
79m	0.6032	0.4247	0.4000	0.5938	0.4189	0.3947	0.5846	0.4133	0.4762	0.5000	0.4054	0.6032	0.4247	0.4412	0.6667	0.4627	0.4286	0.6441	0.4493	0.4478	0.6786	0.4697	0.4516	0.3333	0.3649	0.4286	0.3553	0.3553
93	0.3867	0.3718	0.4026	0.3462	0.3333	0.3974	0.3418	0.3293	0.4769	0.3913	0.4079	0.3506	0.3375	0.4638	0.4000	0.3836	0.4306	0.3699	0.3553	0.4493	0.3857	0.3699	0.5763	0.3582	0.6774	0.8235	0.6563	0.6563
25	0.4507	0.3947	0.3375	0.4054	0.3544	0.3333	0.4000	0.3500	0.3971	0.4179	0.3418	0.4110	0.3590	0.3889	0.4697	0.4085	0.3600	0.4348	0.3784	0.3750	0.4545	0.3944	0.6140	0.3235	0.5606	0.6727	0.5441	0.5441
54	0.5970	0.4286	0.4051	0.5882	0.4231	0.4000	0.5797	0.4177	0.4348	0.4559	0.4103	0.5970	0.4286	0.4054	0.6032	0.4247	0.3947	0.5846	0.4133	0.4110	0.6129	0.4306	0.4118	0.3056	0.3718	0.3913	0.3625	0.3625
79k	0.6032	0.4247	0.4000	0.5938	0.4189	0.3947	0.5846	0.4133	0.6607	0.6909	0.4054	0.6032	0.4247	0.4412	0.6667	0.4627	0.4286	0.6441	0.4493	0.4478	0.6786	0.4697	0.4516	0.3333	0.3649	0.4286	0.3553	0.3553
79q	0.5538	0.3867	0.3636	0.5455	0.3816	0.3590	0.5373	0.3766	0.4091	0.4308	0.3684	0.5538	0.3867	0.4203	0.6379	0.4412	0.4085	0.6167	0.4286	0.4265	0.6491	0.4478	0.4516	0.3333	0.3836	0.4286	0.3733	0.3733
79t	0.5303	0.3684	0.3462	0.5224	0.3636	0.3418	0.5147	0.3590	0.4091	0.4308	0.3506	0.5303	0.3684	0.3803	0.5833	0.4000	0.3699	0.5645	0.3889	0.3857	0.5932	0.4058	0.4516	0.3333	0.3649	0.4286	0.3553	0.3553
79u	0.5072	0.3544	0.3333	0.5000	0.3500	0.3293	0.4930	0.3457	0.3913	0.4118	0.3544	0.5294	0.3718	0.3649	0.5556	0.3836	0.3553	0.5385	0.3733	0.3699	0.5645	0.3889	0.4531	0.3188	0.3506	0.4091	0.3418	0.3418
79z	0.5652	0.4051	0.4000	0.5797	0.4177	0.4125	0.5942	0.4304	0.3699	0.3889	0.3875	0.5652	0.4051	0.3636	0.5455	0.3816	0.3718	0.5522	0.3896	0.3684	0.5538	0.3867	0.4058	0.3014	0.4795	0.3857	0.3924	0.3924
79r	0.5303	0.3684	0.3462	0.5224	0.3636	0.3418	0.5147	0.3590	0.4531	0.4762	0.3506	0.5303	0.3684	0.3803	0.5833	0.4000	0.3889	0.5902	0.4085	0.3857	0.5932	0.4058	0.4516	0.3333	0.3649	0.4286	0.3553	0.3553
79s	0.5938	0.4189	0.3947	0.5846	0.4133	0.3896	0.5758	0.4079	0.4688	0.4921	0.4000	0.5938	0.4189	0.4348	0.6552	0.4559	0.4225	0.6333	0.4429	0.4412	0.6667	0.4627	0.4444	0.3284	0.3600	0.4219	0.3506	0.3506
79n	0.6508	0.4658	0.4400	0.6406	0.4595	0.4342	0.6308	0.4533	0.4545	0.4769	0.4459	0.6508	0.4658	0.4853	0.7193	0.5075	0.4714	0.6949	0.4928	0.4925	0.7321	0.5152	0.4308	0.3188	0.3684	0.4091	0.3590	0.3590
79x	0.8033	0.5915	0.4805	0.6818	0.5000	0.5132	0.7231	0.5333	0.4167	0.4366	0.4868	0.6923	0.5067	0.4459	0.6508	0.4658	0.4342	0.6308	0.4533	0.4521	0.6613	0.4722	0.3944	0.2933	0.3924	0.3750	0.4000	0.4000
79o	0.6613	0.4722	0.4459	0.6508	0.4658	0.4400	0.6406	0.4595	0.4615	0.4844	0.4521	0.6613	0.4722	0.4925	0.7321	0.5152	0.4783	0.7069	0.5000	0.5000	0.7455	0.5231	0.4375	0.3235	0.3733	0.4154	0.3636	0.3636
79v	0.8167	0.6000	0.4868	0.6923	0.5067	0.5200	0.7344	0.5405	0.4225	0.4429	0.4933	0.7031	0.5135	0.4521	0.6613	0.4722	0.4400	0.6406	0.4595	0.4583	0.6721	0.4789	0.4000	0.2973	0.3974	0.3803	0.4051	0.4051
79l	0.6406	0.4595	0.4342	0.6308	0.4533	0.4286	0.6212	0.4474	0.4478	0.4697	0.4400	0.6406	0.4595	0.4783	0.7069	0.5000	0.4648	0.6833	0.4857	0.4853	0.7193	0.5075	0.4242	0.3143	0.3636	0.4030	0.3544	0.3544
79y	0.6716	0.4935	0.4321	0.6143	0.4500	0.4444	0.6286	0.4625	0.4054	0.4247	0.4375	0.6232	0.4557	0.4342	0.6308	0.4533	0.4605	0.6615	0.4800	0.4795	0.6935	0.5000	0.3836	0.2857	0.3827	0.3649	0.3902	0.4805
80a	0.4459	0.4286	0.6567	0.4400	0.4231	0.6471	0.4342	0.4177	0.7069	0.4348	0.6667	0.4459	0.4286	0.7333	0.4853	0.4648	0.7097	0.4714	0.4521	0.7458	0.4925	0.4714	0.3913	0.4242	0.4267	0.4769	0.4156	0.4156
79a	0.6406	0.4595	0.4533	0.6308	0.4533	0.4474	0.6212	0.4474	0.4697	0.4697	0.4595	0.6406	0.4595	0.5000	0.7069	0.5000	0.4857	0.6833	0.4857	0.5075	0.7193	0.5075	0.4242	0.3333	0.3816	0.4242	0.3718	0.3718
82a	0.4595	0.6567	0.4359	0.4533	0.6471	0.4304	0.4474	0.6377	0.4493	0.6949	0.4416	0.4595	0.6567	0.4789	0.5000	0.7213	0.4658	0.4857	0.6984	0.4857	0.5075	0.7333	0.4058	0.3194	0.3671	0.4058	0.3580	0.3580
80a	0.5634	0.5405	0.7692	0.5342	0.5132	0.8125	0.5694	0.5467	0.6613	0.4110	0.7538	0.5205	0.5000	0.6875	0.4583	0.4400	0.6667	0.4459	0.4286	0.6984	0.4648	0.4459	0.3699	0.4000	0.5417	0.4493	0.4487	0.4487
79b	0.8000	0.5857	0.5342	0.7581	0.5556	0.5694	0.8033	0.5915	0.4286	0.4493	0.5205	0.7419	0.5417	0.4583	0.6721	0.4789	0.4459	0.6508	0.4658	0.4648	0.6833	0.4857	0.4058	0.3014	0.4795	0.3857	0.3924	0.3924
82b	0.5857	0.8095	0.5132	0.5556	0.7692	0.5467	0.5915	0.8125	0.4110	0.6613	0.5000	0.5417	0.7538	0.4400	0.4789	0.6875	0.4286	0.4658	0.6667	0.4459	0.4857	0.6984	0.3889	0.2895	0.4605	0.3699	0.3780	0.3780
80c	0.5694	0.5467	0.6957	0.4805	0.4625	0.7353	0.5132	0.4937	0.6406	0.4000	0.7059	0.4868	0.4684	0.6667	0.4459	0.4286	0.6471	0.4342	0.4177	0.6769	0.4521	0.4342	0.3600	0.3889	0.4487	0.4366	0.4557	0.5541
79c	0.8033	0.5915	0.4805	0.6818	0.5000	0.5132	0.7231	0.5333	0.4167	0.4366	0.4868	0.6923	0.5067	0.4459	0.6508	0.4658	0.4342	0.6308	0.4533	0.4521	0.6613	0.4722	0.3944	0.2933	0.3924	0.3750	0.4000	0.4933
82c	0.5915	0.8125	0.4625	0.5000	0.6957	0.4937	0.5333	0.7353	0.4000	0.6406	0.4684	0.5067	0.7059	0.4286	0.4658	0.6667	0.4177	0.4533	0.6471	0.4342	0.4722	0.6769	0.3784	0.2821	0.3780	0.3600	0.3855	0.4744
80d	0.7164	0.6857	0.6761	0.4684	0.4512	0.7143	0.5000	0.4815	0.6212	0.3896	0.6857	0.4744	0.4568	0.6716	0.4533	0.4359	0.6286	0.4231	0.4074	0.6567	0.4400	0.4231	0.3867	0.3784	0.4744	0.4648	0.5811	0.4810
89d	1.0000	0.7424	0.4684	0.6618	0.4872	0.5000	0.7015	0.5195	0.4054	0.4247	0.4744	0.6716	0.4935	0.4533	0.6563	0.4730	0.4231	0.6119	0.4416	0.4400	0.6406	0.4595	0.4225	0.2857	0.4177	0.4028	0.5200	0.4250
82d	0.7424	1.0000	0.4512	0.4872	0.6761	0.4815	0.5195	0.7143	0.3896	0.6212	0.4568	0.4935	0.6857	0.4359	0.4730	0.6716	0.4074	0.4416	0.6286	0.4231	0.4595	0.6567	0.4054	0.2750	0.4024	0.3867	0.5000	0.4096
80e	0.4684	0.4512	1.0000	0.7206	0.6901	0.7286	0.5128	0.4938	0.6119	0.3846	0.7000	0.4872	0.4691	0.6377	0.4286	0.4125	0.6197	0.4177	0.4024	0.6471	0.4342	0.4177	0.3462	0.3733	0.4500	0.4189	0.4048	0.4048
79e	0.6618	0.4872	0.7206	1.0000	0.7463	0.5128	0.7164	0.5325	0.4000	0.4189	0.4872	0.6866	0.5065	0.4286	0.6212	0.4474	0.4177	0.6029	0.4359	0.4342	0.6308	0.4533	0.3784	0.2821	0.3951	0.3600	0.3529	0.3529
82e	0.4872	0.6761	0.6901	0.7463	1.0000	0.4938	0.5325	0.7286	0.3846	0.6119	0.4691	0.5065	0.7000	0.4125	0.4474	0.6377	0.4024	0.4359	0.6197	0.4177	0.4533	0.6471	0.3636	0.2716	0.3810	0.3462	0.3409	0.3409
80f	0.5000	0.4815	0.7286	0.5128	0.4938	1.0000	0.7246	0.6944	0.6029	0.3797	0.6901	0.4810	0.4634	0.6286	0.4231	0.4074	0.6111	0.4125	0.3976	0.6377	0.4286	0.4125	0.3418	0.3684	0.4625	0.4133	0.4167	0.4167
79f	0.7015	0.5195	0.5128	0.7164	0.5325	0.7246	1.0000	0.7500	0.3947	0.4133	0.4810	0.6765	0.5000	0.4231	0.6119	0.4416	0.4125	0.5942	0.4304	0.4286	0.6212	0.4474	0.3733	0.2785	0.4074	0.3553	0.3647	0.3647
82f	0.5195	0.7143	0.4938	0.5325	0.7286	0.6944	0.7500	1.0000	0.3797	0.6029	0.4634	0.5000	0.6901	0.4074	0.4416	0.6286	0.3976	0.4304	0.6111	0.4125	0.4474	0.6377	0.3590	0.2683	0.3929	0.3418	0.3523	0.3523
80k	0.4054	0.3896	0.6119	0.4000	0.3846	0.6029	0.3947	0.3797	1.0000	0.6271	0.6212	0.4054	0.3896	0.6833	0.4412	0.4225	0.6613	0.4286	0.4110	0.6949	0.4478	0.4286	0.4091	0.4444	0.4247	0.5000	0.4133	0.4133
82k	0.4247	0.6212	0.3846	0.4189	0.6119	0.3797	0.4133	0.6029	0.6271	1.0000	0.3896	0.4247	0.6212	0.4225	0.4627	0.6833	0.4110	0.4493	0.6613	0.4286	0.4697	0.6949	0.4308	0.3188	0.3506	0.4091	0.3418	0.3418
80g	0.4744	0.4568	0.7000	0.4872	0.4691	0.6901	0.4810	0.4634	0.6212	0.3896	1.0000	0.7164	0.6857	0.6471	0.4342	0.4177	0.6286	0.4231	0.4074	0.6567	0.4400	0.4231	0.3684	0.3784	0.4375	0.4247	0.4096	0.4096
79g	0.6716	0.4935	0.4872	0.6866	0.5065	0.4810	0.6765	0.5000	0.4054	0.4247	0.7164	1.0000	0.7424	0.4342	0.6308	0.4533	0.4231	0.6119	0.4416	0.4400	0.6406	0.4595	0.4028	0.2857	0.3827	0.3649	0.3571	0.3571
82g	0.4935	0.6857	0.4691	0.5065	0.7000	0.4634	0.5000	0.6901	0.3896	0.6212	0.6857	0.7424	1.0000	0.4177	0.4533	0.6471	0.4074	0.4416	0.6286	0.4231	0.4595	0.6567	0.3867	0.2750	0.3690	0.3506	0.3448	0.3448
80h	0.4533	0.4359	0.6377	0.4286	0.4125	0.6286	0.4231	0.4074	0.6833	0.4225	0.6471	0.4342	0.4177	1.0000	0.6885	0.6563	0.6875	0.4583	0.4400	0.7500	0.5000	0.4789	0.4000	0.4118	0.4342	0.4848	0.4231	0.4231
79h	0.6563	0.4730	0.4286	0.6212	0.4474	0.4231	0.6119	0.4416	0.4412	0.4627	0.4342	0.6308	0.4533	0.6885	1.0000	0.7167	0.4583	0.6721	0.4789	0.5000	0.7368	0.5224	0.4394	0.3099	0.3766	0.4179	0.3671	0.3671
82h	0.4730	0.6716	0.4125	0.4474	0.6377	0.4074	0.4416	0.6286	0.4225	0.6833	0.4177	0.4533	0.6471	0.6563	0.7167	1.0000	0.4400	0.4789	0.6875	0.4789	0.5224	0.7500	0.4203	0.2973	0.3625	0.4000	0.3537	0.3537
80i	0.4231	0.4074	0.6197	0.4177	0.4024	0.6111	0.4125	0.3976	0.6613	0.4110	0.6286	0.4231	0.4074	0.6875	0.4583	0.4400	1.0000	0.6984	0.6667	0.8136	0.5522	0.5286	0.3699	0.4000	0.4051	0.4493	0.3951	0.3951
79i	0.6119	0.4416	0.4177	0.6029	0.4359	0.4125	0.5942	0.4304	0.4286	0.4493	0.4231	0.6119	0.4416	0.4583	0.6721	0.4789	0.6984	1.0000	0.7258	0.5522	0.8036	0.5758	0.4058	0.3014	0.3500	0.3857	0.3415	0.3415
82i	0.4416	0.6286	0.4024	0.4359	0.6197	0.3976	0.4304	0.6111	0.4110	0.6613	0.4074	0.4416	0.6286	0.4400	0.4789	0.6875	0.6667	0.7258	1.0000	0.5286	0.5758	0.8136	0.3889	0.2895	0.3373	0.3699	0.3294	0.3294
80j	0.4400	0.4231	0.6471	0.4342	0.4177	0.6377	0.4286	0.4125	0.6949	0.4286	0.6567	0.4400	0.4231	0.7500	0.5000	0.4789	0.8136	0.5522	0.5286	1.0000	0.6833	0.6508	0.3857	0.4179	0.4211	0.4697	0.4103	0.4103
79j	0.6406	0.4595	0.4342	0.6308	0.4533	0.4286	0.6212	0.4474	0.4478	0.4697	0.4400	0.6406	0.4595	0.5000	0.7368	0.5224	0.5522	0.8036	0.5758	0.6833	1.0000	0.7119	0.4242	0.3143	0.3636	0.4030	0.3544	0.3544
82j	0.4595	0.6567	0.4177	0.4533	0.6471	0.4125	0.4474	0.6377	0.4286	0.6949	0.4231	0.4595	0.6567	0.4789	0.5224	0.7500	0.5286	0.5758	0.8136	0.6508	0.7119	1.0000	0.4058	0.3014	0.3500	0.3857	0.3415	0.3415
32	0.4225	0.4054	0.3462	0.3784	0.3636	0.3418	0.3733	0.3590	0.4091	0.4308	0.3684	0.4028	0.3867	0.4000	0.4394	0.4203	0.3699	0.4058	0.3889	0.3857	0.4242	0.4058	1.0000	0.3333	0.5075	0.6071	0.4928	0.4928
30	0.2857	0.2750	0.3733	0.2821	0.2716	0.3684	0.2785	0.2683	0.4444	0.3188	0.3784	0.2857	0.2750	0.4118	0.3099	0.2973	0.4000	0.3014	0.2895	0.4179	0.3143	0.3014	0.3333	1.0000	0.3200	0.3750	0.3117	0.3117
88b	0.4177	0.4024	0.4500	0.3951	0.3810	0.4625	0.4074	0.3929	0.4247	0.3506	0.4375	0.3827	0.3690	0.4342	0.3766	0.3625	0.4051	0.3500	0.3373	0.4211	0.3636	0.3500	0.5075	0.3200	1.0000	0.7119	0.8387	0.8387
88a	0.4028	0.3867	0.4189	0.3600	0.3462	0.4133	0.3553	0.3418	0.5000	0.4091	0.4247	0.3649	0.3506	0.4848	0.4179	0.4000	0.4493	0.3857	0.3699	0.4697	0.4030	0.3857	0.6071	0.3750	0.7119	1.0000	0.6885	0.6885
88d	0.5200	0.5000	0.4048	0.3529	0.3409	0.4167	0.3647	0.3523	0.4133	0.3418	0.4096	0.3571	0.3448	0.4231	0.3671	0.3537	0.3951	0.3415	0.3294	0.4103	0.3544	0.3415	0.4928	0.3117	0.8387	0.6885	1.0000	0.8413
88c	0.4250	0.4096	0.4048	0.3529	0.3409	0.4167	0.3647	0.3523	0.4133	0.3418	0.4096	0.3571	0.3448	0.4231	0.3671	0.3537	0.3951	0.3415	0.3294	0.4103	0.3544	0.3415	0.4928	0.3117	0.8387	0.6885	0.8413	1.0000
88f	0.3765	0.3636	0.5714	0.5128	0.4938	0.4353	0.3837	0.3708	0.3974	0.3293	0.4118	0.3605	0.3483	0.4074	0.3537	0.3412	0.3810	0.3294	0.3182	0.3951	0.3415	0.3294	0.4722	0.3000	0.7727	0.6563	0.7000	0.7000
88e	0.3797	0.3659	0.3951	0.3415	0.3294	0.3902	0.3373	0.3256	0.4429	0.3649	0.4000	0.3457	0.3333	0.4722	0.4110	0.3947	0.4400	0.3816	0.3671	0.5217	0.4571	0.4384	0.5313	0.3333	0.7031	0.7500	0.6818	0.6818
88i	0.4096	0.3953	0.3908	0.3409	0.3297	0.4023	0.3523	0.3407	0.3974	0.3293	0.3953	0.3448	0.3333	0.4074	0.3537	0.3412	0.3810	0.3294	0.3182	0.3951	0.3415	0.3294	0.4722	0.3000	0.8000	0.6563	0.8030	0.8308
88h	0.4146	0.4000	0.3953	0.3448	0.3333	0.4070	0.3563	0.3444	0.4026	0.3333	0.4000	0.3488	0.3371	0.4125	0.3580	0.3452	0.3855	0.3333	0.3218	0.4000	0.3457	0.3333	0.4789	0.3038	0.7059	0.6667	0.7101	0.8438
88j	0.3882	0.3750	0.4023	0.3523	0.3407	0.4302	0.3793	0.3667	0.3924	0.3253	0.4070	0.3563	0.3444	0.4024	0.3494	0.3372	0.3765	0.3256	0.3146	0.3902	0.3373	0.3256	0.4658	0.2963	0.8154	0.6462	0.7391	0.8182
79p	0.6406	0.4595	0.4342	0.6308	0.4533	0.4286	0.6212	0.4474	0.4478	0.4697	0.4400	0.6406	0.4595	0.4783	0.7069	0.5000	0.4648	0.6833	0.4857	0.4853	0.7193	0.5075	0.4242	0.3143	0.3636	0.4030	0.3544	0.3544
89h	0.3902	0.3765	0.3111	0.3218	0.3111	0.3222	0.3333	0.3222	0.3086	0.3086	0.3146	0.3256	0.3146	0.3214	0.3333	0.3214	0.2989	0.3095	0.2989	0.3095	0.3210	0.3095	0.4507	0.2785	0.4615	0.4507	0.4684	0.5676
89i	0.3855	0.3721	0.3077	0.3182	0.3077	0.3187	0.3295	0.3187	0.3049	0.3049	0.3111	0.3218	0.3111	0.3176	0.3293	0.3176	0.2955	0.3059	0.2955	0.3059	0.3171	0.3059	0.4444	0.2750	0.4935	0.4444	0.5000	0.5195
89g	0.3647	0.3523	0.3187	0.3295	0.3187	0.3444	0.3563	0.3444	0.3012	0.3012	0.3222	0.3333	0.3222	0.3140	0.3253	0.3140	0.2921	0.3023	0.2921	0.3023	0.3133	0.3023	0.4384	0.2716	0.5065	0.4384	0.4568	0.5128
86a	0.4000	0.3846	0.3974	0.3947	0.3797	0.3924	0.3896	0.3750	0.4058	0.3857	0.4026	0.4000	0.3846	0.4366	0.4348	0.4167	0.4247	0.4225	0.4054	0.4429	0.4412	0.4225	0.3429	0.3143	0.3291	0.3623	0.3210	0.3210
86b	0.5352	0.5135	0.4868	0.5068	0.4868	0.5200	0.5417	0.5200	0.3836	0.3836	0.4737	0.4932	0.4737	0.4133	0.4306	0.4133	0.4026	0.4189	0.4026	0.4189	0.4366	0.4189	0.3425	0.2973	0.4342	0.3425	0.3537	0.3537
86c	0.5417	0.5200	0.4375	0.4545	0.4375	0.4684	0.4868	0.4684	0.3733	0.3733	0.4430	0.4605	0.4430	0.4026	0.4189	0.4026	0.3924	0.4079	0.3924	0.4079	0.4247	0.4079	0.3333	0.2895	0.3537	0.3333	0.3614	0.4487
86d	0.6866	0.6571	0.4268	0.4430	0.4268	0.4568	0.4744	0.4568	0.3636	0.3636	0.4321	0.4487	0.4321	0.4103	0.4267	0.4103	0.3827	0.3974	0.3827	0.3974	0.4133	0.3974	0.3600	0.2821	0.3780	0.3600	0.4744	0.3855
86e	0.4430	0.4268	0.6620	0.6912	0.6620	0.4691	0.4872	0.4691	0.3590	0.3590	0.4444	0.4615	0.4444	0.3875	0.4026	0.3875	0.3780	0.3924	0.3780	0.3924	0.4079	0.3924	0.3205	0.2785	0.3571	0.3205	0.3182	0.3182
84a	0.3494	0.3372	0.3488	0.3452	0.3333	0.3448	0.3412	0.3295	0.3333	0.3165	0.3529	0.3494	0.3372	0.3625	0.3590	0.3457	0.3537	0.3500	0.3373	0.3671	0.3636	0.3500	0.2785	0.2857	0.2874	0.2949	0.2809	0.2809
84b	0.4430	0.4268	0.4048	0.4198	0.4048	0.4337	0.4500	0.4337	0.3086	0.3086	0.3929	0.4074	0.3929	0.3373	0.3500	0.3373	0.3294	0.3415	0.3294	0.3415	0.3544	0.3415	0.2716	0.2625	0.3571	0.2716	0.2889	0.2889
84c	0.4500	0.4337	0.3636	0.3765	0.3636	0.3908	0.4048	0.3908	0.3012	0.3012	0.3678	0.3810	0.3678	0.3294	0.3415	0.3294	0.3218	0.3333	0.3218	0.3333	0.3457	0.3333	0.2651	0.2561	0.2889	0.2651	0.2967	0.3721
84d	0.5733	0.5513	0.3556	0.3678	0.3556	0.3820	0.3953	0.3820	0.2941	0.2941	0.3596	0.3721	0.3596	0.3372	0.3494	0.3372	0.3146	0.3256	0.3146	0.3256	0.3373	0.3256	0.2892	0.2500	0.3111	0.2892	0.3953	0.3187
84e	0.3678	0.3556	0.5570	0.5789	0.5570	0.3933	0.4070	0.3933	0.2907	0.2907	0.3708	0.3837	0.3708	0.3182	0.3294	0.3182	0.3111	0.3218	0.3111	0.3218	0.3333	0.3218	0.2558	0.2471	0.2935	0.2558	0.2604	0.2604
89a	0.3611	0.3467	0.3077	0.3200	0.3077	0.3038	0.3158	0.3038	0.3636	0.3636	0.3117	0.3243	0.3117	0.3571	0.3731	0.3571	0.3288	0.3429	0.3288	0.3429	0.3582	0.3429	0.5536	0.3281	0.4627	0.5536	0.4493	0.4493
89b	0.3924	0.3780	0.3571	0.3704	0.3571	0.3690	0.3827	0.3690	0.3247	0.3247	0.3452	0.3580	0.3452	0.3375	0.3506	0.3375	0.3133	0.3250	0.3133	0.3250	0.3377	0.3250	0.4776	0.2933	0.6176	0.4776	0.5135	0.5135
89c	0.4000	0.3855	0.3182	0.3294	0.3182	0.3295	0.3412	0.3295	0.3165	0.3165	0.3218	0.3333	0.3218	0.3293	0.3418	0.3293	0.3059	0.3171	0.3059	0.3171	0.3291	0.3171	0.4638	0.2857	0.5135	0.4638	0.5200	0.6286
89d	0.4933	0.4744	0.3182	0.3294	0.3182	0.3295	0.3412	0.3295	0.3165	0.3165	0.3218	0.3333	0.3218	0.3293	0.3418	0.3293	0.3059	0.3171	0.3059	0.3171	0.3291	0.3171	0.4638	0.2857	0.5135	0.4638	0.6286	0.5200
89e	0.3418	0.3293	0.2941	0.3049	0.2941	0.2907	0.3012	0.2907	0.3243	0.3243	0.2976	0.3086	0.2976	0.3553	0.3699	0.3553	0.3291	0.3421	0.3291	0.3973	0.4143	0.3973	0.4844	0.2917	0.4324	0.4844	0.4211	0.4211
89f	0.3529	0.3409	0.4691	0.4872	0.4691	0.3483	0.3605	0.3483	0.3049	0.3049	0.3258	0.3372	0.3258	0.3176	0.3293	0.3176	0.2955	0.3059	0.2955	0.3059	0.3171	0.3059	0.4444	0.2750	0.4935	0.4444	0.4444	0.4444
90a	0.4167	0.4000	0.3418	0.3733	0.3590	0.3375	0.3684	0.3544	0.4030	0.4242	0.3462	0.3784	0.3636	0.3944	0.4328	0.4143	0.3649	0.4000	0.3836	0.3803	0.4179	0.4000	0.6250	0.3284	0.5000	0.5965	0.4857	0.4857
90b	0.4359	0.4198	0.3810	0.4125	0.3976	0.3929	0.4250	0.4096	0.3506	0.3684	0.3690	0.4000	0.3855	0.3625	0.3947	0.3797	0.3373	0.3671	0.3537	0.3500	0.3816	0.3671	0.5303	0.2857	0.6000	0.5075	0.5000	0.5000
90c	0.4430	0.4268	0.3409	0.3690	0.3563	0.3523	0.3810	0.3678	0.3418	0.3590	0.3448	0.3735	0.3605	0.3537	0.3846	0.3704	0.3294	0.3580	0.3452	0.3415	0.3718	0.3580	0.5147	0.2785	0.5000	0.4928	0.5065	0.6111
90d	0.5405	0.5195	0.3409	0.3690	0.3563	0.3523	0.3810	0.3678	0.3418	0.3590	0.3448	0.3735	0.3605	0.3537	0.3846	0.3704	0.3294	0.3580	0.3452	0.3415	0.3718	0.3580	0.5147	0.2785	0.5000	0.4928	0.6111	0.5065
90e	0.3974	0.3827	0.3294	0.3580	0.3452	0.3256	0.3537	0.3412	0.3649	0.3836	0.3333	0.3625	0.3494	0.3947	0.4306	0.4133	0.3671	0.4000	0.3846	0.4384	0.4783	0.4583	0.5556	0.2973	0.4730	0.5313	0.4605	0.4605
90f	0.3929	0.3793	0.4938	0.5325	0.5125	0.3708	0.4000	0.3864	0.3293	0.3457	0.3483	0.3765	0.3636	0.3412	0.3704	0.3571	0.3182	0.3452	0.3333	0.3294	0.3580	0.3452	0.4930	0.2683	0.5000	0.4722	0.4512	0.4512
90g	0.4048	0.3908	0.3407	0.3678	0.3556	0.3667	0.3953	0.3820	0.3253	0.3415	0.3444	0.3721	0.3596	0.3372	0.3659	0.3529	0.3146	0.3412	0.3295	0.3256	0.3537	0.3412	0.4861	0.2651	0.5128	0.4658	0.4634	0.5190
90h	0.4321	0.4167	0.3333	0.3605	0.3483	0.3444	0.3721	0.3596	0.3333	0.3500	0.3371	0.3647	0.3523	0.3452	0.3750	0.3614	0.3218	0.3494	0.3372	0.3333	0.3625	0.3494	0.5000	0.2716	0.4872	0.4789	0.4937	0.5946
90i	0.4268	0.4118	0.3297	0.3563	0.3444	0.3407	0.3678	0.3556	0.3293	0.3457	0.3333	0.3605	0.3483	0.3412	0.3704	0.3571	0.3182	0.3452	0.3333	0.3294	0.3580	0.3452	0.4930	0.2683	0.4810	0.4722	0.4875	0.5063
91b	0.2955	0.2857	0.2553	0.2637	0.2553	0.2660	0.2747	0.2660	0.2045	0.2045	0.2447	0.2527	0.2447	0.2333	0.2414	0.2333	0.2021	0.2088	0.2021	0.2222	0.2299	0.2222	0.2875	0.2024	0.3735	0.2875	0.3034	0.3034
91c	0.4487	0.4321	0.3448	0.3571	0.3448	0.3563	0.3690	0.3563	0.3291	0.3291	0.3488	0.3614	0.3488	0.3415	0.3544	0.3415	0.3176	0.3293	0.3176	0.3293	0.3418	0.3293	0.4571	0.2821	0.4675	0.4571	0.4744	0.5753
91d	0.5479	0.5263	0.3448	0.3571	0.3448	0.3563	0.3690	0.3563	0.3291	0.3291	0.3488	0.3614	0.3488	0.3415	0.3544	0.3415	0.3176	0.3293	0.3176	0.3293	0.3418	0.3293	0.4571	0.2821	0.4675	0.4571	0.5753	0.4744
91e	0.3544	0.3415	0.3059	0.3171	0.3059	0.3023	0.3133	0.3023	0.3378	0.3378	0.3095	0.3210	0.3095	0.3684	0.3836	0.3684	0.3590	0.3733	0.3590	0.4507	0.4706	0.4507	0.4769	0.2877	0.4267	0.4769	0.4156	0.4156
91a	0.3699	0.3553	0.3165	0.3289	0.3165	0.3125	0.3247	0.3125	0.3731	0.3731	0.3205	0.3333	0.3205	0.3662	0.3824	0.3662	0.3378	0.3521	0.3378	0.3521	0.3676	0.3521	0.5345	0.3182	0.4493	0.5345	0.4366	0.4366
92a	0.4533	0.4359	0.4304	0.4474	0.4304	0.4250	0.4416	0.4250	0.4429	0.4429	0.4359	0.4533	0.4359	0.4722	0.4928	0.4722	0.4595	0.4789	0.4595	0.4789	0.5000	0.4789	0.4000	0.3151	0.3625	0.4000	0.3537	0.3537
92b	0.5775	0.5541	0.5065	0.5479	0.5263	0.5395	0.5833	0.5600	0.4054	0.4247	0.4935	0.5342	0.5132	0.4342	0.4722	0.4533	0.4231	0.4595	0.4416	0.4400	0.4789	0.4595	0.3836	0.2857	0.4545	0.3649	0.3735	0.3735
92c	0.5833	0.5600	0.4568	0.4935	0.4750	0.4875	0.5263	0.5063	0.3947	0.4133	0.4625	0.5000	0.4810	0.4231	0.4595	0.4416	0.4125	0.4474	0.4304	0.4286	0.4658	0.4474	0.3733	0.2785	0.3735	0.3553	0.3810	0.4684
92d	0.7313	0.7000	0.4458	0.4810	0.4634	0.4756	0.5128	0.4938	0.3846	0.4026	0.4512	0.4872	0.4691	0.4304	0.4667	0.4487	0.4024	0.4359	0.4198	0.4177	0.4533	0.4359	0.4000	0.2716	0.3976	0.3816	0.4937	0.4048
67	0.3718	0.3580	0.3373	0.3333	0.3214	0.3333	0.3293	0.3176	0.3944	0.3750	0.3415	0.3375	0.3253	0.3867	0.3836	0.3684	0.3590	0.3553	0.3418	0.3733	0.3699	0.3553	0.5484	0.3239	0.5286	0.6271	0.5139	0.5139
66	0.4571	0.3816	0.3590	0.4110	0.3418	0.3544	0.4054	0.3375	0.4242	0.4030	0.3636	0.4167	0.3462	0.4143	0.4769	0.3944	0.3836	0.4412	0.3649	0.4000	0.4615	0.3803	0.5965	0.3485	0.5000	0.5965	0.4857	0.4857
31	0.3026	0.2911	0.3733	0.2987	0.2875	0.3684	0.2949	0.2840	0.4444	0.3382	0.3784	0.3026	0.2911	0.4118	0.3286	0.3151	0.4000	0.3194	0.3067	0.4179	0.3333	0.3194	0.3538	0.5926	0.3200	0.3750	0.3117	0.3117
90j	0.3974	0.3827	0.3452	0.3580	0.3452	0.3412	0.3537	0.3412	0.3836	0.3836	0.3494	0.3625	0.3494	0.3947	0.4110	0.3947	0.3671	0.3816	0.3671	0.3816	0.3973	0.3816	0.5556	0.3151	0.4932	0.5556	0.4800	0.4800
36	0.3611	0.3467	0.3077	0.3200	0.3077	0.3038	0.3158	0.3038	0.3636	0.3636	0.3117	0.3243	0.3117	0.3571	0.3731	0.3571	0.3288	0.3429	0.3288	0.3429	0.3582	0.3429	0.5536	0.3281	0.4627	0.5536	0.4493	0.4493
33	0.4225	0.6250	0.3462	0.3784	0.5672	0.3418	0.3733	0.5588	0.4091	0.6909	0.3506	0.3836	0.5758	0.4000	0.4394	0.6610	0.3699	0.4058	0.6129	0.3857	0.4242	0.6441	0.6364	0.3333	0.5075	0.6071	0.4928	0.4928
35	0.3250	0.3133	0.2791	0.2892	0.2791	0.2759	0.2857	0.2759	0.2895	0.2895	0.2824	0.2927	0.2824	0.3038	0.3158	0.3038	0.2805	0.2911	0.2805	0.2911	0.3026	0.2911	0.4394	0.2917	0.4133	0.4394	0.4026	0.4026
25	0.5738	0.3944	0.3889	0.5645	0.3889	0.3836	0.5556	0.3836	0.4667	0.4667	0.3944	0.5738	0.3944	0.4308	0.6364	0.4308	0.4179	0.6140	0.4179	0.4375	0.6481	0.4375	0.4912	0.4821	0.3913	0.4655	0.3803	0.3803
23	0.3803	0.3649	0.5938	0.3750	0.3600	0.5846	0.3699	0.3553	0.7308	0.4286	0.6032	0.3803	0.3649	0.6667	0.4154	0.3971	0.6441	0.4030	0.3857	0.6786	0.4219	0.4030	0.4500	0.6038	0.4627	0.5536	0.4493	0.4493

Compound	88f	88e	88i	88h	88j	79p	89h	89i	89g	86a	86b	86c	86d	86e	84a	84b	84c	84d	84e	89a	89b	89c	8	89e	89f	90a	90b	90c
79m	0.3418	0.3803	0.3590	0.3462	0.3375	0.6786	0.3205	0.3333	0.3125	0.4030	0.4000	0.3889	0.3784	0.3733	0.3289	0.3205	0.3125	0.3049	0.3012	0.3810	0.3378	0.3289	0.3289	0.3380	0.3165	0.4444	0.3836	0.3733
93	0.6269	0.7119	0.6269	0.6364	0.6176	0.3857	0.4324	0.4267	0.4211	0.3472	0.3289	0.3205	0.3462	0.3086	0.2840	0.2619	0.2558	0.2791	0.2472	0.5254	0.4571	0.4444	0.4444	0.4627	0.4267	0.5667	0.4857	0.4722
25	0.5211	0.5873	0.5211	0.5286	0.5139	0.4545	0.4384	0.4324	0.4267	0.3333	0.3333	0.3247	0.3506	0.3125	0.2716	0.2651	0.2588	0.2824	0.2500	0.5345	0.4638	0.4507	0.4507	0.4697	0.4324	0.6034	0.5147	0.5000
54	0.3494	0.3506	0.3494	0.3537	0.3452	0.6129	0.3293	0.3253	0.3214	0.3699	0.4054	0.3947	0.3846	0.3797	0.3210	0.3293	0.3214	0.3140	0.3103	0.3478	0.3462	0.3375	0.3375	0.3117	0.3253	0.4058	0.3896	0.3797
79k	0.3418	0.3803	0.3418	0.3462	0.3375	0.6786	0.3205	0.3165	0.3125	0.4030	0.4000	0.3889	0.3784	0.3733	0.3289	0.3205	0.3125	0.3049	0.3012	0.3810	0.3378	0.3289	0.3289	0.3380	0.3165	0.4444	0.3836	0.3733
79q	0.3590	0.4203	0.3590	0.3636	0.3544	0.6207	0.3377	0.3333	0.3291	0.3623	0.3611	0.3514	0.3421	0.3377	0.2949	0.2875	0.2805	0.2738	0.2706	0.3810	0.3562	0.3467	0.3467	0.3768	0.3333	0.4444	0.4028	0.3919
79t	0.3418	0.3803	0.3418	0.3462	0.3375	0.6207	0.3205	0.3165	0.3125	0.3429	0.3425	0.3333	0.3247	0.3205	0.2785	0.2716	0.2651	0.2588	0.2558	0.3810	0.3378	0.3289	0.3289	0.3380	0.3165	0.4677	0.4028	0.3919
79u	0.3293	0.3649	0.3293	0.3333	0.3253	0.5645	0.3086	0.3049	0.3012	0.3288	0.3289	0.3205	0.3125	0.3086	0.2683	0.2619	0.2558	0.2500	0.2472	0.3636	0.3247	0.3165	0.3165	0.3243	0.3049	0.4462	0.3867	0.3766
79z	0.3951	0.3636	0.3780	0.3827	0.4074	0.5538	0.3580	0.3537	0.3827	0.3289	0.4583	0.3718	0.3625	0.3750	0.2857	0.3750	0.3023	0.2955	0.3068	0.3429	0.4521	0.3671	0.3671	0.3247	0.3704	0.4000	0.5000	0.4103
79r	0.3418	0.3803	0.3418	0.3462	0.3375	0.5932	0.3205	0.3165	0.3125	0.3429	0.3425	0.3333	0.3247	0.3205	0.2785	0.2716	0.2651	0.2588	0.2558	0.3810	0.3378	0.3289	0.3289	0.3380	0.3165	0.4444	0.3836	0.3733
79s	0.3375	0.3750	0.3375	0.3418	0.3333	0.7273	0.3165	0.3125	0.3086	0.3971	0.3944	0.3836	0.3733	0.3684	0.3247	0.3165	0.3086	0.3012	0.2976	0.3750	0.3333	0.3247	0.3247	0.3333	0.3125	0.4375	0.3784	0.3684
79n	0.3457	0.3836	0.3625	0.3500	0.3415	0.7321	0.3250	0.3375	0.3171	0.4478	0.4429	0.4306	0.4189	0.4133	0.3684	0.3590	0.3500	0.3415	0.3373	0.3636	0.3421	0.3333	0.3333	0.3425	0.3210	0.4242	0.3867	0.3766
79x	0.3529	0.3544	0.3855	0.3902	0.3647	0.6613	0.3659	0.3614	0.3412	0.4110	0.5507	0.5571	0.5417	0.4545	0.3580	0.4545	0.4615	0.4500	0.3765	0.3333	0.3671	0.3750	0.3750	0.3165	0.3294	0.3889	0.4103	0.4177
79o	0.3500	0.3889	0.3500	0.3544	0.3457	0.9200	0.3291	0.3250	0.3210	0.4545	0.4493	0.4366	0.4247	0.4189	0.3733	0.3636	0.3544	0.3457	0.3415	0.3692	0.3467	0.3377	0.3377	0.3472	0.3250	0.4308	0.3919	0.3816
79v	0.3571	0.3590	0.3902	0.3951	0.3690	0.6721	0.3704	0.3659	0.3452	0.4167	0.5588	0.5652	0.5493	0.4605	0.3797	0.4800	0.4868	0.4744	0.3976	0.3380	0.3718	0.3797	0.3797	0.3205	0.3333	0.3944	0.4156	0.4231
79l	0.3415	0.3784	0.3415	0.3457	0.3373	0.7193	0.3210	0.3171	0.3133	0.4412	0.4366	0.4247	0.4133	0.4079	0.3816	0.3718	0.3625	0.3537	0.3494	0.3582	0.3377	0.3291	0.3291	0.3378	0.3171	0.4179	0.3816	0.3718
79y	0.3448	0.3457	0.3929	0.5065	0.4048	0.6406	0.4805	0.3690	0.3810	0.4000	0.4533	0.5634	0.4487	0.4074	0.3494	0.3735	0.4684	0.3721	0.3371	0.3243	0.3580	0.4545	0.3659	0.3086	0.3218	0.3784	0.4000	0.5000
80a	0.4000	0.4444	0.4000	0.4051	0.3951	0.4925	0.3133	0.3095	0.3059	0.6129	0.4247	0.4133	0.4026	0.3974	0.5070	0.3457	0.3373	0.3294	0.3256	0.3478	0.3291	0.3210	0.3210	0.3289	0.3095	0.3857	0.3544	0.3457
79a	0.3580	0.3973	0.3580	0.3625	0.3537	0.7193	0.3210	0.3171	0.3133	0.6333	0.4366	0.4247	0.4133	0.4079	0.5217	0.3544	0.3457	0.3373	0.3333	0.3582	0.3377	0.3291	0.3291	0.3378	0.3171	0.4179	0.3816	0.3718
82a	0.3452	0.3816	0.3452	0.3494	0.3412	0.5075	0.3095	0.3059	0.3023	0.6032	0.4189	0.4079	0.3974	0.3924	0.5000	0.3415	0.3333	0.3256	0.3218	0.3429	0.3250	0.3171	0.3171	0.3247	0.3059	0.4000	0.3671	0.3580
80a	0.4500	0.4211	0.4321	0.4375	0.4625	0.4648	0.3452	0.3412	0.3690	0.4247	0.6364	0.5278	0.5135	0.4868	0.3704	0.5270	0.4375	0.4268	0.4048	0.3288	0.4342	0.3537	0.3537	0.3125	0.3571	0.3649	0.4605	0.3780
79b	0.3951	0.3636	0.3780	0.3827	0.4074	0.6833	0.3580	0.3537	0.3827	0.4225	0.6667	0.5507	0.5352	0.5068	0.3671	0.5493	0.4545	0.4430	0.4198	0.3429	0.4521	0.3671	0.3671	0.3247	0.3704	0.4000	0.5000	0.4103
82b	0.3810	0.3500	0.3647	0.3690	0.3929	0.4857	0.3452	0.3412	0.3690	0.4054	0.6364	0.5278	0.5135	0.4868	0.3537	0.5270	0.4375	0.4268	0.4048	0.3288	0.4342	0.3537	0.3537	0.3125	0.3571	0.3836	0.4800	0.3951
80c	0.4048	0.4103	0.4568	0.5395	0.4691	0.4521	0.4375	0.3647	0.3765	0.4133	0.5278	0.6471	0.5200	0.4375	0.3614	0.4375	0.5395	0.4337	0.3636	0.3200	0.3537	0.4487	0.3614	0.3049	0.3182	0.3553	0.3780	0.4744
79c	0.3529	0.3544	0.4024	0.4805	0.4146	0.6613	0.4545	0.3780	0.3902	0.4110	0.5507	0.6769	0.5417	0.4545	0.3580	0.4545	0.5616	0.4500	0.3765	0.3333	0.3671	0.4667	0.3750	0.3165	0.3294	0.3889	0.4103	0.5135
82c	0.3409	0.3415	0.3882	0.4625	0.4000	0.4722	0.4375	0.3647	0.3765	0.3947	0.5278	0.6471	0.5200	0.4375	0.3452	0.4375	0.5395	0.4337	0.3636	0.3200	0.3537	0.4487	0.3614	0.3049	0.3182	0.3733	0.3951	0.4935
80d	0.4286	0.4359	0.4634	0.4691	0.4405	0.4400	0.3765	0.3721	0.3523	0.4026	0.5135	0.5200	0.6571	0.4268	0.3529	0.4268	0.4337	0.5513	0.3556	0.3467	0.3780	0.3855	0.4744	0.3293	0.3409	0.3816	0.4024	0.4096
89d	0.3765	0.3797	0.4096	0.4146	0.3882	0.6406	0.3902	0.3855	0.3647	0.4000	0.5352	0.5417	0.6866	0.4430	0.3494	0.4430	0.4500	0.5733	0.3678	0.3611	0.3924	0.4000	0.4933	0.3418	0.3529	0.4167	0.4359	0.4430
82d	0.3636	0.3659	0.3953	0.4000	0.3750	0.4595	0.3765	0.3721	0.3523	0.3846	0.5135	0.5200	0.6571	0.4268	0.3372	0.4268	0.4337	0.5513	0.3556	0.3467	0.3780	0.3855	0.4744	0.3293	0.3409	0.4000	0.4198	0.4268
80e	0.5714	0.3951	0.3908	0.3953	0.4023	0.4342	0.3111	0.3077	0.3187	0.3974	0.4868	0.4375	0.4268	0.6620	0.3488	0.4048	0.3636	0.3556	0.5570	0.3077	0.3571	0.3182	0.3182	0.2941	0.4691	0.3418	0.3810	0.3409
79e	0.5128	0.3415	0.3409	0.3448	0.3523	0.6308	0.3218	0.3182	0.3295	0.3947	0.5068	0.4545	0.4430	0.6912	0.3452	0.4198	0.3765	0.3678	0.5789	0.3200	0.3704	0.3294	0.3294	0.3049	0.4872	0.3733	0.4125	0.3690
82e	0.4938	0.3294	0.3297	0.3333	0.3407	0.4533	0.3111	0.3077	0.3187	0.3797	0.4868	0.4375	0.4268	0.6620	0.3333	0.4048	0.3636	0.3556	0.5570	0.3077	0.3571	0.3182	0.3182	0.2941	0.4691	0.3590	0.3976	0.3563
80f	0.4353	0.3902	0.4023	0.4070	0.4302	0.4286	0.3222	0.3187	0.3444	0.3924	0.5200	0.4684	0.4568	0.4691	0.3448	0.4337	0.3908	0.3820	0.3933	0.3038	0.3690	0.3295	0.3295	0.2907	0.3483	0.3375	0.3929	0.3523
79f	0.3837	0.3373	0.3523	0.3563	0.3793	0.6212	0.3333	0.3295	0.3563	0.3896	0.5417	0.4868	0.4744	0.4872	0.3412	0.4500	0.4048	0.3953	0.4070	0.3158	0.3827	0.3412	0.3412	0.3012	0.3605	0.3684	0.4250	0.3810
82f	0.3708	0.3256	0.3407	0.3444	0.3667	0.4474	0.3222	0.3187	0.3444	0.3750	0.5200	0.4684	0.4568	0.4691	0.3295	0.4337	0.3908	0.3820	0.3933	0.3038	0.3690	0.3295	0.3295	0.2907	0.3483	0.3544	0.4096	0.3678
80k	0.3974	0.4429	0.3974	0.4026	0.3924	0.4478	0.3086	0.3049	0.3012	0.4058	0.3836	0.3733	0.3636	0.3590	0.3333	0.3086	0.3012	0.2941	0.2907	0.3636	0.3247	0.3165	0.3165	0.3243	0.3049	0.4030	0.3506	0.3418
82k	0.3293	0.3649	0.3293	0.3333	0.3253	0.4697	0.3086	0.3049	0.3012	0.3857	0.3836	0.3733	0.3636	0.3590	0.3165	0.3086	0.3012	0.2941	0.2907	0.3636	0.3247	0.3165	0.3165	0.3243	0.3049	0.4242	0.3684	0.3590
80g	0.4118	0.4000	0.3953	0.4000	0.4070	0.4400	0.3146	0.3111	0.3222	0.4026	0.4737	0.4430	0.4321	0.4444	0.3529	0.3929	0.3678	0.3596	0.3708	0.3117	0.3452	0.3218	0.3218	0.2976	0.3258	0.3462	0.3690	0.3448
79g	0.3605	0.3457	0.3448	0.3488	0.3563	0.6406	0.3256	0.3218	0.3333	0.4000	0.4932	0.4605	0.4487	0.4615	0.3494	0.4074	0.3810	0.3721	0.3837	0.3243	0.3580	0.3333	0.3333	0.3086	0.3372	0.3784	0.4000	0.3735
82g	0.3483	0.3333	0.3333	0.3371	0.3444	0.4595	0.3146	0.3111	0.3222	0.3846	0.4737	0.4430	0.4321	0.4444	0.3372	0.3929	0.3678	0.3596	0.3708	0.3117	0.3452	0.3218	0.3218	0.2976	0.3258	0.3636	0.3855	0.3605
80h	0.4074	0.4722	0.4074	0.4125	0.4024	0.4783	0.3214	0.3176	0.3140	0.4366	0.4133	0.4026	0.4103	0.3875	0.3625	0.3373	0.3294	0.3372	0.3182	0.3571	0.3375	0.3293	0.3293	0.3553	0.3176	0.3944	0.3625	0.3537
79h	0.3537	0.4110	0.3537	0.3580	0.3494	0.7069	0.3333	0.3293	0.3253	0.4348	0.4306	0.4189	0.4267	0.4026	0.3590	0.3500	0.3415	0.3494	0.3294	0.3731	0.3506	0.3418	0.3418	0.3699	0.3293	0.4328	0.3947	0.3846
82h	0.3412	0.3947	0.3412	0.3452	0.3372	0.5000	0.3214	0.3176	0.3140	0.4167	0.4133	0.4026	0.4103	0.3875	0.3457	0.3373	0.3294	0.3372	0.3182	0.3571	0.3375	0.3293	0.3293	0.3553	0.3176	0.4143	0.3797	0.3704
80i	0.3810	0.4400	0.3810	0.3855	0.3765	0.4648	0.2989	0.2955	0.2921	0.4247	0.4026	0.3924	0.3827	0.3780	0.3537	0.3294	0.3218	0.3146	0.3111	0.3288	0.3133	0.3059	0.3059	0.3291	0.2955	0.3649	0.3373	0.3294
79i	0.3294	0.3816	0.3294	0.3333	0.3256	0.6833	0.3095	0.3059	0.3023	0.4225	0.4189	0.4079	0.3974	0.3924	0.3500	0.3415	0.3333	0.3256	0.3218	0.3429	0.3250	0.3171	0.3171	0.3421	0.3059	0.4000	0.3671	0.3580
82i	0.3182	0.3671	0.3182	0.3218	0.3146	0.4857	0.2989	0.2955	0.2921	0.4054	0.4026	0.3924	0.3827	0.3780	0.3373	0.3294	0.3218	0.3146	0.3111	0.3288	0.3133	0.3059	0.3059	0.3291	0.2955	0.3836	0.3537	0.3452
80j	0.3951	0.5217	0.3951	0.4000	0.3902	0.4853	0.3095	0.3059	0.3023	0.4429	0.4189	0.4079	0.3974	0.3924	0.3671	0.3415	0.3333	0.3256	0.3218	0.3429	0.3250	0.3171	0.3171	0.3973	0.3059	0.3803	0.3500	0.3415
79j	0.3415	0.4571	0.3415	0.3457	0.3373	0.7193	0.3210	0.3171	0.3133	0.4412	0.4366	0.4247	0.4133	0.4079	0.3636	0.3544	0.3457	0.3373	0.3333	0.3582	0.3377	0.3291	0.3291	0.4143	0.3171	0.4179	0.3816	0.3718
82j	0.3294	0.4384	0.3294	0.3333	0.3256	0.5075	0.3095	0.3059	0.3023	0.4225	0.4189	0.4079	0.3974	0.3924	0.3500	0.3415	0.3333	0.3256	0.3218	0.3429	0.3250	0.3171	0.3171	0.3973	0.3059	0.4000	0.3671	0.3580
32	0.4722	0.5313	0.4722	0.4789	0.4658	0.4242	0.4507	0.4444	0.4384	0.3429	0.3425	0.3333	0.3600	0.3205	0.2785	0.2716	0.2651	0.2892	0.2558	0.5536	0.4776	0.4638	0.4638	0.4844	0.4444	0.6250	0.5303	0.5147
30	0.3000	0.3333	0.3000	0.3038	0.2963	0.3143	0.2785	0.2750	0.2716	0.3143	0.2973	0.2895	0.2821	0.2785	0.2857	0.2625	0.2561	0.2500	0.2471	0.3281	0.2933	0.2857	0.2857	0.2917	0.2750	0.3284	0.2857	0.2785
88b	0.7727	0.7031	0.8000	0.7059	0.8154	0.3636	0.4615	0.4935	0.5065	0.3291	0.4342	0.3537	0.3780	0.3571	0.2874	0.3571	0.2889	0.3111	0.2935	0.4627	0.6176	0.5135	0.5135	0.4324	0.4935	0.5000	0.6000	0.5000
88a	0.6563	0.7500	0.6563	0.6667	0.6462	0.4030	0.4507	0.4444	0.4384	0.3623	0.3425	0.3333	0.3600	0.3205	0.2949	0.2716	0.2651	0.2892	0.2558	0.5536	0.4776	0.4638	0.4638	0.4844	0.4444	0.5965	0.5075	0.4928
88d	0.7000	0.6818	0.8030	0.7101	0.7391	0.3544	0.4684	0.5000	0.4568	0.3210	0.3537	0.3614	0.4744	0.3182	0.2809	0.2889	0.2967	0.3953	0.2604	0.4493	0.5135	0.5200	0.6286	0.4211	0.4444	0.4857	0.5000	0.5065
88c	0.7000	0.6818	0.8308	0.8438	0.8182	0.3544	0.5676	0.5195	0.5128	0.3210	0.3537	0.4487	0.3855	0.3182	0.2809	0.2889	0.3721	0.3187	0.2604	0.4493	0.5135	0.6286	0.5200	0.4211	0.4444	0.4857	0.5000	0.6111
88f	1.0000	0.6522	0.6712	0.6351	0.6849	0.3415	0.4167	0.4286	0.4405	0.3095	0.3571	0.3182	0.3409	0.4691	0.2717	0.2935	0.2604	0.2813	0.3933	0.4306	0.4935	0.4444	0.4444	0.4051	0.6438	0.4658	0.5000	0.4512
88e	0.6522	1.0000	0.6522	0.7121	0.6429	0.3784	0.4416	0.4177	0.4125	0.3421	0.3250	0.3171	0.3415	0.3059	0.2824	0.2614	0.2556	0.2778	0.2473	0.4844	0.4459	0.4342	0.4342	0.5846	0.4177	0.5231	0.4730	0.4605
88i	0.6712	0.6522	1.0000	0.7042	0.7324	0.3415	0.4691	0.6438	0.4578	0.3095	0.3412	0.3647	0.3721	0.3077	0.2717	0.2796	0.3011	0.3085	0.2525	0.4306	0.4935	0.5195	0.5000	0.4051	0.4286	0.4658	0.4810	0.5063
88h	0.6351	0.7121	0.7042	1.0000	0.7183	0.3457	0.6389	0.4691	0.4815	0.3133	0.3452	0.4375	0.3765	0.3111	0.2747	0.2826	0.3636	0.3118	0.2551	0.4366	0.4615	0.5676	0.4684	0.4286	0.4167	0.4722	0.4872	0.5946
88j	0.6849	0.6429	0.7324	0.7183	1.0000	0.3373	0.4815	0.4578	0.6486	0.3059	0.3690	0.3765	0.3523	0.3187	0.2688	0.3043	0.3118	0.2917	0.2626	0.4247	0.5065	0.5128	0.4568	0.4000	0.4405	0.4595	0.5128	0.5190
79p	0.3415	0.3784	0.3415	0.3457	0.3373	1.0000	0.3210	0.3171	0.3133	0.4412	0.4366	0.4247	0.4133	0.4079	0.3636	0.3544	0.3457	0.3373	0.3333	0.3582	0.3377	0.3291	0.3291	0.3378	0.3171	0.4179	0.3816	0.3718
89h	0.4167	0.4416	0.4691	0.6389	0.4815	0.3210	1.0000	0.6957	0.7101	0.3896	0.4416	0.5479	0.4744	0.3976	0.2527	0.2747	0.3563	0.3043	0.2474	0.6393	0.6970	0.8387	0.7015	0.6875	0.6250	0.4444	0.4615	0.5676
89i	0.4286	0.4177	0.6438	0.4691	0.4578	0.3171	0.6957	1.0000	0.7246	0.3846	0.4359	0.4615	0.4684	0.3929	0.2500	0.2717	0.2935	0.3011	0.2449	0.6290	0.7937	0.8254	0.7969	0.6269	0.6620	0.4384	0.4557	0.4810
89g	0.4405	0.4125	0.4578	0.4815	0.6486	0.3133	0.7101	0.7246	1.0000	0.3797	0.4675	0.4744	0.4444	0.4048	0.2473	0.2967	0.3043	0.2842	0.2551	0.6190	0.8095	0.8125	0.7313	0.6176	0.6761	0.4324	0.4872	0.4937
86a	0.3095	0.3421	0.3095	0.3133	0.3059	0.4412	0.3896	0.3846	0.3797	1.0000	0.6721	0.6508	0.6308	0.6212	0.4789	0.3210	0.3133	0.3059	0.3023	0.4677	0.4110	0.4000	0.4000	0.4348	0.3846	0.3380	0.3125	0.3049
86b	0.3571	0.3250	0.3412	0.3452	0.3690	0.4366	0.4416	0.4359	0.4675	0.6721	1.0000	0.8305	0.8033	0.7619	0.3457	0.5205	0.4304	0.4198	0.3976	0.4394	0.5507	0.4533	0.4533	0.4110	0.4545	0.3378	0.4342	0.3537
86c	0.3182	0.3171	0.3647	0.4375	0.3765	0.4247	0.5479	0.4615	0.4744	0.6508	0.8305	1.0000	0.8065	0.6866	0.3373	0.4304	0.5333	0.4268	0.3563	0.4265	0.4533	0.5634	0.4605	0.4000	0.4074	0.3289	0.3537	0.4487
86d	0.3409	0.3415	0.3721	0.3765	0.3523	0.4133	0.4744	0.4684	0.4444	0.6308	0.8033	0.8065	1.0000	0.6667	0.3294	0.4198	0.4268	0.5455	0.3483	0.4559	0.4800	0.4868	0.5915	0.4267	0.4321	0.3553	0.3780	0.3855
86e	0.4691	0.3059	0.3077	0.3111	0.3187	0.4079	0.3976	0.3929	0.4048	0.6212	0.7619	0.6866	0.6667	1.0000	0.3256	0.3976	0.3563	0.3483	0.5513	0.4085	0.4545	0.4074	0.4074	0.3846	0.5811	0.3165	0.3571	0.3182
84a	0.2717	0.2824	0.2717	0.2747	0.2688	0.3636	0.2527	0.2500	0.2473	0.4789	0.3457	0.3373	0.3294	0.3256	1.0000	0.7273	0.7059	0.6857	0.6761	0.2564	0.2644	0.2584	0.2584	0.2471	0.2500	0.2750	0.2727	0.2667
84b	0.2935	0.2614	0.2796	0.2826	0.3043	0.3544	0.2747	0.2717	0.2967	0.3210	0.5205	0.4304	0.4198	0.3976	0.7273	1.0000	0.8438	0.8182	0.7794	0.2500	0.3494	0.2809	0.2809	0.2414	0.2857	0.2683	0.3571	0.2889
84c	0.2604	0.2556	0.3011	0.3636	0.3118	0.3457	0.3563	0.2935	0.3043	0.3133	0.4304	0.5333	0.4268	0.3563	0.7059	0.8438	1.0000	0.8209	0.7083	0.2439	0.2809	0.3647	0.2889	0.2360	0.2526	0.2619	0.2889	0.3721
84d	0.2813	0.2778	0.3085	0.3118	0.2917	0.3373	0.3043	0.3011	0.2842	0.3059	0.4198	0.4268	0.5455	0.3483	0.6857	0.8182	0.8209	1.0000	0.6892	0.2683	0.3034	0.3111	0.3882	0.2584	0.2737	0.2857	0.3111	0.3187
84e	0.3933	0.2473	0.2525	0.2551	0.2626	0.3333	0.2474	0.2449	0.2551	0.3023	0.3976	0.3563	0.3483	0.5513	0.6761	0.7794	0.7083	0.6892	1.0000	0.2353	0.2857	0.2526	0.2526	0.2283	0.3864	0.2529	0.2935	0.2604
89a	0.4306	0.4844	0.4306	0.4366	0.4247	0.3582	0.6393	0.6290	0.6190	0.4677	0.4394	0.4265	0.4559	0.4085	0.2564	0.2500	0.2439	0.2683	0.2353	1.0000	0.6842	0.6610	0.6610	0.7358	0.6290	0.5439	0.4627	0.4493
89b	0.4935	0.4459	0.4935	0.4615	0.5065	0.3377	0.6970	0.7937	0.8095	0.4110	0.5507	0.4533	0.4800	0.4545	0.2644	0.3494	0.2809	0.3034	0.2857	0.6842	1.0000	0.8333	0.8333	0.6774	0.7656	0.4706	0.5714	0.4737
89c	0.4444	0.4342	0.5195	0.5676	0.5128	0.3291	0.8387	0.8254	0.8125	0.4000	0.4533	0.5634	0.4868	0.4074	0.2584	0.2809	0.3647	0.3111	0.2526	0.6610	0.8333	1.0000	0.8361	0.6563	0.6912	0.4571	0.4737	0.5833
89d	0.4444	0.4342	0.5000	0.4684	0.4568	0.3291	0.7015	0.7969	0.7313	0.4000	0.4533	0.4605	0.5915	0.4074	0.2584	0.2809	0.2889	0.3882	0.2526	0.6610	0.8333	0.8361	1.0000	0.6563	0.6912	0.4571	0.4737	0.4805
89e	0.4051	0.5846	0.4051	0.4286	0.4000	0.3378	0.6875	0.6269	0.6176	0.4348	0.4110	0.4000	0.4267	0.3846	0.2471	0.2414	0.2360	0.2584	0.2283	0.7358	0.6774	0.6563	0.6563	1.0000	0.6269	0.4769	0.4324	0.4211
89f	0.6438	0.4177	0.4286	0.4167	0.4405	0.3171	0.6250	0.6620	0.6761	0.3846	0.4545	0.4074	0.4321	0.5811	0.2500	0.2857	0.2526	0.2737	0.3864	0.6290	0.7656	0.6912	0.6912	0.6269	1.0000	0.4384	0.4744	0.4268
90a	0.4658	0.5231	0.4658	0.4722	0.4595	0.4179	0.4444	0.4384	0.4324	0.3380	0.3378	0.3289	0.3553	0.3165	0.2750	0.2683	0.2619	0.2857	0.2529	0.5439	0.4706	0.4571	0.4571	0.4769	0.4384	1.0000	0.6721	0.6508
90b	0.5000	0.4730	0.4810	0.4872	0.5128	0.3816	0.4615	0.4557	0.4872	0.3125	0.4342	0.3537	0.3780	0.3571	0.2727	0.3571	0.2889	0.3111	0.2935	0.4627	0.5714	0.4737	0.4737	0.4324	0.4744	0.6721	1.0000	0.8387
90c	0.4512	0.4605	0.5063	0.5946	0.5190	0.3718	0.5676	0.4810	0.4937	0.3049	0.3537	0.4487	0.3855	0.3182	0.2667	0.2889	0.3721	0.3187	0.2604	0.4493	0.4737	0.5833	0.4805	0.4211	0.4268	0.6508	0.8387	1.0000
90d	0.4512	0.4605	0.4875	0.4937	0.4634	0.3718	0.4684	0.4625	0.4390	0.3049	0.3537	0.3614	0.4744	0.3182	0.2667	0.2889	0.2967	0.3953	0.2604	0.4493	0.4737	0.4805	0.5833	0.4211	0.4268	0.6508	0.8387	0.8413
90e	0.4430	0.5821	0.4430	0.4487	0.4375	0.3973	0.4231	0.4177	0.4125	0.3247	0.3250	0.3171	0.3415	0.3059	0.2674	0.2614	0.2556	0.2778	0.2473	0.4844	0.4459	0.4342	0.4342	0.5373	0.4177	0.7069	0.7031	0.6818
90f	0.6267	0.4430	0.4353	0.4405	0.4471	0.3580	0.4167	0.4118	0.4235	0.2941	0.3571	0.3182	0.3409	0.4691	0.2581	0.2935	0.2604	0.2813	0.3933	0.4306	0.4744	0.4268	0.4268	0.4051	0.6000	0.6212	0.7727	0.7000
90g	0.4471	0.4375	0.4643	0.5062	0.6316	0.3537	0.4815	0.4405	0.6053	0.2907	0.3690	0.3765	0.3523	0.3187	0.2553	0.3043	0.3118	0.2917	0.2626	0.4247	0.4872	0.4937	0.4390	0.4000	0.4235	0.6119	0.8154	0.8182
90h	0.4405	0.4487	0.4938	0.6216	0.5062	0.3625	0.5946	0.4691	0.4815	0.2976	0.3452	0.4375	0.3765	0.3111	0.2609	0.2826	0.3636	0.3118	0.2551	0.4366	0.4615	0.5676	0.4684	0.4103	0.4167	0.6308	0.7059	0.8438
90i	0.4353	0.4430	0.6267	0.4938	0.4643	0.3580	0.4691	0.6000	0.4405	0.2941	0.3412	0.3647	0.3721	0.3077	0.2581	0.2796	0.3011	0.3085	0.2525	0.4306	0.4557	0.4810	0.4625	0.4051	0.4118	0.6212	0.8000	0.8308
91b	0.3077	0.2907	0.2935	0.2967	0.3187	0.2159	0.3488	0.3448	0.3721	0.2442	0.3875	0.3140	0.3372	0.3034	0.2128	0.3182	0.2553	0.2766	0.2474	0.3333	0.4359	0.3571	0.3571	0.3333	0.3605	0.2840	0.3735	0.3034
91c	0.4217	0.4286	0.4750	0.5600	0.4875	0.3418	0.6912	0.5890	0.6027	0.4133	0.5068	0.6232	0.5405	0.4375	0.2697	0.3218	0.4096	0.3523	0.2766	0.5714	0.5857	0.7121	0.5915	0.5286	0.5263	0.4507	0.4675	0.5753
91d	0.4217	0.4286	0.4568	0.4625	0.4337	0.3418	0.5753	0.5676	0.5395	0.4133	0.5068	0.5135	0.6522	0.4375	0.2697	0.3218	0.3295	0.4337	0.2766	0.5714	0.5857	0.5915	0.7121	0.5286	0.5263	0.4507	0.4675	0.4744
91e	0.4000	0.5294	0.4000	0.4051	0.3951	0.3514	0.5139	0.5068	0.5000	0.4493	0.4247	0.4133	0.4400	0.3974	0.2588	0.2529	0.2472	0.2697	0.2391	0.6316	0.5441	0.5286	0.5286	0.6833	0.5068	0.4697	0.4267	0.4156
91a	0.4189	0.4697	0.4189	0.4247	0.4133	0.3676	0.5455	0.5373	0.5294	0.4762	0.4478	0.4348	0.4638	0.4167	0.2658	0.2593	0.2530	0.2771	0.2442	0.7200	0.5806	0.5625	0.5625	0.6207	0.5373	0.5254	0.4493	0.4366
92a	0.3412	0.3766	0.3412	0.3452	0.3372	0.5000	0.3059	0.3023	0.2989	0.5938	0.4133	0.4026	0.3924	0.3875	0.4932	0.3373	0.3294	0.3218	0.3182	0.3380	0.3210	0.3133	0.3133	0.3205	0.3023	0.6500	0.4730	0.4605
92b	0.3765	0.3457	0.3605	0.3647	0.3882	0.4789	0.3412	0.3372	0.3647	0.4000	0.6269	0.5205	0.5067	0.4805	0.3494	0.5200	0.4321	0.4217	0.4000	0.3243	0.4286	0.3494	0.3494	0.3086	0.3529	0.6190	0.6000	0.5000
92c	0.3371	0.3373	0.3837	0.4568	0.3953	0.4658	0.4321	0.3605	0.3721	0.3896	0.5205	0.6377	0.5132	0.4321	0.3412	0.4321	0.5325	0.4286	0.3596	0.3158	0.3494	0.4430	0.3571	0.3012	0.3146	0.6000	0.5000	0.6111
92d	0.3596	0.3614	0.3908	0.3953	0.3708	0.4533	0.3721	0.3678	0.3483	0.3797	0.5067	0.5132	0.6479	0.4217	0.3333	0.4217	0.4286	0.5443	0.3516	0.3421	0.3735	0.3810	0.4684	0.3253	0.3371	0.6308	0.5263	0.5325
67	0.4933	0.5522	0.4933	0.5000	0.4868	0.3699	0.4156	0.4103	0.4051	0.3158	0.3165	0.3086	0.3333	0.2976	0.2588	0.2529	0.2472	0.2697	0.2391	0.5000	0.4384	0.4267	0.4267	0.4429	0.4103	0.5397	0.4658	0.4533
66	0.4658	0.5231	0.4658	0.4722	0.4595	0.4615	0.4444	0.4384	0.4324	0.3380	0.3378	0.3289	0.3553	0.3165	0.2750	0.2683	0.2619	0.2857	0.2529	0.5439	0.4706	0.4571	0.4571	0.4769	0.4384	0.5862	0.5000	0.4857
31	0.3000	0.3333	0.3000	0.3038	0.2963	0.3333	0.2785	0.2750	0.2716	0.3143	0.2973	0.2895	0.2821	0.2785	0.2857	0.2625	0.2561	0.2500	0.2471	0.3281	0.2933	0.2857	0.2857	0.2917	0.2750	0.3485	0.3026	0.2949
90j	0.4615	0.5143	0.4615	0.4675	0.4557	0.3973	0.4231	0.4177	0.4125	0.3973	0.3250	0.3171	0.3415	0.3059	0.3293	0.2614	0.2556	0.2778	0.2473	0.4844	0.4459	0.4342	0.4342	0.4507	0.4177	0.7069	0.7031	0.6818
36	0.4306	0.4844	0.4306	0.4366	0.4247	0.3582	0.5625	0.5538	0.5455	0.6250	0.5833	0.5645	0.5968	0.5385	0.2564	0.2500	0.2439	0.2683	0.2353	0.7500	0.6000	0.5806	0.5806	0.6429	0.5538	0.5439	0.4627	0.4493
33	0.4722	0.5313	0.4722	0.4789	0.4658	0.4242	0.4507	0.4444	0.4384	0.3429	0.3425	0.3333	0.3600	0.3205	0.2785	0.2716	0.2651	0.2892	0.2558	0.5536	0.4776	0.4638	0.4638	0.4844	0.4444	0.6250	0.5303	0.5147
35	0.3875	0.4110	0.3875	0.3924	0.3827	0.3026	0.3846	0.3797	0.3750	0.2692	0.2875	0.2805	0.3049	0.2706	0.6825	0.6615	0.6418	0.6716	0.6143	0.4154	0.4054	0.3947	0.3947	0.3889	0.3797	0.4328	0.4133	0.4026
25	0.3649	0.4091	0.3649	0.3699	0.3600	0.6481	0.3425	0.3378	0.3333	0.3692	0.3676	0.3571	0.3472	0.3425	0.2973	0.2895	0.2821	0.2750	0.2716	0.4138	0.3623	0.3521	0.3521	0.3636	0.3378	0.4828	0.4118	0.4000
23	0.4306	0.4844	0.4306	0.4366	0.4247	0.4219	0.3333	0.3289	0.3247	0.3788	0.3571	0.3472	0.3378	0.3333	0.3067	0.2821	0.2750	0.2683	0.2651	0.4000	0.3521	0.3425	0.3425	0.3529	0.3289	0.4426	0.3803	0.3699

Compound	90d	90e	90f	90g	90h	90i	91b	91c	91d	91e	91a	92a	92b	92c	92d	67	66	31	90j	36	33	35	25	23
79m	0.3733	0.4000	0.3590	0.3544	0.3636	0.3766	0.2118	0.3421	0.3421	0.3521	0.3906	0.4627	0.4429	0.4306	0.4189	0.3913	0.4918	0.3538	0.4000	0.3810	0.4516	0.3014	0.7000	0.4500
93	0.4722	0.5075	0.4533	0.4474	0.4595	0.4533	0.2771	0.4384	0.4384	0.4559	0.5082	0.3836	0.3506	0.3418	0.3671	0.7368	0.5667	0.3582	0.5303	0.5254	0.5763	0.4203	0.4426	0.5254
25	0.5000	0.5385	0.4795	0.4730	0.4861	0.4795	0.2805	0.4444	0.4444	0.4627	0.5167	0.3889	0.3733	0.3636	0.3896	0.7500	0.5763	0.3433	0.5385	0.5345	0.6140	0.4265	0.5263	0.4355
54	0.3797	0.3684	0.3659	0.3614	0.3704	0.3659	0.2247	0.3500	0.3500	0.3247	0.3571	0.4247	0.4459	0.4342	0.4231	0.3600	0.4478	0.3239	0.3684	0.3478	0.4118	0.2949	0.6250	0.4091
79k	0.3733	0.4000	0.3590	0.3544	0.3636	0.3590	0.2118	0.3421	0.3421	0.3521	0.3906	0.4627	0.4429	0.4306	0.4189	0.3913	0.4918	0.3538	0.4000	0.3810	0.4516	0.3014	0.7000	0.4500
79q	0.3919	0.4412	0.3766	0.3718	0.3816	0.3766	0.2262	0.3421	0.3421	0.3714	0.3692	0.4203	0.4028	0.3919	0.3816	0.3913	0.4918	0.3538	0.4203	0.3810	0.4516	0.3194	0.7000	0.4500
79t	0.3919	0.4203	0.3766	0.3718	0.3816	0.3766	0.1977	0.3247	0.3247	0.3333	0.3692	0.4203	0.4028	0.3919	0.3816	0.3913	0.4918	0.3538	0.4203	0.3810	0.4516	0.3014	0.7000	0.4500
79u	0.3766	0.4028	0.3625	0.3580	0.3671	0.3625	0.1910	0.3125	0.3125	0.3200	0.3529	0.4028	0.3867	0.3766	0.3671	0.3750	0.4688	0.3382	0.4028	0.3636	0.4308	0.2895	0.6604	0.4286
79z	0.4103	0.3816	0.4125	0.4250	0.4000	0.3951	0.2941	0.3625	0.3625	0.3205	0.3333	0.3816	0.5000	0.4103	0.4000	0.3553	0.4412	0.3194	0.3816	0.3429	0.4058	0.3077	0.6140	0.4030
79r	0.3733	0.4000	0.3590	0.3544	0.3636	0.3590	0.1977	0.3247	0.3247	0.3333	0.3692	0.4000	0.3836	0.3733	0.3636	0.3913	0.4918	0.3538	0.4000	0.3810	0.4516	0.3014	0.7000	0.4500
79s	0.3684	0.3944	0.3544	0.3500	0.3590	0.3544	0.2093	0.3377	0.3377	0.3472	0.3846	0.4559	0.4366	0.4247	0.4133	0.3857	0.4839	0.3485	0.3944	0.3750	0.4444	0.2973	0.6863	0.4426
79n	0.3766	0.4028	0.3625	0.3580	0.3671	0.3797	0.2184	0.3462	0.3462	0.3562	0.3731	0.5075	0.4857	0.4722	0.4595	0.3750	0.4688	0.3382	0.4028	0.3636	0.4308	0.3067	0.6604	0.4286
79x	0.4177	0.3718	0.3690	0.3810	0.4074	0.4024	0.2727	0.4231	0.4231	0.3291	0.3425	0.4658	0.5942	0.6000	0.5833	0.3462	0.4286	0.3108	0.3718	0.3333	0.3944	0.3000	0.5932	0.3913
79o	0.3816	0.4085	0.3671	0.3625	0.3718	0.3671	0.2209	0.3506	0.3506	0.3611	0.3788	0.5152	0.4928	0.4789	0.4658	0.3803	0.4762	0.3433	0.4085	0.3692	0.4375	0.3108	0.6731	0.4355
79v	0.4231	0.3766	0.3735	0.3855	0.4125	0.4074	0.2759	0.4286	0.4286	0.3333	0.3472	0.4722	0.6029	0.6087	0.5915	0.3506	0.4348	0.3151	0.3766	0.3380	0.4000	0.3205	0.6034	0.3971
79l	0.3718	0.3973	0.3580	0.3537	0.3625	0.3580	0.2159	0.3418	0.3418	0.3514	0.3676	0.5000	0.4789	0.4658	0.4533	0.3699	0.4615	0.3333	0.3973	0.3582	0.4242	0.3200	0.6481	0.4219
79y	0.4074	0.3625	0.3605	0.4217	0.5263	0.4096	0.2391	0.4675	0.3780	0.3375	0.3333	0.4533	0.4933	0.6056	0.4872	0.3375	0.4167	0.3026	0.3625	0.3243	0.3836	0.2927	0.5738	0.3803
80a	0.3457	0.3684	0.3333	0.3294	0.3373	0.3333	0.2111	0.3333	0.3333	0.3421	0.3571	0.6508	0.4459	0.4342	0.4231	0.3784	0.4058	0.4242	0.4444	0.3478	0.3913	0.2949	0.4444	0.6909
79a	0.3718	0.3973	0.3580	0.3537	0.3625	0.3580	0.2159	0.3418	0.3418	0.3514	0.3676	0.7000	0.4789	0.4658	0.4533	0.3699	0.4615	0.3529	0.4783	0.3582	0.4242	0.3026	0.6481	0.4444
82a	0.3580	0.3816	0.3452	0.3412	0.3494	0.3452	0.2088	0.3293	0.3293	0.3377	0.3521	0.6667	0.4595	0.4474	0.4359	0.3553	0.3803	0.3380	0.4583	0.3429	0.6441	0.2911	0.4375	0.4242
80a	0.3780	0.3500	0.3810	0.3929	0.3690	0.3647	0.3294	0.4000	0.4000	0.3250	0.3378	0.4595	0.6567	0.5479	0.5333	0.3590	0.3836	0.4000	0.3671	0.3288	0.3699	0.2963	0.4179	0.6441
79b	0.4103	0.3816	0.4125	0.4250	0.4000	0.3951	0.3415	0.4156	0.4156	0.3377	0.3521	0.4789	0.7143	0.5942	0.5775	0.3553	0.4412	0.3194	0.3816	0.3429	0.4058	0.3077	0.6140	0.4030
82b	0.3951	0.3671	0.3976	0.4096	0.3855	0.3810	0.3294	0.4000	0.4000	0.3250	0.3378	0.4595	0.6818	0.5694	0.5541	0.3418	0.3649	0.3067	0.3671	0.3288	0.6129	0.2963	0.4179	0.3857
80c	0.3855	0.3415	0.3409	0.4000	0.4625	0.3882	0.2637	0.5000	0.4074	0.3171	0.3289	0.4474	0.5479	0.6667	0.5395	0.3500	0.3733	0.3889	0.3580	0.3200	0.3600	0.2892	0.4058	0.6230
79c	0.4177	0.3718	0.3690	0.4321	0.5000	0.4198	0.2727	0.5205	0.4231	0.3291	0.3425	0.4658	0.5942	0.7231	0.5833	0.3462	0.4286	0.3108	0.3718	0.3333	0.3944	0.3000	0.5932	0.3913
82c	0.4024	0.3580	0.3563	0.4167	0.4810	0.4048	0.2637	0.5000	0.4074	0.3171	0.3289	0.4474	0.5694	0.6912	0.5600	0.3333	0.3553	0.2987	0.3580	0.3200	0.5938	0.2892	0.4058	0.3750
80d	0.5000	0.3659	0.3636	0.3750	0.4000	0.3953	0.2857	0.4321	0.5263	0.3415	0.3553	0.4359	0.5333	0.5395	0.6761	0.3750	0.4000	0.3784	0.3827	0.3467	0.3867	0.3133	0.3944	0.6032
89d	0.5405	0.3974	0.3929	0.4048	0.4321	0.4268	0.2955	0.4487	0.5479	0.3544	0.3699	0.4533	0.5775	0.5833	0.7313	0.3718	0.4571	0.3026	0.3974	0.3611	0.4225	0.3250	0.5738	0.3803
82d	0.5195	0.3827	0.3793	0.3908	0.4167	0.4118	0.2857	0.4321	0.5263	0.3415	0.3553	0.4359	0.5541	0.5600	0.7000	0.3580	0.3816	0.2911	0.3827	0.3467	0.6250	0.3133	0.3944	0.3649
80e	0.3409	0.3294	0.4938	0.3407	0.3333	0.3297	0.2553	0.3448	0.3448	0.3059	0.3165	0.4304	0.5065	0.4568	0.4458	0.3373	0.3590	0.3733	0.3452	0.3077	0.3462	0.2791	0.3889	0.5938
79e	0.3690	0.3580	0.5325	0.3678	0.3605	0.3563	0.2637	0.3571	0.3571	0.3171	0.3289	0.4474	0.5479	0.4935	0.4810	0.3333	0.4110	0.2987	0.3580	0.3200	0.3784	0.2892	0.5645	0.3750
82e	0.3563	0.3452	0.5125	0.3556	0.3483	0.3444	0.2553	0.3448	0.3448	0.3059	0.3165	0.4304	0.5263	0.4750	0.4634	0.3214	0.3418	0.2875	0.3452	0.3077	0.5672	0.2791	0.3889	0.3600
80f	0.3523	0.3256	0.3708	0.3667	0.3444	0.3407	0.2660	0.3563	0.3563	0.3023	0.3125	0.4250	0.5395	0.4875	0.4756	0.3333	0.3544	0.3684	0.3412	0.3038	0.3418	0.2759	0.3836	0.5846
79f	0.3810	0.3537	0.4000	0.3953	0.3721	0.3678	0.2747	0.3690	0.3690	0.3133	0.3247	0.4416	0.5833	0.5263	0.5128	0.3293	0.4054	0.2949	0.3537	0.3158	0.3733	0.2857	0.5556	0.3699
82f	0.3678	0.3412	0.3864	0.3820	0.3596	0.3556	0.2660	0.3563	0.3563	0.3023	0.3125	0.4250	0.5600	0.5063	0.4938	0.3176	0.3375	0.2840	0.3412	0.3038	0.5588	0.2759	0.3836	0.3553
80k	0.3418	0.3649	0.3293	0.3253	0.3333	0.3293	0.2045	0.3291	0.3291	0.3378	0.3731	0.4429	0.4054	0.3947	0.3846	0.3944	0.4242	0.4444	0.3836	0.3636	0.4091	0.2895	0.4667	0.7308
82k	0.3590	0.3836	0.3457	0.3415	0.3500	0.3457	0.2045	0.3291	0.3291	0.3378	0.3731	0.4429	0.4247	0.4133	0.4026	0.3750	0.4030	0.3382	0.3836	0.3636	0.6909	0.2895	0.4667	0.4286
80g	0.3448	0.3333	0.3483	0.3444	0.3371	0.3333	0.2447	0.3488	0.3488	0.3095	0.3205	0.4359	0.4935	0.4625	0.4512	0.3415	0.3636	0.3784	0.3494	0.3117	0.3506	0.2824	0.3944	0.6032
79g	0.3735	0.3625	0.3765	0.3721	0.3647	0.3605	0.2527	0.3614	0.3614	0.3210	0.3333	0.4533	0.5342	0.5000	0.4872	0.3375	0.4167	0.3026	0.3625	0.3243	0.3836	0.2927	0.5738	0.3803
82g	0.3605	0.3494	0.3636	0.3596	0.3523	0.3483	0.2447	0.3488	0.3488	0.3095	0.3205	0.4359	0.5132	0.4810	0.4691	0.3253	0.3462	0.2911	0.3494	0.3117	0.5758	0.2824	0.3944	0.3649
80h	0.3537	0.3947	0.3412	0.3372	0.3452	0.3412	0.2333	0.3415	0.3415	0.3684	0.3662	0.4722	0.4342	0.4231	0.4304	0.3867	0.4143	0.4118	0.3947	0.3571	0.4000	0.3038	0.4308	0.6667
79h	0.3846	0.4306	0.3704	0.3659	0.3750	0.3704	0.2414	0.3544	0.3544	0.3836	0.3824	0.4928	0.4722	0.4595	0.4667	0.3836	0.4769	0.3286	0.4110	0.3731	0.4394	0.3158	0.6364	0.4154
82h	0.3704	0.4133	0.3571	0.3529	0.3614	0.3571	0.2333	0.3415	0.3415	0.3684	0.3662	0.4722	0.4533	0.4416	0.4487	0.3684	0.3944	0.3151	0.3947	0.3571	0.6610	0.3038	0.4308	0.3971
80i	0.3294	0.3671	0.3182	0.3146	0.3218	0.3182	0.2021	0.3176	0.3176	0.3590	0.3378	0.4595	0.4231	0.4125	0.4024	0.3590	0.3836	0.4000	0.3671	0.3288	0.3699	0.2805	0.4179	0.6441
79i	0.3580	0.4000	0.3452	0.3412	0.3494	0.3452	0.2088	0.3293	0.3293	0.3733	0.3521	0.4789	0.4595	0.4474	0.4359	0.3553	0.4412	0.3194	0.3816	0.3429	0.4058	0.2911	0.6140	0.4030
82i	0.3452	0.3846	0.3333	0.3295	0.3372	0.3333	0.2021	0.3176	0.3176	0.3590	0.3378	0.4595	0.4416	0.4304	0.4198	0.3418	0.3649	0.3067	0.3671	0.3288	0.6129	0.2805	0.4179	0.3857
80j	0.3415	0.4384	0.3294	0.3256	0.3333	0.3294	0.2222	0.3293	0.3293	0.4507	0.3521	0.4789	0.4400	0.4286	0.4177	0.3733	0.4000	0.4179	0.3816	0.3429	0.3857	0.2911	0.4375	0.6786
79j	0.3718	0.4783	0.3580	0.3537	0.3625	0.3580	0.2299	0.3418	0.3418	0.4706	0.3676	0.5000	0.4789	0.4658	0.4533	0.3699	0.4615	0.3333	0.3973	0.3582	0.4242	0.3026	0.6481	0.4219
82j	0.3580	0.4583	0.3452	0.3412	0.3494	0.3452	0.2222	0.3293	0.3293	0.4507	0.3521	0.4789	0.4595	0.4474	0.4359	0.3553	0.3803	0.3194	0.3816	0.3429	0.6441	0.2911	0.4375	0.4030
32	0.5147	0.5556	0.4930	0.4861	0.5000	0.4930	0.2875	0.4571	0.4571	0.4769	0.5345	0.4000	0.3836	0.3733	0.4000	0.5484	0.5965	0.3538	0.5556	0.5536	0.6364	0.4394	0.4912	0.4500
30	0.2785	0.2973	0.2683	0.2651	0.2716	0.2683	0.2024	0.2821	0.2821	0.2877	0.3182	0.3151	0.2857	0.2785	0.2716	0.3239	0.3485	0.5926	0.3151	0.3281	0.3333	0.2917	0.4821	0.6038
88b	0.5000	0.4730	0.5000	0.5128	0.4872	0.4810	0.3735	0.4675	0.4675	0.4267	0.4493	0.3625	0.4545	0.3735	0.3976	0.5286	0.5000	0.3200	0.4932	0.4627	0.5075	0.4133	0.3913	0.4627
88a	0.4928	0.5313	0.4722	0.4658	0.4789	0.4722	0.2875	0.4571	0.4571	0.4769	0.5345	0.4000	0.3649	0.3553	0.3816	0.6271	0.5965	0.3750	0.5556	0.5536	0.6071	0.4394	0.4655	0.5536
88d	0.6111	0.4605	0.4512	0.4634	0.4937	0.4875	0.3034	0.4744	0.5753	0.4156	0.4366	0.3537	0.3735	0.3810	0.4937	0.5139	0.4857	0.3117	0.4800	0.4493	0.4928	0.4026	0.3803	0.4493
88c	0.5065	0.4605	0.4512	0.5190	0.5946	0.5063	0.3034	0.5753	0.4744	0.4156	0.4366	0.3537	0.3735	0.4684	0.4048	0.5139	0.4857	0.3117	0.4800	0.4493	0.4928	0.4026	0.3803	0.4493
88f	0.4512	0.4430	0.6267	0.4471	0.4405	0.4353	0.3077	0.4217	0.4217	0.4000	0.4189	0.3412	0.3765	0.3371	0.3596	0.4933	0.4658	0.3000	0.4615	0.4306	0.4722	0.3875	0.3649	0.4306
88e	0.4605	0.5821	0.4430	0.4375	0.4487	0.4430	0.2907	0.4286	0.4286	0.5294	0.4697	0.3766	0.3457	0.3373	0.3614	0.5522	0.5231	0.3333	0.5143	0.4844	0.5313	0.4110	0.4091	0.4844
88i	0.4875	0.4430	0.4353	0.4643	0.4938	0.6267	0.2935	0.4750	0.4568	0.4000	0.4189	0.3412	0.3605	0.3837	0.3908	0.4933	0.4658	0.3000	0.4615	0.4306	0.4722	0.3875	0.3649	0.4306
88h	0.4937	0.4487	0.4405	0.5062	0.6216	0.4938	0.2967	0.5600	0.4625	0.4051	0.4247	0.3452	0.3647	0.4568	0.3953	0.5000	0.4722	0.3038	0.4675	0.4366	0.4789	0.3924	0.3699	0.4366
88j	0.4634	0.4375	0.4471	0.6316	0.5062	0.4643	0.3187	0.4875	0.4337	0.3951	0.4133	0.3372	0.3882	0.3953	0.3708	0.4868	0.4595	0.2963	0.4557	0.4247	0.4658	0.3827	0.3600	0.4247
79p	0.3718	0.3973	0.3580	0.3537	0.3625	0.3580	0.2159	0.3418	0.3418	0.3514	0.3676	0.5000	0.4789	0.4658	0.4533	0.3699	0.4615	0.3333	0.3973	0.3582	0.4242	0.3026	0.6481	0.4219
89h	0.4684	0.4231	0.4167	0.4815	0.5946	0.4691	0.3488	0.6912	0.5753	0.5139	0.5455	0.3059	0.3412	0.4321	0.3721	0.4156	0.4444	0.2785	0.4231	0.5625	0.4507	0.3846	0.3425	0.3333
89i	0.4625	0.4177	0.4118	0.4405	0.4691	0.6000	0.3448	0.5890	0.5676	0.5068	0.5373	0.3023	0.3372	0.3605	0.3678	0.4103	0.4384	0.2750	0.4177	0.5538	0.4444	0.3797	0.3378	0.3289
89g	0.4390	0.4125	0.4235	0.6053	0.4815	0.4405	0.3721	0.6027	0.5395	0.5000	0.5294	0.2989	0.3647	0.3721	0.3483	0.4051	0.4324	0.2716	0.4125	0.5455	0.4384	0.3750	0.3333	0.3247
86a	0.3049	0.3247	0.2941	0.2907	0.2976	0.2941	0.2442	0.4133	0.4133	0.4493	0.4762	0.5938	0.4000	0.3896	0.3797	0.3158	0.3380	0.3143	0.3973	0.6250	0.3429	0.2692	0.3692	0.3788
86b	0.3537	0.3250	0.3571	0.3690	0.3452	0.3412	0.3875	0.5068	0.5068	0.4247	0.4478	0.4133	0.6269	0.5205	0.5067	0.3165	0.3378	0.2973	0.3250	0.5833	0.3425	0.2875	0.3676	0.3571
86c	0.3614	0.3171	0.3182	0.3765	0.4375	0.3647	0.3140	0.6232	0.5135	0.4133	0.4348	0.4026	0.5205	0.6377	0.5132	0.3086	0.3289	0.2895	0.3171	0.5645	0.3333	0.2805	0.3571	0.3472
86d	0.4744	0.3415	0.3409	0.3523	0.3765	0.3721	0.3372	0.5405	0.6522	0.4400	0.4638	0.3924	0.5067	0.5132	0.6479	0.3333	0.3553	0.2821	0.3415	0.5968	0.3600	0.3049	0.3472	0.3378
86e	0.3182	0.3059	0.4691	0.3187	0.3111	0.3077	0.3034	0.4375	0.4375	0.3974	0.4167	0.3875	0.4805	0.4321	0.4217	0.2976	0.3165	0.2785	0.3059	0.5385	0.3205	0.2706	0.3425	0.3333
84a	0.2667	0.2674	0.2581	0.2553	0.2609	0.2581	0.2128	0.2697	0.2697	0.2588	0.2658	0.4932	0.3494	0.3412	0.3333	0.2588	0.2750	0.2857	0.3293	0.2564	0.2785	0.6825	0.2973	0.3067
84b	0.2889	0.2614	0.2935	0.3043	0.2826	0.2796	0.3182	0.3218	0.3218	0.2529	0.2593	0.3373	0.5200	0.4321	0.4217	0.2529	0.2683	0.2625	0.2614	0.2500	0.2716	0.6615	0.2895	0.2821
84c	0.2967	0.2556	0.2604	0.3118	0.3636	0.3011	0.2553	0.4096	0.3295	0.2472	0.2530	0.3294	0.4321	0.5325	0.4286	0.2472	0.2619	0.2561	0.2556	0.2439	0.2651	0.6418	0.2821	0.2750
84d	0.3953	0.2778	0.2813	0.2917	0.3118	0.3085	0.2766	0.3523	0.4337	0.2697	0.2771	0.3218	0.4217	0.4286	0.5443	0.2697	0.2857	0.2500	0.2778	0.2683	0.2892	0.6716	0.2750	0.2683
84e	0.2604	0.2473	0.3933	0.2626	0.2551	0.2525	0.2474	0.2766	0.2766	0.2391	0.2442	0.3182	0.4000	0.3596	0.3516	0.2391	0.2529	0.2471	0.2473	0.2353	0.2558	0.6143	0.2716	0.2651
89a	0.4493	0.4844	0.4306	0.4247	0.4366	0.4306	0.3333	0.5714	0.5714	0.6316	0.7200	0.3380	0.3243	0.3158	0.3421	0.5000	0.5439	0.3281	0.4844	0.7500	0.5536	0.4154	0.4138	0.4000
89b	0.4737	0.4459	0.4744	0.4872	0.4615	0.4557	0.4359	0.5857	0.5857	0.5441	0.5806	0.3210	0.4286	0.3494	0.3735	0.4384	0.4706	0.2933	0.4459	0.6000	0.4776	0.4054	0.3623	0.3521
89c	0.4805	0.4342	0.4268	0.4937	0.5676	0.4810	0.3571	0.7121	0.5915	0.5286	0.5625	0.3133	0.3494	0.4430	0.3810	0.4267	0.4571	0.2857	0.4342	0.5806	0.4638	0.3947	0.3521	0.3425
89d	0.5833	0.4342	0.4268	0.4390	0.4684	0.4625	0.3571	0.5915	0.7121	0.5286	0.5625	0.3133	0.3494	0.3571	0.4684	0.4267	0.4571	0.2857	0.4342	0.5806	0.4638	0.3947	0.3521	0.3425
89e	0.4211	0.5373	0.4051	0.4000	0.4103	0.4051	0.3333	0.5286	0.5286	0.6833	0.6207	0.3205	0.3086	0.3012	0.3253	0.4429	0.4769	0.2917	0.4507	0.6429	0.4844	0.3889	0.3636	0.3529
89f	0.4268	0.4177	0.6000	0.4235	0.4167	0.4118	0.3605	0.5263	0.5263	0.5068	0.5373	0.3023	0.3529	0.3146	0.3371	0.4103	0.4384	0.2750	0.4177	0.5538	0.4444	0.3797	0.3378	0.3289
90a	0.6508	0.7069	0.6212	0.6119	0.6308	0.6212	0.2840	0.4507	0.4507	0.4697	0.5254	0.6500	0.6190	0.6000	0.6308	0.5397	0.5862	0.3485	0.7069	0.5439	0.6250	0.4328	0.4828	0.4426
90b	0.8387	0.7031	0.7727	0.8154	0.7059	0.8000	0.3735	0.4675	0.4675	0.4267	0.4493	0.4730	0.6000	0.5000	0.5263	0.4658	0.5000	0.3026	0.7031	0.4627	0.5303	0.4133	0.4118	0.3803
90c	0.8413	0.6818	0.7000	0.8182	0.8438	0.8308	0.3034	0.5753	0.4744	0.4156	0.4366	0.4605	0.5000	0.6111	0.5325	0.4533	0.4857	0.2949	0.6818	0.4493	0.5147	0.4026	0.4000	0.3699
90d	1.0000	0.6818	0.7000	0.7391	0.7101	0.8030	0.3034	0.4744	0.5753	0.4156	0.4366	0.4605	0.5000	0.5065	0.6389	0.4533	0.4857	0.2949	0.6818	0.4493	0.5147	0.4026	0.4000	0.3699
90e	0.6818	1.0000	0.6522	0.6429	0.7121	0.6522	0.2907	0.4286	0.4286	0.5294	0.4697	0.4930	0.4730	0.4605	0.4868	0.4857	0.5231	0.3151	0.7377	0.4844	0.5556	0.4110	0.4308	0.3971
90f	0.7000	0.6522	1.0000	0.6849	0.6351	0.6712	0.3077	0.4217	0.4217	0.4000	0.4189	0.4430	0.5000	0.4512	0.4756	0.4359	0.4658	0.2840	0.6522	0.4306	0.4930	0.3875	0.3836	0.3553
90g	0.7391	0.6429	0.6849	1.0000	0.7183	0.7324	0.3187	0.4875	0.4337	0.3951	0.4133	0.4375	0.5128	0.5190	0.4878	0.4304	0.4595	0.2805	0.6429	0.4247	0.4861	0.3827	0.3784	0.3506
90h	0.7101	0.7121	0.6351	0.7183	1.0000	0.7042	0.2967	0.5600	0.4625	0.4051	0.4247	0.4487	0.4872	0.5946	0.5190	0.4416	0.4722	0.2875	0.6618	0.4366	0.5000	0.3924	0.3889	0.3600
90i	0.8030	0.6522	0.6712	0.7324	0.7042	1.0000	0.2935	0.4750	0.4568	0.4000	0.4189	0.4430	0.4810	0.5063	0.5125	0.4359	0.4658	0.2840	0.6522	0.4306	0.4930	0.3875	0.3836	0.3553
91b	0.3034	0.2907	0.3077	0.3187	0.2967	0.2935	1.0000	0.4744	0.4744	0.3797	0.3600	0.2065	0.3256	0.2609	0.2826	0.2674	0.2840	0.2024	0.2759	0.3333	0.2875	0.3012	0.2099	0.2048
91c	0.4744	0.4286	0.4217	0.4875	0.5600	0.4750	0.4744	1.0000	0.8387	0.6615	0.6557	0.3253	0.3951	0.4935	0.4268	0.4211	0.4507	0.2821	0.4286	0.5714	0.4571	0.3896	0.3472	0.3378
91d	0.5753	0.4286	0.4217	0.4337	0.4625	0.4568	0.4744	0.8387	1.0000	0.6615	0.6557	0.3253	0.3951	0.4024	0.5195	0.4211	0.4507	0.2821	0.4286	0.5714	0.4571	0.3896	0.3472	0.3378
91e	0.4156	0.5294	0.4000	0.3951	0.4051	0.4000	0.3797	0.6615	0.6615	1.0000	0.7273	0.3333	0.3210	0.3133	0.3373	0.4366	0.4697	0.2877	0.4444	0.6316	0.4769	0.3836	0.3582	0.3478
91a	0.4366	0.4697	0.4189	0.4133	0.4247	0.4189	0.3600	0.6557	0.6557	0.7273	1.0000	0.3472	0.3333	0.3247	0.3506	0.4844	0.5254	0.3182	0.4697	0.7200	0.5345	0.4030	0.4000	0.3871
92a	0.4605	0.4930	0.4430	0.4375	0.4487	0.4430	0.2065	0.3253	0.3253	0.3333	0.3472	1.0000	0.7031	0.6818	0.6618	0.3506	0.3750	0.3333	0.5821	0.3380	0.4000	0.2875	0.4308	0.4179
92b	0.5000	0.4730	0.5000	0.5128	0.4872	0.4810	0.3256	0.3951	0.3951	0.3210	0.3333	0.7031	1.0000	0.8387	0.8125	0.3375	0.3600	0.3026	0.4730	0.3243	0.3836	0.2927	0.4118	0.3803
92c	0.5065	0.4605	0.4512	0.5190	0.5946	0.5063	0.2609	0.4935	0.4024	0.3133	0.3247	0.6818	0.8387	1.0000	0.8154	0.3293	0.3506	0.2949	0.4605	0.3158	0.3733	0.2857	0.4000	0.3699
92d	0.6389	0.4868	0.4756	0.4878	0.5190	0.5125	0.2826	0.4268	0.5195	0.3373	0.3506	0.6618	0.8125	0.8154	1.0000	0.3537	0.3766	0.2875	0.4868	0.3421	0.4000	0.3095	0.3889	0.3600
67	0.4533	0.4857	0.4359	0.4304	0.4416	0.4359	0.2674	0.4211	0.4211	0.4366	0.4844	0.3506	0.3375	0.3293	0.3537	1.0000	0.7321	0.3239	0.4857	0.5000	0.5484	0.4028	0.4444	0.4308
66	0.4857	0.5231	0.4658	0.4595	0.4722	0.4658	0.2840	0.4507	0.4507	0.4697	0.5254	0.3750	0.3600	0.3506	0.3766	0.7321	1.0000	0.3485	0.5231	0.5439	0.5965	0.4328	0.5636	0.4667
31	0.2949	0.3151	0.2840	0.2805	0.2875	0.2840	0.2024	0.2821	0.2821	0.2877	0.3182	0.3333	0.3026	0.2949	0.2875	0.3239	0.3485	1.0000	0.3333	0.3281	0.3538	0.2917	0.5091	0.6038
90j	0.6818	0.7377	0.6522	0.6429	0.6618	0.6522	0.2759	0.4286	0.4286	0.4444	0.4697	0.5821	0.4730	0.4605	0.4868	0.4857	0.5231	0.3333	1.0000	0.4844	0.5556	0.4110	0.4308	0.4179
36	0.4493	0.4844	0.4306	0.4247	0.4366	0.4306	0.3333	0.5714	0.5714	0.6316	0.7200	0.3380	0.3243	0.3158	0.3421	0.5000	0.5439	0.3281	0.4844	1.0000	0.5536	0.4154	0.4138	0.4000
33	0.5147	0.5556	0.4930	0.4861	0.5000	0.4930	0.2875	0.4571	0.4571	0.4769	0.5345	0.4000	0.3836	0.3733	0.4000	0.5484	0.5965	0.3538	0.5556	0.5536	1.0000	0.4394	0.4912	0.4500
35	0.4026	0.4110	0.3875	0.3827	0.3924	0.3875	0.3012	0.3896	0.3896	0.3836	0.4030	0.2875	0.2927	0.2857	0.3095	0.4028	0.4328	0.2917	0.4110	0.4154	0.4394	1.0000	0.3235	0.3143
25	0.4000	0.4308	0.3836	0.3784	0.3889	0.3836	0.2099	0.3472	0.3472	0.3582	0.4000	0.4308	0.4118	0.4000	0.3889	0.4444	0.5636	0.5091	0.4308	0.4138	0.4912	0.3235	1.0000	0.6400
23	0.3699	0.3971	0.3553	0.3506	0.3600	0.3553	0.2048	0.3378	0.3378	0.3478	0.3871	0.4179	0.3803	0.3699	0.3600	0.4308	0.4667	0.6038	0.4179	0.4000	0.4500	0.3143	0.6400	1.0000