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NEW SYNTHETIC STRATEGIES INVOLVING DEAROMATIZATION

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Chapter 1: Dearomatization as a Synthetic Tool

1.1 Dearomatization: State of the Art

Aromatic compounds (**1.1**) represent some of the most abundant feedstock chemicals as they are produced annually on a million-metric ton scale by the petrochemical and coal industries. These molecules play a fundamental role in modern society as their derivatives are employed in manufacturing fuels, paints, polymers, pharmaceuticals, and agrochemicals. Despite their widespread application, they remain one of the most inexpensive sources of materials and are extensively used across all areas of molecular sciences. Not surprisingly, the chemistry of these molecules is an exceptionally rich field and is distinctive due to their unique reactivity patterns and inherent stability. One area of particular interest for synthetic organic chemists is that of dearomatizations, transformations capable of converting the aromatic π-system to provide unsaturated, and often functionalized, products. By utilizing arenes as starting materials, dearomative strategies offer rapid access to more complex, value-added, and synthetically versatile intermediates from readily available sources of hydrocarbons. This direct, simplicity-to-complexity synthetic logic is becoming increasingly popular in the fields of natural product synthesis and small-molecule medicinal chemistry, where a high degree of functionality and structural diversity (sp^3-content) is often desired.[1] Despite the strategic use of dearomative methodologies in total synthesis, as they are capable of enabling disconnects otherwise difficult to break, these processes do not introduce significant functional diversity, and most dearomatized compounds require subjection to further manipulations to install the desired level of functionalization.[1–4] Transformations of benzene derivatives that result in permanent loss of aromaticity have since become a cornerstone of synthetic methodology; over the last century, dearomative reactions have revolutionized the way chemists make molecules. Highlighted are some of the principal methodologies that have been developed in this field.[5] These can be classified into several categories including reductive[6], oxidative[4], transition-metal-mediated[7], cycloaddition-based[8] and also enzymatic mediated[9] processes (Figure 1.1). Numerous bioactive compounds and drugs, such as the analgesic morphine (**1.9**)[10], the antifungal agent jesterone (**1.11**)[11], and the antiviral drug oseltamivir (**1.10**)[12], have been obtained using one of these transformations as the key step.

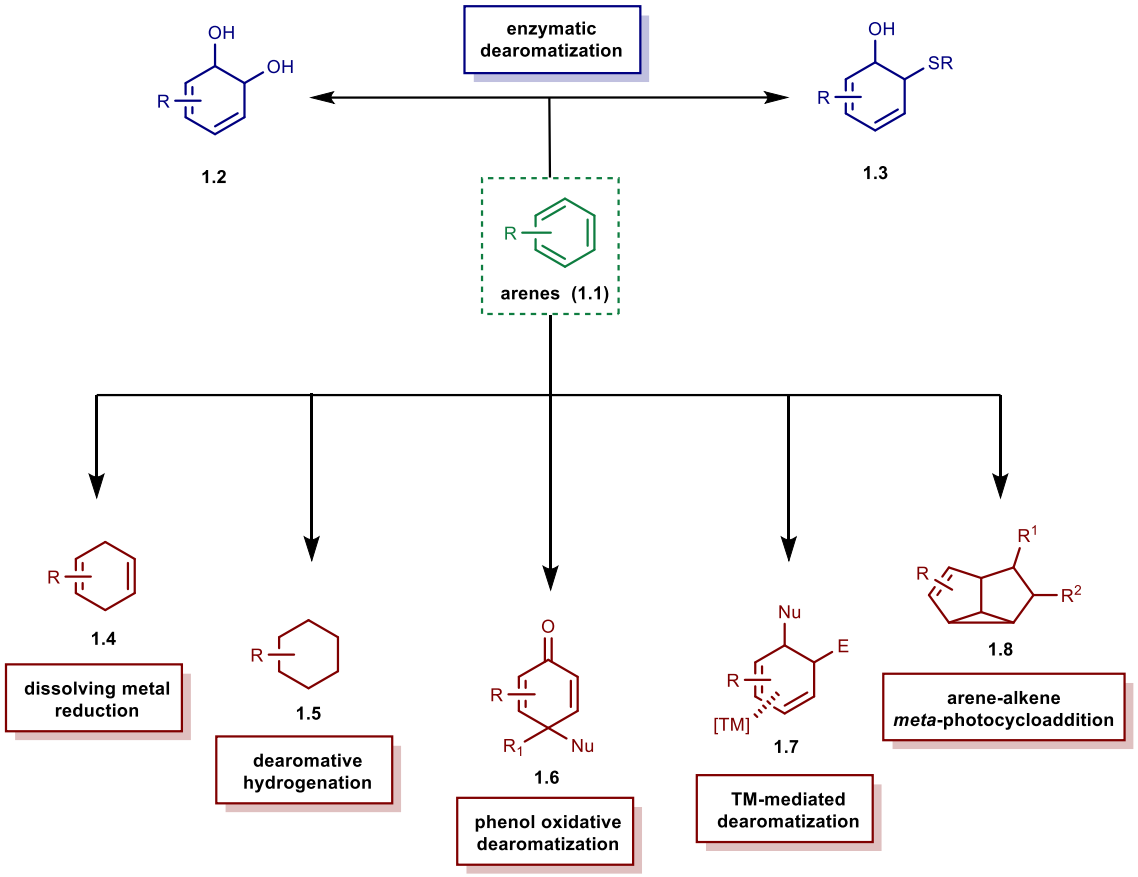

Figure 1.1. Current strategies for arene dearomatization.

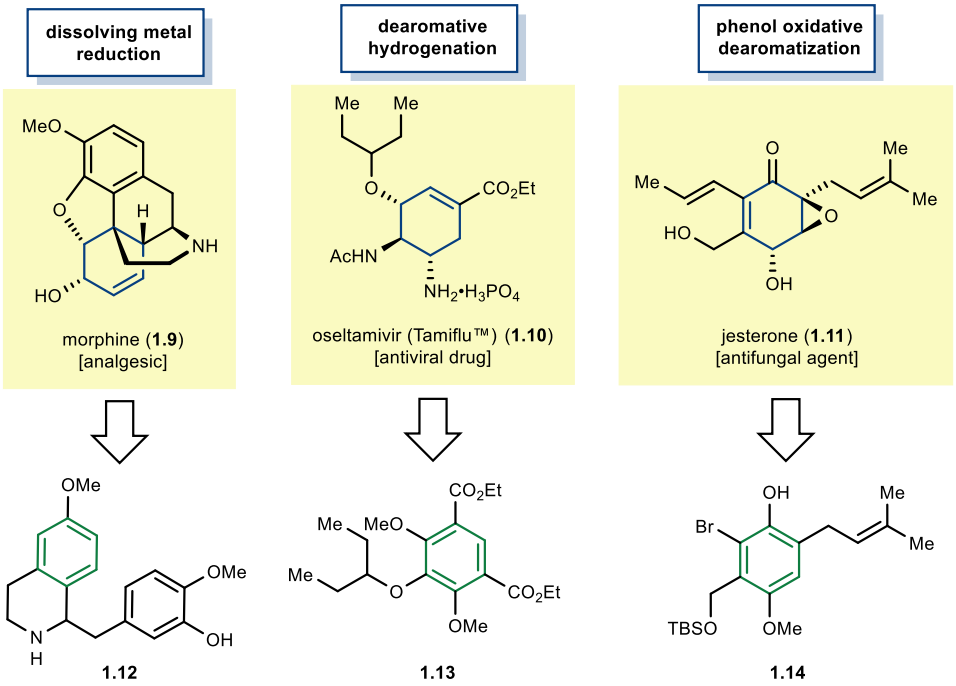

Figure 1.2. Examples of natural products synthesized using dearomatization as a key step.

Heteroaromatic compounds, which possess lower resonance stabilization than carbogenic arenes, have an equally rich canon of robust dearomative transforms, given the inherent

functionalities that they store.[13] Electron-poor heteroarenes such as pyridine (**1.15**) and its polynuclear derivatives (**1.16-1.17**) provide a class of interesting substrates for the synthesis of complex alkaloidal structures. Usually, these compounds need to be activated as pyridinium salts (**1.18**) to be dearomatized with a nucleophile, that attacks either at the C2 or C4 position generating a more reactive dihydropyridine intermediate (**1.19-1.20**) that can be further exploited.[14] Dearomatization of electron-rich arenes such as indole, pyrrole, or furan has also been employed as a key part of complex total synthesis endeavors. For instance, substituted indoles (**1.21**) can generate many indolic alkaloid frameworks through either [3+2]/[4+2] cycloaddition (**1.23**) or stepwise nucleophilic dearomatization at C3 followed by successive trapping at C2 (**1.22**). Pyrrole and furan instead (**1.24**) have been extensively used in intra-molecular Diels–Alder (IMDA) and [4+3] cycloadditions to generate complex ring structures (**1.25-1.27**).[3]

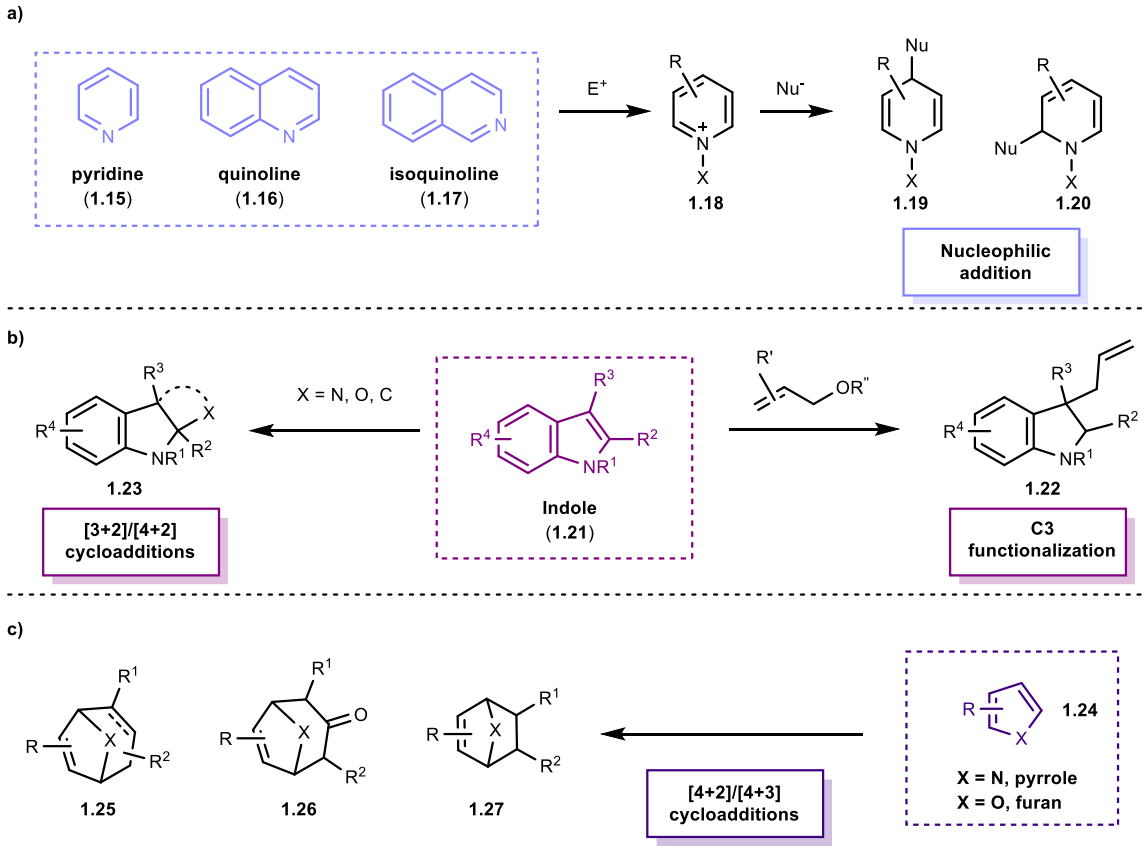

Figure 1.3. Dearomatization of heteroaromatic compounds.

A few examples of natural products synthesized through one of these strategies are shown in Figure 1.4.[15–17]

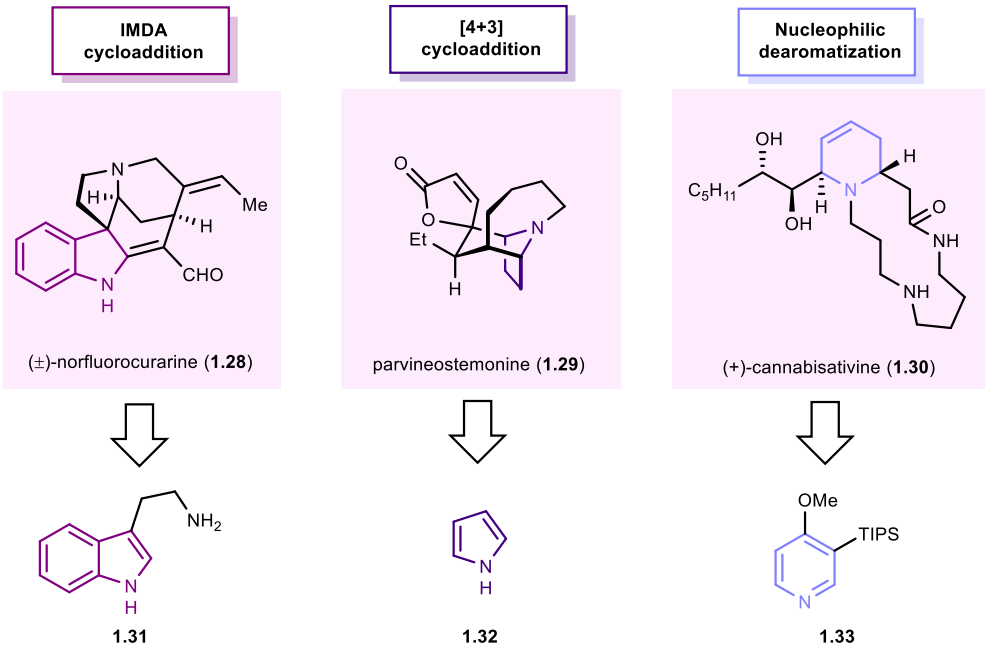

Figure 1.4. Examples of natural products derived from heteroarene dearomatization.

As underlined, these dearomative strategies offer rapid access to more complex, and synthetically useful intermediates from readily available and cheap sources of chemicals. In this dissertation, I will describe our recent efforts to expand the utility of this chemistry. This proposal describes how we intend to build upon our preliminary work in the chemistry of dearomative functionalizations to provide new synthetic pathways to small functionalized molecules. It is our aim to secure a greater understanding of these processes and to provide new synthetic methods, strategies, and functionalization guidelines that will result in the direct conversion of abundant aromatic entities to compounds of higher value.

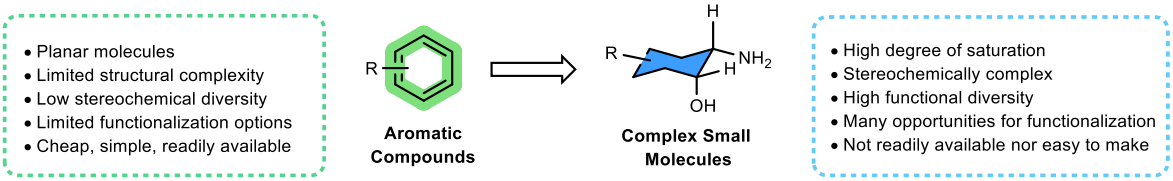

Figure 1.5. Thesis proposal.

For instance, Chapter 2 will focus on the description of the development of a novel programmable dearomative approach for the synthesis of (amino)cyclitols. Chapter 3 will describe instead a divergent synthetic pathway for the synthesis of N-saturated heterocycles isosteres from pyridine.

1.2 References

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Chapter 2: Diversification of Simple Arenes into Complex (Amino) Cyclitols

2.1 Aminocyclitols: Introduction

Aminocyclitols are a class of natural products of significant relevance in medicinal chemistry, as they are structural components of a variety of antibiotics, glycosidase inhibitors, and other families of biologically active compounds. From a structural point of view, aminocyclitols are cycloalkanes containing at least one free or functionalized amino group and a number of additional hydroxy groups on the ring atoms. Because of their close structural relationship with sugars, they are also referred to as aminocarbasugars. These molecules display a remarkable variety of biological activities, going from antidiabetic, antibiotic, or antiviral to antitumoral agents.[1] Representative examples include the α-glucosidase inhibitor voglibose (**2.1**)[2], the anticancer Amaryllidaceae alkaloid pancratistatin (**2.2**)[3], and the potent aminoglycoside antibiotic streptomycin (**2.3**).[4] The notable biological activity of these small yet densely functionalized molecules highlights (amino)cyclitols as privileged motifs in drug design. The biological significance conferred by these structures serves as motivation for the development of synthetic methods to access analogs with improved bioactivity and drug-like qualities. However, the efficient production of small, functionally dense complex molecules still represents a largely unmet challenge. This is typical for the synthesis of such compounds, as the introduction of multiple vicinal functionalities is a lengthy process that often results in an unfavorable step economy.

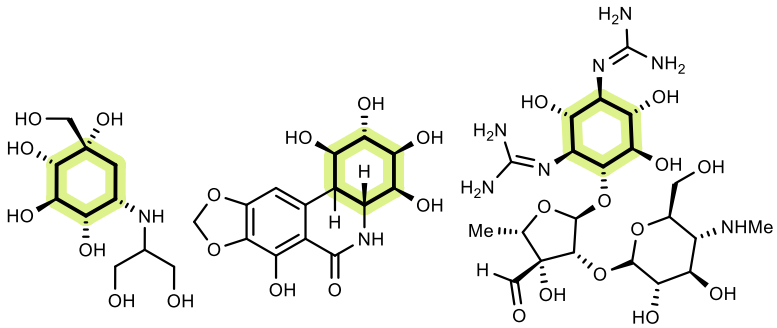

Figure 2.1. Selected aminocyclitol-containing natural products.

2.2 Prior Synthetic Approaches

The synthesis of (amino)cyclitols has been regarded with intense interest by the synthetic community, and recent efforts have culminated in successful campaigns featuring innovative solutions.[5,6] Readily available chiral pool materials (e.g. quinic acid **2.4** and D-glucose **2.6**, Figure 2.2) have become popular heteroatom-rich molecular templates which efficiently provide preinstalled functionality. While the chiral pool strategy obviates the need to install functional groups and/or set stereochemistry, manipulations of the intrinsic functional groups are often arduous. Several general synthetic strategies have emerged along this line and mainly include cyclization, annulation, and dearomatization reactions, both chemical or enzyme-mediated.

2.2.1 Chiral pool

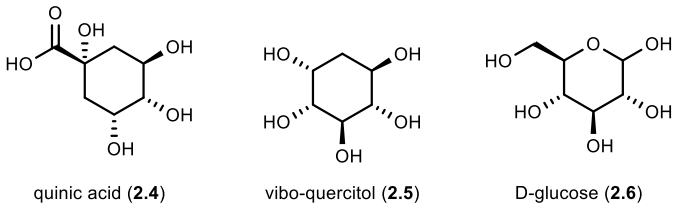

Figure 2.2. Chiral natural sources of starting materials.

Most of the reported syntheses of aminocyclitols make use of the chiral pool as the main source of starting materials. Several natural products containing polyhydroxy cyclohexane skeletons, such as vibo-quercitol (**2.5**) or quinic acid (**2.4**)[7], have frequently been used as starting materials in the synthesis of aminocyclitol derivatives. A classical example, as shown in Figure 2.3, is the synthesis of valiolamine (**2.10**) and related amino-carbasugars from quinic acid.[8] However, carbohydrate derivatives are probably the most common starting materials, due to the well-established protocols for their conversion into suitable functionalized carbocycles.

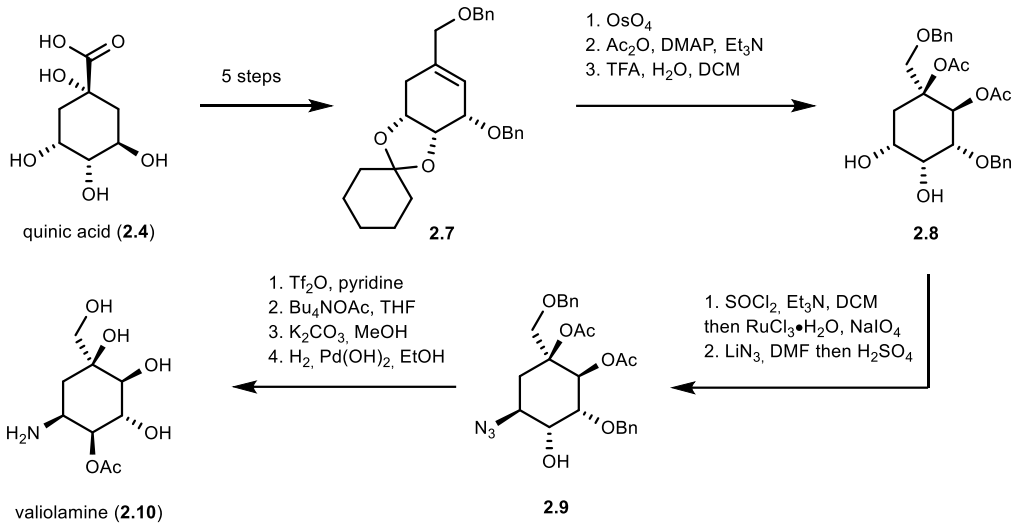

Figure 2.3. Valiolamine synthesis from quinic acid.

2.2.2 Cyclization approaches

The most used strategy within the cyclization-based synthetic approach is clearly ring-closing metathesis. For example, RCM of aminodiene **2.12**, obtained by a multi-step sequence from a suitably protected furanoside **2.11**, afforded conduramine (**2.13**), a key intermediate in the synthesis of diaminocyclitols **2.14** related to 2-deoxystreptamine aminoglycoside antibiotics.[9] Interestingly, by use of a suitable carbohydrate precursor, both enantiomers of the key conduramine intermediate **2.13** can be obtained. In a similar approach, Garner's aldehyde **2.15**, obtained from L-serine by a multistep sequence, has been employed as starting material for the elaboration of aminodiene **2.16.**[10] This precursor was used in RCM reactions to provide amino-cycloalkyl **2.17**, which was further functionalized by diastereoselective olefin dihydroxylation to afford the target aminocyclitol **2.18**. Another strategy worth mentioning is the intramolecular aldol reaction: as a matter of fact, Mukaiyama-type condensation (**2.19** to **2.20**, Figure 2.4) can be used to synthesize such cores.[11] Moreover, chemoenzymatic nitroaldol reaction has been reported within this field.[12]

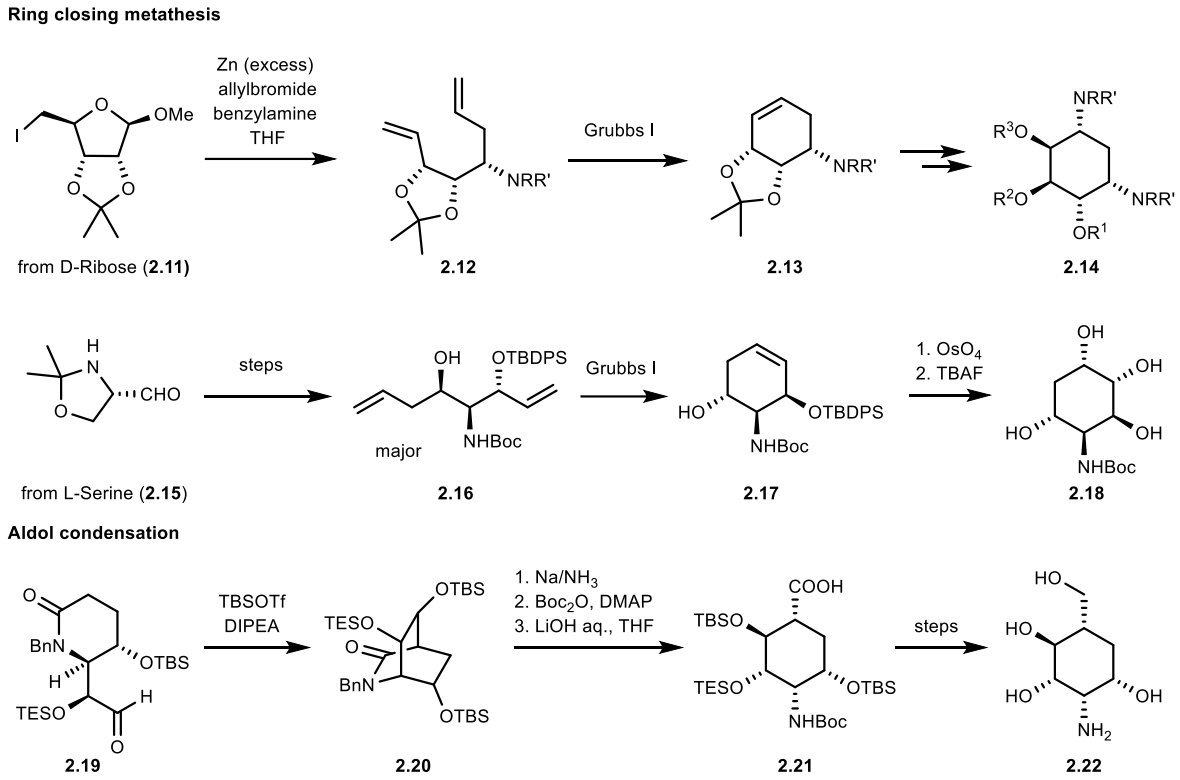

Figure 2.4. Examples of Cyclization approaches for the synthesis of aminocyclitols.

2.2.3 Annulation Approaches

Among annulations, Diels–Alder cycloadditions[13] (Figure 2.5) or nitrile oxide/nitrone–alkene 1,3-intramolecular dipolar cycloadditions (Figure 2.6) represent reliable methods to obtain aminocyclitol cores.[14]

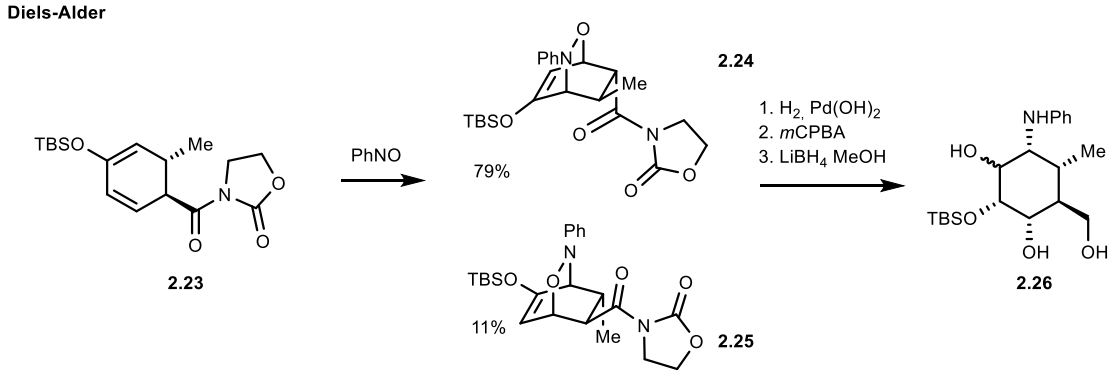

Figure 2.5. Nitroso Diels–Alder cycloaddition towards aminocyclitol core.

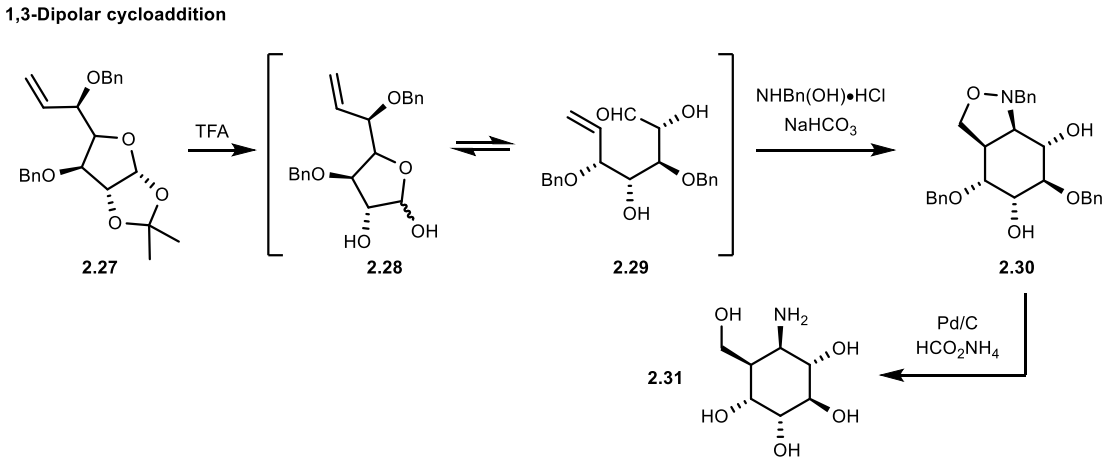

Figure 2.6. 1,3-Dipolar cycloaddition as key step for the synthesis of aminocyclitol core.

2.2.4 Dearomatization Approaches

Dearomatization is included among the synthetic approaches toward the synthesis of aminocyclitols. Except for reductive conditions such as Birch reduction of fully functionalized arenes, the most used strategy in this field is enzymatic-mediated dearomatization, which is usually oxidative in nature. In this way, novel and densely functionalized aminocyclitols were obtained from simple aromatic compounds: for example, the enantioselective synthesis of the aminocyclitol moiety of the antibiotic hygromycin (**2.37**, Figure 2.7) was realized in eight steps and 39% overall yield from homochiral cis-dihydrocatechol **2.33**, achieved from bromobenzene **2.32** with the use of benzene dioxygenase (Figure 2.7).[15] It was found to be the shortest synthesis of the aminocyclitol portion of hygromycin A reported to date and obtained the highest overall yield. Moreover, the toluene dioxygenase enzymatic complex was used within the first enantioselective synthesis of protected aminocyclitol **2.43** using benzyl azide **2.38** as a starting material.[16] Despite the above examples, literature reports demonstrated that the direct formation of aminocyclitols by chemoenzymatic methods is restricted.

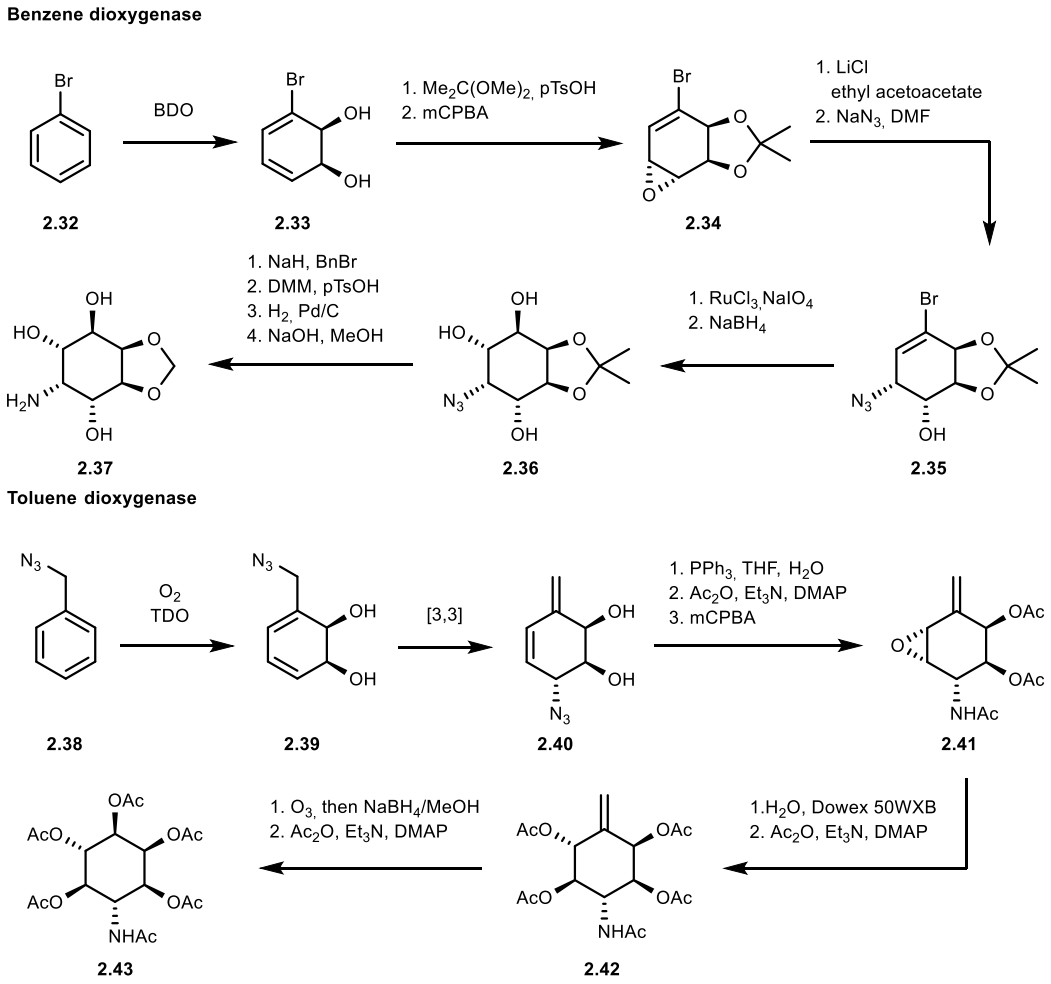

Figure 2.7. Examples of Chemoenzymatic synthesis of aminocyclitols.

2.3 Development of a New Synthetic Strategy

While a number of successful synthetic routes toward these compounds already exist, a general diversification approach to access this stereochemically dense and complex class of molecules is still missing. Herein, we envisioned the use of dearomatized derivatives from arenophile chemistry (**2.45**-**2.47**), which our group has a strong background on, as starting points towards downstream transformations. Starting from simple arenes (**2.44**, Figure 2.8), several guidelines and directions were devised, resulting in the practical and selective preparation of a library of natural and non-natural (amino)cyclitols.

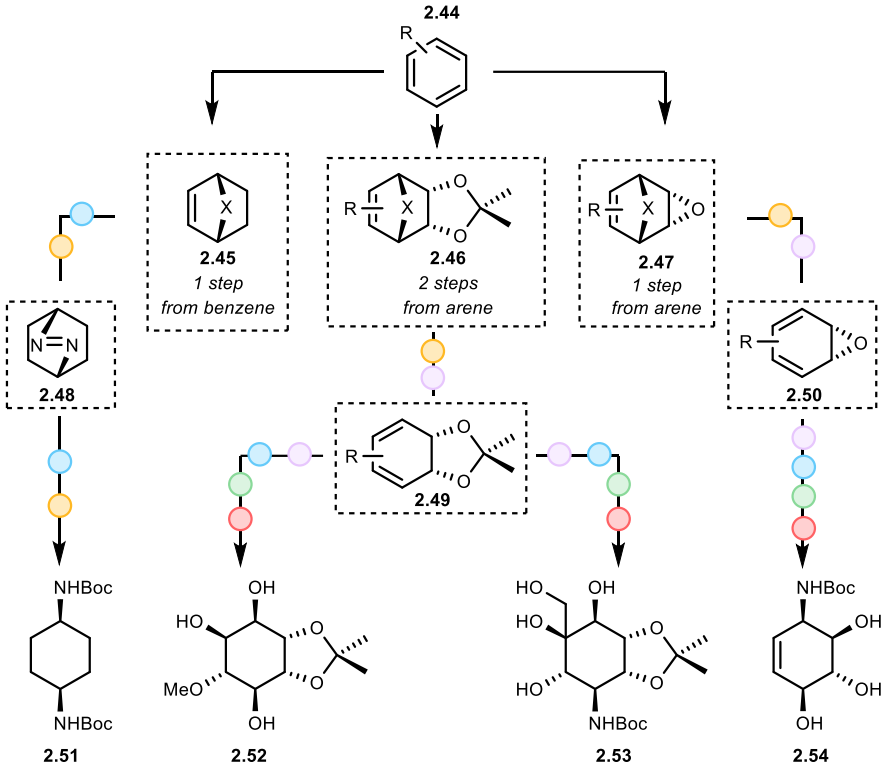

Figure 2.8. Programmable strategy for the synthesis of aminocyclitols from arenes.

2.3.1 Arenophile-Mediated Dearomatization

In the 1980s Sheridan et al. reported that 4-methyl 1,2,4-triazoline-3, dione (MTAD, **2.55**, Figure 2.9) undergoes unusual *para*-selective [4+2] cycloaddition reactions with benzene (**2.58**) or naphthalene (**2.56**) under visible light irradiation at low temperatures.[17,18] The resulting 1,4-cycloadducts (**2.59**-**2.57**) cannot be isolated, as retro-cycloaddition proceeds above –10 °C. Even though several studies have been performed, this process is still mechanistically ambiguous and could occur through multiple reaction trajectories, including photoinduced electron-transfer or charge-transfer complexes between the arene **2.44** and the excited state of the arenophile **2.61**, MTAD.[17,19] These two pathways lead to either excited charge-separated intimate ion radical pair (**2.62**, Figure 2.10), or three-electron stabilized exciplex (**2.63**, Figure 2.10), respectively, both of which can undergo formal cycloaddition reactions. Nevertheless, the energy provided by visible light is sufficient to electronically excite only the arenophile (**2.60**), given its much lower-lying and narrower HOMO-LUMO gap compared to that of the arene (**2.44**). A crucial electronic requirement for the photoreactivity of an arenophile is that both the HOMO and LUMO energies are within the range of the energy of the HOMO of the arene.

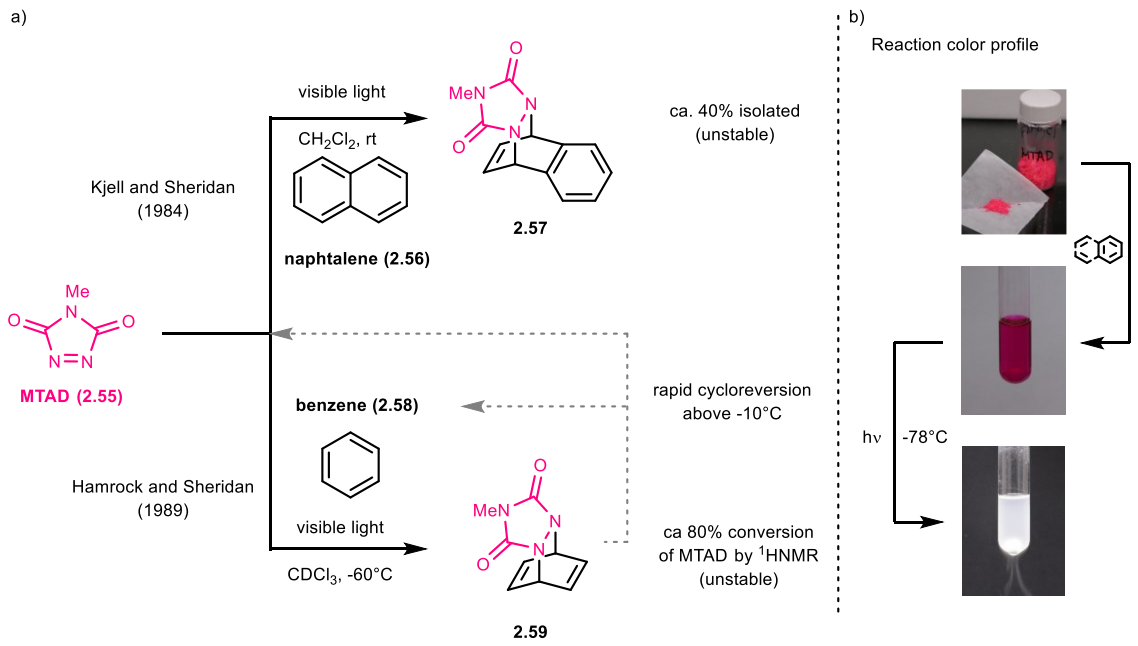

Figure 2.9. Discovery of MTAD-arene cycloaddition and b) Reaction color profile.

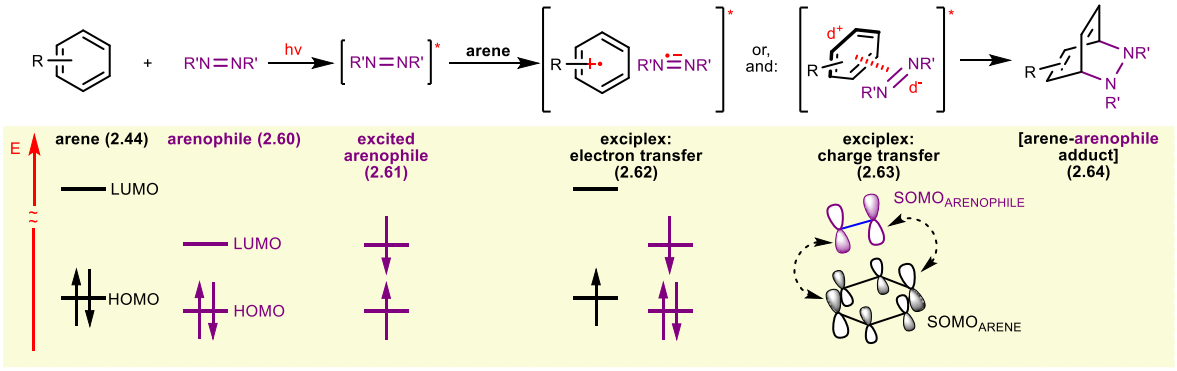

Figure 2.10. MTAD-arene cycloadduct formation mechanistic hypothesis.

Considering the synthetic potential that these arene-MTAD cycloadducts possess, over the past nine years our laboratory has been exploring the reactivity of these compounds. The underlying principle of this approach is that cycloaddition with arenophiles can be seen as the isolation of two π-bonds in the aromatic system via the formation of the bicyclic intermediate **2.64**. In general, two main paradigms of reactivity were established: 1) olefin functionalization, in which the newly isolated double bond is subjected to known olefin chemistry, and 2) allylic substitution, in which the bis-allylic bridgehead amide bond can be exploited as a leaving group in an allylic substitution reaction. These reaction manifolds have proven highly synthetically useful, and we have been able to access a variety of unique compounds that have allowed for the facile synthesis of multiple medicinally relevant compounds.

Considering olefin functionalization, one of the first transformation that was explored was dearomative dihydroxylation: subjecting MTAD-arene cycloadducts to in situ modified Upjohn dihydroxylation delivered functionalized bicyclic diols (**2.66**, Figure 2.11).[20] Tosyl amide proved to be crucial, as it facilitated osmate ester hydrolysis at lower temperatures. After acetonide protection, cycloreversion was accomplished via urazole hydrolysis to the bicyclic hydrazine and subsequent oxidation to the diazene. This could be achieved in one pot using hydrazine or KOH for hydrolysis and Cu(II) chloride as the oxidant. Using this sequence, a range of mono-substituted benzene and naphthalene derivatives were converted to the corresponding dihydrodiols **2.67**. The bicyclic hydrazine could also be cleaved to the corresponding 1,4-diamino diols upon benzoylation and treatment with SmI_2. Importantly, single constitutional and diastereoisomers were obtained since cycloaddition/dihydroxylation proceeded in a highly regio- and diastereoselective fashion. With this strategy, different bioactive products like **2.68** were synthesized. Following the same principle, diimide reduction was successfully performed on these cycloadducts to access dearomative reduction products (**2.69**, Figure 2.11).[21] These products were derivatized with the same sequence mentioned before, providing substituted 1,3-cyclohexadienes (**2.70**) as well as 1,4-diamino cyclohexanes (**2.71**). Another transformation that was explored was dearomative epoxidation[22]; in this case, when cycloreversion is performed on the monoarene epoxidated cycloadducts, the resulting arene oxide **2.73** is found in equilibrium with the oxepine species, the former being favored. On the other hand, in the case of naphthalene-derived epoxides, it was observed that they selectively form the benzoxepine species **2.74**. Using this dearomative epoxidation strategy it was then possible to synthesize several interesting functionalized benzoxepines. Another reported methodology is the dearomative hydroboration.[23] While it is highly limited in its scope, only providing the desired products on polynuclear arenes, its synthetic utility is very promising. We have been able to employ this reaction toward a total synthesis of idarubicinone, the aglycone of the FDA-approved anthracycline idarubicin. The latest published olefin functionalization is the dearomative cyclopropanation, followed by ring expansion, of polycyclic arenes, producing benzocycloheptenes derivatives.[24]

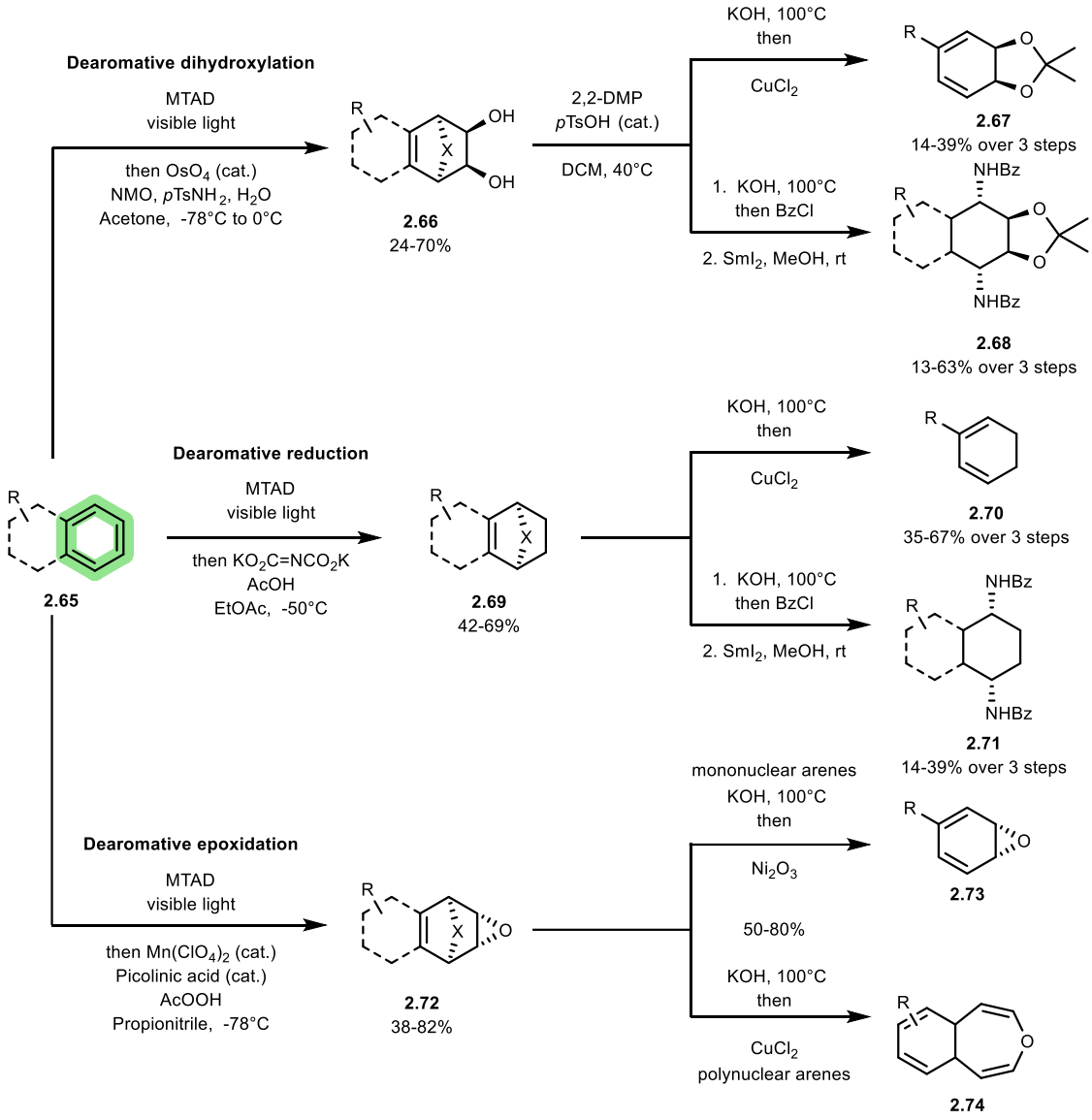

Figure 2.11. Olefin functionalization pathways of the arene-MTAD cycloadducts.

Aside from our advances in the olefin functionalization of these cycloadducts, we have also made strides in the allylic substitution of these intermediates. As a matter of fact, arene–arenophile cycloadducts are also competent substrates for transition metal-catalyzed reactions. Specifically, low-valent metals could undergo oxidative addition, expelling one of the bis-allylic bridgehead nitrogens and forming unsaturated complexes amenable to nucleophilic addition. Along these lines, different catalytic and enantioselective dearomative 1,2 or 1,4-functionalizations were achieved, providing synthetically useful intermediates. For instance, if MTAD-benzene cycloadduct is exposed to nickel catalyst and Grignard reagents in the presence of a chiral ligand, *trans*-1,2-carboamination is achieved with high enantioselectivity (98:2 er).[25] Using this desymmetrization strategy, it was possible to synthesize (+)-Pancratistatin (**2.2**) from

benzene.[26] Enolates can also be employed in a very similar transformation, using a palladium catalyst in place of nickel, resulting in an enantioselective dearomative *syn*-1,4-carboamination that produces chiral 1,4-cyclohexadienes **2.75** that could be further elaborated to various substituted cyclohexanes and tetrahydronaphthalenes.[27] Tuning the reaction conditions, Grignard reagents could be also employed to provide similarly substituted products.[28] Enantioselective dearomative *syn*-1,4-diamination[29] or 1,4-oxamination[30] were also developed using a palladium catalyst and amine or oxygen nucleophiles (**2.77**, Figure 2.12). Lastly, catalytic enantioselective 1,2-hydroamination was developed to achieve the synthesis of (+)-Ribostamycin from benzene.[31]

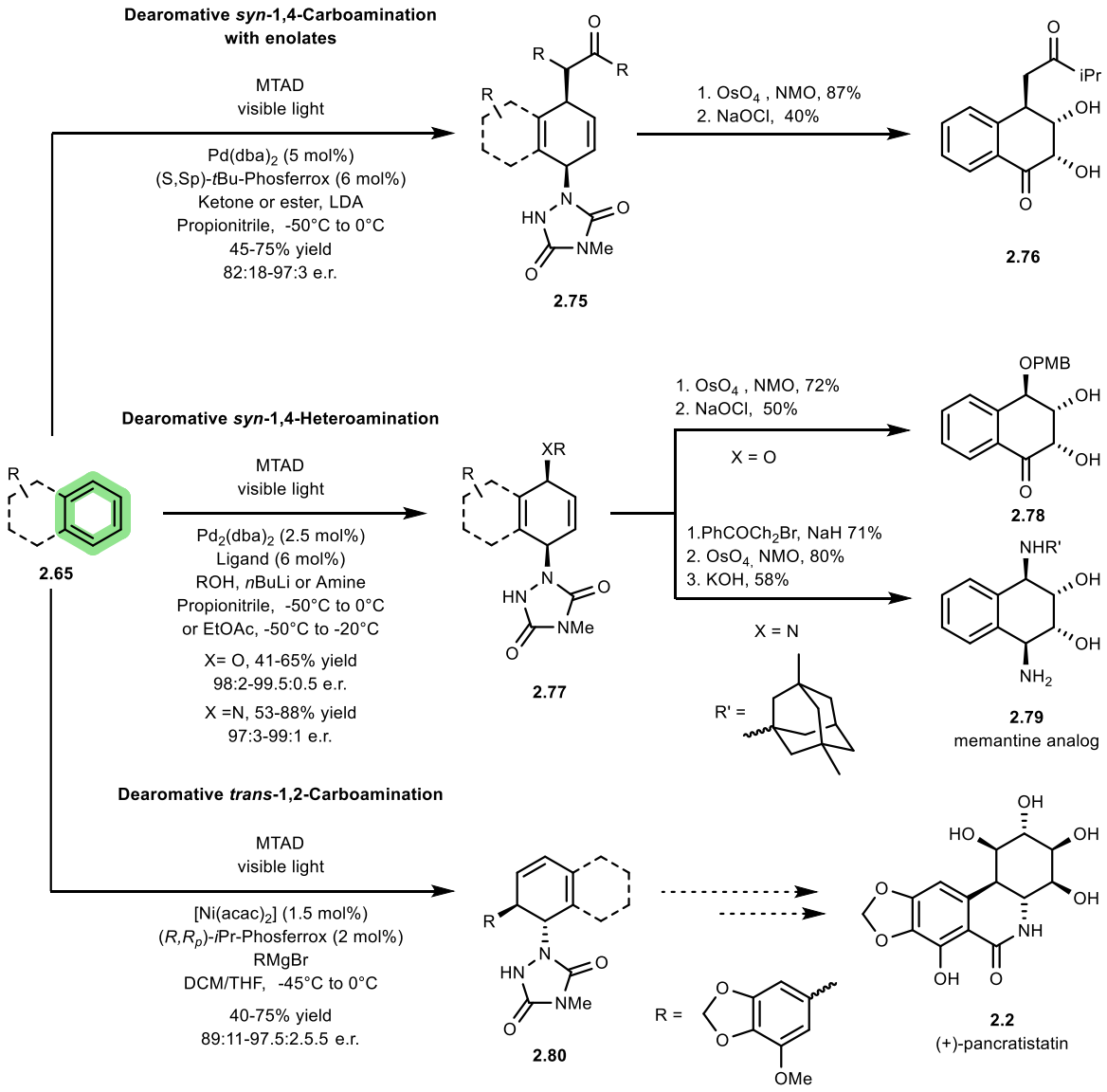

Figure 2.12. Allylic substitution examples of arene-MTAD cycloadducts.

2.3.2 Results

All the results that we were able to obtain are presented in the draft version of the attached paper "Diversification of Simple Arenes into Complex (Amino)cyclitols" on page 22, followed by the related supplementary material. https://doi.org/10.1002/chem.202303262

2.4 Summary and Future Directions

In this work, arenophile chemistry was leveraged to access dearomatized intermediates that were amenable to controlled functionalization events. The construction of a diverse library of (amino)cyclitols was guided by strategic and iterative olefin functionalization. Notably, this diversification platform enabled the rapid conversion of simple and abundant arenes into biologically relevant motifs occupying underexplored regions of chemical space (ca. 40 heteroatom and sp^3-rich compounds). The described synthetic methods will facilitate further study of (amino)cyclitol fragments in the contexts of chemical biology and complex natural product synthesis. For instance, our group is currently working on the synthesis of Hygromycin A analogs using the aforementioned aminocyclitol library.

2.5 Acknowledgements of Contributions

Elisa Angelini and Matteo Martinelli equally contributed to the project as first authors, as stated in the article. Elisa Angelini developed the general synthetic pathways and applied them on benzene; she also synthetized (±)-Valienamine. Matteo Martinelli elaborated benzyl alcohol substrate. Eugenio Roà elaborated polyaromatic compounds. Chad Ungarean helped organizing and developing research. Spirochem team (Christophe Salome, Quentin Lefebvre, and Colin Bournez) took care of the PMI analysis.

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Diversification of Simple Arenes into Complex (Amino)cyclitols

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Abstract: Highly oxygenated cyclohexanes, including (amino)cyclitols, are featured in natural products possessing a notable range of biological activities. As such, these building blocks are valuable tools for medicinal chemistry. While de novo synthetic strategies have provided access to select compounds, challenges including stereochemical density and complexity have hindered the development of a general approach to (amino)cyclitol structures. Herein, we report the use of arenophile chemistry to access dearomatized intermediates which are amenable to diverse downstream transformations. Practical guidelines were developed for the synthesis of natural and non-natural (amino)cyclitols from simple arenes through a series of strategic functionalization events.

The critical need to access new chemical space presents a significant challenge and is an important goal of contemporary synthetic chemistry.[1] The overuse and reliance on low-diversity combinatorial chemistry combined with the departure from natural products led to decreased sp^3 fraction and increased the occurrence of nitrogen-containing heterocycles in drug discovery libraries.[2] This has been described as adding more hay to the (screening) haystacks,[3] and a logical argument for a renewed focus on natural product-like motifs to address the diminishing natural product likeness.[4] The importance of pseudo-natural products, defined as natural product-like fragments not accessible through biosynthesis,[5] is increasingly being recognized as an important tactic in drug design. This is particularly the case with cyclic structures, where the incorporation of diverse cyclic fragments in libraries has been slower than expected.[6] Therefore, developing strategies that could access functionalized natural-like cyclic compounds is an essential consideration for the future of drug discovery.

Highly functionalized 6-membered carbocycles are prevalent in natural products and biologically active compounds.[7] Aminocyclitols, inositols, and carbasugars have been shown to possess antidiabetic, antibiotic, antiviral, and antitumor activities

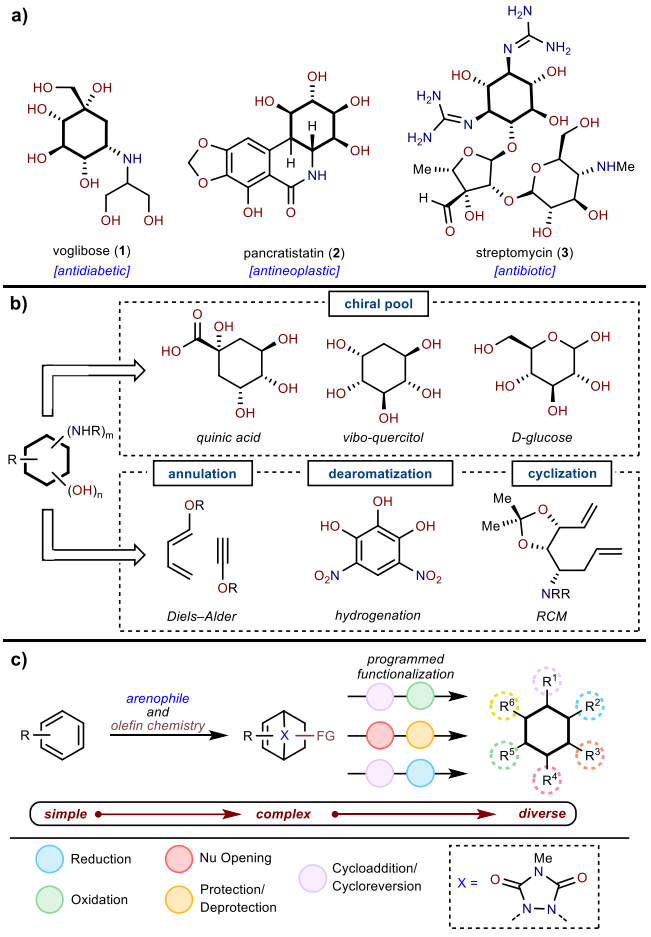


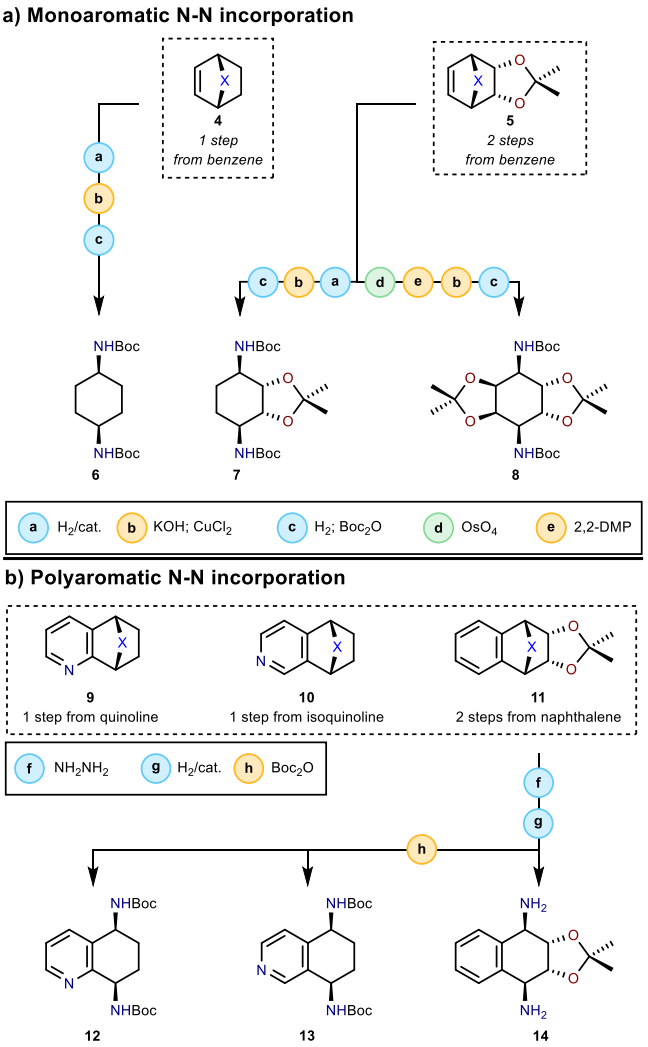
Figure 1. a) Selected aminocyclitol-containing natural products. b) Representative strategies used for the synthesis of (amino)cyclitols. c) This work: programmed (amino)cyclitol synthesis through diversification of arenophile-based products.

(Figure 1a).[8] Representative examples include the α-glucosidase inhibitor voglibose (**1**),[9] the anticancer Amaryllidaceae alkaloid pancratistatin (**2**),[10] and the potent aminoglycoside antibiotic streptomycin (**3**).[11] The notable biological activity of these small yet densely functionalized molecules highlights (amino)cyclitols as privileged motifs in drug design. The biological significance conferred by these structures serves as motivation for the development of synthetic methods to access analogs with improved bioactivity and drug-like qualities.

The synthesis of (amino)cyclitols has been regarded with intense interest by the synthetic community,[12] and recent efforts have culminated in successful campaigns featuring innovative solutions (Figure 1b). Readily available chiral pool materials (e.g. quinic acid and D-glucose) have become popular heteroatom-rich molecular templates which efficiently provide preinstalled functionality.[13] While the chiral pool strategy obviates the need to install functional groups and/or set stereochemistry, manipulations of the intrinsic functional groups are often arduous. Ring formation through annulation or cyclization is a common alternative strategy.[14] However, narrow substrate scope and/or demanding linear construction of the necessary precursors limits the generality and utility of both strategies. Additionally, arenes have shown promise as starting materials.[15] Dearomative hydrogenation is a powerful and facile approach towards sp^3 core scaffolds. Unfortunately, this approach introduces hydrogen atoms with global *syn*-addition and is incompatible with stereodivergency and late-stage functionalization. As a result of these limitations, few (amino)cyclitols have been synthesized to date. There is an unmet need for the development of a general approach to (amino)cyclitol synthesis. An ideal strategy would provide access to diverse (amino)cyclitol structures through careful stereochemical and functionalization control.

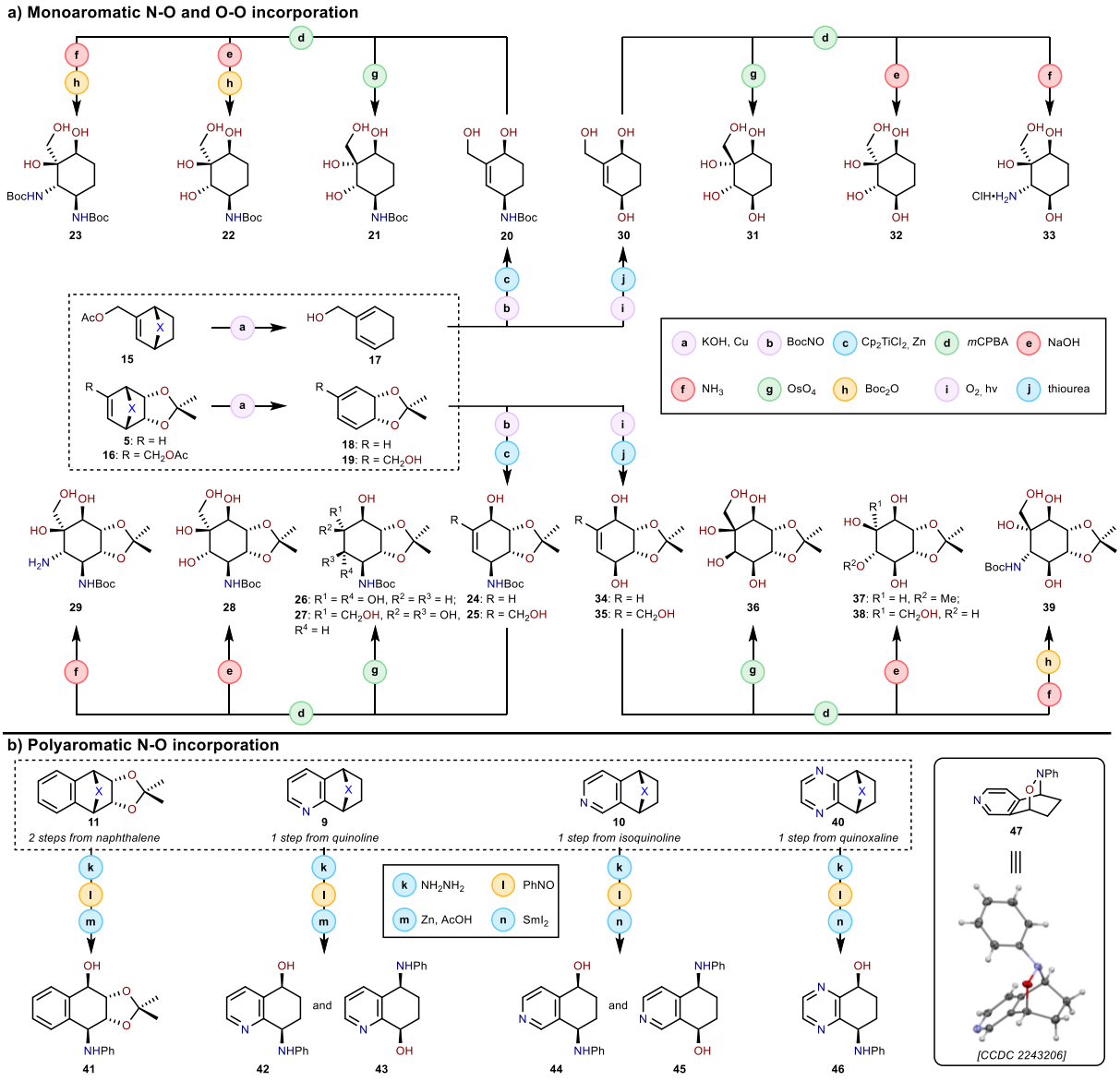
We recently reported a conceptually distinct approach toward dearomative functionalization involving photoactivated 2π-components – arenophiles – that react with arenes in *para*-fashion.[16] Although dearomatization reactions have not been used in diversification strategies previously,[17] we were intrigued by the possibility of employing an arenophile platform to achieve systematic, expedient, and divergent syntheses of (amino)cyclitols (Figure 1c). Accordingly, a variety of readily available simple (hetero)arenes would serve as templates to facilitate the introduction of diverse functionalities during a dearomatization event. A wide selection of established olefin chemistry would then enable facile functional group incorporation onto the dearomatized intermediate. Transformations on the [2.2.2]-bicyclic system and further elaborated cyclohexene structures would follow predictable stereocontrol, and the arenophile's urazole subunit could serve as a surrogate for either an amine or diene. The strategic use of broadly applicable reactions on diverse substrates (highlighted in Figure 1c) would maximize the expansion of (amino)cyclitol chemical space and facilitate the synthesis of structures which cannot be readily accessed through more traditional, single target-driven approaches.

The first demonstration of our strategy employed the urazole motif as a masked *syn*-1,4-diamine (Scheme 1). We began our campaign with benzene-derived bicycles **4** and **5**, which were readily obtained by arenophile-mediated dearomative diimide reduction[18] and dearomative dihydroxylation,[19] respectively. Bicycle **4** was transformed into diamine **6** through a three-step sequence involving hydrogenation of the cyclic alkene,



Scheme 1. Diversification of arenophile-based dearomatized products towards *syn*-1,4-diaminocyclohexane derivatives using a) benzene-derived and b) polycyclic (hetero)arenes-derived products. *Reactions and conditions*: (a) H_2 (1 atm), Pd/C (0.1 equiv), MeOH, rt, 12 h, to **6**: 99%; to **7**: 66%; (b) KOH (10 equiv), *i*PrOH, 80 °C, 12 h, *then* $CuCl_2$ (2 equiv), NH_4OH (aq, 20 equiv), rt, 2 h, to **6**: 93%; to **7**: 54%; to **8**: 68%; (c) H_2 (6 atm), Raney-Ni (0.1 equiv), EtOH, rt, 12 h, *then* Boc_2O (5 equiv), Et_3N (1 equiv), DMAP (0.01 equiv), dioxane:H_2O 1:1, rt, 12 h, to **6**: 53%; to **7**: 88%; to **8**: 70% (d) OsO_4 (0.1 equiv), NMO (1.2 equiv), H_2O (20 equiv), acetone, rt, 24 h, 78%; (e) *p*TsOH (0.1 equiv), 2,2-DMP (5 equiv), DCM, 0 °C to rt, 5 h, 82%. b) Diamines derived from polyaromatics. *Reactions and conditions*: (f) NH_2NH_2 (20 equiv), 100 °C, 12 h, intermediates taken forward; (g) to **12** and **13**: H_2 (1 atm), PtO_2 (0.1 equiv) TFA (3 equiv), EtOH, 50 °C, taken forward; to **14**: H_2 (1 atm), Raney-Ni (0.1 equiv), EtOH, 50 °C, 12 h, to **13**: taken forward; to **14**: 60% over 2 steps; (h) Boc_2O (10 equiv), $NaHCO_3$ (10 equiv), *t*BuOH:H_2O (2:1), 50 °C, 12 h, **12**: 31% over 3 steps; **13**: 42% over 3 steps. NMO = *N*-methylmorpholine *N*-oxide, DMP = 2,2-dimethoxypropane, DCM = dichloromethane, TFA = trifluoroacetic acid

hydrolysis of the urazole with subsequent oxidation to bicyclic diazo, and hydrogenative cleavage of the diazene bridge. More densely functionalized structures were accessed by employing the same reaction sequence on dihydroxylated dearomatized intermediate **5**, thus delivering diaminodiol derivative **7**. A divergent pathway provided hexasubstituted aminocyclitol **8** from **5** through dihydroxylation[20] and acetonide diol protection prior to the previously described reaction sequence.



Scheme 2. Diversification of arenophile-based dearomatized products towards (amino)cyclitols using a) benzene-derived **5**,**15**, and **16** dearomatized adducts; and b) polycyclic (hetero)arenes-derived **9**–**11**, and **40** adducts. *Reactions and conditions*: (a) ref.; (b) for R = H: BocNHOH (2 equiv), Bu_4NIO_4 (2 equiv), DCM, –20 °C to rt, 12 h, to **24**: 97%; for R = OH: BocNHOH (1.3 equiv), $NaIO_4$ (1.2 equiv), MeOH:H_2O, –20 °C to rt, 3 h, to **20**: 79%; to **25**: taken forward; (c) Cp_2TiCl_2 (2.5 equiv), Zn (5 equiv), THF:MeOH 1:1, –30°C, 1 h, **20**: 84%; **24**: 92%; **25**: 74%* (94% brsm); (d) for R = H: *m*CPBA (2.0 equiv), $NaHCO_3$ (10 equiv), DCM, 0°C to rt, 12 h, from **24**: 74%; from **34**: 47%; for R = OH: *m*CPBA (2 equiv), MeCN, 35 °C, 24 h, from **20**: 86%; from **25**: 94%; from **30**: 91%; from **35**: 60%; (e) For R = H: NaOH (5 equiv), MeOH, 80 °C, 2 d, **37**: 55%; for R = OH: H_2O (pH > 10), 55 °C, 24 h, **22**: 44% (91% brsm); **28**: 54%; **32**: 99%; **38**: 57%; (f) NH_3 (7 M in MeOH), 95 °C, 24 h, to **23**: taken forward; **29**: 48%; **33**: 80%; to **39**: taken forward; (g) OsO_4 (0.1 eq), NMO (1.2 equiv), H_2O (20 equiv), acetone, rt, 24 h, **21**: 95%; **26**: 51%; **27**: 80%; **31**: 57%; **36**: 86%; (h) Boc_2O (5 equiv), Et_3N (5 equiv), dioxane:H_2O 1:1, 55 °C, 5 h; **23**: 60%*; **39**: 52%*; (i) TPP (0.01 equiv), O_2 (1 atm), hv, DCM, –50 °C, to **30**: 87%; to **34**: 70%; to **35**: 75%; (j) thiourea (2.0 equiv), MeOH, 0°C to rt, 12 h, **30**: 96%; **34**: 87%; **35**: 78%; (k) NH_2NH_2 (20 equiv), 100 °C, 12 h, intermediates taken forward; (l) PhNO (3 equiv), THF, 60 °C, 30 min, **41**: THF as solvent: 58%; from **9**: THF as solvent; 75%* (1:1.6 r.r.); from **10**: DMF as solvent; 56%* (1:1.3 r.r.); from **40**: MeOH as solvent: 75%*; (m) Zn (7 equiv), AcOH, rt, 4 h, **41**: 97%; **42**+**43**: 75% (1:1.6 r.r.)**;** (n) SmI_2 (5 equiv), THF, 0 °C to rt, 12 h, **44**+**45**: 41% (1:1.3 r.r); **46**: 71%. *yield over 2 steps. DCM = dichloromethane, THF = tetrahydrofuran, DMF = dimethylformamide, TPP = tetraphenylporphyrin, *m*CPBA = *meta*-chloroperbenzoic acid; NMO = *N*-methylmorpholine *N*-oxide

Motivated by the recent emergence of (aza)benzofused aminocyclitols in medicinal chemistry,[21] we sought to construct functionalized sp^2-sp^3 hybrid building blocks (Scheme 1b) from polycyclic (hetero)aromatic derivatives. Accordingly, we validated our strategy on several representative dearomatized intermediates including quinoline- and isoquinoline-derived **9** and **10** and naphthalene-derived **11**. An identical sequence involving hydrazinolysis of the urazole (operation f) and reduction of the resultant bicyclic hydrazine intermediate (operation g) revealed a *syn*-1,4-diamine motif on each substrate, exemplified by diamine product **14** and Boc-protected variants **12** and **13**.

Advancing beyond the use of bridgehead urazole as a *syn*-1,4-diamine surrogate, we desired to install other functionalities by using the urazole motif as a diene surrogate which could engage in hetero-Diels–Alder reactions with either nitroso compounds or singlet oxygen (Scheme 2a).[22] Thus, diimide-reduced product **15** and dihydroxylated derivatives **5** and **16** were subjected to a one-pot urazole cleavage/cycloreversion protocol

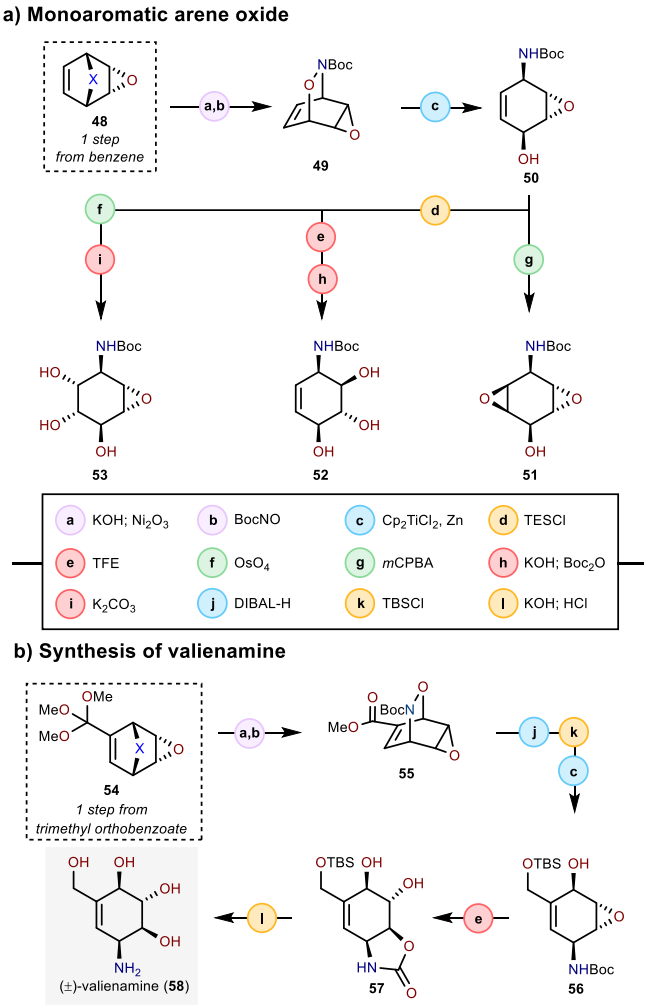
to unveil the corresponding dienes **17**–**19**. The benzyl alcohol-derived diene **17** readily underwent regioselective cycloaddition with an acylnitroso species[23] followed by N–O bond cleavage[24] (steps b and c) to deliver aminodiol derivative **20**. This intermediate was then advanced in a divergent fashion. Aminotetraol **21** was secured through dihydroxylation (step g), while epoxidation of **20** (step d) and subsequent ring-opening with sodium hydroxide (step e) or ammonia (step f) provided aminotetraol **22** and diaminotriol **23**, respectively. Analogous functionalizations were performed on dihydroxylated diene variants **18** and **19**. Nitroso-[4+2] followed by reductive N–O bond cleavage afforded **24** and **25**, and subsequent dihydroxylation yielded aminopentaol **26** and aminohexanol **27**. Furthermore, epoxidation of benzyl alcohol congener **25** followed by nucleophilic opening with sodium hydroxide or methanolic ammonia yielded complementary hexasubstituted aminocyclitols **28** and **29.**

Dienes **17**–**19** were also functionalized with a *syn*-1,4-diol motif through cycloaddition of singlet oxygen followed by mild reduction of the resulting endoperoxides with thiourea[25] (steps i and j). Accordingly, diene **17** was effectively converted to triol **30**. The remaining olefin was then subjected to dihydroxylation (step g) or epoxidation (step d) with subsequent nucleophilic opening (step e or f) to yield final compounds **31**–**33** as single diastereoisomers. Similarly, hexafunctionalized cyclitols **34**–**39** were expediently accessed from dihydrodiols **18** and **19**. Rapid conversion of distinct dearomatized substates (i.e. **5**, **15**, **16**) into 20 uniquely functionalized (amino)cyclitols (**20**–**39**) showcases the generality and modularity of this diversification sequence.

In an analogous manner to monoaromatic N-O incorporation, aminohydroxy functionality was introduced to polycyclic (hetero)arene-derived substrates (Scheme 2b). Representative compounds including dihydroxylated naphthalene **11**, reduced quinoline **9**, isoquinoline **10,** and quinoxaline **40** were subjected to the previously described sequence to deliver **41**–**46**. Hydrazinolysis (step k) converted the bridgehead urazole motif to hydrazine and treatment with excess nitrosobenzene (step l) induced oxidation and concurrent dinitrogen expulsion. This afforded *ortho*-quinonedimethide, which reacted with nitrosobenzene in a [4+2] cycloaddition (see inset Scheme 2b for the X-ray crystallographic image of adduct **47** derived from **10**).[26] The N–O bond was then reductively cleaved (step m or n) to afford hybrids **46**–**48**. In cases of nitroso cycloaddition with quinoline and isoquinoline-derived intermediates (**9** and **10,** respectively), constitutional isomers were formed.

Our strategy provides access to additional (amino)cyclitols from arene oxides (Scheme 3). We were pleased to find that capture of transient benzene oxide, derived from surrogate **48**,[27] with an acyl nitroso species delivered cycloadduct **49** (steps a and b, Scheme 3a). Divergent downstream transformations including epoxidation (step g), carbamate-assisted intramolecular epoxide opening (step e), and dihydroxylation (step f) provided aminocyclitols **51**–**53**.

We pursued the synthesis of naturally occurring aminocyclitol valienamine (**58**),[28] a motif found in the antidiabetic drug acarbose and the antibiotic validamycin, to showcase the utility of our method (Scheme 3b).[29] Our route began with arenophile-mediated epoxidation product **54**, obtained in a single step from trimethylorthobenzoate. One pot cycloreversion to a highly labile arene oxide and acyl nitroso Diels–Alder (step a/b) afforded compound **55** as the main constitutional isomer.



Scheme 3. Diversification of arenophile-based dearomatized products based on a) benzene oxide, and b) application of this strategy towards valienamine (**58**). *Reactions and conditions*: (a) ref. 27; (b) Bu_4NaIO_4 (2 equiv), BocNHOH (2 equiv), DCM, –20 °C to rt, 12 h, 71%; (c) Cp_2TiCl_2 (2.5 equiv), Zn (5 equiv), THF:MeOH 1:1, –30°C to –10 °C, 1 h, 90%; (d) TESCl (1.1 equiv), imidazole (2 equiv), DMF, 0 °C to rt, 12 h, 89%; (e) TFE (neat), 60 °C, 24 h, 98%; (f) OsO_4 (0.1 equiv), NMO (1.2 equiv), H_2O (20 equiv), acetone, rt, 24 h, 45%; (g) *m*CPBA (2 equiv), $NaHCO_3$ (10 equiv), DCM, 0 °C to rt, 12 h, 42%; (h) KOH (10 equiv), EtOH, 80 °C, 12 h, *then* Boc_2O (3 equiv), Et_3N (1 equiv), DMAP (0.01 eq), dioxane:H_2O (1:1), rt, 12 h 79% (i) K_2CO_3 (1 equiv), MeOH, rt, 12 h, 76%. (a) KOH (10 equiv), *i*-PrOH, 80 °C, 2 h, *then* Ni_2O_3 (3 equiv), DCM, rt, 2 min, taken forward crude; (b) Bu_4NaIO_4 (2 equiv), BocNHOH (2 equiv), DCM, –20°C to rt, 12 h, *then* HCl, 20 min, 33% over 4 steps; (j) DIBAL-H (2 equiv), DCM, –78 °C to –50 °C, 5 h, 55%; (k) TBSCl (1.1 eq), imidazole (2.1 equiv), DMF, 0 °C to rt, 12 h, 83%; (c) Cp_2TiCl_2 (2.5 equiv), Zn (5 equiv), THF:MeOH, –30 °C, 1 h, 57%; (e) TFE (neat), 60 °C, 3 h, 80%; (l) KOH (10 equiv), EtOH, 80 °C, 12 h, 71%. TESCl = triethylsilyl chloride, TFE = trifluoroethanol, TBSCl = *tert*-butyldimethylsilyl chloride DCM = dichloromethane, DMF = *N,N*-dimethylformamide, NMO = *N*-methylmorpholine *N*-oxide.

Sequential DIBAL-H reduction, TBS protection, and titanocene/Zn mediated N–O bond cleavage (steps j, k, and c), furnished aminocyclitol precursor **56**. Intramolecular Boc-assisted epoxide opening (step l) yielded carbamate **57,** and cleavage of the carbamate and TBS groups delivered valienamine (**58**) as the corresponding freebase. Our strategy enables rapid diversification of simple arenes into structures that are relevant to and/or underexplored in drug discovery, as demonstrated with a

comparison plot of the principal moments of inertia (PMI) for FDA-approved drugs (Figure 2).[30] The PMI method computationally calculates the moments of inertia of a particular conformation of a molecule around its three principal axes, which are then sorted and converted into two normalized PMI ratios. Plotting these values against each other in a two-dimensional triangular graph allows for quick visualization of the molecular shape.[30] In the polyaromatic series (Figure 2a), compounds derived from N–N incorporation (**12**–**14**) occupy regions of chemical space heavily populated by existing and relatively 2-dimensional drug molecules. While compounds derived from N–O incorporation (**41**–**46**) occupy a region less populated by existing drug molecules, they are still fairly flat molecules. Strikingly, 3-dimensional benzyl alcohol-derived (amino)cyclitols occupy underexplored regions of chemical space (Figure 3b). While the initial dearomative functionalization places cyclohexene intermediates containing two or four heteroatom stereocenters (**20**, **30**, **25**, **35**) at the boundary of 2D/3D space, additional diversification events project the densely functionalized and fully saturated carbocycles into broader regions of 3D topological space. As demonstrated by the recent synthetic efforts in this area, there is an interest in more thoroughly investigating the use of 3D fragments in medicinal chemistry, not only to better explore the impact of the 3D character on the fragment screening hit rates, but also to allow the identification of novel structures as starting points for hit optimisation studies.

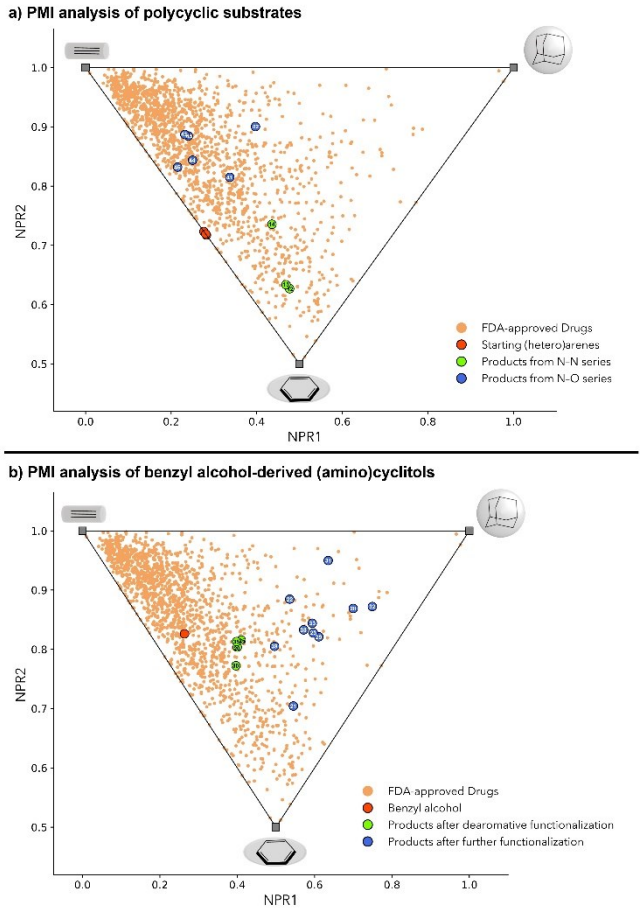


Figure 2. Diversification of arenes using dearomative functionalization visualized with PMI analysis. Results are plotted using unprotected intermediates in comparison with FDA-approved drugs (orange dots). a) Diversification of polycyclic (hetero)arenes. b) Diversification of benzyl alcohol.

Conclusion

In this work, arenophile chemistry was leveraged to access dearomatized intermediates that were amenable to controlled functionalization events. Construction of a diverse library of (amino)cyclitols was guided by strategic and iterative olefin functionalization. Notably, this diversification platform enabled the rapid conversion of simple and abundant arenes into biologically relevant motifs occupying underexplored regions of chemical space. The described synthetic methods will facilitate further study of (amino)cyclitol fragments in the contexts of chemical biology and complex natural product synthesis.

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Keywords: dearomatization • aminocyclitols • arenes • diversification • drug discovery

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2.7 Experimental

General Procedures

Unless otherwise noted, all reactions were carried out under an ambient atmosphere. All chemicals were purchased from commercial suppliers and used as received. *N*-Methyl-1,2,4-triazoline-3,5-dione (MTAD) was prepared based on the literature procedures[1] and was resublimed before use. Nickel oxide was synthesized according to literature procedures.[1] Raney®-Nickel was bought from Sigma Aldrich. Dry dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and tetrahydrofuran (THF) were obtained by passing commercially available anhydrous, oxygen-free HPLC-grade solvents through activated alumina columns. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 aluminum plates. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$). Retention factor (R_f) values reported were measured using a 5 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash® P60 (SiO_2, 40-63 μm particle size, 230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on Bruker 400 (400 MHz, ^1H; 101 MHz, ^{13}C), Bruker 500 (500 MHz, ^1H; 126 MHz, ^{13}C), Varian Unity Inova 500 (500 MHz, ^1H; 126 MHz, ^{13}C), or Varian 600 (600 MHz, ^1H; 151 MHz, ^{13}C) spectrometers. Spectra are referenced to residual chloroform (δ = 7.26 ppm, ^1H; 77.16 ppm, ^{13}C), residual methanol (δ = 3.31 ppm, ^1H; 49.00 ppm, ^{13}C), residual benzene (δ = 7.16 ppm, ^1H; 128.06 ppm, ^{13}C), residual H_2O (δ = 4.76 ppm, ^1H) or residual dimethyl sulfoxide (δ = 2.50 ppm, ^1H; 39.5 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants J are reported in Hertz (Hz). Mass spectrometry (MS) was performed either by the University of Illinois Mass Spectrometry Laboratory or at the University of Pavia. Electrospray ionization (ESI+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100). Infrared spectra were measured neat on either a Perkin-Elmer spectrum BX FT-IR spectrometer or Agilent Cary 630 FTIR with ATR. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad). Visible-light spectrum of LED was recorded using an Avantes Sensline Avaspec-ULS TEC Spectrometer. Melting points of solids, compounds that solidified after chromatography, were measured on a Buchi B-540 melting point apparatus and are uncorrected. The x-ray diffraction experiments were conducted using Bruker D8 Venture/Photon 100 diffractometer or Bruker APEX-II CCD

diffractometer. Using Olex the structure was solved with ShelXT7 structure solution program using Intrinsic Phasing solution method, and the XL8 refinement package using Least Squares minimization.

Abbreviations

MTAD = 4-Methyl-1,2,4-triazoline-3,5-dione, THF = tetrahydrofuran, DMF = *N*,*N*-Dimethylformamide, DMSO = Dimethylsulfoxide, *m*CPBA = *meta*-3-chloroperbenzoic acid, TESCl = triethylsilyl chloride, TBSCl = *tert*-butyldimethylsilyl chloride, 2,2-DMP = 2,2-dimethoxypropane, DMAP = 4-dimethylaminopyridine.

Photochemical Set-Up

LED light source: Generic cool white light LED corn bulbs were used for the photochemical experiments. These can be obtained from several manufactures over amazon.com and proved to give consistent results as well as identical visible spectra. Detailed info:

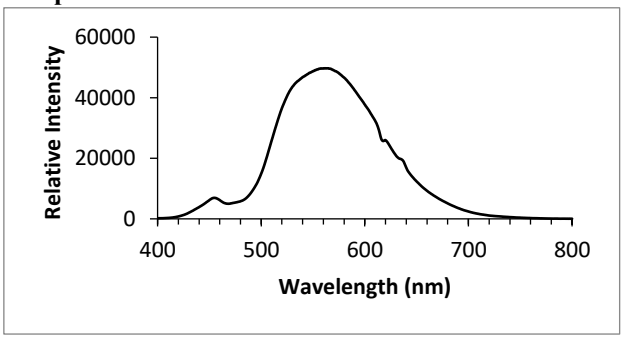


Figure S1. Spectrum of LED bulb used.

Socket: G4

LED Chip: 48 LEDs SMD 2835

Consume wattage: 4W

Input voltage: AC / DC 12V

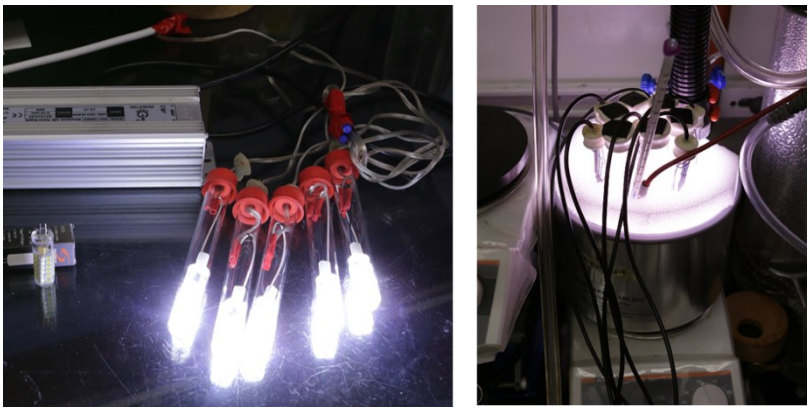
Beam degree: 360 degrees

Color temperature: 6500K (Cool White)

Initial Lumens (lm): 290

Photochemical set-up for small scale reactions (up to 2.0 mmol scale)

Five 4 W LED corn bulbs (12V, cool white light 6500K) were wired to a suitable 12V power supply, then sealed into test tubes and capped with septa (Picture S1). Lights and reaction tubes were arranged in a carrousel fashion for maximal exposure of each reaction vessel to light source and were submerged in a −78 °C bath. Generally, up to four 0.2-2.0 mmol scale reactions can be run in the same bath using five 4 W lamps.



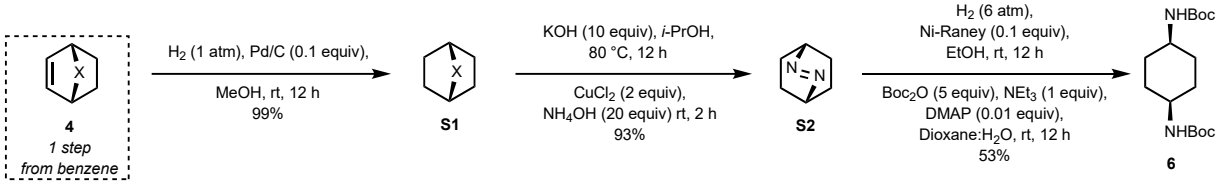
Picture S1. Assembly of LED bulbs for small-scale photochemical reactions.

Photochemical set-up for medium scale reactions (up to 25 mmol scale)

Eight 4 W LED corn bulbs (12V, cool white light 6500K) were wired to a suitable 12V power supply, then sealed into test tubes and capped with septa. Lights were arranged in a carrousel fashion around a 500 mL Schlenk flask. The whole set-up was kept submerged in a −78 °C bath during the photochemical reactio

Experimental Procedures and Characterization Data

Derivatizations from Benzene



Scheme S1. Conversion of intermediate **4** to **6**.

S1

Bicycle S1. To a degassed solution of **4** (253 mg, 1.29 mmol, 1.0 eq.)[2] in MeOH (13 mL, 0.1 M) was added Pd/C (138 mg, 0.13 mmol, 0.1 eq., 10 wt%). Then, the reaction was purged with hydrogen gas and thereafter left under 1 atm of hydrogen (balloon). After reaction completion, the mixture was degassed with argon, filtered through Celite, and rinsed with additional MeOH. The combined organics were dried *in vacuo* and the crude material was purified by column chromatography (SiO_2, hexane:EtOAc 3:1 to 1:2) to afford **S1** (250 mg, 1.28 mmol, 99%) as a white solid.

R_f 0.3 (*n*-hexanes:EtOAc = 1:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (s, 2H), 3.07 (s, 3H), 2.07 – 1.73 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 48.0, 25.3, 24.8.

IR (ATR, neat, cm^{-1}) 2952 (s), 2870 (s), 1751 (m), 1695 (w), 1453 (m), 1394 (m), 1248 (m), 1010 (s), 924 (s), 853 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{14}N_3O_2$ $[M+H]^+$ calc.: 196.1081; found: 196.1075.

m.p. 103 – 104 °C.

S2

Diazene S2. The protocol was adapted from a reported protocol.[3] A solution of **S1** (250 mg, 1.28 mmol, 1.0 eq.) in *i*-PrOH (13 mL, 0.1 M) and KOH (798 mg, 12.8 mmol, 10 eq.) was degassed with argon and heated in a sealed vial at 80 °C for 12 hours. After cooling to room temperature and neutralization to pH 7 with the addition of AcOH (1 M aq. sol.), the resulting mixture was treated with $CuCl_2$ (344 mg, 2.56 mmol, 2.0 eq.) and allowed to stir for an additional 2 hours. The mixture was then treated with ammonium hydroxide (1 M aq. sol., 3 mL) and extracted with EtOAc (3 × 20 mL). The resulting organics were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, 2:1 to 1:2 hexanes:EtOAc) to afford **S2** (132 mg, 1.20 mmol, 93%) in the form of colorless crystals.

R_f 0.3 (*n*-hexanes:EtOAc = 1:2, Vanillin).

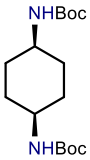
^{1}H NMR ($CDCl_3$) δ 5.13 – 5.07 (m, 2H), 1.57 (m, *J* = 7.7 Hz, 4H), 1.39 – 1.20 (m, 4H).

^{13}C NMR ($CDCl_3$) δ 61.1, 21.3.

IR (ATR, neat, cm^{-1}) 2959 (m), 2937 (s), 2866 (m), 1722 (s), 1517 (s), 1446 (s), 1319 (s), 1259 (s), 1170 (s), 1133 (s), 1025 (s), 887 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_6H_{11}N_2$ $[M+H]^+$ calc.: 111.0917; found: 111.0913.

m.p. 138 – 140 °C.



6

***Bis*-amide 6**. To a degassed solution of **S2** (30 mg, 0.27 mmol, 1.0 eq.) in EtOH (2.7 mL, 0.1 M) was added Raney®-Nickel (0.5 mL, W.R. Grace and Co. Raney® 2400, slurry, in H_2O). Then, the reaction vessel was placed inside an autoclave and subjected to hydrogen (6 atm) for 12 h. After reaction completion, the mixture was degassed with argon, filtered through Celite, and rinsed with additional EtOH. The combined organics were dried *in vacuo* and the crude material was then diluted with 1,4-dioxane:water (1:1, 2.7 mL, 0.1 M) and treated sequentially with Et_3N (38 µl, 0.27 mmol, 1.0 eq.), Boc_2O (300 mg, 1.4 mmol, 5.0 eq.) and DMAP (0.3 mg, 2.7 µmol, 0.01 eq.). The resulting solution was stirred at rt overnight. Thereafter, the reaction was quenched with sodium bicarbonate (sat. aq. sol., 3 mL) and diluted with EtOAc. The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified by column chromatography (SiO_2, hexane:EtOAc 9:1 to 1:1) to afford **6** (45 mg, 0.14 mmol, 53%) as a white solid.

R_f 0.4 (*n*-hexanes:EtOAc = 7:3, $KMnO_4$).

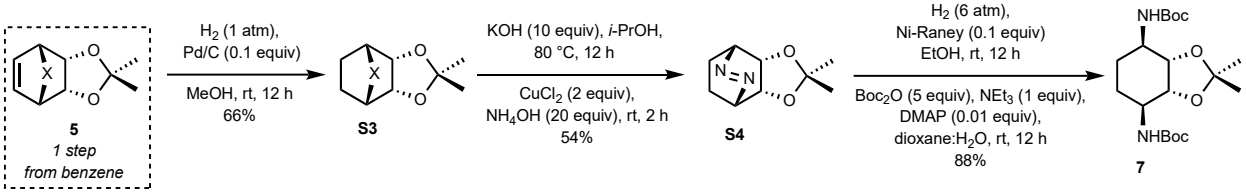
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (s, 2H), 3.58 (s, 2H), 1.78 – 1.65 (m, 4H), 1.52 (m, *J* = 12.2, 6.4 Hz, 4H), 1.44 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 79.4, 46.9, 28.8, 28.6.

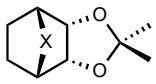
IR (ATR, neat, cm^{-1}) 3451 (b), 3339 (b), 2974 (s), 2933 (m), 2862 (s), 1684 (w), 1498 (w), 1390 (m), 1248 (m), 1155 (w), 1043 (m), 782 (m), 700 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{16}H_{30}N_2O_4Na$ $[M+Na]^+$ calc.: 337.2098; found: 337.2085.

m.p. 136 – 137 °C.



Scheme S2. Conversion of intermediate **5** to **7**.



S3

Acetonide S3. To a degassed solution of **5** (100 mg, 0.377 mmol, 1.0 eq.)[3] in MeOH (3.8 mL, 0.1 M) was added Pd/C (40 mg, 0.1 eq., 10 wt%). Then, the reaction was purged with hydrogen gas using a balloon and thereafter left under 1 atm of hydrogen (balloon). After reaction completion, the mixture was degassed with argon, filtered through Celite, and rinsed with additional MeOH. The combined organics were dried *in vacuo* and the crude material was purified by column chromatography (SiO_2, hexane:EtOAc 7:3 to 1:1) to afford **S3** (66 mg 0.25 mmol, 66%) as a white solid.

R_f 0.1 (*n*-hexanes:EtOAc = 7:3, $KMnO_4$).

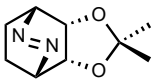
^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.40 – 4.31 (m, 4H), 3.03 (s, 3H), 2.15 – 1.99 (m, 2H), 1.76 – 1.60 (m, 2H), 1.52 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 154.9, 111.9, 72.6, 51.0, 26.0, 25.8, 24.5, 17.6.

IR (ATR, neat, cm^{-1}) 2981 (s), 2933 (s), 1763 (m), 1692 (m), 1438 (m), 1394 (m), 1259 (m), 1218 (m), 1058 (m), 928 (s), 872 (m), 831 (s), 715 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{18}N_3O_4$ $[M+H]^+$ calc.: 268.1292; found: 268.1283.

m.p. 216 – 218 °C.



S4

Diazene S4. The protocol was adapted from a reported protocol.[4] A solution of **S3** (100 mg, 0.374 mmol, 1.0 eq.) in *i*-PrOH (2 mL, 0.1 M) and KOH (233 mg, 3.74 mmol, 10 eq.) was degassed with argon and heated in a sealed vial at 80 °C for 12 hours. After cooling to room temperature and neutralization to pH 7 with the addition of AcOH (1 M, aq. sol.), the resulting mixture was treated with $CuCl_2$ (101 mg, 0.748 mmol, 2.0 eq.) and allowed to stir for additional 2 hours. The mixture was then extracted with treated with ammonium hydroxide solution (10% aq. sol., 1 mL) and extracted with EtOAc

(3 × 10 mL). The resulting organics were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexanes:EtOAc 3:1 to 1:1) to afford **S4** (37 mg, 0.20 mmol, 54%) in the form of colorless crystals.

R_f 0.4 (*n*-hexanes:EtOAc = 1:2, Vanillin).

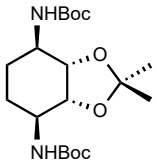
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.50 (m, 2H), 3.80 (t, *J* = 2.3 Hz, 2H), 2.00 – 1.88 (m, 2H), 1.51 (s, 3H), 1.29 (s, 3H), 1.08 – 0.95 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 111.4, 69.3, 67.2, 26.1, 24.5, 14.5.

IR (ATR, neat, cm^{-1}) 2989 (m), 2929 (m), 2862 (s), 1722 (s), 1453 (s), 1263 (m), 1237 (m), 1200 (m), 1162 (m), 1099 (m), 972 (m), 920 (s), 868 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_9H_{15}N_2O_2$ $[M+H]^+$ calc.: 183.1128; found: 183.1125.

m.p. 111 – 112 °C.



7

***Bis*-amide 7**. To a degassed solution of **S4** (40 mg, 0.22 mmol, 1.0 eq.) in EtOH (2.2 mL, 0.1 M) was added Raney®-Nickel (0.7 mL, W.R. Grace and Co. Raney® 2400, slurry, in H_2O). Then, the reaction vessel was placed inside an autoclave and subjected to hydrogen (6 atm) for 12 h. After reaction completion, the mixture was degassed with argon and filtered through Celite washing with additional EtOH. The combined organics were dried *in vacuo* and the crude material was then diluted with 1,4-dioxane:water 1:1 (2.2 mL, 0.1 M) and Et_3N (31 µl, 0.22 mmol, 1.0 eq.), Boc_2O (240 mg, 1.1 mmol, 5.0 eq.) and DMAP (0.3 mg, 2.2 µmol, 0.01 eq.) were added in sequence. The resulting solution was left stirring at rt overnight. Thereafter, the reaction was quenched with sodium bicarbonate (sat. aq. sol., 2 mL) and diluted with EtOAc. The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified by column chromatography (SiO_2, hexane:EtOAc 9:1 to 1:1) to afford **7** (75 mg, 0.19 mmol, 88%) as a white solid.

R_f 0.3 (*n*-hexanes:EtOAc = 2:1, UV, $KMnO_4$).

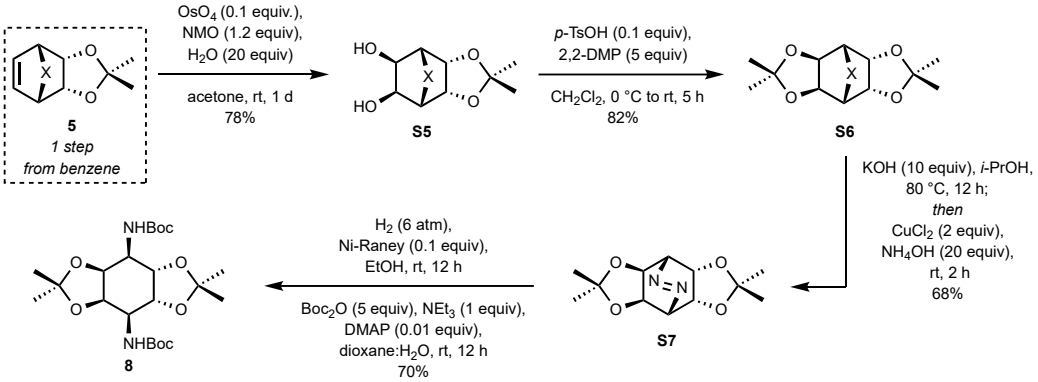
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 2H), 4.01 (d, *J* = 4.4 Hz, 2H), 3.77 (dp, *J* = 8.2, 4.1 Hz, 2H), 1.93 – 1.82 (m, 2H), 1.54 (s, 3H), 1.43 (s, 18H), 1.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 109.2, 79.8, 50.2, 28.5, 28.3, 26.5, 25.2.

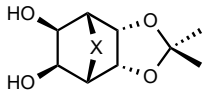
IR (ATR, neat, cm^{-1}) 3332 (b), 2981 (s), 2937 (s), 1681 (w), 1513 (w), 1453 (s), 1367 (m), 1244 (m), 1162 (w), 868 (m), 782 (s), 730 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{19}H_{34}N_2O_6Na$ $[M+Na]^+$ calc.: 409.2309; found: 409.2301.

m.p. 210 – 211 °C.



Scheme S3. Conversion of intermediate **5** to **8**.



Diol S5. To a solution of **5** (179 mg, 0.675 mmol, 1.0 eq.)[3] and *N*-methylmorpholine *N*-oxide (94.9 mg, 0.810 mmol, 1.2 eq.) in acetone (6.75 mL, 0.1 M) at rt was added H_2O (0.240 mL, 20 eq.) followed by a solution of OsO_4 (0.2 M in MeCN, 0.169 mL 0.03 mmol, 0.05 eq.). After completion, the reaction was quenched with a sodium thiosulfate (10% aq. sol., 5 mL). The mixture was directly concentrated *in vacuo*, absorbed on Celite and purified *via* column chromatography (SiO_2, hexane:EtOAc 2:1 to 1:2 with 10% MeOH) to afford **S5** (158 mg, 0.528 mmol, 78%) as a white solid.

R_f 0.2 (*n*-hexanes:EtOAc = 1:2, $KMnO_4$).

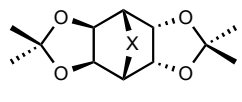
^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.60 – 4.50 (m, 4H), 4.36 (s, 2H), 3.05 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 155.5, 112.6, 73.3, 62.8, 56.7, 25.9, 25.8, 24.1.

IR (ATR, neat, cm^{-1}) 3488 (b), 3347 (s), 2981 (s), 2929 (s), 1759 (m), 1677 (m), 1457 (m), 1397 (m), 1315 (s), 1248 (m), 1159 (m), 1010 (m), 931 (s), 831 (s), 670 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{12}H_{17}N_3O_6Na$ $[M+Na]^+$ calc.: 322.1010; found: 322.0988.

m.p. 241 °C decomp.



***Bis*-acetonide S6**. To a solution of **S5** (158 mg, 0.528 mmol, 1.0 eq.) in CH_2Cl_2 (2.64 mL, 0.2 M) was added 2,2-DMP (323 µL, 2.64 mmol, 5.0 eq.). The solution was cooled to 0 °C, *p*-toluenesulfonic acid monohydrate (20 mg, 0.106 mmol, 0.2 eq.) was added, and the reaction was warmed to rt until completion (*ca.* 5 h). Thereafter, the reaction was quenched with sodium bicarbonate (sat. aq. sol., 2 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified by column chromatography (SiO_2, hexane:EtOAc 9:1 to 1:1) to afford **S6** (148 mg, 0.436 mmol, 82%) as a white solid.

R_f 0.3 (*n*-hexanes:EtOAc = 7:3, $KMnO_4$).

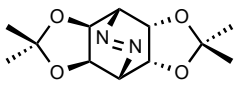
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (dq, *J* = 3.2, 1.6 Hz, 2H), 4.62 (dd, *J* = 2.9, 1.7 Hz, 2H), 4.48 (d, *J* = 1.6 Hz, 2H), 3.06 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 112.1, 109.2, 72.6, 70.0, 52.7, 25.6, 25.4, 24.9, 23.5, 23.0.

IR (ATR, neat, cm^{-1}) 2978 (s), 1766 (m), 1707. (w), 1457 (m), 1379 (m), 1308 (m), 1263 (w), 1203 (w), 1058 (w), 965 (m), 857 (m), 745 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{21}N_3O_6Na$ $[M+Na]^+$ calc.: 362.1323; found: 362.1307.

m.p. 275 – 277 °C.



S7

Diazene S7. The protocol was adapted from a reported protocol.[4] A solution of **S6** (150 mg, 0.442 mmol, 1.0 eq.) in *i*-PrOH (4.4 mL, 0.1 M) and KOH (248 mg, 4.42 mmol, 10 eq.) was degassed with argon and heated in a sealed vial at 80 °C for 12 hours. After cooling to room temperature and neutralization to pH 7 with the addition of AcOH (1 M, aq. sol.), the resulting mixture was treated with $CuCl_2$ (119 mg, 0.884 mmol, 2.0 eq.) and allowed to stir for additional 2 hours. The mixture was then extracted with treated with ammonium hydroxide (10% aq. sol., 1 mL) and extracted with EtOAc (4 × 10 mL). The resulting organics were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexane:EtOAc 7:3 to 1:2) to afford **S7** (76 mg, 0.30 mmol, 68%) in the form of colorless crystals.

R_f 0.2 (*n*-hexanes:EtOAc = 1:1, $KMnO_4$).

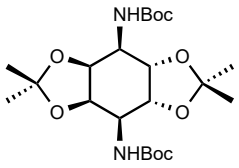
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 3.0, 1.6 Hz, 2H), 4.59 (d, *J* = 1.7 Hz, 2H), 3.91 (dt, *J* = 2.7, 1.5 Hz, 2H), 1.43 (s, 3H), 1.28 – 1.23 (m, 6H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 111.9, 109.0, 71.2, 69.2, 69.1, 25.8, 25.3, 24.1, 23.6.

IR (ATR, neat, cm^{-1}) 2981 (s), 2937 (s), 1528 (s), 1457 (s), 1379 (w), 1304 (s), 1263 (w), 1162 (w), 1058 (w), 969 (s), 924 (s), 801 (s), 663 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{12}H_{18}N_2O_4Na$ $[M+Na]^+$ calc.: 277.1159; found: 277.1152.

m.p. 203 – 205 °C.



8

***Bis*-amide 8**. To a degassed solution of **S7** (30 mg, 0.12 mmol, 1.0 eq.) in EtOH (1.2 mL, 0.1 M) was added Raney®-Nickel (0.5 mL, W.R. Grace and Co. Raney® 2400, slurry, in H_2O). Then, the reaction vessel was placed inside an autoclave and subjected to hydrogen (6 atm) for 12 h. After reaction completion, the mixture was degassed with argon, filtered through Celite, and rinsed with additional EtOH. The combined organics were dried *in vacuo* and the crude material was then diluted with 1,4-dioxane:water (1:1, 1.2 mL, 0.1 M) and

treated sequentially with Et_3N (16 µL, 0.12 mmol, 1.0 eq.), Boc_2O (130 mg, 0.59 mmol, 5.0 eq.) and DMAP (0.15 mg, 1.2 µmol, 0.01 eq.). The resulting solution was left stirring at rt overnight. Thereafter, the reaction was quenched with sodium bicarbonate (sat. aq. sol., 2 mL) and diluted with EtOAc. The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified by column chromatography (SiO_2, hexane:EtOAc 9:1 to 7:3) to afford **8** (38 mg, 0.083 mmol, 70%) as a foamy, white solid.

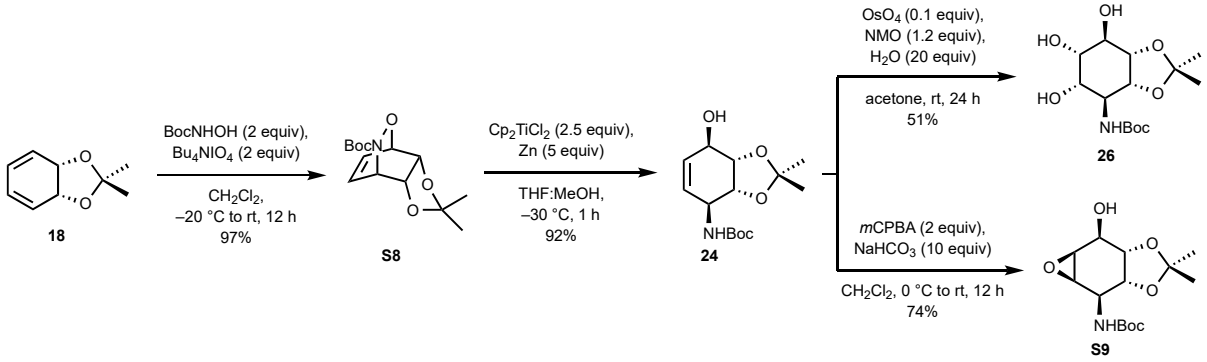
R_f 0.3 (*n*-hexanes:EtOAc = 2:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, *J* = 9.0 Hz, 2H), 4.45 (s, 2H), 4.18 – 4.06 (m, 2H), 3.81 (d, *J* = 10.5 Hz, 2H), 1.48 (s, 3H), 1.44 (s, 18H), 1.40 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H).

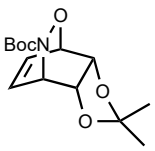
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.37, 109.43, 109.15, 79.88, 75.27, 74.84, 60.51, 51.70, 28.48, 27.44, 25.81, 25.02, 23.63.

IR (ATR, neat, cm^{-1}) 3436 (s), 3347 (s), 3056 (s), 2981 (s), 2933 (s), 1707 (w), 1502 (w), 1453 (s), 1364 (w), 1256 (m), 1162 (w), 1043 (w), 980 (m), 939 (m), 730 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{22}H_{38}N_2O_8Na$ $[M+Na]^+$ calc.: 481.2520; found: 481.2515.



Scheme S4. Conversion of intermediate **18** to **26**.



S8

Cycloadduct S8. To a solution of diene **18** (600 mg, 3.94 mmol, 1.0 eq.)[3] and BocNHOH (1.2 g, 7.88 mmol, 2.0 eq.) in CH_2Cl_2 (18 mL) at –20 °C under inert atmosphere was added dropwise a solution of Bu_4NIO_4 (3.42 g, 7.88 mmol, 2.0 eq.) in CH_2Cl_2 (10 mL). The resulting reaction was warmed to rt and stirred overnight. After this time, the reaction was quenched with a sodium thiosulfate (10% aq. sol., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were washed with sodium chloride (sat. aq. sol., 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexane:EtOAc 10:1 to 8:2) to afford **S8** (1.08 g, 3.80 mmol, 97%) as a white solid.

R_f 0.4 (*n*-hexane:EtOAc = 8:2, UV, $KMnO_4$).

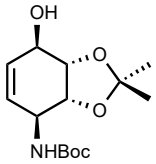
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 – 6.36 (m, 2H), 4.98 (ddd, J = 5.8, 4.0, 2.1 Hz, 1H), 4.87 (ddd, J = 5.8, 4.3, 1.8 Hz, 1H), 4.57 – 4.46 (m, 2H), 1.45 (s, 9H), 1.31 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 130.5, 129.6, 111.0, 82.6, 73.4, 72.9, 71.2, 53.2, 28.2, 25.7, 25.5.

IR (ATR, neat, cm^{-1}): 2981 (b), 2933 (b), 1707 (s), 1371 (m), 1252 (w), 1207 (m), 991 (w), 834 (w), 726 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{22}NO_5$ $[M+H]^+$ calc.: 284.1414; found: 284.1484.

m.p. 130 – 132 °C.



24

Alcohol 24. The protocol was adapted from a reported protocol.[5] A degassed and dry THF solution (20 mL, 0.08 M) of Cp_2TiCl_2 (1.04 g, 4.18 mmol, 2.5 eq.) and activated zinc powder (574 mg, 8.37 mmol, 5.0 eq.) was stirred at rt under N_2 for 45 min, during which the reaction mixture changed color from dark red to olive green. The reaction mixture was cooled to –30 °C and charged with a MeOH solution (16 mL) of substrate **S8** (474 mg, 1.67 mmol, 1.0 eq.) dropwise over 3 min. The reaction mixture was stirred for 45 min as the bath temperature was maintained between –10 °C and –30 °C. The reaction mixture was warmed to rt, partitioned between K_2CO_3 (sat. aq. sol., 15 mL) and EtOAc (40 mL) and filtered through a plug of Celite. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined filtered organics were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexane:EtOAc 3:1 to 2:1) to afford **24** (440 mg, 1.54 mmol, 92%) as a sticky, white solid.

R_f 0.4 (*n*-hexanes:EtOAc = 3:1, UV, $KMnO_4$).

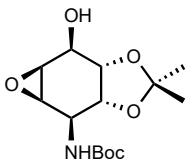
^{1}H NMR (400 MHz, MeOD) δ 5.77 (dt, J = 9.9, 2.6 Hz, 1H), 5.61 (dt, J = 9.8, 2.7 Hz, 1H), 4.13 (dq, J = 4.4, 2.4 Hz, 1H), 4.11 – 4.03 (m, 2H), 3.97 (d, J = 5.9 Hz, 1H), 1.45 (m, 12H), 1.34 (s, 3H).

^{13}C NMR (101 MHz, MeOD) δ 157.9, 132.7, 130.9, 110.1, 81.1, 80.4, 78.1, 71.0, 52.5, 28.7, 27.6, 25.1.

IR (ATR, neat, cm^{-1}): 3518 (b), 3488 (s), 3384 (m), 2929 (s), 1684 (m), 1513 (m), 1297 (m), 1084 (m), 730 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{24}NO_6$ $[M+H]^+$ calc.: 286.1655; found: 286.1642.

m.p. 109 – 110 °C.



S9

Epoxide S9. To a solution of **24** (200 mg, 0.7 mmol, 1.0 eq.) in CH_2Cl_2 (5.3 mL, 0.2 M) at 0 °C was added $NaHCO_3$ (600 mg, 7.0 mmol, 10 eq.) followed by *m*CPBA (75 wt%, 323 mg, 1.4 mmol, 2.0 eq.). The resulting reaction was warmed up to rt and stirred overnight. Thereafter, the reaction was quenched with a sodium thiosulfate (10% aq. sol., 3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic

phases were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexane:EtOAc 2:1 to 1:1) to afford **S9** (156 mg, 0.5 mmol, 74%) as white solid.

R_f 0.3 (*n*-hexanes:EtOAc = 1:1, $KMnO_4$).

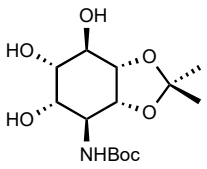
^{1}H NMR (400 MHz, MeOD) δ 4.12 – 4.04 (m, 3H), 3.93 (d, J = 7.1 Hz, 1H), 3.27 (d, J = 4.6 Hz, 1H), 3.24 (d, J = 4.6 Hz, 1H), 1.47 (s, 9H), 1.43 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (101 MHz, MeOD) δ 158.0, 108.9, 80.5, 79.8, 76.6, 72.4, 56.4, 55.8, 53.2, 28.7, 27.3, 24.3.

IR (ATR, neat, cm^{-1}): 3466 (b), 3391 (s), 2974 (s), 2929 (s), 1692 (m), 1513 (m), 1367 (w), 1166 (w), 965 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{24}NO_6$ $[M+H]^+$ calc.: 302.1520; found: 302.1591.

m.p. 140 – 142 °C.



26

Triol 26. To a solution of **24** (150 mg, 0.526 mmol, 1.0 eq.) and *N*-methylmorpholine *N*-oxide (74 mg, 0.631 mmol, 1.2 eq.) in acetone (4 mL, 0.1 M) at rt was added H_2O (0.190 mL, 20 eq.) followed by a solution of OsO_4 (0.2 M in MeCN, 0.131 mL, 0.026 mmol, 0.05 eq.). After completion, the reaction was quenched with a sodium thiosulfate (10% aq. sol., 3 mL). The mixture was directly concentrated *in vacuo*, absorbed on Celite and purified *via* column chromatography (SiO_2, CH_2Cl_2:MeOH 20:1 to 10:1) to afford **26** (86 mg, 0.27 mmol, 51%) as a foamy white solid.

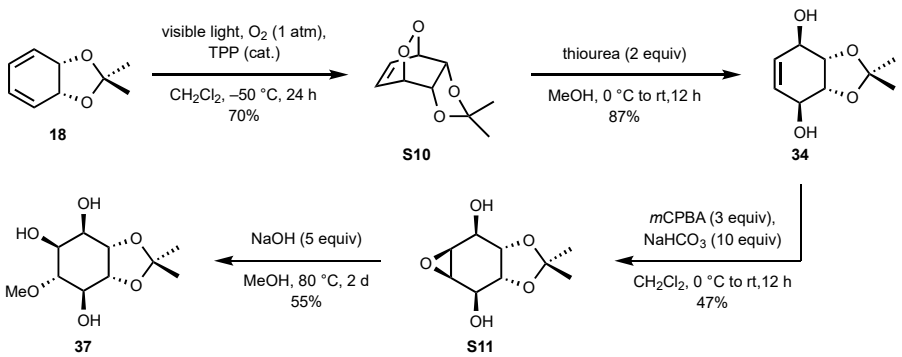
R_f 0.3 (CH_2Cl_2:MeOH = 9:1, $KMnO_4$).

^{1}H NMR (400 MHz, MeOD) δ 4.25 – 4.15 (m, 2H), 3.95 (t, *J* = 4.6 Hz, 1H), 3.90 – 3.83 (m, 3H), 1.47 (s, 3H), 1.45 (s, 9H), 1.34 (s, 3H).

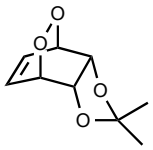
^{13}C NMR (101 MHz, MeOD) δ 158.0, 110.2, 80.4, 79.1, 77.6, 73.2, 72.8, 71.1, 54.5, 28.7, 28.6, 26.5.

IR ((ATR, neat, cm^{-1}): 3391 (b), 2981 (s), 2937 (s), 1681 (m), 1416 (m), 1312 (s), 1244 (s), 1222 (m), 1062 (w), 864 (m), 790 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{26}NO_7$ $[M+H]^+$ calc.: 320.1709; found: 320.1694.



Scheme S5. Conversion of intermediate **18** to **37**.



S10

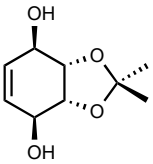
Endoperoxide S10. Diene **18** (400 mg, 2.63 mmol, 1.0 eq.)[3] was dissolved in CH_2Cl_2 (26 mL, 0.1 M) and tetraphenylporphyrin (16 mg, 0.026 mmol, 0.01 eq.) was added. The solution was cooled to –50 °C and oxygen gas was bubbled through while the flask was irradiated with white LEDs at –50 °C until completion (*ca.* 24 h). Once full conversion was observed by TLC, nitrogen gas was bubbled through the solution to purge the remaining oxygen before warming it up to room temperature. The crude material was purified *via* column chromatography (SiO_2, hexane:EtOAc 20:1 to 9:1) to provide endoperoxide **S10** (340 mg, 4.01 mmol, 70%) as a foamy white solid matching the literature data.[6]

Note: It has been observed that on small scale an oxygen-filled balloon is sufficient to push the reaction to completion, while for larger scales the reaction gains efficiency if it is connected directly to an oxygen tank and purged using a porous sparger.

R_f 0.4 (*n*-hexanes:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 4.6, 3.3 Hz, 2H), 4.92 – 4.85 (m, 2H), 4.56 (dd, *J* = 3.0, 1.7 Hz, 2H), 1.36 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 130.7, 110.5, 72.0, 71.7, 25.8, 25.6.



34

Diol 34. A solution of endoperoxide **S10** (160 mg, 0.869 mmol, 1.0 eq.) in MeOH (4 mL, 0.2 M) was cooled to 0 °C and thiourea (132 mg, 1.74 mmol, 2.0 eq.) was added. The solution was allowed to warm up to room temperature and stirred for 12 h. Upon completion, the crude material was purified *via* column chromatography (SiO_2, hexane:EtOAc 1:2 to 1:4) to provide diol **34** (140 mg, 0.752 mmol, 87%) as a foamy white solid.

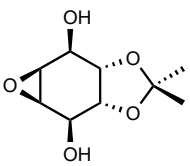
R_f 0.2 (*n*-hexanes:EtOAc = 1:2, $KMnO_4$).

^{1}H NMR (400 MHz, MeOD) δ 5.70 (d, *J* = 0.9 Hz, 2H), 4.11 – 3.99 (m, 4H), 1.45 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (101 MHz, MeOD) δ 132.1, 110.2, 80.9, 71.7, 27.5, 25.0.

IR (ATR, neat, cm^{-1}): 3362 (b), 2985 (s), 2929 (s), 1375 (w), 1211 (m), 1162 (m), 1058 (w), 984 (m), 1058 (w), 984 (m), 957 (m), 875 (m), 697 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_9H_{15}O_4$ $[M+H]^+$ calc.: 209.0784; found: 209.0783.



S11

Epoxy diol S11. To a solution of **34** (128 mg, 0.687 mmol, 1.0 eq.) in CH_2Cl_2 (3.44 mL, 0.2 M) at 0 °C was added $NaHCO_3$ (577 mg, 6.87 mmol, 10 eq.) followed by *m*CPBA (75 wt%, 474 mg, 2.06 mmol, 3.0 eq.). The resulting reaction was warmed up to rt and left stirring overnight. Thereafter, the reaction was quenched with a sodium

thiosulfate (10% aq. sol., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexane:EtOAc 2:1 to 1:2) to afford **S11** (65 mg, 0.32 mmol, 47%) as a foamy, white solid.

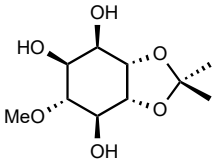
R_f 0.3 (*n*-hexanes:EtOAc = 1:2, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 4.5, 1.8 Hz, 2H), 4.08 (s, 2H), 3.39 (s, 2H), 2.42 (s, 2H), 1.47 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 108.6, 78.5, 72.1, 54.8, 27.0, 24.0.

IR (ATR, neat, cm^{-1}): 3399 (b), 2989 (s), 2933 (s), 1379 (s), 1263 (s), 1211 (s), 1162 (m), 969 (s), 879 (m), 812 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_9H_{14}O_5Na$ $[M+Na]^+$ calc.: 225.0733; found: 225.0727.



37

Triol 37. Epoxide **S11** (20 mg, 0.10 mmol, 1.0 eq.) was dissolved in MeOH (1.0 ml, 0.1 M) and solid NaOH (20 mg, 0.50 mmol, 5.0 eq.) was added. The reaction was heated to reflux until reaction completion. The solvent was removed *in vacuo* and the crude material directly purified by column chromatography (SiO_2, CH_2Cl_2:MeOH 20:1 to 4:1) to afford **37** (12 mg, 0.054 mmol, 55%) as a foamy white solid.

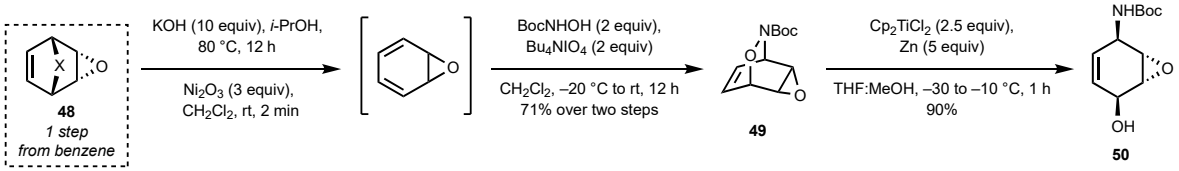
R_f 0.2 (CH_2Cl_2:MeOH = 9:1, $KMnO_4$).

^{1}H NMR (400 MHz, MeOD) δ 4.25 (dd, *J* = 6.3, 4.6 Hz, 1H), 4.09 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.95 (dd, *J* = 4.6, 2.9 Hz, 1H), 3.72 (dd, *J* = 6.4, 3.0 Hz, 1H), 3.54 (s, 3H), 3.51 (d, *J* = 8.4 Hz, 1H), 3.22 (dd, *J* = 8.6, 6.4 Hz, 1H), 1.45 (s, 3H), 1.33 (s, 3H).

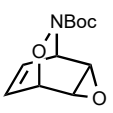
^{13}C NMR (101 MHz, MeOD) δ 110.3, 85.0, 80.0, 78.9, 76.3, 73.1, 71.3, 59.8, 28.2, 25.8.

IR (ATR, neat, cm^{-1}): 3362 (b), 2933 (m), 1640 (m), 1457 (m), 1379 (m), 1244 (m), 1222 (w), 1118 (w), 957 (m), 887 (m), 790 (m), 719 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{10}H_{18}O_6Na$ $[M+Na]^+$ calc.: 257.0996; found: 257.0986.



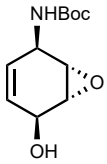
Scheme S6. Conversion of intermediate **48** to **50**.



49

Epoxide 49. To a vial containing finely ground KOH (1.35 g, 24.1 mmol, 10 eq.), and substrate **48** (500 mg, 2.41 mmol, 1.0 eq.) under nitrogen was added *i*-PrOH (24 mL, 0.1 M) and degassed using nitrogen and sonication for 15 min. The reaction was heated to 40 °C with vigorous stirring until complete conversion by TLC (ca. 2 h). Upon completion, the reaction was cooled in

an ice bath and H_2O was added. AcOH was then carefully added dropwise until pH 5. The semicarbazide intermediate was then extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried with sodium bicarbonate (sat. aq. sol.) and concentrated *in vacuo*. This mixture containing the semicarbazide was added to vial, followed by CH_2Cl_2 (24 mL, 0.1 M), and sparged with nitrogen for 15 minutes. Next, nickel oxide (1.20 g, 7.24 mmol, 3.0 eq., 30% active basis) was added as a solid under a stream of nitrogen (***note: vigorous gas evolution was observed***). The solution was agitated manually for 1 minute, filtered through a Celite plug, and the Celite was washed thoroughly with CH_2Cl_2 to yield the resulting arene-oxide as a solution (0.1 M). To this solution, *N*-acetohydroxyamic acid (353 mg, 2.65 mmol, 1.1 eq.) was added and the mixture was cooled to 0 °C. A solution of Bu_4NIO_4 (1.15 g, 2.65 mmol, 1.1 eq.) in CH_2Cl_2 (5 mL) was added dropwise. After 15 h at room temperature, the reaction mixture was quenched with sodium thiosulfate (sat. aq. sol., 10 mL) and the aqueous fraction was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with sodium chloride (sat. aq. sol.), dried over $MgSO_4$, filtered and the solvent was removed under vacuum. Purification of the residue by flash column chromatography (SiO_2, hexanes:EtOAc 1:1) afforded the desired cycloadduct **49** as a yellowish solid (390 mg, 1.7 mmol, 71%) which matched the literature data.[7]



50

Allylic alcohol 50. The protocol was adapted from a reported protocol.[5] A degassed and dry THF solution (61 mL) of Cp_2TiCl_2 (3 g, 12 mmol, 2.5 eq.) and activated zinc (1.6 g, 24 mmol, 5.0 eq.) was stirred at rt under N_2 for 45 min, during which the reaction mixture changed color from dark red to olive green. The reaction mixture was cooled to –30 °C and charged with a solution of substrate **49** (1.1 g, 4.9 mmol, 1.0 eq.) in MeOH (49 mL) dropwise over 3 min. The reaction mixture was stirred for 45 min as the bath temperature was maintained between –10 and –30 °C. The reaction mixture was warmed to rt, partitioned between K_2CO_3 (sat. aq. sol., 20 mL) and EtOAc (60 mL) and filtered through a plug of Celite. The aqueous layer was extracted with EtOAc (3 × 60 mL). The combined filtered organics were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexane:EtOAc 4:1 to 3:2) to afford the **50** as a sticky, white solid (1.0 g, 4.0 mmol, 90%).

R_f 0.2 (*n*-hexanes:EtOAc = 7:3, UV, $KMnO_4$).

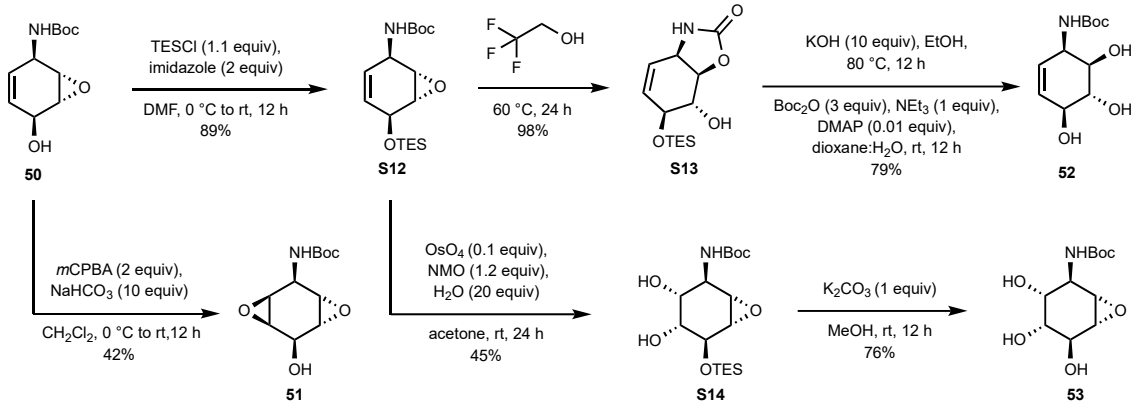
^{1}H NMR (400 MHz, MeOD) δ 5.72 (ddt, J = 10.2, 4.6, 1.6 Hz, 1H), 5.54 (ddd, J = 10.5, 4.7, 1.9 Hz, 1H), 4.36 – 4.26 (m, 2H), 3.20 (dq, J = 3.2, 1.6 Hz, 1H), 3.16 (dt, J = 3.1, 1.8 Hz, 1H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, MeOD) δ 157.7, 127.8, 125.5, 80.7, 63.0, 53.9, 53.3, 45.4, 28.7.

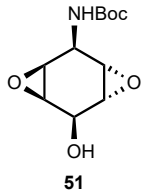
IR (ATR, neat, cm^{-1}): 3287 (b), 2974 (s), 2903 (s), 2564 (s), 2415 (s), 1681 (m), 1550 (s), 1423 (m), 1367 (m), 1252 (m), 1155 (w), 1043 (m), 1017 (m), 872 (m), 726 (m).

HRMS (ESI, m/z) calcd. for $C_{11}H_{17}NO_4Na$ $[M+Na]^+$ calc.: 250.1055; found: 250.1048.

m.p. 119 – 120 °C.



Scheme S7. Conversion of intermediate **50** to **51-53**.



***Bis*-epoxide 51**. To a solution of **50** (200 mg, 0.88 mmol, 1.0 eq.) in CH_2Cl_2 (4.4 mL, 0.2 M) at rt was added $NaHCO_3$ (370 mg, 4.4 mmol, 5.0 eq.) and subsequently *m*CPBA (75 wt%, 607 mg, 2.64 mmol, 3.0 eq.) and the resulting reaction was left stirring until completion (*ca*. 48 h). Thereafter, the reaction was quenched with a sodium thiosulfate (10% aq. sol., 3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, hexane:EtOAc 3:1 to 1:1) to afford **51** (90 mg, 0.37 mmol, 42%) as a sticky white solid.

R_f 0.4 (*n*-hexanes:EtOAc = 1:1, $KMnO_4$).

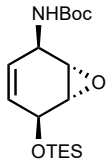
^{1}H NMR (400 MHz, MeOD) δ 4.18 (dd, *J* = 11.7, 3.2 Hz, 2H), 3.32 (d, *J* = 2.0 Hz, 1H), 3.27 (td, *J* = 3.6, 1.8 Hz, 1H), 3.00 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H), 2.97 – 2.91 (m, 1H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, MeOD) δ 157.80, 80.86, 64.59, 54.75, 54.47, 54.33, 53.39, 46.30, 28.68.

IR (ATR, neat, cm^{-1}) 3347 (b), 2978 (s), 1692 (m), 1509 (m), 1394 (m), 1367 (m), 1308 (m), 1244 (m), 1162 (w), 1051 (m), 1006 (m), 909 (m), 853 (m), 797 (s), 685 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{17}NO_5Na$ $[M+Na]^+$ calc.: 266.1004; found: 266.0995.

m.p. 121 – 123 °C.



S12

Silyl ether S12. To a solution of **50** (1.2 g, 5.3 mmol, 1.0 eq.) in DMF (53 mL, 0.1 M) at 0 °C was added imidazole (720 mg, 11 mmol, 2.0 eq.) and TESCl (880 mg, 5.8 mmol, 1.1 eq.) The reaction was warmed up to rt and stirred overnight. Thereafter, it was diluted with water (20 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were washed with sodium chloride (sat. aq. sol.), dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified *via* column chromatography (SiO_2, hexane:EtOAc 20:1 to 9:1) to afford **S12** (1.6 g, 4.7 mmol, 89%) as a colorless oil.

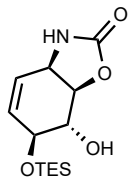
R_f 0.4 (*n*-hexanes:EtOAc = 9:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 – 5.55 (m, 2H), 4.69 – 4.50 (m, 2H), 4.44 (s, 1H), 3.29 – 3.23 (m, 1H), 3.16 (d, *J* = 3.4 Hz, 1H), 1.46 (s, 9H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.65 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 127.7, 124.7, 80.2, 63.0, 53.0, 52.3, 44.0, 28.5, 6.9, 4.9.

IR (ATR, neat, cm^{-1}) 3332 (b), 2955 (s), 2914 (s), 2877 (s), 1714 (m), 1494 (m), 1390 (s), 1304 (m), 1237 (m), 1166 (w), 1066 (w), 1010 (w), 898 (m), 849 (w), 726 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{17}H_{31}NO_4SiNa$ $[M+Na]^+$ calc.: 364.1915; found: 364.1901.



S13

Cyclic carbamate S13. Silyl ether **S12** (300 mg, 0.878 mmol, 1.0 eq.) was dissolved in trifluoroethanol (8.8 mL, 0.1 M) and heated at 60 °C for 1 d. The solvent was removed *in vacuo* and the residue was purified *via* column chromatography (SiO_2, hexane:EtOAc 2:1 to 1:2) to afford **S13** (248 mg, 0.869 mmol, 98%) as a white solid.

R_f 0.3 (*n*-hexanes:EtOAc = 1:1, UV, $KMnO_4$).

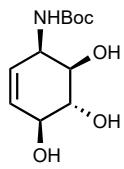
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.79 (dt, *J* = 10.1, 1.6 Hz, 1H), 5.64 (dt, *J* = 10.1, 2.7 Hz, 1H), 4.57 (t, *J* = 8.8 Hz, 1H), 4.46 (ddd, *J* = 8.9, 3.2, 1.6 Hz, 1H), 4.10 (dq, *J* = 8.4, 1.8 Hz, 1H), 3.72 (td, *J* = 8.7, 2.7 Hz, 1H), 2.73 (d, *J* = 2.7 Hz, 1H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.73 – 0.59 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 134.5, 122.4, 78.3, 74.2, 70.2, 51.3, 6.9, 5.3, 5.0, 4.7.

IR (ATR, neat, cm^{-1}) 3440 (b), 3272 (b), 2955 (m), 2877 (m), 1744 (w), 1379 (w), 1248 (w), 1218 (w), 1077 (w), 1036 (w), 943 (w), 909 (m), 760 (w), 685 (w).

HRMS (ESI-TOF, m/z) calcd. for C1H123NO4SiNa $[M+Na]^+$ calc.: 308.1289.; found: 308.1282.

m.p. 183 – 185 °C.



52

Triol 52. To a solution of **S13** (125 mg, 0.438 mmol, 1.0 eq.) in EtOH (4.38 mL, 0.1 M) was added KOH (246 mg, 4.38 mmol, 10 eq.) and the reaction was heated to reflux overnight. Thereafter, it was cooled to rt, neutralized with HCl (1 M aq. sol.) and EtOH was removed *in vacuo*. The aqueous phase was then diluted with 1,4-dioxane (2 mL) and sequentially treated

with Et_3N (61 µL, 0.438 mmol, 1.0 eq.), Boc_2O (287 mg, 1.31 mmol, 3.0 eq.) and DMAP (0.5 mg, 0.01 eq.). The resulting solution was stirred at rt overnight. Thereafter, the reaction was quenched with sodium bicarbonate (sat. aq. sol., 3 mL). The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified *via* column chromatography (SiO_2, CH_2Cl_2:MeOH 20:1 to 4:1) to afford **52** (85 mg, 0.35 mmol, 79%) as a colorless oil.

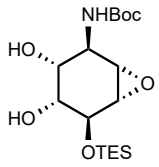
R_f 0.3 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 – 5.64 (m, 2H), 5.06 – 4.94 (m, 1H), 4.74 (s, 1H), 4.58 (d, *J* = 4.4 Hz, 1H), 4.44 (s, 1H), 4.09 (t, *J* = 5.9 Hz, 1H), 3.81 – 3.63 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 132.0, 126.0, 80.3, 73.6, 72.2, 70.3, 28.6.

IR (ATR, neat, cm^{-1}) 3306 (b), 2974 (s), 2922 (s), 1681 (w), 1520 (m), 1453 (m), 1394 (m), 1300 (m), 1248 (w), 1162 (w), 954 (m), 805 (m), 771 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{11}H_{19}NO_5Na$ $[M+Na]^+$ calc.:268.1155.; found: 286.1146.



S14

Diol S14. To a solution of **S12** (100 mg, 0.293 mmol, 1.0 eq.) and *N*-Methylmorpholine *N*-oxide (41.2 mg, 0.351 mmol, 1.2 eq.) in acetone (2 mL, 0.1 M) at rt was added H_2O (106 µL, 20 eq.) and a solution of OsO_4 (0.2 M in MeCN, 146 µL, 29.3 µmol, 0.1 eq.). After completion, the reaction was quenched with a sodium thiosulfate (10% aq. sol., 1 mL). The mixture was directly concentrated *in vacuo*, absorbed on Celite and purified *via* column chromatography (SiO_2, hexane:EtOAc 2:1 to 1:2) to afford **S14** (50 mg, 0.13 mmol, 45%) as a white solid.

R_f 0.6 (*n*-hexanes:EtOAc = 1:2, $KMnO_4$).

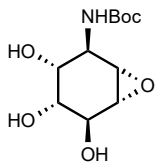
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (d, *J* = 6.5 Hz, 1H), 4.30 (dd, *J* = 3.9, 1.9 Hz, 1H), 4.08 (d, *J* = 21.1 Hz, 1H), 3.63 (d, *J* = 8.8 Hz, 2H), 3.31 (d, *J* = 3.3 Hz, 1H), 3.19 (t, *J* = 2.6 Hz, 1H), 2.56 (dd, *J* = 24.6, 9.9 Hz, 2H), 1.47 (s, 9H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.65 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 80.5, 73.7, 69.8, 68.2, 56.2, 56.0, 50.9, 28.5, 6.9, 4.7.

IR (ATR, neat, cm^{-1}) 3436 (b), 3272 (b), 3160 (s), 2952 (s), 2877 (m), 1744 (w), 1379 (m), 1248 (m), 1218 (m), 1077 (w), 1036 (w), 943 (w), 853 (m), 760 (w), 685 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{17}H_{33}NO_6SiNa$ $[M+Na]^+$ calc.: 398.1969; found 398.1970.

m.p. 186 – 187 °C.



53

Triol 53. To a solution of diol **S14** (326 mg, 0.868 mmol, 1.0 eq.) in MeOH (8.68 mL, 0.1 M) at rt was added K_2CO_3 (120 mg, 0.868 mmol, 1.0 eq.) and the contents were stirred overnight. After completion, the reaction was directly concentrated *in vacuo*, absorbed on

Celite and purified *via* column chromatography (SiO_2, CH_2Cl_2:MeOH 10:1 to 4:1) to afford **53** (170 mg, 0.66 mmol, 76%) as a fluffy solid.

R_f 0.2 (CH_2Cl_2:MeOH = 9:1, $KMnO_4$).

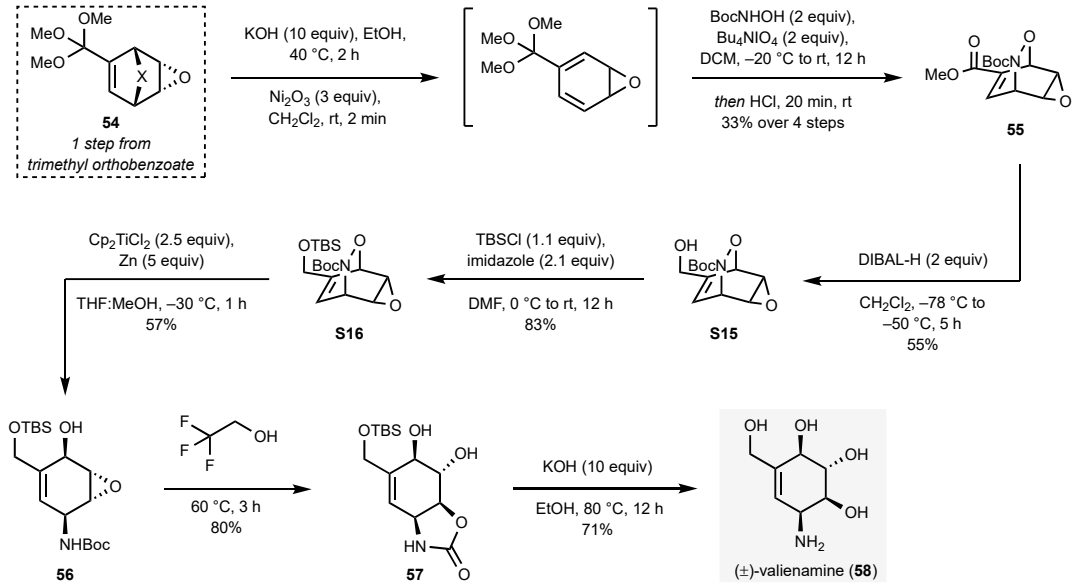
^{1}H NMR (400 MHz, MeOD) δ 4.25 (t, *J* = 3.0 Hz, 1H), 3.74 (dd, *J* = 8.5, 1.0 Hz, 1H), 3.66 – 3.57 (m, 1H), 3.39 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.30 – 3.25 (m, 1H), 3.11 (dd, *J* = 3.5, 0.8 Hz, 1H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, MeOD) δ 159.6, 80.3, 71.4, 68.9, 68.6, 57.6, 56.9, 55.1, 28.8.

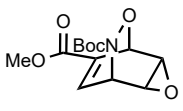
IR (ATR, neat, cm^{-1}) 3328 (b), 2978 (s), 2933 (s), 1684 (m), 1520 (m), 1364 (m), 1319 (s), 1293 (s), 1244 (m), 1162 (w), 1058 (m), 864 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{19}NO_6Na$ $[M+Na]^+$ calc.: 284.2638; found: 284.1102.

Derivatization of Trimethylorthobenzoate



Scheme S8. Conversion of intermediate **54** to valienamine **58**.



Ester 55. To a vial containing finely ground KOH (1.44 g, 25.7 mmol, 10 eq.) and substrate **54** (800 mg, 2.57 mmol, 1.0 eq.) under nitrogen was added *i*-PrOH (25.7 mL, 0.1 M) and degassed with sonication and nitrogen for 15 min. The reaction was heated to 40 °C with vigorous stirring until complete conversion by TLC (ca. 2 h). Upon completion, the reaction was cooled in an ice bath and H_2O (4 mL) was added. Glacial AcOH was then carefully added dropwise until pH 6. The semicarbazide intermediate was then extracted out with EtOAc (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated *in vacuo*. This mixture containing the semicarbazide was added to vial, followed by CH_2Cl_2 (25.7 mL, 0.1 M), and sparged with nitrogen for 15 minutes. Next, nickel oxide (Ni_2O_3, 30% active basis, 4.25 g, 7.71 mmol, 3.0 eq.) was added as a solid under a stream of nitrogen (***note: vigorous gas evolution was observed***). The solution was agitated

manually for 1 minute, filtered through a Celite plug, and the Celite was washed thoroughly with CH_2Cl_2 to yield the resulting arene-oxide as a solution. To this solution, *N*-acetohydroxyamic acid (411 mg, 3.08 mmol, 1.2 eq.) was added and the mixture was cooled to –20 °C. A solution of Bu_4NIO_4 (1.34 g, 3.08 mmol, 1.2 eq.) in CH_2Cl_2 (10 mL) was added dropwise under nitrogen atmosphere and the reaction was warmed up and left stirring overnight. Thereafter, the reaction mixture was quenched with sodium thiosulfate (10% aq. sol., 10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with sodium chloride (sat. aq. sol., 30 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude material was dissolved in CH_2Cl_2 (25 mL) and acidified to pH 4 with HCl (1 M aq. sol.). At this point the organic phase was dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified *via* column chromatography (SiO_2, hexane:EtOAc 9:1 to 1:1) to afford **55** (274 mg, 0.832 mmol, 33%) as a yellowish oil.

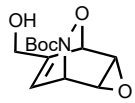
R_f 0.3 (*n*-hexanes:EtOAc = 2:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (ddd, J = 6.3, 2.2, 0.9 Hz, 1H), 5.60 (dd, J = 4.3, 2.2 Hz, 1H), 5.31 (dd, J = 6.3, 4.5 Hz, 1H), 3.80 (s, 3H), 3.73 – 3.62 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 156.9, 134.0, 130.4, 83.4, 73.9, 54.4, 52.4, 41.8, 41.4, 28.2, 28.1.

IR (ATR, neat, cm^{-1}) 3082 (s), 2978 (s), 1725 (m), 1438 (s), 1367 (m), 1312 (m), 1252 (m), 1151 (m), 1103 (m), 1017 (m), 969 (s), 935 (m), 887 (m), 764 (m), 663 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{13}H_{17}NO_6Na$ $[M+Na]^+$ calc.: 306.0948; found: 306.0939.



S15

Allylic alcohol S15. A solution of **55** (134 mg, 0.473 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (4.7 mL, 0.1 M) was cooled down to –78 °C and DIBAL-H (0.95 mL, 1 M sol. in CH_2Cl_2, 0.946 mmol, 2.0 eq.) was added dropwise under nitrogen atmosphere and the reaction was left stirring for 3 h and warmed to –50°C. Thereafter, potassium sodium tartrate (sat. aq. sol., 5 mL) was added and after 20 min the aqueous phase was extracted with CH_2Cl_2 (4 × 4 mL). The combined organics were dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified *via* column chromatography (SiO_2, hexane:EtOAc 2:1 to 1:2) to afford **S15** (66 mg, 0.26 mmol, 55%) as a yellowish oil.

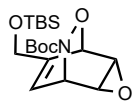
R_f 0.35 (*n*-hexanes:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (ddt, *J* = 6.1, 2.2, 1.3 Hz, 1H), 5.17 – 5.08 (m, 2H), 4.24 (d, *J* = 1.7 Hz, 2H), 3.70 – 3.57 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 139.8, 119.4, 82.9, 77.5, 77.2, 76.8, 75.6, 62.0, 54.6, 42.1, 41.9, 28.3.

IR (ATR, neat, cm^{-1}) 3332 (b), 2974 (s), 2929 (s), 2877 (s), 1699 (m), 1517 (m), 1453 (m), 1367 (m), 1252 (m), 1166 (m), 1088 (m), 752 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{17}NO_5Na$ $[M+Na]^+$ calc.: 275.1366; found: 275.1368.



S16

Silyl Ether S16. To a solution of **S15** (106 mg, 0.417 mmol, 0.417 mmol, 1.0 eq.) in DMF (4.17 mL, 0.1 M) at 0 °C was added imidazole (60 mg, 0.876 mmol, 2.1 eq.) and TBSCl (69 mg, 0.459 mmol, 1.1 eq.) The reaction was warmed to rt and stirred overnight. Thereafter, it was diluted with water (10 mL) and EtOAc and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were washed with sodium chloride (sat. aq. sol.), dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified by column chromatography (SiO_2, hexane:EtOAc 6:1 to 3:1) to afford **S16** (128 mg, 0.346 mmol, 83%) as a colorless oil.

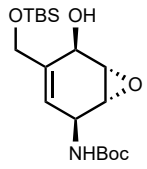
R_f 0.3 (*n*-hexanes:EtOAc = 4:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (dtd, *J* = 6.3, 2.1, 1.1 Hz, 1H), 5.16 – 5.07 (m, 1H), 5.02 – 4.93 (m, 1H), 4.24 (dd, *J* = 1.9, 1.0 Hz, 2H), 3.59 (dt, *J* = 14.2, 4.3 Hz, 2H), 1.46 (s, 9H), 0.89 (s, 9H), 0.06 (d, *J* = 2.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 139.9, 117.9, 82.7, 82.6, 75.3, 61.8, 54.6, 42.1, 42.0, 28.3, 25.9, 18.5, 18.4, -5.21, -5.28.

IR (ATR, neat, cm^{-1}) 2929 (m), 2884 (s), 2858 (m), 1729 (w), 1468 (m), 1394 (m), 1338 (m), 1285 (w), 1248 (w), 1080 (w), 1010 (m), 939 (m), 782 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{18}H_{31}NO_5SiNa$ [M+Na]+ calc.: 392.1864; found: 392.1848.



56

Allylic alcohol 56. The protocol was adapted from a reported protocol.[5] A degassed THF solution (4.33 mL, 0.08 M) of Cp_2TiCl_2 (216 mg, 0.866 mmol, 2.5 eq.) and activated zinc (113 mg, 1.73 mmol, 5.0 eq.) was stirred at rt under N_2 for 45 min. The reaction mixture changed colour from dark red to olive green. The reaction mixture was cooled to –30 °C and charged with a solution of **S16** (128 mg, 0.346 mmol, 1.0 eq.) in MeOH (4.33 mL, 0.08 M) dropwise over 3 min. The reaction mixture was stirred for 45 min as the bath temperature was maintained between –10 and –30 °C. The reaction mixture was warmed to rt and partitioned between K_2CO_3 (sat. aq. sol., 2 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the organic layer was filtered through a Celite pad after extraction. The combined filtered organics were dried over $MgSO_4$, filtered, and dried *in vacuo*. The crude material was purified *via* column chromatography (SiO_2, hexane:EtOAc 2:1 to 1:2) to afford **56** (73 mg, 0.20 mmol, 57%) as a sticky, white solid.

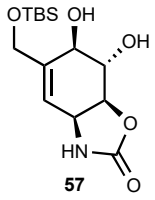
R_f 0.3 (hexanes:EtOAc = 2:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 5.56 – 5.51 (m, 1H), 4.39 – 4.34 (m, 1H), 4.28 (d, J = 2.4 Hz, 1H), 4.25 – 4.13 (m, 2H), 3.27 (dt, J = 3.4, 1.6 Hz, 1H), 3.18 (s, 1H), 1.45 (s, 9H), 0.92 (s, 9H), 0.08 (d, J = 5.3 Hz, 6H).

^{13}C NMR (126 MHz, MeOD) δ 157.7, 138.6, 119.2, 80.7, 64.9, 63.1, 54.2, 53.2, 49.5, 49.3, 49.1, 49.0, 48.8, 48.7, 48.5, 45.6, 28.7, 26.4, 19.2, -5.2, -5.3.

IR (ATR, neat, cm^{-1}) 3287 (b), 2974 (s), 2875 (s), 2564 (s), 2415 (s), 1681 (m), 1550 (m), 1423 (m), 1367 (m), 1252 (m), 1155 (w), 1043 (m), 1010 (m), 939 (m), 782 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{18}H_{33}NO_5SiNa$ $[M+Na]^+$ calc.: 394.2026; found: 394.2027.



57

Diol 57. A solution of **56** (100 mg, 0.269 mmol, 1.0 eq.) in trifluoroethanol (2.7 mL, 0.1 M) was heated to 60 °C for 3 h. The reaction mixture was warmed to rt and filtered over PTFE with MeOH. The reaction was dried *in vacuo* and the residue was purified *via* column chromatography (SiO_2, hexane:EtOAc 1:4 to 1:6 with 10% MeOH) to afford **57** (68 mg, 0.215 mmol, 80%) as sticky, white solid.

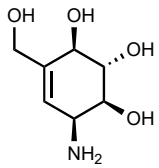
R_f 0.3 (*n*-hexanes:EtOAc = 1:4, UV, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 5.72 (dq, J = 3.8, 1.9 Hz, 1H), 4.57 (t, J = 8.4 Hz, 1H), 4.49 – 4.43 (m, 1H), 4.39 (dq, J = 15.5, 1.6 Hz, 1H), 4.28 (dq, J = 15.3, 2.0 Hz, 1H), 4.05 (dt, J = 7.9, 1.7 Hz, 1H), 3.68 (t, J = 8.0 Hz, 1H), 0.94 (s, 9H), 0.10 (d, J = 1.5 Hz, 6H).

^{13}C NMR (126 MHz, MeOD) δ 161.0, 143.7, 117.2, 80.0, 74.3, 70.4, 63.3, 52.2, 26.4, 19.2, -5.31, -5.35.

IR (ATR, neat, cm^{-1}) 3443 (b), 3320 (b), 2951 (m), 2929(m), 2874 (m), 1744 (w), 1248 (w), 1215 (w), 1080 (w), 1036 (w), 943 (w), 909 (m), 760 (w), 681 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{14}H_{26}NO_5Si$ $[M+H]^+$ calc.: 316.1580; found: 316.1580.



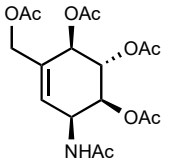
(±)-valienamine (**58**)

Valienamine 58. To a solution of **57** (43 mg, 0.14 mmol, 1.0 eq.) in EtOH (1.4 mL, 0.1 M) was added KOH (77 mg, 1 mmol, 10 eq.) and the reaction was heated to reflux overnight. Thereafter, it was cooled to rt, and EtOH was removed *in vacuo*. The residue was diluted with water and was purified with Amberlyst A26 hydroxide form ionic exchange resin using NH_4OH (48 wt%, aq. sol.) as eluent to obtain **58** (17 mg, 0.097 mmol, 71%) as a colorless syrup, matching literature data.[8]

R_f 0.3 (CH_2Cl_2:MeOH = 3:1, UV, $KMnO_4$)

^{1}H NMR (400 MHz, D_2O) δ 5.73 – 5.67 (m, 1H), 4.15 (d, *J* = 13.7 Hz, 1H), 4.10 – 3.96 (m, 2H), 3.67 – 3.54 (m, 2H), 3.41 (t, *J* = 4.7 Hz, 1H).

Valienamine pentaacetate 58•OAc. To a solution of **58** (17 mg, 0.097 mmol, 1.0 eq.) in pyridine (1.4 mL, 0.07 M) and acetic anhydride (0.65 mL, 0.15 M) containing a catalytic amount of DMAP (0.59 mg, 4.9 µmol, 0.05 eq.). The resulting solution was stirred overnight at room temperature, then was diluted with EtOAc (2 mL) and washed with sodium bicarbonate (sat. aq. sol., 5 mL). The aqueous layer was further extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with sodium chloride (sat. aq. sol.), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified *via* column chromatography (SiO_2, hexane:EtOAc 3:1 to 1:4) to give **58•OAc** (27 mg, 70 µmol, 72%) as a white solid, matching literature data.[9]

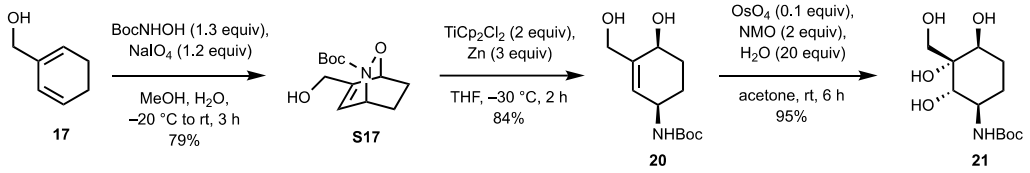


(±)-valienamine (**58•OAc**)

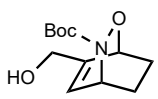
R_f 0.3 (hexanes:EtOAc = 1:4, UV, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dq, *J* = 5.4, 1.4 Hz, 1H), 5.66 (d, *J* = 8.8 Hz, 1H), 5.46 (dd, *J* = 9.8, 6.4 Hz, 1H), 5.36 (d, *J* = 6.4 Hz, 1H), 5.12 – 4.99 (m, 2H), 4.64 (dq, *J* = 13.3, 1.2 Hz, 1H), 4.39 (d, *J* = 13.3 Hz, 1H), 2.11 – 1.98 (m, 15H).

Derivatization of Benzyl Acetate



Scheme S9. Conversion of intermediate **17** to **21**.



S17

Nitroso cycloadduct S17. Diene **17** (2.62 g, 23.8 mmol, 1.0 eq.)[2] and *N*-Boc-hydroxylamine (4.12 g, 30.9 mmol, 1.3 eq.) were dissolved in MeOH (476 mL, 0.05 M) and the solution was cooled to −10 °C. In a separate flask, $NaIO_4$ (6.10 g, 28.5 mmol, 1.2 eq.) was dissolved in H_2O (143 mL, 0.2 M relative to $NaIO_4$) and added dropwise *via* cannula into the aforementioned MeOH solution over 15 minutes. The reaction mixture was allowed to slowly warm to room temperature and then stirred for 3 h. Thereafter, the reaction was quenched by addition of sodium thiosulfate (10 wt% aq. sol., 50 mL) and H_2O (100 mL). After 30 minutes, MeOH was removed *in vacuo* and the remaining aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 100 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified *via* column chromatography (SiO_2, 4:1-1:2 hexanes:EtOAc) to afford **S17** (4.53 g, 18.8 mmol, 79%) as a colorless oil which solidified upon standing.

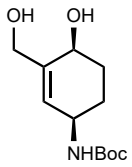
R_f 0.4 (*n*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dq, J = 5.7, 1.7 Hz, 1H), 4.70 (dt, J = 3.7, 1.8 Hz, 1H), 4.66 (dt, J = 6.1, 3.0 Hz, 1H), 4.24 – 4.14 (m, 2H), 2.14 (ddt, J = 13.0, 9.5, 3.7 Hz, 1H), 2.03 (ddt, J = 12.8, 9.3, 3.5 Hz, 1H), 1.38 (m, 10H), 1.32 (dddd, J = 13.0, 11.6, 3.6, 1.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 144.7, 124.3, 81.9, 72.0, 61.9, 50.7, 28.3, 23.8, 21.6.

IR (ATR, neat, cm^{-1}) 3396 (b), 2975 (m), 2937 (m), 1703 (s), 1368 (s), 1255 (m), 1168 (s), 1148 (s), 1075 (m), 1025 (m), 891 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{19}NO_4Na^+$ $[M+Na]^+$ calc.: 264.1212; found: 264.1211.



20

Diol 20. The protocol was adapted from a reported protocol.[5] Cp_2TiCl_2 (262 mg, 1.05 mmol, 2.0 eq.) and zinc powder (103 mg, 1.58 mmol, 3.0 eq.) were suspended in dry degassed THF (5.26 mL, 0.2 M relative to titanocene) and stirred under inert atmosphere for 1 h at room temperature. Thereafter, the green suspension was cooled to −30 °C, and a solution of nitroso cycloadduct **S17** in dry degassed THF (5.26 mL, 0.1 M) was added dropwise over 15 minutes. The reaction mixture was stirred for 2 h at −30 °C, then warmed to room temperature. Thereafter, the reaction was quenched by addition of sodium phosphate monobasic (sat. aq. sol., 10 mL) under vigorous stirring. After 2 h, the orange biphasic mixture was filtered, the organic phase was separated, and the aqueous phase was extracted with EtOAc (5 × 10 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 50 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified *via* column chromatography (SiO_2, 1:1-1:4 hexanes:EtOAc) to afford diol **20** (107 mg, 0.44 mmol, 84%) as a light yellow oil which solidified upon standing.

Note: The reaction can be run on multi-gram scale following the same procedure with slightly lower yields observed.

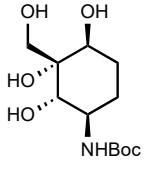
R_f 0.4 (*n*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1H), 4.17 – 4.10 (m, 2H), 4.08 (m, 1H), 4.00 (br, 1H), 1.86 – 1.69 (m, 3H), 1.68 – 1.56 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 142.5, 127.9, 80.1, 64.5, 64.2, 48.2, 31.0, 28.8, 25.9.

IR (ATR, neat, cm^{-1}) 3323 (b), 2976 (w), 2937 (m), 2870 (w), 1683 (s), 1520 (m), 1366 (m), 1249 (m), 1167 (s), 1060 (m), 984 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{21}NO_4Na^+$ $[M+Na]^+$ calc.: 266.1368; found: 266.1367.



21

Tetraol 21. To a solution of diol **20** (152 mg, 0.63 mmol, 1.0 eq.) in acetone (6.25 mL, 0.1 M) was added *N*-methylmorpholine *N*-oxide (146 mg, 1.25 mmol, 2.0 eq.), H_2O (225 µL, 20 eq.), and OsO_4 (0.2 M in MeCN, 312 µL, 63 µmol, 0.1 eq.). The solution was stirred for 6 h at room temperature. Thereafter, the reaction was quenched by addition of sodium thiosulfate (10 wt% aq. sol., 2 mL). After 30 minutes, the mixture was dried *in vacuo*. The crude materials were sonicated in MeOH (10 mL) and the mixture was filtered through a frit before dry loading on silica

for column chromatography (SiO_2, 30:1-10:1 CH_2Cl_2:MeOH). Tetraol **21** (164 mg, 0.59 mmol, 95%) was obtained as a sticky, white foam.

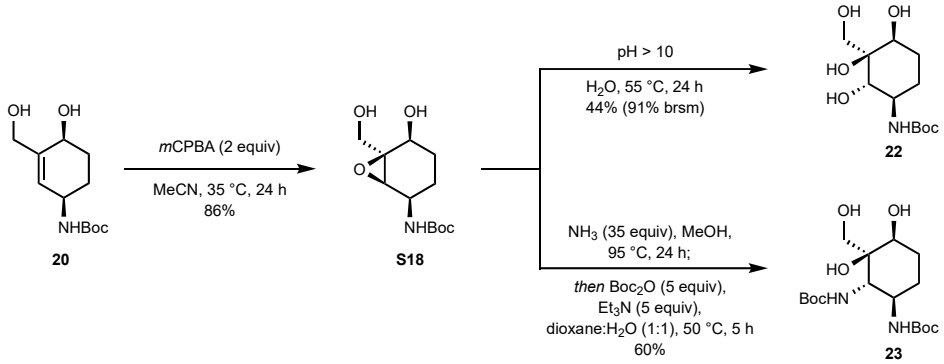
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 3.89 (s, 1H), 3.81 (d, J = 11.1 Hz, 1H), 3.76 – 3.67 (m, 2H), 3.56 (d, J = 10.2 Hz, 1H), 1.97 (dt, J = 15.8, 7.5 Hz, 1H), 1.72 – 1.55 (m, 3H), 1.46 (s, 9H).

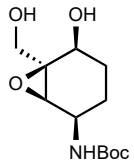
^{13}C NMR (126 MHz, MeOD) δ 158.9, 79.9, 76.2, 73.4, 71.8, 66.5, 52.9, 28.8, 28.1, 26.6.

IR (ATR, neat, cm^{-1}) 3339 (b), 2972 (m), 2937 (m), 1681 (s), 1530 (m), 1366 (s), 1314 (m), 1248 (m), 1167 (s), 1076 (s), 1015 (s), 859 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{23}NO_6Na^+$ $[M+Na]^+$ calc.: 300.1423; found: 300.1417.



Scheme S10. Conversion of intermediate **20** to **22** and **23**.



S18

Epoxide S18. To a solution of diol **20** (500 mg, 2.06 mmol, 1.0 eq.) in MeCN (20.6 mL, 0.1 M) was added *m*CPBA (75 wt%, 978 mg, 4.11 mmol, 2.0 eq.). The solution was stirred at 35 °C for 24 h. Thereafter, the reaction was cooled to room temperature and quenched by addition of sodium thiosulfate (10 wt% aq. sol., 10 mL). After 30 minutes, the organic phase was separated, and the aqueous phase was extracted with EtOAc (5 × 10 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 50 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were purified *via* column chromatography (SiO_2, 30:1-10:1 CH_2Cl_2:MeOH) to afford epoxide **S18** (460 mg, 1.77 mmol, 86%) as a sticky, white foam.

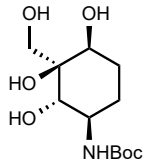
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 4.06 (t, J = 4.5 Hz, 1H), 3.87 (d, J = 11.9 Hz, 2H), 3.48 (d, J = 12.0 Hz, 1H), 3.35 (d, J = 3.0 Hz, 1H), 1.65 – 1.56 (m, 1H), 1.46 (m, 12H).

^{13}C NMR (126 MHz, MeOD) δ 157.8, 80.3, 65.7, 65.1, 63.4, 60.8, 47.7, 29.4, 28.7, 24.5.

IR (ATR, neat, cm^{-1}) 3347 (b), 2971 (m), 2938 (m), 1683 (s), 1519 (m), 1366 (s), 1249 (m), 1168 (s), 1061 (m), 877 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{21}NO_5Na^+$ $[M+Na]^+$ calc.: 282.1317; found: 282.1317.



22

Tetraol 22. A mixture of epoxide **S18** (30 mg, 0.12 mmol, 1.0 eq.) in H_2O (1.2 mL, 0.1 M) was basified to pH > 10 by addition of NaOH (2 M aq. sol., *sat. aq. sol. of $NaHCO_3$ for basifying also works with the same efficiency*). The solution was stirred at 55 °C for 24 h, thereafter cooled to room temperature. The solvent was completely removed *in vacuo*. The crude materials were sonicated in MeOH (10 mL) and the mixture was filtered before dry loading on silica gel for column chromatography (SiO_2, 40:1-15:1 CH_2Cl_2:MeOH). Tetraol **22** (14 mg, 50 μmol, 44%) was obtained as a colorless oil along with recovered starting material **S18** (14 mg, 54 μmol, 47%).

Note: The reaction can be pushed longer or at higher temperature to convert more starting material, but significant amounts of Boc deprotection occurs.

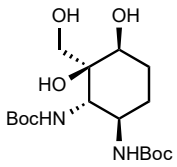
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 3.92 (dt, *J* = 12.9, 3.7 Hz, 1H), 3.84 (dd, *J* = 11.4, 2.1 Hz, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.73 – 3.65 (m, 2H), 2.08 – 1.97 (m, 1H), 1.81 (qd, *J* = 13.2, 3.8 Hz, 1H), 1.68 (dq, *J* = 13.9, 3.2 Hz, 1H), 1.36 – 1.59 (m, 10H).

^{13}C NMR (126 MHz, MeOD) δ 75.4, 75.1, 71.9, 69.4, 65.4, 28.0, 24.3.

IR (ATR, neat, cm^{-1}) 3357 (b), 2932 (m), 1683 (s), 1511 (m), 1367 (m), 1250 (m), 1166 (s), 1063 (s), 968 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{23}NO_6Na^+$ $[M+Na]^+$ calc.: 300.1423; found: 300.1422.



23

Triol 23. In a pressure tube, epoxide **S18** (16 mg, 62 μmol, 1.0 eq.) was dissolved in methanolic ammonia (7 M in MeOH, 620 μL, 0.2 M, 35 eq.). The pressure tube was sealed, placed behind a blast shield, and the solution was stirred at 95 °C for 24 h. Thereafter, the mixture was cooled to room temperature and volatiles were removed *in vacuo*. The crude was redissolved in 1:1 dioxane:H_2O (1.24 mL, 0.05 M), followed by addition of triethylamine (43 μL, 0.31 mmol, 5.0 eq.) and Boc_2O (67 mg, 0.31 mmol, 5.0 eq.). The mixture was stirred at 50 °C for 5 h, then cooled to room temperature, quenched with sodium bicarbonate (sat. aq. sol., 1 mL), and diluted with EtOAc (5 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 15 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were purified *via* column chromatography (SiO_2, 1:2 hexanes:EtOAc) to afford triol **23** (14 mg, 37 μmol, 60%) as a colorless oil.

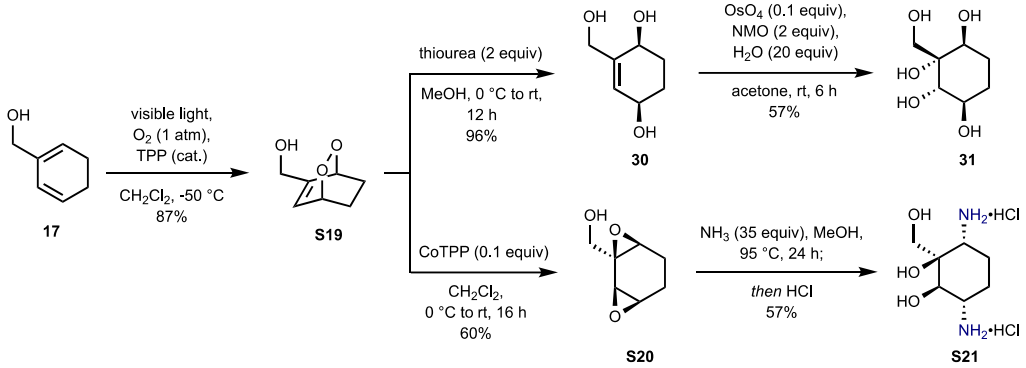
R_f 0.2 (*n*-hexane:EtOAc = 1:2, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 3.83 – 3.75 (m, 2H), 3.70 (d, J = 11.7 Hz, 1H), 3.57 (m, J = 21.5, 10.2 Hz, 2H), 1.81 – 1.61 (m, 4H), 1.44 (s, 9H), 1.43 (s, 9H).

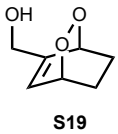
^{13}C NMR (126 MHz, MeOD) δ 159.6, 158.3, 80.5, 80.2, 77.1, 70.7, 64.9, 58.2, 52.2, 28.8, 27.6, 27.0.

IR (ATR, neat, cm^{-1}) 3355 (b), 2976 (m), 2933 (m), 1687 (s), 1522 (s), 1366 (m), 1249 (m), 1171 (s), 1046 (m), 1022 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{17}H_{32}N_2O_7Na^+$ $[M+Na]^+$ calc.: 399.2107; found: 399.2097.



Scheme S11. Conversion of intermediate **17** to **31** and **S21**.



S19

Endoperoxide S19. Diene **17** (510 mg, 4.63 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (46 mL, 0.1 M) and tetraphenylporphyrin (28 mg, 46.3 μmol, 0.01 eq.) was added. The solution was cooled to –50 °C and oxygen gas was bubbled through while the flask was irradiated with white LEDs at –50 °C until completion (*usually about 5 h*). Once full conversion was observed by TLC, nitrogen gas was bubbled through the solution to purge the remaining oxygen before warming it up to room temperature. The crude material was purified *via* column chromatography (SiO_2, 2:1-1:2 hexanes:EtOAc) to provide endoperoxide **S19** (570 mg, 4.01 mmol, 87%) as a colorless oil. *Note: It has been observed that on small scale an oxygen-filled balloon is sufficient to push the reaction to completion, while for larger scales the reaction gains efficiency if it is connected directly to an oxygen tank.*

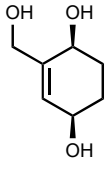
R_f 0.4 (*n*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (dq, J = 5.8, 1.8 Hz, 1H), 4.70 – 4.62 (m, 2H), 4.29 (d, J = 2.0 Hz, 2H), 2.46 (s, 1H), 2.33 – 2.19 (m, 2H), 1.52 – 1.40 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 125.0, 72.2, 71.3, 62.0, 22.5, 21.9.

IR (ATR, neat, cm^{-1}) 3379 (b), 2937 (m), 2861 (w), 1602 (w), 1398 (m), 1049 (m), 918 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_7H_{10}O_3^+$ $[M]^+$ calc.: 142.0630; found: 142.0633.



30

Triol 30. A solution of endoperoxide **S19** (1.01 g, 7.11 mmol, 1.0 eq.) in MeOH (36 mL, 0.2 M) was cooled to 0 °C and thiourea (1.08 g, 14.2 mmol, 2.0 eq.) was added. The solution was allowed to warm up to room temperature and stirred for 12 h. Upon completion, the crude

material was purified *via* column chromatography (SiO_2, 30:1-8:1 CH_2Cl_2:MeOH) to provide triol **30** (981 mg, 6.80 mmol, 96%) as a colorless oil.

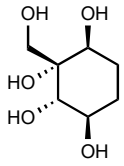
R_f 0.1 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 5.78 (s, 1H), 4.19 – 4.05 (m, 4H), 1.89 – 1.76 (m, 2H), 1.76 – 1.66 (m, 2H).

^{13}C NMR (126 MHz, MeOD) δ 142.2, 129.5, 67.3, 65.0, 64.1, 30.2, 28.3.

IR (ATR, neat, cm^{-1}) 3307 (b), 2942 (m), 2868 (m), 1416 (m), 1281 (m), 1049 (s), 978 (s).

HRMS (ES+/TOF, m/z) calcd. For $C_7H_{12}O_3Na^+$ $[M+Na]^+$ calc.: 167.0684; found: 167.0677.



31

Pentaol 31. To a solution of triol **30** (99 mg, 0.69 mmol, 1.0 eq.) in acetone (6.9 mL, 0.1 M) were added *N*-Methylmorpholine *N*-oxide (160 mg, 1.4 mmol, 2.0 eq.), H_2O (250 µL, 20 eq.), and OsO_4 (0.2 M in MeCN, 340 µL, 69 µmol, 0.1 eq.). The solution was stirred for 6 h at room temperature. Thereafter, the reaction was quenched by addition of sodium thiosulfate (10 wt% aq. sol., 2 mL). After 30 minutes, the mixture was completely dried *in vacuo*. The crude materials were sonicated in MeOH (10 mL) and the mixture was filtered through a frit before dry loading on silica gel for column chromatography (SiO_2, 10:1-5:1 CH_2Cl_2:MeOH). Pentaol **31** (29 mg, 0.34 mmol, 60%) was obtained as a colorless oil.

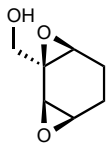
R_f 0.2 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 3.83 (t, J = 2.9 Hz, 1H), 3.81 – 3.67 (m, 3H), 3.55 (d, J = 9.1 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.75 – 1.66 (m, 2H), 1.60 (dq, J = 14.0, 3.4 Hz, 1H).

^{13}C NMR (126 MHz, MeOD) δ 76.8, 75.5, 72.2, 72.0, 66.6, 27.8, 27.6.

IR (ATR, neat, cm^{-1}) 3356 (b), 2943 (w), 1644 (w), 1398 (m), 1087 (m), 1061 (m), 1019 (m), 980 (w), 885 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_7H_{14}O_5Na^+$ $[M+Na]^+$ calc.: 201.0739; found: 201.0739.



S20

***Bis*-epoxide S20**. A solution of endoperoxide **S19** (48 mg, 0.34 mmol, 1.0 eq.) in CH_2Cl_2 (3.4 mL, 0.1 M) was cooled to 0 °C and cobalt(II) *meso*-tetraphenylporphine (4.5 mg, 6.8 µmol, 0.02 eq.) was added. The solution was allowed to warm up to room temperature and stirred overnight. Upon completion, the crude material was purified *via* column chromatography (SiO_2, 1:1-1:4 hexanes:EtOAc) to provide *bis*-epoxide **S20** (29 mg, 0.34 mmol, 60%) as a colorless oil.

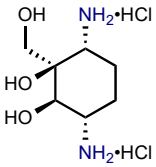
R_f 0.33 (*n*-hexane:EtOAc = 1:4, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (dd, J = 12.5, 5.6 Hz, 1H), 3.77 (dd, J = 12.5, 7.4 Hz, 1H), 3.28 (d, J = 4.1 Hz, 1H), 3.18 – 3.11 (m, 2H), 1.97 (dd, J = 7.4, 5.8 Hz, 1H), 1.90 – 1.77 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 63.7, 56.6, 51.9, 48.5, 48.5, 20.1, 20.0.

IR (ATR, neat, cm^{-1}) 3366 (b), 1927 (m), 1634 (w), 1426 (m), 1233 (m), 1037 (s), 956 (s), 921 (m), 881 (s), 866 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_7H_{10}O_3Na^+$ $[M+Na]^+$ calc.: 165.0528; found: 165.0534.



S21

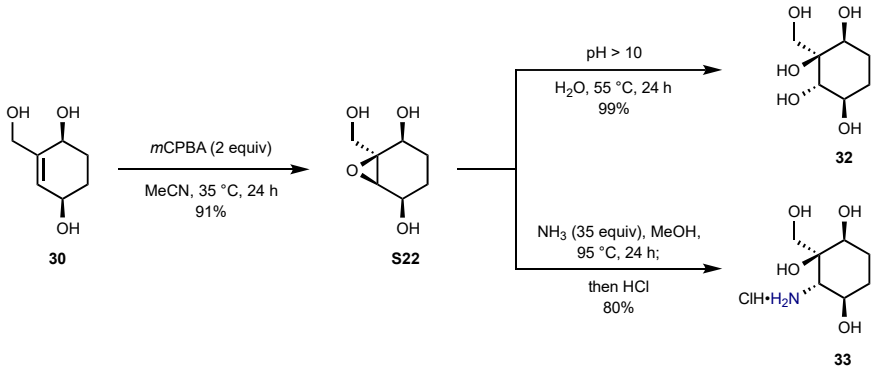
Diaminotriol 21. In a pressure tube, *bis*-epoxide **S20** (24 mg, 0.17 mmol, 1.0 eq.) was dissolved in ammonia (7 M in MeOH, 840 µL, 0.2 M, 35 eq.). The pressure tube was sealed and the solution was stirred at 95 °C for 24 h. ***WARNING: the reaction was placed behind a blast shield for safety measures.*** Thereafter, the mixture was cooled to room temperature and volatiles were removed *in vacuo*. The crude was acidified with concentrated HCl (conc. aq. sol., 0.5 mL), and dried *in vacuo*. The crude materials were triturated with *i*-PrOH (3 × 3 mL) and dried under high-vacuum, affording diaminotriol **21** (24 mg, 96 umol, 57%) as a brown, sticky foam.

^{1}H NMR (500 MHz, MeOD) δ 3.93 (dd, J = 23.1, 10.7 Hz, 2H), 3.65 (d, J = 11.0 Hz, 1H), 3.49 (q, J = 2.3 Hz, 1H), 3.41 (ddd, J = 12.3, 10.3, 4.2 Hz, 1H), 2.24 (tt, J = 15.4, 4.7 Hz, 1H), 2.04 (m, 1H), 1.92 – 1.74 (m, 2H).

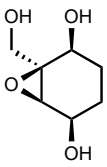
^{13}C NMR (126 MHz, MeOD) δ 74.1, 69.1, 65.3, 55.7, 52.8, 24.4, 24.3.

IR (ATR, neat, cm^{-1}) 3325 (b), 2939 (b), 1606 (m), 1518 (s), 1446 (m), 1390 (m), 1215 (w), 1086 (s), 1043 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_7H_{17}N_2O_3^+$ $[M+H]^+$ calc.: 177.1239; found: 177.1241.



Scheme S12. Conversion of intermediate **30** to **32** and **33**.



S22

Epoxide S22. To a solution of triol **30** (215 mg, 1.49 mmol, 1.0 eq.) in MeCN (14.9 mL, 0.1 M) was added *m*CPBA (75 wt%, 710 mg, 2.98 mmol, 2.0 eq.). The solution was stirred at 35 °C for 24 h. Thereafter, the reaction was cooled to room temperature and quenched by addition of sodium thiosulfate (10 wt% aq. sol., 2 mL). After 30 minutes, the mixture was dried *in vacuo*. The crude materials were sonicated in MeOH (20 mL) and the mixture was filtered through a frit before dry loading on silica gel for column chromatography (SiO_2, 30:1-5:1 CH_2Cl_2:MeOH). Epoxide **S22** (218 mg, 1.36 mmol, 91%) was obtained as a colorless oil.

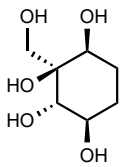
R_f 0.1 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 4.03 (t, J = 4.7 Hz, 1H), 3.94 (ddd, J = 7.8, 5.3, 2.6 Hz, 1H), 3.86 (d, J = 12.0 Hz, 1H), 3.47 (d, J = 12.0 Hz, 1H), 3.34 (d, J = 2.6 Hz, 1H), 1.66 (m, 2H), 1.55 – 1.43 (m, 2H).

^{13}C NMR (126 MHz, MeOD) δ 67.9, 65.5, 65.3, 63.7, 61.7, 29.6, 26.0.

IR (ATR, neat, cm^{-1}) 3339 (b), 2925 (s), 1738 (m), 1637 (m), 1365 (m), 1217 (m), 1056 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_7H_{12}O_4Na^+$ $[M+Na]^+$ calc.: 183.0633; found: 183.0627.



32

Pentaol 32. A solution of epoxide **S22** (87 mg, 0.54 mmol, 1.0 eq.) in H_2O (5.4 mL, 0.1 M) was basified to pH > 10 by addition of NaOH (2 M aq. sol., *sat. aq. sol. of $NaHCO_3$ for basifying also works with the same efficiency*). The solution was stirred at 55 °C for 24 h. Thereafter, the contents were cooled to room temperature and the solvent was removed *in vacuo*. The crude materials were sonicated in MeOH (10 mL) and the mixture was filtered through a frit before dry loading on silica gel for column chromatography (SiO_2, 10:1-5:1 CH_2Cl_2:MeOH). Pentaol **32** (96 mg, 0.54 mmol, 99%) was obtained as a colorless oil.

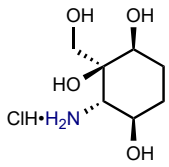
R_f 0.2 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 3.95 (dq, J = 9.9, 3.4 Hz, 1H), 3.85 (q, J = 11.4, 2H), 3.70 (s, 1H), 3.65 (s, 1H), 1.98 – 1.82 (m, 2H), 1.72 (m, 1H), 1.60 – 1.52 (m, 1H).

^{13}C NMR (126 MHz, MeOD) δ 75.4, 75.1, 71.9, 69.4, 65.4, 28.0, 24.3.

IR (ATR, neat, cm^{-1}) 2925 (s), 1735 (m), 1245 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_7H_{14}O_5Na^+$ $[M+Na]^+$ calc.: 201.0739; found: 201.0741.



33

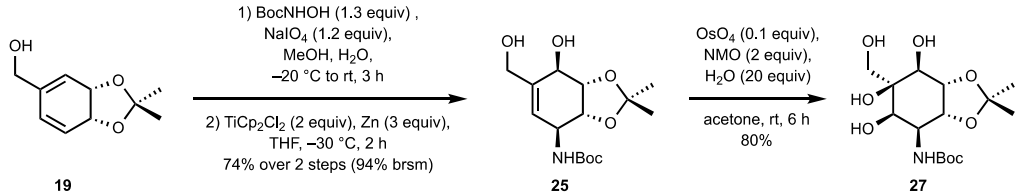
Aminotetraol 33. In a pressure tube, epoxide **S22** (30 mg, 0.19 mmol, 1.0 eq.) was dissolved in ammonia (7 M in MeOH, 940 µL, 0.2 M, 65.8 mmol, 35 eq.). The pressure tube was sealed, placed behind a blast shield, and the solution was stirred at 95 °C for 24 h. Thereafter, the mixture was cooled to room temperature and volatiles were removed *in vacuo*. The crude was acidified with HCl (12 M aq. sol., 0.5 mL), and dried *in vacuo*. The crude materials were triturated with *i*-PrOH (3 × 3 mL) and dried *in vacuo*, affording aminotetraol **33** (32 mg, 0.15 mmol, 80%) as a brown sticky foam.

^{1}H NMR (500 MHz, MeOD) δ 3.85 – 3.75 (m, 2H), 3.71 (m, 1H), 3.58 (d, J = 11.8 Hz, 1H), 3.24 (d, J = 10.8 Hz, 1H), 1.90 – 1.70 (m, 3H), 1.67 – 1.56 (m, 1H).

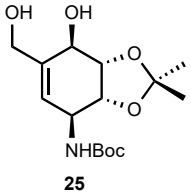
^{13}C NMR (126 MHz, MeOD) δ 75.2, 70.5, 68.8, 65.0, 61.5, 29.2, 27.

IR (ATR, neat, cm^{-1}) 3338 (b), 2944 (m), 1617 (w), 1506 (w), 1456 (w), 1364 (w), 1278 (w), 1227 (w), 1103 (m), 1052 (s), 972 (m), 846 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_7H_{16}NO_4^+$ $[M+H]^+$ calc.: 178.1079; found: 178.1084.



Scheme S13. Conversion of intermediate **19** to **27**.



25

Diol 25. Diene **19** (649 mg, 3.56 mmol, 1.0 eq.) and *N*-Boc-hydroxylamine (617 mg, 4.63 mmol, 1.3 eq.) were dissolved in MeOH (71 mL, 0.05 M) and the solution was cooled to −10 °C. In a separate flask, sodium periodate (914 mg, 4.27 mmol, 1.2 eq.) was dissolved in H_2O (18 mL, 0.2 M relative to sodium periodate) and added dropwise *via* cannula into the aforementioned MeOH solution over 15 minutes. The reaction mixture was allowed to slowly warm to room temperature and then it was stirred for 3 h. Thereafter, the reaction was quenched by addition of sodium thiosulfate (10 wt% aq. sol., 50 mL) and H_2O (100 mL). After 30 minutes, MeOH was removed by *in vacuo* and the remaining aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol. 100 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was taken forward without further purification. Titanocene dichloride (1.77 g, 7.12 mmol, 2.0 eq.) and zinc powder (699 mg, 10.7 mmol, 3.0 eq.) were suspended in dry degassed THF (35.6 mL, 0.2 M relative to titanocene) and stirred under inert atmosphere for 1 h at room temperature. Thereafter, the green suspension was cooled to −30 °C, and a solution of the previously obtained crude in dry degassed THF (35.6 mL, 0.1 M) was added dropwise over 15 minutes. The reaction mixture was stirred for 2 h at −30 °C, then warmed to room temperature. Thereafter, the reaction was quenched by addition of sodium phosphate monobasic (sat. aq. sol., 100 mL) under vigorous stirring. After 2 h, the orange biphasic mixture was filtered, the organic phase was separated, and the aqueous phase was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 100 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified *via* column chromatography (SiO_2, 4:1-1:1 CH_2Cl_2:EtOAc + 1% *i*-PrOH) to afford diol **25** (831 mg, 2.64 mmol, 74%) as a sticky white foam, along with recovered starting diene **19** (130 mg, 0.71 mmol, 20%).

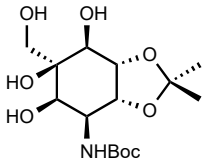
R_f 0.3 (CH_2Cl_2:EtOAc = 2:1 + 1% *i*-PrOH, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 5.69 (dd, J = 4.3, 2.1 Hz, 1H), 4.24 (dd, J = 7.2, 4.1 Hz, 1H), 4.19 (dd, J = 7.3, 4.8 Hz, 1H), 4.15 (q, J = 1.8 Hz, 3H), 4.11 (m, 1H), 1.45 (s, 9H), 1.39 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 157.8, 143.5, 124.1, 109.9, 80.8, 80.4, 78.3, 69.9, 63.3, 51.0, 28.7, 27.3, 24.9.

IR (ATR, neat, cm^{-1}) 3356 (b), 2979 (w), 2933 (w), 1687 (s), 1512 (m), 1368 (s), 1248 (m), 1213 (m), 1163 (s), 1043 (s), 880 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{25}NO_6Na^+$ $[M+Na]^+$ calc.: 338.1580; found: 338.1576.



27

Tetraol 27. To a solution of diol **25** (121 mg, 0.38 mmol, 1.0 eq.) in acetone (3.8 mL, 0.1 M) were added *N*-Methylmorpholine *N*-oxide (90 mg, 0.77 mmol, 2.0 eq.), H_2O (138 μL, 7.7 mmol 20 eq.), and OsO_4 (0.2 M in MeCN, 192 μL, 38 μmol, 0.1 eq.). The solution was stirred for 6 h at room temperature. Thereafter, the reaction was quenched by addition of sodium thiosulfate (10 wt% aq. sol., 1 mL). After 30 minutes, the mixture was completely dried through rotary evaporation and high-vacuum. The crude materials were sonicated in MeOH (5 mL) and the mixture was filtered through a frit before dry loading on column chromatography for purification (SiO_2, 40:1-10:1 CH_2Cl_2:MeOH). Tetraol **27** (107 mg, 0.31 mmol, 80%) was obtained as a colorless oil.

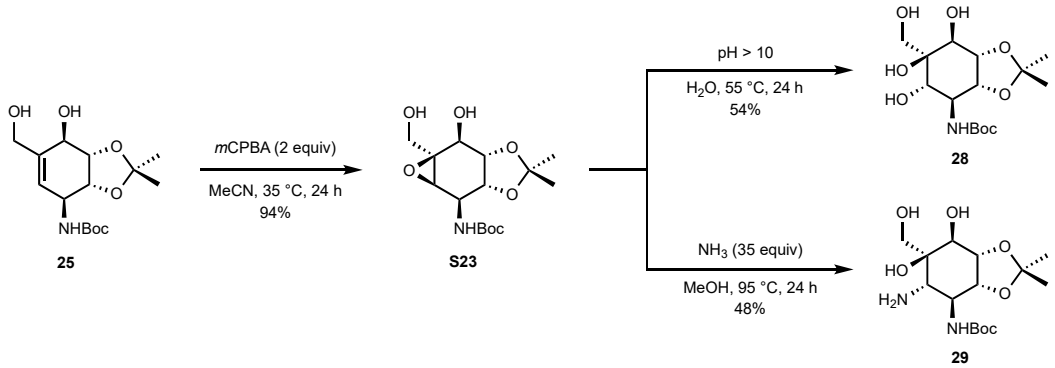
R_f 0.3 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 4.24 – 4.14 (m, 2H), 4.11 (t, J = 4.6 Hz, 1H), 3.93 (d, J = 4.9 Hz, 1H), 3.69 (d, J = 7.7 Hz, 1H), 3.59 (s, 2H), 1.46 (m, 12H), 1.34 (s, 3H).

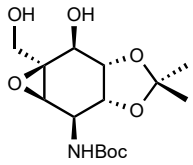
^{13}C NMR (126 MHz, MeOD) δ 158.0, 110.2, 80.5, 79.5, 77.9, 72.2, 67.1, 62.8, 53.5, 28.7, 28.5, 26.3.

IR (ATR, neat, cm^{-1}) 3391 (b), 2981 (w), 1688 (s), 1504 (m), 1367 (s), 1219 (s), 1165 (s), 1048 (s), 868 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{27}NO_8Na^+$ $[M+Na]^+$ calc.: 372.1634; found: 372.1634.



Scheme S14. Conversion of intermediate **25** to **28** and **29**.



S23

Epoxide S23. To a solution of diol **25** (320 mg, 1.01 mmol, 1.0 eq.) in MeCN (10 mL, 0.1 M) was added *m*CPBA (75 wt%, 483 mg, 2.03 mmol, 2.0 eq.). The solution was stirred at 35 °C for 24 h. Thereafter, the reaction was cooled to room temperature, diluted with EtOAc (5 mL) and quenched by addition of sodium thiosulfate (10 wt%

aq. sol., 5 mL) and sodium bicarbonate (sat. aq. sol, 5 mL). After 30 minutes, the organic phase was separated, and the aqueous phase was extracted with EtOAc (5 × 5 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 25 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were purified *via* column chromatography (SiO_2, 30:1-10:1 CH_2Cl_2:MeOH) to afford epoxide **S23** (460 mg, 1.77 mmol, 94%) as a sticky, white foam.

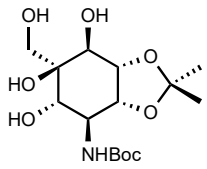
R_f 0.4 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 4.17 – 4.06 (m, 3H), 3.97 (m, 2H), 3.64 (d, J = 12.6 Hz, 1H), 3.28 (s, 1H), 1.47 (s, 9H) 1.44 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 158.0, 109.1, 80.6, 80.5, 77.0, 72.4, 63.0, 60.6, 59.6, 53.1, 28.7, 27.4, 24.3.

IR (ATR, neat, cm^{-1}) 3346 (b), 2980 (w), 2935 (w), 1960 (s), 1525 (m), 1368 (m), 1247 (m), 1163 (s), 1050 (s), 879 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{25}NO_7Na^+$ $[M+Na]^+$ calc.: 255.0845; found: 255.0846.



28

Tetraol 28. A mixture of epoxide **S23** (28 mg, 84 μmol, 1.0 eq.) in H_2O (0.84 mL, 0.1 M) was basified to pH > 10 by addition of NaOH (2 M aq. sol., *sat. aq. sol. of $NaHCO_3$ for basifying also works with the same efficiency*). The solution was stirred at 55 °C for 24 h, thereafter cooled to room temperature. The solvent was completely removed through rotary evaporation and high-vacuum. The crude materials were sonicated in MeOH (5 mL) and the mixture was filtered before dry loading on silica gel for column chromatography (SiO_2, 40:1-10:1 CH_2Cl_2:MeOH). Tetraol **28** (16 mg, 46 μmol, 54%) was obtained as a sticky, white foam.

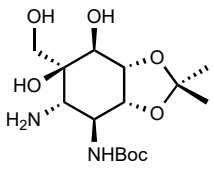
R_f 0.3 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 4.29 (m, 2H), 4.11 (d, J = 8.1, 1H), 3.88 (d, J = 4.8 Hz, 1H), 3.79 (m, 3H), 1.50 (s, 3H), 1.46 (s, 9H), 1.34 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 158.1, 110.2, 80.2, 80.0, 77.1, 76.0, 75.6, 74.2, 64.8, 52.9, 28.8, 28.4, 26.2.

IR (ATR, neat, cm^{-1}) 3372 (b), 2982 (w), 1682 (m), 1572 (s), 1369 (s), 1220 (m), 1165 (m), 1066 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{27}NO_8Na^+$ $[M+Na]^+$ calc.: 372.1634; found: 372.1617.



29

Aminotriol 29. In a pressure tube, epoxide **S23** (32 mg, 97 μmol, 1.0 eq.) was dissolved in methanolic ammonia (7 M in MeOH, 970 μL, 0.2 M, 35 eq.). The pressure tube was sealed, placed behind a blast shield, and the solution was stirred at 95 °C for 24 h. Thereafter, the mixture was cooled to room temperature and volatiles

were removed *in vacuo*. The crude materials were purified *via* column chromatography (SiO_2, 20:1-5:1 CH_2Cl_2:MeOH) to afford aminotriol **29** (16 mg, 46 μmol, 48%) as a colorless oil.

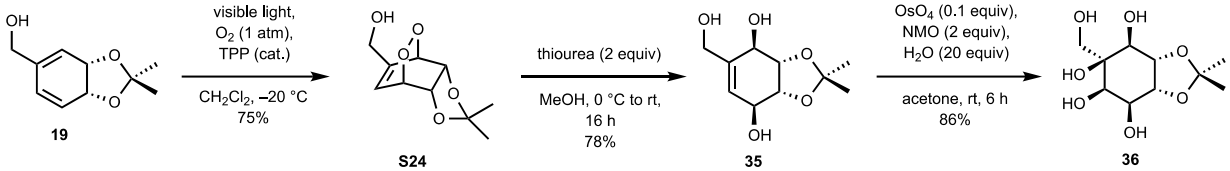
R_f 0.4 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 4.28 – 4.15 (m, 2H), 3.96 (d, J = 11.5 Hz, 1H), 3.89 (d, J = 5.2 Hz, 1H), 3.76 (t, J = 8.5 Hz, 1H), 3.69 (d, J = 11.6, 1H), 3.03 (d, J = 9.3 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 9H), 1.34 (s, 3H).

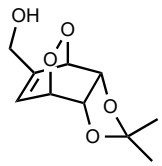
^{13}C NMR (126 MHz, MeOD) δ 160.9, 112.9, 83.1, 82.1, 80.9, 78.9, 73.0, 67.7, 60.5, 57.8, 31.2, 30.8, 28.5.

IR (ATR, neat, cm^{-1}) 3343 (b), 2982 (w), 2934 (w), 1689 (m), 1518 (w), 1368 (s), 1219 (m), 1164 (s), 1048 (m), 858 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{29}N_2O_7^+$ $[M+H]^+$ calc.: 349.1975; found: 349.1973.



Scheme S15. Conversion of intermediate **19** to **36**.



Endoperoxide S24. Diene **19** (1.45 g, 7.96 mmol, 1.0 eq.)[3] was dissolved in CH_2Cl_2 (80 mL, 0.1 M) and tetraphenylporphyrin (49 mg, 79.6 μmol, 0.01 eq.) was added. The solution was cooled to –20 °C and oxygen gas was bubbled through while the flask was irradiated with white LEDs at –20 °C until completion (*usually about 8 h*). Once full conversion is observed by TLC, nitrogen gas was bubbled through the solution to remove the remaining oxygen before warming it to room temperature. The crude material was purified *via* column chromatography (SiO_2, 4:1-2:1 hexanes:EtOAc) to provide endoperoxide **S24** (1.27 g, 5.93 mmol, 75%) as an amorphous white foam. *Note: It has been observed that on small scale an oxygen-filled balloon is sufficient to push the reaction to completion, while for larger scales the reaction is much more efficient if it is connected straight to an oxygen tank and purged with a porous sparger.*

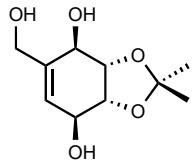
R_f 0.2 (*n*-hexane:EtOAc = 2:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dt, J = 6.0, 1.8 Hz, 1H), 4.94 (dt, J = 4.7, 1.8 Hz, 1H), 4.88 (ddd, J = 6.2, 4.4, 1.7 Hz, 1H), 4.61 – 4.53 (m, 2H), 4.27 (t, J = 1.9 Hz, 2H), 1.33 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 114.5, 95.5, 82.4, 45.1, 43.8, 43.4, 43.1, 34.7, -2.3, -2.7.

IR (ATR, neat, cm^{-1}) 3401 (b), 2989 (w), 2935 (w), 1681 (w), 1373 (m), 1214 (m), 1050 (s), 1023 (s), 859 (m).

HRMS (CI+/TOF, m/z) calcd. For $C_{10}H_{15}O_5^+$ $[M+H]^+$ calc.: 215.0920; found: 215.0918.



35

Triol 35. A solution of endoperoxide **S24** (798 mg, 3.73 mmol, 1.0 eq.) in MeOH (19 mL, 0.2 M) was cooled to 0 °C and thiourea (567 mg, 7.45 mmol, 2.0 eq.) was added. The solution was allowed to warm up to room temperature and stirred for 16 h. Upon completion, the crude material was purified *via* column chromatography (SiO_2, 3:1-1:3 CH_2Cl_2:EtOAc) to provide triol **35** (627 mg, 2.90 mmol, 78%) as a colorless oil.

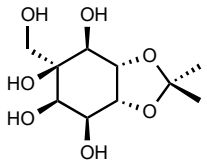
R_f 0.2 (CH_2Cl_2:EtOAc = 1:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 5.75 (dq, J = 3.6, 1.8 Hz, 1H), 4.18 (m, 3H), 4.16 – 4.10 (m, 3H), 1.41 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 142.7, 125.7, 110.2, 80.9, 80.6, 71.2, 70.6, 62.7, 27.4, 24.9.

IR (ATR, neat, cm^{-1}) 3339 (b), 2987 (w), 2920 (w), 1638 (w), 1376 (m), 1210 (m), 1060 (s), 1027 (s), 860 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{10}H_{17}O_5^+$ $[M+H]^+$ calc.: 217.1498; found: 217.1501.



36

Pentaol 36. To a solution of triol **35** (99 mg, 0.46 mmol, 1.0 eq.) in acetone (4.6 mL, 0.1 M) were added *N*-Methylmorpholine *N*-oxide (110 mg, 0.92 mmol, 2.0 eq.), H_2O (170 µL, 9.2 mmol 20 eq.), and OsO_4 (0.2 M in MeCN, 230 µL, 46 µmol, 0.1 eq.). The solution was stirred for 6 h at room temperature. Thereafter, the reaction was quenched by addition of sodium thiosulfate (10 wt% aq. sol., 2 mL). After 30 minutes, the mixture was completely dried through rotary evaporation and high-vacuum. The crude materials were sonicated in MeOH (10 mL) and the mixture was filtered through a frit before dry loading on column chromatography for purification (SiO_2, 90:10:0.5-80:20:1 $CHCl_3$:MeOH:H_2O). Pentaol **36** (99 mg, 0.40 mmol, 86%) was obtained as a colorless oil.

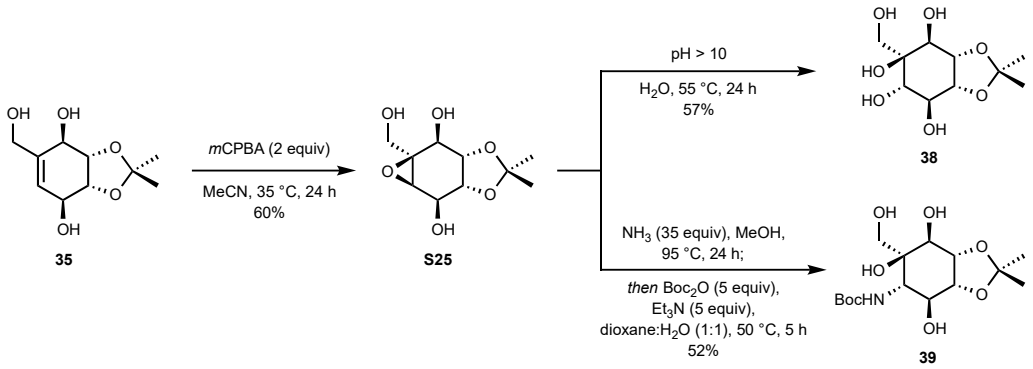
R_f 0.3 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{1}H NMR (500 MHz, MeOD) δ 4.33 (dd, J = 6.1, 4.3 Hz, 1H), 4.24 (dd, J = 8.1, 6.0 Hz, 1H), 4.03 (t, J = 4.0 Hz, 1H), 3.84 (d, J = 3.7 Hz, 1H), 3.65 (d, J = 8.0 Hz, 1H), 3.58 (s, 2H), 1.47 (s, 3H), 1.35 (s, 3H).

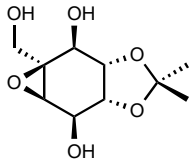
^{13}C NMR (126 MHz, MeOD) δ 110.2, 79.6, 79.0, 78.0, 72.5, 72.3, 68.8, 62.9, 28.4, 26.

IR (ATR, neat, cm^{-1}) 3347 (b), 2932 (w), 1737 (w), 1375 (m), 1217 (s), 1051 (s), 850 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{10}H_{18}O_7Na^+$ $[M+Na]^+$ calc.: 273.0950; found: 273.0949.



Scheme S16. Conversion of intermediate **35** to **38** and **39**.



S25

Epoxide S25. To a solution of triol **34** (448 mg, 2.07 mmol, 1.0 eq.) in MeCN (20.6 mL, 0.1 M) was added *m*CPBA (75 wt%, 715 mg, 4.14 mmol, 2.0 eq.). The solution was stirred at 35 °C for 24 h. Thereafter, the reaction was cooled to room temperature and quenched by addition of sodium thiosulfate (10 wt% aq. sol., 10 mL). After 30 minutes, the mixture was completely dried *in vacuo*. The crude materials were sonicated in MeOH (20 mL) and the mixture was filtered through a frit before dry loading on silica gel for column chromatography (SiO_2, 40:1-10:1 CH_2Cl_2:MeOH). Epoxide **S25** (290 mg, 1.25 mmol, 60%) was obtained as a colorless oil.

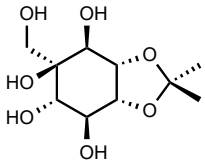
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 4.15 – 4.03 (m, 3H), 4.02 – 3.94 (m, 2H), 3.64 (d, J = 12.5 Hz, 1H), 3.33 (s, 1H), 1.43 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 109.1, 80.5, 80.0, 72.5, 72.3, 63.0, 60.6, 60.2, 27.3, 24.2.

IR (ATR, neat, cm^{-1}) 3380 (b), 2988 (w), 2932 (w), 1709 (w), 1378 (m), 1209 (m), 1071 (s), 1040 (s), 868 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{10}H_{16}O_6Na^+$ $[M+Na]^+$ calc.: 255.0845; found: 255.0846.



38

Pentaol 38. A mixture of epoxide **S25** (178 mg, 0.77 mmol, 1.0 eq.) in H_2O (7.7 mL, 0.1 M) was basified to pH > 10 by addition of NaOH (2 M aq. sol., *sat. aq. sol. of $NaHCO_3$ for basifying also works with the same efficiency*). The solution was stirred at 55 °C for 24 h, thereafter cooled to room temperature. The solvent was removed *in vacuo*. The crude materials were sonicated in MeOH (10 mL) and the mixture was filtered through a frit before dry loading on silica gel for column chromatography (SiO_2, 10:1-5:1 CH_2Cl_2:MeOH). Pentaol **38** (110 mg, 0.44 mmol, 57%) was obtained as a colorless oil.

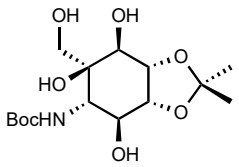
R_f 0.1 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 4.32 – 4.21 (m, 3H), 3.96 (dd, J = 12.0, 1.9 Hz, 1H), 3.81 – 3.72 (m, 2H), 3.69 – 3.62 (m, 1H), 1.46 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 110.2, 80.7, 79.4, 79.2, 73.6, 72.1, 65.5, 54.3, 28.3, 26.2.

IR (ATR, neat, cm^{-1}) 2924 (m), 1737 (s), 1365 (m), 1216 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{10}H_{18}O_7Na^+$ $[M+Na]^+$ calc.: 273.0950; found: 273.0959.



39

Tetraol 39. In a pressure tube, epoxide **S25** (18 mg, 78 μmol, 1.0 eq.) was dissolved in ammonia (7 M in MeOH, 620 μL, 0.2 M, 35 eq.). ***The pressure tube was sealed, placed behind a blast shield***, and the solution was stirred at 95 °C for 24 h. Thereafter, the mixture was cooled to room temperature and volatiles were removed *in vacuo*. The crude was redissolved in 1:1 dioxane:H_2O (1.56 mL, 0.05 M), followed by addition of triethylamine (54 μL, 0.39 mmol, 5.0 eq.) and Boc_2O (85 mg, 0.39 mmol, 5.0 eq.). The mixture was stirred at 50 °C for 5 h, then cooled to room temperature, quenched with sodium bicarbonate (sat. aq. sol., 1 mL), and diluted with EtOAc (5 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 15 mL) and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were purified *via* column chromatography (SiO_2, 40:1-10:1 CH_2Cl_2:MeOH) to afford tetraol **39** (14 mg, 40 μmol, 52%) as a sticky, white foam.

R_f 0.18 (CH_2Cl_2:MeOH = 20:1, $KMnO_4$).

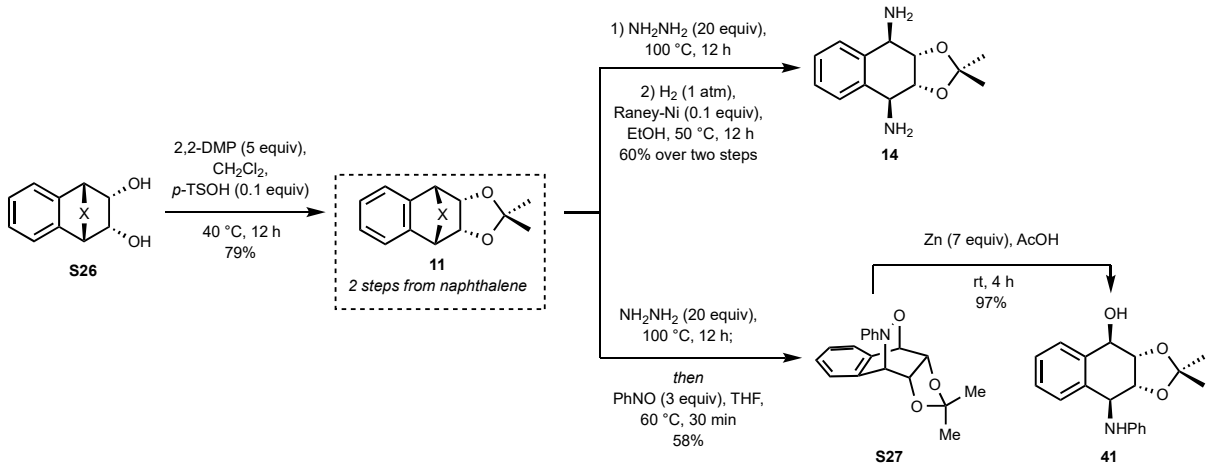
^{1}H NMR (500 MHz, MeOD) δ 4.30 (t, J = 6.8 Hz, 1H), 4.20 (t, J = 7.0 Hz, 1H), 3.78 (d, J = 6.7 Hz, 1H), 3.70 (m, 3H), 3.58 (d, J = 11.3 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 9H), 1.35 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 159.3, 110.4, 80.7, 80.5, 78.9, 77.0, 72.9, 71.1, 64.5, 58.7, 28.7, 28.1, 25.6.

IR (ATR, neat, cm^{-1}) 3396 (b), 2981 (w), 2934 (w), 1687 (s), 1514 (m), 1368 (s), 1247 (m), 1219 (m), 1165 (s), 1054 (s), 869 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{27}NO_8Na^+$ $[M+Na]^+$ calc.: 372.1634; found: 372.1629.

Derivatization from Naphthalene



Scheme S16. Conversion of intermediate **S26** to **14** and **41**.

11

Acetonide 11. To a solution of diol **S26** (3.0 g, 11.0 mmol, 1.0 eq.)[2] in CH_2Cl_2 (44.0 mL, 0.25 M) was added 2,2-DMP (6.7 mL, 54.0 mmol, 5.0 eq.) and *p*-toluenesulfonic acid monohydrate (210.0 mg, 1.1 mmol, 0.1 eq.). The reaction mixture was heated and stirred at 40 °C under a nitrogen atmosphere overnight. The reaction was cooled, diluted with CH_2Cl_2 and washed with NaOH (0.2 M aq. sol., 2 × 30 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 100 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude organics were purified *via* column chromatography (SiO_2, 10:1 – 7:3 hexane:EtOAc mixture) to afford **11** (3.0 g, 9.5 mmol, 87%) as a white solid.

R_f 0.3 (*n*-hexane:EtOAc = 10:1, UV).

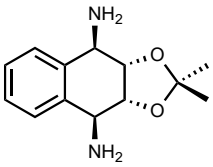
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 4H), 5.41 (s, 2H), 4.80 (s, 2H), 2.87 (s, 3H), 1.27 (s, 3H), 0.60 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 131.4, 129.3, 126.5, 112.4, 74.1, 56.2, 25.7, 25.5, 25.4.

IR (ATR, neat, cm^{-1}): 3009 (w), 2980 (w), 2932 (w), 1769 (m), 1700 (s), 1453 (s), 1375 (s), 1212 (s) 1075 (s), 862 (m), 750 (s), 556 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{16}H_{18}N_3O_4^+$ $[M+H]^+$ calc.: 316.1297; found: 316.1296.

m.p. 235 – 236 °C.



14

Diamine 14. The experimental procedure was adjusted from a reported protocol.[2] A mixture of the acetonide protected cycloadduct **11** (200 mg, 0.63 mmol, 1.0 eq.) and anhydrous hydrazine (0.520 mL, 16.4 mmol, 20 eq.) was stirred at 100 °C until full conversion of the cycloadduct was observed (*ca.* 16 hours). The reaction was allowed to cool to 50 °C and volatiles were removed *in vacuo*. EtOH (4.1 mL, 0.2 M) was added under a 1 atm of hydrogen (balloon) followed by Raney®-Nickel (400 μL, W.R. Grace and Co. Raney® 2400, slurry, in H_2O). The resulting mixture was stirred under a hydrogen atmosphere at 50 °C for 8 h, then filtered through a plug of Celite. The resulting crude material purified purified *via* column chromatography (SiO_2; 5 % - 40 % MeOH in CH_2Cl_2) to provide the title compound **14** (89.8 mg, 0.383 mmol, 60%) as a colorless foam.

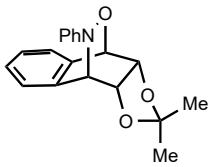
R_f 0.2 (*n*-hexane:EtOAc = 3:7, UV, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 7.40 (ddd, *J* = 45.3, 5.5, 3.3 Hz, 4H), 4.12 (dd, *J* = 4.6, 1.8 Hz, 2H), 3.95 (dd, *J* = 4.7, 1.9 Hz, 2H), 1.38 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 137.9, 128.6, 126.0, 111.0, 81.4, 55.0, 27.2, 24.6.

IR (ATR, neat, cm^{-1}): 3359 (m), 3293 (m), 2985 (m), 2893 (m), 1666 (m), 1599 (w), 1373 (m), 1208 (s), 1162 (m), 1047 (s), 874 (w), 824 (w), 747 (s), 519 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{13}H_{19}N_2O_2^+$ $[M+H]^+$ calc.: 235.1447; found: 235.1447.



S27

Cycloadduct S27. The procedure was adjusted from a reported protocol.[3] Acetonide **11** (500 mg, 1.59 mmol, 1.0 eq.) was refluxed in hydrazine (1.54 mL,31.7 mmol, 20 eq.) at 100 °C until full conversion of the cycloadduct was observed (*ca.* 16 hours). Volatiles were removed *in vacuo* and the residue was dissolved in THF (7.9 mL). Nitrosobenzene (510 mg, 4.76 mmol, 3.0 eq.) was added and the reaction mixture was stirred at 60 °C for 30 min. The crude product was purified by column chromatography (SiO_2, 10:1-7:3 hexane:EtOAc) to provide the title compound **S27** (285 mg, 0.835 mmol, 58%) as a white solid.

Note: It has been observed that elimination of hydrazine became difficult on scales larger than 500 mg. Residual hydrazine can consume nitrosobenzene, so multiple azeotropic evaporations with toluene are recommended.

R_f 0.3 (*n*-hexane:EtOAc = 10:1, UV).

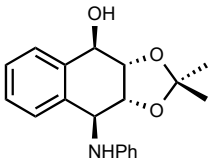
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.24 (m, 1H), 7.1 (m, 2H), 7.04 (dd, *J* = 7.37, 1.1 Hz, 1H), 6.85 (m,3H), 5.33 (d, *J* = 4.55 Hz, 1H), 4.96 (m, 2H), 4.85 (dd, *J* = 6.62, 4.6 Hz, 1H), 1.28 (s, 3H), 0.62 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 133.9, 131.6, 128.6, 128.1, 126.8, 125.8, 123.0, 117.7, 110.9, 73.8, 74.0, 73.6, 25.5, 25.6.

IR (ATR, neat, cm^{-1}): 3076 (w), 3035 (w), 2932 (m), 1582 (m), 1486 (s), 1374 (s), 1260 (s), 1064 (s), 751 (s), 688 (s), 630 (m), 576 (s), 524 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{20}NO_3^+$ $[M+H]^+$ calc.: 310.1443; found: 310.1439.

m.p. 167 – 168 °C.



41

Alcohol 41. To a solution of the benzene condensed cycloadduct **S27** (93.3 mg 0.30 mmol, 1.0 eq.) in glacial AcOH (1.0 mL, 0.3 M) activated zinc powder (237.3 mg, 2.1 mmol, 7.0 eq.) was added. The reaction mixture was stirred at room temperature until full conversion was observed by TLC (*ca.* 4 hours). The reaction mixture was diluted with toluene, filtered through Celite, and concentrated *in vacuo*. The title compound **41** was isolated by column chromatography (SiO_2, 10:1-7:3 hexane:EtOAc) as a white solid (91.5 mg, 0.29 mmol, 97%).

R_f 0.3 (*n*-hexane:EtOAc = 8:2, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.20 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.79 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.74 – 6.68 (m, 2H), 4.87 (d, *J* = 5.7 Hz, 1H), 4.46 – 4.40 (m, 2H), 4.36 (td, *J* = 5.7, 2.3 Hz, 1H), 1.56 (s, 2H), 1.37 (d, *J* = 5.0 Hz, 6H).

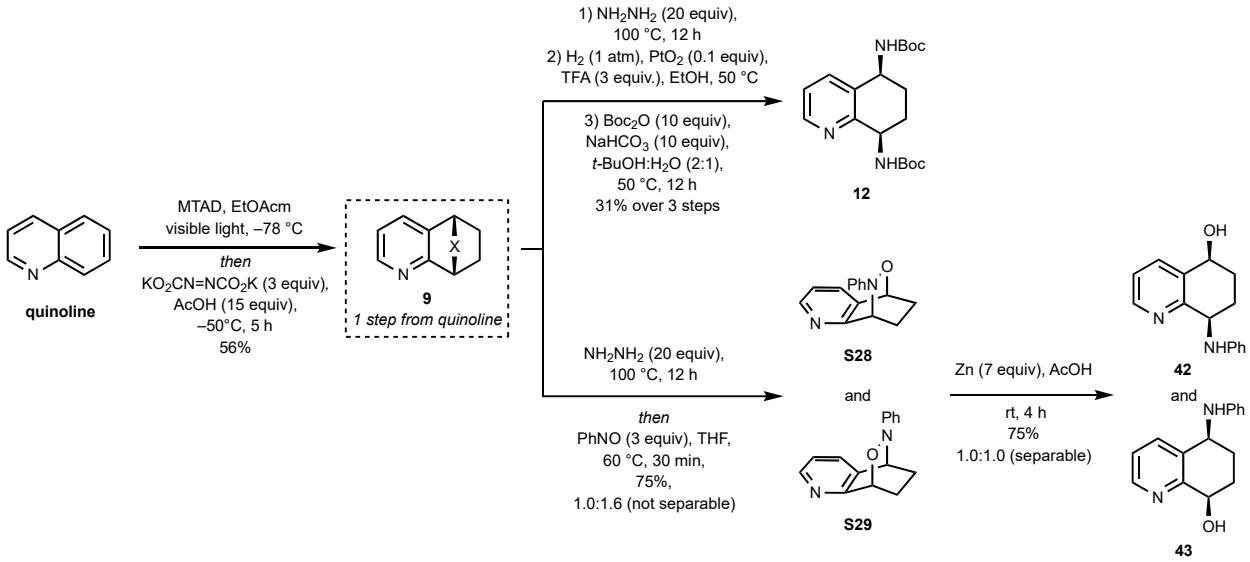
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 136.5, 135.1, 129.4, 128.2, 128.1, 127.1, 125.7, 118.9, 114.5, 110.3, 79.7, 72.0, 57.2, 26.9, 24.6.

IR (ATR, neat, cm^{-1}): 3469 (s), 3357 (s), 3034 (w), 2982 (w), 2923 (w), 1602 (m), 1519 (m), 1380 (m), 1268 (m), 1204 (m), 1125 (m), 1048 (s), 832 (m), 755 (s), 697 (s), 529 (m).

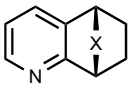
HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{22}NO_3^+$ $[M+H]^+$ calc.: 312.1600; found: 312.1599.

m.p. 155 – 157 °C.

Derivatization from Quinoline



Scheme S17. Conversion of intermediate **quinoline** to **12**, **42**, and **43**.



9

Cycloadduct 9. The protocol was adjusted from the reported procedure.[2] Quinoline (6.2 mL, 53.1 mmol, 2.0 eq.). was added to a solution of MTAD (3.0 g, 26.5 mmol, 1.0 eq.) in EtOAc (265 mL, 0.1 M) under inert atmosphere at –78 °C. The mixture was then stirred under irradiation with LED lights at –78 ºC until full decolorization of the reaction mixture was observed (*pink to colorless solution, usually 36 hours*). After turning the lights off, potassium azodicarboxylate (15.5 g, 79.6 mmol, 3.0 eq.) was added in one portion, followed by the addition of AcOH (22.8 mL, 398.0 mmol, 15 eq.) EtOAc (240.0 mL) at –78 ºC. After stirring the resulting suspension at –50 ºC for 5 hours, the reaction was warmed up to room temperature in a water bath, then quenched with water (120.0 mL). Sodium bicarbonate (sat. aq. sol., 400 mL) was added, and then the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated sodium chloride (sat. aq. sol., 1 × 400 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (SiO_2, 10:1 – 3:7 hexane:EtOAc) to provide compound **9** (3.6 g, 15.0 mmol, 56 %) as a white solid.

R_f 0.3 (*n*-hexane:EtOAc = 3:7, UV).

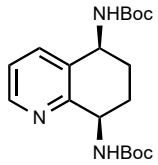
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.49 (dd, J = 5.2, 2.6 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.42 (dd, J = 7.5, 5.0 Hz, 1H), 5.48 (t, J = 2.8 Hz, 1H), 5.28 (t, J = 2.8 Hz, 1H), 2.72 (s, 3H), 2.37 – 2.23 (m, 2H), 1.79 – 1.56 (m, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 156.4, 156.3, 154.2, 149.1, 131.6, 129.9, 124.2, 55.2, 52.7, 25.0, 22.7, 22.2.

IR (ATR, neat, cm^{-1}): 3073 (w), 2973 (w), 1765 (m), 1696 (s), 1458 (s), 1395 (m), 1058 (s), 835 (s) 542 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{13}N_4O_2^+$ $[M+H]^+$ calc.: 245.1039; found: 245.1039.

m.p. 166 – 167 °C.



12

***Bis*-amide 12**. The experimental procedure was adjusted from the reported protocol.[2] The urazole containing cycloadduct **9** (500 mg, 2.05 mmol, 1.0 eq.) was placed in a flame dried round bottom flask along with anhydrous hydrazine (1.31 mL, 40.9 mmol, 20 eq.). The flask was purged with nitrogen and stirred at 100 °C for 16 hours. The reaction was allowed to cool down to 50 °C and volatiles were removed *in vacuo*. The crude reaction mixture was dissolved in EtOH (10.2 mL, 0.2 M) and Adams' catalyst (46.6 mg, 0.205 mmol, 0.1 eq.) was added along with trifluoroacetic acid (470 mL, 6.14 mmol, 3.0 eq.). The reactor was purged with nitrogen and then with hydrogen. The reaction mixture was stirred under 1 atm of hydrogen (balloon) at 50 °C for 8 hours and then filtered through a plug of Celite. The resulting crude material was dissolved in a 2:1 mixture of *t*-BuOH:H_2O (4.1 mL, 0.5 M) then Boc_2O (4.7 mL, 20.5 mmol, 10 eq.) and $NaHCO_3$ (1.72 g, 20.5 mmol, 10 eq.) were added. The reaction mixture was stirred ad 50 °C overnight, cooled at room temperature, diluted with water (15 mL) and extracted with EtOAc (3 × 150 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The resulting crude was purified by column chromatography (SiO_2; 10:1-1:1 hexanes:EtOAc) to provide the title compound **12** (234 mg, 0.641 mmol, 31%) as a light brown solid.

R_f 0.3 (*n*-hexane:EtOAc = 1:1, UV, $KMnO_4$).

m.p. 178 – 180 °C.

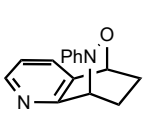
^{1}H NMR (500 MHz, MeOD) δ 8.41 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.71 (dd, *J* = 8.5, 5.3 Hz, 1H), 4.66 (t, *J* = 5.1 Hz, 1H), 2.17 – 1.80 (m, 4H), 1.48 (d, *J* = 5.2 Hz, 18H).

^{13}C NMR (126 MHz, MeOD) δ 158.1, 157.7, 156.3, 149.2, 138.2, 136.2, 124.5, 80.5, 80.3, 51.6, 49.3*, 28.8, 28.76, 28.2, 26.9.

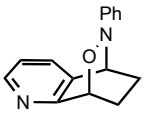
IR (ATR, neat, cm^{-1}): 3275 (m), 2970 (m), 2941 (m), 1700 (s), 1675 (s), 1525 (s), 1309 (m), 1249 (m), 1160 (s), 1086 (m), 967 (w), 653 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{30}N_3O_4^+$ $[M+H]^+$ calc.: 364.2236; found: 364.2230.

**Covered by the MeOD but well visible from the HSQC.*



S28



S29

Cycloadducts S28 and S29. The procedure was adjusted from the reported protocol. The pyridine fused cycloadduct **9** (500 mg, 2.05 mmol, 1.0 eq.) was refluxed in hydrazine (1.31 mL, 41.0 mmol, 20 eq.) at 100 °C until full conversion of the cycloadduct was observed (*ca.* 16 hours). Volatiles were removed *in vacuo* and the residue was dissolved in dry THF (10.2 mL). Nitrosobenzene (660 mg, 6.15 mmol, 3.0 eq.) was added and the reaction mixture was stirred at 60 °C for 30 min. The crude product was purified by column chromatography (SiO_2, 10:1-3:7 hexane:EtOAc) to provide the title compounds **S28** and **S29** as an inseparable mixture of regioisomers (368 mg, 1.54 mmol, 75%, 1.0:1.6).

Note: It has been observed that elimination of hydrazine became difficult on scales larger than 500 mg. Residual hydrazine can consume nitrosobenzene, so multiple azeotropic evaporations with toluene are recommended.

R_f 0.3 (*n*-hexane:EtOAc = 3:7, UV).

S28 + S29

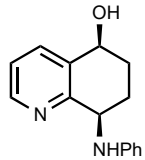
^{1}H NMR (500 MHz, MeOD) δ 8.39 (dd, *J* = 5.2, 1.5 Hz, 0.6H), 8.29 (dd, *J* = 5.1, 1.5 Hz, 0.4H), 7.82 (dd, *J* = 7.7, 1.6 Hz, 0.4H), 7.48 (dd, *J* = 7.5, 1.6 Hz, 0.6H), 7.34 (dd, *J* = 7.5, 5.2 Hz, 0.4H), 7.27 (dd, *J* = 7.5, 5.1 Hz, 0.6H), 7.07 (td, *J* = 8.7, 7.1 Hz, 1.8H), 6.92 – 6.78 (m, 2.6H), 5.41 (dd, *J* = 4.2, 1.4 Hz, 0.4H), 5.26 (d, *J* = 3.2 Hz, 0.6H), 5.06 (t, *J* = 2.8 Hz, 0.6H), 4.97 (t, *J* = 3.1 Hz, 0.4H), 2.62 – 2.37 (m, 2H), 1.92 – 1.69 (m, 1H), 1.66 – 1.41 (m, 1H).

^{13}C NMR (126 MHz, MeOD) δ 157.7, 155.7, 152.6, 152.5, 149.1, 148.8, 134.5, 134.2, 132.8, 132.3, 129.5, 129.5, 125.2, 124.9, 123.9, 123.8, 118.4, 118.3, 75.3, 73.8, 62.8, 61.0, 25.6, 24.9, 23.2, 22.6.

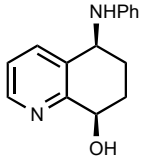
IR (ATR, neat, cm^{-1}): 3054 (w), 2966 (m), 2932 (m), 1730 (m), 1586 (m), 1468 (m), 1431 (m), 1265 (m), 959 (m), 854 (m), 827 (s), 734 (s), 695 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{15}N_2O^+$ $[M+H]^+$ calc.: 239.1184; found: 239.1182.

Alcohols 42 and 43. To a 1.0:1.6 mixture of the cycloadducts **S28** and **S29** (200 mg 0.839 mmol, 1.0 eq.) in glacial AcOH (2.8 mL, 3.0 M) activated zinc (384 mg, 5.88 mmol, 7.0 eq.) was added. The reaction mixture was stirred at room temperature until full conversion was observed by TLC (*ca.* 4 hours). The reaction mixture was diluted in toluene, filtered through Celite and concentrated *in vacuo*. The title compounds were isolated by reverse Biotage® Isolera™ One (AQ C18 column Spherical; 20 – 35µm; 100A; 20 g, 20 %-55 % MeCN in H_2O, detection at λ = 275 nm) getting **42** and **43**, both as a brown foams (151 mg, 0.629 mmol, combined yield 75 %, 1.0:1.0). *Note: While we take a 1:1.6 ratio of S28:S29 forward, we observe a 1:1 ratio of 42:43*



42



43

following chromatography. We believe that this ratio diminishment may be due to either the decomposition of 43 (product of S29) during column chromatography or low reactivity of S29 comparison to S28.

42

R_f 0.3 (*n*-hexane:EtOAc = 6:4, UV, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 8.43 (dd, J = 4.8, 1.7 Hz, 1H), 7.98 (dd, J = 7.1, 1.5 Hz, 1H), 7.35 (dd, J = 7.9, 4.7 Hz, 1H), 7.12 (dd, J = 8.6, 7.2 Hz, 2H), 6.74 (d, J = 7.5 Hz, 2H), 6.63 (dd, J = 7.9, 6.7 Hz, 1H), 4.74 (dd, J = 7.7, 5.0 Hz, 1H), 4.56 (t, J = 4.5 Hz, 1H), 2.32 – 1.82 (m, 4H).

^{13}C NMR (126 MHz, MeOD): δ 157.3, 149.3, 149.2, 138.1, 137.9, 130.1, 124.25, 118.1, 114.4, 68.3, 53.9, 29.0, 25.7.

IR (ATR, neat, cm^{-1}): 3360 (s), 3258 (s), 3047 (w), 2948 (s), 2862 (w), 1738 (w), 1602 (m), 1497 (m), 1322 (m), 966 (m), 912 (m), 807 (m), 743 (s), 866 (s), 692 (s), 505 (s).

HRMS (ESI-TOF, m/z) calcd.. For $C_{15}H_{16}N_2O^+$ $[M+H]^+$ calc.: 241.1341; found: 241.1342.

43

R_f 0.3 (*n*-hexane:EtOAc = 6:4, UV, $KMnO_4$).

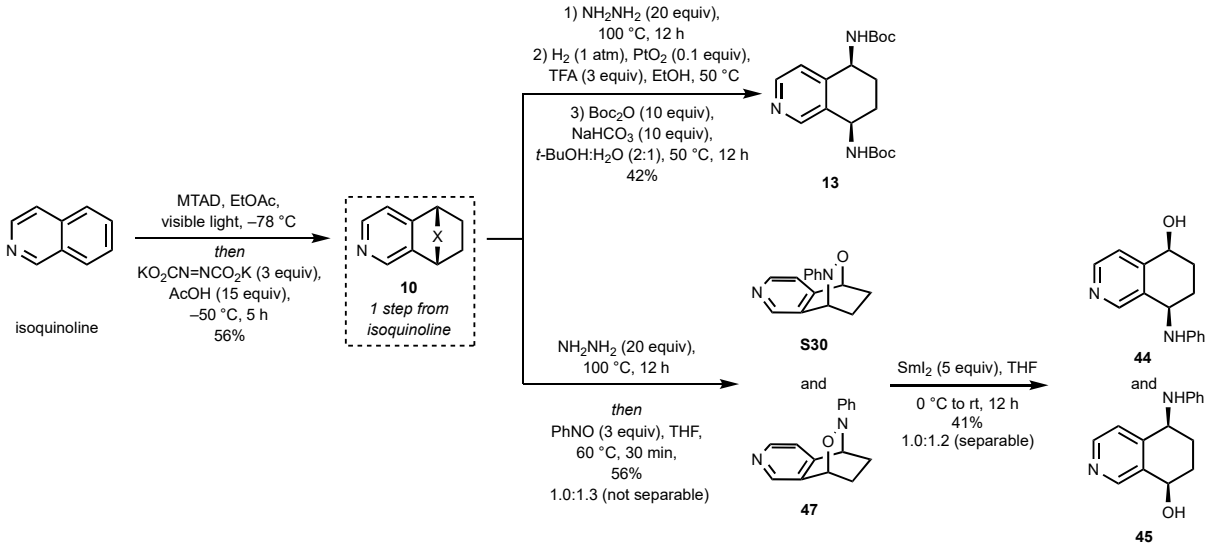
^{1}H NMR (500 MHz, MeOD) δ 8.45 – 8.43 (m, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.28 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.11 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.75 – 6.64 (m, 2H), 6.62 (tt, *J* = 7.4, 1.1 Hz, 1H), 4.73 (m, 1H), 4.67 – 4.57 (m, 1H), 2.13 – 1.95 (m, 4H).

^{13}C NMR (126 MHz, MeOD) δ 158.2, 149.4, 148.9, 138.4, 136.9, 130.2, 124.5, 118.1, 114.2, 69.2, 52.3, 30.0, 25.4.

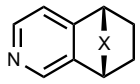
IR (ATR, neat, cm^{-1}): 3326 (m), 3219 (m), 2939 (m), 2890 (m), 2401 (m), 1597 (s), 1494 (s), 1435 (m), 964 (m), 767 (s), 721 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{16}N_2O^+$ $[M+H]^+$ calc.: 241.1341; found: 241.1341.

Derivatization from Isoquinoline



Scheme S18. Conversion of intermediate **isoquinoline** to **13**, **44**, and **45**.



10

Cycloadduct 10. The protocol was adjusted from the reported procedure.[2] Isoquinoline (6.2 mL, 53.1 mmol, 2.0 eq.) was added to a solution of MTAD (3.0 g, 26.5 mmol, 1.0 eq.) in EtOAc (265 mL, 0.1 M) under inert atmosphere at –78 °C. The mixture was then stirred under the irradiation with LED lights at –78 ºC until full decolorization of the reaction mixture was observed (*pink to colorless solution, usually about 36 hours*). After turning the lights off, potassium azodicarboxylate (15.5 g, 79.6 mmol, 3.0 eq.) was added in one portion, followed by the addition of AcOH (22.8 mL, 398 mmol, 15 eq.) in EtOAc (240 mL) at –78 ºC. After stirring the resulting suspension at –50 ºC for 5 hours, the reaction was warmed up to room temperature in water bath, then quenched with water (120 mL). Sodium bicarbonate (sat. aq. sol., 400 mL) was added, and then the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated sodium chloride (sat. aq. sol., 1 × 400 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (SiO_2, 10:1 – 3:7 hexane:EtOAc mixture) to provide compound **10** (3.6 g, 15.0 mmol, 56%) as a light brown solid.

R_f 0.2 (*n*-hexane:EtOAc = 3:7, UV).

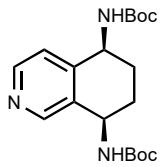
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.62 (d, J = 4.6 Hz, 1H), 8.59 (s, 1H), 7.44 (d, J = 4.8 Hz, 1H), 5.46 (s, 1H), 5.42 (s, 1H), 2.71 (s, 3H), 2.38 – 2.23 (m, 2H), 1.64 (d, J = 8.8 Hz, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 156.5, 156.4, 150.3, 143.8, 142.9, 130.6, 118.4, 52.0, 50.8, 25.0, 22.7, 22.0.

IR (ATR, neat, cm^{-1}): 3001 (w), 2946 (w), 1764 (m), 1701 (s), 1456 (s), 1207 (m), 1033 (m), 763 (s), 599 (s), 542 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{13}N_4O_2^+$ $[M+H]^+$ calc.: 245.1039; found: 245.1043.

m.p. 176 – 177 °C.



13

***Bis*-amide 13**. The experimental procedure was adjusted from the reported protocol.[32] The urazole containing cycloadduct **10** (500 mg, 2.05 mmol, 1.0 eq.) was placed in a flame dried round bottom flask along with anhydrous hydrazine (1.31 mL, 40.9 mmol, 20 eq.). The flask was purged with nitrogen and stirred at 100 °C for 16 hours. The reaction was allowed to cool down to 50 °C and volatiles were removed *in vacuo*. The crude reaction mixture was dissolved in EtOH (10.2 mL, 0.2 M) and PtO_2 (546.5 mg, 0.205, 0.1 eq.) along with trifluoroacetic acid (470 μL, 6.14 mmol, 3.0 eq.) were added. The reactor was purged with nitrogen and then with H_2. The reaction mixture was stirred under 1 atm of hydrogen (balloon) at 50 °C for 8 hours then filtered through a plug of Celite. The resulting crude material was dissolved in a 2 : 1 mixture of *t*-BuOH : H_2O (4.1 mL, 0.5 M) then Boc_2O (4.7 mL, 20.5 mmol, 10 eq.) and $NaHCO_3$ (1.72 g, 20.5 mmol, 10 eq.) were added. The

reaction mixture was stirred at 50 °C overnight, cooled at room temperature, diluted with water (15 mL), and extracted with EtOAc (3 × 150 mL). The combined organic phases were dried on anhydrous $MgSO_4$, filtered and purified by column chromatography (SiO_2; 10:1-1:1 hexanes:EtOAc) to provide the title compound **13** (314 mg, 0.860 mmol, 42%) as a bright yellow solid.

R_f 0.2 (*n*-hexane:EtOAc = 3:7, UV, $KMnO_4$).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 – 8.25 (m, 2H), 7.24 – 6.95 (m, 2H), 4.73 – 4.47 (m, 2H), 4.66 – 4.54 (m, 1H), 3.33 (s, 1H), 2.17 – 1.59 (m, 4H), 1.43 (d, J = 3.5 Hz, 18H).

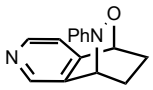
^{13}C NMR (126 MHz, DMSO-d_6)* δ 155.8, 155.8, 155.7, 155.5, 155.5, 155.2, 155.1, 149.5, 149.3, 148.9, 148.8, 147.9, 147.8, 147.7, 147.5, 147.3, 147.1, 134.3, 133.7, 121.6, 121.6, 121.3, 79.24, 79.0, 78.7, 78.2, 78.1, 78.1, 47.9, 47.8, 46.9, 46.8, 46.6, 46.5, 45.1, 45.0, 28.2, 26.6, 25.4.

IR (ATR, neat, cm^{-1}): 3323 (m), 2976 (m), 2931 (m), 1683 (s), 1513 (s), 1244 (s), 1160 (s), 1045 (w), 841 (w), 620 (w).

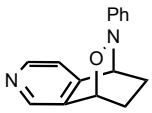
HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{30}N_3O_4^+$ $[M+H]^+$ calc.: 364.2236; found: 364.2234.

m.p. 178 – 179 °C.

**Mixture of rotamers confirmed by VT NMR.*



S30



47

Cycloadducts S30 and 47. The procedure was adjusted from the reported protocol.[3] The pyridine fused cycloadduct **10** (500 mg, 2.05 mmol, 1.0 eq.) was refluxed in hydrazine (1.31 mL, 41.0 mmol, 20 eq.) at 100 °C until full conversion of the cycloadduct was observed (*ca.* 16 hours). Volatiles were removed *in vacuo* and the residue was dissolved in DMF (10.2 mL, 0.2 M). Nitrosobenzene (660 mg, 6.15 mmol, 3.0 eq.) was added and the reaction mixture was stirred at 60 °C for 30 min. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 50 mL). The organic phases were washed with a saturated sodium chloride (sat. aq. sol., 3 × 50 mL), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 7:3-1:9 hexane:EtOAc) to provide the title compounds **47** and **S30** (275 mg, 1.15 mmol, 56%, 1.0:1.3) as a complex mixture of the two regioisomers along with products of degradation of the nitrosobenzene. The mixture was crystallized in EtOH two times getting **47** as colorless crystals (31.0 mg, 0.129 mmol). The EtOH phase was evaporated recovering the rest of the material (240 mg, 1.00 mmol) that was purified by preparative TLC (SiO_2, 2:8 hexane:EtOAc) getting a clean mixture of the two regioisomers (236 mg, 0.991 mmol, 1.0:2.1) as a reddish brown foam.

Note: It has been observed that elimination of hydrazine became difficult on scales larger than 500 mg. Residual hydrazine can consume nitrosobenzene, so multiple azeotropic evaporations with toluene are recommended.

S30 + 47

R_f 0.3 (*n*-hexane:EtOAc = 1:9, UV).

^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 – 8.53 (m, 1H), 8.48 (d, *J* = 4.82 Hz, 0.3H), 8.25 (s, 0.7H), 7.26 (m, 0.6H)*, 7.14 – 7.03 (m, 2H), 6.92 (d, *J* = 4.85 Hz, 0.3H), 6.88 – 6.76 (m, 3H), 5.31 (dd, *J* = 4.2, 1.5 Hz, 0.3H), 5.20 (dd, *J* = 4.3, 1.5 Hz, 0.7H), 4.82 (t, *J* = 3.0 Hz, 0.7H), 4.76 (t, *J* = 3.0 Hz, 0.3H), 2.68 – 2.45 (m, 2.1H), 1.73 (ddq, *J* = 15.7, 9.3, 3.1 Hz, 1H), 1.50 (dddt, *J* = 13.5, 12.1, 3.4, 1.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 149.8, 143.5, 143.4, 133.5, 128.7, 122.9, 119.3, 117.2, 70.4, 59.7, 24.8, 22.1.

IR (ATR, neat, cm^{-1}): 3031 (w), 2994 (w), 2936 (w), 1738 (w), 1480 (m), 962 (s), 851 (s), 761 (s), 695 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{15}N_2O^+$ $[M+H]^+$ calc.: 239.1184; found: 239.1184.

m.p. 182 – 183 °C.

**Partially covered by $CDCl_3$, visible from the HSQC.*

47

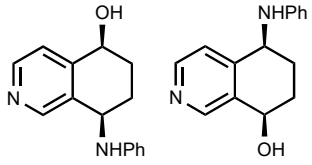
R_f 0.3 (*n*-hexane:EtOAc = 1:9, UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.48 (d, *J* = 4.9 Hz, 1H), 7.17 – 6.99 (m, 2H), 6.91 (d, *J* = 4.8 Hz, 1H), 6.87 – 6.69 (m, 3H), 5.40 – 5.23 (m, 1H), 4.76 (t, *J* = 3.0 Hz, 1H), 2.71 – 2.43 (m, 2H), 1.74 (tt, *J* = 12.4, 3.0 Hz, 1H), 1.59 – 1.37 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 149.8, 143.5, 143.4, 133.5, 128.7, 122.9, 119.3, 117.2, 70.4, 59.7, 24.8, 22.1.

IR (ATR, neat, cm^{-1}): 3158 (m), 2968 (m), 2935 (s), 1595 (s), 1486 (s), 1421 (m), 1184 (m), 962 (m), 835 (s), 760 (s), 696 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{15}N_2O^+$ $[M+H]^+$ calc.: 239.1184; found: 239.1182.



44 **45**

Alcohols 44 and 45. A 1.0:2.1 mixture of the pyridine condensed cycloadducts **S30** and **47** (100.0 mg, 0.420 mmol, 1.0 eq.) was placed in a flame dried round bottom flask under nitrogen atmosphere. Dry and degassed THF (4.2 mL, 0.1 M) was added to the flask, the suspension was cooled in an ice bath for around 10 min. A freshly prepared solution of SmI_2 (0.1 M in THF, 21.0 mL, 2.1 mmol, 5.0 eq.) was added to the reaction mixture dropwise getting a deep blue solution. The mixture was heated at room temperature overnight. When complete conversion was observed by TLC the excess of SmI_2 was quenched sodium bicarbonate (sat. aq. sol., 15 mL), diluted with EtOAc (25 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The titled compounds were isolated from the crude by reverse Biotage® Isolera™ One (AQ C18 column Spherical; 20 – 35μm; 100A; 20 g, 20 %-55 % MeCN in H_2O, detection a λ = 275 nm) to afford **44** and **45**, both as a brown foams (41.2

mg, 0.172 mmol, combined yield 41% 1.2:1.0). *Note: While we take a 1:2.1 ratio of S30:47 forward, we observe a 1:1 ratio of 44:45 following chromatography. We believe that this ratio diminishment may be due to either the decomposition of 45 (product of 47) during column chromatography or low reactivity of 47 in comparison to S30.*

44

R_f 0.3 (*n*-hexane:EtOAc = 3:7, UV, $KMnO_4$).

^{1}H NMR (500 MHz, MeOD) δ 8.51 (s, 1H), 8.40 (s, 1H), 7.56 (d, *J* = 5.2 Hz, 1H), 7.13 (dd, *J* = 8.7, 7.2 Hz, 2H), 6.79 – 6.68 (m, 2H), 6.64 (t, *J* = 7.3, 1H), 4.68 (m, 2H), 2.16 – 1.88 (m, 4H).

^{13}C NMR (126 MHz, MeOD)* δ 151.6, 150.6, 149.1, 148.0, 130.2, 123.4**, 118.2, 114.2, 67.8, 49.3***, 29.1, 25.9.

IR (ATR, neat, cm^{-1}): 3334 (w), 2928 (w), 1601 (s), 1498 (s), 1413 (m),1311 (w), 1072 (w), 750 (m), 694 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{17}N_2O^+$ $[M+H]^+$ calc.: 241.1341; found: 241.1342.

**One quaternary carbon is not ^{13}C NMR active.*
*** Slightly visible from ^{13}C, well visible from HSQC.*
****Covered by MeOD, well visible from HSQC.*

45

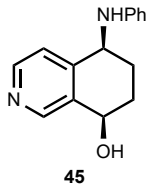
R_f 0.3 (*n*-hexane:EtOAc = 3:7, UV, $KMnO_4$).

^{1}H NMR (600 MHz, MeOD) δ 8.58 (s, 1H), 8.34 (d, *J* = 5.3 Hz, 1H), 7.48 (d, *J* = 5.3 Hz, 1H), 7.12 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.71 (dt, *J* = 7.7, 1.1 Hz, 2H), 6.63 (tt, *J* = 7.3, 1.1 Hz, 1H), 4.82 (m, 1H), 4.57 (t, *J* = 5.4 Hz, 1H), 2.34 – 1.78 (m, 4H).

^{13}C NMR (151 MHz, MeOD) δ 151.1, 150.7, 149.4, 148.5, 137.0, 130.2, 124.0, 118.2, 114.2, 65.9, 52.0, 30.5, 25.3.

IR (ATR, neat, cm^{-1}): 3293 (s), 3108 (s), 2944 (m), 2852 (m), 1600 (s), 1493 (s), 1292 (m), 1251 (m), 1088 (m), 1049 (m), 968 (s), 830 (m), 748 (s), 695 (s).

HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{17}N_2O^+$ $[M+H]^+$ calc.: 241.1341; found: 241.1345.

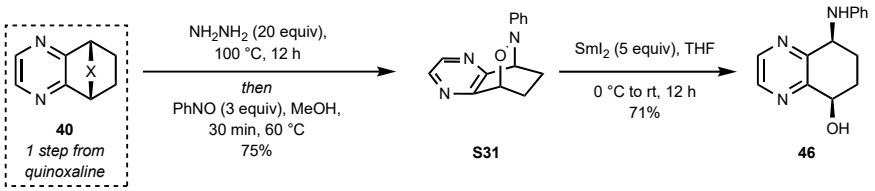


45

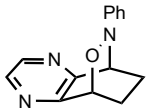
Alcohol 45. The cycloadduct **47** (100.0 mg, 0.420 mmol, 1.0 eq.) was placed in a flame dried round bottom flask under nitrogen atmosphere. Dry and degassed THF (4.2 mL, 0.1 M) was added to the flask, the suspension was cooled in an ice bath for around 10 min. SmI_2 (0.1 M in THF, 21 mL, 5.0 eq.) was added to the reaction mixture dropwise getting a deep blue solution. The mixture was heated at room temperature overnight. When complete conversion was observed by TLC the excess of SmI_2 was quenched with sodium bicarbonate (sat. aq. sol., 15 mL), diluted with EtOAc (25 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed *in*

vacuo. The crude material was purified by column chromatography (SiO_2, 7:3-1:9 hexane:EtOAc) to afford **45** as a light brown foam (95.5 mg, 0.398 mmol, 95%).

Derivatization from Quinoxaline



Scheme S19. Conversion of intermediate **40** to **46**.



S31

Cycloadduct S31. The procedure was adjusted from a reported protocol.[3] The urazole containing cycloadduct **40** (500 mg, 2.05 mmol, 1.0 eq.)[2] was refluxed in hydrazine (1.31 mL, 41.0 mmol, 20 eq.) at 100 °C until full conversion of the cycloadduct was observed (*ca.* 16 hours). Volatiles were removed *in vacuo* and the residue was dissolved in MeOH (10.2 mL). Nitrosobenzene (660 mg, 6.15 mmol, 3.0 eq.) was added and the reaction mixture was stirred at 60 °C for 30 min. The crude product was purified by column chromatography (SiO_2, 10:1-7:3 hexane:EtOAc) to provide the title compound **S31** (366 mg, 1.53 mmol, 75%) as a brown solid.

Note: It has been observed that elimination of hydrazine became difficult on scales larger than 500 mg. Residual hydrazine can consume nitrosobenzene, so multiple azeotropic evaporations with toluene are recommended.

R_f 0.4 (*n*-hexane:EtOAc = 3:7, UV).

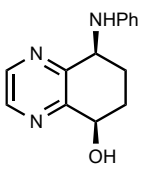
^{1}H NMR (500 MHz, MeOD) δ 8.43 (dd, *J* = 41.5, 2.9 Hz, 2H), 7.08 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.90 – 6.75 (m, 3H), 5.45 – 5.35 (m, 1H), 5.11 (t, *J* = 3.1 Hz, 1H), 2.66 – 2.42 (m, 2H), 1.94 – 1.76 (m, 1H), 1.68 – 1.44 (m, 1H).

^{13}C NMR (126 MHz, MeOD) δ 153.0, 152.2, 151.7, 145.5, 145.2, 129.6, 124.1, 118.2, 75.6, 62.8, 24.8, 22.4.

IR (ATR, neat, cm^{-1}): 3058 (w), 2990 (w), 2973 (s), 2937 (w), 1590 (m), 1481 (m), 1402 (m), 1348 (m), 949 (m), 854 (m), 768 (s),704 (s) 514 (m).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{14}N_3O^+$ $[M+H]^+$ calc.: 240.1137; found: 240.1134.

m.p. 134 – 135 °C.



46

Pyrazine fused alcohol 46. The cycloadduct **S31** (100.0 mg, 0.418 mmol, 1.0 eq.) was placed in a flame dried round bottom flask under nitrogen atmosphere. Dry and degassed THF (4.2 mL, 0.1 M) was added to the flask, the suspension was cooled in an ice bath for 10 min. A freshly prepared solution of SmI_2 (0.1 M in THF, 21 mL 5.0 eq.) was added to the reaction mixture dropwise and the resulting deep blue solution was heated at room temperature overnight. When complete conversion was observed by TLC, the excess of SmI_2 was quenched with sodium

bicarbonate (sat. aq. sol., 15 mL), diluted with EtOAc (25 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (SiO_2, 7:3-1:9 hexane:EtOAc) to obtain **46** as a brown foam (71.4 mg, 0.296 mmol, 71%).

R_f 0.3 (*n*-hexane:EtOAc = 3:7, UV, $KMnO_4$).

^{1}H NMR (600 MHz, MeOD) δ 8.54 (m, 2H), 7.13 (m, 2H), 6.77 (m, 2H), 6.65 (m, 1H), 4.80 (m, 1H), 4.64 (m, 1H), 2.21 – 2.07 (m, 4H).

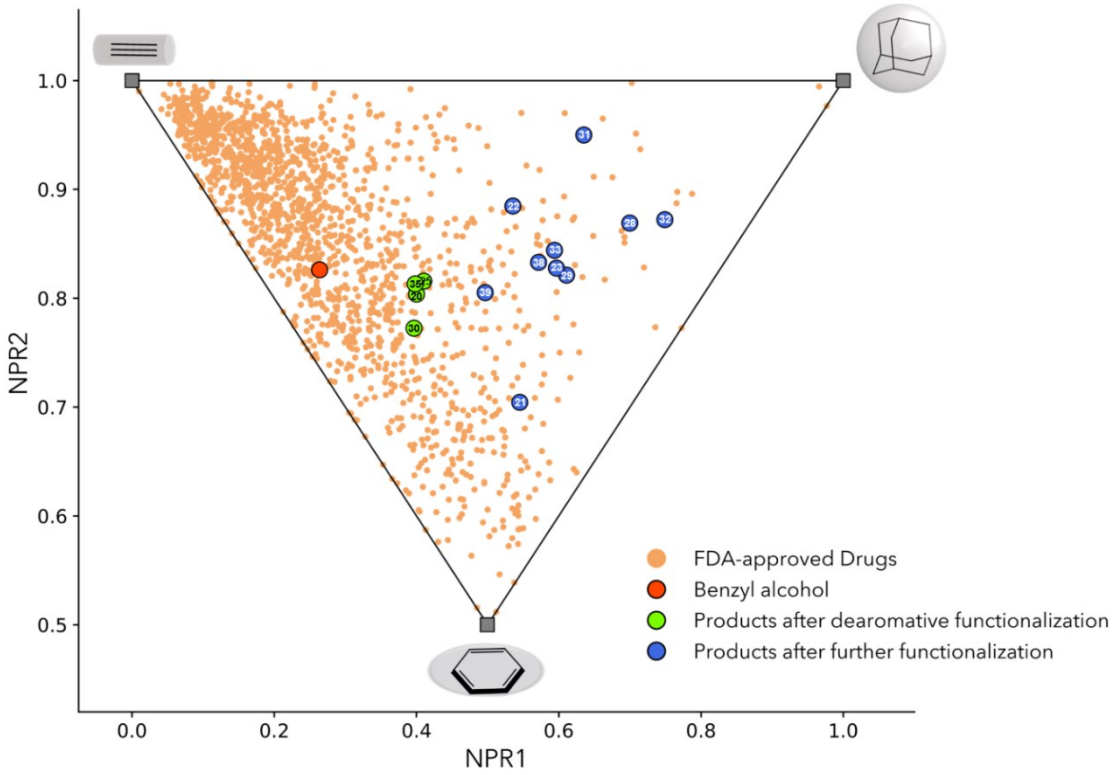
^{13}C NMR (151 MHz, MeOD) δ 155.2, 154.4, 149.4, 144.8, 144.7, 130.1, 118.5, 114.7, 69.4, 54.6, 28.8, 25.4.

IR (ATR, neat, cm^{-1}): 3356 (s), 3049 (m), 2927 (s), 1649 (m), 1600 (s), 1497 (s), 1071 (s), 747 (s), 693 (s).

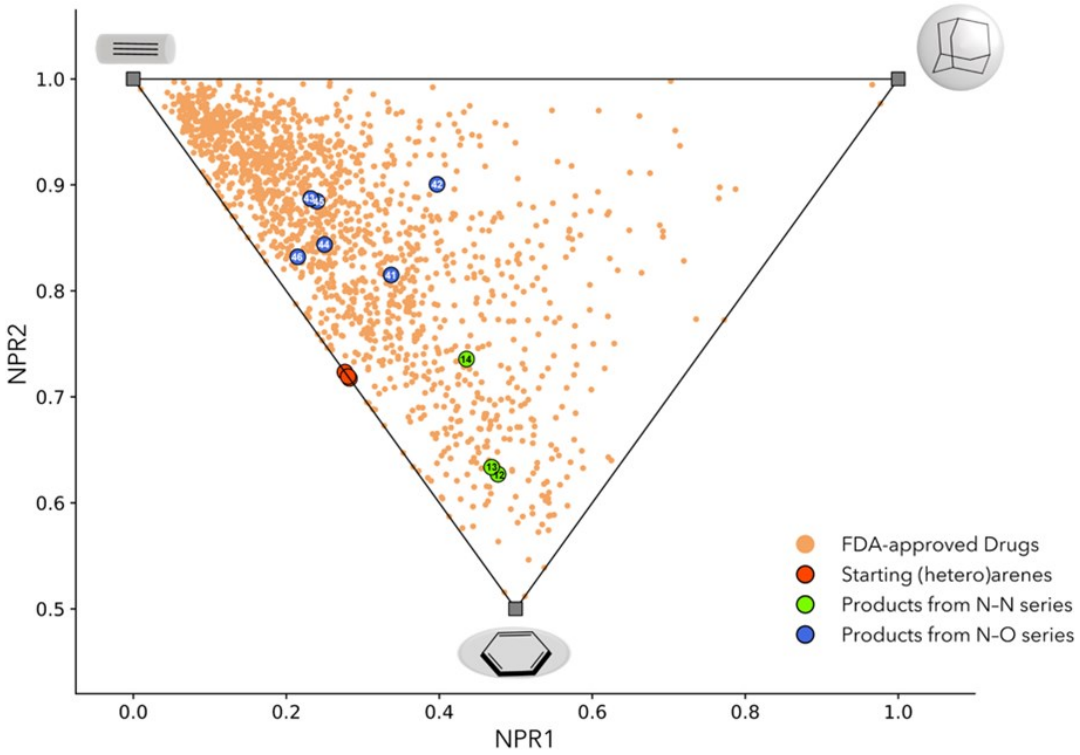
HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{16}N_3O^+$ $[M+H]^+$ calc.: 242.1293; found: 242.1293.

PMI Calculation and Plotting

To evaluate the structural shape diversity of our molecules, we conducted a principal moments of inertia (PMI) analysis.[10] As a complement to this analysis and to enable a comparison, we selected a dataset of 1,683 FDA-approved compounds from ChEMBL (as of November 2022).[11] We calculated molecular descriptors for the PMI analysis using RDKit (version 2022.03.4),[12] on the 3D conformations generated using the ETKDG method[13] followed by energy minimization with the MMFF94 force field.[14] The corners of the PMI triangle were delimited using three distinct compounds, namely diacetylene in the top-left corner, benzene in the bottom corner, and adamantane in the top-right corner. All experiments and calculations were performed with Python 3.9.12, and the figures were created using the matplotlib[15] and seaborn[16] packages.



Picture S2. PMI analysis graph of benzyl alcohol and products following functionalization.



Picture S3. PMI analysis graph of heteroarenes and products following functionalization.

Molecule Name	MW	TPSA	LogP	Num HAcceptors	Num HDonors	Num Rotatable Bonds	Num HeavyAtoms	Num Aromatic Rings	FractionCSP3	LabuteASA	NPR1	NPR2
Compound_12	163,224	64,93	0,875	3	2	2	12	1	0,444444	90,281613	0,476803	0,627048
Compound_13	163,224	64,93	0,875	3	2	2	12	1	0,444444	90,281613	0,468347	0,633655
Compound_14	194,234	92,5	-0,5784	4	4	4	14	1	0,4	102,228743	0,435638	0,735772
Compound_20	143,186	66,48	-0,6129	3	3	4	10	0	0,714286	78,715898	0,400021	0,803877
Compound_21	177,2	106,94	-2,4473	5	5	6	12	0	1	91,97725	0,545168	0,704481
Compound_22	177,2	106,94	-2,4473	5	5	6	12	0	1	91,97725	0,535474	0,884759
Compound_23	176,216	112,73	-2,4809	5	5	6	12	0	1	93,957321	0,596619	0,827688
Compound_25	175,184	106,94	-2,6713	5	5	6	12	0	0,714286	88,477706	0,410108	0,815672
Compound_27	209,198	147,4	-4,5057	7	7	8	14	0	1	101,739058	0,494237	0,847501
Compound_28	209,198	147,4	-4,5057	7	7	8	14	0	1	101,739058	0,699705	0,869095
Compound_29	208,214	153,19	-4,5393	7	7	8	14	0	1	103,719129	0,610859	0,821327
Compound_30	144,17	60,69	-0,5793	3	3	4	10	0	0,714286	76,735828	0,396376	0,772582
Compound_31	178,184	101,15	-2,4137	5	5	6	12	0	1	89,99718	0,635144	0,949984
Compound_32	178,184	101,15	-2,4137	5	5	6	12	0	1	89,99718	0,749072	0,872265
Compound_33	177,2	106,94	-2,4473	5	5	6	12	0	1	91,97725	0,593903	0,84412
Compound_35	176,168	101,15	-2,6377	5	5	6	12	0	0,714286	86,497636	0,398078	0,813234
Compound_36	210,182	141,61	-4,4721	7	7	8	14	0	1	99,758988	0,587971	0,719353
Compound_38	210,182	141,61	-4,4721	7	7	8	14	0	1	99,758988	0,571489	0,832971
Compound_39	209,198	147,4	-4,5057	7	7	8	14	0	1	101,739058	0,496463	0,805234
Compound_41	271,316	72,72	1,6086	4	4	5	20	2	0,25	141,077564	0,336971	0,815067
Compound_42	240,306	45,15	3,062	3	2	3	18	2	0,266667	129,130433	0,396919	0,90055
Compound_43	240,306	45,15	3,062	3	2	3	18	2	0,266667	129,130433	0,231899	0,887181
Compound_44	240,306	45,15	3,062	3	2	3	18	2	0,266667	129,130433	0,249916	0,843741
Compound_45	240,306	45,15	3,062	3	2	3	18	2	0,266667	129,130433	0,240199	0,8846
Compound_46	241,294	58,04	2,457	4	2	3	18	2	0,285714	126,945111	0,21499	0,832117
Isoquinoline	129,162	12,89	2,2348	1	0	0	10	2	0	69,167509	0,276518	0,723482
Naphtalene	128,174	0	2,8398	0	0	0	10	2	0	71,352832	0,28073	0,71927
Quinoline	129,162	12,89	2,2348	1	0	0	10	2	0	69,167509	0,282545	0,717455
benzyl alcohol	108,14	20,23	1,1789	1	1	2	8	1	0,142857	59,917013	0,263744	0,826074

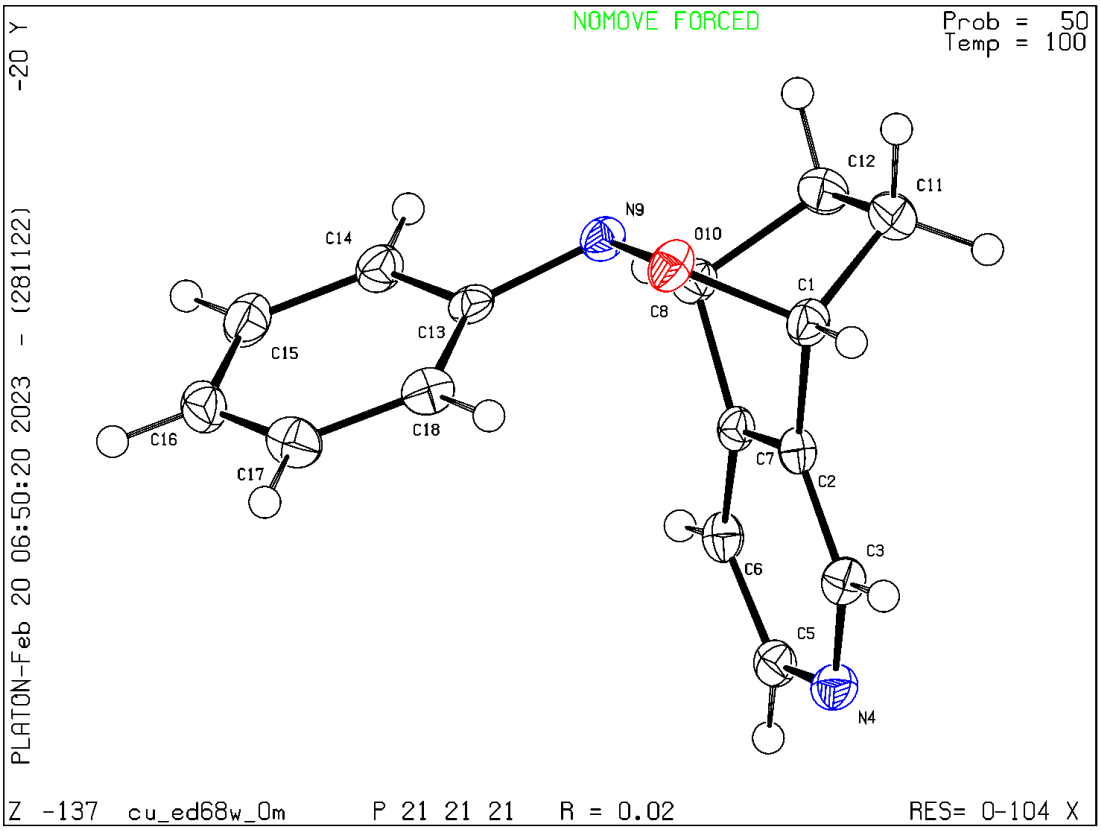
Table S1. PMI values.

Crystallographic Data

Single crystals of $C_{15}H_{14}N_2O$ **47** were recrystallized from ethanol. A suitable crystal was selected and [Mounted using Paratone-N oil (Exxon) on a cryo-loop (Hampton) with (-2 3 5) face roughly perpendicular to the spindle axis] on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.00 K during data collection. Using Olex2,[17] the structure was solved with the XT[18] structure solution program using Intrinsic Phasing and refined with the XL[19,20] refinement package using Least Squares minimization.

Table S1. Crystal data and structure refinement for **47.**

Identification code	cu_ed68w_0m
Empirical formula	$C_{15}H_{14}N_2O$
Formula weight	238.28
Temperature/K	100.00
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.3242(4)
b/Å	9.9190(5)
c/Å	12.8658(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1189.92(10)
Z	4
ρ_{calc}g/cm^3	1.330
μ/mm^{-1}	0.675
F(000)	504.0
Crystal size/mm^3	0.482 × 0.481 × 0.126
Radiation	MoKα (λ = 1.54178)
2Θ range for data collection/°	11.264 to 136.454
Index ranges	$-11 \le h \le 11$, $-11 \le k \le 11$, $-15 \le l \le 15$
Reflections collected	16020
Independent reflections	2182 [R_{int} = 0.0232, R_{sigma} = 0.0140]
Data/restraints/parameters	2182/0/165
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0243, wR_2 = 0.0632
Final R indexes [all data]	R_1 = 0.0244, wR_2 = 0.0633
Largest diff. peak/hole / e Å^{-3}	0.17/-0.12
Flack parameter	0.4(3)


NOMOVE FORCED
Prob = 50
Temp = 100
-20 Y
PLATON-Feb 20 06:50:20 2023 - (281122)
C12
C11
N9
O10
C14
C1
C8
C13
C15
C7
C2
C16
C18
C17
C6
C3
C5
N4
Z -137 cu_ed68w_0m
P 21 21 21
R = 0.02
RES= 0-104 X

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Chapter 3: Dearomative Approach Towards the Synthesis of Pyridine-Derived Isosteres

3.1 Bioisosterism: Introduction

The concept of bioisosterism, together with the implementation of bioisosteric replacement, is fundamental in the field of medicinal chemistry. Its broadest definition, provided by Burger in 1991, states that bioisosteres are "*Compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physicochemical properties....*"[1] As a matter of fact, the exploration of bioisosteres provides valuable design elements that can be used to adjust the structural and pharmacokinetic characteristics of bioactive compounds towards viable drug candidates. Precisely, the concept can be traced back to Langmuir, who originated the term isosteres in 1919 to describe molecules of a similar shape and size that exhibited analogous physical-chemical properties.[2] The first experiments that explored the potential of bioisosterism were reported by Erlenmeyer a few years later: he observed that antibodies recognizing ortho-substituted tyrosine moieties in synthetic antigens, derived by reaction with diazonium ions, were not able to distinguish between phenyl and thiophene ring or O, NH, and CH_2 in a linker element.[3] Though, the deployment of a bioisostere maintains high value in the field of drug design by providing an opportunity to probe the effect of steric size and shape, the modulation of dipole and electronic properties, lipophilicity, polarity, or pKa on biological response. In addition to affecting potency and function, isosteres have proven to be useful in addressing problems associated with pharmacokinetic and pharmaceutical properties, specificity, toxicity, and metabolic activation pathways in addition to being a source of novel intellectual property.[3–5]

3.1.1 Classification of Bioisosteres

In the 1970s, Alfred Bruger categorized bioisosteres as either classical (atom number, number of valence electrons, and degree of unsaturation) or non-classical (similar pKa, electrostatic potentials, orbital occupation/HOMOs, and LUMOs). Classical bioisosteres can be further subdivided into five classes, as shown in Figure 3.1.[1,4] Unlike their classical counterparts, nonclassical bioisosteres do not conform to Langmuir's broad definition of "isostere". They represent groups capable of emulating the steric or electronic profile of the original functional group instead. As non-classical bioisosteres can significantly differ

in electronic distribution, physicochemical, steric, and topological properties, they have found beneficial applications in drug discovery research. Non-classical bioisosteres are subdivided into two groups: 1) exchangeable functional groups or 2) cyclic vs. non-cyclic.

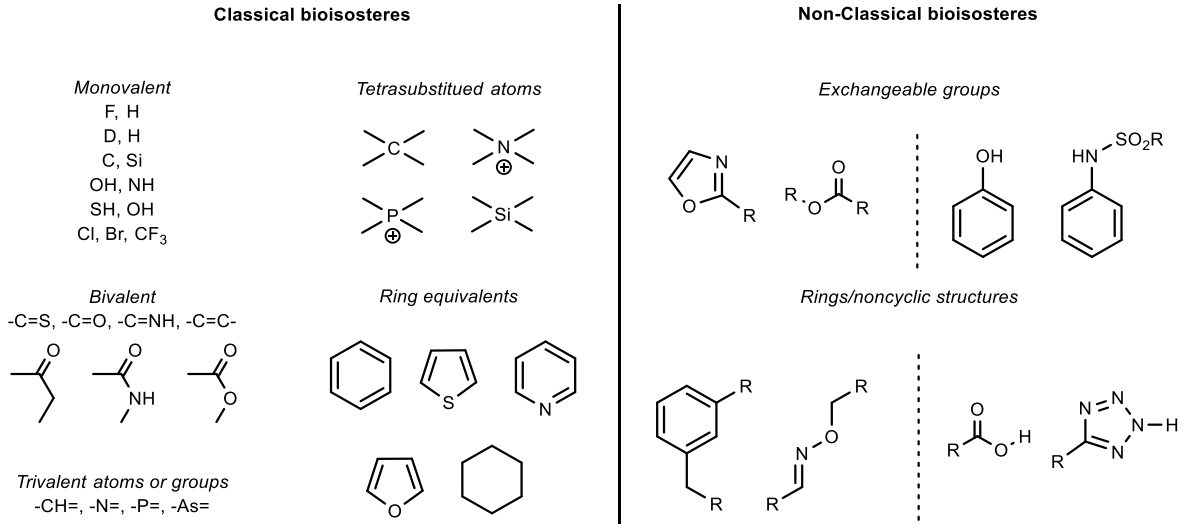


Figure 3.1. Examples of Classical and Non-Classical bioisosteres.

3.1.2 Examples of Bioisosteric Replacement

3.1.2.1 Hydrogen-Fluorine

One of the most common examples of bioisosteric replacement in drug design is the substitution of hydrogen with fluorine. F is 20% larger than H, actually closer in size to a C=O moiety, and is the most electronegative atom of the periodic table. The large dipole associated with the C—F moiety interacts electronically with proximal polar substituents and is in the same direction as C=O, C—OH, C—CN, for which it can act also as a bioisosteric replacement, but is the reverse of the C—H. The C—F bond dissociation energy is very high at 105.4 kcal/mol, which compares to 98.8 kcal/mol for C—H. The powerful electron-withdrawing properties of fluorine can modulate the p*K*a values of proximal functionalities in a predictable and additive fashion, reducing the basicity of amines and increasing the acidity of acids and alcohols.[4] This logic has been applied to the development of a Fentanyl analog. This famous drug (**3.1A**, Figure 3.2) is a very potent centrally and peripherally active μ-opioid receptor agonist used to treat pain: unfortunately, besides several adverse side effects, it is also addictive. Based on the hypotheses that μ-opioid receptors in peripheral sensory neurons are important contributors to painful syndromes and that damaged local tissues are inflamed and acidic,

the concept of reducing the basicity of Fentanyl as a means of conferring tissue selectivity was examined. The binding of this molecule to the μ-opioid receptor is not pH-dependent between pH=6.5 and 7.4. However, the reduced basicity of the fluoro derivative **3.1B** results in pH-dependent receptor binding, with high affinity observed only at low pH when the amine is protonated. As a consequence, the μ-opioid receptor binding of the analog would have been expected to be restricted to tissues where the pH is low enough to affect amine protonation. As a matter of fact, NFEPP (**3.1B**, Figure 3.2) proved to be active in two models of pain, not associated with the respiratory depression, sedation, or constipation that **3.1A** might bring, and exhibited reduced potential for addiction based on evaluation in a conditioned place preference model.[6]

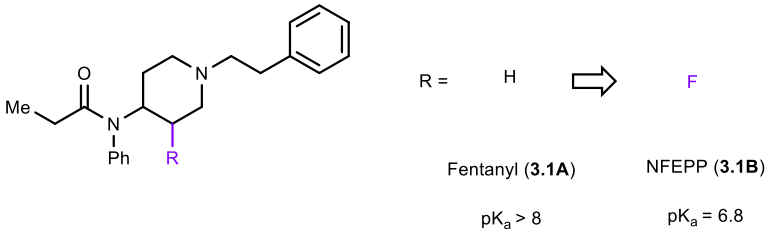


Figure 3.2. Hydrogen-Fluorine replacement for the generation of a Fentanyl analog.

3.1.2.2 Bioisosteres of Carbonyl-containing Functionality

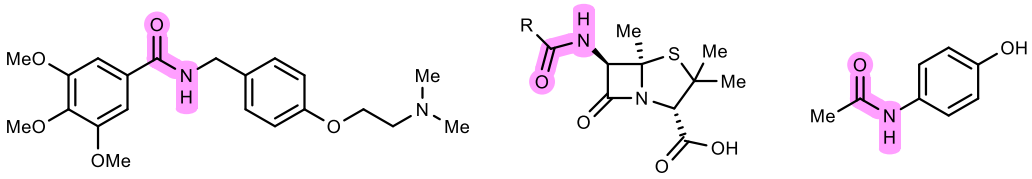


Figure 3.3. Amide bond containing marketed drugs.

In drug discovery, amide bond formation is the most common reaction, exploiting the vast amine and carboxylic acid libraries available to pharmaceutical companies. Amides are therefore prevalent motifs in commercial pharmaceutical and agrochemical compounds, such as Penicillin, Paracetamol, and many more, and display valuable features such as being more stable than other carbonyl derivatives, being powerful hydrogen-bond donors and acceptors, as well as being ubiquitous as critical bonding units in natural peptides and proteins. Consequently, bioisosteres of amides are also diffused, providing a mimic of the features of the amide and adjusting the global properties of a compound.[7] One of the latest examples is provided by the amino-oxetane motif. 3,3-

disubstituted oxetanes have gained considerable interest as carbonyl replacements due to their similar dipole moments, hydrogen-bonding capacities, and oxygen lone pair orientation.[8] Their use as bioisosteres might also introduce tridimensionality and, in the case of amides, provide fragments with increased stability towards hydrolysis. One example was provided with the discovery of Thalidomide analog (**3.5B**, Figure 3.3). This compound (**3.5A**), despite its unfortunate story, it's therapeutically useful, but its distribution to patients is limited due to the inherent teratogenic properties it bears. Carreira's group tried to address this issue, mainly linked to the in vivo stability/metabolism and consequent racemization of this molecule. Substituting the amide moiety with an oxetane ring provided an analog with stronger plasma stability, without significant differences in the physicochemical and in vitro metabolic profiles.[9]

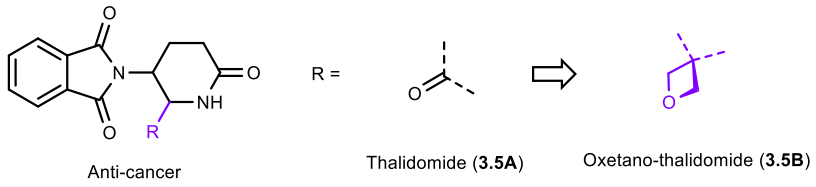


Figure 3.4. Amide-Oxetane replacement for the generation of a Thalidomide analog.

3.1.2.3 Phenyl Ring Bioisosteres

Aromatic rings are ubiquitous in bioactive molecules, with the phenyl ring being the most prevalent, a component of approximately 45% of marketed small-molecule drugs. However, the deployment of planar aromatic rings in drug design has been highlighted as potentially problematic concerning the durability of a compound as it navigates the development process. For instance, phenyl rings are relatively non-polar; they may be engaged in π–π stacking interactions that can contribute to low aqueous solubility or have limited bioavailability; and they can be a metabolic liability. Several strategies have been developed to address these kinds of issues: hydrophobicity can be reduced by appending charged or polar groups such as alcohol or amine moieties to the parent compound, with the risk of altering potency. Similar effects may be seen through the use of heterocyclic ring replacements, but again these may alter the potency of the desired compound. Alternatively, modifications can be made to alter the crystal packing of a compound by removal of phenyl rings, changing the molecular geometry or topology. For example, the replacement of a phenyl ring by an alkyl group (linear, cyclic, or caged) may help improve solubility by eliminating π–π stacking interactions with the advantage of introducing potential reactivity plus a higher level of three-dimensionality, accessing new chemical

space. These changes can heavily influence the binding interactions between a drug and its ultimate biological target. In conclusion, the ideal features of a phenyl ring bioisotere are: retained structural rigidity, reduced lipophilicity, and increased sp^3 incorporation without introducing metabolic instability.[10] A nice example is provided by the use of cubane and bicyclo[1.1.1]pentane (BCP) as 1,4-disubstituted phenyl ring replacements. Considering Imatinib (**3.6A**, Figure 3.5), a potent inhibitor of ABL1 kinase and widely prescribed drug for the treatment of a variety of leukemias, a med-chem study for the development of improved derivatives revealed that the BCP and cubane-containing analogs (**3.6B**, **3.6C**) were found to possess higher thermodynamic solubility, with the cubane derivative also manifesting the highest inhibitory activity against ABL1 kinase and the most potent cytotoxicity values against cancer cell lines.[11]

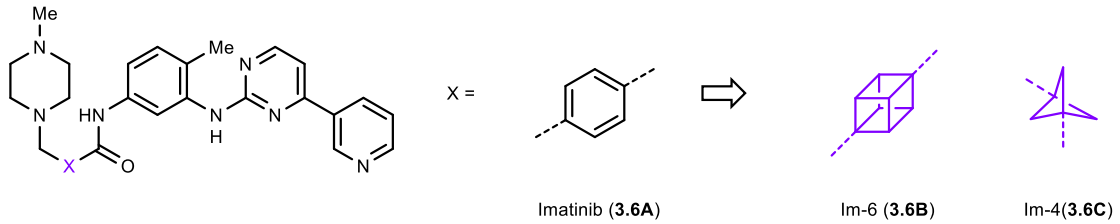


Figure 3.5. Phenyl ring replacement for the generation of an Imatinib analog.

3.1.3 Saturated Nitrogen Heterocycles

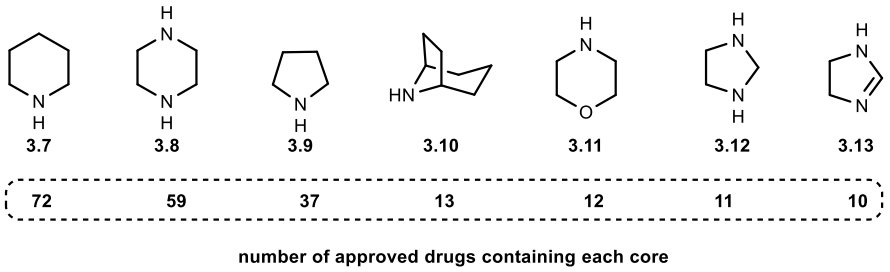


Figure 3.6. Most frequently used saturated nitrogen heterocycles in FDA-approved pharmaceuticals.

Saturated N-heterocycles are prevalent in biologically active molecules and are increasingly attractive scaffolds within the development of new pharmaceuticals.[12] The core units of aliphatic nitrogen heterocycles such as piperazine (**3.8**), piperidine (**3.7**), and morpholine (**3.11**) have been targets for metabolic attack by P450s and other drug-metabolizing enzymes such as aldehyde oxidase and monoamine oxidase (MAOs). The electron-rich nitrogen and/or a-carbons are often major sites of the metabolism of alicyclic amines. The most common biotransformations include N-oxidation, N-conjugation, oxidative N-dealkylation, ring oxidation, and ring-opening (Figure 3.7). In some instances, the metabolic pathways generate electrophilic reactive intermediates and

cause bioactivation.[13] However, potential bioactivation-related adverse events can be attenuated by structural modifications. Expanding the scope of accessible functionality with the discovery of new building blocks of this kind with increased metabolic stability could greatly impact the rate of success in drug development.

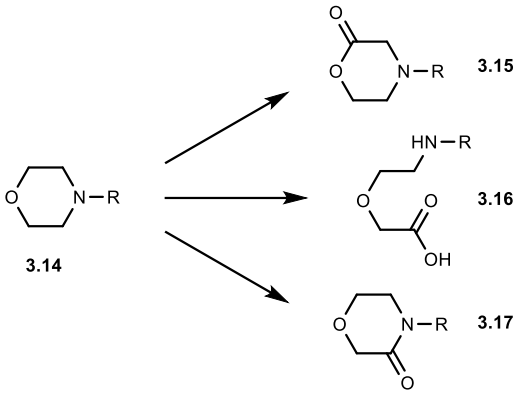
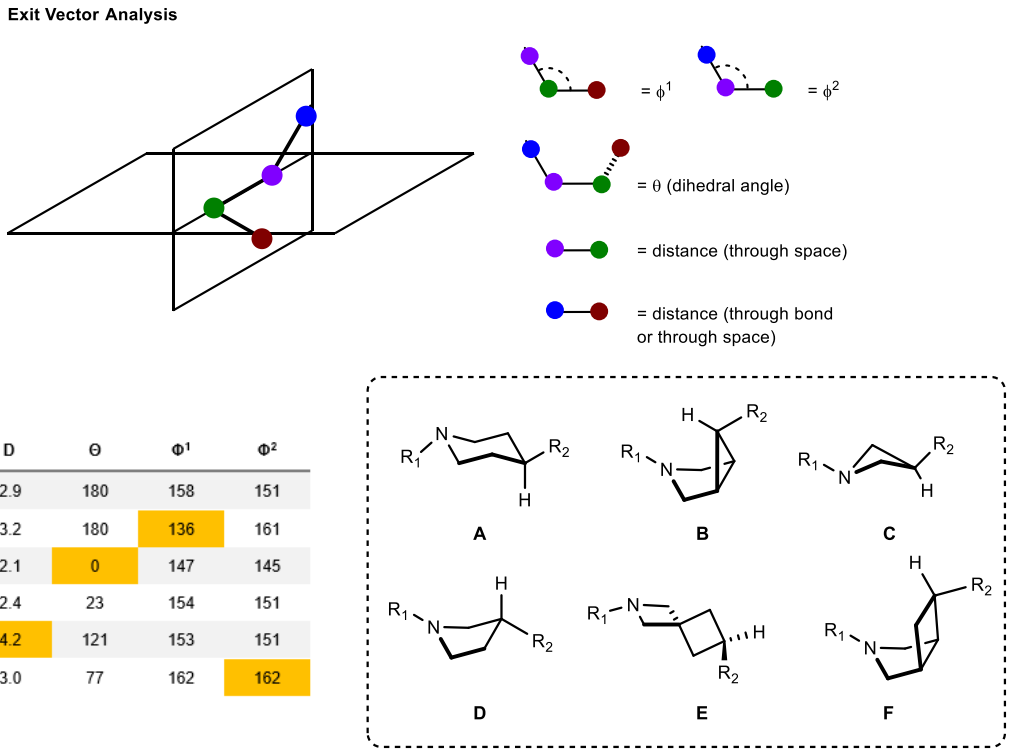


Figure 3.7. Example of oxidative metabolic pathways of N-substituted morpholine ring.

Curiously, despite the major prevalence of these cores in drug design, the space of their existing analogs has experienced a more placid growth compared to benzene surrogates. For instance, established piperidine (**A**) bioisosteres (**B-F**) are commonly used in early lead development to alter the spatial orientation and distances between vectors and to optimize the binding affinity, as evident from the exit vector analysis (EVA, Figure **3.8**).[14,15]



	D	Θ	Φ¹	Φ²
A	2.9	180	158	151
B	3.2	180	136	161
C	2.1	0	147	145
D	2.4	23	154	151
E	4.2	121	153	151
F	3.0	77	162	162

Figure 3.8. Exit vector analysis of most common piperidine isosteres.

However, a different stratagem is necessary for later stages of lead advancement – namely, optimization of the ADME (absorption, distribution, metabolism, excretion) profile without significantly perturbing the molecular topology. As mentioned, one of the major liabilities of these substructures is the presence of metabolic hotspots. In some cases, the introduction of alkyl substituents has shown to increase resistance towards hepatic metabolism: for example, piperidine-tropane replacement within the β-tryptase inhibitor (**3.18A** to **3.18B**) significantly improved stability in rat and human microsomes (Figure 3.9, a).[16] However, this positive effect can be offset by the increase in molecular weight, total surface area, and overall lipophilicity, features commonly associated with off-target toxicity.[17] These building blocks are also conformationally flexible, which might translate into a dilution of the concentration of the bioactive conformation and entropic penalties due to the conformational sampling within the targeted enzyme. Therefore, a more rigid core with fewer available conformations can offer a significant boost in potency.[18] Perhaps the best illustration of this paradigm is the case of orexin receptor antagonist **3.19A**, where the incorporation of a single methyl group (**3.19B**) changes the conformational landscape and leads to a 505-fold increase in potency (Figure 3.9, b).[19]

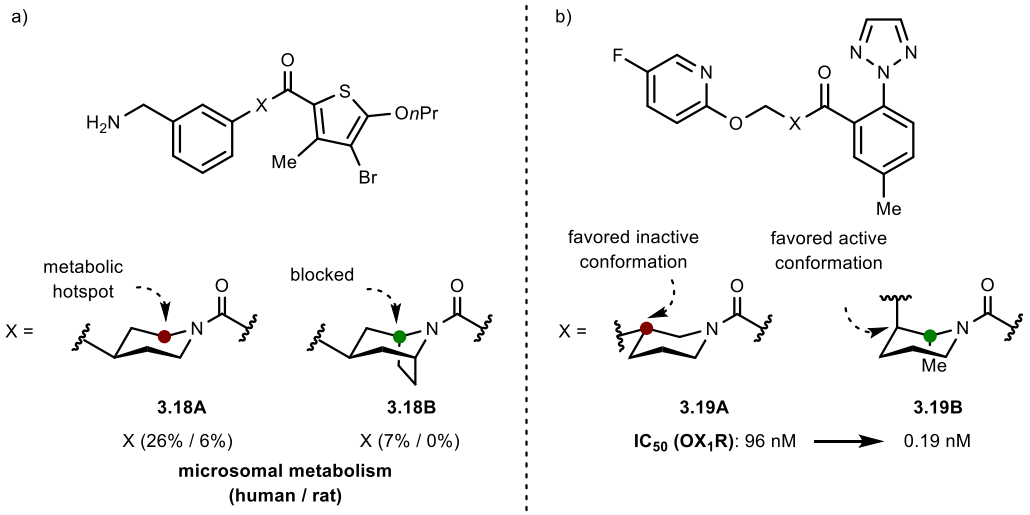


Figure 3.9. Examples of improvements in metabolic profile or potency by rigidifying the piperidine linker.

3.2 Synthetic Strategy

3.2.1 State of the Art: Dewar Pyridines

In this context, our research group has become interested in 4H-Dewar pyridines (4H-DPs, **3.24**) as potential piperidine (**3.23**) bioisosteres. The origin of this "aza-ladderane" core can be traced back to 1972, with Fowler's work on 2H-Dewar pyridine (2H-DP, **3.22**), obtained through reductive dearomatization of pyridine (**3.20**) followed by photochemical 4π- electrocyclization.[20]

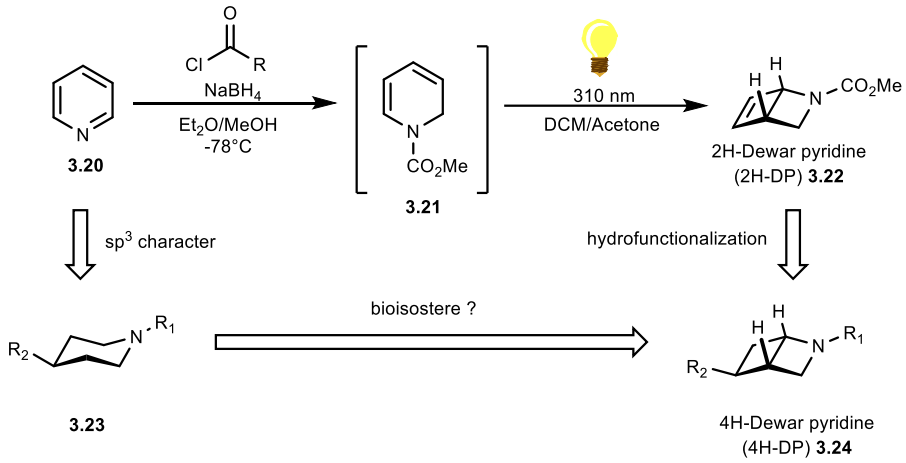


Figure 3.10. Inspiration for more rigid piperidine isosteres with the same number of carbon atoms.

This methodology remained largely unexplored with only a few follow-up studies, as the corresponding products were mostly leveraged as polymer precursors. In contrast, we were intrigued by these [2.2.0]-bicyclic products (**3.22**) and improved the already existing methodology to build a library of these compact N-heterocyclic compounds to showcase their utility, developing a toolkit for their incorporation into drug molecules as piperidine bioisosteres in the form of hydrofunctionalized sp^3-rich 4H-Dewar pyridines (**3.24**).[15] Computational analysis of the respective geometries revealed that interatomic distance across the ring system and the directionality of exit vectors of the 4H-DP structure matched well with that of the parent piperidine, with both fragments occupying nearly identical volumes, thus validating the envisioned design, which has several benefits: 1) substituted pyridines are commodity chemicals and are thus readily available 2) the spring-loaded nature of the olefin in **3.22** can facilitate its functionalization and structural diversification.

After an optimization study on Fowler's methodology, the pyridine scope was evaluated. Unsubstituted pyridine as well as C3 and C4 substituted pyridines were successfully

converted to the desired azabicyclo[2.2.0]hexenes **3.22** with modest to good yields through dearomatization using methyl chloroformate as an electrophile and sodium borohydride as nucleophile followed by light-mediated 4π-electrocyclization. C2 substitution was achieved using other kinds of nucleophiles in the dearomatization step. Afterward, the reactivity profile of these 2H-Dewar pyridines was examined, specifically concerning the olefin functionality (Figure 3.11). Selective double bond hydrogenation (**3.22** to **3.26**) and hydroboration (**3.22** to **3.25**) were achieved; halogenated substrates smoothly underwent Suzuki coupling, giving 4H-Dewar pyridines after reduction (**3.27** to **3.30**). As expected, profound substrate bias afforded exquisite stereoselectivity in all cases: therefore, this building block provides an opportunity to selectively access pseudo-equatorial or pseudo-axial piperidine isosteres without the need for auxiliary groups, which could disturb interactions with their targets.[15]

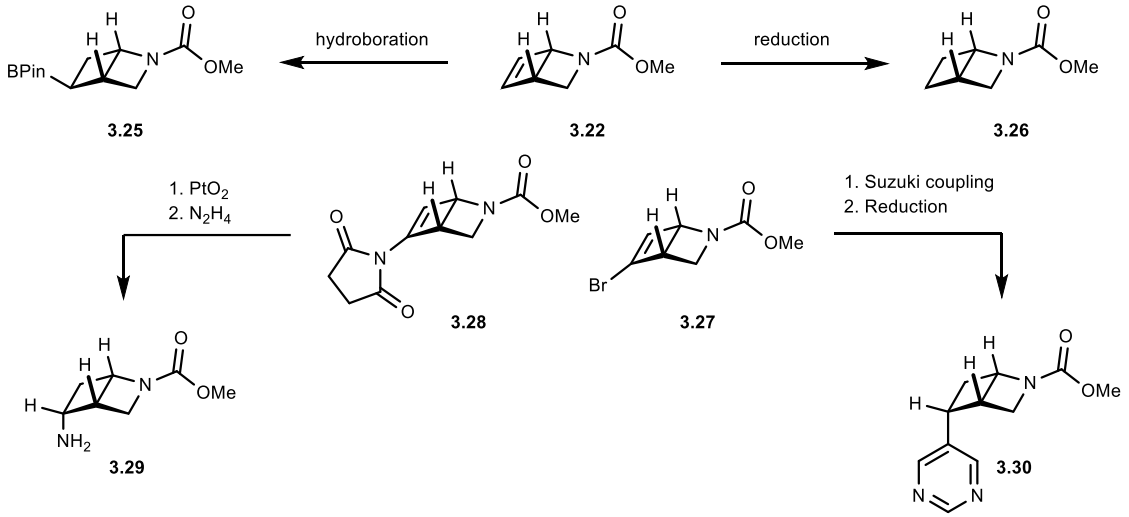


Figure 3.11. Formal "hydrofunctionalizations" of 3.22 and skeletal editing of the Dewar pyridine scaffold.

As alluded to before, the conformational flexibility of piperidine can decrease the potency of a certain drug due to the dilution of bioactive conformation. 4H-Dewar pyridine analogs can address this drawback as their transverse C–C bond substantially increases the energy barrier for a ring flip, as shown in Figure 3.12 with the case of a pseudo-axial substitution vs. axial substituted piperidine.

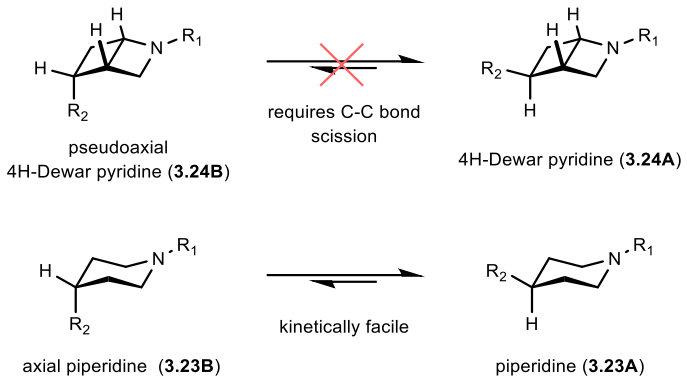


Figure 3.12. "Ring flip" in 4-substituted piperidine and its 4H-Dewar pyridine isostere.

In this study, our group has introduced 4H-Dewar pyridines as innovative isosteres of piperidines, with the support of geometry optimization and exit vector analysis. The bicyclic design brings several notable advantages such as precise control over spatial orientation of exit vectors and rigidification of the core and could be a great tool in the hands of a medicinal chemist.

3.2.2 Development of New Pyridine-derived Isosteres

Being the general aim of the project the generation of new isosteres from Dewar pyridine, we decided to further exploit the intrinsic olefin reactivity of 2H-Dewar pyridines (**3.32**) to expand the scope of functionalized derivatives. With this in mind, we envisioned a systematic development towards a novel library of fused, small-ring bioisosteres of morpholine, piperidine, and piperazine, respectively. As a matter of fact, the 2H-Dewar pyridine core can be considered a common, divergent intermediate in the generation of the three distinct groups of isosteres, depending on the olefin transformation applied (i.e. epoxidation **3.33**, cyclopropanation **3.34**, or aziridination **3.35**) with successive hydrogenation of the 3,4-fused ring junction to give azabicyclo[3.2.0]heptane cores (**3.36**, **3.37**, **3.38**). With this in mind, after an optimization study related to the synthesis of novel azabicyclo[2.2.0]hexenes **3.32**, we thus set focus on each of the three functionalization routes. This unconventional strategy could greatly simplify and expand the few already existing ways to access these isosteres, which also provide differential vectors and rigidity in comparison to their parent heterocycles.

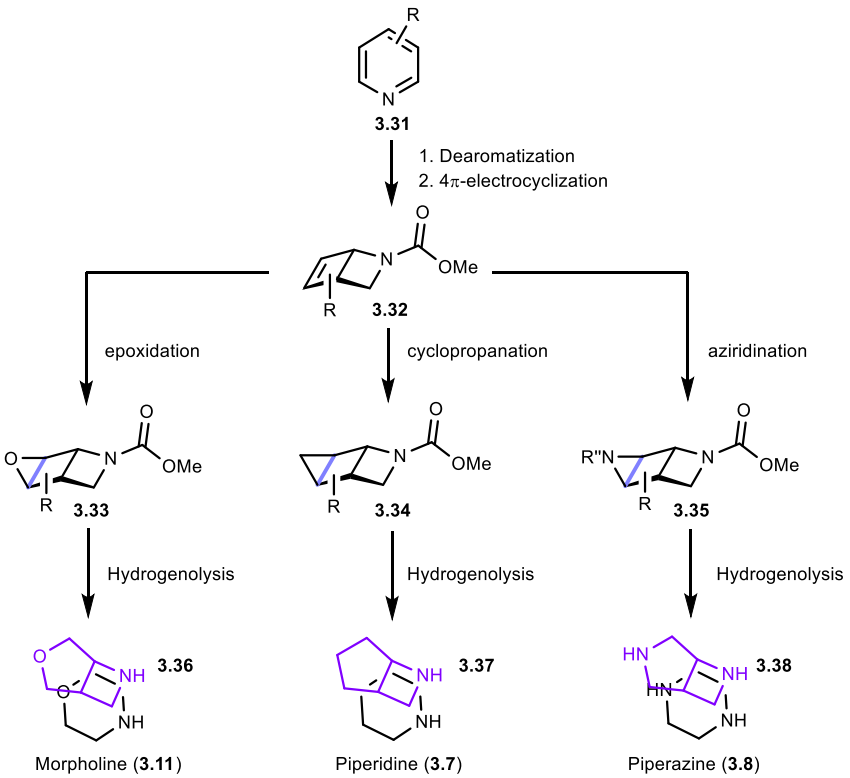


Figure 3.13. Aim of the project: divergent synthesis of pyridine-derived isosteres.

3.2.2.1 Synthesis of 2H-Dewar pyridines library

The first step we focused our attention on was the generation of a suitable library of 2H-Dewar pyridines, expanding the already existing scope. The dearomatization of C3 and C4 substituted pyridines was realized following Fowler's optimized methodology, using methyl chloroformate as electrophile and sodium borohydride as a reductive agent. In this reaction, performed at cryogenic temperature, methyl chloroformate is attacked by the nitrogen atom of pyridine generating an N-acyl pyridinium intermediate **3.39**, that is subsequently reduced by $NaBH_4$ forming the 1,2-dihydropyridine **3.21**. This species easily rearomatizes with prolonged exposure to air, so it is directly subjected to the photochemical step without purification. In these conditions, the 4π-electrocyclization takes place with a disrotatory closure due to its photochemical nature. The photochemical reaction, which needs 7 days to complete, can be achieved using either dichloromethane, acetone, or ethyl acetate as a solvent and Pyrex Erlenmeyer flasks as reaction vessels (See the experimental part for more details).

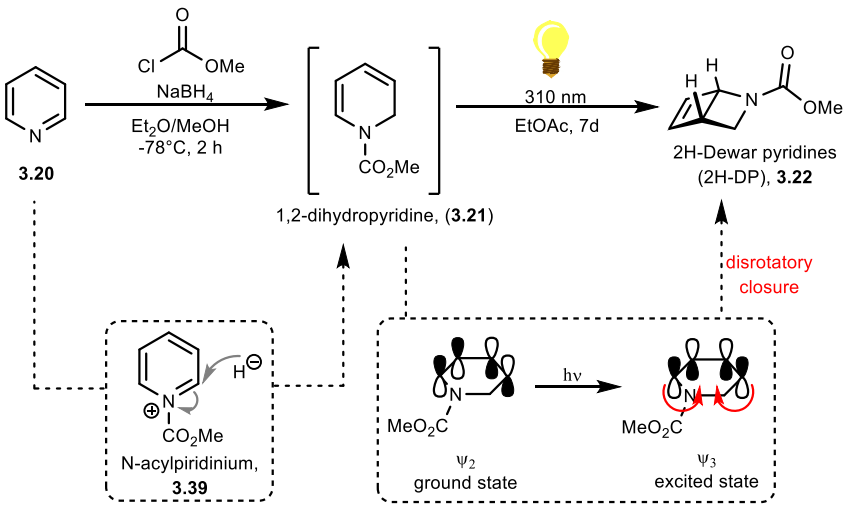


Figure 3.14. Dearomatization and 4π-electrocyclization procedure with mechanistic explanations.

With these conditions in hand, we could perform a substrate scope on C4 and C3 substituted pyridines (**3.20A**, Figure 3.15). After achieving a 58% yield on pyridine (**3.22**), we initiated our investigation with the 4-substituted pyridines, particularly using the 4-methyl, 4-ethyl, 4-methanol (previously protected with a TBS *tert*-butyl-dimethyl silyl group to avoid issues within the photochemical step) and 4-phenyl pyridines. The corresponding C5 substituted methyl azabicyclo[2.2.0]hex-5-ene carboxylates were obtained with a 40-60% yield over 2 steps, especially using Ethyl Acetate as a solvent for the photochemical step (**3.40-3.43**, Figure 3.15). We next applied the same procedure to 3-substituted pyridines, considering the 3-methyl, 3-ethyl, and 3-methanol (previously protected with a TBS group) pyridines. Unfortunately, in this case, the two-step reaction provides lower yields than C4 substituted pyridines, around 10-40% yield over 2 steps (**3.44-3.46**, Figure 3.15). As the dearomatization step always gives an NMR yield comparable to the 4-substituted, a possible reason for the poorer output of C3 substituted pyridines could be attributed to the 4π-electrocyclization step, in which a quaternary carbon is generated in a highly constrained system, a process that probably requires very high activation energy. However, the cost of the reagents, the unchallenged IP space, and the utility of the products offset this shortcoming. We also achieved C2 substitution by changing the nucleophilic partner in the dearomative step. Instead of $NaBH_4$, we used a Grignard reagent to attack the N-acyl pyridinium intermediate. The main difference is that the 2-alkyl-1,2-dihydropyridines **3.21B** are more stable compared to the parent 1,2-dihydropyridines **3.21A**, so that they can be purified by column chromatography. The photochemical step[21] is then realized in the same way and reaction yields are approximately around 40% over 2 steps (**3.47-3.48**, Figure 3.15), comparable with the

previous ones. Having generated a library of 10 compounds, we started exploring the divergent synthetic pathways towards the three isosteres.

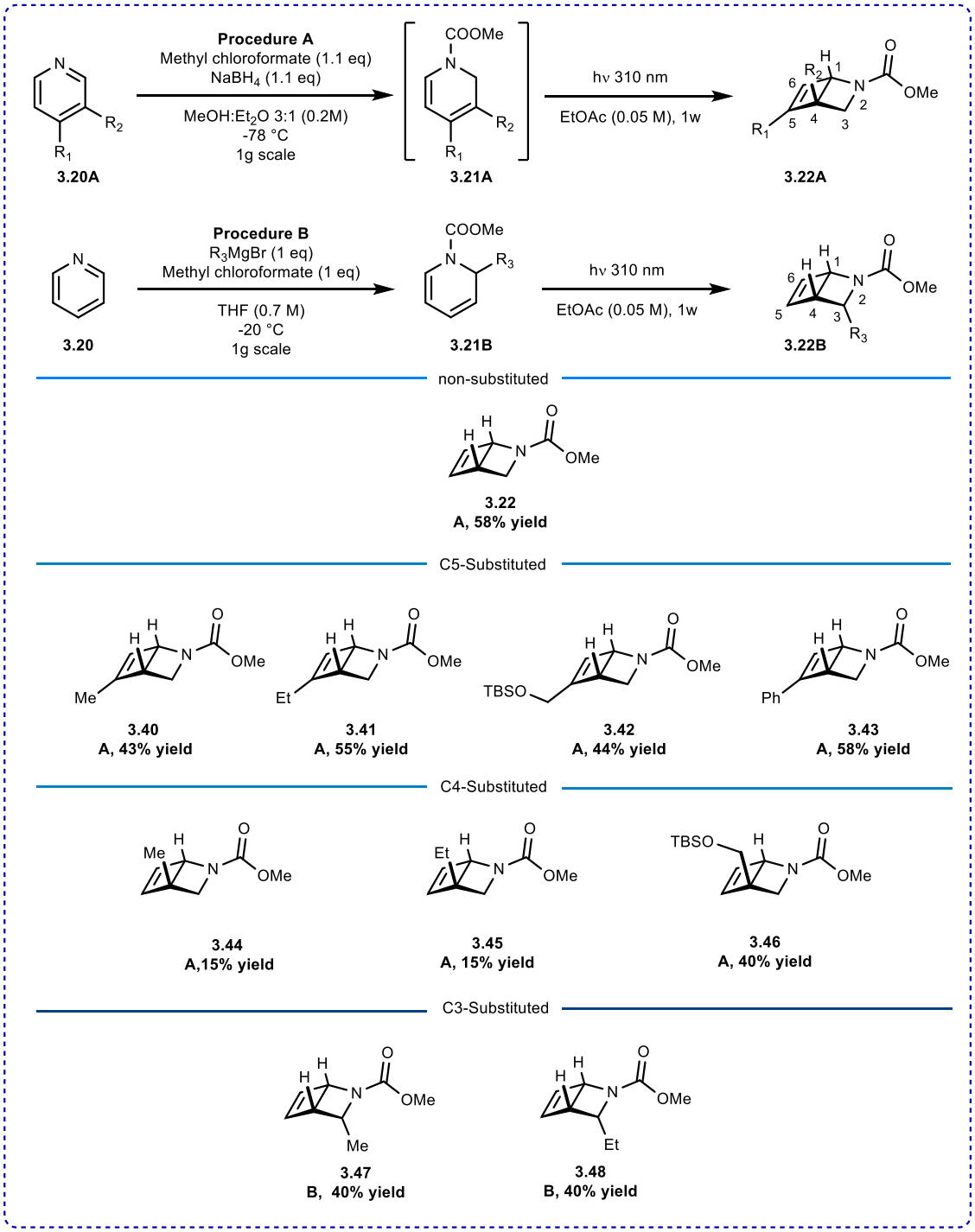


Figure 3.15. Substrate scope.

3.2.2.2 Epoxidation-Hydrogenation of 2H-DPs towards Morpholine Isosteres

The first coupled transformations that were investigated are the epoxidation-hydrogenation of the 2H-DPs core **3.32** to access methyl 3-oxa-6-azabicyclo[3.2.0]heptane-6-carboxylate scaffolds **3.49** as morpholine isosteres.

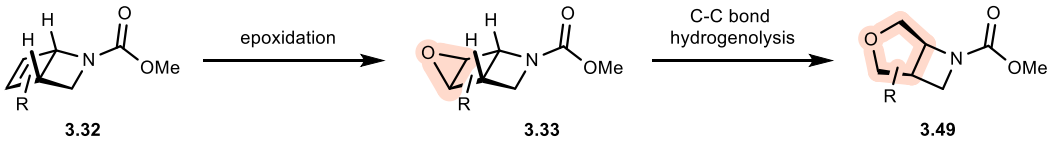
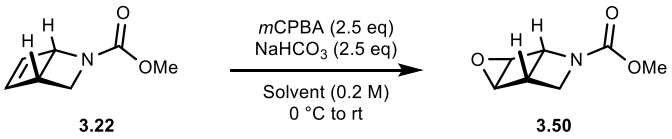


Figure 3.16. Epoxidation-hydrogenation sequence of 2H-DPs to access morpholine isosteres.

The epoxidation step was first performed on the model substrate **3.22** to find the best conditions, as shown in Table 3.1. *m*CPBA was used, as reported in the literature.[22]

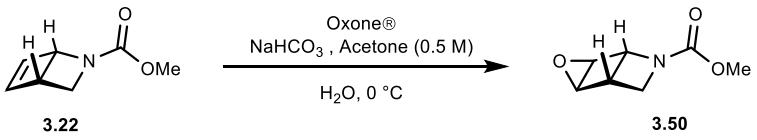


Entry	Solvent	Scale (mmol)	Time (h)	Yield (%)
1	DCM	0.8	48	53
2	DCM	1.4	24	37
3	DCM	1.4	60	35
4	DCM	1.8	24	44
5	DCM	1.8	48	56
6	DCM	3.6	48	34
7	CH_3CN	1.8	48	57

Table 3.1: *m*CPBA epoxidation screening.

The main problem we encountered while performing this procedure was the incomplete conversion of the starting material even after multiple days, especially when increasing the scale, and the formation of an uncomfortable slurry within the reaction vessel. The best solution we found was to switch from Dichloromethane to Acetonitrile as a solvent, which improved the solubility of the reaction components for the whole duration of the procedure, even if not improving the yield or the conversion. The best result we have obtained is a 57% yield on a 1.8 mmol scale.

In order to solve the problem, we decided to test a second procedure that employs Dimethyldioxirane (DMDO) as the epoxidizing agent. The general protocol implies the use of acetone, sodium bicarbonate, and Oxone®, which is slowly added dropwise as an aqueous solution in the reaction vessel to generate DMDO at such a rate to avoid overoxidation of the substrate.[23] Also in this case, we performed an optimization of the reaction conditions for the model substrate **3.22**, as shown in Table 3.2.



3.22 **3.50**

Entry	Scale (mmol)	Oxone (eq.)	$NaHCO_3$ (eq.)	Acetone (eq.)	Time (h)	Yield (%)
1	0.36	1	2	4	12	36
2	0.55	2	4	4	24	30
3	1.8	2	4	4	12	35
4	1.8	4	8	8	2	76
5	1.8	10	20	20	3	71

Table 3.2: DMDO-mediated epoxidation screening.

The major parameters that proved to be fundamental for this reaction are the time and the equivalents of Oxone® added to the mix. The amount of Oxone® exponentially reduced the reaction time, making for better yields and higher conversion rates, compared to *m*CPBA-mediated epoxidation.

With the library of azabicyclo[2.2.0]hex-5-enes in hand, the optimized epoxidation conditions were used to run a substrate scope, creating a new class of diversly substituted 3-oxa-6-azatricyclo[3.2.0.$0^{2,4}$]heptane-6-carboxylates (**3.33**, Figure 3.17): both procedures were used, even though only Procedure A managed to fully convert the starting material and made the reaction much faster, with higher yields. Only C5-Alkyl substituted azabicyclo [2.2.0]hex-5-enes **3.32** showed overoxidation when subjected to DMDO-mediated epoxidation. Nonetheless, they could react via the more traditional *m*CPBA route, although with lower overall yields.

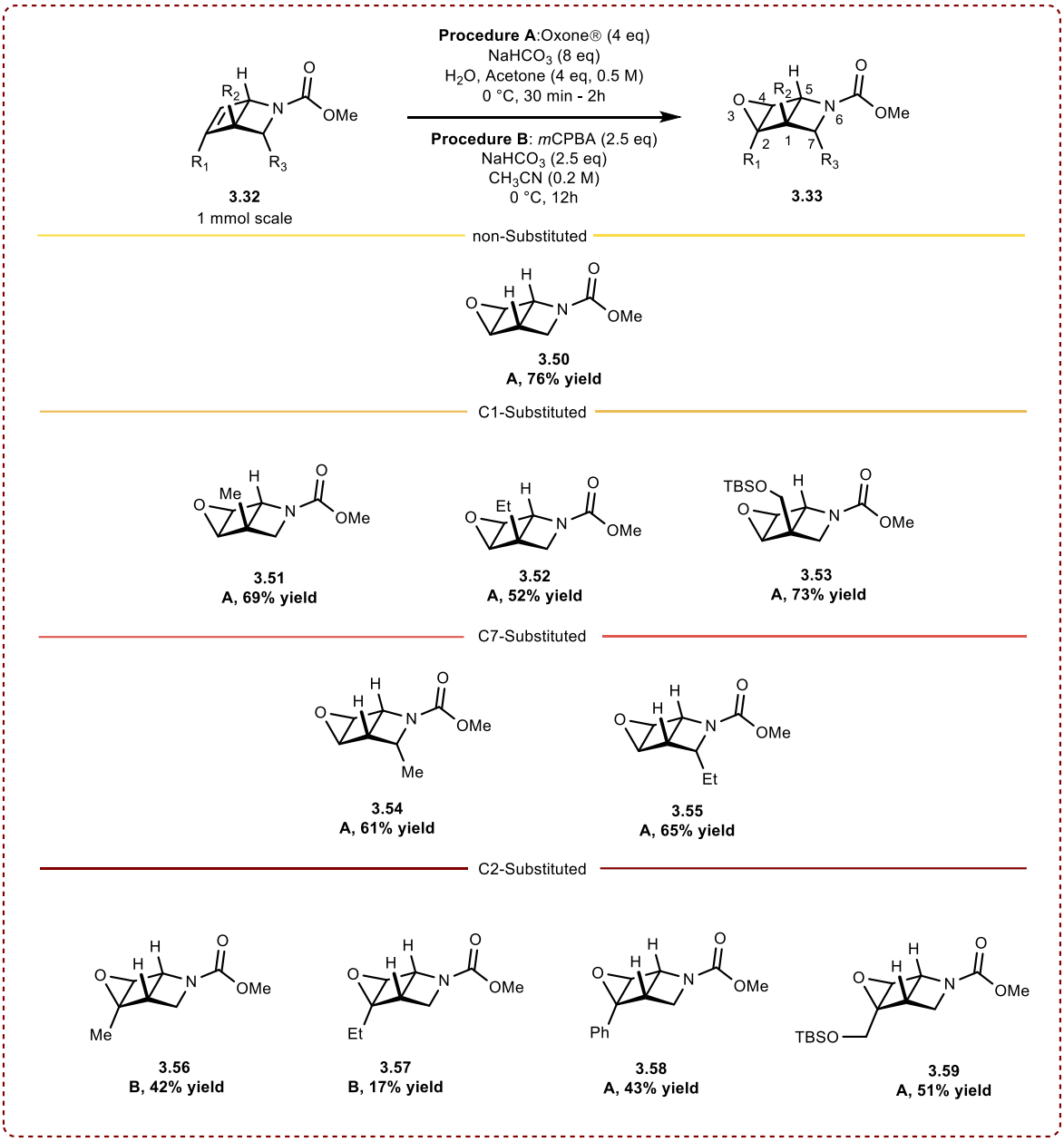
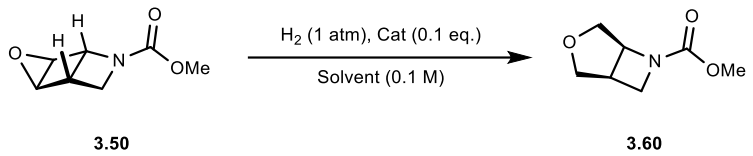


Figure 3.17. Epoxidation scope.

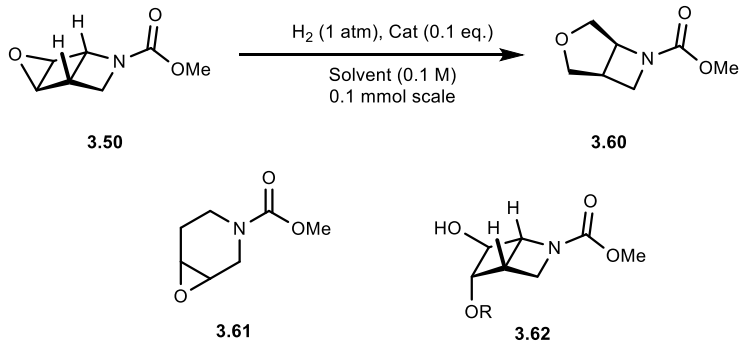
Having obtained a library of differently substituted epoxides, our aim was to subject them to heterogeneous hydrogenation conditions, since we have found out that reacting the non-substituted epoxide with H_2 in the presence of catalytic Pd/C results in a C-C bond hydrogenolysis (**3.60**, Figure 3.18), rather than a reductive epoxide opening, to form a tetrahydrofuran ring.



3.50 **3.60**

Figure 3.18. Hydrogenolysis of the [3,4]-ring junction reveals the tetrahydrofuran moiety.

In order to find optimal conditions to further employ for a substrate scope, we began by screening conditions on the non-substituted epoxide **3.50**, as shown in Table 3.3:



3.50 **3.60**

3.61
observed as trace

3.62
observed as major impurity when ROH solvents used

Entry	Catalyst (0.1 eq.)	Solvent (0.1 M)	Time (h)	3.60, Yield (%)
1	Pd/C	MeOH	2	48
2	Pd/C	EtOH	2	48
3	Pd/C	*i*PrOH	2	50
4	Pd/C	*t*BuOH	24	poor conv.
5	Pd/C	EtOAc	12	nc
6	Pd/C	Cyclohexane	12	35
7	Pd/C	HFIP	24	poor conv.
8	none	MeOH	12	nc
9	Ni-Raney	EtOH	12	nc
10	$Pd(OH)_2$	MeOH	12	27
11	PtO_2	MeOH	12	nc
12	Rh/Al_2O_3	EtOAc	12	nc
13	Lindlar	EtOAc	12	nc

Table 3.3. Hydrogenation conditions screening on model substrate **3.50.**

The best conditions proved to be using Pd/C as a catalyst and isopropanol as the solvent (Entry 3) since we have observed the formation of an epoxide-opened product by the solvent as a major impurity (**3.62**, Table 3.3) when using methanol or ethanol (Entries 1

and 2). The success of isopropanol can be attributed to its steric hindrance so that the epoxide opening is unfavored. Aprotic solvents were also screened, but a slow or even no conversion was observed (Entries 5 to 7). Traces of the internal C-C bond hydrogenolysis were also found, but no reductive epoxide opened product was ever observed. Only a Palladium-based catalyst proved to work; other metal catalysts gave no conversion (Entry 9, 11-13). Considering the nature of the main byproduct of the reaction (**3.62**), we can hypothesize that the metal might activate the epoxide acting like a Lewis Acid.

Having optimized the hydrogenation conditions, they were applied to the scope of previously obtained epoxide compounds. This procedure proved to work nicely on C1 substituted 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylates **3.33A**, but it proved to be harder than expected to perform on C2 or C7 substituted ones. Having said that, with the use of the reported optimized conditions, we were able to run a little scope on C1 substituted epoxides so that a library of 3-oxa-6-azabicyclo[3.2.0]heptane-6-carboxylates **3.49A** was achieved with nice yields, as shown in Figure 3.19:

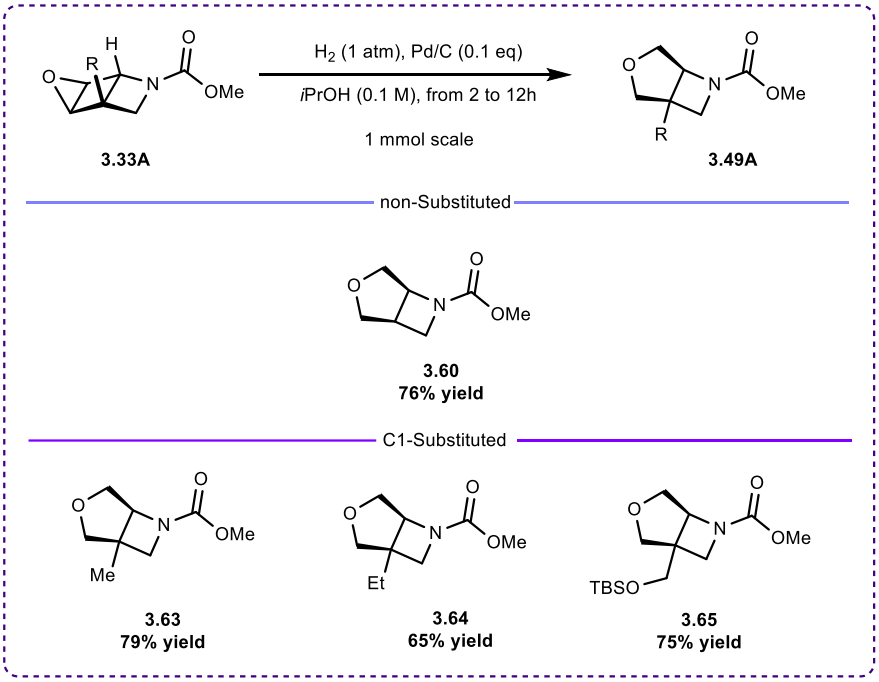
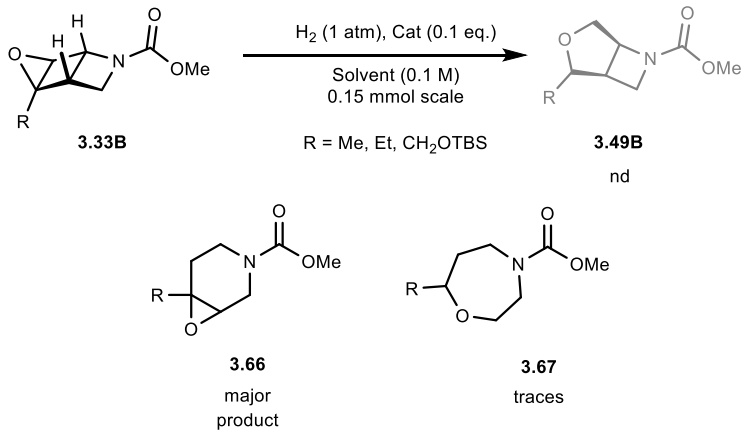


Figure 3.19. Hydrogenation scope on non-substituted or C1 substituted epoxides.

Considering C2 or C7 substituted epoxides instead, we had to perform another screening of the hydrogenation conditions, which resulted in 2 different sets of results.

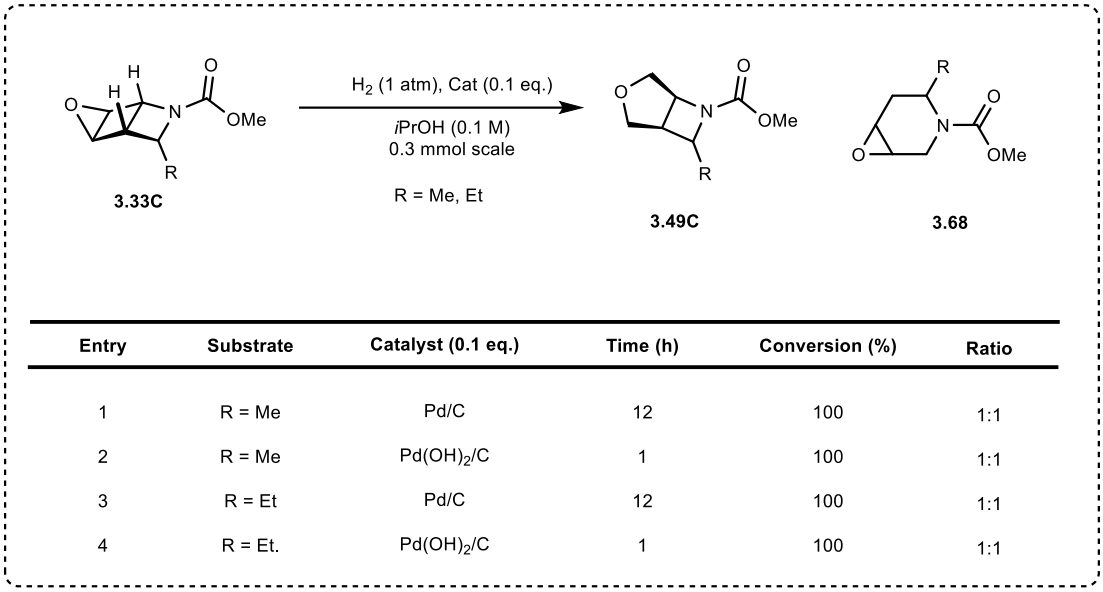
For instance, considering C2 substituted epoxides **3.33B**, we found out that if we subjected them to the optimized reaction conditions for the model substrate, not only they showed no conversion, but after trying to use harsher conditions to push the hydrogenolysis, we were able to get only 7-oxa-3-azabicyclo[4.1.0]heptane ring **3.66** as major product, which was just obtained as traces for the previous substrates, together with methyl tetrahydro-1,4-oxazepine-4(5H)-carboxylate **3.67**. We even tried to change solvents or catalysts, also increasing reaction temperature, but without success. Results are summarized in Table 3.4.



Entry	Catalyst (0.1 eq.)	Solvent (0.1 M), T (°C)	Time (h)	Conversion (%)
1	Pd/C	iPrOH	24	nc
2	Pd/C	MeOH	24	nc
3	Pd/C	EtOH + AcOH cat.	24	50
4	Pd/C	MeOH + AcOH cat.	24	50
5	Pd/C	MeOH, 50°C	6h	100
6	Ni-Raney	MeOH	24	nc
7	PtO_2	MeOH	24	nc

Table 3.4 Hydrogenation conditions screening for C2 substituted epoxides.

Given the unsuccessful results related to C2 substituted epoxides, we focused our efforts on C7 substituted ones **3.33C**. Also in this case, as shown in Table 3.5, we observed a different trend. C7 substituted epoxides were subjected to either Pd/C or $Pd(OH)_2$ catalyzed hydrogenation in *i*PrOH, which is the best solvent to avoid epoxide opening when the epoxide is not substituted. The desired product **3.49C** was obtained, but unfortunately as a 1:1 inseparable mixture with the internal C-C bond hydrogenolysis product **3.68**.



Entry	Substrate	Catalyst (0.1 eq.)	Time (h)	Conversion (%)	Ratio
1	R = Me	Pd/C	12	100	1:1
2	R = Me	$Pd(OH)_2/C$	1	100	1:1
3	R = Et	Pd/C	12	100	1:1
4	R = Et.	$Pd(OH)_2/C$	1	100	1:1

Table 3.5 Hydrogenation conditions screening for C7 substituted epoxides.

We are currently trying to further optimize the reaction conditions for this class of substrates to avoid the formation of undesired byproducts and eventually find the best method for the purification of these constitutional isomers.

3.2.2.3 Aziridination-Hydrogenation of 2H-DPs towards Piperazine Isosteres

The second transformation we investigated is the aziridination-hydrogenation of the 2H-DP core in order to access 3,6-diazabicyclo[3.2.0]heptane-6-carboxylates **3.69** as piperazine isosteres.

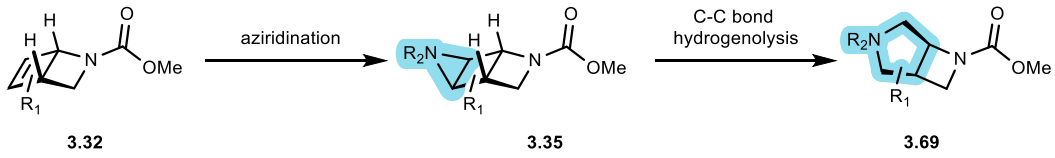


Figure 3.20. Aziridination-hydrogenation of 2H-DPs to access piperazine isosteres.

Considering the aziridination step, we decided at first to replicate the reported procedure on our system.[22] We though tested the reactivity of N-Ethoxycarbonyl-p-nitrobenzenesulfonamide-derived nitrene on the model substrate **3.22**; The reaction gives the desired product **3.70** in 19%, which provides a useful intermediate with two orthogonally protected nitrogens. After unsuccessful attempts to improve the yield, we

decided to move to other strategies so that we could find more reproducible and reliable conditions to run a substrate scope with.

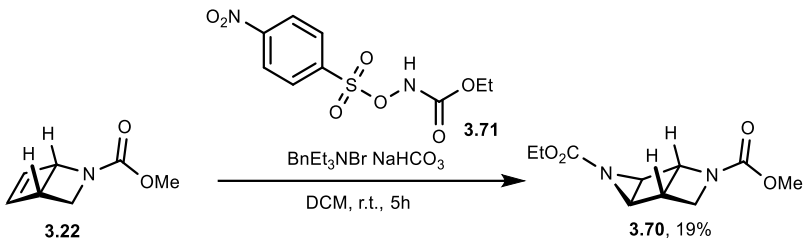


Figure 3.21. Aziridination of 2H-DP with N-Ethoxycarbonyl-p-nitrobenzenesulfonamide-derived nitrene.

The second strategy we tried involved (N-(p-toluenesulfonyl)imino)phenyliodinane **3.72** as a nitrene source. This compound has a characteristic I=N bond, that can easily break in reductive conditions leaving a nitrene species that rapidly reacts. We tested this reagent in a metal-free aziridination in the presence of iodine I_2 and tetrabutylammonium iodide (Bu_4NI).[24] The mechanism of this reaction is still not clear, but it is thought that a radical pathway is involved. We tested the reaction in various conditions: even if the starting material is always totally consumed, *p*-toluensulfonamide is the main product. Though, we were able to observe the formation of a free aziridine **3.74** with a 37% NMR yield.

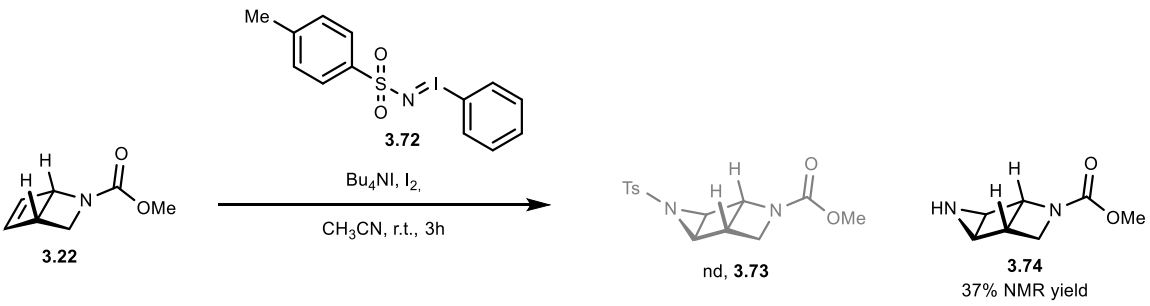


Figure 3.22. Aziridination with (N-(p-toluenesulfonyl)imino)phenyliodinane as nitrene source.

To confirm this result, we realized a Boc (tert-butyloxycarbonyl) protection directly on the crude and analyzed the NMR spectra. We did not investigate the reaction outcome we observed, but it could be associated with the radical nature of this reaction. We tried to further explore this route, but we were not able to obtain reproducible results (Figure 3.22).

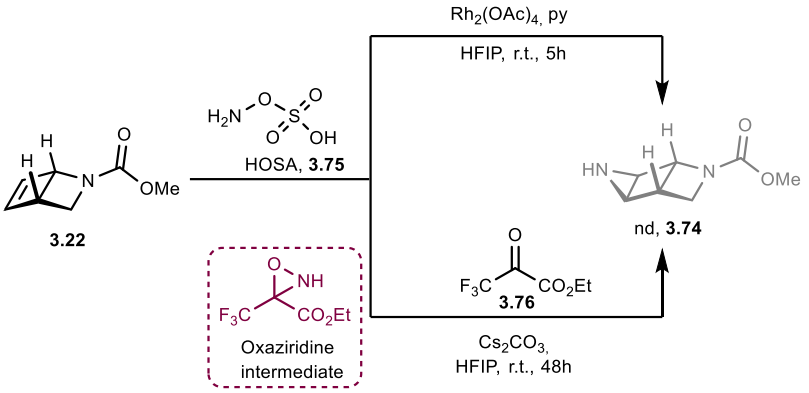


Figure 3.23. Kurti's aziridination procedures performed on substrate 3.22.

Another strategy that we applied is an aziridination protocol developed by Kurti et al.[25] in which rhodium (II) tetraacetate ($Rh_2(OAc)_4$) is used as a catalyst and hydroxylamine-O-sulfonic acids (HOSA, **3.75**) as inexpensive, readily available and nitro group-free aminating agents. Since this reaction is known to convert non-activated olefins to the corresponding aziridines with excellent yields, we tried it with the 2H-DP substrate **3.22**. Again, no reactivity was observed. We also tested a similar procedure developed by the same group, this time in an organocatalytic version. The aminating agent is still HOSA and the reaction occurs in the presence of cesium carbonate Cs_2CO_3 as a base and ethyl 3,3,3-trifluoropyruvate **3.76** as organocatalyst (Figure 3.23).[26] Unfortunately, no conversion was observed, recovering starting material in all cases. We also tried other metal-catalyzed aziridination conditions without any success. Even if the hydrogenation of intermediate **3.70** proved to be successful in order to obtain building block **3.77** as piperidine isostere[15], we are currently trying to find suitable aziridination conditions to run a substrate scope in a reliable fashion.

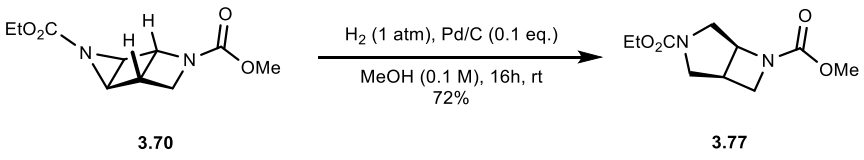


Figure 3.24. Hydrogenation of aziridine 3.70 to give plain piperazine isostere 3.77.

3.2.2.4 Cyclopropanation-Hydrogenation of 2H-DPs towards Piperidine Isosteres

The last sequence we focused our attention on is the cyclopropanation-hydrogenation of the 2H-DP scaffold to obtain 6-azabicyclo[3.2.0]heptane-6-carboxylates **3.78** as piperidine isosteres.

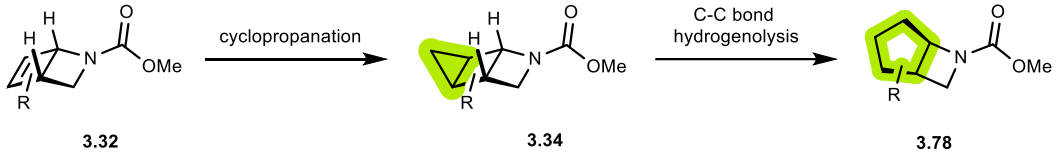


Figure 3.25. Cyclopropanation-Hydrogenation of 2H-DPs to access piperidine isosteres.

This kind of olefin functionalization was already known in the literature on the same substrate and implied the use of diazomethane.[22] While successful, the toxicity and safety concerns related with the use of this reagent encouraged us to attempt of alternative conditions. Our screening started with a classical haloform reaction for the generation of a 1,1-dihalocyclopropane.[27] Our attempted conditions failed with either low reactivity or decomposition of the starting material (A, Figure 3.26). We then shifted our focus toward palladium-catalyzed cyclopropanations. The first reaction we tested is a cyclopropanation with 3-pinacolatoboryl-1-arylallyl carboxylate **3.80**.[28] Even if these conditions are suitable for strained alkenes, we were not able to observe any reactivity (B, Figure 3.26). After a series of non-productive results, we decided to go back to the use of diazo compounds. Firstly, we performed the reaction using trimethylsilyl-diazomethane $TMSCHN_2$ and tris(dibenzylidenacetone)dipalladium (0) $Pd_2(dba)_3$ as catalyst (C, Figure 3.26)[29]: this strategy proved to be successful, as we finally isolated the desired product **3.82**, without observing any side-reactivity. We also tested the reactivity of alpha diazo carbonyl compounds, e.g. methyl (2Z)-2-diazo-pheylacetate (**3.83**), employing either silver hexafluoroantimonate $AgSbF_6$ or rhodium (II) acetate dimer, $Rh_2(OAc)_4$ as catalyst, in this case without success (D, Figure 3.26).[30]

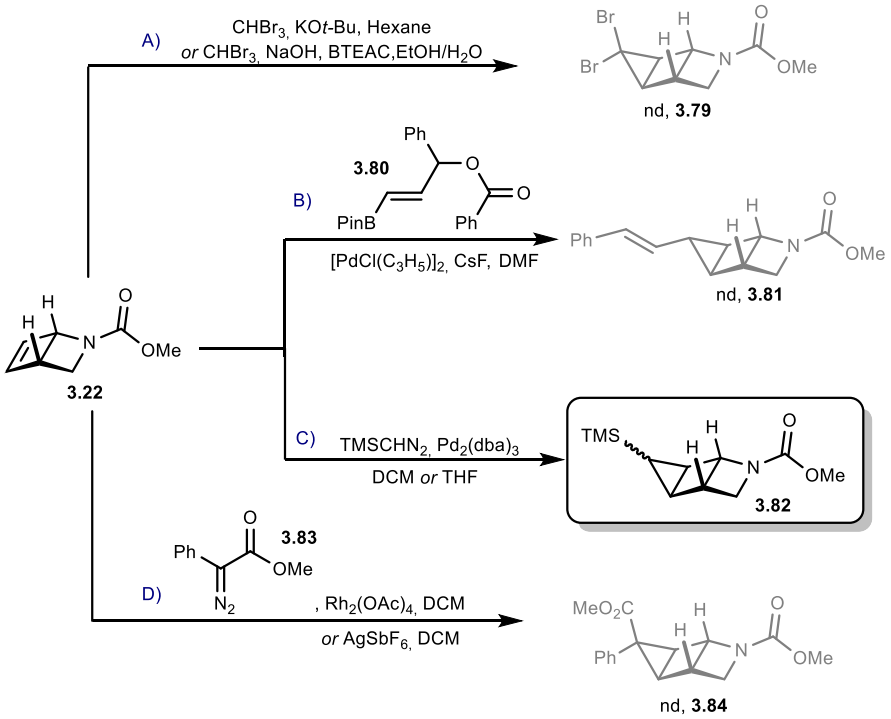


Figure 3.26. Cyclopropanation trials.

Having these preliminary results in hand, we decided to further investigate the palladium-catalyzed cyclopropanation with TMS-diazomethane, performing an optimization of the reaction conditions in order to run a substrate scope.

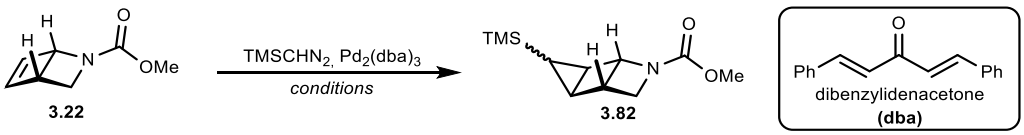


Figure 3.27. Cyclopropanation reaction selected for the optimization.

The optimization was conducted on the model substrate. The first condition we tried implied the use of 0.1 equivalents of $Pd_2(dba)_3$, 3 equivalents of $TMSCHN_2$ and THF as a solvent, performing the addition at 0°C and letting the reaction to warm up to room temperature: after 6h we observed full conversion of the starting material, but a lot of side products forming (Table 3.6, Entry 1). So, we decided to change the reaction temperature at first: adding $TMSCHN_2$ at -50°C and -20°C and letting the reaction warm up to room temperature gave a yield of 52% and 60% respectively (Table 3.6, Entry 2,3). We also decided to change the solvent, using DCM instead of THF, and reducing the equivalents of $TMSCHN_2$ to 1.5, obtaining a cleaner reaction profile with a 74% yield (Table 3.6, Entry 4). We also tested $Pd_2(dba)_3CHCl_3$ as catalyst, with the same conditions, but the result was inferior (Table 3.6, Entry 5). Even if lowering the temperature of $TMSCH_2N_2$ addition proved to be beneficial, full conversion of the starting material was not observed.

Other modifications were applied, such as increasing the reaction time, adding $TMSCHN_2$ at 0°C, keeping this temperature for 12 hours, and leaving the reaction mixture at room temperature for additional 12 hours. With these final conditions, we obtained a 90% yield with a full conversion of SM (Table 3.6, Entry 7).

Entry	Scale (mmol)	Catalyst (0.1 eq.)	$TMSCHN_2$ (eq.)	Solvent (0.1 M)	Time (h)	Temperature	3.82, Yield (%)
1	0.14	$Pd_2(dba)_3$	3	THF	6	0°C to rt	30
2	0.14	$Pd_2(dba)_3$	3	THF	6	-50°C to rt	52
3	0.14	$Pd_2(dba)_3$	3	THF	6	-20°C to rt	60
4	0.14	$Pd_2(dba)_3$	1.5	DCM	6	-20°C to rt	74
5	0.14	$Pd_2(dba)_3CHCl_3$	1.5	DCM	6	-20°C to rt	63
6	0.7	$Pd_2(dba)_3$	1.5	DCM	12	0°C to rt	82
7	0.7	$Pd_2(dba)_3$	1.5	DCM	24	0°C to rt	90

Table 3.6. Optimization of the reaction conditions.

A detailed analysis of the product revealed that the TMS-cyclopropane forms on the top face of the C=C bond, but as a 1:1.5 mixture of inseparable epimers. Since the NMR spectra of these molecules are complicated, as they also show rotameric behaviour, it's not easy to determine which is the major epimer; but, since we planned to remove the TMS group to obtain a non-substituted cyclopropane, we thought it would be not a problem for the purposes of this project.

The mechanism of this reaction is still unknown, even if some studies about the reactivity of diazomethane with olefins in the presence of Pd(0) are reported.[31,32] We can assume that $TMSCHN_2$ reacts similarly; for this reason, we can propose a mechanism in which a palladium (0) carbene species is involved (Figure 3.28). Firstly Pd(0) coordinates the olefin, forming a π-complex (**3.85**). Then, palladium coordinates also to $TMSCHN_2$ generating the η^2-complex **3.86** that rapidly releases nitrogen and produces a palladacarbene species **3.87**, the reactive species of this process. At this point, a migratory insertion occurs, forming intermediate **3.88**, a palladacyclobutane system that undergoes reductive elimination to form the desired product **3.82** and close the catalytic cycle.

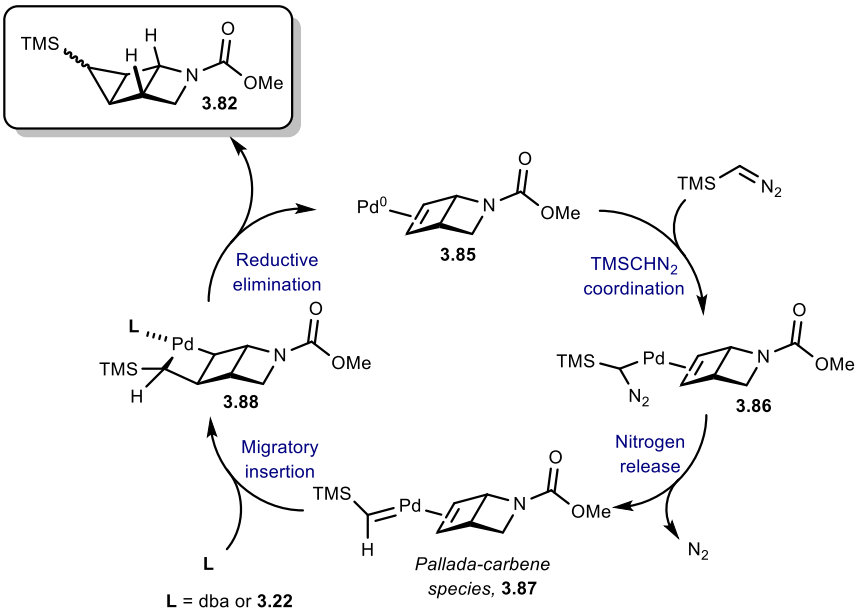
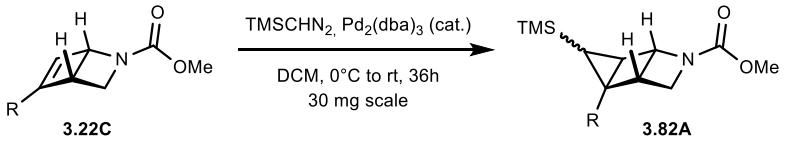


Figure 3.28. Mechanistic proposal.

With optimized conditions in hand, we applied these conditions (general procedure A, Figure 3.29) on the C4 and C3 substituted 2H-Dewar pyridines, observing an almost complete conversion into the desired products with satisfying yields. On the other hand, the C5 substituted ones (**3.22C**, Table 3.7) showed low conversion and reactivity; for this reason, a modification of the reaction's conditions was needed.

The parameters involved in this investigation were the temperature, time, catalyst loading, and the equivalents of $TMSCHN_2$. Firstly, we did the reaction at room temperature instead of 0°C overnight and the reaction time was increased up to 36 hours; secondly, we did some attempts with a 25 mol% of catalyst loading and finally, we tested the reaction with 3 and 5 equivalents of $TMSCHN_2$. Table 3.7 represents a summary of the obtained results.

Even though after 36 hours all reactions were incomplete, they were quenched anyway because of the catalyst degradation. An increased catalyst loading did not significantly affect the reaction but running the reaction at room temperature and increasing the equivalents of $TMSCHN_2$ (5.0 eq.) improved both the conversion and the reaction yields (Entries 2,6,9, Table 3.7).



Entry	R	Scale	Catalyst (eq.)	$TMSCHN_2$ (eq.)	3.82A, Yield (%)
1	Et	30 mg	0.1	1.5	8
2	Et	30 mg	0.1	5	15
3	Ph	50 mg	0.1	1.5	21
4	Ph	50 mg	0.1	3	36
5	Ph	50 mg	0.25	3	26
6	Ph	30 mg	0.1	5	42
7	CH_2OTBS	50 mg	0.1	1.5	nr
8	CH_2OTBS	50 mg	0.25	3	5
9	CH_2OTBS	30 mg	0.1	5	32

Table 3.7. Optimization of the reaction conditions for the C5 substituted 2H-DPs.

The optimized conditions (procedures A and B, Figure 3.29) were applied to the substrates, with the scope reported in Figure 3.29; all the products were obtained as a mixture of inseparable epimers. In general, the yields are satisfying, around 60-80%, except for the C2 alkyl substituted structures, where the yields are 20-30%.

The C5 substituted 2H-Dewar pyridines are not very reactive in these conditions, and it is probably attributed to electronic and steric reasons. As described before, the Pd catalyst coordinates the olefin in the first steps of the reaction and its steric hindrance could affect this process; in addition, the reaction generates a non-classical sp^3-carbon in 5-position, with very contract bond angles, that might have slowed off this process. Only the 5-phenyl-2H-DP structure (**3.43**, Figure 3.15) has shown a good yield, probably due to the high reactivity of conjugate olefins instead of aliphatic ones.

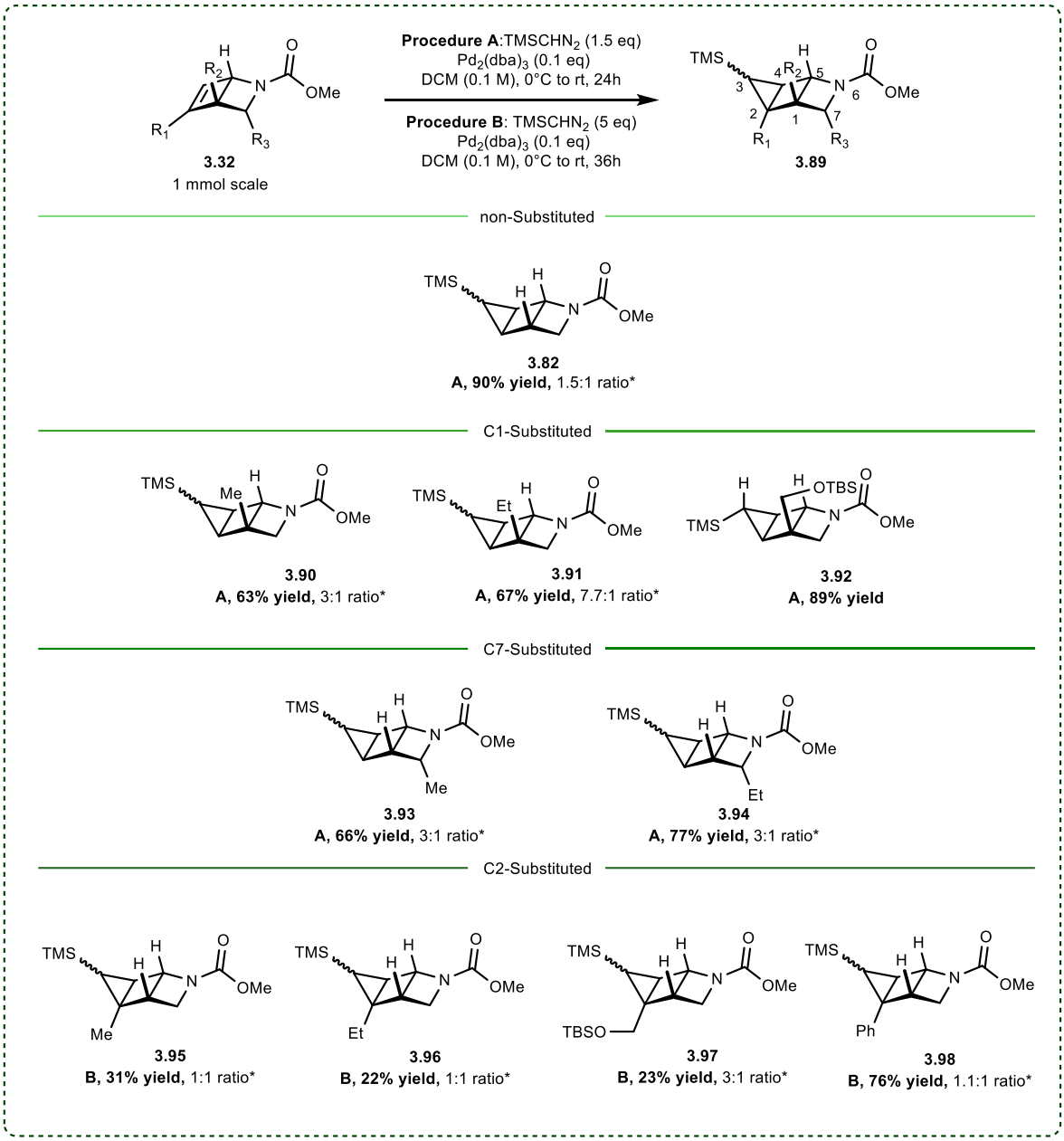
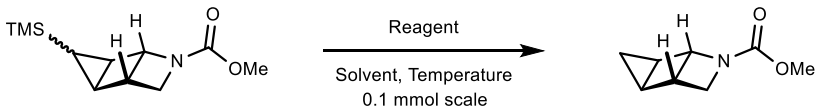


Figure 3.29. TMS-Cyclopropanation scope. Ratio* refers to epimeric ratio

At this point, in order to achieve the 6-Azabicyclo[3.2.0]heptane core **3.78** (Figure 3.25), the cleavage of the C-Si bond on the cyclopropane was necessary before the final hydrogenation step. We tested different conditions on the model substrate, such as treatment with tetrabutylammonium fluoride (TBAF)[33], cesium fluoride (CsF) or potassium hydride (KH)[29]. Table 3.8 summarizes all the attempts: in particular, the best result was achieved using 10 equivalents of TBAF (1 M solution in THF) heating at 65°C for ten days (Entry 4).



3.82 3.99

Entry	Reagent	Equivalents	Temperature	Time	3.99, Yield (%)
1	TBAF	1.3	rt	16h	nr
2	TBAF	3	rt	16h	nr
3	TBAF	3	65°C	5d	10
4	TBAF	10	65°C	10d	65
5	CsF	3	rt	16h	nr
6	KH	1	-78°C	6h	nr
7	KH	1	-78°C to rt	16h	nr

Table 3.8. Protodesilylation conditions screening.

The optimized procedure was then applied to all the substrates, as shown in Figure 3.30. The yields are medium-high, around 40-70%; the substrate with 3-CH_2OTBS as a substituent is the only one with a low yield, 13%. As the protodesilylation is usually not a smooth reaction to perform, these results could be considered satisfying. Moreover, we did not observe any side-products or decomposition of the starting material and if necessary we could recover the unreacted starting material and re-subject it to the cleavage conditions.

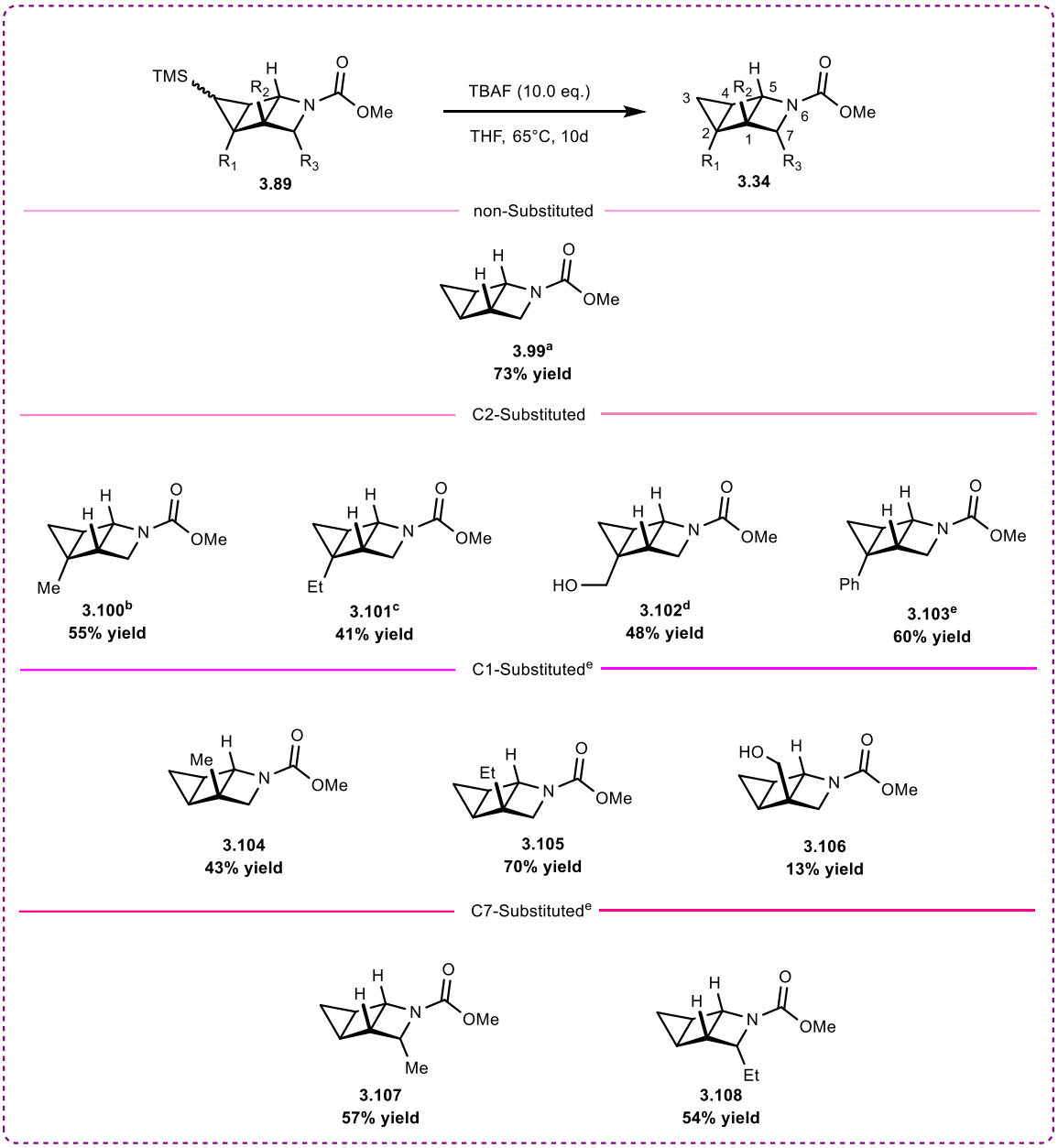
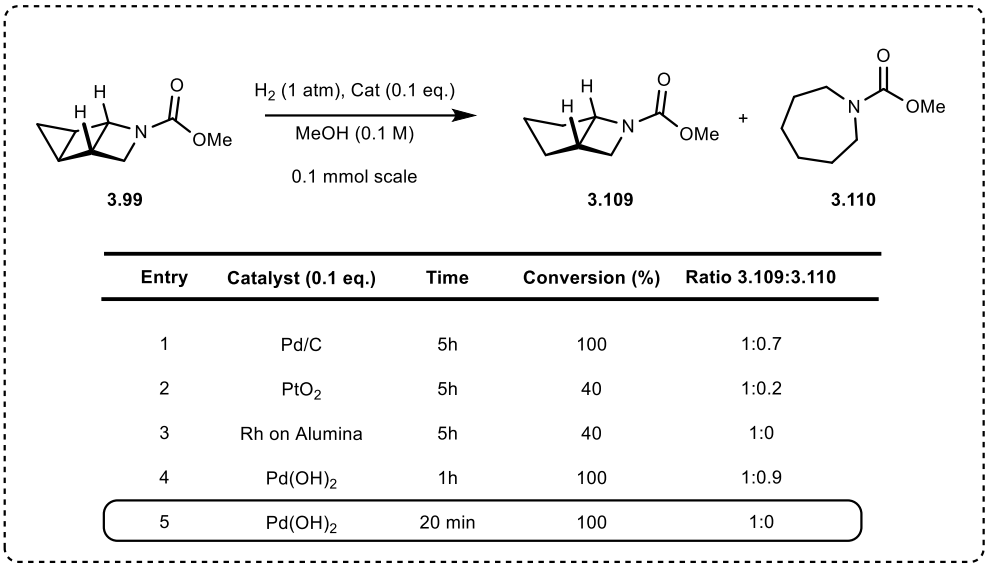


Figure 3.30. Protodesilylation scope a) 1.8 mmol scale b) 0.20 mmol scale, c) 0.30 mmol scale, d) 0.15 mmol scale, e) 0.40 mmol scale.

Having obtained methyl 6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylate cores **3.34**, the last goal of this project was to access the 6-azabicyclo[3.2.0]heptane core through selective hydrogenation of the cyclopropane-cyclobutane junction. We then started to test different heterogeneous hydrogenation conditions on the model substrate to see if we could obtain significant results. All the trials, run on 0.1 mmol of model substrate **3.99**, are summarized in Table 3.9.



Entry	Catalyst (0.1 eq.)	Time	Conversion (%)	Ratio 3.109:3.110
1	Pd/C	5h	100	1:0.7
2	PtO_2	5h	40	1:0.2
3	Rh on Alumina	5h	40	1:0
4	$Pd(OH)_2$	1h	100	1:0.9
5	$Pd(OH)_2$	20 min	100	1:0

Table 3.9. Hydrogenation screening on model substrate 3.99.

Using Pd/C, a full conversion was observed after 5h; unfortunately, an inseparable mixture of the fully hydrogenated product **3.110** and the desired one **3.109** was obtained. Switching to other metal catalysts such as PtO_2 or Rh on Alumina improved the product ratio, favoring **3.109**, but lowered the conversion. The best result was achieved with Pearlman's catalyst $Pd(OH)_2$ in 20 minutes of reaction (Entry 5, Table 3.9). With the best conditions in hand, we scaled up the reaction (50 mg scale), isolating the desired product **3.109** with 77% yield. The scope on the other substrates is ongoing.

3.2.2.5 Synthesis-oriented Manipulation of Novel Scaffolds

The last efforts were spent to find a straightforward route to make these novel scaffolds synthetically useful. To do so, we decided to start with the 3-oxa-6-azabicyclo[3.2.0]heptane, which was to us the easiest substrate to achieve. We thus explored a way to free the nitrogen moiety, that is protected as a methyl carbamate. Our strategy was to do a protecting group exchange from methyl carbamate to *tert*-butyl carbamate and then make the amine salt upon treatment with a strong acid like HCl or TFA.

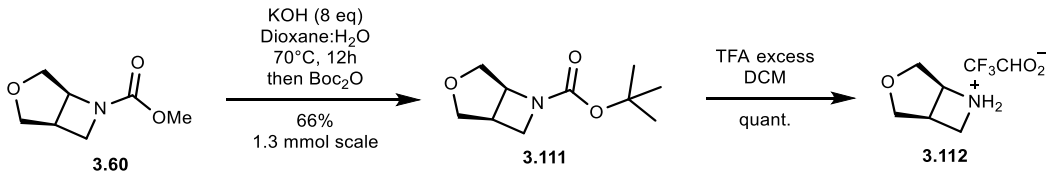


Figure 3.31: Scaffold manipulation.

As shown in Figure 3.31, we were able to get to the Boc-protected Nitrogen after basic cleavage and treatment of the crude with Boc_2O. Intermediate **3.111** was then treated with excess of trifluoroacetic acid and in this way we were able to obtain the corresponding salt **3.112** with a quantitative yield. This straightforward sequence can be potentially applied to the other building blocks library so that the nitrogen moiety is ready to react.

3.3 Summary and Future Directions

The culmination of this work represents a novel and programmable synthetic strategy for the generation of new isosteres of saturated nitrogen heterocycles from cheap and available starting materials such as pyridines, employing unique transformations. Even if this design proved to be successful considering the preliminary results within the synthesis of morpholine and piperidine isosteres, additional work is going to be needed for the piperazine one, given the lack of finding of reliable methodology to perform aziridination on 2H-Dewar pyridines. Going deeper into the subject, even the epoxidated and cyclopropanated substrates could be considered morpholine and piperidine isosteres themselves, expanding the goal of this design. With all these motifs in hand, the next step of this project is going to be the synthesis of few drug analogs that could be subjected to biological tests, with the support of computational studies to uncover the features of these building blocks compared to their parent counterparts.

3.4 Acknowledgements of Contributions

Elisa Angelini was involved in and/or developed the majority of the transformations on 2H-Dewar pyridines (epoxidation, aziridination, cyclopropanation and related hydrogenolysis). Giorgio Grosso and Patrik Pedrotti had joint roles in the synthetic efforts and assisted in scale-up, route scouting studies, and characterization of the compounds described.

3.5 Experimental

General Procedures

Unless otherwise noted, all reactions were carried out under an ambient atmosphere. All chemicals were purchased from commercial suppliers and used as received. Dry dichloromethane (DCM), diethyl ether (Et_2O), ethyl acetate (EtOAc), and tetrahydrofuran (THF) were obtained by passing commercially available anhydrous, oxygen-free HPLC-grade solvents through activated alumina columns. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 aluminum plates. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$) and/or vanillin-H_2SO_4. Retention factor (R_f) values reported were measured using a 5 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash® P60 (SiO_2, 40-63 μm particle size, 230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on Bruker 400 (400 MHz, ^1H; 101 MHz, ^{13}C) spectrometers. Spectra are referenced to residual chloroform (δ = 7.26 ppm, ^1H; 77.16 ppm, ^{13}C), residual methanol (δ = 3.31 ppm, 1H; 49.00 ppm, 13C), and residual H_2O (δ = 1.5 ppm, or δ = 4.87 ppm, ^1H). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants J are reported in Hertz (Hz). Infrared spectra were measured neat on Agilent Cary 630 FTIR with ATR. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad).

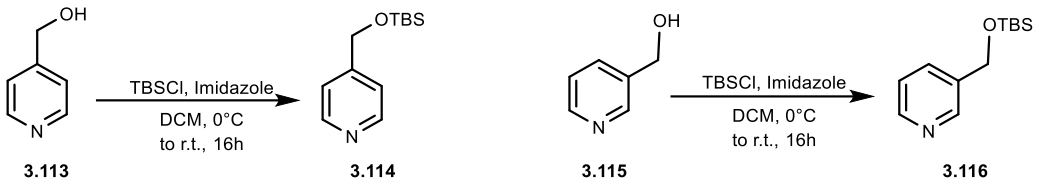
Photochemical reactions were performed in Pyrex reaction vessels placed in the center of a Rayonet RPR-100 photochemical reactor equipped with 12 G8T5E UV lamps (310 nm).

Abbreviations

Brine = saturate aqueous solution of NaCl, Boc_2O = Di-*tert*-butyl decarbonate, DMAP = 4-dimethylaminopyridine, DCM = dichloromethane, THF = tetrahydrofuran, EtOAc = ethyl acetate, Et_2O = diethyl ether, MeCN = acetonitrile, MeOH = methanol, $NaBH_4$ = sodium borohydride, $NaHCO_3$ = sodium bicarbonate, NIS = N-iodo succinimide, *m*CPBA = meta-Chloroperoxybenzoic acid, Oxone® = Potassium peroxymonosulfate, SiO_2 = silica, TBSCl = tert-butyldimethylsilyl chloride, 2H-DP = 2H-Dewar pyridine.

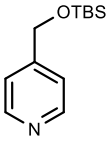
Procedures and Characterization data

General procedure for TBS protection of C4 and C3 methanol pyridines



Scheme S1

In a round-bottom flask, 4- or 3-pyridinemethanol (1.0 g, 9.2 mmol, 1 eq.) was dissolved in DCM (92 mL, 0.1 M) and cooled at 0°C. Imidazole (1.3 g, 18 mmol, 2.0 eq) and TBSCl (1.7 g, 11 mmol, 1.2 eq) were subsequently added to the reaction mixture, and it was stirred overnight at room temperature. The reaction was quenched with an aqueous solution of $NaHCO_3$, extracted with DCM (3 × 20 mL), dried over $MgSO_4$, filtered and the solvent was removed under pressure. The crude was purified *via* column chromatography (SiO_2, hexane: EtOAc mixtures) isolating the desired products.

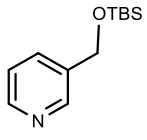


3.114

Synthesis of 3.114: Following the general procedure, the title compound was isolated *via* column chromatography (SiO_2, hexanes:EtOAc 6:1 to 4:1) as a slightly yellow clear oil (1.6 g, 7.22 mmol, 80%), matching the literature data.[34]

R_f 0.40 (SiO_2, hexanes:EtOAc = 4:1, UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.49 (m, 2H), 7.26 – 7.22 (m, 2H), 4.74 (t, *J* = 0.9 Hz, 2H), 0.96 (s, 9H), 0.12 (s, 6H).



3.116

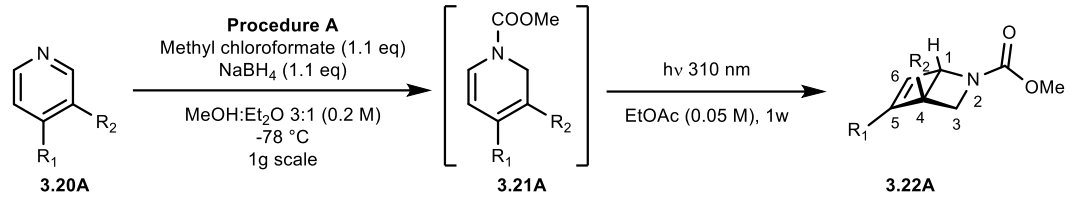
Synthesis of 3.116: Following the general procedure, the title compound was isolated *via* column chromatography (SiO_2, hexanes:EtOAc 6:1 to 4:1) as a slightly yellow clear oil (2.0 g, 9.02 mmol, 98%) matching the literature data.[35]

R_f 0.38 (SiO_2, hexanes: EtOAc = 4:1, UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.50 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.66 (dtt, *J* = 7.8, 1.7, 0.8 Hz, 1H), 7.30 – 7.22 (m, 1H), 4.76 (d, *J* = 0.8 Hz, 2H), 0.94 (s, 9H), 0.11 (s, 6H).

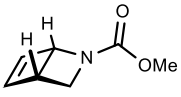
Dearomatization-4π electrocyclization

General procedure A: dearomatization-4π electrocyclization of C3 and C4 substituted pyridines for the synthesis of C4 and C5 substituted Methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylates



Scheme S2.

A flame-dried two-neck round bottom flask was charged with the desired pyridine (1 g, 1.0 eq.), $NaBH_4$ (1.1 eq.), and anhydrous Et_2O (0.8 M) under a nitrogen atmosphere. The reaction mixture was cooled to -78 °C in an acetone/dry ice cooling bath and MeOH (0.3 M) was added slowly. Methyl chloroformate (1.220 g/mL, 1.1 eq.) was then added dropwise to the reaction mixture over the course of 15 minutes. The resulting mixture was stirred for 2 hours at -78 °C. Afterward, the reaction mixture was diluted with Et_2O and quenched with water (Careful! Exothermic! Gas evolution!). The organic phase was separated from the aqueous phase, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by passing through a short plug of basic alumina (activated, Brockmann I) with Et_2O to yield the corresponding 1,2-dihydropyridine. EtOAc solution (0.05 M) of the 1,2-dihydropyridine was degassed by sparging with argon for 10 minutes in an ultrasonic bath. The degassed solution was then irradiated in the photoreactor equipped with 310 nm lamps for 7 days. The solvent was removed, and the product was purified *via* column chromatography (SiO_2, hexane: EtOAc mixtures). The reported yields are over two steps.[15] All reactions were performed on 1.0 g scale. In case of variations of this procedure, it is specified for the substrate involved.



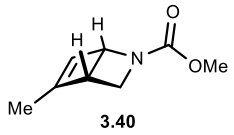
3.22

2H-DP 3.22: Following the general procedure A, reaction was performed on pyridine (1.0 g, 12.6 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 4:1) as a slightly yellow clear oil (1.0 g, 7.3 mmol, 58%), matching the literature data.[15]

R_f 0.33 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.60 – 6.41 (m, 2H), 4.83 (d, *J* = 20.7 Hz, 1H), 3.96 (t, *J* = 7.9 Hz, 1H), 3.67 (s, 3H), 3.49 (ddd, *J* = 8.7, 2.7, 1.4 Hz, 1H), 3.41 (dq, *J* = 7.7, 2.6 Hz, 1H).

IR (ATR, neat, cm^{-1}) 2957 (w), 1700 (s), 1445 (s), 1362 (m), 1190 (m), 1155 (m), 1110 (m), 766 (w).



3.40

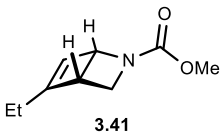
2H-DP 3.40: Following the general procedure A, reaction was performed on 4-methylpyridine (1.0 g, 10.7 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 4:1) as a slightly yellow clear oil (712 mg, 4.65 mmol, 43%).

R_f 0.35 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.27– 6.06 (m, 1H), 4.70 – 4.57 (m, 1H), 3.88 (t, *J* = 7.9 Hz, 1H), 3.65 (s, 3H), 3.48 – 3.40 (m, 1H), 3.26 (dt, *J* = 7.0, 2.8 Hz, 1H), 1.81 (d, *J* = 1.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 158.0, 153.9, 133.4, 133.0, 62.3, 61.7, 52.2, 49.3, 48.6, 39.7, 15.5.

IR (ATR, neat, cm^{-1}) 2952 (w), 2872 (w), 1705 (s), 1444 (m), 1361 (m), 1193 (w), 985 (w), 763 (w).



3.41

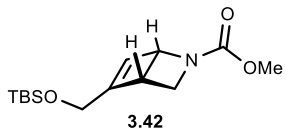
2H-DP 3.41: Following the general procedure A, reaction was performed on 4-ethylpyridine (1.0 g, 9.3 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 4:1) as a slightly yellow clear oil (854 mg, 5.11 mmol, 55%).

R_f 0.34 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.31 – 6.07 (m, 1H), 4.75 – 4.59 (m, 1H), 3.90 (t, *J* = 7.9 Hz, 1H), 3.66 (s, 3H), 3.44 (ddd, *J* = 8.7, 2.8, 1.4 Hz, 1H), 3.28 (dq, *J* = 5.6, 2.6 Hz, 1H), 2.23 – 2.04 (m, 2H), 1.06 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 159.4, 158.1, 131.2, 130.8, 77.5, 77.2, 76.8, 62.1, 61.5, 52.2, 49.6, 48.9, 38.3, 23.1, 10.8.

IR (ATR, neat, cm^{-1}) 2960 (w), 2881 (w), 1700 (s), 1446 (m), 1357 (s), 1111 (m), 831 (m), 768 (m).



3.42

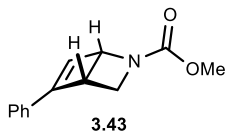
2H-DP 3.42: Following the general procedure A, reaction was performed on 4-(Dimethyl-tert-butylsilyloxymethyl)pyridine (1.0 g, 4.9 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 9:1 to 4:1) as a slightly yellow clear oil (555 mg, 1.96 mmol, 44%).

R_f 0.44 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.44 – 6.24 (m, 1H), 4.78 – 4.62 (m, 1H), 4.28 – 4.17 (m, 2H), 3.92 (t, *J* = 8.0 Hz, 1H), 3.66 (s, 3H), 3.51 (ddd, *J* = 8.7, 2.7, 1.5 Hz, 1H), 3.38 – 3.31 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.8, 132.4, 131.9, 62.3, 61.8, 60.2, 52.30, 48.9, 37.0, 25.9, 18.5, -5.22, -5.3.

IR (ATR, neat, cm^{-1}) 2952 (w), 2884 (w), 2855 (w), 1707 (s), 1446 (m), 1356 (m), 1088 (m), 834 (s), 775 (s).



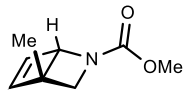
3.43

2H-DP 3.43: Following the general procedure A with a slight modification (changing the solvent ratio to Et_2O:MeOH 2:1 0.2 M and adding both MeOH and Methyl chloroformate at -25°C), reaction was performed on 4-phenylpyridine (1.0 g, 6.3 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 9:1 to 4:1) as a slightly yellow clear solid (796 mg, 3.7 mmol, 58%), matching literature data.[22]

R_f 0.37 (SiO_2, hexanes: EtOAc = 4:1, UV/Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.43 – 7.29 (m, 5H), 6.81 – 6.59 (m, 1H), 4.95 – 4.77 (m, 1H), 4.08 (t, J = 7.9 Hz, 1H), 3.76 – 3.60 (m, 4H), 3.57 (ddd, J = 8.7, 2.7, 1.4 Hz, 1H).

IR (ATR, neat, cm^{-1}) 2952 (w), 2885 (w), 1685 (s), 1446 (s), 1360 (s), 1111 (m), 972 (m), 820 (m), 756 (s), 693 (s).



3.44

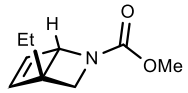
2H-DP 3.44: Following the general procedure A, reaction was performed on 3-methylpyridine (1.0 g, 10.7 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 4:1) as a slightly yellow clear oil (245 mg, 1.6 mmol, 15%).

R_f 0.32 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.51 – 6.33 (m, 2H), 4.55 – 4.39 (m, 1H), 3.69 – 3.61 (m, 4H), 3.57 (dd, *J* = 8.6, 1.5 Hz, 1H), 1.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.7, 146.6, 137.9, 137.5, 68.6, 68.0, 55.7, 55.0, 52.3, 46.7, 18.1.

IR (ATR, neat, cm^{-1}) 2952 (w), 2877 (w), 1700 (m), 1446 (m), 1364 (m), 1193 (w), 984 (w), 764 (w).



3.45

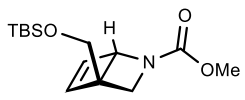
2H-DP 3.45: Following the general procedure A, reaction was performed on 3-Ethylpyridine (1.0 g, 9.3 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 4:1) as a slightly yellow clear oil (234 mg, 1.4 mmol, 15%).

R_f 0.35 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.60 – 6.28 (m, 2H), 4.60 – 4.43 (m, 1H), 3.71 – 3.63 (m, 4H), 3.53 (dd, *J* = 8.6, 1.5 Hz, 1H), 1.68 (qt, *J* = 14.0, 6.7 Hz, 2H), 0.89 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.8, 145.2, 138.5, 138.0, 66.7, 66.0, 54.4, 53.3, 52.3, 51.5, 24.8, 9.7.

IR (ATR, neat, cm^{-1}) 2950 (w), 2871 (w), 1701 (s), 1449 (s), 1365 (m), 1190 (w), 980 (w), 761 (m).



3.46

2H-DP 3.46: Following the general procedure A, reaction was performed on 3-(Dimethyl-tert-butylsilyloxymethyl)pyridine (1 g, 4.5 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 9:1 to 4:1) as a slightly yellow clear oil (510 mg, 1.8 mmol, 40%).

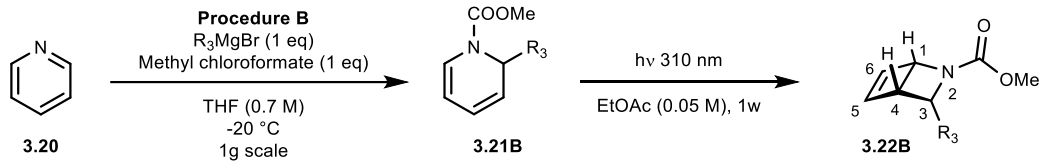
R_f 0.35 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.59 – 6.38 (m, 2H), 4.67 – 4.51 (m, 1H), 3.96 – 3.84 (m, 1H), 3.76 (d, *J* = 1.5 Hz, 2H), 3.66 (s, 3H), 3.49 (dd, *J* = 8.5, 1.5 Hz, 1H), 0.88 (s, 9H), 0.04 (d, *J* = 1.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.8, 143.6, 139.4, 139.0, 77.5, 77.2, 76.8, 65.9, 65.3, 62.6, 52.3, 51.5, 51.1, 50.4, 26.0, 18.4, -5.3.

IR (ATR, neat, cm^{-1}) 2955 (w), 2882 (w), 2851 (w), 1701 (s), 1447 (m), 1353 (m), 1083 (m), 831 (m), 771 (s).

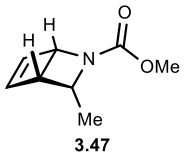
General procedure B: dearomatization-4π electrocyclization of pyridine for the synthesis of C3 substituted Methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylates



3.20 **3.21B** **3.22B**

Scheme S3.

A flame-dried two-neck round bottom flask was charged with pyridine (1 g scale, 13 mmol, 1.0 eq.) and anhydrous THF (26 mL, 0.5 M) under a nitrogen atmosphere; the reaction mixture was cooled to -20°C in an acetone/dry ice cooling bath. Grignard reagent (1.0 eq.) was slowly added, followed by methyl chloroformate (1 mL, 1.220 g/mL, 13 mmol, 1.0 eq.) that was added dropwise to the resulting mixture over the course of 15 minutes. The reaction was then stirred for 20 minutes at -20 °C and 20 minutes at room temperature. Afterwards, the reaction mixture was diluted with Et_2O and quenched with water (Careful! Exothermic!). The organic phase was separated from the aqueous phase, washed with a saturated solution of $CuSO_4$, $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified *via* column chromatography (SiO_2, hexane: EtOAc mixtures). An EtOAc solution (260 mL, 0.05 M) of the resulting 1,2-dihydropyridine was degassed by sparging with argon for 10 minutes in an ultrasonic bath. The degassed solution was then irradiated in the photoreactor equipped with 310 nm lamps for 7 days. The solvent was removed, and the product was purified *via* column chromatography (SiO_2, hexane: EtOAc mixtures).



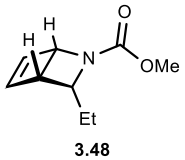
3.47

2H-DP 3.47: Following the general procedure B, using Methyl Magnesium Bromide (4 mL, 13 mmol, 3M solution in Et_2O, 1 eq.), the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 10:1 to 4:1) as a slightly yellow oil (814 mg, 5.31 mmol, 40%).

R_f 0.5 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.56 (s, 1H), 6.38 (t, *J* = 3.0 Hz, 1H), 4.73 (s, 1H), 4.28 (s, 1H), 3.67 (s, 3H), 3.51 (d, *J* = 7.3 Hz, 1H), 1.31 (s, 3H).

IR (ATR, neat, cm^{-1}) 2951 (w), 2881 (w), 2852 (w), 1701 (s), 1442 (m), 1352 (m), 1081 (m), 832 (s), 776 (s).



3.48

2H-DP 3.48: Following the general procedure B using Ethyl Magnesium Bromide (10 mL, 13 mmol, 13% wt, 1 eq.), the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 10:1 to 4:1) as a slightly yellow oil (818 mg, 4.89 mmol, 40%).

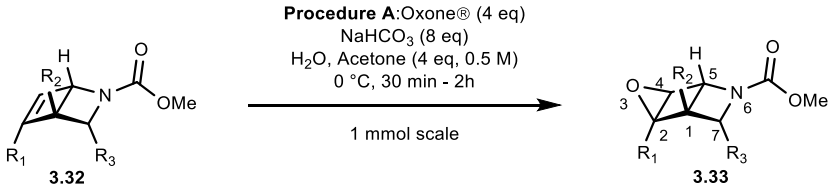
R_f 0.6 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.53 (s, 1H), 6.37 (dd, *J* = 3.4, 2.5 Hz, 1H), 4.75 (s, 1H), 4.02 (s, 1H), 3.66 (s, 3H), 3.54 (ddd, *J* = 7.4, 3.2, 2.1 Hz, 1H), 1.55 – 1.41 (m, 2H), 0.85 (t, *J* = 7.5 Hz, 3H).

IR (ATR, neat, cm^{-1}) 2951 (w), 2880 (w), 2850 (w), 1705 (s), 1441 (m), 1351 (m), 1086 (m), 831 (s), 771 (s).

Epoxidation of 2H-Dewar pyridines

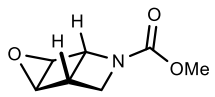
General procedure A: Epoxidation of 2H-DPs with DMDO



3.32 **3.33**

Scheme S4.

This procedure was modified from the literature protocol.[23] To a stirred mixture of the olefin (1.00 mmol, 1 eq.), $NaHCO_3$ (0.672 g, 8 mmol, 8 eq.), and acetone (8 mL, d= 0.791 g/mL, 0.5 M, 4 eq.), at 0°C, a solution of Oxone® (2.45 g, 4 mmol, 4 eq.) in water (12 mL) was added dropwise. The resulting mixture was stirred at 0°C until completion. At this point, the reaction was quenched by the addition of sodium thiosulfate (10 wt% aq. sol.), then extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified *via* column chromatography (SiO_2, Hexane: EtOAc) to yield the corresponding epoxide.

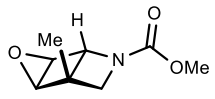


3.50

Epoxide 3.50: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 3:1) as a colorless oil (120 mg, 0.76 mmol, 76%), matching the literature data.[15]

R_f 0.45 (SiO_2, hexanes: EtOAc = 2:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.51 – 4.35 (m, 1H), 4.34 – 4.10 (m, 1H), 4.10 – 4.00 (m, 2H), 3.87 (d, J = 9.5 Hz, 1H), 3.67 (s, 3H), 2.98 – 2.90 (m, 1H).



3.51

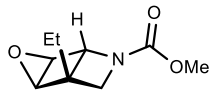
Epoxide 3.51: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 6:1 to 3:1) as a colorless oil (117 mg, 0.69 mmol, 69%).

R_f 0.36 (SiO_2, hexanes: EtOAc = 2.5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.22 – 4.06 (m, 2H), 3.96 (d, J = 9.2 Hz, 1H), 3.90 (dd, J = 4.2, 1.9 Hz, 1H), 3.75 (d, J = 9.1 Hz, 1H), 3.68 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.7, 69.7, 69.2, 57.5, 54.3, 53.6, 53.3, 52.5, 48.2, 15.9.

IR (ATR, neat, cm^{-1}) 2959 (m), 2885 (w), 1670 (s), 1449 (m), 1386 (m), 1230 (w), 1151 (w), 1095 (w), 991 (w), 842 (w).



3.52

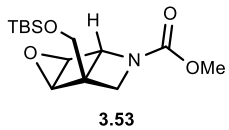
Epoxide 3.52: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 7:1 to 3:1) as a colorless oil (95 mg, 0.52 mmol, 52%).

R_f 0.42 (SiO_2, hexanes: EtOAc = 2.5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.25 – 4.08 (m, 2H), 3.96 (dd, J = 4.1, 2.0 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.81 (s, 1H), 3.69 (s, 3H), 1.72 – 1.48 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.8, 68.2, 67.7, 56.4, 53.1, 52.7, 52.5, 52.4, 51.4, 22.5, 8.8.

IR (ATR, neat, cm^{-1}) 2971 (m), 2885 (w), 1669 (s), 1451 (m), 1386 (m), 1235 (w), 1151 (w), 1095 (w), 991 (w), 835 (w).



3.53

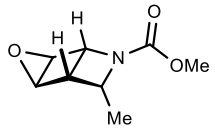
Epoxide 3.53: Following the general procedure A, the reaction was performed on **3.46** (200 mg, 0.705 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 3:1) as a colorless oil (153 mg, 0.51 mmol, 73%).

R_f 0.38 (SiO_2, hexanes: EtOAc = 2.5:2, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.29 – 4.12 (m, 2H), 4.04 (d, J = 9.0 Hz, 1H), 4.00 (dd, J = 4.2, 1.9 Hz, 1H), 3.87 (d, J = 9.2 Hz, 1H), 3.73 (d, J = 10.8 Hz, 1H), 3.70 (s, 3H), 3.62 (d, J = 10.8 Hz, 1H), 0.87 (s, 9H), 0.04 (d, J = 3.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.9, 156.8, 67.4, 67.0, 60.5, 55.5, 53.5, 52.6, 50.8, 50.1, 25.9, 18.4, -5.3, -5.3, -5.6.

IR (ATR, neat, cm^{-1}) 2952 (m), 2885 (m), 2884 (m), 1710 (s), 1450 (s), 1375 (s), 1252 (w), 1080 (m), 835 (m), 775 (w).



3.54

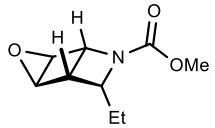
Epoxide 3.54: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc = 3:1) as a colorless oil (103 mg, 0.61 mmol, 61%).

R_f 0.36 (SiO_2, hexanes: EtOAc = 2.5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.53 – 4.35 (m, 2H), 4.20 (s, 1H), 4.01 (dd, J = 4.3, 1.8 Hz, 1H), 3.67 (s, 3H), 2.98 (dt, J = 6.9, 3.3 Hz, 1H), 1.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.9, 156.1, 66.4, 65.6, 57.2, 57.0, 56.8, 53.9, 52.2, 45.0, 44.8, 17.6, 17.1.

IR (ATR, neat, cm^{-1}) 2978 (m), 1696 (s), 1449 (s), 1375 (s), 1197 (m), 1141 (m), 1036 (w), 849 (m), 767 (m).



3.55

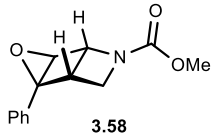
Epoxide 3.55: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 3:1) as a colorless oil (119 mg, 0.65 mmol, 65%).

R_f 0.43 (SiO_2, hexanes: EtOAc = 2.5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.43 (s, 1H), 4.30 – 4.17 (m, 1H), 4.00 (dd, J = 4.4, 1.8 Hz, 1H), 3.68 (s, 3H), 3.01 (dt, J = 6.9, 3.3 Hz, 1H), 2.14 (bs, 1H), 1.78 (ddq, J = 13.5, 10.5, 7.4 Hz, 2H), 0.95 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.7, 77.5, 77.2, 76.8, 66.0, 65.8, 62.5, 56.9, 53.9, 52.3, 44.1, 25.0, 9.7.

IR (ATR, neat, cm^{-1}) 2959 (m), 2881 (w), 1699 (s), 1446 (s), 1379 (s), 1196 (w), 1125 (m), 1035 (w), 849 (m), 767 (m).



3.58

Epoxide 3.58: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 6:1 to 3:1) as a colorless oil (99 mg, 0.43 mmol, 43%).

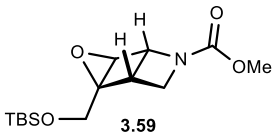
R_f 0.35 (SiO_2, hexanes: EtOAc = 3:1, UV/Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.43 – 7.30 (m, 3H), 7.25 – 7.17 (m, 2H), 4.71 (d, J = 43.3 Hz, 1H), 4.55 (d, J = 17.4 Hz, 1H), 4.25 (dd, J = 9.4, 7.0 Hz, 1H), 4.01 (d, J = 8.9 Hz, 1H), 3.74 – 3.64 (m, 3H), 3.36 (ddt, J = 6.8, 4.0, 2.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.6, 131.8, 128.8, 126.6, 77.5, 77.2, 76.8, 66.0, 65.7, 65.3, 63.4, 52.5, 49.3, 48.7, 40.0.

IR (ATR, neat, cm^{-1}) 3091 (m), 3065 (m), 3040 (m), 2948 (m), 2890 (w), 1695 (s), 1501 (m), 1453 (s), 1382 (s), 1200 (w), 1148 (w), 1121 (w), 1065 (w), 950 (w), 857 (w), 739

(w).



3.59

Epoxide 3.59: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 4:1 to 2:1) as a colorless oil (152 mg, 0.51 mmol, 51%).

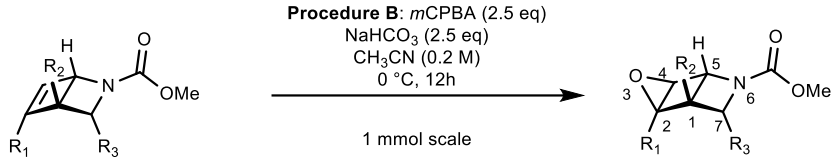
R_f 0.34 (SiO_2, hexanes: EtOAc = 2:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.49 – 4.31 (m, 2H), 4.29 – 4.01 (m, 3H), 3.92 (dd, J = 25.7, 12.1 Hz, 1H), 3.69 (s, 3H), 3.04 (dt, J = 6.5, 3.4 Hz, 1H), 0.90 (s, 9H), 0.08 (d, J = 3.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.6, 66.3, 65.9, 59.9, 59.8, 59.2, 52.5, 48.8, 48.1, 39.9, 26.0, 18.5, -5.2, -5.3.

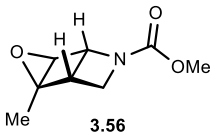
IR (ATR, neat, cm^{-1}) 2949 (m), 2897 (m), 2884 (m), 1698 (s), 1456 (s), 1375 (s), 1252 (w), 1080 (m), 835 (m), 770 (w).

General procedure B: Epoxidation of 2H-DPs with *m*CPBA



Scheme S5.

To a solution of starting material (1 mmol, 1.0 eq.) in MeCN (5 mL, 0.2 M) was added $NaHCO_3$ (200 mg, 2.56 mmol, 2.5 eq.) and *m*CPBA (75 wt%, 630 mg, 2.56 mmol, 2.5 eq.) at 0°C. The solution was stirred for 12-24 h. Thereafter, the reaction was diluted with EtOAc and quenched by the addition of sodium thiosulfate (10 wt% aq. sol., 5 mL) and sodium bicarbonate (sat. aq. sol, 5 mL). After 30 minutes, the organic phase was separated, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 20 mL) and thereafter dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. To afford pure epoxides, the crude materials were purified *via* column chromatography (SiO_2, Hexane: EtOAc).



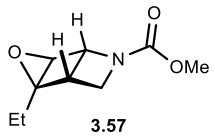
3.56

Epoxide 3.56: Following the general procedure B, reaction was performed on **3.40** (200 mg, 1.31 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 5:1 to 3:1) as a colorless oil (93 mg, 0.55 mmol, 42%), matching literature data.[22]

R_f 0.36 (SiO_2, hexanes: EtOAc = 2.5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.41 – 4.32 (m, 1H), 4.28 – 4.12 (m, 1H), 4.09 (dd, J = 9.4, 7.0 Hz, 1H), 3.89 – 3.82 (m, 1H), 3.69 (s, 3H), 2.92 (ddt, J = 6.8, 4.0, 2.6 Hz, 1H),

1.59 (s, 3H).



3.57

Epoxide 3.57: Following the general procedure B, reaction was performed on **3.41** (300 mg, 1.8 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 8:1 to 3:1) as a colorless oil (55 mg, 0.3 mmol, 17%).

R_f 0.43 (SiO_2, hexanes: EtOAc = 2.5:1, Vanillin-H_2SO_4).

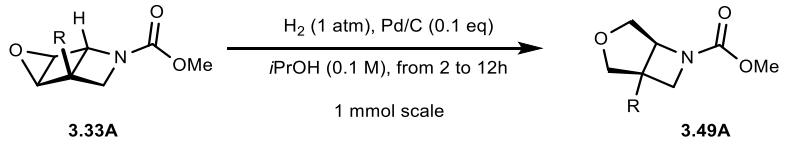
^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.44 – 4.31 (m, 1H), 4.31 – 4.13 (m, 1H), 4.07 (dd, J = 9.4, 7.0 Hz, 1H), 3.89 – 3.81 (m, 1H), 3.68 (s, 3H), 2.94 (ddt, J = 6.9, 4.1, 2.6 Hz, 1H), 2.11 (dq, J = 14.9, 7.4 Hz, 1H), 1.83 (dq, J = 15.0, 7.5 Hz, 1H), 0.93 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.7, 68.1, 66.0, 65.6, 60.1, 52.5, 48.8, 48.1, 40.8, 18.9, 8.7.

IR (ATR, neat, cm^{-1}) 2959 (m), 2892 (w), 1703 (s), 1453 (s), 1382 (s), 1200 (w), 1148 (w), 1121 (w), 950 (w), 857 (w), 719 (w).

Hydrogenation of 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylates

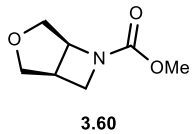
General Conditions for Hydrogenation of non-substituted or C1 substituted 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylates



3.33A 3.49A

Scheme S6.

To a degassed solution of epoxide (1.16 mmol, 1.0 eq.) in *i*PrOH (12 mL, 0.1 M) was added Pd/C (123 mg, 0.16 mmol, 10 wt%, 0.1 eq.). Then, the reaction was subjected to a hydrogen atmosphere (balloon) until full consumption of starting material (2 to 12h). The reaction mixture was then degassed with Argon, filtered through Celite, and rinsed with MeOH. The combined organics were dried *in vacuo* and the crude material was purified by column chromatography (SiO_2, hexanes: EtOAc) to afford products.



3.60

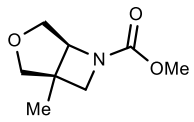
Compound 3.60: Following the general procedure, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 2:1 to 1:2) as a colorless oil (140 mg, 0.88 mmol, 76%).

R_f 0.25 (SiO_2, hexanes: EtOAc = 1:2, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.76 (s, 1H), 4.25 (dd, J = 52.3, 10.7 Hz, 1H), 4.07 – 3.97 (m, 2H), 3.67 – 3.61 (m, 4H), 3.48 (dd, J = 9.8, 5.0 Hz, 1H), 3.31 (dd, J = 10.6, 3.2 Hz, 1H), 3.14 – 3.03 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.8, 71.5, 66.8, 66.2, 53.5, 52.6, 52.2, 34.8.

IR (ATR, neat, cm^{-1}) 2969 (m), 2855 (m), 1688 (s), 1453 (s), 1386 (s), 1140 (m), 984 (w), 909 (w), 857 (w), 767 (w).



3.63

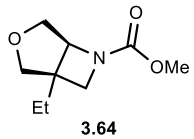
Compound 3.63: Following the general procedure, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 2:1 to 1:2) as a colorless oil (157 mg, 0.91 mmol, 79%).

R_f 0.30 (SiO_2, hexanes: EtOAc = 1:2, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.30 – 4.21 (m, 1H), 4.17 – 4.09 (m, 1H), 3.91 (d, J = 9.5 Hz, 1H), 3.78 (d, J = 8.4 Hz, 1H), 3.68 (d, J = 7.8 Hz, 1H), 3.64 (s, 3H), 3.41 (dd, J = 10.7, 3.2 Hz, 1H), 3.19 (d, J = 9.5 Hz, 1H), 1.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.8, 72.1, 71.6, 71.0, 59.0, 58.1, 52.2, 42.6, 18.7.

IR (ATR, neat, cm^{-1}) 2985 (m), 2861 (m), 1702 (s), 1453 (s), 1325 (s), 1219 (w), 1140 (m), 971 (w), 909 (w), 885 (w), 857 (w), 767 (w).



3.64

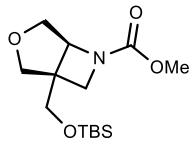
Compound 3.64: Following the general procedure, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 2:1 to 1:2) as a colorless oil (139 mg, 0.75 mmol, 65%).

R_f 0.35 (SiO_2, hexanes: EtOAc = 1:2, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.28 (t, J = 15.1 Hz, 2H), 3.96 (dd, J = 32.4, 7.9 Hz, 1H), 3.74 (d, J = 3.0 Hz, 2H), 3.64 (s, 3H), 3.39 (dd, J = 10.7, 3.2 Hz, 1H), 3.27 (d, J = 9.5 Hz, 1H), 1.85 – 1.60 (m, 2H), 0.89 (dt, J = 20.1, 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.1, 73.1, 71.5, 70.9, 59.1, 58.7, 52.5, 42.6, 27.6, 18.7.

IR (ATR, neat, cm^{-1}) 2985 (m), 2854 (m), 1691 (s), 1494 (s), 1301 (s), 1253 (w), 1140 (m), 971 (w), 914 (w), 885 (w), 857 (w), 766 (w).



3.65

Compound 3.65: Following the general procedure, the title compound was isolated *via* column chromatography (SiO_2, hexanes: EtOAc 3:1 to 1:1) as a colorless oil (260 mg, 0.87 mmol, 75%).

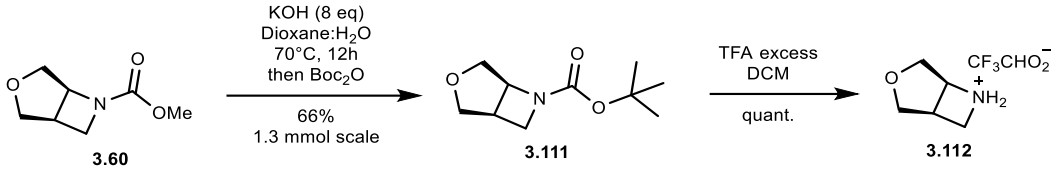
R_f 0.4 (SiO_2, hexanes: EtOAc = 1:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.53 – 4.40 (m, 1H), 4.19 (dd, J = 51.6, 10.6 Hz, 1H), 3.92 (d, J = 9.5 Hz, 1H), 3.83 (d, J = 8.4, 1.0 Hz, 1H), 3.78 (d, J = 2.4 Hz, 2H), 3.77 – 3.70 (m, 1H), 3.65 (s, 3H), 3.45 (d, J = 9.7 Hz, 1H), 3.39 (dd, 1H), 0.87 (s, 9H), 0.05 (d, J = 1.6 Hz, 6H).

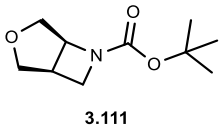
^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.00, 73.6, 72.2, 71.8, 68.6, 67.9, 63.0, 55.4, 54.5, 52.3, 48.7, 25.9, 18.3, -5.4.

IR (ATR, neat, cm^{-1}) 2952 (s), 2855 (s), 1703 (s), 1449 (s), 1379 (s), 1254 (w), 1181 (w), 1092 (m), 834 (s), 767 (s), 730 (w).

Derivatization of 3.60 to 3.112



Scheme S7.



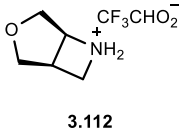
Carbamate 3.111: To a solution of **3.60** (200 mg, 1.27 mmol, 1.0 eq.) in 1,4-dioxane: water (1:1, 13 mL, 0.1 M) was added KOH (571 mg, 10.2 mmol, 8 eq.), and the reaction mixture was heated up to 70°C for 12h. Then, after cooling down the reaction to room temperature, Boc_2O (3.33 g, 15.3 mmol, 12 eq.) was added and the resulting solution was stirred for an additional 2h. Thereafter, the reaction was quenched with sodium bicarbonate (sat. aq. sol., 3 mL) and diluted with EtOAc. The aqueous phase was extracted with EtOAc (4 × 10 mL) and the combined organics were dried over MgSO4, filtered, and dried *in vacuo*. The crude material was purified *via* column chromatography (SiO_2, hexane: EtOAc 3:1 to 1:1) to afford **3.111** (167 mg, 0.83 mmol, 66%) as a colorless oil.

R_f 0.35 (SiO_2, hexanes: EtOAc = 1:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.69 (s, 1H), 4.23 (d, J = 37.3 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.59 (dd, J = 8.5, 4.3 Hz, 1H), 3.47 (dd, J = 9.8, 5.1 Hz, 1H), 3.30 (dd, J = 10.4, 3.2 Hz, 1H), 3.03 (ddd, J = 11.9, 7.2, 4.6 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.0, 154.7, 79.6, 71.8, 71.6, 66.8, 65.8, 53.6, 52.2, 34.3, 28.6.

IR (ATR, neat, cm^{-1}) 2987 (m), 2843 (m), 1705 (s), 1454 (s), 1386 (s), 1139 (m), 984 (w), 909 (w), 857 (w), 767 (w).



TFA salt 3.112: Compound **3.111** (167 mg, 0.83 mmol, 1 eq.) was dissolved in DCM: TFA (2:1, 4.2 mL, 0.2 M). After 3h, the organics were dried *in vacuo* and the title compound was isolated as a yellowish oil without the need for further purification (175 mg, 0.82 mmol, 98%).

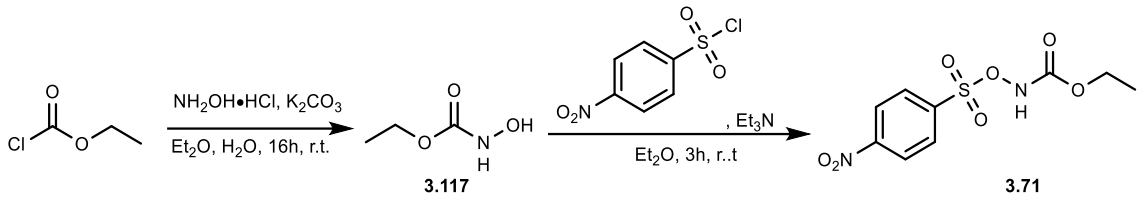
R_f 0.1 (SiO_2, hexanes: EtOAc = 3:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, CD_3OD) δ 4.95 (dd, J = 6.8, 3.7 Hz, 1H), 4.31 (d, J = 11.9 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.62 (dd, J = 11.1, 5.3 Hz, 1H), 3.58 – 3.49 (m, 2H), 3.38 (ddt, J = 8.5, 6.8, 5.0 Hz, 1H).

^{13}C NMR (101 MHz, CD_3OD) δ 162.8, 162.5, 162.1, 161.7, 122.2, 119.3, 116.4, 113.5, 73.1, 71.6, 66.2, 38.6.

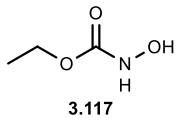
Aziridination of 2H-Dewar pyridines

Synthesis of N-Ethoxycarbonyl-p-nitrobenzenesulfonamide 3.71

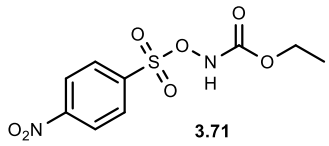


Scheme S8.

The synthesis was performed following a reported procedure.[36]

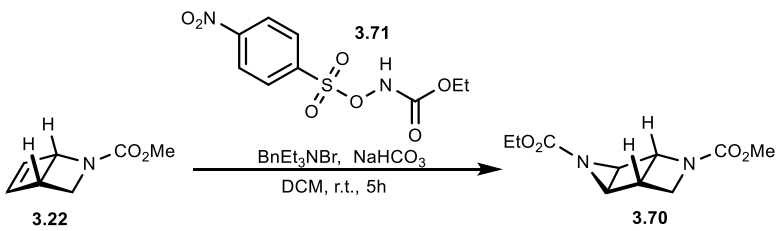


Synthesis of Carbamate 3.117: A stirred suspension of Hydroxylamine Hydrochloride (3.2 g, 47 mmol, 1.01 eq.) and anhydrous Potassium Carbonate (6.4 g, 47 mmol, 1.01 eq.) in Et_2O (26 ml, 2M) and H_2O (0.33 mL, 0.4 eq) was cooled down to 0°C. Subsequently, Ethyl Chloroformate (4.4 mL, 1.140 g/mL, 46 mmol, 1.0 eq.) was added to the stirred mixture within 1 h. After the addition, the reaction was left stirring overnight at room temperature. After completion, KCl was removed by filtration, and the filtrate was evaporated under vacuum. The resulting colorless oil was taken forward to the next step without purification.



Synthesis of sulfonamide 3.71: To a two-necked, round-bottom flask containing a solution of Ethyl N-hydroxycarbamate **3.117** (5.0 g, 47 mmol, 1 eq.) in anhydrous Et_2O (75.6 mL, 0.6 M), p-Nitrobenzenesulfonyl chloride (10.5 g, 47 mmol, 1 eq.) was added dropwise at 0°C. A solution of Triethylamine (5.64 mL, 0.726 g/mL, 40.5 mmol, 0.85 eq.) in Et_2O was slowly added with a drip funnel at such a rate as to always keep the mixture acidic. After the addition, the reaction mixture was stirred for 3 h at room temperature and then it was filtered to remove salts. The yellow filtrate was evaporated to dryness to yield a white solid which was recrystallized from toluene (6.9 g, 23.8 mmol, 50%), matching the literature data.[36,37]

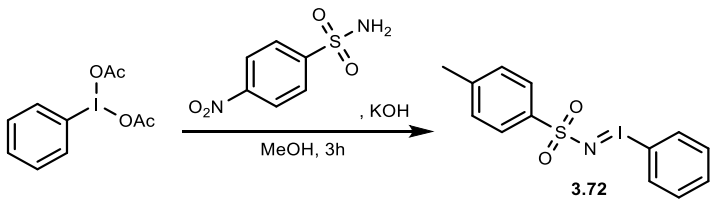
Aziridination of Methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate with N-Ethoxycarbonyl-p-nitrobenzenesulfonamide



Scheme S9.

N-Ethoxycarbonyl-p-nitrobenzenesulfonamide (156 mg, 0.54 mmol, 1.5 eq.) and Triethylbenzylammonium bromide (16.4 mg, 0.07 mmol, 0.2 eq.) were added to a solution of the bicyclic compound **3.22** (50 mg, 0.36 mmol, 1 eq.) in DCM (1.89 mL, 0.57 M). Then, $NaHCO_3$ aq. (2.16 mL, 4 wt%, 1.1 mmol, 3 eq) was added dropwise at room temperature. The reaction mixture was stirred for further 5 h. After that, it was diluted with DCM, the organic layer was separated, washed with Brine, dried with $MgSO_4$, and evaporated in vacuo. The residue was purified by column cromatography (SiO_2, hexane:EtOAc 3:1 to 4:1) and the corresponding aziridine **3.70** was isolated as a yellow oil. (15.5 g, 0.07 mmol, 19%), matching the literature data.[15,22]

Synthesis of (N-(p-toluenesulfonyl)imino)phenyliodinane 3.72

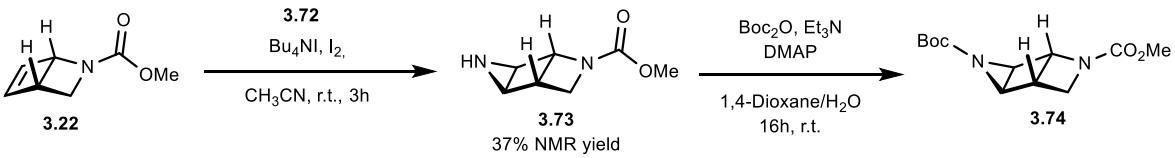


Scheme S10.

The synthesis was performed following a reported procedure.[38]

(Diacetoxyiodo) benzene (1.6 g, 5 mmol, 1.0 eq.) was added to a stirred mixture of p-Toluenesulfonamide (0.86 g, 5 mmol, 1.0 eq.), Potassium Hydroxide (701 mg, 12.5 mmol, 2.5 eq.) and Methanol (20 ml, 0.25M) at 10°C. The resulting yellow solution was stirred for 3h at room temperature. After that, the reaction mixture was poured into water so that a yellow solid could precipitate over-night and then recrystallized from methanol to give N-tosyliminophenyliodinane **3.72** (1.2 g, 3.2 mmol, 66%) matching the literature data.

Aziridination of Methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate with (N-(p-toluenesulfonyl)imino)phenyliodinane



Scheme S11.

The procedure was adapted from a reported protocol.[24] To a solution of Bu_4NI (33 mg, 0.09 mmol, 0.5 eq.) and I_2 (46 mg, 0.18 mmol, 1.0 eq) in acetonitrile (0.72 mL, 0.25 M), PhI=NTs (67 mg, 0.18 mmol, 1 eq.)

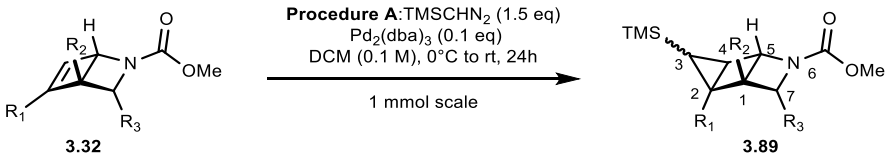
and starting material **3.22** (25 mg, 0.18 mmol, 1.0 eq.) were added. The reaction mixture was stirred for 3 h at room temperature, and then quenched by $Na_2S_2O_3$ aq (1 M, 5 mL). The mixture was extracted with Et_2O (3 × 10 mL). The collected organic layers were dried over Na_2SO_4 and evaporation of volatiles gave the crude product, which was obtained with 37% NMR yield using 1,1,2,2-tetrachloroethylene as an internal standard. The crude product was directly taken forward to the next step. Boc_2O (0.12 g, 0.54 mmol, 3 eq.), DMAP (22 mg, 0.18 mmol, 1 eq.), and Triethylamine (38 μL, 0.726 g/mL, 0.27 mmol, 1.5 eq.) were subsequently added at 0°C to a stirred solution of the crude product **3.73** (0.18 mmol, 1.0 eq.) in 1,4-dioxane: water (1:1, 1.8 mL, 0.1 M). The reaction was stirred at room temperature overnight, then quenched with aqueous solution of $NaHCO_3$, and the organic phase was extracted with EtOAc (3 × 5 mL). The collected organic layers were dried on Na_2SO_4 and evaporation gave the crude product which was purified *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 4:1) giving the desired product **3.74** (27.5 mg, 0.11 mmol, 64% over two steps).

R_f 0.35 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 5.24 (s, 1H), 4.52 (s, 1H), 4.37 – 4.28 (m, 1H), 4.19 (dd, J = 9.3, 7.3 Hz, 1H), 3.69 (s, 3H), 3.43 (tdd, J = 7.2, 4.3, 2.7 Hz, 1H), 1.49 (s, 9H).

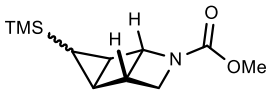
Cyclopropanation of 2H-Dewar pyridines

General procedure A: TMS-cyclopropanation of C4 and C3 susbstituted Methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylates



Scheme S12.

A solution of 2H-DP **3.32** (1.0 mmol, 1.0 eq.) in anhydrous DCM (10 mL, 0.1 M) was degassed by sparging with argon for 3 minutes in an ultrasonic bath and was added to a flame-dried vial containing $Pd_2(dba)_3$ (91.6 mg, 0.1 mmol, 0.1 eq.). The reaction mixture was cooled at 0°C and $TMSCHN_2$ (0.75 mL, 1.5 mmol, 2 M in THF, 1.5 eq.) was slowly added. The reaction was left stirring at 0°C overnight, then it was warmed up at room temperature and left stirring for additional 6 hours. The reaction mixture was quenched by adding formic acid (0.06 mL, 1.22 g/mL, 1.5 mmol, 1.5 eq.) and left stirring until no gas evolution was observed. The resulting mixture was filtered through a celite pad to remove the catalyst and the solvent was removed under pressure. The crude was purified *via* column chromatography (SiO_2, hexane: EtOAc, or toluene: EtOAc mixtures) giving the desired product.



3.82

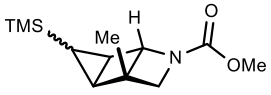
TMS-Cyclopropane 3.82: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 20:1 to 6:1) as a colorless oil (203 mg, 0.90 mmol, 90%, 1:1.5 epimeric ratio).

R_f 0.35 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.33 (m 0.4H), 4.20 (bs, 0.6H), 4.16 – 4.05 (m, 1H), 3.90 (dd, J = 14.3, 8.8 Hz, 1H), 3.70 (s, 3H), 2.65 (dt, J = 6.6, 2.7 Hz, 0.4H), 2.55 (dq, J = 5.8, 2.8 Hz, 0.6H), 2.35 (m, 0.4H), 2.18 – 1.92 (m, 1H), 1.75 – 1.70 (m, 0.6H), 0.09 (s, 3H), -0.04 (s, 6H), -0.010 (t, J = 5.9 Hz, 0.4H), -0.25 (d, J = 2.3 Hz, 0.6H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.1, 66.0, 65.5, 65.0, 52.9, 52.2, 36.9, 35.2, 25.5, 24.0, 23.8, 23.4, 22.0, 10.7, 9.3, 0.7, -2.1.

IR (ATR, neat, cm^{-1}) 2952 (w), 2885 (w), 1707 (s), 1446 (m), 1372 (m), 1249 (m), 1148 (m), 1118 (m), 984 (w), 835 (s), 764 (m).



3.90

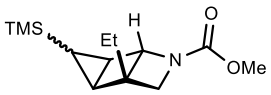
TMS-Cyclopropane 3.90: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 4:1) as a colorless oil (150 mg, 0.63 mmol, 63%, 3:1 epimeric ratio).

R_f 0.38 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.22 – 4.06 (m, 0.3H), 4.00 (s, 1H), 3.92 – 3.82 (m, 0.7H), 3.76 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.70 (s, 3H), 2.34 – 2.13 (m, 0.2H), 2.05 – 1.92 (m, 0.5H), 1.85 (s, 0.3H), 1.67 (td, *J* = 3.6, 2.2 Hz, 0.8H), 1.64 – 1.52 (m, 0.2H), 1.16 (s, 0.7H), 1.05 (s, 2.3H), 0.13 (s, 2H), -0.04 (s, 7H), -0.17 (t, *J* = 5.9 Hz, 0.3H), -0.23 (t, *J* = 2.3 Hz, 0.7H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.2, 67.7, 67.1, 66.6, 66.1, 59.0, 58.6, 57.8, 52.2, 42.9, 41.9, 26.9, 25.3, 22.0, 20.7, 20.6, 20.3, 18.5, 9.7, 8.7, 0.9, -2.1.

IR (ATR, neat, cm^{-1}) 2952 (w), 2877 (w), 1703 (s), 1446 (m), 1379 (m), 1249 (m), 1152 (m), 1103 (m), 834 (s), 768 (m).



3.91

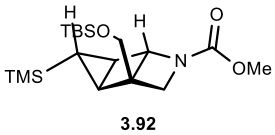
TMS-Cyclopropane 3.91: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 4:1) as a colorless oil (169 mg, 0.67 mmol, 67%, 7.7:1 epimeric ratio).

R_f 0.39 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.19 – 4.05 (m, 0.16H), 3.98 – 3.83 (m, 1.88H), 3.80 (d, *J* = 8.5 Hz, 1H), 3.69 (s, 3H), 2.33 – 2.13 (m, 0.12H), 2.08 – 1.92 (m, 0.5H), 1.86 (bs, 0.5H), 1.76 – 1.61 (m, 1H), 1.52 – 1.25 (m, 2H), 0.78 (q, *J* = 8.1, 7.4 Hz, 3H), 0.10 (s, 1H), -0.05 (s, 8H), -0.16 – -0.23 (m, 0.16H), -0.26 (s, 0.89H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.25, 157.07, 77.48, 77.16, 76.84, 66.14, 65.57, 65.06, 64.54, 57.26, 56.59, 56.41, 55.67, 52.28, 52.18, 47.12, 46.07, 26.21, 25.32, 24.72, 23.74, 21.85, 21.64, 20.53, 20.23, 9.60, 8.34, 7.85, 0.85, -2.09.

IR (ATR, neat, cm^{-1}) 2952 (w), 2877 (w), 1707 (s), 1446 (m), 1375 (m), 1249 (m), 1144 (m), 857 (m), 768 (m).



3.92

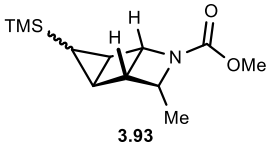
TMS-Cyclopropane 3.92: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 4:1) as a colorless oil (329 mg, 0.89 mmol, 89%).

R_f 0.42 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.11 – 4.01 (m, 1H), 3.98 (bs, 1H), 3.93 – 3.84 (m, 1H), 3.71 (s, 3H), 3.56 – 3.41 (m, 2H), 2.14 – 1.79 (m, 1H), 1.70 (td, *J* = 3.7, 2.2 Hz, 1H), 0.87 (s, 9H), 0.03 (d, *J* = 2.9 Hz, 6H), -0.01 (s, 9H), -0.15 (t, *J* = 2.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.16, 65.2, 64.7, 63.6, 62.9, 54.1, 52.3, 47.0, 46.2, 26.0, 25.9, 24.1, 22.5, 18.4, 18.3, 9.7, 8.5, 0.8, -2.0, -5.2, -5.2.

IR (ATR, neat, cm^{-1}) 2952 (w), 2885 (w), 2855 (w), 1707 (m), 1446 (m), 1371 (m), 1245 (m), 1077 (m), 835 (s), 775 (s).



3.93

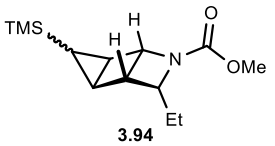
TMS-Cyclopropane 3.93: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 4:1) as a colorless oil (158 mg, 0.66 mmol, 66%, 3:1 epimeric ratio).

R_f 0.38 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.45 (bs, 1H), 4.32 – 4.03 (m, 1H), 3.67 (s, 3H), 2.70 (dt, *J* = 5.9, 2.5 Hz, 0.2H), 2.61 (dt, *J* = 6.3, 2.9 Hz, 0.8H), 2.28 (bs, 0.2H), 2.10 – 1.89 (m, 1H), 1.72 (s, 0.8H), 1.53 (s, 3H), 0.09 (s, 2H), 0.01 – -0.11 (m, 7.2H), -0.19 – -0.25 (m, 0.8H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.0, 156.4, 64.2, 63.4, 58.6, 58.3, 51.9, 42.3, 41.7, 39.9, 26.7, 25.2, 18.3, 17.1, 16.4, 10.6, 9.3, 0.8, -2.0.

IR (ATR, neat, cm^{-1}) 2952 (w), 2900 (w), 1703 (s), 1445 (m), 1379 (m), 1249 (m), 1144 (m), 835 (s), 764 (m).



3.94

TMS-Cyclopropane 3.94: Following the general procedure A, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 4:1) as a colorless oil (195 mg, 0.77 mmol, 77%, 3:1 epimeric ratio).

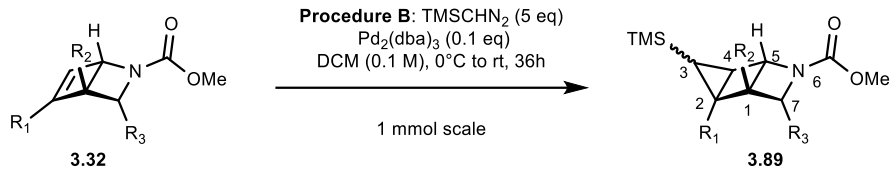
R_f 0.37 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.15 (bs, 2H), 3.67 (s, 3H), 2.72 (dt, *J* = 6.1, 2.6 Hz, 0.2H), 2.63 (dt, *J* = 6.5, 3.0 Hz, 0.8H), 2.32 – 1.85 (m, 3.2H), 1.67 (dt, *J* = 5.7, 2.5 Hz, 0.8H), 0.90 (td, *J* = 7.5, 4.0 Hz, 3H), 0.10 (s, 2H), -0.04 (s, 7H), -0.09 (t, *J* = 5.9 Hz, 0.2H), -0.22 (t, *J* = 2.2 Hz, 0.8H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.9, 156.5, 64.0, 63.5, 63.3, 52.1, 51.9, 41.1, 40.7, 38.8, 38.9, 26.5, 25.0, 23.9, 18.3, 17.0, 10.7, 9.7, 9.6, 9.4, 0.8, -2.0.

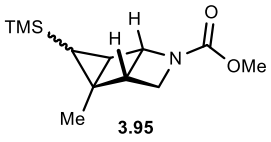
IR (ATR, neat, cm^{-1}) 2956 (w), 1703 (s), 1446 (m), 1379 (m), 1245 (m), 1126 (m), 835 (s), 764 (m).

General procedure B: TMS-cyclopropanation of C5 substituted Methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylates



Scheme S13.

A solution of 2H-DP (1.0 mmol, 1.0 eq) in anhydrous DCM (10 ml, 0.1 M) was degassed by sparging with argon for 3 minutes in an ultrasonic bath and was added to a flame-dried pressure tube containing $Pd_2(dba)_3$ (91.6 mg, 0.1 mmol, 0.1 eq.). The reaction mixture was cooled at 0°C and $TMSCHN_2$ (2.5 mL, 5.0 mmol, 2 M in THF, 5.0 eq.) was slowly added. The reaction was left at 0°C for 2 hours, then it was warmed up at room temperature and left stirring for additional 34 hours. The reaction mixture was then quenched by adding formic acid (0.189 ml, 1.5 mmol, 5 eq.) and left stirring until no gas evolution was observed. The resulting mixture was filtered through a celite pad to remove the catalyst and the solvent was removed under pressure. The crude was purified by flash chromatography (SiO_2, hexane: EtOAc, or toluene: EtOAc mixtures) giving the desired product.



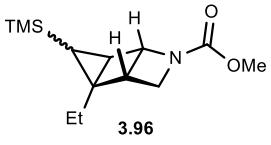
TMS-Cyclopropane 3.95: Following the general procedure B, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 7:1) as a colorless oil (74 mg, 0.31 mmol, 31%, 1:1 epimeric ratio).

R_f 0.43 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.25 (s, 0.5H), 4.11 (s, 0.5H), 4.08 – 3.95 (m, 2H), 3.72 – 3.66 (m, 3H), 2.69 (dq, J = 5.6, 2.7 Hz, 0.5H), 2.57 (dq, J = 6.2, 3.1 Hz, 0.5H), 2.23 (d, J = 31.1 Hz, 0.5H), 2.02 (d, J = 43.9 Hz, 0.5H), 1.38 – 1.29 (m, 3H), 0.08 (s, 4.5H), 0.03 (s, 4.5H), -0.27 (d, J = 6.0 Hz, 0.5H), -0.33 (d, J = 2.2 Hz, 0.5H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.0, 64.0, 52.2, 52.2, 49.6, 49.1, 40.7, 37.6, 31.1, 29.3, 29.0, 28.0, 16.4, 15.8, 15.6, 12.6, 0.8, -0.6.

IR (ATR, neat, cm^{-1}) 2951 (w), 2905 (w), 1704 (s), 1441 (m), 1373 (m), 1247 (m), 1142 (m), 831 (s), 767 (m)



TMS-Cyclopropane 3.96: Following the general procedure B, the title compound was isolated by *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 7:1) as a colorless oil (56 mg, 0.22 mmol, 22%, 1:1 epimeric ratio).

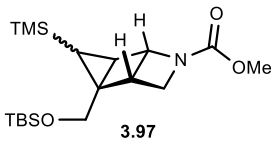
R_f 0.41 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.28 (d, *J* = 28.8 Hz, 0.5H), 4.19 – 4.06 (m, 0.5H), 4.07 – 3.94 (m, 2H), 3.71 – 3.66 (m, 3H), 2.73 (dq, *J* = 5.4, 2.6 Hz, 0.5H), 2.62 (dq, *J* = 6.2, 3.1 Hz, 0.5H), 2.38 – 1.92 (m, 2H), 1.18 (ddd, *J* = 21.9, 14.7, 7.8 Hz, 1H), 0.91 (dt, *J* = 20.3,

7.4 Hz, 3H), 0.09 (s, 4.5H), 0.03 (s, 4.5H), -0.28 (d, *J* = 5.9 Hz, 0.5H), -0.31 – -0.34 (m, 0.5H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.9, 64.3, 63.9, 63.6, 52.2, 52.2, 49.5, 38.7, 36.3, 35.0, 33.7, 31.8, 30.5, 28.6, 28.4, 22.8, 19.6, 15.5, 14.3, 11.8, 11.6, 0.7, -0.5.

IR (ATR, neat, cm^{-1}) 2954 (w), 2901 (w), 1705 (s), 1444 (m), 1371 (m), 1243 (m), 1141 (m), 837 (m), 765 (m).



3.97

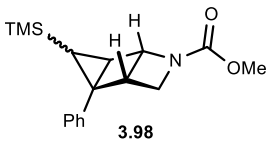
TMS-Cyclopropane 3.97: Following the general procedure B, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 7:1) as a colorless oil (85 mg, 0.23 mmol, 23%, 3:1 epimeric ratio).

R_f 0.39 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.36 – 3.98 (m, 4H), 3.68 (s, 3H), 3.58 – 3.35 (m, 1H), 2.79 (dq, *J* = 5.5, 2.6 Hz, 0.8H), 2.68 (s, 0.2H), 2.51 – 2.30 (m, 0.8H), 2.30 – 2.06 (m, 0.2H), 0.88 (s, 9H), 0.10 (s, 6H), 0.06 – 0.00 (m, 6H), -0.03 – -0.10 (m, 0.8H), -0.19 (s, 0.2H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.9, 64.0, 63.6, 62.9, 52.2, 49.9, 49.0, 38.9, 35.9, 35.8, 34.4, 33.5, 30.2, 28.3, 26.1, 26.0, 25.8, 18.5, 15.9, 14.6, 0.8, 0.2, -0.5, -5.2, -5.2.

IR (ATR, neat, cm^{-1}) 2951 (w), 2902 (w), 1700 (s), 1441 (m), 1373 (m), 1246 (m), 1143 (m), 839 (m), 769 (w).



3.98

TMS-Cyclopropane 3.98: Following the general procedure B, the title compound was isolated *via* column chromatography (SiO_2, toluene: EtOAc 10:1 to 6:1) as a colorless oil (230 mg, 0.76 mmol, 76%, 1.1:1 epimeric ratio).

R_f 0.42 (SiO_2, hexanes: EtOAc = 6:1, UV/Vanillin-H_2SO_4).

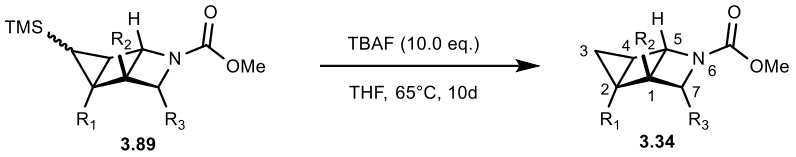
^{1}H NMR (400 MHz, $CDCl_3$, rotamers) 7.34 – 7.20 (m, 3H), 7.20 – 7.12 (m, 1H), 7.01 – 6.94 (m, 1H), 4.45 (s, 0.6H), 4.30 (s, 0.4H), 4.08 (dd, J = 9.1, 6.7 Hz, 0.6H), 3.91 (dd, J = 9.2, 6.6 Hz, 0.4H), 3.86 – 3.59 (m, 4H), 3.13 (dq, J = 6.7, 2.6 Hz, 0.6H), 3.04 – 2.84 (m, 1H), 2.58 (bs, 0.4H), 0.29 (d, J = 6.2 Hz, 0.6H), 0.22 (d, J = 2.4 Hz, 0.4H), 0.14 (s, 5H), -0.24 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.8, 140.5, 140.2, 139.8, 134.9, 129.9, 128.7, 128.5, 128.3, 128.2, 127.1, 126.0, 125.9, 125.8, 125.7, 125.4, 124.8, 66.9, 63.4, 62.9, 52.3, 52.2, 50.5, 49.8, 41.7, 36.8, 36.7, 36.3, 33.0, 29.8, 22.5, 22.2, 18.5, 0.8, -1.2, -3.2, -4.3.

IR (ATR, neat, cm^{-1}) 2952 (w), 2885 (w), 1700 (s), 1446 (m), 1375 (m), 1245 (m), 1125 (m), 991 (w), 835 (s), 757 (s), 701 (s).

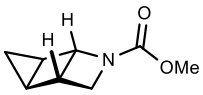
Prototesilylation

General procedure for protodesilylation



Scheme S14.

A flame-dried vial was charged with the starting material **3.89** (1 eq.) and TBAF (1 M solution in THF, 10 eq.) was added dropwise under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 65°C for ten days, then it was diluted with Et_2O and quenched adding an aqueous solution of NH_4Cl. The organic phase was extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified *via* column chromatography (SiO_2, hexane: EtOAc mixtures) giving the desired product.



3.99

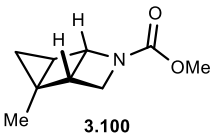
Cyclopropane 3.99: Following the general procedure, reaction was performed on **3.82** (410 mg, 1.8 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 4:1) as a clear oil (200 mg, 1.3 mmol, 73%).

R_f 0.31 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.22 (d, *J* = 22.1 Hz, 1H), 4.13 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 3.70 (s, 3H), 2.54 (dq, *J* = 6.6, 2.7 Hz, 1H), 2.16 (d, *J* = 47.3 Hz, 1H), 1.84 (ddt, *J* = 5.8, 3.8, 1.8 Hz, 1H), 0.84 (q, *J* = 5.5 Hz, 1H), 0.42 (d, *J* = 5.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.2, 65.2, 64.8, 53.3, 52.6, 52.2, 35.5, 20.7, 20.5, 18.6, 9.9.

IR (ATR, neat, cm^{-1}) 2956 (w), 2885 (w), 1696 (s), 1446 (s), 1371 (s), 1200 (m), 1121 (s), 984 (m), 767 (m).



3.100

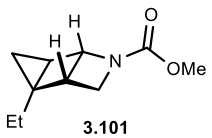
Cyclopropane 3.100: Following the general procedure, reaction was performed on **3.95** (50 mg, 0.2 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 5:1) as a clear oil (18.6 mg, 0.11 mmol, 55%).

R_f 0.33 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.18 – 3.99 (m, 3H), 3.69 (s, 3H), 2.56 (dq, J = 6.5, 3.2 Hz, 1H), 2.05 (d, J = 46.5 Hz, 1H), 1.31 (s, 3H), 0.65 (t, J = 5.4 Hz, 1H), 0.49 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 63.5, 63.0, 56.2, 52.2, 50.1, 49.4, 37.7, 25.7, 24.6, 16.2, 14.0. C=O peak absent due to low concentration but confirmed by HMBC.

IR (ATR, neat, cm^{-1}) 2951 (w), 2884 (w), 1698 (s), 1443 (m), 1372 (m), 1205 (m), 1122 (m), 980 (m), 671 (m).



3.101

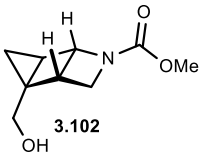
Cyclopropane 3.101: Following the general procedure, reaction was performed on **3.96** (80 mg, 0.3 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 5:1) as a clear oil (22.1 mg, 0.12 mmol, 41%).

R_f 0.35 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.17 (s, 1H), 4.11 (s, 1H), 4.04 (d, J = 5.0 Hz, 2H), 3.69 (s, 3H), 2.60 (dq, J = 6.2, 2.2, 1.4 Hz, 1H), 2.02 (dt, J = 14.5, 7.2 Hz, 1H), 1.40 – 1.28 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H), 0.67 (t, J = 5.5 Hz, 1H), 0.43 – 0.37 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 72.7, 63.4, 52.2, 49.2, 36.6, 29.9, 24.9, 20.5, 18.8, 13.8, 11.4, 11.0. C=O peak absent due to low concentration but confirmed by HMBC.

IR (ATR, neat, cm^{-1}) 2955 (w), 2885 (w), 1699 (s), 1440 (m), 1371 (m), 1208 (m), 1124 (m), 982 (m), 766 (m).



3.102

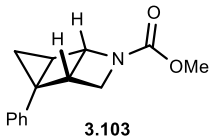
Cyclopropane 3.102: Following the general procedure, reaction was performed on **3.97** (55 mg, 0.15 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 4:1 to 1:1) as a clear oil (13 mg, 0.07 mmol, 48%).

R_f 0.37 (SiO_2, hexanes: EtOAc = 1:2, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.24 – 4.18 (m, 1H), 4.14 – 4.05 (m, 1H), 3.69 (s, 2H), 3.52 (d, J = 12.3 Hz, 1H), 2.73 (dq, J = 5.9, 2.8 Hz, 1H), 2.30 (d, J = 46.4 Hz, 1H), 1.44 – 1.22 (m, 3H), 0.92 – 0.83 (m, 1H), 0.65 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.0, 63.4, 63.0, 62.0, 61.7, 52.3, 50.3, 49.6, 35.7, 32.1, 30.5, 29.9, 29.8, 25.3, 25.2, 22.8, 14.3.

IR (ATR, neat, cm^{-1}) 3412 (br w), 2954 (w), 2882 (w), 1686 (s), 1455 (m), 1393 (m), 1204 (w), 1151 (m), 1039 (w), 763 (w).



3.103

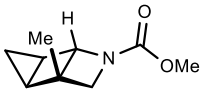
Cyclopropane 3.103: Following the general procedure, reaction was performed on **3.98** (100 mg, 0.4 mmol) and tthe title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 4:1) as a clear oil (55 mg, 0.24 mmol, 60%).

R_f 0.40 (SiO_2, hexanes: EtOAc = 4:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.00 – 6.94 (m, 2H), 4.38 – 4.23 (m, 1H), 4.12 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.97 (t, *J* = 9.1 Hz, 1H), 3.67 (d, *J* = 23.3 Hz, 3H), 3.02 (dq, *J* = 6.5, 2.9 Hz, 1H), 2.74 (d, *J* = 56.3 Hz, 1H), 1.17 (t, *J* = 5.6 Hz, 1H), 1.06 (d, *J* = 6.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.9, 139.4, 139.0, 128.5, 128.2, 125.9, 62.7, 62.2, 52.3, 52.2, 51.0, 50.3, 36.9, 36.8, 31.7, 28.6, 20.9, 20.6.

IR (ATR, neat, cm^{-1}) 3026 (w), 2952 (w), 2885 (w), 1700 (s), 1446 (s), 1364 (s), 1193 (m), 1126 (m), 1021 (m), 980 (m), 749 (s), 697 (s).



3.104

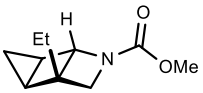
Cyclopropane 3.104: Following the general procedure, reaction was performed on **3.90** (96 mg, 0.4 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 5:1) as a clear oil (30 mg, 0.18 mmol, 43%).

R_f 0.35 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.04 (t, J = 8.6 Hz, 1H), 3.93 – 3.82 (m, 1H), 3.79 (d, J = 8.5 Hz, 1H), 3.69 (s, 3H), 2.11 – 1.92 (m, 1H), 1.79 (dtd, J = 5.2, 3.6, 1.3 Hz, 1H), 1.05 (s, 3H), 0.76 (q, J = 5.6 Hz, 1H), 0.42 (d, J = 5.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.3, 66.9, 66.4, 59.0, 58.3, 52.3, 41.8, 29.8, 21.8, 18.2, 17.3, 17.1, 8.4.

IR (ATR, neat, cm^{-1}) 2951 (w), 2881 (w), 1696 (s), 1445 (m), 1370 (m), 1203 (m), 1122 (m), 985 (m), 761 (m).



3.105

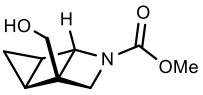
Cyclopropane 3.105: Following the general procedure, reaction was performed on **3.91** (101 mg, 0.4 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 4:1) as a clear oil (49 mg, 0.27 mmol, 70%).

R_f 0.37 (SiO_2, hexanes: EtOAc = 5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.00 – 3.86 (m, 2H), 3.83 (d, J = 8.5 Hz, 1H), 3.69 (s, 3H), 2.14 – 1.94 (m, 1H), 1.81 (q, J = 4.4 Hz, 1H), 1.37 (p, J = 7.4 Hz, 2H), 0.82 – 0.69 (m, 4H), 0.41 (t, J = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.3, 157.0, 65.3, 64.8, 56.7, 56.0, 52.3, 46.0, 24.4, 20.3, 17.1, 16.9, 8.3, 8.0.

IR (ATR, neat, cm^{-1}) 2951 (w), 2882 (w), 1698 (s), 1445 (m), 1373 (m), 1205 (m), 1122 (m), 981 (m), 765 (m).



3.106

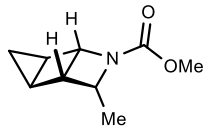
Cyclopropane 3.106: Following the general procedure, reaction was performed on **3.92** (150 mg, 0.4 mmol) and tthe title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 4:1 to 1:1) as a clear oil (9 mg, 0.05 mmol, 13%).

R_f 0.25 (SiO_2, hexanes: EtOAc = 1:2, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.16 – 3.94 (m, 3H), 3.70 (s, 3H), 3.55 (q, *J* = 11.6 Hz, 2H), 2.14 (d, *J* = 47.5 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.55 (bs, 1H), 0.82 (q, *J* = 5.7 Hz, 1H), 0.55 (dt, *J* = 5.8, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.2, 64.4, 63.8, 62.5, 55.1, 54.4, 52.3, 45.7, 18.8, 17.7, 17.5, 8.2.

IR (ATR, neat, cm^{-1}) 3414 (br w), 2952 (w), 2881 (w), 1681 (s), 1453 (m), 1390 (m), 1200 (w), 1155 (m), 1036 (w), 768 (w).



3.107

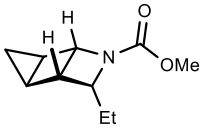
Cyclopropane 3.107: Following the general procedure, reaction was performed on **3.93** (95 mg, 0.4 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 10:1 to 6:1) as a clear oil (38 mg, 0.23 mmol, 57%).

R_f 0.44 (SiO_2, hexanes: EtOAc = 6:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.49 (s, 1H), 4.21 – 4.09 (m, 1H), 3.67 (s, 3H), 2.60 (dt, *J* = 6.4, 2.9 Hz, 1H), 2.15 – 2.01 (m, 1H), 1.89 – 1.77 (m, 1H), 1.64 – 1.44 (m, 3H), 0.86 (q, *J* = 5.5 Hz, 1H), 0.45 (dt, *J* = 5.2, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.1, 156.4, 63.3, 62.5, 58.9, 58.4, 51.9, 40.7, 40.4, 21.9, 17.0, 16.4, 13.8, 10.1.

IR (ATR, neat, cm^{-1}) 2956 (w), 1700 (s), 1446 (m), 1379 (s), 1196 (m), 1141 (m), 1051 (m), 768 (m).



3.108

Cyclopropane 3.108: Following the general procedure, reaction was performed on **3.94** (101 mg, 0.4 mmol) and the title compound was isolated *via* column chromatography (SiO_2, hexane: EtOAc 12:1 to 4:1) as a clear oil (39.4 mg, 0.22 mmol, 54%).

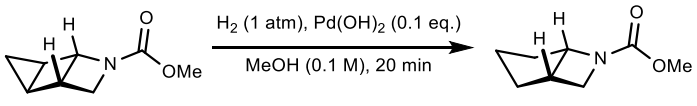
R_f 0.46 (SiO_2, hexanes: EtOAc = 5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.18 (d, *J* = 26.1 Hz, 2H), 3.66 (s, 3H), 2.62 (dt, *J* = 6.5, 2.9 Hz, 1H), 2.33 – 2.01 (m, 2H), 1.94 (ddq, *J* = 13.3, 10.5, 7.4 Hz, 1H), 1.79 (qd, *J* = 3.8, 1.9 Hz, 1H), 0.96 – 0.81 (m, 4H), 0.45 (dt, *J* = 5.2, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.1, 156.7, 63.9, 63.0, 62.4, 51.9, 39.6, 39.3, 24.3, 24.0, 21.7, 13.7, 10.2, 9.6.

IR (ATR, neat, cm^{-1}) 2960 (w), 2876 (w), 1700 (s), 1446 (s), 1375 (s), 1193 (m), 1126 (m), 768 (m).

Hydrogenation of Methyl 6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylate



3.99 3.109

Scheme S15.

To a degassed solution of **3.99** (50 mg, 0.33 mmol, 1.0 eq.) in MeOH (3.3 mL, 1 M) was added $Pd(OH)_2$ (23 mg, 0.03 mmol, 20 wt%). Then, the reaction was subjected to a hydrogen atmosphere (balloon) for 20 min. After reaction completion, the mixture was degassed with argon, filtered through Celite, and rinsed with additional MeOH. The combined organics were dried *in vacuo* to afford **3.109** as a colorless oil (39.4 mg, 0.25 mmol, 77%).

R_f 0.51 (SiO_2, hexanes: EtOAc = 5:1, Vanillin-H_2SO_4).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.60 (d, J = 18.1 Hz, 1H), 3.98 (t, J = 8.5 Hz, 1H), 3.61 (s, 3H), 3.34 (dd, J = 8.8, 4.1 Hz, 1H), 2.89 – 2.78 (m, 1H), 2.18 – 1.92 (m, 2H), 1.95 – 1.77 (m, 1H), 1.72 – 1.63 (m, 1H), 1.61 – 1.37 (m, 1H), 1.37 – 1.20 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.3, 155.9, 67.5, 67.0, 53.5, 52.3, 52.5, 52.0, 46.1, 44.3, 40.1, 33.7, 32.2, 31.7, 31.0, 30.7, 30.2, 30.1, 25.3, 25.2, 23.5, 23.4.

IR (ATR, neat, cm^{-1}) 2962 (w), 2871 (w), 1702 (s), 1442 (s), 1371 (s), 1191 (m), 1121 (m), 763 (m).

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