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Synthesis of sp^3-enriched medicinal chemistry-relevant fragments

and

Studies towards the total synthesis of nimbolide

Tesi di Dottorato di
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Part I:

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.

Sp^2-sp^3 fragments play a vital role in fragment-based drug design (FBDD). Strategies to chemically modify them and efficiently access libraries of these compounds have been goals of the highest priority in the last decades. In this work, a series of sp^2-sp^3 fragments is synthesized and validated for that purpose, based on their measured physical-chemical properties. Selective C-H cyanation and allylation of these fragments is demonstrated by simple heating in presence of an appropriate hydrogen-atom transfer reagent and a radical acceptor. These conditions enable a streamlined access to covalent fragments in a single step, by direct introduction of the desired covalent binder. Preliminary results on vinylation, as well as late-stage functionalization of a drug analogue are disclosed.

Part II:

Nimbolide, a natural product belonging to the limonoids family, has attracted much attention thanks to its biological properties, especially against cancer cell lines. However, clinical studies still struggle to proceed due to the not fully understood metabolism and its poor pharmacokinetic properties. A flexible total synthesis would help addressing these problems by allowing access to a variety of analogues with the desired physical-chemical characteristics. The studies towards the synthesis of the two main fragments identified in our retrosynthetic analysis are here presented.

Part I: Synthesis of sp^3-enriched medicinal chemistry-relevant fragments

1.1 Diversification of arenes into complex (amino)cyclitols

1.1.1 Manuscript

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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.

Introduction

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 incorporation of diverse cyclic fragments in libraries has been slower than expected.[6] Therefore, developing strategies that could access functionalized natural-like

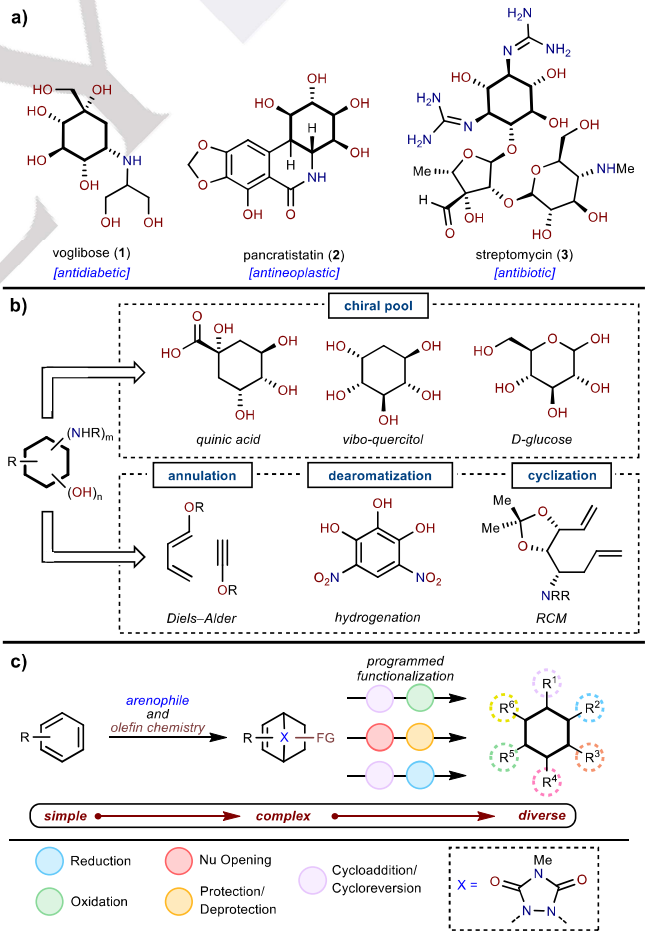

Figure 1. a) Selected aminocyclitol-containing natural products. b) Representative strategies used for the synthesis of (amino)cyclitols. c) This work: programmed (amino)cyclitol synthesis through diversification of arenophile-based products.

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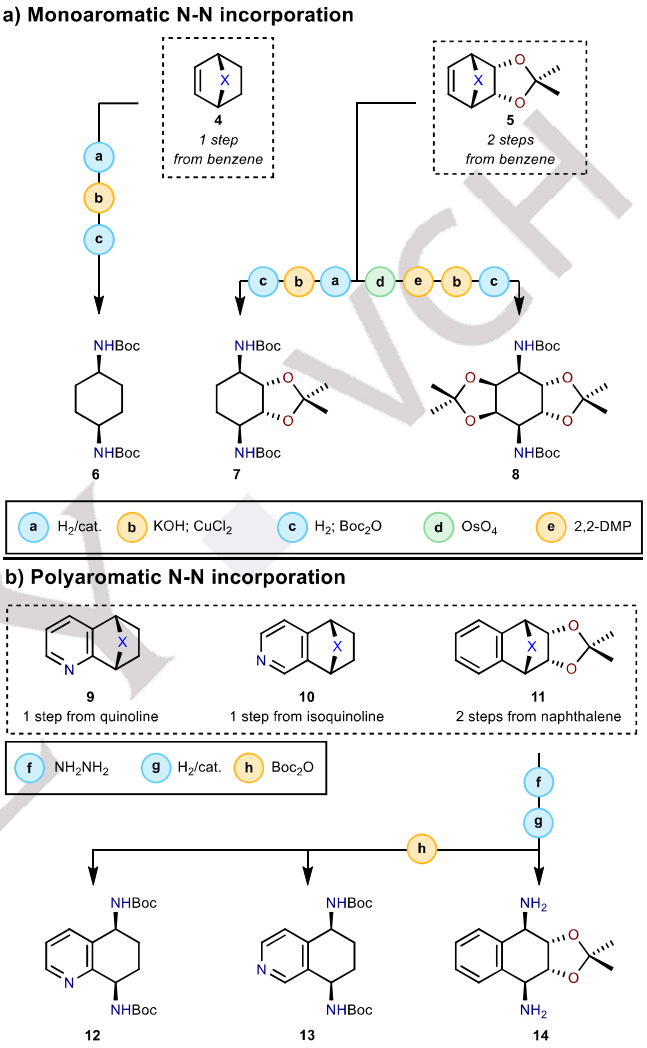
cyclic compounds is an essential consideration for the future of drug discovery.

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 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.

Results and Discussion



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.

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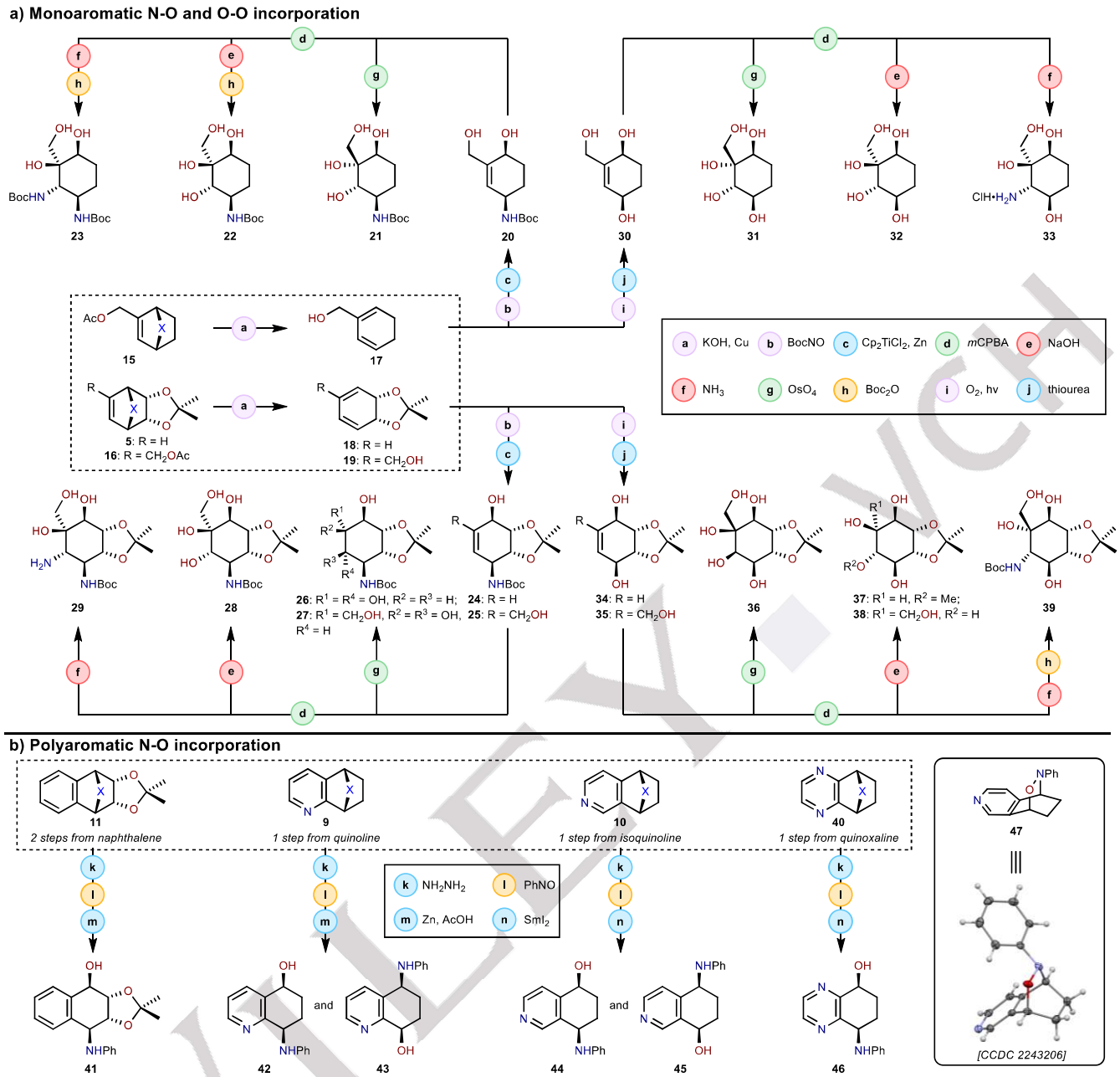

Scheme 2. Diversification of arenophile-based dearomatized products towards (amino)cyclitols using a) benzene-derived **5**,**15**, and **16** dearomatized adducts; and b) polycyclic (hetero)arenes-derived **9–11**, and **40** adducts. *Reactions and conditions*: (a) ref.; (b) for R = H: BocNHOH (2 equiv), 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.

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

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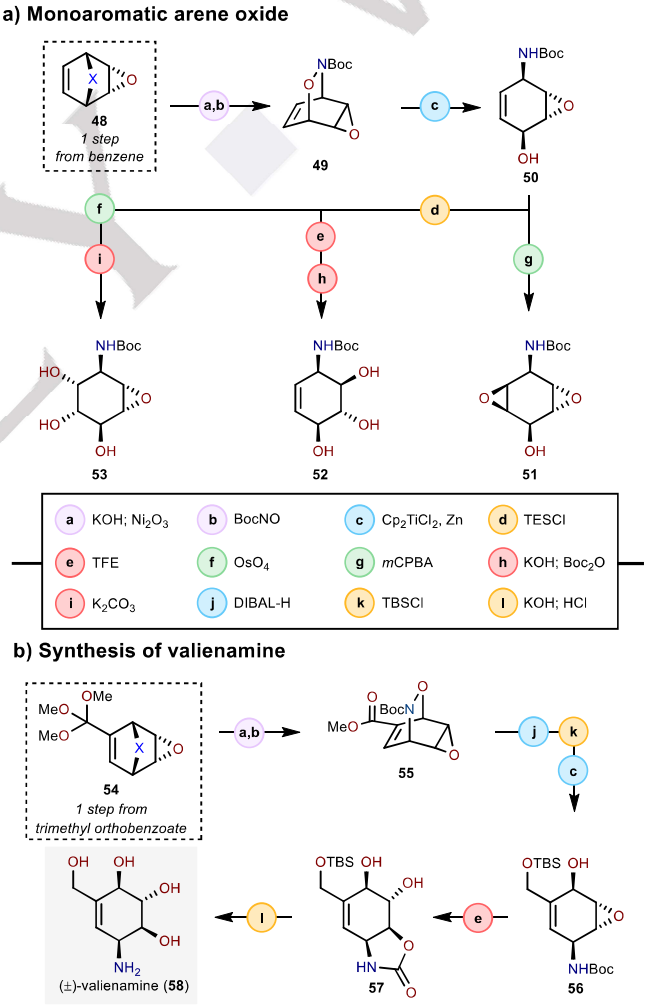
reduction[18] and dearomative dihydroxylation,[19] respectively. Bicycle **4** was transformed into diamine **6** through a three-step sequence involving hydrogenation of the cyclic alkene, hydrolysis of the urazole with subsequent oxidation to bicyclic diazo, and hydrogenative cleavage of the diazene 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.

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.



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

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(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.

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. 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] 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.

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.

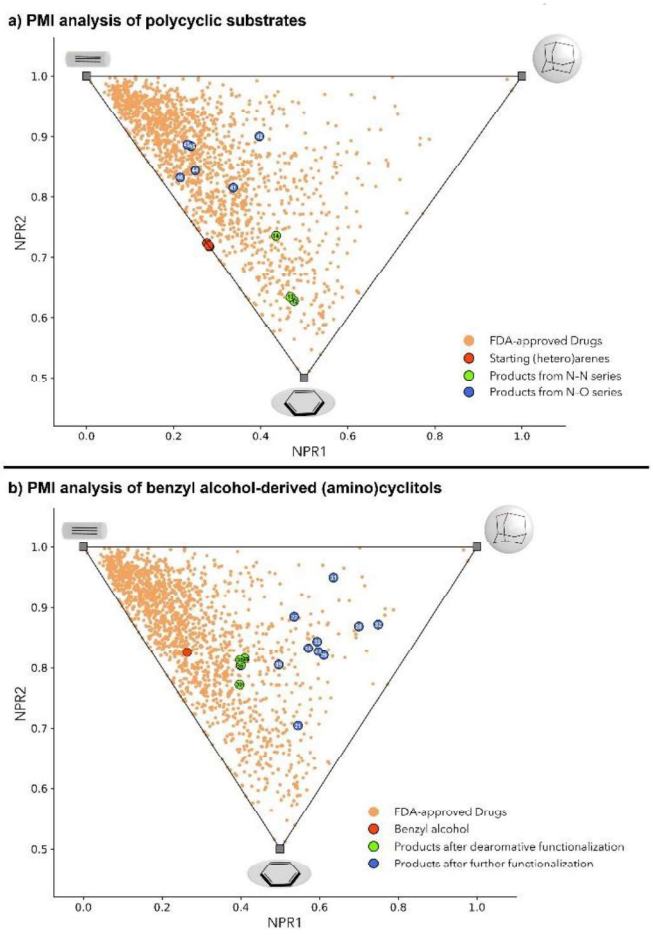

Figure 2. Diversification of arenes using dearomative functionalization visualized with PMI analysis. Results are plotted using unprotected intermediates in comparison with FDA-approved drugs (orange dots). a) Diversification of polycyclic (hetero)arenes. b) Diversification of benzyl alcohol.

Supporting Information

The Supporting Information contains extensive further experimental and spectroscopic detail beyond the above example of a typical procedure. The authors have cited additional references within the Supporting Information (Ref. [31-45]).

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

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1.1.2 Experimental section

Diversification of Simple Arenes into Complex (Amino)cyclitols

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Supporting Information

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 procedures1 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 SilicaFlash® 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:

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

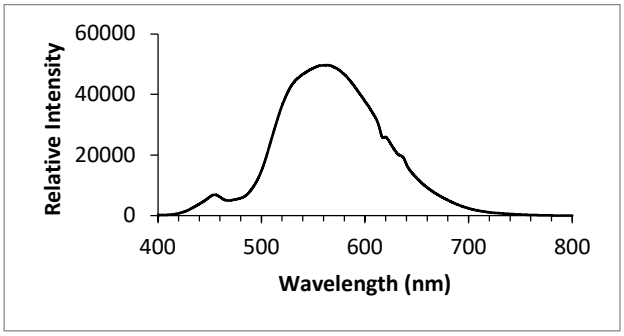
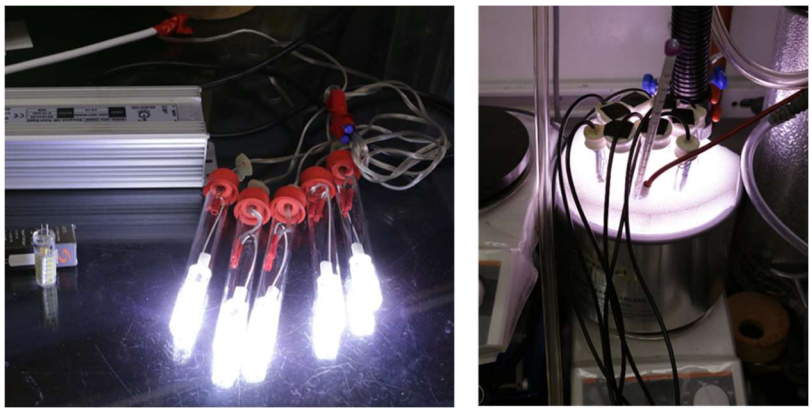


Figure S1. Spectrum of LED bulb used.

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.



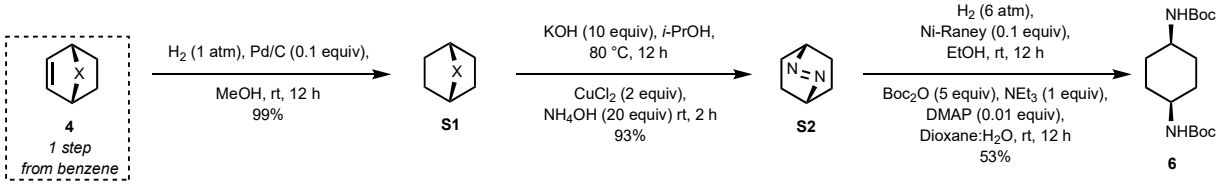
Picture S1. Assembly of LED bulbs for small-scale photochemical reactions.

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 reaction.

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, hexanes: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).

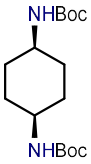
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 – 5.07 (m, 2H), 1.57 (m, *J* = 7.7 Hz, 4H), 1.39 – 1.20 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) 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, $KMnO_4$).

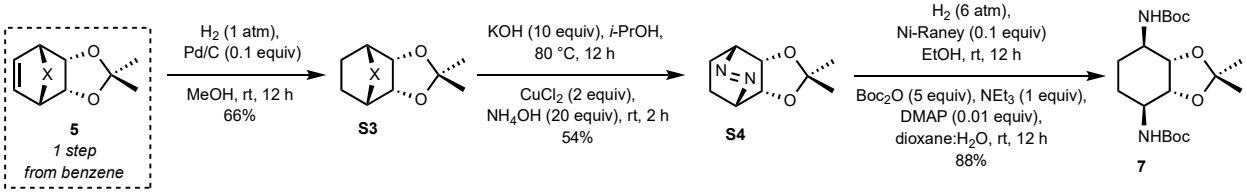
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (s, 2H), 3.58 (s, 2H), 1.78 – 1.65 (m, 4H), 1.52 (m, *J* = 12.2, 6.4 Hz, 4H), 1.44 (s, 18H).

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

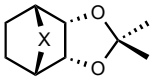
IR (ATR, neat, cm^{-1}) 3451 (b), 3339 (b), 2974 (s), 2933 (m), 2862 (s), 1684 (w), 1498 (w), 1390 (m), 1248 (m), 1155 (w), 1043 (m), 782 (m), 700 (m).

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, $KMnO_4$).

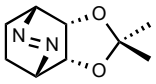
^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.40 – 4.31 (m, 4H), 3.03 (s, 3H), 2.15 – 1.99 (m, 2H), 1.76 – 1.60 (m, 2H), 1.52 (s, 3H), 1.35 (s, 3H).

^{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).

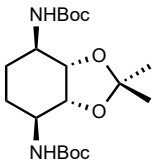
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.50 (m, 2H), 3.80 (t, J = 2.3 Hz, 2H), 2.00 – 1.88 (m, 2H), 1.51 (s, 3H), 1.29 (s, 3H), 1.08 – 0.95 (m, 2H).

^{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, $KMnO_4$).

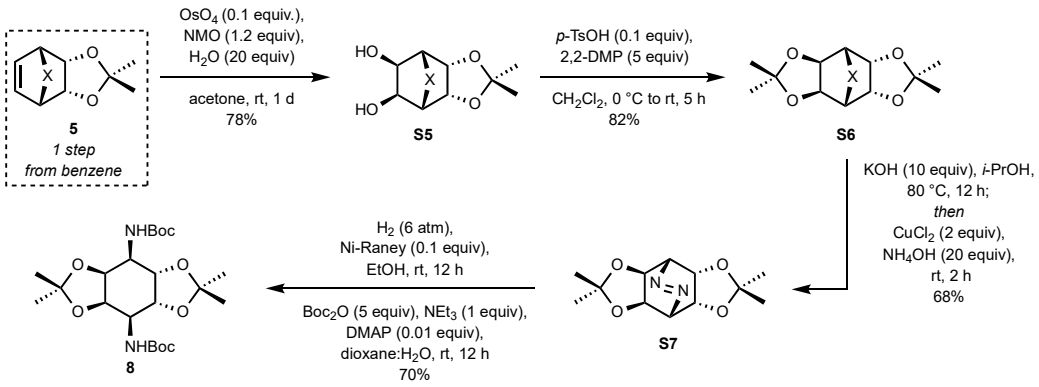
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 2H), 4.01 (d, *J* = 4.4 Hz, 2H), 3.77 (dp, *J* = 8.2, 4.1 Hz, 2H), 1.93 – 1.82 (m, 2H), 1.54 (s, 3H), 1.43 (s, 18H), 1.34 (s, 3H).

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

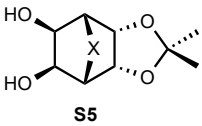
IR (ATR, neat, cm^{-1}) 3332 (b), 2981 (s), 2937 (s), 1681 (w), 1513 (w), 1453 (s), 1367 (m), 1244 (m), 1162 (w), 868 (m), 782 (s), 730 (m).

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**.



S5

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, $KMnO_4$).

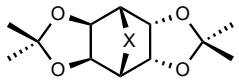
^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.60 – 4.50 (m, 4H), 4.36 (s, 2H), 3.05 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H).

^{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.



S6

***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, $KMnO_4$).

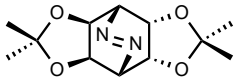
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (dq, J = 3.2, 1.6 Hz, 2H), 4.62 (dd, J = 2.9, 1.7 Hz, 2H), 4.48 (d, J = 1.6 Hz, 2H), 3.06 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H).

^{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, $KMnO_4$).

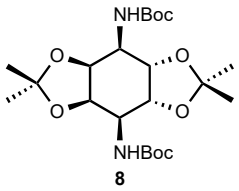
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 3.0, 1.6 Hz, 2H), 4.59 (d, *J* = 1.7 Hz, 2H), 3.91 (dt, *J* = 2.7, 1.5 Hz, 2H), 1.43 (s, 3H), 1.28 – 1.23 (m, 6H), 1.20 (s, 3H).

^{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.

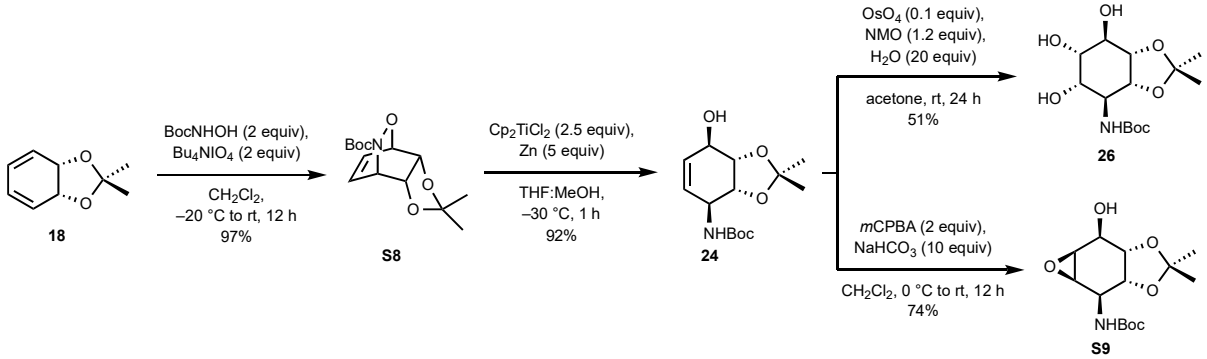
R_f 0.3 (*n*-hexanes:EtOAc = 2:1, $KMnO_4$).

^{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).

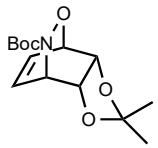
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.37, 109.43, 109.15, 79.88, 75.27, 74.84, 60.51, 51.70, 28.48, 27.44, 25.81, 25.02, 23.63.

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, $KMnO_4$).

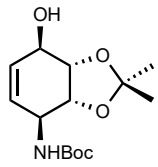
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 – 6.36 (m, 2H), 4.98 (ddd, J = 5.8, 4.0, 2.1 Hz, 1H), 4.87 (ddd, J = 5.8, 4.3, 1.8 Hz, 1H), 4.57 – 4.46 (m, 2H), 1.45 (s, 9H), 1.31 (s, 3H), 1.30 (s, 3H).

^{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, $KMnO_4$).

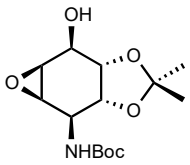
^{1}H NMR (400 MHz, MeOD) δ 5.77 (dt, J = 9.9, 2.6 Hz, 1H), 5.61 (dt, J = 9.8, 2.7 Hz, 1H), 4.13 (dq, J = 4.4, 2.4 Hz, 1H), 4.11 – 4.03 (m, 2H), 3.97 (d, J = 5.9 Hz, 1H), 1.45 (m, 12H), 1.34 (s, 3H).

^{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, $KMnO_4$).

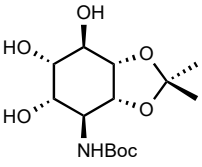
^{1}H NMR (400 MHz, MeOD) δ 4.12 – 4.04 (m, 3H), 3.93 (d, J = 7.1 Hz, 1H), 3.27 (d, J = 4.6 Hz, 1H), 3.24 (d, J = 4.6 Hz, 1H), 1.47 (s, 9H), 1.43 (s, 3H), 1.28 (s, 3H).

^{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.

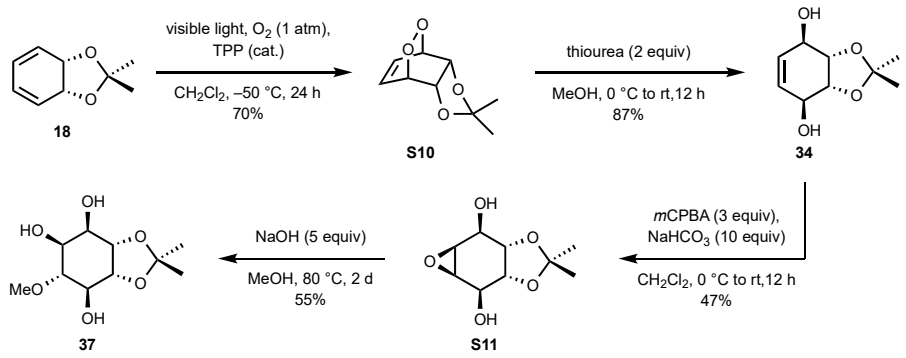
R_f 0.3 (CH_2Cl_2:MeOH = 9:1, $KMnO_4$).

^{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).

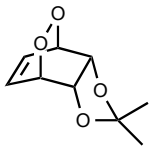
^{13}C NMR (101 MHz, MeOD) δ 158.0, 110.2, 80.4, 79.1, 77.6, 73.2, 72.8, 71.1, 54.5, 28.7, 28.6, 26.5.

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**.



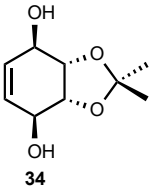
S10

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.

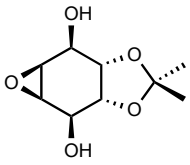
R_f 0.2 (*n*-hexanes:EtOAc = 1:2, $KMnO_4$).

^{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.

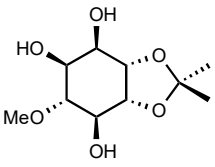
R_f 0.3 (*n*-hexanes:EtOAc = 1:2, $KMnO_4$).

^{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.

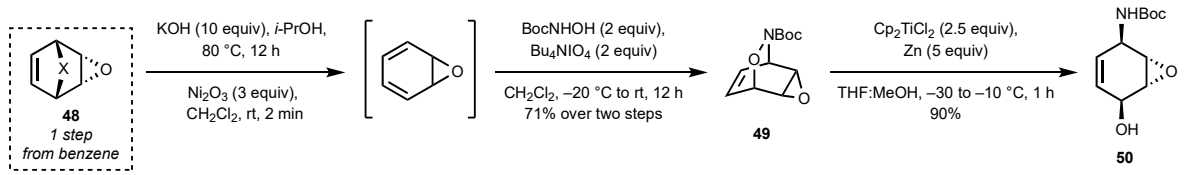
R_f 0.2 (CH_2Cl_2:MeOH = 9:1, $KMnO_4$).

^{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).

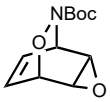
^{13}C NMR (101 MHz, MeOD) δ 110.3, 85.0, 80.0, 78.9, 76.3, 73.1, 71.3, 59.8, 28.2, 25.8.

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.

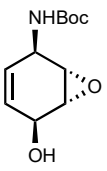


Scheme S6. Conversion of intermediate **48** to **50**.



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.[8] 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, $KMnO_4$).

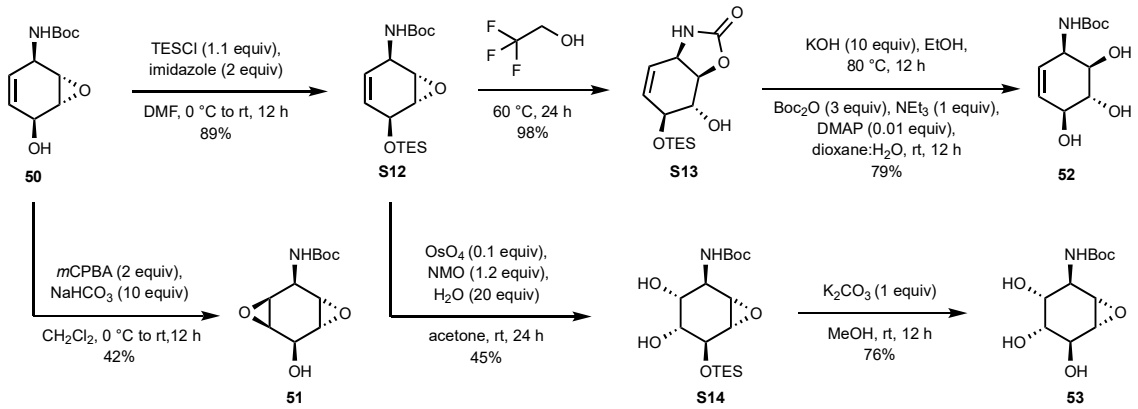
^{1}H NMR (400 MHz, MeOD) δ 5.72 (ddt, J = 10.2, 4.6, 1.6 Hz, 1H), 5.54 (ddd, J = 10.5, 4.7, 1.9 Hz, 1H), 4.36 – 4.26 (m, 2H), 3.20 (dq, J = 3.2, 1.6 Hz, 1H), 3.16 (dt, J = 3.1, 1.8 Hz, 1H), 1.46 (s, 9H).

^{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.

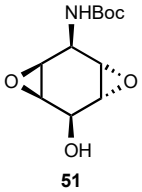
IR (ATR, neat, cm^{-1}): 3287 (b), 2974 (s), 2903 (s), 2564 (s), 2415 (s), 1681 (m), 1550 (s), 1423 (m), 1367 (m), 1252 (m), 1155 (w), 1043 (m), 1017 (m), 872 (m), 726 (m).

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**.



51

***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, $KMnO_4$).

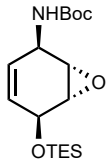
^{1}H NMR (400 MHz, MeOD) δ 4.18 (dd, *J* = 11.7, 3.2 Hz, 2H), 3.32 (d, *J* = 2.0 Hz, 1H), 3.27 (td, *J* = 3.6, 1.8 Hz, 1H), 3.00 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H), 2.97 – 2.91 (m, 1H), 1.48 (s, 9H).

^{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.

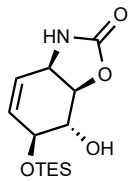
R_f 0.4 (*n*-hexanes:EtOAc = 9:1, UV, $KMnO_4$).

^{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, $KMnO_4$).

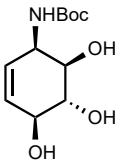
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.79 (dt, *J* = 10.1, 1.6 Hz, 1H), 5.64 (dt, *J* = 10.1, 2.7 Hz, 1H), 4.57 (t, *J* = 8.8 Hz, 1H), 4.46 (ddd, *J* = 8.9, 3.2, 1.6 Hz, 1H), 4.10 (dq, *J* = 8.4, 1.8 Hz, 1H), 3.72 (td, *J* = 8.7, 2.7 Hz, 1H), 2.73 (d, *J* = 2.7 Hz, 1H), 0.98 (t, *J* = 7.9 Hz,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

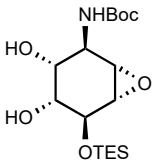
R_f 0.3 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

^{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, $KMnO_4$).

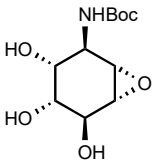
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (d, *J* = 6.5 Hz, 1H), 4.30 (dd, *J* = 3.9, 1.9 Hz, 1H), 4.08 (d, *J* = 21.1 Hz, 1H), 3.63 (d, *J* = 8.8 Hz, 2H), 3.31 (d, *J* = 3.3 Hz, 1H), 3.19 (t, *J* = 2.6 Hz, 1H), 2.56 (dd, *J* = 24.6, 9.9 Hz, 2H), 1.47 (s, 9H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.65 (q, *J* = 7.9 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, $KMnO_4$).

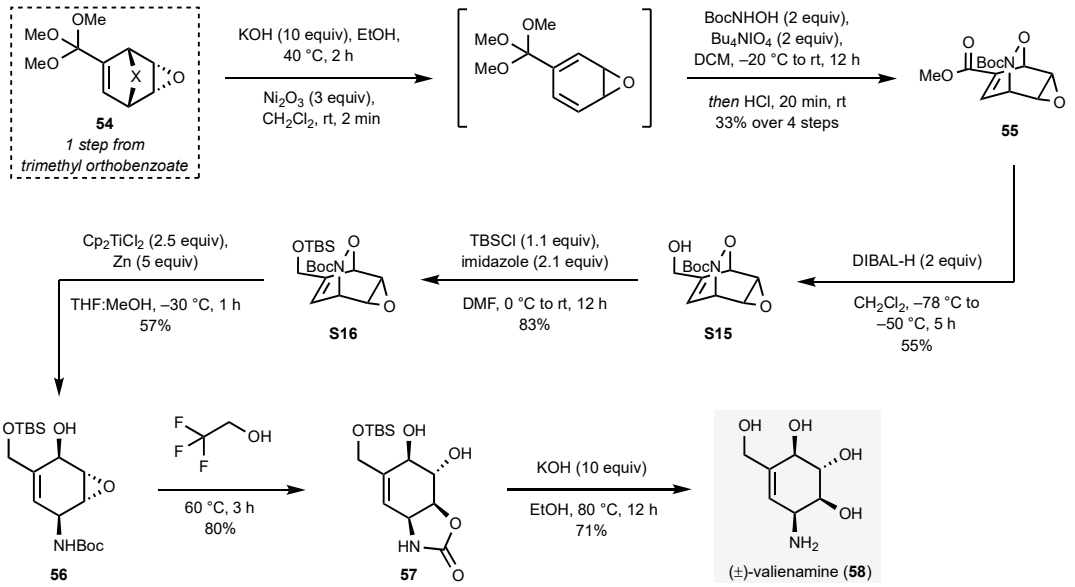
^{1}H NMR (400 MHz, MeOD) δ 4.25 (t, *J* = 3.0 Hz, 1H), 3.74 (dd, *J* = 8.5, 1.0 Hz, 1H), 3.66 – 3.57 (m, 1H), 3.39 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.30 – 3.25 (m, 1H), 3.11 (dd, *J* = 3.5, 0.8 Hz, 1H), 1.45 (s, 9H).

^{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.

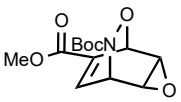
IR (ATR, neat, cm^{-1}) 3328 (b), 2978 (s), 2933 (s), 1684 (m), 1520 (m), 1364 (m), 1319 (s), 1293 (s), 1244 (m), 1162 (w), 1058 (m), 864 (s).

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**.



55

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.

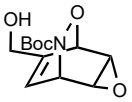
R_f 0.3 (*n*-hexanes:EtOAc = 2:1, UV, $KMnO_4$).

^{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.

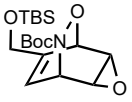
R_f 0.35 (*n*-hexanes:EtOAc = 1:2, UV, $KMnO_4$).

^{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.

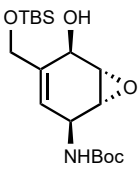
R_f 0.3 (*n*-hexanes:EtOAc = 4:1, UV, $KMnO_4$).

^{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.[8] 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.

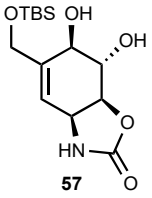
R_f 0.3 (hexanes:EtOAc = 2:1, UV, $KMnO_4$).

^{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.

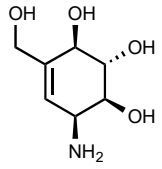
R_f 0.3 (*n*-hexanes:EtOAc = 1:4, UV, $KMnO_4$).

^{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.



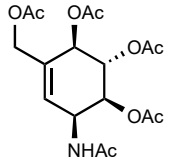
(±)-valienamine (**58**)

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.[9]

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.[10]

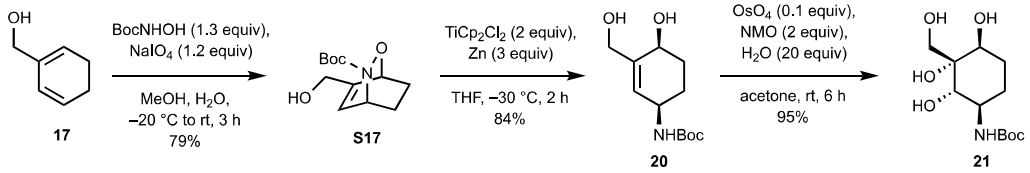


(±)-valienamine (**58•OAc**)

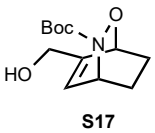
R_f 0.3 (hexanes:EtOAc = 1:4, UV, $KMnO_4$)

^{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.

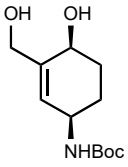
R_f 0.4 (*n*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{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.[8] 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.

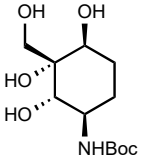
R_f 0.4 (*n*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{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.

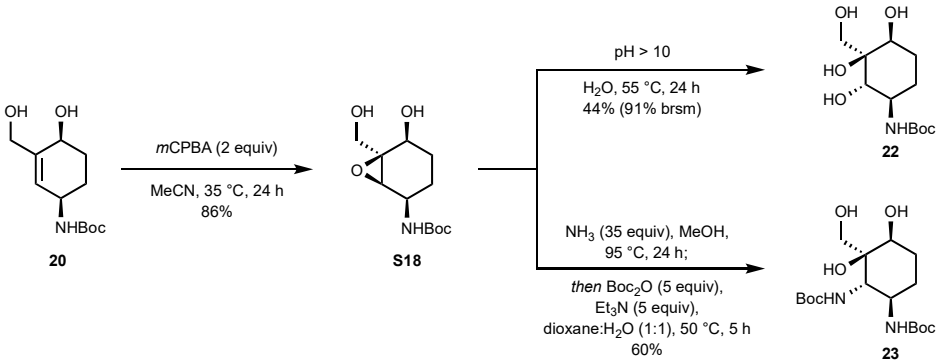
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{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).

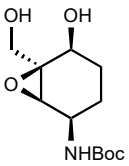
^{13}C NMR (126 MHz, MeOD) δ 158.9, 79.9, 76.2, 73.4, 71.8, 66.5, 52.9, 28.8, 28.1, 26.6.

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.

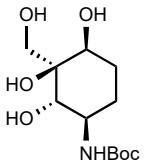
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{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.

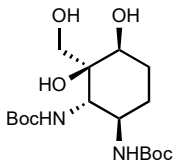
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{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.

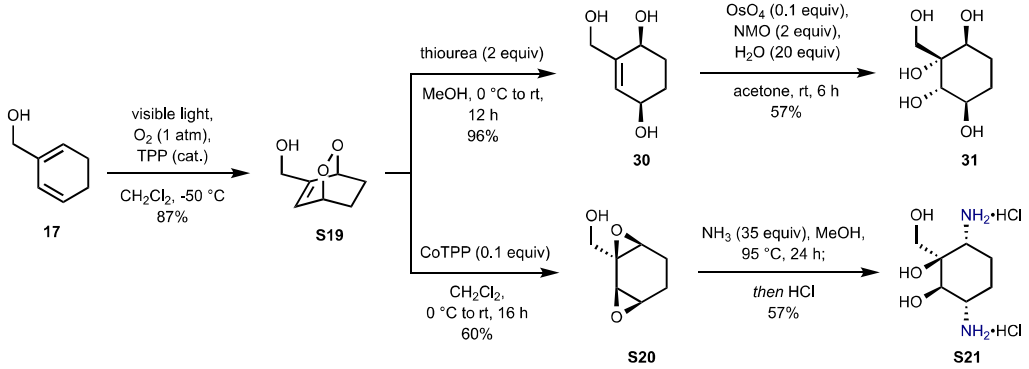
R_f 0.2 (*n*-hexane:EtOAc = 1:2, $KMnO_4$).

^{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).

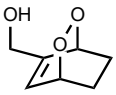
^{13}C NMR (126 MHz, MeOD) δ 159.6, 158.3, 80.5, 80.2, 77.1, 70.7, 64.9, 58.2, 52.2, 28.8, 27.6, 27.0.

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.*

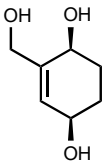
R_f 0.4 (*n*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{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.

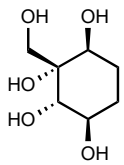
R_f 0.1 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{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.

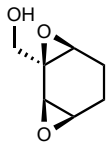
R_f 0.2 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{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.

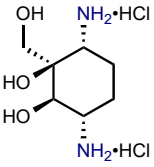
R_f 0.33 (*n*-hexane:EtOAc = 1:4, $KMnO_4$).

^{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

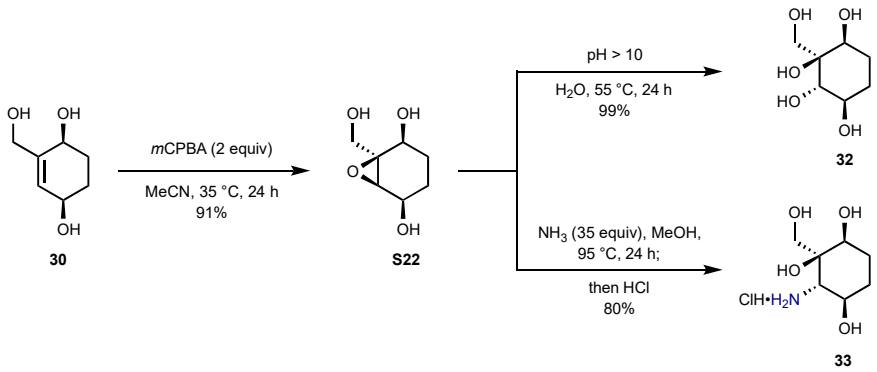
Diaminotriol 21. In a pressure tube, *bis*-epoxide **S20** (24 mg, 0.17 mmol, 1.0 eq.) was dissolved in ammonia (7 M in MeOH, 840 µL, 0.2 M, 35 eq.). The pressure tube was sealed and the solution was stirred at 95 °C for 24 h. ***WARNING: the reaction was placed behind a blast shield for safety measures.*** 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 µmol, 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).

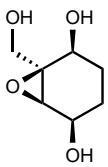
^{13}C NMR (126 MHz, MeOD) δ 74.1, 69.1, 65.3, 55.7, 52.8, 24.4, 24.3.

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.

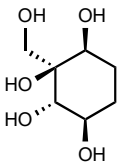
R_f 0.1 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{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.

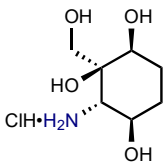
R_f 0.2 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{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

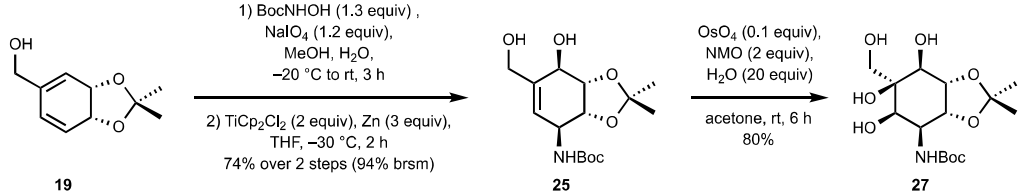
Aminotetraol 33. In a pressure tube, epoxide **S22** (30 mg, 0.19 mmol, 1.0 eq.) was dissolved in ammonia (7 M in MeOH, 940 µL, 0.2 M, 65.8 mmol, 35 eq.). The pressure tube was sealed, placed behind a blast shield, and the solution was stirred at 95 °C for 24 h. Thereafter, the mixture was cooled to 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.

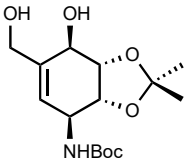
IR (ATR, neat, cm^{-1}) 3338 (b), 2944 (m), 1617 (w), 1506 (w), 1456 (w), 1364 (w), 1278 (w), 1227 (w), 1103 (m), 1052 (s), 972 (m), 846 (w).

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



19 **25** **27**

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%).

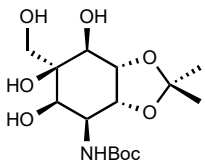
R_f 0.3 (CH_2Cl_2:EtOAc = 2:1 + 1% *i*-PrOH, $KMnO_4$).

^{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.

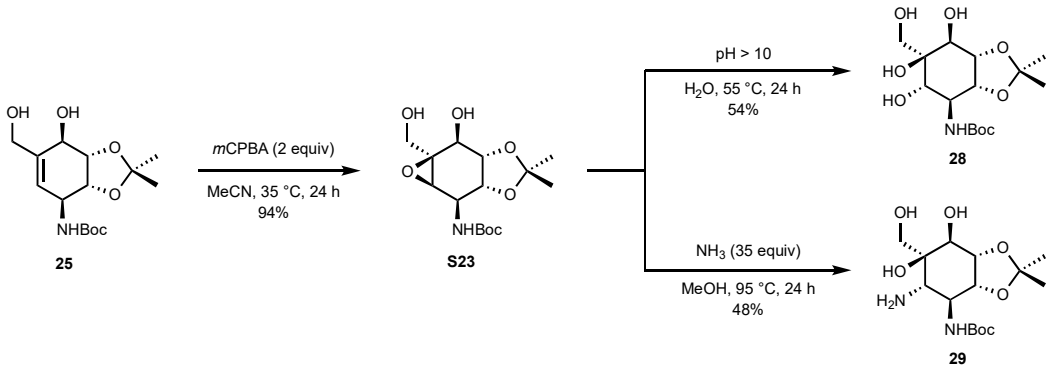
R_f 0.3 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$).

^{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).

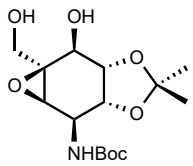
^{13}C NMR (126 MHz, MeOD) δ 158.0, 110.2, 80.5, 79.5, 77.9, 72.2, 67.1, 62.8, 53.5, 28.7, 28.5, 26.3.

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.

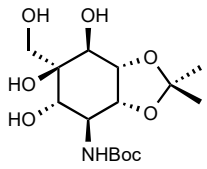
R_f 0.4 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{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.

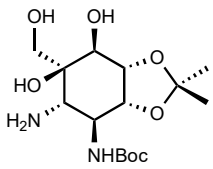
R_f 0.3 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$)

^{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.

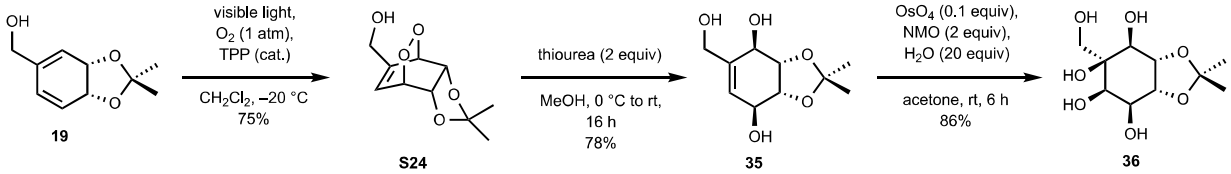
R_f 0.4 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{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.

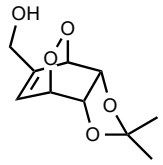
IR (ATR, neat, cm^{-1}) 3343 (b), 2982 (w), 2934 (w), 1689 (m), 1518 (w), 1368 (s), 1219 (m), 1164 (s), 1048 (m), 858 (w).

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



19 S24 35 36

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



S24

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.*

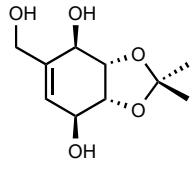
R_f 0.2 (*n*-hexane:EtOAc = 2:1, UV, $KMnO_4$)

^{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.

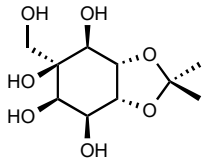
R_f 0.2 (CH_2Cl_2:EtOAc = 1:1, $KMnO_4$)

^{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.

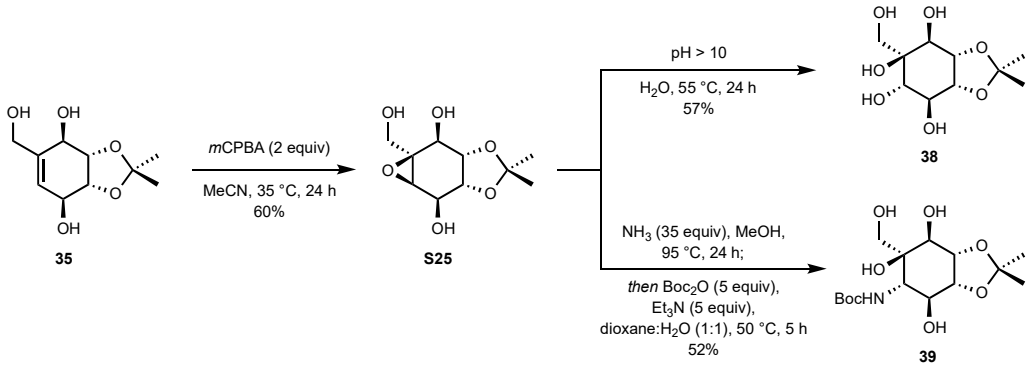
R_f 0.3 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$)

^{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).

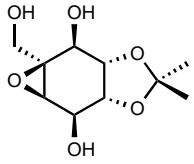
^{13}C NMR (126 MHz, MeOD) δ 110.2, 79.6, 79.0, 78.0, 72.5, 72.3, 68.8, 62.9, 28.4, 26.

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.

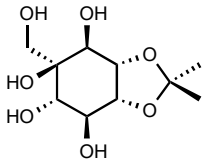
R_f 0.2 (CH_2Cl_2:MeOH = 10:1, $KMnO_4$).

^{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.

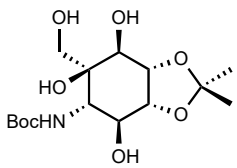
R_f 0.1 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$).

^{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, $KMnO_4$).

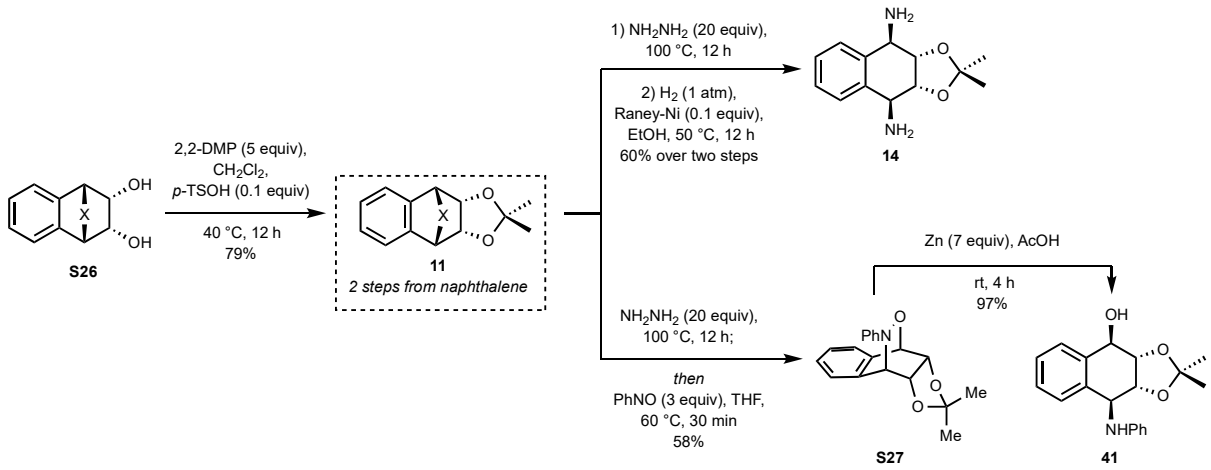
^{1}H NMR (500 MHz, MeOD) δ 4.30 (t, J = 6.8 Hz, 1H), 4.20 (t, J = 7.0 Hz, 1H), 3.78 (d, J = 6.7 Hz, 1H), 3.70 (m, 3H), 3.58 (d, J = 11.3 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 9H), 1.35 (s, 3H).

^{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).

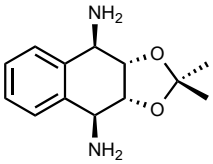
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 4H), 5.41 (s, 2H), 4.80 (s, 2H), 2.87 (s, 3H), 1.27 (s, 3H), 0.60 (s, 3H).

^{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 *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.

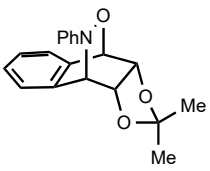
R_f 0.2 (*n*-hexane:EtOAc = 3:7, UV, $KMnO_4$).

^{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).

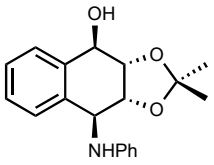
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.24 (m, 1H), 7.1 (m, 2H), 7.04 (dd, *J* = 7.37, 1.1 Hz, 1H), 6.85 (m,3H), 5.33 (d, *J* = 4.55 Hz, 1H), 4.96 (m, 2H), 4.85 (dd, *J* = 6.62, 4.6 Hz, 1H), 1.28 (s, 3H), 0.62 (s, 3H).

^{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).

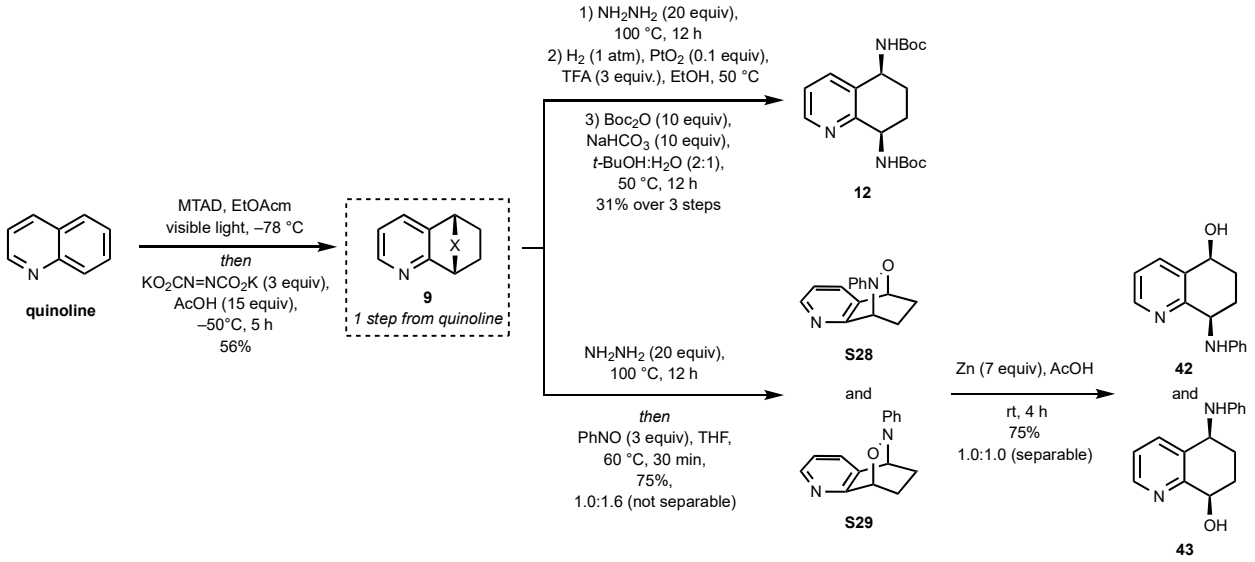
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 136.5, 135.1, 129.4, 128.2, 128.1, 127.1, 125.7, 118.9, 114.5, 110.3, 79.7, 72.0, 57.2, 26.9, 24.6.

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).

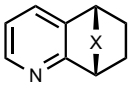
HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{22}NO_3^+$ $[M+H]^+$ calc.: 312.1600; found: 312.1599.

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).

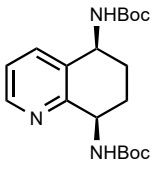
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.49 (dd, *J* = 5.2, 2.6 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.42 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.48 (t, *J* = 2.8 Hz, 1H), 5.28 (t, *J* = 2.8 Hz, 1H), 2.72 (s, 3H), 2.37 – 2.23 (m, 2H), 1.79 – 1.56 (m, 2H).

^{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.

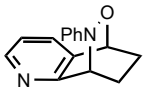
^{1}H NMR (500 MHz, MeOD) δ 8.41 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.71 (dd, *J* = 8.5, 5.3 Hz, 1H), 4.66 (t, *J* = 5.1 Hz, 1H), 2.17 – 1.80 (m, 4H), 1.48 (d, *J* = 5.2 Hz, 18H).

^{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.

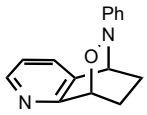
IR (ATR, neat, cm^{-1}): 3275 (m), 2970 (m), 2941 (m), 1700 (s), 1675 (s), 1525 (s), 1309 (m), 1249 (m), 1160 (s), 1086 (m), 967 (w), 653 (w).

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

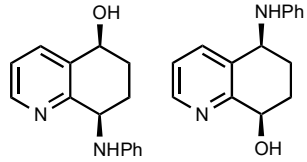
^{1}H NMR (500 MHz, MeOD) δ 8.39 (dd, *J* = 5.2, 1.5 Hz, 0.6H), 8.29 (dd, *J* = 5.1, 1.5 Hz, 0.4H), 7.82 (dd, *J* = 7.7, 1.6 Hz, 0.4H), 7.48 (dd, *J* = 7.5, 1.6 Hz, 0.6H), 7.34 (dd, *J* = 7.5, 5.2 Hz, 0.4H), 7.27 (dd, *J* = 7.5, 5.1 Hz, 0.6H), 7.07 (td, *J* = 8.7, 7.1 Hz, 1.8H), 6.92 – 6.78 (m, 2.6H), 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



42 **43**

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 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, $KMnO_4$).

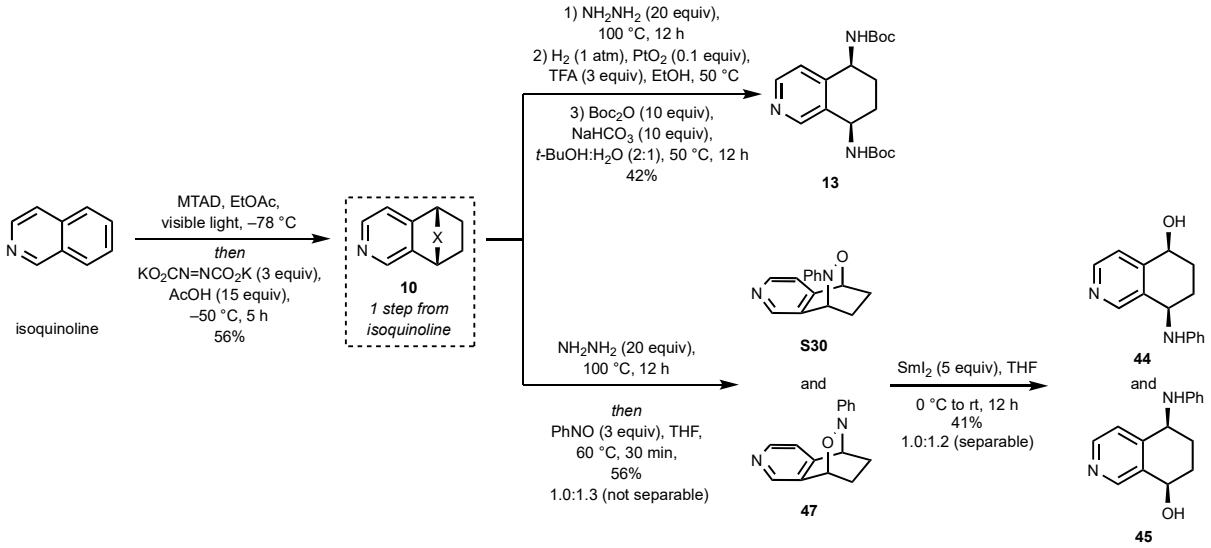
^{1}H NMR (500 MHz, MeOD) δ 8.45 – 8.43 (m, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.28 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.11 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.75 – 6.64 (m, 2H), 6.62 (tt, *J* = 7.4, 1.1 Hz, 1H), 4.73 (m, 1H), 4.67 – 4.57 (m, 1H), 2.13 – 1.95 (m, 4H).

^{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.

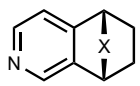
IR (ATR, neat, cm^{-1}): 3326 (m), 3219 (m), 2939 (m), 2890 (m), 2401 (m), 1597 (s), 1494 (s), 1435 (m), 964 (m), 767 (s), 721 (s).

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).

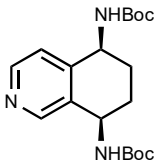
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.62 (d, J = 4.6 Hz, 1H), 8.59 (s, 1H), 7.44 (d, J = 4.8 Hz, 1H), 5.46 (s, 1H), 5.42 (s, 1H), 2.71 (s, 3H), 2.38 – 2.23 (m, 2H), 1.64 (d, J = 8.8 Hz, 2H).

^{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.[2] 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).

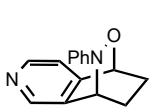
^{13}C NMR (126 MHz, DMSO-d_6)* δ 155.8, 155.8, 155.7, 155.5, 155.5, 155.2, 155.1, 149.5, 149.3, 148.9, 148.8, 147.9, 147.8, 147.7, 147.5, 147.3, 147.1, 134.3, 133.7, 121.6, 121.6, 121.3, 79.24, 79.0, 78.7, 78.2, 78.1, 78.1, 47.9, 47.8, 46.9, 46.8, 46.6, 46.5, 45.1, 45.0, 28.2, 26.6, 25.4.

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).

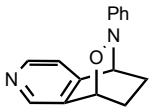
HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{30}N_3O_4^+$ $[M+H]^+$ calc.: 364.2236; found: 364.2234.

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

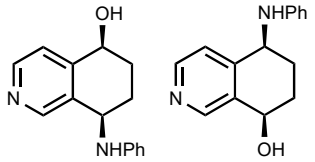
R_f 0.3 (*n*-hexane:EtOAc = 1:9, UV).

^{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

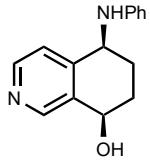
R_f 0.3 (*n*-hexane:EtOAc = 3:7, UV, $KMnO_4$).

^{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).

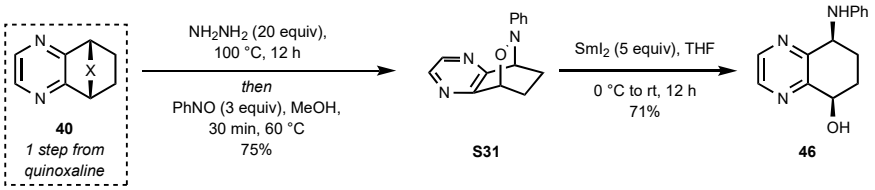
HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{17}N_2O^+$ $[M+H]^+$ calc.: 241.1341; found: 241.1345.



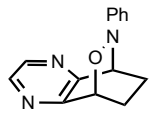
45

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).

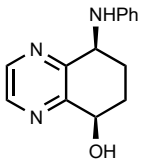
^{1}H NMR (500 MHz, MeOD) δ 8.43 (dd, *J* = 41.5, 2.9 Hz, 2H), 7.08 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.90 – 6.75 (m, 3H), 5.45 – 5.35 (m, 1H), 5.11 (t, *J* = 3.1 Hz, 1H), 2.66 – 2.42 (m, 2H), 1.94 – 1.76 (m, 1H), 1.68 – 1.44 (m, 1H).

^{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).

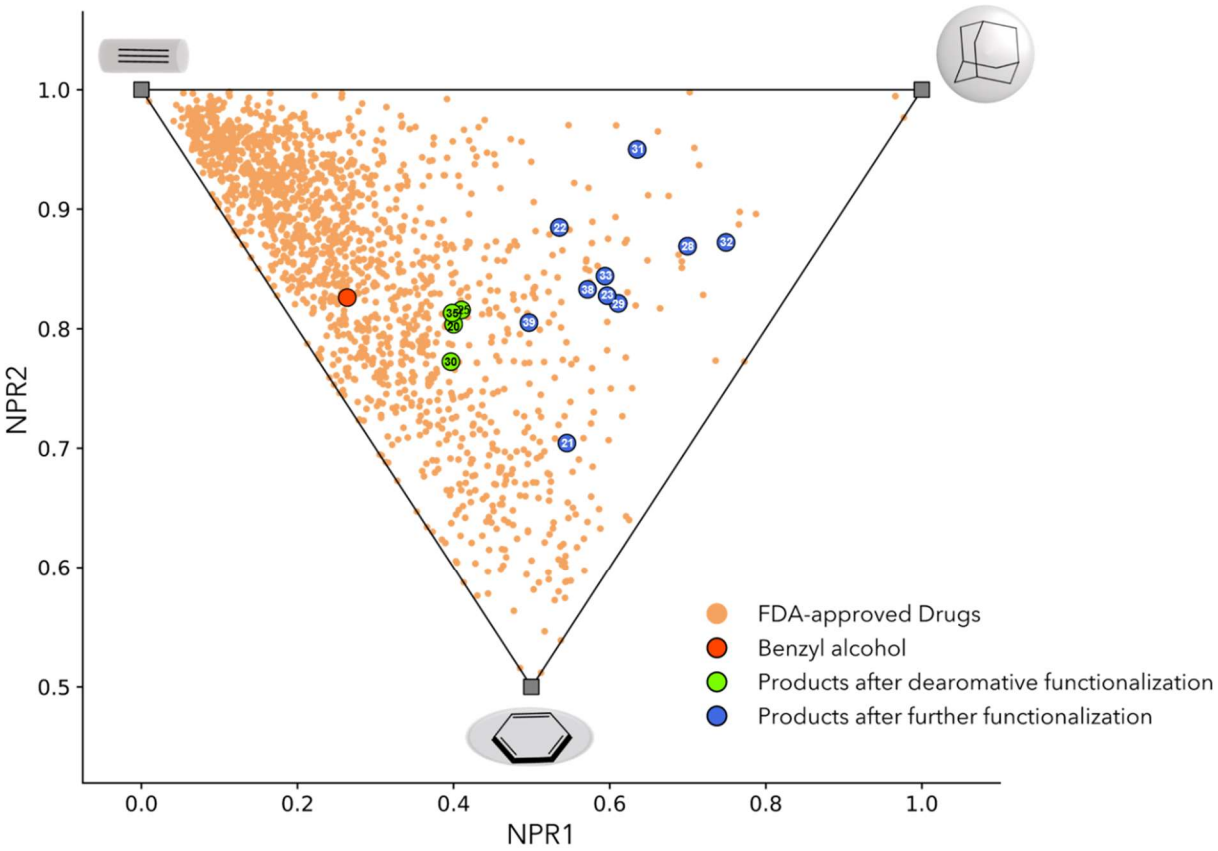
^{13}C NMR (151 MHz, MeOD) δ 155.2, 154.4, 149.4, 144.8, 144.7, 130.1, 118.5, 114.7, 69.4, 54.6, 28.8, 25.4.

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

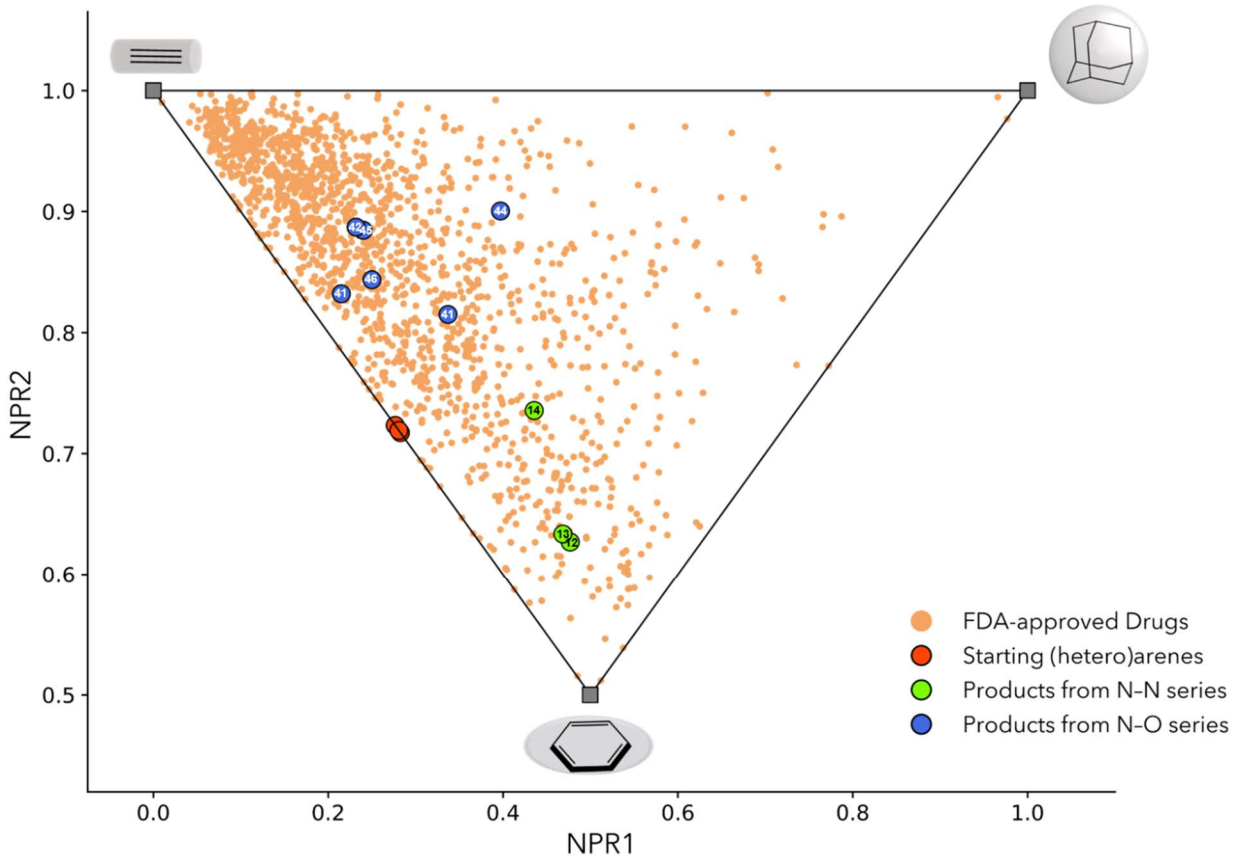
HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{16}N_3O^+$ $[M+H]^+$ calc.: 242.1293; found: 242.1293.

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.



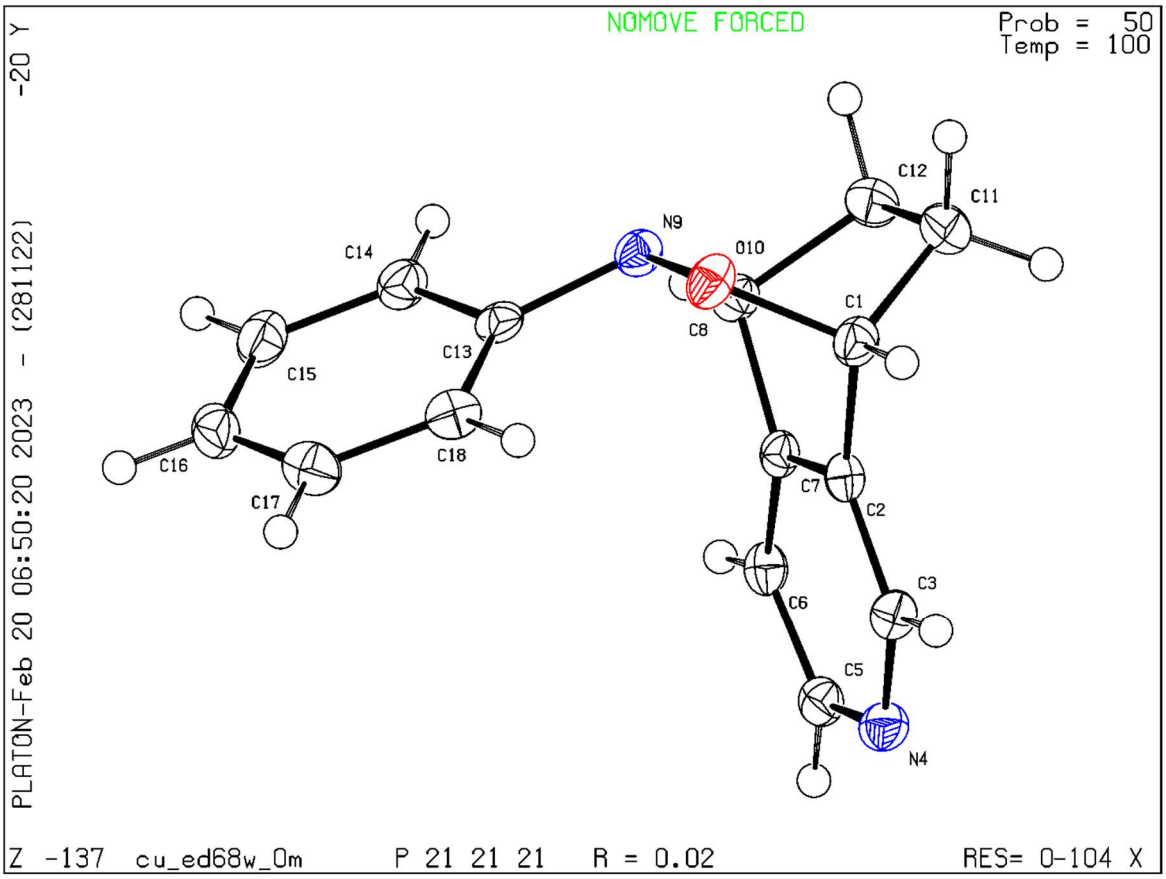
Picture S3. PMI analysis graph of heteroarenes and products following functionalization.

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	$-11 \leq h \leq 11$, $-11 \leq k \leq 11$, $-15 \leq l \leq 15$
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)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C12
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C1
C8
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C5
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1.2 Introducing covalent warheads on sp^2-sp^3 fragments by innate C-H functionalization

1.2.1 Manuscript

ARTICLE

Introducing covalent warheads on sp^2-sp^3 fragments by innate C-H functionalization

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Sp^2-sp^3 fragments play a vital role in fragment-based drug design (FBDD). Strategies to chemically modify them and efficiently access libraries of these compounds have been goals of the highest priority in the last decades. In this work, a series of sp^2-sp^3 fragments is synthesized and validated for that purpose, based on their measured physical-chemical properties. Selective C-H cyanation and allylation of these fragments is demonstrated by simple heating in presence of an appropriate hydrogen-atom transfer reagent and a radical acceptor. These conditions enable a streamlined access to covalent fragments in a single step, by driect introduction of the desired covalent binder. Preliminary results on vinylation, as well as late-stage functionalization of a drug analogue are disclosed.

Introduction

In the crowded space of drug discovery, R&D has more than ever become a numbers' game. High attrition rates at all stages of the process (hit finding, hit-to-lead, and lead optimization) led to the widespread adoption of high-throughput screening (HTS) to fill the drug discovery pipeline with as many compounds as possible at the hit finding stage. In recent years, a more modular approach, fragment-based drug design (FBDD) was developed: rather than testing millions of lead-like compounds looking for high activity, testing of thousands of smaller molecules looking for hits was identified as more efficient. Once one or several hits have been found, fragment growing, linking, or fusing are all valid strategies to get to a lead compound. The quality and drug-likeness of the initial fragment is of paramount importance to avoid lengthy re-optimization when building onto that hit to generate a viable lead. Such fragments should usually follow the 'Rule of three', having a molecular weight ≤300 Da, ≤3 hydrogen bond donors (HBD), ≤3 hydrogen bond acceptors (HBA) and a LogP ≤3.

While FBDD allows for screening of a rather limited set of ligands compared to HTS, the low intrinsic binding affinity of these small fragments is difficult to quantify. To address that concern, medicinal chemists have drawn inspiration from targeted covalent inhibitors. Such inhibitors contain a warhead that engages in a covalent bond (in a reversible or irreversible manner), giving a much longer residence time than their non-covalent counterpart. Translating this feature to a FBDD-campaign eases the quantification of binding, and recent studies showed there is little promiscuity with moderately electrophilic warheads.

Commercial fragment libraries often over-represent sp^2-rich fragments as they are the most synthetically accessible. At SpiroChem, we have developed a strong interest on bicyclo- and spiroalkane-containing fragments, as their rigid scaffold provides fixed conformations and well-defined exit-vectors, angles, and distances. Their use in isosteric replacement has been demonstrated in multiple reports, but their high sp^3-content sometimes leads to undesirable ADME (absorption, distribution, metabolism, excretion) properties according to customers' feedback. We reasoned that the issue could potentially lie in the high lipophilicity of these sp^3-rich fragments and thus be counterbalanced by linking them to a basic heteroaromatic core, creating heterocyclic sp^2-sp^3 fragments hybrids.

With these considerations in mind, we embarked on a large-scale campaign to generate high-quality covalent fragments libraries, with a broad range of warheads to cover all our customers' needs. Using traditional strategies, we could generate libraries of several hundreds of sp^2-sp^3 hybrid covalent fragments, but a limitation of such strategies was identified. There is often no overlap between fragments and covalent-fragments campaigns, since most warheads usually require the presence of a predefined functional group in order to be installed (Scheme 1a). Operationally, this translates into a divergent workflow from the starting materials, which limits its efficiency.

As an alternative, innate C-H late-stage functionalization has emerged as a powerful tool to create exit vectors which were not pre-installed in the parent molecule. We envisioned to use this strategy to introduce the desired warheads on our sp^2-sp^3 hybrid fragments (Scheme 1b), without the need of a specific functional group already present. If effective, this approach

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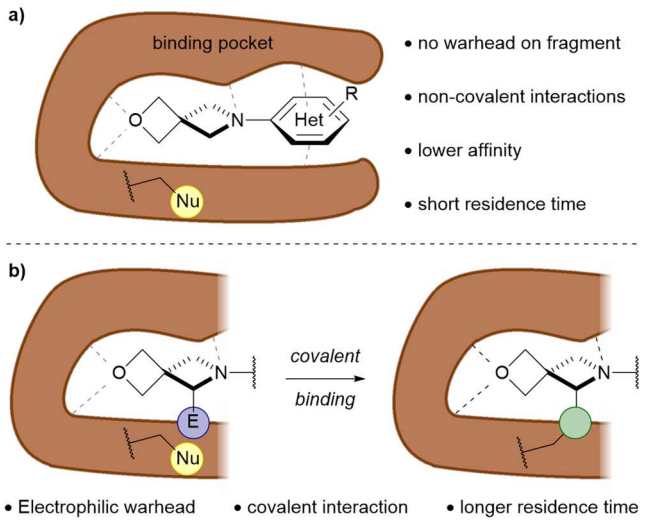
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme 1. a) Divergent workflow with pre-installed functional group. b) Streamlined workflow with innate C-H functionalization.

could potentially be applied to the general fragment library, streamlining the general workflow.

In the absence of directing groups, the selectivity of such C-H functionalization reactions is solely driven by electronic and steric effects. Understanding of these effects can be a precious guide for the application of conditions to selectively synthesize one or two products from a starting material containing a multitude of C-H bonds.

Herein, we show how we generated a high-quality fragment library and converted it to a covalent fragment library in one step by using innate C-H functionalization.

Results and discussion

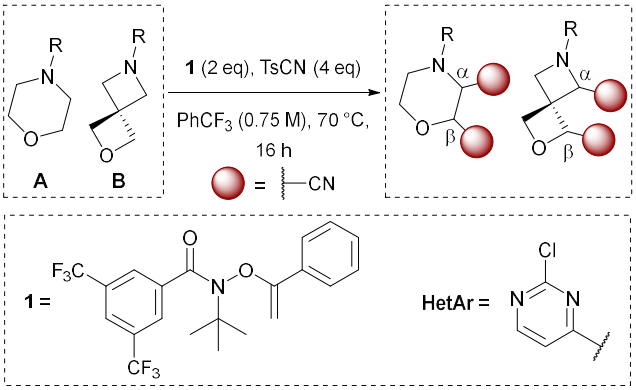
Preliminary results and optimization

Starting from N-protected or functionalized morpholine and its spirocyclic counterpart as models, we performed a literature survey on late-stage functionalization methods and quicky identified C-H cyanation as an appropriate transformation for our goals. Indeed, several protease inhibitors have been developed using this warhead, which acts in a reversible fashion. We also wanted to benchmark a less reversible warhead, and substituted acrylamides were considered viable. Allyl sulfones have been used extensively as very reactive acceptors for radical reactions, but to the best of our knowledge, never with the purpose of generating a covalent warhead.

Substrates with different protecting groups attached to the nitrogen of morpholine and 2-oxa-6-azaspiro[3.3]heptane ("spiromorpholine") were submitted to the conditions for HAT-cyanation reported by Alexanian (Table 1), using hydroxamic ester derivative **1** as the radical generator and tosyl cyanide as the radical trap.[12] When derivatized with benzoyl- (Bz-), carboxybenzyl- (Cbz-), and trifluoroacetyl- (TFA-), the morpholine core proved to be unreactive, with full recovery of starting material (entries A). In stark contrast, selective derivatization α to the nitrogen was observed in the cases of *tert*-butyloxycarbonyl- (Boc-). As expected, the corresponding spiroheterocyclic analogue proved to be a more activated substrate towards this type of reactivity, with cyanated products isolated in all cases (entries B).

Table 1

R =	*Bz*	*Cbz*	*Boc*	*TFA*	*HetAr*
A	n.r.	n.r.	40% α	n.r.	35% α
B	44% (1:1 α:β)	8% α	40% α	34% β	63% α



n.r. = no reaction

Interestingly, different selectivity was observed depending on the functional group present on the nitrogen. Exclusive α-functionalization products were isolated in the cases of Cbz-, and Boc-; a 1:1 α:β mixture was afforded in the case of Bz-; exclusive β-functionalization was observed with TFA-. When we directly tested an sp^2-sp^3 hybrid fragment bearing the 4-(2-chloropyrimidinyl)- group (HetAr), productive and selective functionalization at the α-carbon was observed. This was remarkable, as it completely suited our goal of direct functionalization of such fragments. A brief screening of reaction conditions on that substrate (**2**) was then performed to see whether they could be further optimized for this specific class of compounds (Table 2). The standard reported conditions afforded full conversion (entry Stand.), with 63% mono-derivatized product **2a** and 36% double-derivatized products, as a complex mixture of regio- and diastereo-isomers.

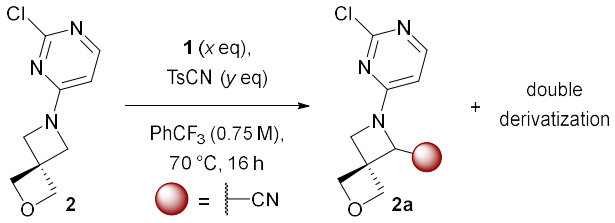


Table 2

Entry	*x*	*y*	*T (°C)*	*Yield (**2**:**2a**:**double**) %*
Stand.	2	4	70	0:63:36
1	1.5	4	70	10:64:10
2	1.5	2	70	20:68:10
3[a]	2	4	70	30:52:0

a = non-distilled trifluorotoluene was used.

Lowering the amount of HAT reagent **1** (entry 1) did not affect the yield of mono-derivatization and showed less double-derivatization. Although, this was at the expenses of conversion, with some recovered starting material from the product mixture. A lower loading of radical trap (entry 2) did not show significant differences in the outcome. The robustness of the reaction was tested by using an old bottle of non-distilled trifluorotoluene (entry 3), and lower conversion was observed compared to the reaction with freshly distilled solvent. Rising the temperature of the reaction to 90 °C (entry 4) had a deleterious effect on the isolated yields of both mono- and double-derivatization products.

After securing conditions for cyanation, we then moved onto the optimization of the analogous allylation reaction using reagent **3** as a radical trap. Testing of the transformation on the same substrate used for cyanation (**2**) showed that a very laborious purification process was required for separating the remaining starting material from the radical trap, hampering the reaction outcome analysis. A simple change of the heteroaromatic ring made the process more expedite, therefore substrate **4** was eventually chosen for the optimization (Table 3). The general profile of the reaction was noticed to be different: the use of the same conditions applied for cyanation (entry 1) afforded only 35% of mono-derivatized product **4b**, and 52% of double-derivatized products (as a mixture of diastereomers). As previously, lowering the loading of radical trap proved to not influence the outcome significantly (entry 2). Instead, lowering the loading of HAT reagent (entry 3) to 1.5 eq favored the desired outcome, with 59% of mono-derivatized product, and the rest of the mass being recovered starting material and double derivatization. When the amount of **1** was further decreased to 1.1 eq, the lower conversion was counterbalanced by less double derivatization, not significantly affecting the yield of **4b** overall. We decided to use entry 3 conditions for the substrate scope in order to maximize conversion.

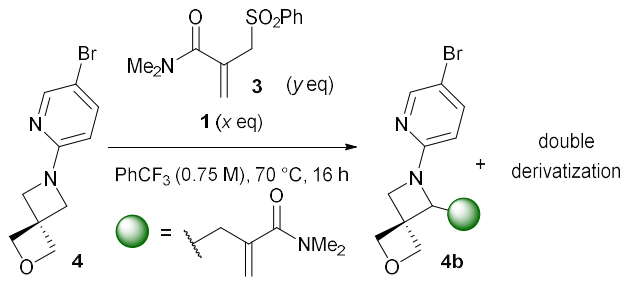


Table 3

Entry	*x*	*y*	*T (°C)*	*Yield (**4**:**4b**:**double**) %*
1	2	4	70	0:35:52
2	2	2	70	0:37:44
3	1.5	2	70	10:59:26
4	1.1	2	70	25:57:15

The lower selectivity towards mono-derivatization compared to the cyanation reaction can be explained by the minimal change of hydricity of the α-protons upon allylation, in contrast to the significant one upon cyanation. In this latter case, the installed nitrile group partially deactivates the mono-derivatized product towards a second hydrogen-atom abstraction due to its electron-withdrawing character. Such effect can also be taken into account to explain why allylation forms double-derivatization product only on the azetidine moiety, whereas cyanation unselectively goes for both the azetidine and oxetane moieties after first derivatization.

Synthesis of sp2-sp3 fragments and their physical-chemical properties

Lead-likeness of fragments is of paramount importance to anticipate the needs in the hit-to-lead and lead-optimization stages. We generated a small library of sp^2-sp^3 fragments by S_NAr reactions, which are typically high-yielding and give interesting products with well-balanced properties. The alicyclic part provides some lipophilicity, while the heteroaromatic provides mild basicity, aqueous solubility and opportunities for further derivatization using standard cross-coupling reactions. We selected 14 of these fragments for an early assessment of key parameters such as molecular weight, pKa, logP and aqueous solubility. We measured the physical-chemical properties using an automatic UV-VIS and pH-metric titrator Sirius T3 (Pion, UK, Table 4, see ESI for experimental details) and confirmed that the values were in line with the Rule of Three, with aqueous solubilities usually in the 1-100 mM range. Pyridine- and pyrazine-containing derivatives were significantly more soluble than pyridazine- and pyrimidine-based products. Although

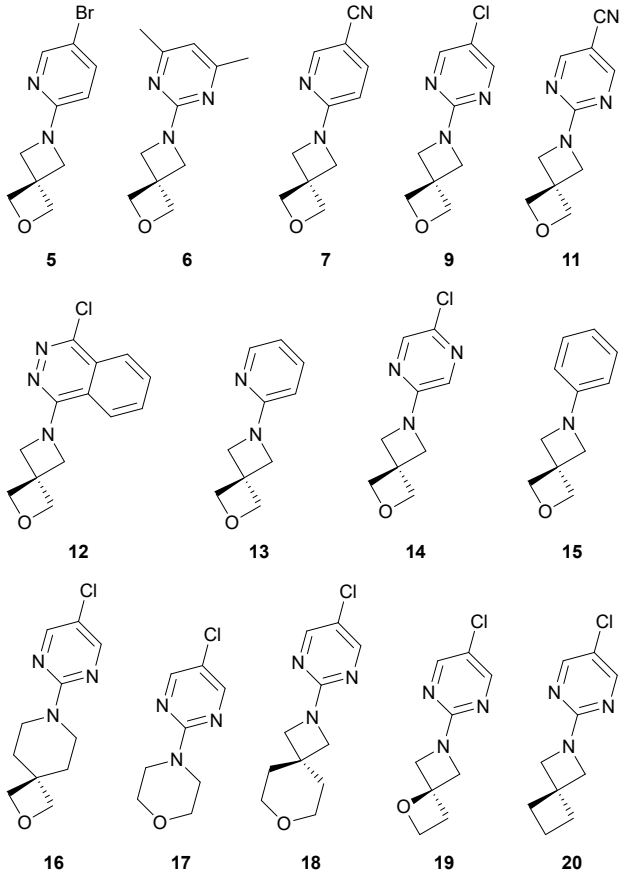


Table 4

Compound	*HetAr*	*MW*	*pKa*	*LogP*	*Solubility (mM)*
5	Pyridine	255	4.18	1.86	35.0
6	Pyrimidine	205	4.50	0.9	0.032
7	Pyridine	201	2.69	0.42	50.0
9	Pyrimidine	212	2.82	1.31	2.20
11	Pyrimidine	202	2.32	0.85	0.088
12	Pyridazine	262	4.62	1.54	10.0
13	Pyridine	176	6.12	1.02	104
14	Pyrazine	212	2.01	0.8	100
15	Phenyl	175	2.95	1.60	49.0
16	Pyrimidine	240	2.50	2.54	0.802
17	Pyrimidine	200	3.15	1.08	2.00
18	Pyrimidine	240	2.5	2.39	0.315
19	Pyrimidine	212	3.30	1.45	0.504
20	Pyrimidine	210	3.30	n.d.	0.505

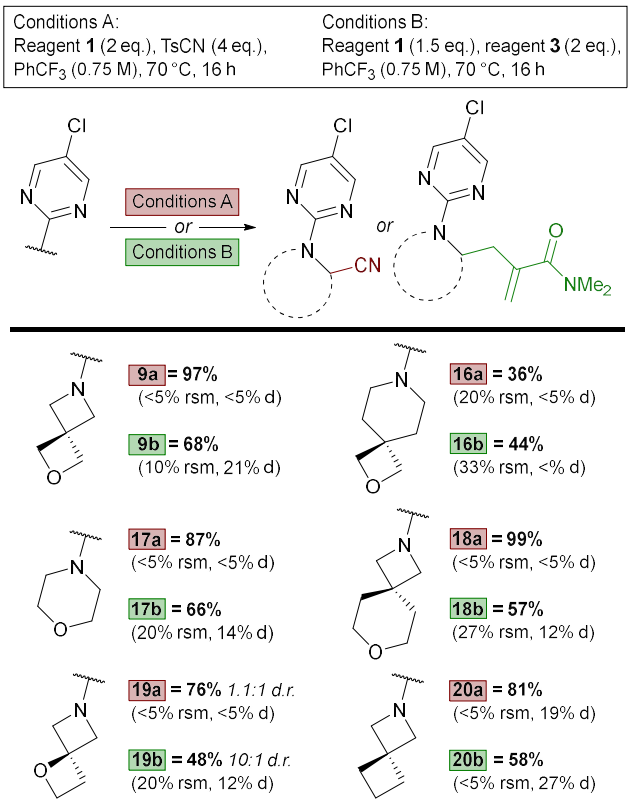
there was no clear correlation pattern between structure and LogP or pKa, it is evident how with simple changes in the alkyl and aryl moieties the physical-chemical properties can be significantly influenced. This can be used for a tuning of such properties according to the desired outcome.

Substrate scope

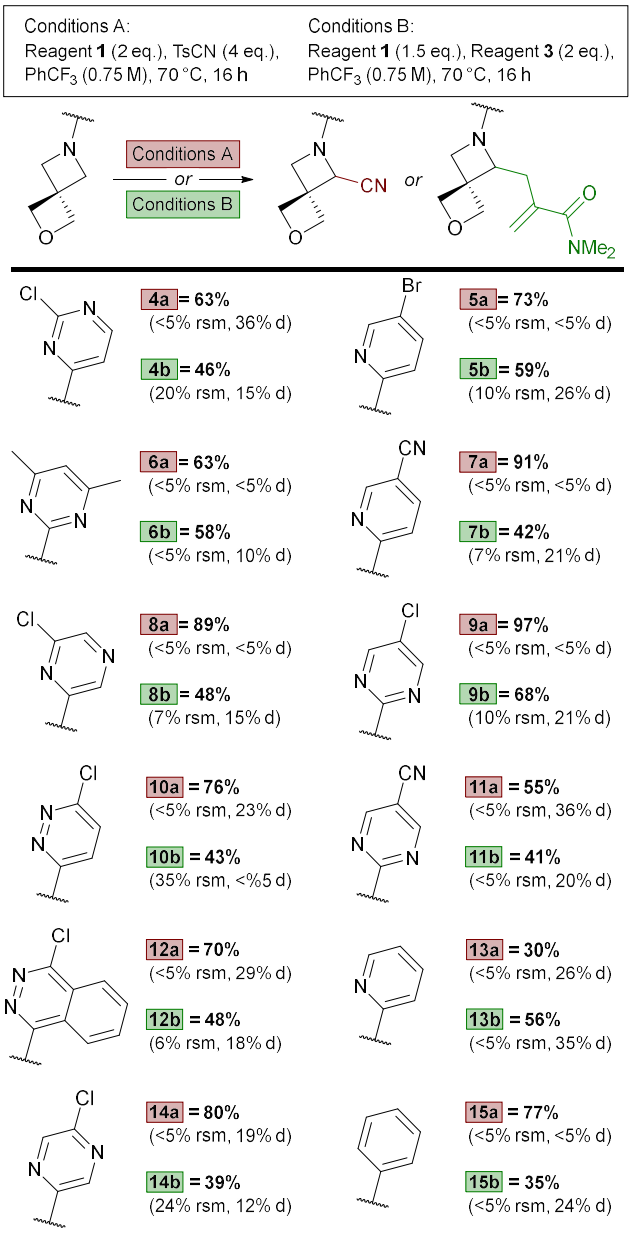
With satisfying conditions in hand for both cyanation and allylation, we evaluated the reaction scope with respect to the alkyl heterocyclic moiety (Scheme 2). Not surprisingly, allylation was in general less efficient than cyanation because of the factors presented before (significant amounts of recovered starting material and double derivatized product). α-Functionalization of azetidine could be successfully achieved in the presence of spirocycles including an oxetane (**9** and **19**), tetrahydropyrane (**19**), and cyclobutane (**20**). In the latter case two diastereomers were obtained in a 1.1:1 and 10:1 ratio for cyanation and allylation, respectively. Interestingly, selective functionalization next to the nitrogen is observed even when it is part of a six-membered ring, and an oxetane is present (**16**). Such behavior might suggest some important implications of the (hetero)aromatic ring on the selectivity of the reaction in comparison to other groups [ref.]. Lastly, functionalization of morpholine derivative **17** could be performed successfully.

Next, we evaluated the reaction on a variety of (hetero)aromatics (Scheme 3), keeping a spiromorpholine aliphatic part. Halo-diazine isomers showed good performances with pyrimidine (**4** and **9**), pyrazine (**8** and **14**), and pyridazine

Scheme 3. Scope of the alkyl moiety.

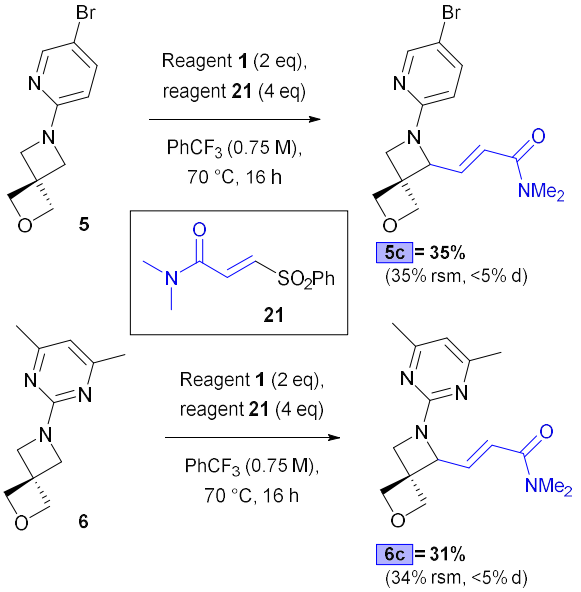


Scheme 2. Scope of the aromatic moiety.



(**10**) derivatives tolerated. Phthalazine derivative **12** also worked for both transformations. More electron-deficient substrates containing an aromatic nitrile (**7** and **11**) afforded the desired product in moderate to excellent yields. However, more electron-poor analogues containing a nitro group did not undergo productive transformation (not shown). Heteroaromatic bromides were also tolerated (**5**), a key factor

Scheme 4. Preliminary vinylation results.



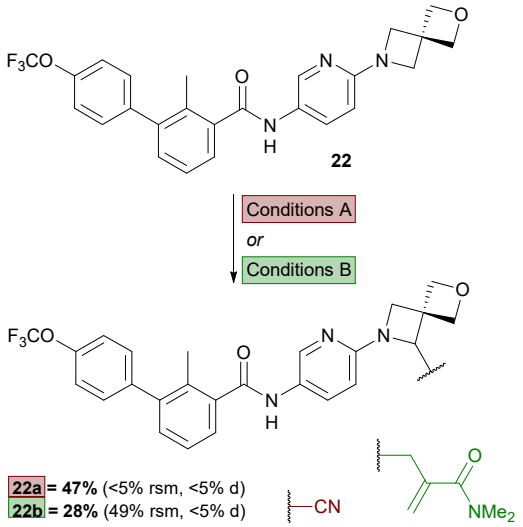
when thinking about potential further derivatizations. Benzylic positions remained untouched (**6**), showing a selective preference for the azetidine derivatization. The transformation could be performed also on simple non-substituted (hetero)aromatics as shown in the case of pyridyl (**13**) and phenyl (**15**).

Finally, as a preliminary study (Scheme 4), we also performed vinylation reactions using a vinyl sulfone radical acceptor (**21**) on two fragments (**5** and **6**), affording the corresponding products with the installed warhead. The conversions were only moderate, and the yields far from optimial, but these promising hits are currently under investigation and results will be reported in due course.

Drug analog synthesis

To go beyond fragments and demonstrate the application of this method to late-stage functionalization of drug compounds, cyanation and allylation conditions were performed on spiromorpholine analogue of sonidegib (**22**), a drug prescribed for treatment of locally advanced basal-cell carcinoma (Scheme 5). The compound was synthesized starting from spiromorpholine hemioxalate through a three-step sequence involving S_NAr, hydrogenation, and coupling with the carboxylic acid moiety. Pleasingly, the treatment of this compound with the standard conditions presented before gave direct access to the expected C-H functionalized compounds in acceptable yields. This showcases the potential utility of this transformation to evolve hits, leads or drugs

Scheme 5. Sonidegib analogue late-stage functionalization.



into covalent inhibitors without the need for already present functional group handles or *de-novo* resynthesis.

Conclusions

Spirocyclic amines were easily coupled to heteroaromatics to give sp^2-sp^3 hybrid fragments with well-balanced physical chemical properties suitable with fragment-based drug design. Under thermal conditions in the presence of a hydrogen-atom-transfer reagent, these fragments readily reacted with radical acceptors to give covalent fragments with a cyano- or an acrylamide warhead. Application of this strategy to late-stage functionalization of a sonidegib analogue was demonstrated, and preliminary results on vinylation were disclosed. Further investigations on late-stage installation of warheads on medicinal chemistry-relevant molecules are ongoing and will be reported in due course.

Experimental

See SI for experimental.

Author Contributions

M. M. performed the synthetic experimental work, analyzed the data, and co-wrote the manuscript. C. G. performed the physical-chemical properties measurements and collected the analytical data. T. C. F. provided guidance for fragments selection. Q. L. designed and directed the project, analyzed the data, and co-wrote the manuscript.

Conflicts of interest

The authors are employees and CEO (T. C. F.) of SpiroChem AG, a Innovative Contract Research Organization (iCRO) commercializing building blocks, fragments and virtual libraries.

Acknowledgements

The acknowledgements come at the end of an article after the conclusions and before the notes and references.

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
§
§§
etc.

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1.2.2 Experimental section

Introducing covalent warheads on sp^2-sp^3 fragments by innate C-H functionalization

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Supporting Information

General Methods

All reactions were carried out in round-bottom flasks or microwave tubes under a positive flow of nitrogen, unless otherwise stated. Commercially available reagents and solvents were used without further purification, except trifluorotoluene, which was distilled over P_2O_5 before use. They were supplied by Astatech, Merck, Combi-Blocks or SpiroChem and were of technical grade. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin-layer chromatography using Biotage KP-NH TLC Glass plates and visualized by fluorescence under UV light or by development with an aqueous $KMnO_4$ solution with gentle heating. Medium-Pressure Liquid Chromatography (MPLC) purifications of crude residues were performed on a Biotage Isolera IV System with Agela technologies pre-packed silica gel. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried under high vacuum or with a lyophilizer after reverse-phase. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a Bruker Ultrashield at 300 or 400 MHz (^{1}H), 75 or 101 MHz (^{13}C), and 376 MHz (^{19}F) at 298K in the indicated deuterated solvent, unless otherwise stated. Chemical shifts are reported in ppm with the solvent resonance as the internal standard relative to, CDCl3 (δ = 7.26 for ^{1}H, δ = 77.16 for ^{13}C) and MeOD-d_4 (δ = 3.31 for ^{1}H, δ = 49.00 for ^{13}C). All ^{13}C spectra were measured with complete proton decoupling. Data are reported as follows : s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, qt = quartet of triplets, qd = quartet of doublets, dd = doublet of doublets, ddd = doublet of doublets of doublets, ddt = doublet of doublet of triplets, dtt = doublet of triplet of triplet, dt = doublet of triplets, tdt = triplet of doublets of triplets, qdd= quartet of doublets of doublets, coupling constants *J* in Hz. Low resolution mass spectra by ESI-MS were recorded on Shimadzu LCMS-2020, coupled with Shimadzu LC-2040C Plus from the analytical service of SpiroChem. Masses on TLC were checked with the TLC-MS device from Advion using the Low Fragmentation and Low Temperature mode. High resolution mass spectrometry was perfomed by ESI-TOF using a standard deviation of 0.500 ppm on a Bruker Daltonics maXis. Physical-chemical properties were measured in the following way.

Sirius T3 is an automated instrument that allows the screening of compounds and the preparation of detailed physical chemical profiles. The device consists of a pH-meter electrode, a robot that prepares the solutions needed to perform the measurements, and a UVVIS spectrophotometer. If basic titration is needed, basic titration will be performed with a 0.1M KOH buffer. If acidic titration is needed, this titration will be

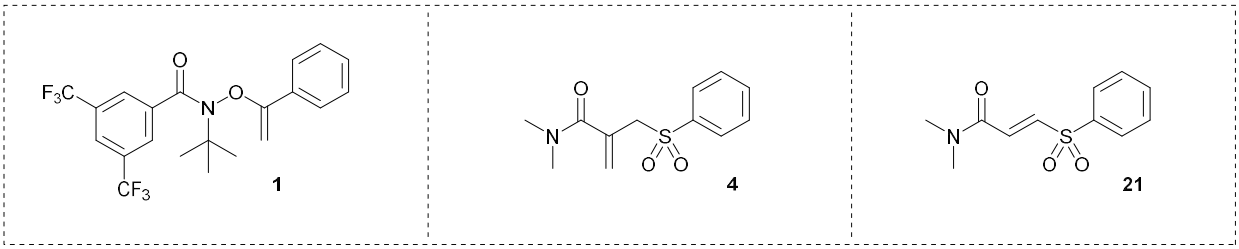
performed with a 0.1M HCl buffer. To obtain the pKa value of our molecules, a pH-metric titration experiment was carried out. Potentiometric measurement was done from pH 2 to pH 12 by adding 0.5M KCl solution. Measurement point was done every 0.2 pH value. After each addition, the sample is stirred for 60 seconds, and the pH value is then collected. The titration experiment was done 3 times. The given value is an average value of the 3 measurements. Log P was determined potentiometrically by using the "Shake flask" method, which consists of dissolving part of the solute in question in a volume of octanol and water, then performing pH titration. LogD was determined as the value of log P at a pH where the molecule was completely not ionised. Solubility measurements were performed using the CheqSol method developed by Pion. As in most cases, compounds are more soluble at pH where they ionized, the analyte was solubilized in acidic water, then pH-titration was performed, measuring the UV-Vis spectrum after each addition. The precipitation point was detected from the reduction of the light transmission during UV-VIS measurement, or manually when not obvious. The pH-titration was repeated several times around the precipitation point to determine the solubility value by averaging.

Abbreviations

HAT = hydrogen atom transfer; DMF = *N*,*N*-dimethylformamide; HATU = hexafluorophosphate azabenzotriazole tetramethyl uronium.

Experimental Procedures and Characterization Data

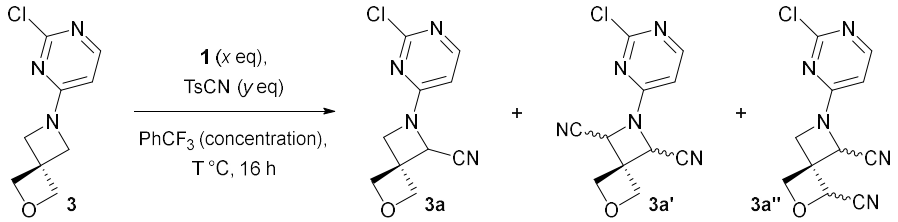
Reactants synthesis



HAT reagent **1**[1] and allylic sulfone **4**[2] were synthesized according to literature reported procedures. Vinyl sulfone **21** was synthesized adapting a reported procedure, using sodium benzenesulfinate instead of sodium *p*-toluenesulfinate.[3]

Optimization tables

HAT cyanation

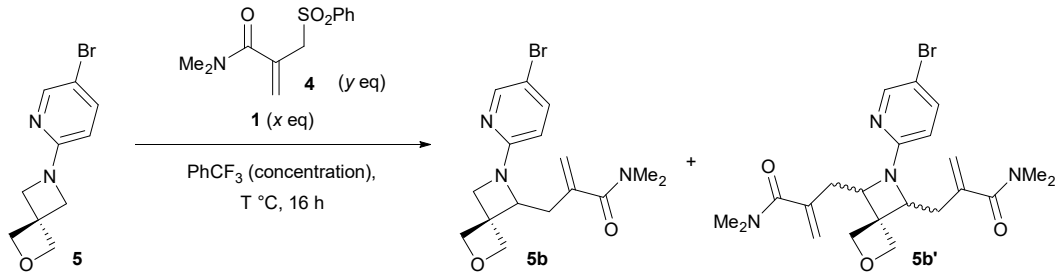


Entry	x	y	Concentration (M)	T (°C)	Yield (2:2a:2a'+2a''+2a''') %
1	2	4	1	70	0:63:36
2	2	4	0.75	70	0:63:36
3	1.5	4	0.75	70	10:64:10
4	1.5	2	0.75	70	20:68:10
5[a]	2	4	0.75	70	30:52:0
6	2	4	0.75	90	0:51:25
7	2	6	0.75	70	0:63:36
8	3	4	0.75	70	0:40:50
9	3	6	0.75	70	0:40:55
10	4	6	0.75	70	0:40:46

a = non-distilled trifluorotoluene was used.

Note: the double-derivatized products were considered together because they were afforded as complex mixtures of regio- and diastereoisomers.

HAT allylation



Entry	x	y	Concentration (M)	T (°C)	Yield (4:4a:4b') %
1	2	4	0.75	70	0:35:52
2	2	2	0.75	70	0:37:44
3	1.5	2	0.75	70	10:59:26
4	1.1	2	0.75	70	25:57:15

General procedures

General procedure A: Nucleophilic aromatic substitution

The amine (1 eq), the aromatic electrophile (1 or 2 eq), and potassium carbonate (5 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Acetonitrile (0.2 M) was added, and the mixture was stirred at 85 °C for 16 h. Afterwards, the mixture was cooled down, and filtered, rinsing with ethyl acetate. The volatiles were removed *via* rotary evaporation, and the crude was purified with silica gel column chromatography to afford the desired product.

General procedure B: HAT cyanation

Adapted from a reported procedure.[1] The substrate (0.20 mmol, 1 eq), HAT reagent **1** (170 mg, 0.40 mmol, 2 eq), and tosyl cyanide (140 mg, 0.80 mmol, 4 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Distilled trifluorotoluene (270 µL, 0.75 M) was added and the mixture was stirred at 70 °C for 16 h. Afterwards, the mixture was cooled down and volatiles were

removed *via* rotary evaporation. The crude was purified with silica gel column chromatography followed by reverse-phase column chromatography to afford the desired product.

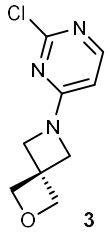
General procedure C: HAT allylation

The substrate (0.20 mmol, 1 eq), HAT reagent **1** (0.30 mmol, 1.5 eq), and allylic sulfone **3** (0.40 mmol, 2 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Distilled trifluorotoluene (270 µL, 0.75 M) was added and the mixture was stirred at 70 °C for 16 h. Afterwards, the mixture was cooled down and volatiles were removed *via* rotary evaporation. The crude was purified with silica gel column chromatography followed by reverse-phase column chromatography to afford the desired product.

General procedure D: HAT vinylation

The substrate (0.20 mmol, 1 eq), HAT reagent **1** (0.40 mmol, 2 eq), and vinyl sulfone **21** (0.80 mmol, 4 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Distilled trifluorotoluene (270 µL, 0.75 M) was added and the mixture was stirred at 70 °C for 16 h. Afterwards, the mixture was cooled down and volatiles were removed *via* rotary evaporation. The crude was purified with silica gel column chromatography followed by reverse-phase column chromatography to afford the desired product.

Substrates synthesis



Compound 3.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (300 mg, 1.04 mmol, 1 eq), 2,5-dichloropyrimidine (310 mg, 2.08 mmol, 2 eq), and potassium carbonate (720 mg, 5.21 mmol, 5 eq) in acetonitrile (5.2 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (290 mg, 1.37 mmol, 66% yield) as an amorphous white solid.

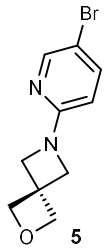
R_f 0.17 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 5.8 Hz, 1H), 6.05 (d, *J* = 5.9 Hz, 1H), 4.82 (s, 4H), 4.25 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 161.0, 156.6, 100.7, 80.8, 59.5, 39.2.

IR (ATR, neat, cm^{-1}) 2939 (w), 2867 (w), 1580 (s), 1498 (s), 1352 (s), 1314 (m), 1144 (m), 968 (s), 812 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{11}ClN_3O$ $[M+H]^+$ calc.: 212.0585; found: 212.0584.



Compound 5.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 5-bromo-2-fluoro-pyridine (305 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (441 mg, 1.73 mmol, 100% yield) as an amorphous white solid.

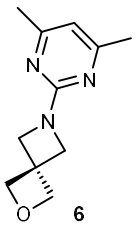
R_f 0.54 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.17 (dd, *J* = 8.8, 0.7 Hz, 1H), 4.82 (s, 4H), 4.13 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 148.9, 139.6, 108.1, 107.5, 81.2, 60.4, 39.0.

IR (ATR, neat, cm^{-1}) 2943 (m), 2872 (m), 2851 (m), 1578 (m), 1490 (m), 1400 (m), 1306 (m), 1089 (m), 966 (s), 813 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{12}BrN_2O$ $[M+H]^+$ calc.: 255.0128; found: 255.0127.



Compound 6.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2-chloro-4,6-dimethyl-1,3-diazine (247 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (314 mg, 1.53 mmol, 88% yield) as an amorphous white solid.

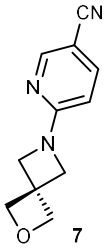
R_f 0.23 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.82 (s, 4H), 4.25 (s, 4H), 2.28 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 163.1, 110.2, 81.4, 60.0, 38.7, 24.0.

IR (ATR, neat, cm^{-1}) 2863 (w), 1558 (s), 1497 (s), 1464 (s), 1381 (m), 1338 (m), 1210 (w), 972 (s), 789 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{16}N_3O$ $[M+H]^+$ calc.: 206.1288; found: 206.1285.



Compound 7.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 6-chloronicotinonitrile (240 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (147 mg, 0.73 mmol, 42% yield) as an amorphous white solid.

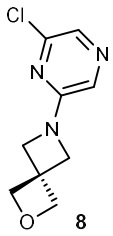
R_f 0.31 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, J = 2.2, 0.8 Hz, 1H), 7.57 (dd, J = 8.8, 2.2 Hz, 1H), 6.22 (dd, J = 8.8, 0.8 Hz, 1H), 4.85 (s, 4H), 4.26 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 153.2, 139.5, 118.6, 105.2, 97.1, 80.9, 59.9, 39.0.

IR (ATR, neat, cm^{-1}) 2209 (m), 1597 (s), 1543 (m), 1513 (m), 1438 (m), 1309 (m), 1109 (w), 967 (m), 827 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{12}N_3O$ $[M+H]^+$ calc.: 202.0975; found: 202.0974.



Compound 8.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2,6-dichloro-pyrazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (282 mg, 1.33 mmol, 77% yield) as an amorphous white solid.

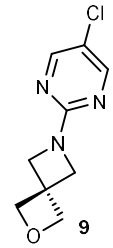
R_f 0.40 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.59 (s, 1H), 4.82 (s, 4H), 4.24 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 147.3, 131.4, 127.4, 80.9, 60.3, 39.6.

IR (ATR, neat, cm^{-1}) 2945 (w), 2863 (w), 1567 (s), 1504 (s), 1465 (m), 1411 (m), 1315 (w), 1175 (s), 1106 (m), 989 (m), 973 (s), 836 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{11}ClN_3O$ $[M+H]^+$ calc.: 212.0585; found: 212.0586.



Compound 9.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2,5-dichloro-1,3-diazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (357 mg, 1.69 mmol, 97% yield) as an amorphous white solid.

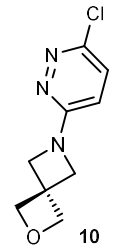
R_f 0.49 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 2H), 4.82 (s, 4H), 4.24 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 156.2, 119.5, 81.1, 59.9, 38.6.

IR (ATR, neat, cm^{-1}) 2933 (m), 2864 (m), 1577 (s), 1508 (s), 1462 (s), 1385 (m), 1310 (w), 1214 (w), 1135 (m), 940 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{11}ClN_3O$ $[M+H]^+$ calc.: 212.0585; found: 212.0584.



Compound 10.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 3,6-dichloro pyridazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (319 mg, 1.51 mmol, 87% yield) as an amorphous white solid.

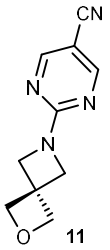
R_f 0.14 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 9.2 Hz, 1H), 6.52 (d, *J* = 9.3 Hz, 1H), 4.84 (s, 4H), 4.27 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 147.3, 128.9, 114.3, 81.0, 60.5, 39.6.

IR (ATR, neat, cm^{-1}) 3040 (w), 2947 (m), 2872 (m), 2859 (w), 1588 (s), 1532 (m), 1525 (m), 1475 (s), 1320 (w), 1155 (m), 1085 (w), 967 (s), 848 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{11}ClN_3O$ $[M+H]^+$ calc.: 212.0585; found: 212.0588.



11

Compound 11.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (100 mg, 0.35 mmol, 1 eq), 2-chloro-5-pyrimidinecarbonitrile (97 mg, 0.69 mmol, 2 eq), and potassium carbonate (240 mg, 1.73 mmol, 5 eq) in acetonitrile (1.7 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (76 mg, 0.38 mmol, 54% yield) as an amorphous white solid.

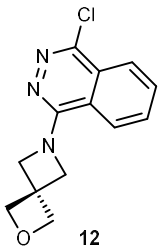
R_f 0.34 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 2H), 4.85 (s, 4H), 4.36 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 160.5, 116.6, 96.7, 80.8, 59.6, 38.7.

IR (ATR, neat, cm^{-1}) 2949 (w), 2877 (w), 2216 (m), 1600 (s), 1558 (s), 1509 (m), 1400 (m), 1228 (m), 959 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{11}N_4O$ $[M+H]^+$ calc.: 203.0927; found: 203.0927.



12

Compound 12.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 1,4-dichlorophthalazine (345 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.34 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (256 mg, 0.98 mmol, 56% yield) as an amorphous white solid.

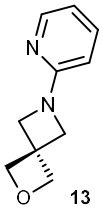
R_f 0.20 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.12 (m, 1H), 7.95 – 7.76 (m, 3H), 4.89 (s, 4H), 4.65 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 147.5, 132.6, 131.9, 126.9, 125.9, 123.9, 121.0, 81.2, 63.4, 40.2.

IR (ATR, neat, cm^{-1}) 2936 (w), 2864 (m), 1570 (w), 1499 (s), 1443 (s), 1351 (s), 1317 (m), 1295 (w), 974 (m), 766 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{13}H_{13}ClN_3O$ $[M+H]^+$ calc.: 262.0742; found: 262.0736.


13

Compound 13.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2-fluoropyridine (168 mg, 149 µL, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (123 mg, 0.70 mmol, 40% yield) as a colorless oil.

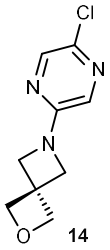
R_f 0.18 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (ddd, *J* = 5.1, 1.9, 0.9 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.2, 1.9 Hz, 1H), 6.61 (ddd, *J* = 7.2, 5.1, 1.0 Hz, 1H), 6.28 (dt, *J* = 8.4, 1.0 Hz, 1H), 4.83 (s, 4H), 4.15 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 148.3, 137.3, 113.4, 106.2, 81.4, 60.3, 39.1.

IR (ATR, neat, cm^{-1}) 2931 (w), 2862 (m), 1591 (s), 1558 (w), 1489 (m), 1469 (m), 1438 (s), 1345 (m), 1149 (w), 974 (m), 774 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{13}N_2O$ $[M+H]^+$ calc.: 177.1022; found: 177.1026.


14

Compound 14.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 3,6-dichloropyrazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (304 mg, 1.44 mmol, 83% yield) as an amorphous white solid.

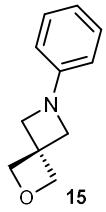
R_f 0.57 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.4 Hz, 1H), 7.48 (d, *J* = 1.4 Hz, 1H), 4.82 (s, 4H), 4.20 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 141.5, 137.0, 128.6, 81.0, 60.4, 39.6.

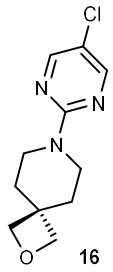
IR (ATR, neat, cm^{-1}) 2941 (m), 2920 (m), 2864 (s), 1569 (s), 1510 (s), 1490 (s), 1474 (s), 1354 (m), 1312 (m), 1198 (m), 1154 (s), 1000 (m), 965 (s), 774 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{11}ClN_3O$ $[M+H]^+$ calc.: 212.0585; found: 212.0583.



Compound 15.

Bromobenzene (130 mg, 87 µL, 0.83 mmol, 1 eq), 2-oxa-6-azaspiro[3.3]heptane hemioxalate (263 mg, 0.91 mmol, 1.1 eq), $Pd_{2(}dba)_3$ (38 mg, 0.04 mmol, 5 mol %), Xphos (40 mg, 0.08 mmol, 10 mol %), and cesium carbonate (1.35 g, 4.14 mmol, 5 eq) were added in a vial. The vial was sealed with a microwave cap and purged with nitrogen. Anhydrous toluene (8.3 mL, 0.1 M) was added, and the mixture was stirred at 100 °C for 16 h. Afterwards, the vial was cooled down to room temperature and the mixture was filtered through a pad of celite, rinsing with ethyl acetate. The solvents were removed *via* rotary evaporation, and the crude was purified with silica gel flash column chromatography using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate), affording the desired product (136 mg, 0.78 mmol, 94% yield) as an amorphous white solid. The analytical data is consistent with reported literature.[4]



Compound 16.

Prepared following general procedure A, using 2-oxa-7-azaspiro[3.5]nonane hemioxalate (210 mg, 0.61 mmol, 1 eq), 2,5-dichloro-1,3-diazine (182 mg, 1.22 mmol, 2 eq), and potassium carbonate (421 mg, 3.05 mmol, 5 eq) in acetonitrile (3.05 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate), affording the desired product (282 mg, 1.18 mmol, 97% yield) as an amorphous white solid.

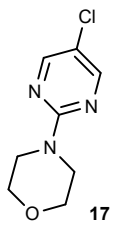
R_f 0.33 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 4.48 (s, 2H), 3.75 – 3.67 (m, 2H), 1.92 – 1.85 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 156.0, 118.1, 81.7, 41.4, 39.2, 34.6.

IR (ATR, neat, cm^{-1}) 2862 (m), 1581 (s), 1525 (m), 1501 (s), 1459 (m), 1398 (w), 1356 (s), 1301 (m), 1251 (s), 1170 (w), 1137 (w), 969 (m), 940 (m), 885 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{15}ClN_3O$ $[M+H]^+$ calc.: 240.0898; found: 240.0895.



Compound 17.

Prepared following general procedure A, using morpholine (100 mg, 99 µL, 1.15 mmol, 1 eq), 2,5-dichloro-1,3-diazine (171 mg, 1.15 mmol, 1 eq), and potassium carbonate (397 mg, 2.87 mmol, 2.5 eq) in acetonitrile (5.7 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate), affording the desired product (228 mg, 1.14 mmol, >99% yield) as an amorphous white solid.

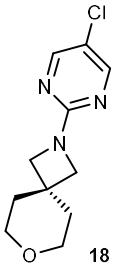
R_f 0.56 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H), 3.74 – 3.64 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 156.0, 118.8, 66.8, 44.6.

IR (ATR, neat, cm^{-1}) 2963 (w), 2854 (w), 1581 (s), 1528 (m), 1488 (s), 1445 (s), 1391 (w), 1356 (s), 1299 (w), 1259 (s), 1168 (w), 1140 (w), 1117 (m), 957 (m), 787 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_8H_{11}ClN_3O$ $[M+H]^+$ calc.: 200.0585; found: 200.0585.



18

Compound 18.

Prepared following general procedure A, using 7-oxa-2-azaspiro[3.5]nonane hemioxalate (200 mg, 0.58 mmol, 1 eq), 2,5-dichloro-1,3-diazine (173 mg, 1.16 mmol, 2 eq), and potassium carbonate (401 mg, 2.90 mmol, 5 eq) in acetonitrile (2.9 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (176 mg, 0.73 mmol, 63% yield) as an amorphous white solid.

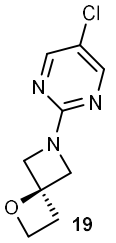
R_f 0.58 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 2H), 3.86 (s, 4H), 3.68 – 3.61 (m, 4H), 1.86 – 1.79 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 156.2, 118.9, 65.0, 60.4, 36.4, 33.6.

IR (ATR, neat, cm^{-1}) 2968 (w), 2931 (w), 2863 (w), 1572 (s), 1523 (s), 1511 (s), 1476 (m), 1389 (w), 1257 (w), 878 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{15}ClN_3O$ $[M+H]^+$ calc.: 240.0898; found: 240.0895.



19

Compound 19.

Prepared following general procedure A, using 1-oxa-6-azaspiro[3.3]heptane hemioxalate (200 mg, 0.69 mmol, 1 eq), 2,5-dichloro-1,3-diazine (207 mg, 1.39 mmol, 2 eq), and potassium carbonate (4.79 mg, 3.47 mmol, 5 eq) in acetonitrile (3.5 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (156 mg, 0.74 mmol, 53% yield) as an amorphous white solid.

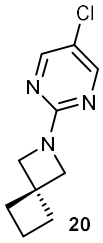
R_f 0.58 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 2H), 4.57 (t, J = 7.5 Hz, 2H), 4.36 – 4.24 (m, 4H), 2.91 (t, J = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 156.3, 119.4, 83.3, 66.6, 65.0, 32.1.

IR (ATR, neat, cm^{-1}) 2922 (w), 2896 (w), 1575 (s), 1522 (s), 1496 (s), 1452 (s), 1378 (m), 1286 (w), 1246 (m), 1131 (m), 1118 (m), 973 (w), 951 (m), 785 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{11}ClN_3O$ $[M+H]^+$ calc.: 212.0585; found: 212.0582.



Compound 20t.

Prepared following general procedure A, using 2-azaspiro[3.3]heptane hemioxalate (200 mg, 0.70 mmol, 1 eq), 2,5-dichloro-1,3-diazine (210 mg, 1.41 mmol, 2 eq), and potassium carbonate (486 mg, 3.52 mmol, 5 eq) in acetonitrile (3.5 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 30% ethyl acetate), affording the desired product (251 mg, 1.20 mmol, 85% yield) as an amorphous white solid.

R_f 0.63 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 2H), 4.08 (s, 4H), 2.23 (t, J = 7.6 Hz, 4H), 1.95 – 1.83 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 156.2, 118.6, 62.9, 38.6, 33.3, 16.3.

IR (ATR, neat, cm^{-1}) 2975 (m), 2953 (m), 2936 (m), 2866 (m), 1574 (s), 1529 (s), 1472 (m), 1381 (m), 1313 (m), 1130 (m), 936 (w), 787 (m).

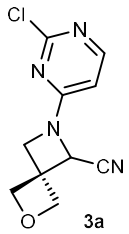
HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{13}ClN_3$ $[M+H]^+$ calc.: 210.0793; found: 210.0790.

pKa and solubility measurements table

Structure	Theoretical pKa*	Measured pKa (in Water)	Theoretical Log P*	Measured Log P	Theoretical Solubility*	Measured Solubility
5	5.89	4.18	1.17	1.86	68 mM	35 mM
6	6.28	4.50	1.51	0.90	3 mM	32 µM
7	4.81	2.69	0.36	0.42	79 mM	50 mM
9	3.34	2.82	1.42	1.31	2.35 mM	2.2 mM
11	2.06	2.32	0.63	0.85	98 µM	88 µM
12	5.66	4.62	1.26	1.54	8 mM	10 mM
13	5.96	6.12	1.13	1.02	66 mM	103.6 mM
14	2.26	2.01	0.77	0.80	276 mM	100 mM
15	2.65	2.95	1.06	1.60	74 mM	49 mM
16	3.52	2.50	2.03	2.54	805 µM	802 µM
17	3.23	3.15	1.35	1.08	5.4 mM	2 mM
18	3.5	2.5	2.03	2.39	805 µM	315 µM

19	3.23	3.30	1.51	1.45	2 mM	504 µM
20	3.64	3.30	-	-	527 µM	505 µM

HAT cyanation products



3a

Compound 3a.

Prepared following general procedure B, using compound **3** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (30 mg, 0.13 mmol, 63% yield) was isolated as an amorphous white solid, alongside the double derivatized products (19 mg, 0.07 mmol, 36% yield).

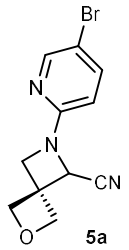
R_f 0.19 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 5.7 Hz, 1H), 6.28 (d, *J* = 5.7 Hz, 1H), 5.13 (d, *J* = 8.0 Hz, 1H), 5.07 (s, 1H), 4.89 (d, *J* = 8.0 Hz, 1H), 4.86 (s, 2H), 4.38 (d, *J* = 9.1 Hz, 1H), 4.25 (d, *J* = 9.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 161.1, 158.1, 114.3, 101.5, 78.8, 77.6, 58.7, 57.2, 42.3.

IR (ATR, neat, cm^{-1}) 1574 (s), 1537 (m), 1487 (m), 1459 (m), 1350 (s), 1305 (w), 1153 (w), 971 (s), 868 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{10}ClN_4O$ $[M+H]^+$ calc.: 237.0538; found: 237.0531.



5a

Compound 5a.

Prepared following general procedure B, using compound **5** (51 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (41 mg, 0.15 mmol, 73% yield) was isolated as an amorphous white solid.

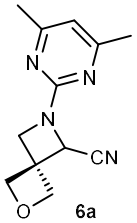
R_f 0.61 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 2.4, 0.8 Hz, 1H), 7.63 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.35 (dd, *J* = 8.7, 0.8 Hz, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 4.91 (m, 3H), 4.81 (s, 3H), 4.26 (d, *J* = 8.3, Hz, 1H), 4.07 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 149.3, 140.3, 115.7, 111.1, 108.2, 78.9, 78.2, 59.3, 57.7, 42.0.

IR (ATR, neat, cm^{-1}) 2948 (w), 2872 (w), 1579 (s), 1552 (w), 1462 (s), 1385 (s), 1339 (m), 1304 (w), 1294 (w), 1091 (m), 976 (m), 736 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{11}BrN_3O$ $[M+H]^+$ calc.: 280.0080; found: 280.0084.



6a

Compound 6a.

Prepared following general procedure B, using compound **6** (41 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (29 mg, 0.13 mmol, 63% yield) was isolated as an amorphous white solid.

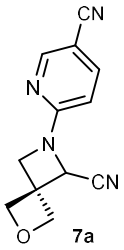
R_f 0.42 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.17 (d, *J* = 7.6 Hz, 1H), 4.99 (s, 1H), 4.89 (d, *J* = 7.7 Hz, 1H), 4.81 (s, 2H), 4.35 (dd, *J* = 9.0, 0.9 Hz, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 161.5, 116.1, 112.4, 79.3, 78.2, 58.8, 57.6, 41.6, 24.0.

IR (ATR, neat, cm^{-1}) 2951 (w), 2974 (w), 1582 (s), 1558 (s), 1444 (s), 1382 (m), 1328 (m), 1297 (w), 978 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{12}H_{15}N_4O$ $[M+H]^+$ calc.: 231.1240; found: 231.1236.



7a

Compound 7a.

Prepared following general procedure B, using compound **7** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (41 mg, 0.18 mmol, 91% yield) was isolated as an amorphous white solid.

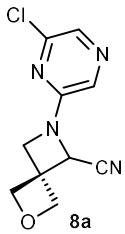
R_f 0.41 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.44 (dd, *J* = 8.6, 0.8 Hz, 1H), 5.18 (d, *J* = 7.9 Hz, 1H), 5.05 (s, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 4.85 (s, 2H), 4.38 (dd, *J* = 8.6, 1.0 Hz, 1H), 4.22 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 153.0, 140.5, 117.7, 115.0, 106.0, 100.4, 78.9, 77.9, 59.0, 57.5, 42.03.

IR (ATR, neat, cm^{-1}) 2949 (w), 2875 (w), 2220 (m), 1594 (s), 1496 (s), 1409 (m), 1308 (m), 1212 (w), 1158 (w), 977 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{12}H_{11}N_4O$ $[M+H]^+$ calc.: 227.0927; found: 227.0926.



Compound 8a.

Prepared following general procedure B, using compound **8** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (42 mg, 0.18 mmol, 89% yield) was isolated as a colorless oil.

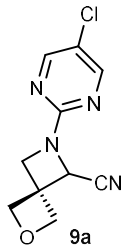
R_f 0.46 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.81 (s, 1H), 5.18 (d, *J* = 7.9 Hz, 1H), 5.03 (s, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 4.84 (s, 2H), 4.41 (dd, *J* = 8.6, 1.0 Hz, 1H), 4.23 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 147.5, 134.8, 127.7, 114.8, 78.8, 77.9, 59.5, 57.8, 42.6.

IR (ATR, neat, cm^{-1}) 2949 (w), 2875 (w), 1564 (s), 1511 (s), 1455 (s), 1410 (s), 1344 (w), 1175 (m), 1111 (m), 977 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{10}ClN_4O$ $[M+H]^+$ calc.: 237.0538; found: 237.0533.



Compound 9.

Prepared following general procedure B, using compound **9** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (46 mg, 0.19 mmol, 97% yield) was isolated as an amorphous white solid.

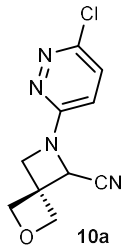
R_f 0.59 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 2H), 5.15 (d, *J* = 7.8 Hz, 1H), 5.00 (s, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 4.83 (s, 2H), 4.35 (dd, *J* = 9.3, 1.0 Hz, 1H), 4.25 (d, *J* = 9.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 156.6, 122.4, 115.4, 79.1, 78.0, 58.9, 57.7, 41.7.

IR (ATR, neat, cm^{-1}) 1576 (s), 1521 (m), 1500 (s), 1384 (m), 1282 (w), 1132 (w), 973 (m), 943 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{10}ClN_4O$ $[M+H]^+$ calc.: 237.0538; found: 237.0539.



10a

Compound 10a.

Prepared following general procedure B, using compound **10** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (36 mg, 0.15 mmol, 76% yield) was isolated as an amorphous white solid, alongside the double derivatized products (12 mg, 0.05 mmol, 23% yield).

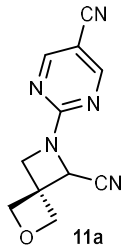
R_f 0.27 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, Acetone-d6) δ 7.55 (d, *J* = 9.3 Hz, 1H), 7.08 (d, *J* = 9.2 Hz, 1H), 5.44 (s, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.97 (d, *J* = 7.5 Hz, 1H), 4.88 (d, *J* = 7.5 Hz, 1H), 4.80 (d, *J* = 7.5 Hz, 1H), 4.47 (d, *J* = 8.4 Hz, 1H), 4.38 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (75 MHz, Acetone-d6) δ 160.2, 149.7, 130.1, 116.9, 116.7, 79.0, 78.4, 60.3, 58.6, 43.4.

IR (ATR, neat, cm^{-1}) 2876 (w), 1580 (m), 1534 (w), 1433 (s), 1348 (w), 1112 (m), 977 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{10}ClN_4O$ $[M+H]^+$ calc.: 237.0538; found: 237.0534.



11a

Compound 11a.

Prepared following general procedure B, using compound **11** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (25 mg, 0.11 mmol, 55% yield) was isolated as an amorphous white solid, alongside the double derivatized products (18 mg, 0.07 mmol, 36%).

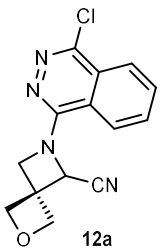
R_f 0.43 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 2H), 5.21 – 5.09 (m, 2H), 4.96 – 4.81 (m, 3H), 4.52 – 4.34 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 160.2, 115.6, 114.5, 99.9, 79.0, 77.4, 58.7, 57.5, 41.9.

IR (ATR, neat, cm^{-1}) 2925 (w), 2874 (w), 2221 (m), 1738 (w), 1595 (s), 1519 (s), 1454 (m), 1226 (m), 958 (w).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{10}N_5O$ $[M+H]^+$ calc.: 228.0880; found: 228.0878.



12a

Compound 12a.

Prepared following general procedure B, using compound **12** (52 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (40 mg, 0.14 mmol, 70% yield) was isolated as a white foam, alongside the double derivatized products (18 mg, 0.06 mmol, 29% yield).

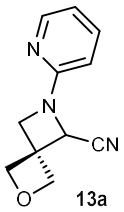
R_f 0.32 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 – 8.18 (m, 1H), 8.03 – 7.80 (m, 3H), 5.63 (s, 1H), 5.32 (d, *J* = 7.7 Hz, 1H), 5.02 (d, *J* = 7.7 Hz, 1H), 4.91 – 4.83 (m, 2H), 4.79 (d, *J* = 7.6 Hz, 1H), 4.45 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 150.4, 133.5, 132.9, 127.1, 126.3, 123.4, 120.9, 115.6, 78.6, 63.9, 57.7, 42.6. (*Note: The peak at 78.6 ppm is two different carbons, as it can be seen by HSQC*).

IR (ATR, neat, cm^{-1}) 2874 (w), 1571 (w), 1494 (s), 1417 (s), 1374 (m), 1295 (m), 1097 (w), 978 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{14}H_{12}ClN_4O$ $[M+H]^+$ calc.: 287.0694; found: 287.0695.



13a

Compound 13a.

Prepared following general procedure B, using compound **13** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (12 mg, 0.06 mmol, 30% yield) was isolated as a colorless oil, alongside the double derivatized products (11 mg, 0.05 mmol, 24% yield).

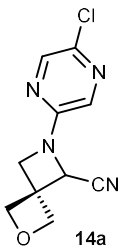
R_f 0.30 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H), 7.57 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H), 6.81 (ddd, *J* = 7.3, 5.1, 0.9 Hz, 1H), 6.46 (dt, *J* = 8.3, 0.9 Hz, 1H), 5.20 (d, *J* = 7.7 Hz, 1H), 4.98 – 4.87 (m, 2H), 4.81 (s, 2H), 4.30 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.11 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 148.3, 138.0, 116.0, 115.9, 107.0, 79.0, 78.4, 59.3, 57.7, 42.0.

IR (ATR, neat, cm^{-1}) 2948 (w), 2873 (w), 1594 (s), 1563 (m), 1478 (s), 1436 (s), 1341 (m), 1304 (w), 1140 (w), 977 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{12}N_3O$ $[M+H]^+$ calc.: 202.0975; found: 202.0975.



14a

Compound 14a.

Prepared following general procedure B, using compound **14** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (38 mg, 0.16 mmol, 80% yield) was isolated as an amorphous white solid, alongside the double derivatized products (10 mg, 0.04 mol, 19% yield).

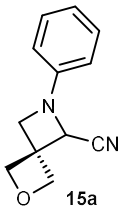
R_f 0.54 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 5.01 – 4.88 (m, 2H), 4.83 (s, 2H), 4.37 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.18 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 141.9, 140.1, 129., 115.1, 78.7, 78.0, 59.5, 57.9, 42.6.

IR (ATR, neat, cm^{-1}) 2950 (w), 2875 (w), 1567 (s), 1519 (m), 1471 (s), 1386 (m), 1350 (m), 1319 (w), 1168 (w), 1136 (w), 1110 (m), 982 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{10}ClN_4O$ $[M+H]^+$ calc.: 237.0538; found: 237.0536.



15a

Compound 15a.

Prepared following general procedure B, using compound **15** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (31 mg, 0.15 mmol, 77% yield) was isolated as an amorphous white solid.

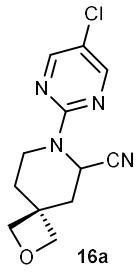
R_f 0.26 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 2H), 6.98 – 6.86 (m, 1H), 6.65 – 6.54 (m, 2H), 5.20 (d, *J* = 7.6 Hz, 1H), 4.97 – 4.86 (m, 1H), 4.79 (s, 2H), 4.67 (d, *J* = 0.8 Hz, 1H), 4.20 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.94 (d, *J* = 7.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 129.5, 120.6, 116.0, 112.5, 78.7, 78.6, 60.2, 59.2, 42.1.

IR (ATR, neat, cm^{-1}) 2948 (w), 2872 (w), 1736 (w), 1599 (s), 1500 (s), 1364 (w), 1330 (m), 1180 (w), 978 (m), 754 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_{12}H_{13}N_2O$ $[M+H]^+$ calc.: 201.1022; found: 201.1022.



16a

Compound 16a.

Prepared following general procedure B, using compound **16** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (19 mg, 0.07 mmol, 36% yield) was isolated as an amorphous white solid, alongside recovered starting material (9 mg, 0.04 mol, 20% yield).

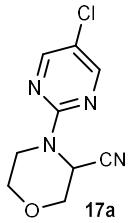
R_f 0.22 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 2H), 5.83 (dt, *J* = 5.8, 1.7 Hz, 1H), 5.02 (dd, *J* = 6.6, 1.5 Hz, 1H), 4.74 (ddt, *J* = 14.2, 4.2, 1.7 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.51 (d, *J* = 6.0 Hz, 1H), 4.37 (d, *J* = 6.0 Hz, 1H), 3.08 (td, *J* = 13.6, 2.7 Hz, 1H), 2.56 (dt, *J* = 13.9, 2.2 Hz, 1H), 2.43 (dq, *J* = 13.5, 2.6 Hz, 1H), 1.87 (dd, *J* = 13.9, 5.8 Hz, 1H), 1.72 (tdd, *J* = 13.3, 4.7, 1.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.3, 121.4, 117.9, 81.8, 80.6, 42.2, 38.5, 37.9, 35.7, 34.0.

IR (ATR, neat, cm^{-1}) 2931 (w), 2866 (w), 1579 (s), 1536 (m), 1475 (m), 1440 (s), 1361 (m), 1209 (m), 1175 (m), 981 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{12}H_{14}ClN_4O$ $[M+H]^+$ calc.: 265.0851; found: 265.0847.



17a

Compound 17a.

Prepared following general procedure B, using compound **17** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (39 mg, 0.17 mmol, 87% yield) was isolated as an amorphous white solid.

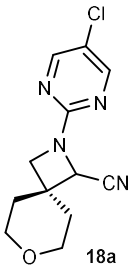
R_f 0.44 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 2H), 5.45 (d, *J* = 2.8 Hz, 1H), 4.40 (ddt, *J* = 13.6, 2.7, 1.2 Hz, 1H), 4.24 – 4.16 (m, 1H), 4.10 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.75 (dd, *J* = 11.9, 3.1 Hz, 1H), 3.62 (td, *J* = 11.9, 2.9 Hz, 1H), 3.31 (ddd, *J* = 13.7, 12.1, 3.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.4, 122.0, 116.9, 67.7, 66.8, 44.8, 41.7.

IR (ATR, neat, cm^{-1}) 1577 (m), 1536 (m), 1435 (s), 1387 (w), 1297 (w), 1263 (w), 1171 (m), 1121 (m), 1075 (m), 950 (s).

HRMS (ESI-TOF, m/z) calcd. for $C_9H_{10}ClN_4O$ $[M+H]^+$ calc.: 225.0538; found: 225.0537.



18a

Compound 18a.

Prepared following general procedure B, using compound **18** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (53 mg, 0.20 mmol, >99% yield) was isolated as an amorphous white solid.

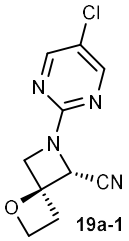
R_f 0.14 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H), 4.60 (s, 1H), 4.02 – 3.83 (m, 3H), 3.76 (ddd, *J* = 12.0, 5.7, 3.9 Hz, 1H), 3.62 (dddd, *J* = 17.0, 11.8, 8.3, 3.3 Hz, 2H), 2.15 (ddd, *J* = 12.6, 8.3, 3.9 Hz, 1H), 2.02 (dddd, *J* = 13.6, 5.8, 3.2, 1.4 Hz, 1H), 1.97 – 1.81 (m, 2H).

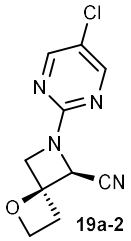
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 156.6, 121.8, 115.9, 64.5, 64.4, 59.6, 58.2, 37.6, 36.3, 33.8.

IR (ATR, neat, cm^{-1}) 1574 (s), 1536 (m), 1488 (s), 1464 (s), 1386 (w), 1229 (m), 1128 (w), 1104 (m), 788 (w), 678 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{12}H_{14}ClN_4O$ $[M+H]^+$ calc.: 265.0851; found: 265.0845.



19a-1



19a-2

Compounds 19a-1 and 19a-2.

Prepared following general procedure B, using compound **19** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 60% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). Compound **19a-1** (19 mg, 0.08 mmol, 40% yield) and compound **19a2-2** (17 mg, 0.07 mol, 36% yield) were isolated independently as amorphous white solids.

19a-1:

R_f 0.24 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 2H), 4.95 (s, 1H), 4.66 (ddt, *J* = 22.9, 8.5, 6.0 Hz, 2H), 4.39 – 4.23 (m, 2H), 3.35 (ddd, *J* = 12.5, 8.4, 6.0 Hz, 1H), 3.03 (ddd, *J* = 12.5, 8.6, 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 156.6, 122.4, 115.8, 84.4, 67.5, 64.3, 62.5, 29.7.

IR (ATR, neat, cm^{-1}) 2901 (w), 1575 (s), 1536 (m), 1487 (s), 1473 (s), 1453 (s), 1381 (w), 1329 (w), 1249 (w), 1099 (m), 972 (m), 945 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{10}ClN_4O$ $[M+H]^+$ calc.: 237.0538; found: 237.0539.

19a-2:

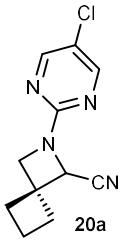
R_f 0.10 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H), 5.05 (s, 1H), 4.76 (ddd, *J* = 8.2, 7.0, 5.9 Hz, 1H), 4.65 (dt, *J* = 8.6, 5.9 Hz, 1H), 4.42 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.29 (d, *J* = 10.2 Hz, 1H), 3.05 (ddd, *J* = 12.3, 8.6, 7.0 Hz, 1H), 2.92 (ddd, *J* = 12.3, 8.2, 5.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 156.6, 122.0, 114.3, 83.1, 67.5, 64.1, 62.7, 31.6.

IR (ATR, neat, cm^{-1}) 1573 (m), 1540 (m), 1463 (s), 1444 (s), 1380 (m), 1249 (w), 1138 (m), 933 (s), 858 (s), 793 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{10}H_{10}ClN_4O$ $[M+H]^+$ calc.: 237.0538; found: 237.0535.



20a

Compound 20a.

Prepared following general procedure B, using compound **20** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 35% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (38 mg, 0.16 mmol, 81% yield) was isolated as an inseparable mixture containing the double derivatized product (10 mg, 0.04 mmol, 19% yield).

R_f 0.48 (*c*-hexane:EtOAc = 3:1, UV, $KMnO_4$).

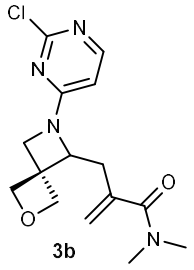
^{1}H NMR (400 MHz, $CDCl_3$) **20a**: δ 8.26 (s, 2H), 4.71 (s, 1H), 4.09 (d, *J* = 8.5 Hz, 1H), 3.99 (d, *J* = 8.5 Hz, 1H), 2.58 (dd, *J* = 12.4, 7.9 Hz, 1H), 2.28 – 2.18 (m, 3H), 1.91 (p, *J* = 7.7 Hz, 2H); **20a-double**: δ 8.37 (s, 2H), 4.81 (s, 2H), 2.72 – 2.58 (m, 2H), 2.39 – 2.24 (m, 2H), 2.01 (p, *J* = 7.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) **20a**: δ 159.8, 156.5, 121.6, 116.4, 61.8, 59.4, 41.8, 32.7, 30.7, 16.0; **20a-double**: δ 157.5, 156.8, 124.0, 115.0, 58.4, 44.8, 30.1, 15.8.

IR (ATR, neat, cm^{-1}) 2941 (w), 1574 (s), 1535 (m), 1457 (s), 1379 (w), 1325 (w), 1132 (w), 935 (w), 790 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{12}ClN_4$ $[M+H]^+$ calc.: 235.0745; found: 235.0740.

HAT allylation products



Compound 3b.

Prepared following general procedure C, using compound **3** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (30 mg, 0.09 mmol, 46% yield) was isolated as a colorless oil, alongside recovered starting material (9 mg, 0.04 mmol, 20% yield), and double derivatized products (9 mg, 0.02 mmol, 10% yield).

R_f 0.39 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

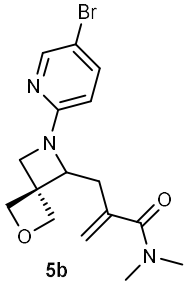
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 5.9 Hz, 1H), 6.32 (s, 1H), 5.42 (s, 1H), 5.29 (d, 1H), 5.07 (d, *J* = 7.4 Hz, 1H), 4.76 (q, *J* = 6.9 Hz, 2H), 4.67 (d, *J* = 7.4 Hz, 1H), 4.59 (dd, *J* = 8.0, 4.5 Hz, 1H), 4.32 (d, *J* = 9.7 Hz, 1H), 4.13 (d, *J* = 9.7 Hz, 1H), 3.16 – 2.83 (m, 8H).

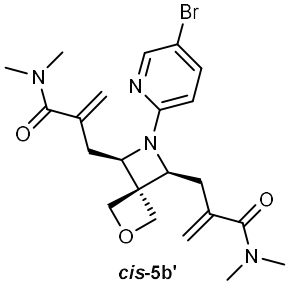
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 163.9, 160.7, 156.8, 140.4, 119.1, 101.9, 81.2, 76.6, 67.7, 59.0, 43.3, 38.9, 35.7, 34.9.

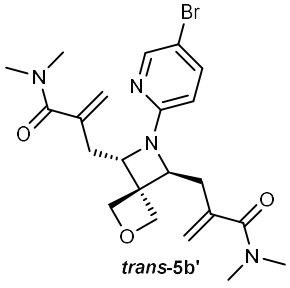
IR (ATR, neat, cm^{-1}) 2970 (w), 2939 (w), 2870 (w), 1738 (m), 1615 (m), 1583 (s), 1494 (m), 1393 (w), 1352 (s), 1217 (m), 1116 (w), 970 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{20}ClN_4O_2$ $[M+H]^+$ calc.: 323.1269; found: 323.1264.

Compounds 5b, *cis*-5b', and *trans*-5b'.







Prepared following general procedure C, using compound **5** (51 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product **5b** (43 mg, 0.12 mmol, 59% yield) was isolated as an amorphous white solid, alongside recovered starting material (5 mg, 0.02 mmol, 10%

yield), and double derivatized products ***cis*-5b'** (12 mg, 0.03 mmol, 13% yield) and ***trans*-5b'** (13 mg, 0.03 mmol, 14% yield).

5b:

R_f 0.65 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 – 8.06 (m, 1H), 7.47 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.39 – 6.28 (m, 1H), 5.45 (s, 1H), 5.26 (s, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 4.74 – 4.62 (m, 3H), 4.34 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.18 (d, *J* = 9.0 Hz, 1H), 3.93 (d, *J* = 8.8 Hz, 1H), 3.18 – 2.88 (m, 7H), 2.77 (dd, *J* = 15.4, 9.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 159.1, 148.7, 140.7, 139.5, 118.3, 108.5, 108.4, 82.0, 77.2, 67.3, 59.7, 43.0, 39.0, 36.5, 34.9.

IR (ATR, neat, cm^{-1}) 2359 (s), 2342 (s), 1639 (m), 1614 (s), 1580 (s), 1476 (s), 1460 (s), 1390 (s), 1342 (w), 1297 (w), 1090 (m), 974 (m), 813 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{16}H_{21}BrN_3O_2$ $[M+H]^+$ calc.: 366.0812; found: 366.0809.

***Cis*-5b':**

R_f 0.48 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 5.50 (s, 2H), 5.29 (s, 2H), 4.92 (s, 2H), 4.68 (s, 2H), 4.24 (dd, *J* = 9.5, 4.1 Hz, 2H), 3.21 – 2.93 (m, 16H), 2.72 (dd, *J* = 15.6, 9.4 Hz, 2H).

^{13}C NMR ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 148.6, 140.8, 139.8, 118.2, 109.3, 109.1, 81.5, 72.4, 66.8, 47.1, 39.2, 37.8, 35.1.

IR (ATR, neat, cm^{-1})

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

***Trans*-5b':**

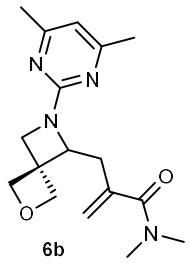
R_f 0.41 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.37 (d, *J* = 8.8 Hz, 1H), 5.44 (d, *J* = 1.7 Hz, 2H), 5.28 (d, *J* = 1.4 Hz, 2H), 5.09 (d, *J* = 7.3 Hz, 2H), 4.62 (d, *J* = 7.3 Hz, 2H), 4.49 (dd, *J* = 10.0, 2.7 Hz, 2H), 3.22 (dq, *J* = 15.9, 2.0 Hz, 2H), 3.10 (s, 6H), 2.96 (s, 6H), 2.47 (dd, *J* = 15.9, 10.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 155.2, 148.9, 141.1, 139.6, 117.8, 109.8, 108.2, 76.8, 64.7, 47.1, 39.0, 35.0, 33.3.

IR (ATR, neat, cm^{-1})

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



Compound 6b.

Prepared following general procedure C, using compound **6** (41 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (37 mg, 0.12 mmol, 58% yield) was isolated as an amorphous white solid, alongside double derivatized products (9 mg, 0.02 mmol, 10% yield).

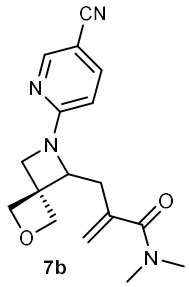
R_f 0.52 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 5.43 (s, 1H), 5.29 (s, 1H), 5.11 (d, *J* = 7.1 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.73 – 4.63 (m, 2H), 4.49 (dd, *J* = 10.1, 3.0 Hz, 1H), 4.23 (d, *J* = 9.3 Hz, 1H), 4.11 (d, *J* = 9.3 Hz, 1H), 3.29 (ddt, *J* = 16.0, 3.2, 1.7 Hz, 1H), 3.10 (s, 3H), 2.96 (s, 3H), 2.71 (ddt, *J* = 16.0, 10.1, 1.2 Hz, 1H), 2.25 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 167.3, 163.3, 142.0, 116.9, 110.4, 81.0, 77.5, 66.7, 58.9, 42.7, 38.8, 35.4, 34.9, 24.0.

IR (ATR, neat, cm^{-1}) 1617 (m), 1575 (s), 1558 (s), 1495 (m), 1455 (s), 1382 (m), 1338 (m), 1313 (m), 1118 (m), 975 (m), 789 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{17}H_{25}N_4O_2$ $[M+H]^+$ calc.: 317.1972; found: 317.1967.



Compound 7b.

Prepared following general procedure C, using compound **7** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (26 mg, 0.08 mmol, 42% yield) was isolated as an amorphous white solid, alongside recovered starting material (3 mg, 0.01 mmol, 7% yield), and double derivatized products (18 mg, 0.04 mmol, 21% yield).

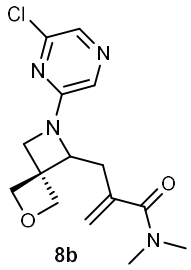
R_f 0.52 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 2.3, 0.8 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.45 (dd, *J* = 8.8, 0.8 Hz, 1H), 5.46 (s, 1H), 5.30 (s, 1H), 5.10 (d, *J* = 7.3 Hz, 1H), 4.81 – 4.65 (m, 3H), 4.56 (dd, *J* = 8.6, 4.1 Hz, 1H), 4.30 (dd, *J* = 9.4, 1.1 Hz, 1H), 4.11 (d, *J* = 9.4 Hz, 1H), 3.19 – 2.76 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 160.5, 152.9, 140.4, 139.5, 118.8, 118.7, 106.3, 97.5, 81.2, 76.8, 67.6, 59.3, 43.1, 39.0, 36.0, 35.0.

IR (ATR, neat, cm^{-1}) 2933 (w), 2869 (w), 2216 (m), 1613 (m), 1595 (s), 1500 (s), 1417 (m), 1395 (w), 1309 (w), 975 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{17}H_{21}N_4O_2$ $[M+H]^+$ calc.: 313.1659; found: 313.1661.



8b

Compound 8b.

Prepared following general procedure C, using compound **8** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (31 mg, 0.10 mmol, 48% yield) was isolated as an amorphous white solid, alongside recovered starting material (3 mg, 0.01 mmol, 7% yield), and double derivatized products (13 mg, 0.03 mmol, 15% yield).

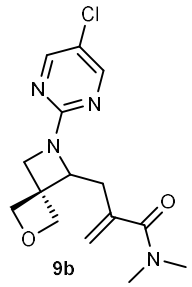
R_f 0.53 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.75 (s, 1H), 5.45 (s, 1H), 5.31 (s, 1H), 5.12 (d, *J* = 7.3 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 1H), 4.74 – 4.62 (m, 2H), 4.56 (dd, *J* = 8.6, 4.1 Hz, 1H), 4.32 (dd, *J* = 9.1, 1.1 Hz, 1H), 4.09 (d, *J* = 9.1 Hz, 1H), 3.17 – 2.79 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 155.2, 147.1, 140.6, 131.9, 128.2, 118.6, 80.9, 77.0, 67.8, 59.7, 43.7, 38.9, 36.1, 34.9.

IR (ATR, neat, cm^{-1}) 1613 (s), 1563 (s), 1501 (s), 1456 (s), 1407 (s), 1394 (s), 1345 (m), 1317 (w), 1202 (w), 1173 (s), 1104 (s), 989 (m), 974 (s), 943 (m), 834 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{20}ClN_4O_2$ $[M+H]^+$ calc.: 323.1269; found: 323.1268.



Compound 9b.

Prepared following general procedure C, using compound **9** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (44 mg, 0.14 mmol, 68% yield) was isolated as an amorphous white solid, alongside recovered starting material (5 mg, 0.02 mmol, 10% yield), and double derivatized products (18 mg, 0.04 mmol, 21% yield).

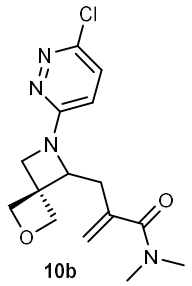
R_f 0.53 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 2H), 5.48 – 5.41 (m, 1H), 5.30 (s, 1H), 5.13 (d, *J* = 7.2 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.75 – 4.64 (m, 2H), 4.53 (dd, *J* = 9.8, 3.4 Hz, 1H), 4.24 (dd, *J* = 9.5, 1.1 Hz, 1H), 4.13 (d, *J* = 9.5 Hz, 1H), 3.22 (ddt, *J* = 16.0, 3.4, 1.7 Hz, 1H), 3.11 (s, 3H), 2.97 (s, 3H), 2.78 (ddt, *J* = 16.1, 9.9, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 161.1, 156.2, 141.2, 119.9, 117.6, 81.0, 77.2, 67.2, 59.1, 42.9, 39.0, 35.3, 35.0.

IR (ATR, neat, cm^{-1}) 2868 (w), 1639 (m), 1615 (m), 1575 (s), 1525 (s), 1489 (s), 1458 (s), 1389 (m), 1367 (m), 1135 (m), 1124 (m), 975 (m), 789 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{20}ClN_4O_2$ $[M+H]^+$ calc.: 323.1269; found: 323.1267.



Compound 10b.

Prepared following general procedure C, using compound **10** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (28 mg, 0.09 mmol, 43% yield) was isolated as an amorphous white solid, alongside recovered starting material (15 mg, 0.07 mmol, 35% yield).

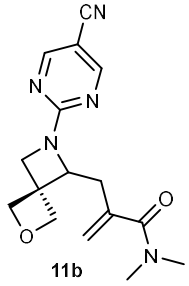
R_f 0.39 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 9.3 Hz, 1H), 6.87 (d, *J* = 9.3 Hz, 1H), 5.45 (s, 1H), 5.26 (s, 1H), 5.11 (d, *J* = 7.3 Hz, 1H), 4.81 – 4.67 (m, 3H), 4.56 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.34 (dd, *J* = 9.2, 1.0 Hz, 1H), 4.15 (d, *J* = 9.2 Hz, 1H), 3.16 – 2.81 (m, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 160.2, 147.7, 140.4, 128.9, 118.9, 115.6, 81.1, 76.9, 68.1, 59.9, 43.7, 39.0, 36.8, 34.9.

IR (ATR, neat, cm^{-1}) 2933 (w), 2868 (w), 1639 (m), 1611 (s), 1582 (s), 1529 (m), 1434 (s), 1393 (m), 1348 (m), 1153 (m), 975 (m), 758 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{20}ClN_4O_2$ $[M+H]^+$ calc.: 323.1269; found: 323.1270.



11b

Compound 11b.

Prepared following general procedure C, using compound **11** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (26 mg, 0.08 mmol, 41% yield) was isolated as an amorphous white solid, alongside double derivatized products (17 mg, 0.04 mmol, 20% yield).

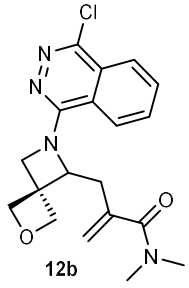
R_f 0.48 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 2H), 5.47 (t, J = 1.6 Hz, 1H), 5.35 (s,1H), 5.15 (d, J = 7.3 Hz, 1H), 4.88 – 4.76 (m, 2H), 4.75 – 4.66 (m, 2H), 4.39 – 4.25 (m, 2H), 3.28 (ddt, J = 16.0, 3.4, 1.7 Hz, 1H), 3.13 (s, 3H), 2.98 (s, 3H), 2.82 (ddt, J = 16.0, 9.8, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 161.0, 160.9, 140.7, 117.9, 116.6, 97.0, 81.0, 77.4, 67.5, 58.8, 42.9, 39.0, 35.0, 34.5.

IR (ATR, neat, cm^{-1}) 2938 (w), 2873 (w), 2220 (m), 1615 (m), 1595 (s), 1541 (m), 1513 (m), 1399 (m), 1227 (w), 1125 (w), 975 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{16}H_{20}N_5O_2$ $[M+H]^+$ calc.: 314.1612; found: 314.1609.



12b

Compound 12b.

Prepared following general procedure C, using compound **12** (52 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (34 mg, 0.09 mmol, 46% yield) was isolated as an amorphous white solid, alongside recovered starting material (3 mg, 0.01 mmol, 6% yield), and double derivatized products (17 mg, 0.04 mmol, 18% yield).

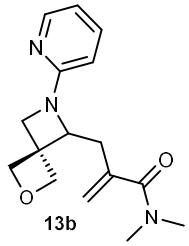
R_f 0.47 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.13 (m, 1H), 7.94 – 7.77 (m, 3H), 5.47 (td, *J* = 1.5, 0.7 Hz, 1H), 5.34 – 5.23 (m, 2H), 5.09 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.96 – 4.82 (m, 2H), 4.76 (dd, *J* = 7.3, 0.7 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.34 (d, *J* = 8.3 Hz, 1H), 3.16 – 2.93 (m, 5H), 2.84 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 157.2, 147.9, 141.6, 132.7, 132.1, 127.0, 125.8, 124.0, 121.2, 117.9, 80.9, 77.5, 67.4, 64.8, 44.0, 39.0, 35.1, 34.9.

IR (ATR, neat, cm^{-1}) 2359 (s), 2329 (s), 1614 (m), 1494 (m), 1419 (m), 1348 (m), 1295 (w), 1120 (w), 974 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{19}H_{22}ClN_4O_2$ $[M+H]^+$ calc.: 373.1426; found: 373.1427.



Compound 13b.

Prepared following general procedure C, using compound **13** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (32 mg, 0.11 mmol, 56% yield) was isolated as a colorless oil, alongside recovered starting material (3 mg, 0.02 mmol, 9% yield), and double derivatized products (28 mg, 0.07 mmol, 35% yield).

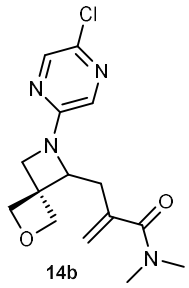
R_f 0.47 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (ddd, *J* = 5.1, 2.0, 0.9 Hz, 1H), 7.50 – 7.38 (m, 1H), 6.62 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.50 (s, 1H), 5.30 (s, 1H), 5.14 (d, *J* = 7.2 Hz, 1H), 4.76 – 4.65 (m, 3H), 4.39 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.24 (d, *J* = 8.8 Hz, 1H), 4.01 (d, *J* = 8.8 Hz, 1H), 3.20 – 3.06 (m, 4H), 2.95 (s, 3H), 2.82 (dd, *J* = 15.6, 9.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 160.4, 147.9, 141.0, 137.4, 118.2, 113.8, 107.1, 81.1, 77.4, 67.2, 59.7, 43.1, 39.1, 36.6, 35.0.

IR (ATR, neat, cm^{-1}) 2929 (w), 2865 (w), 1639 (m), 1613 (s), 1591 (s), 1560 (w), 1481 (s), 1436 (s), 1392 (m), 1123 (w), 975 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{16}H_{22}N_3O_2$ $[M+H]^+$ calc.: 288.1707; found: 288.1701.



14b

Compound 14b.

Prepared following general procedure C, using compound **14** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (25 mg, 0.08 mmol, 39% yield) was isolated as an amorphous white solid, alongside recovered starting material (10 mg, 0.05 mmol, 24% yield), and double derivatized products (10 mg, 0.02 mmol, 12% yield).

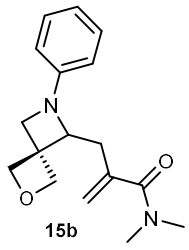
R_f 0.59 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.4 Hz, 1H), 7.66 (d, *J* = 1.4 Hz, 1H), 5.47 (t, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 1.2 Hz, 1H), 5.12 (d, *J* = 7.3 Hz, 1H), 4.81 – 4.66 (m, 3H), 4.53 (dd, *J* = 8.7, 4.3 Hz, 1H), 4.28 (d, *J* = 9.0 Hz, 1H), 4.03 (d, *J* = 8.9 Hz, 1H), 3.13 – 2.93 (m, 7H), 2.83 (ddd, *J* = 15.3, 8.7, 1.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 154.9, 141.4, 140.4, 137.5, 129.5, 118.6, 80.8, 77.1, 67.9, 59.8, 43.7, 39.0, 36.0, 35.0.

IR (ATR, neat, cm^{-1}) 2931 (w), 2869 (w), 2308 (w), 1738 (w), 1615 (s), 1567 (s), 1511 (m), 1473 (s), 1392 (m), 1345 (m), 1210 (w), 1171 (w), 1126 (m), 975 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{20}ClN_4O_2$ $[M+H]^+$ calc.: 323.1269; found: 323.1270.



15b

Compound 15b.

Prepared following general procedure C, using compound **15** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (20 mg, 0.07 mmol, 35% yield) was isolated as an amorphous white solid, alongside double derivatized products (19 mg, 0.05 mmol, 24% yield).

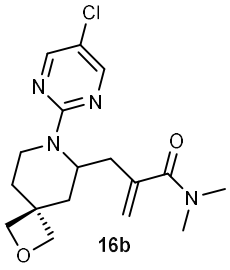
R_f 0.30 (*c*-hexane/EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.15 (m, 2H), 6.77 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.62 – 6.51 (m, 2H), 5.54 (s, 1H), 5.35 – 5.28 (m, 1H), 5.16 (d, *J* = 7.1 Hz, 1H), 4.73 (d, *J* = 7.1 Hz, 1H), 4.66 (s, 2H), 4.25 – 4.10 (m, 2H), 3.74 (d, *J* = 8.0 Hz, 1H), 3.20 – 2.93 (m, 7H), 2.77 (ddd, *J* = 15.6, 9.8, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 151.1, 140.7, 129.2, 118.6, 118.4, 112.5, 80.8, 68.0, 61.4, 43.1, 39.1, 37.1, 35.1.

IR (ATR, neat, cm^{-1}) 2927 (w), 2864 (w), 1640 (m), 1613 (s), 1598 (s), 1496 (s), 1455 (w), 1392 (m), 1324 (m), 1123 (m), 974 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{17}H_{23}N_2O_2$ $[M+H]^+$ calc.: 287.1754; found: 287.1751.



Compound 16b.

Prepared following general procedure C, using compound **16** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (31 mg, 0.09 mmol, 44% yield) was isolated as an amorphous white solid, alongside recovered starting material (16 mg, 0.07 mmol, 33% yield).

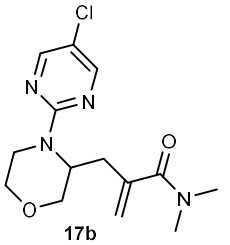
R_f 0.20 (*c*-hexane/EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H), 5.33 (s, 1H), 5.18 – 5.08 (m, 2H), 4.75 (d, *J* = 5.7 Hz, 1H), 4.67 – 4.52 (m, 2H), 4.44 (d, *J* = 5.7 Hz, 1H), 4.21 (d, *J* = 5.7 Hz, 1H), 3.11 – 2.89 (m, 2H), 2.81 (d, *J* = 55.0 Hz, 6H), 2.57 – 2.43 (m, 2H), 2.26 (dq, *J* = 13.3, 2.4 Hz, 1H), 2.16 (dt, *J* = 13.8, 1.9 Hz, 1H), 1.59 (ddd, *J* = 24.0, 13.4, 5.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 159.8, 156.0, 141.4, 118.1, 118.0, 83.2, 82.4, 49.6, 39.0, 38.0, 36.4, 35.9, 35.7, 35.0, 34.5.

IR (ATR, neat, cm^{-1}) 2928 (w), 2853 (w), 1615 (m), 1582 (s), 1491 (s), 1399 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{17}H_{23}ClN_4NaO_2$ $[M+Na]^+$ calc.: 373.1402; found: 373.1394.



Compound 17b.

Prepared following general procedure C, using compound **17** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (41 mg, 0.13 mmol, 66% yield) was isolated as a colorless oil, alongside recovered starting material (8 mg, 0.04 mmol, 20% yield), and double derivatized products (12 mg, 0.03 mmol, 14% yield).

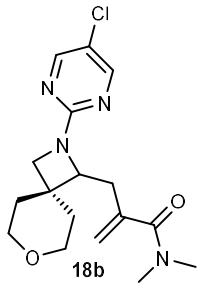
R_f 0.43 (*c*-hexane/EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 2H), 5.37 (s, 1H), 5.16 (s, 1H), 4.83 – 4.74 (m, 1H), 4.34 (dd, *J* = 13.7, 2.9 Hz, 1H), 4.02 – 3.87 (m, 2H), 3.60 – 3.44 (m, 2H), 3.28 (ddd, *J* = 13.8, 12.3, 3.7 Hz, 1H), 2.99 – 2.75 (m, 7H), 2.68 (dd, *J* = 14.0, 6.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 159.5, 156.0, 141.6, 118.4, 118.4, 68.3, 67.0, 50.0, 39.7, 38.8, 34.9, 33.2.

IR (ATR, neat, cm^{-1}) 1614 (m), 1580 (s), 1526 8m), 1478 (s), 1448 (s), 1393 (m), 1229 (m), 1124 (m), 1018 (m), 951 (m), 785 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{14}H_{20}ClN_4O_2$ $[M+H]^+$ calc.: 311.1269; found: 311.1265.



Compound 18b.

Prepared following general procedure C, using compound **18** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (40 mg, 0.11 mmol, 57% yield) was isolated as an amorphous white solid, alongside recovered starting material (13 mg, 0.06 mmol, 27% yield), and double derivatized products (11 mg, 0.02 mmol, 12% yield).

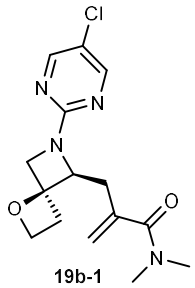
R_f 0.63 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 2H), 5.29 (s, 1H), 5.19 (s, 1H), 4.20 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.99 – 3.76 (m, 5H), 3.37 (tdd, *J* = 11.9, 6.4, 2.3 Hz, 2H), 3.19 – 3.06 (m, 4H), 2.99 (s, 3H), 2.74 (dd, *J* = 15.8, 10.2 Hz, 1H), 2.03 – 1.89 (m, 2H), 1.84 (dq, *J* = 13.2, 2.4 Hz, 1H), 1.64 (dq, *J* = 13.3, 2.3 Hz, 1H).

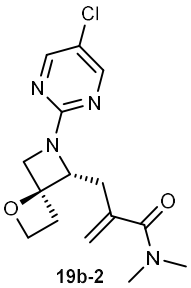
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 161.5, 156.1, 142.3, 119.5, 116.8, 69.3, 64.9, 64.7, 58.8, 39.0, 37.6, 37.4, 35.0, 33.4, 31.7.

IR (ATR, neat, cm^{-1}) 2931 (w), 2843 (w), 1737 (w), 1641 (m), 1621 (m), 1577 (s), 1526 (m), 1496 (s), 1469 (s), 1388 (w), 1106 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{17}H_{24}ClN_4O_2$ $[M+H]^+$ calc.: 351.1582; found: 351.1584.



19b-1



19b-2

Compound 19b-1 and 19b-2.

Prepared following general procedure C, using compound **19** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired products (31 mg, 0.10 mmol, 48% yield) were isolated as an inseparable mixture of the two diastereomers in a 10:1 ratio as a colorless oil, alongside recovered starting material (9 mg, 0.04 mmol, 20% yield), and double derivatized products (10 mg, 0.02 mmol, 12% yield).

Note: because of the overlapping signals, especially as regards the ^{1}H NMR, a precise assignment of the peaks of the minor diastereomer is prohibitive.

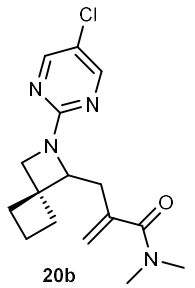
R_f 0.63 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) **major:** δ 8.19 (s, 2H), 5.42 (s, 1H), 5.27 (s, 1H), 4.60 (ddd, *J* = 10.1, 3.7, 1.5 Hz, 1H), 4.55 – 4.44 (m, 2H), 4.26 – 4.10 (m, 2H), 3.18 – 2.96 (m, 8H), 2.93 – 2.74 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) **major:** δ 171.8, 160.8, 156.1, 142.4, 119.5, 117.2, 85.1, 72.5, 67.3, 63.4, 38.8, 34.9, 33.3, 31.3.

IR (ATR, neat, cm^{-1}) 1618 (m), 1574 (s), 1525 (m), 1488 (s), 1449 (s), 1388 (m), 1242 (w), 1143 (m), 976 (m), 952 (m), 789 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{20}ClN_4O_2$ $[M+H]^+$ calc.: 323.1269; found: 323.1264.



20b

Compound 20b.

Prepared following general procedure C, using compound **20** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (37 mg, 0.12 mmol, 58% yield) was isolated as a colorless oil, alongside double derivatized products (23 mg, 0.05 mmol, 27% yield).

R_f 0.57 (*c*-hexane/EtOAc = 1:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H), 5.34 (s, 1H), 5.23 (s, 1H), 4.31 (dd, *J* = 9.8, 3.5 Hz, 1H), 4.07 (dd, *J* = 8.8, 1.0 Hz, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 3.13 – 3.02 (m, 4H), 2.98 (s, 3H), 2.69 (ddt,

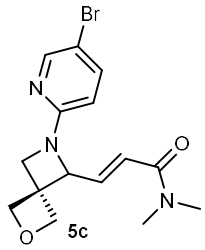
J = 15.8, 9.7, 1.1 Hz, 1H), 2.56 – 2.44 (m, 1H), 2.23 (dt, *J* = 11.3, 8.5 Hz, 1H), 2.08 (ddt, *J* = 11.9, 8.5, 4.2 Hz, 1H), 1.97 (dtd, *J* = 14.5, 9.3, 5.2 Hz, 1H), 1.92 – 1.76 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 161.1, 156.0, 142.4, 119.1, 116.6, 68.7, 62.6, 42.8, 38.9, 35.1, 35.0, 33.5, 28.6, 16.4.

IR (ATR, neat, cm^{-1}) 2930 (w), 1640 (m), 1619 (m), 1574 (s), 1523 (m), 1488 (s), 1460 (s), 1388 (m), 1366 (m), 1296 (w), 1122 (m), 977 (w), 786 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{16}H_{22}ClN_4O$ $[M+H]^+$ calc.: 321.1477; found: 321.1473.

HAT vinylation products



Compound 5c.

Prepared following general procedure D, using compound **5** (51 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (25 mg, 0.07 mmol, 35% yield) was isolated as an amorphous white solid, alongside recovered starting material (18 mg, 0.07 mmol, 35% yield).

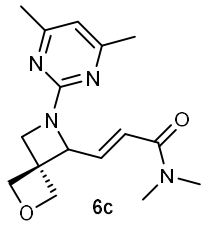
R_f 0.47 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.09 (dd, *J* = 15.0, 5.2 Hz, 1H), 6.58 (dd, *J* = 15.0, 1.5 Hz, 1H), 6.23 (dd, *J* = 8.8, 0.7 Hz, 1H), 4.87 (d, *J* = 7.2 Hz, 1H), 4.79 – 4.62 (m, 5H), 4.21 (dd, *J* = 8.9, 1.2 Hz, 1H), 4.09 (d, *J* = 8.9 Hz, 1H), 3.04 (s, 3H), 3.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 158.8, 148.9, 140.5, 139.9, 123.1, 109.3, 108.5, 80.0, 77.8, 70.2, 59.0, 44.2, 37.6, 35.9.

IR (ATR, neat, cm^{-1}) 2866 (w), 1660 (m), 1615 (m), 1579 (s), 1547 (w), 1462 (s), 1391 (s), 1343 (m), 1292 (w), 1148 (m), 1091 (w), 974 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{19}BrN_3O_2$ $[M+H]^+$ calc.: 352.0655; found: 352.0645.



Compound 6c.

Prepared following general procedure D, using compound **6** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (37 mg, 0.12 mmol, 58% yield) was isolated as an amorphous white solid, alongside double derivatized products (23 mg, 0.05 mmol, 27% yield).

R_f 0.31 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

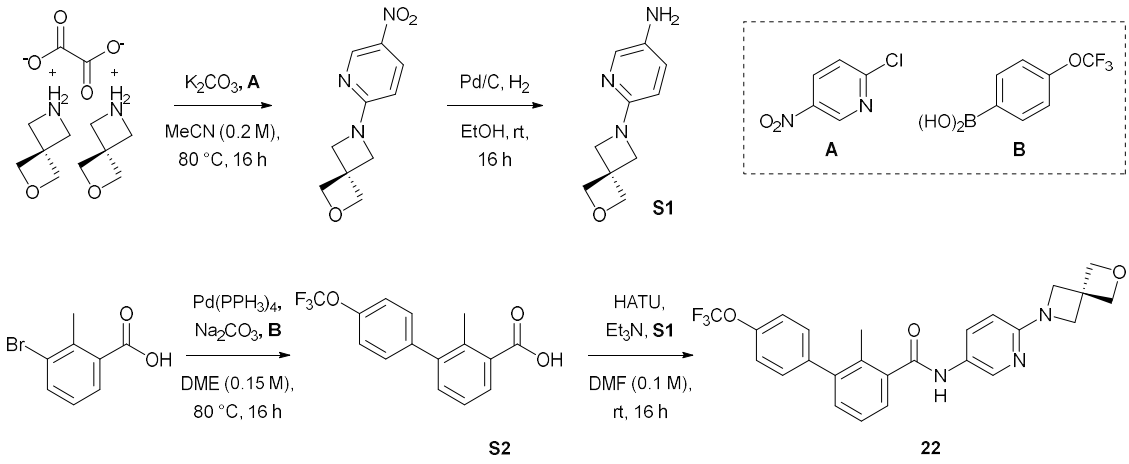
^{1}H NMR ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 15.0, 5.3 Hz, 1H), 6.58 (dd, *J* = 15.0, 1.6 Hz, 1H), 6.37 (s, 1H), 4.91 (t, *J* = 6.6 Hz, 2H), 4.78 (q, *J* = 7.0 Hz, 2H), 4.63 (d, *J* = 7.2 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.02 (d, *J* = 10.1 Hz, 6H), 2.27 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 166.4, 163.3, 140.6, 123.0, 111.0, 80.7, 77.8, 69.3, 58.9, 43.5, 37.5, 35.8, 24.0.

IR (ATR, neat, cm^{-1}) 2868 (w), 1662 (m), 1618 (m), 1578 (s), 1455 (s), 1382 (m), 1335 (m), 1299 (w), 1149 (w), 974 (m).

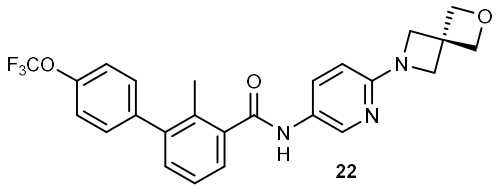
HRMS (ESI-TOF, m/z) calcd. for $C_{16}H_{23}N_4O_2$ $[M+H]^+$ calc.: 303.1816; found: 303.1814.

Synthesis and derivatization of sonidegib analogue



Compounds S1 and S2.

Compounds **S1**[5] and **S2**[6] were synthesized according to reported literature procedures.



22

Compound 22.

Aminopyridine **S1** (165 mg, 0.86 mmol, 1 eq) and carboxylic acid **S2** (256 mg, 0.86 mmol, 1 eq) were weighted in an over dried round-bottom flask. DMF (8.6 mL, 0.1 M) was added, followed by triethylamine (105 mg, 145 µL, 1.04 mmol, 1.2 eq), and HATU (329 mg, 0.86 mmol, 1 eq). The mixture was stirred at room temperature for 16 h. After completion, most of the DMF was removed *via* rotary evaporation, and the crude dissolved in the remaining DMF was directly purified with reverse-phase column chromatography using a water/acetonitrile mixture as eluent (5% to 95% acetonitrile). The desired product (182 mg, 0.39 mmol, 45% yield) was isolated as an amorphous white solid.

Note: because of coupling with fluorine, the trifluoromethyl carbon signals are clearly visible only as regards the two central peaks of the quartet at 121.9 and 119.4 ppm.

R_f 0.13 (*c*-hexane/EtOAc = 1:2, UV, $KMnO_4$).

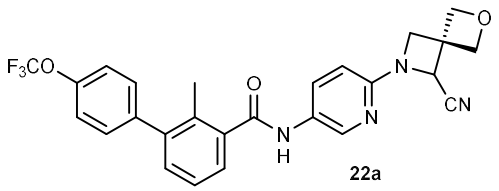
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.6 Hz, 1H), 8.04 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.37 – 7.24 (m, 5H), 6.35 (d, *J* = 8.9 Hz, 1H), 4.85 (s, 4H), 4.17 (s, 4H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 158.0, 148.6, 142.4, 140.5, 140.0, 137.7, 133.6, 131.8, 131.7, 130.7, 126.2, 126.0, 125.9, 121.9, 120.9, 119.4, 106.3, 81.4, 60.6, 39.1, 17.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ -57.78.

IR (ATR, neat, cm^{-1}) 1646 (m), 1505 (m), 1306 8s), 1163 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{25}H_{23}F_3N_3O_3$ $[M+H]^+$ calc.: 470.1686; found: 470.1687.



22a

Compound 22a.

Prepared following general procedure B, using compound **22** (47 mg, 0.10 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (23 mg, 0.05 mmol, 47% yield) was isolated as an amorphous white solid.

Note: because of coupling with fluorine, the trifluoromethyl carbon signals are clearly visible only as regards three peaks of the quartet at 124.5, 121.9, and 119.4 ppm.

R_f 0.47 (*c*-hexane:EtOAc = 1:2, UV, $KMnO_4$).

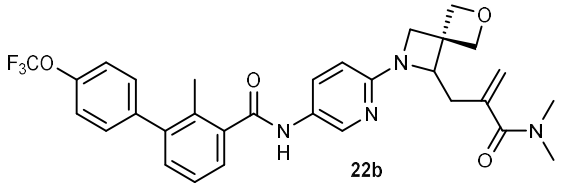
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 2.6 Hz, 1H), 8.16 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.36 – 7.24 (m, 5H), 6.50 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 7.7 Hz, 1H), 4.96 – 4.89 (m, 2H), 4.82 (s, 2H), 4.29 (d, *J* = 8.1 Hz, 1H), 4.09 (d, *J* = 8.1 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 155.4, 148.7, 142.5, 140.4, 139.9, 137.5, 133.7, 132.0, 131.5, 130.7, 128.1, 126.1, 126.1, 124.5, 121.9, 120.9, 119.4, 116.0, 107.0, 79.0, 78.3, 59.5, 57.8, 42.0, 17.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ -57.78.

IR (ATR, neat, cm^{-1}) 2874 (w), 1653 (w), 1609 (w), 1493 (s), 1389 (w), 1255 (s), 1219 (m), 1163 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{26}H_{22}F_3N_4O_3$ $[M+H]^+$ calc.: 495.1639; found: 495.1633.



22b

Compound 22b.

Prepared following general procedure C, using compound **22** (48 mg, 0.10 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (16 mg, 0.03 mmol, 28% yield) was isolated as an amorphous white solid. *Note: because of rotamerism, one quaternary and one non-quaternary aromatic carbons do not present intensities high enough to be detected in the ^{13}C NMR spectrum. This phenomenon can be clearly seen through comparison of the ^{13}C aromatic region of the starting material with the product one since the chemical shifts of the aromatic moieties are largely unaffected by the transformation.*

R_f 0.56 (EtOAc:MeOH = 10:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.05 (s, 1H), 7.50 (dd, *J* = 6.7, 2.4 Hz, 1H), 7.35 – 7.23 (m, 5H), 6.53 (d, *J* = 8.9 Hz, 1H), 5.49 (s, 1H), 5.28 (s, 1H), 5.11 (d, *J* = 7.3 Hz, 1H), 4.71 (dd, *J* = 7.0, 4.0 Hz, 3H), 4.44 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.28 (d, *J* = 8.8 Hz, 2H), 4.02 (d, *J* = 8.8 Hz, 1H), 3.20 – 2.91 (m, 7H), 2.81 (dd, *J* = 15.3, 8.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 168.9, 148.6, 142.3, 140.4, 140.1, 137.6, 133.7, 132.3, 131.8, 130.8, 126.6, 126.4, 126.0, 124.5, 121.9, 120.9, 119.4, 118.6, 116.8, 107.5, 81.0, 77.4, 67.7, 60.1, 43.1, 39.1, 37.0, 35.1, 17.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ -57.77.

IR (ATR, neat, cm^{-1}) 1611 (m), 1493 (s), 1392 (m), 1256 (s), 733 (m).

HRMS (ESI-TOF, m/z) calcd. for $C_{31}H_{32}F_3N_4O_4$ $[M+H]^+$ calc.: 581.2370; found: 581.2359.

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Part II: Studies towards the total synthesis of nimbolide

2.1 Introduction

2.1.1 Nimbolide biochemical properties

Limonoids are a large class of natural products commonly found in the leaves, seeds, fruits, twigs, and roots of a variety of plants including *Meliaceae*, *Rutaceae*, *Cneoraceae* and *Simaroubaceae*.[1] The term derives from the first isolated tetranortriterpenoid of the class, limonin (**1**), found in *citrus* in 1841 (figure 1). Currently, more than 1500 limonoids have been isolated and are known in the literature, evidencing a broad spectrum of biological properties including insect antifeedant,[2] insecticidal,[3] antibacterial,[4] antifungal,[5] antimalarial,[6] antioxidant,[7] cytotoxic,[8] anticancer,[9] antiviral,[10] and anti-inflammatory.[11]

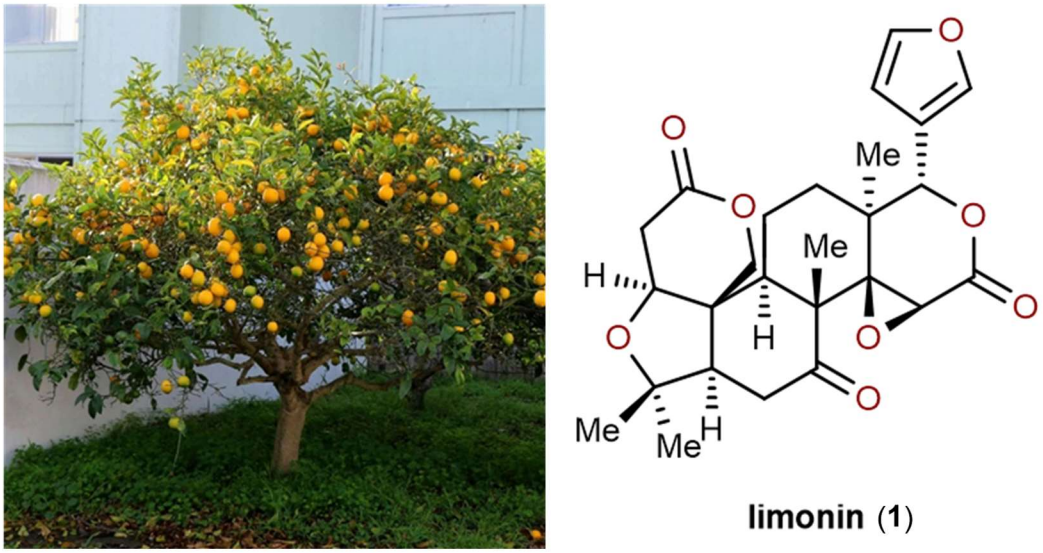


Figure 1. The citrus tree and limonin chemical structure.

Recently, nimbolide (**2**), one of the members of the limonoids family, has attracted much attention from the scientific community because of its peculiar properties. Nimbolide is naturally produced by *Azadirachta indica*, also known as neem, a tree belonging to the *Meliceae* family, which is widespread in different regions of Asia including India, Bangladesh, Burma, Cambodia, Laos, Thailand, and Vietnam (figure 2).[12] The extracts of such plant are known as neem oil, which has been used for centuries in traditional

ayurvedic medicine[13] to treat acne, wounds, gastric ulcers, infections, and it is known to have properties such as anti-malaria,[14] antibacterial (against *S. aureus* and *S. coagulase*),[15] antifeedant,[16] insecticidal,[17] and antioxidant.[18] Nimbolide is one of the major chemical components of neem oil, alongside other limonoids such as azadirachtin,

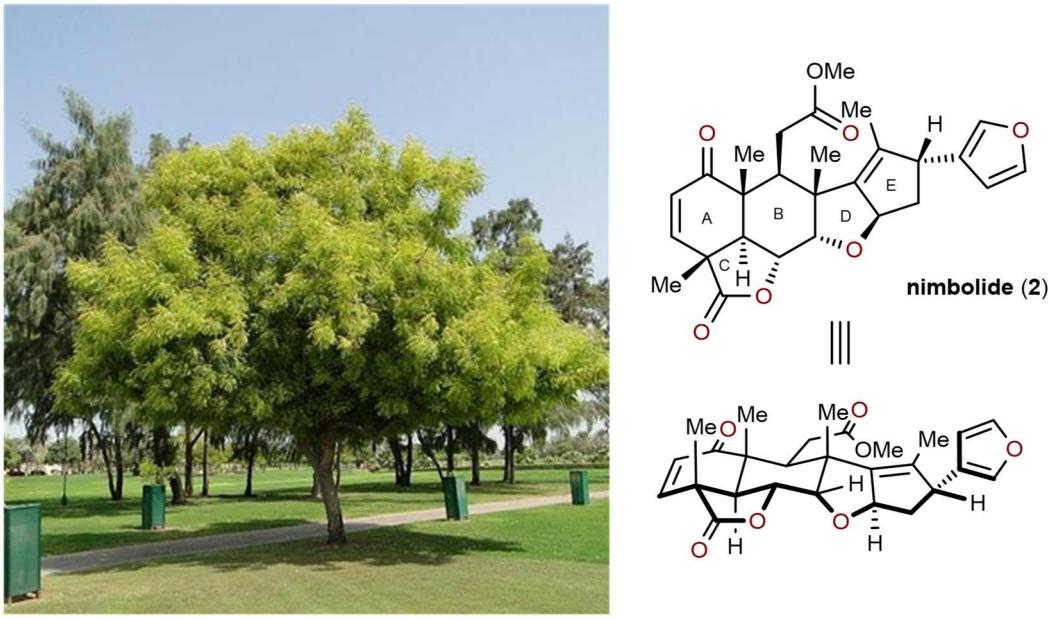


Figure 2. The neem tree and nimbolide chemical structure.

salannin, nimbin, and nimbic acid.[19]

Chemically, nimbolide possesses six cycles, five of which are fused in a pentacyclic system, which confers a relatively rigid three-dimensional conformation, and the other one being a monosubstituted furan.[20] Nine stereogenic centers are present, seven of which are contiguous along the A–B ring skeleton structure. Despite not being heavily oxidized, nimbolide has an interesting enone functionality on the A-ring, alongside a relatively strained γ-lactone, which forms the C-ring, and a side chain on the B-ring bearing a methyl ester.

In recent investigations, nimbolide was the neem oil component that showed the most potent anticancer activity,[21] hence the aforementioned attention on it. Currently, it is at the stage of preclinical pharmacological investigation, with both *in vitro* and *in vivo* studies flourishing in the last decade. For example, through studies on a variety of cancer cell lines, it was shown to be effective at fighting prostate, cervical, breast, colorectal, and brain cancers, Waldenstrom macroglobulinemia (WM), hepatocarcinoma cells, and lymphoma, with the IC_{50} values in the range between 0.2 to 15 µM.[22] The presented functionalities play a key role in the biochemical mechanism of action, which was

identified to be the disruption of the cell cycle through induction of apoptosis on the targeted cancer cells.[23] Recent studies have identified several molecular targets, and showed that the significant cell cytotoxicity and anticancer effect is mostly due to the presence of the α,β-unsaturated ketone functionality.[24] In addition, the γ-lactone moiety was also reported to play an active role in this sense. A series of modifications to the chemical structure have also been analyzed, showcasing that various amide derivatives conferred improved cytotoxicity to the corresponding nimbolide analogue.[25] Besides the strong apoptotic effect, nimbolide remarkably possesses both an inhibitory role on metastasis and a chemopreventive property against carcinogenesis.[26] Such characteristics are of extreme interest, considering that an estimated 90% of cancer deaths are caused by metastases and/or newly formed tumoral masses.[27] These properties have been confirmed by several studies. For example, *in vitro* treatment of breast cancer cell lines presented a significantly decreased cell invasion and migration in the analyzed assays.[28] In another case regarding colorectal cancer xenografts in mice, it was observed that intraperitoneal injections of 5 mg/kg of nimbolide for 10 days caused a 67% reduction in the tumoral volume.[22] At 20 mg/kg, an even more substantial and remarkable 90% reduction was achieved, accompanied by inhibition of angiogenesis and tumor metastasis. The chemopreventive property of nimbolide was highlighted through an *in vivo* study using 7,12-dimethylbenz[*a*]anthracene (**3**)-induced hamster buccal pouch (HBP) carcinogenesis as a model (figure 3).[18] Upon oral administration of 0.01 mg/kg of nimbolide for 14 weeks, the incidence of tumor and pre-neoplastic lesions was significantly reduced, with peaks up to 50%.

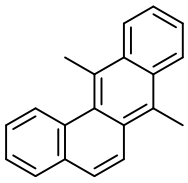


Figure 3. The used carcinogenic compound for inducing HBP.

However, nimbolide is still far from being considered for clinical studies because of several reasons. One of them is that a lot of discrepancies have been noticed between *in vitro* and *in vivo* studies. For example, *in vitro* analysis showed that nimbolide was more potent against WM cells (IC_{50} = 0.2 μM) than colorectal cancer cells (IC_{50} = 1.25 μM). Oppositely, a WM tumor investigation made on mice reported that after 26 days of intraperitoneal treatment, nimbolide was effective only at very high doses (100-200 mg/kg), while significantly lower amounts (5-20 mg/kg) of administration *via* the same intraperitoneal route were found to achieve a good *in vivo* anticancer effect against

colorectal cancer.[29] It should also be pointed out that the doses involved in WM tumor treatment are dangerously close to the reported median lethal dose of nimbolide (LD_{50} = 280 mg/kg) in adult female mice,[30] rising questions on its toxicity, which are still unsolved. Another example is given by a different investigation on glioblastoma multiforme, for which *in vitro* studies indicated a relatively high IC_{50} (3 µM), while *in vivo* treatment with nimbolide was effective at doses as low as 0.01 mg/kg *via* intravenous injection for 7 days.[31] Although such result may be positively received, it actually highlights the current poor understanding and predictability of nimbolide's biochemical behavior.

The incongruencies can be partially explained with the lack of metabolic studies, and partially with nimbolide's intrinsic poor pharmacokinetic properties, the other major problem that is preventing it from reaching clinical studies. In fact, the currently only study on the pharmacokinetic profile of nimbolide presented slow absorption, middle-speed elimination, and very poor absolute bioavailability, especially when administered orally (figure 4a).[32] Taking these facts into account, it is not surprising that in the aforementioned biological studies, the treatment was almost always administered intravenously or intraperitoneally, and orally only once. More specifically, the absolute bioavailability of nimbolide in rats after 10 h from the oral administration was found to be, 1.76%, 2.72%, and 3.06% with doses of 10, 30 and 50 mg/kg, respectively. Moreover, even when decent levels of bioavailability can be reached through intravenous injection, the metabolic elimination is fast, with almost no active compound remaining after less than 10 h (figure 4b).

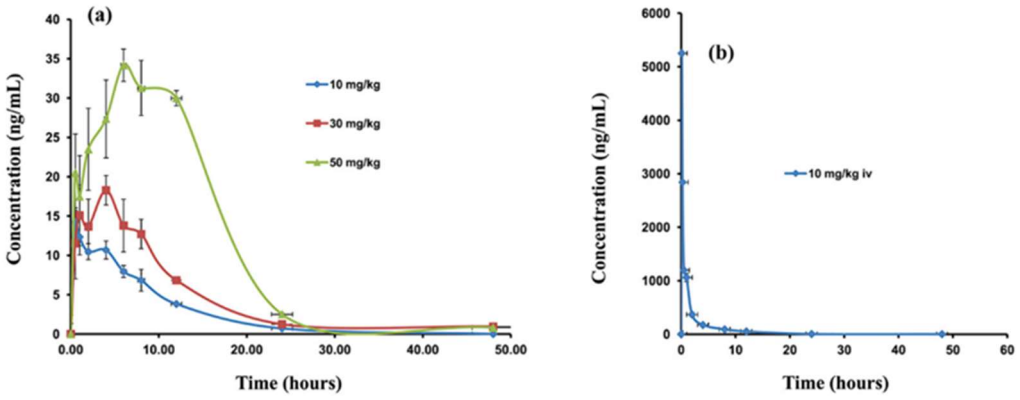


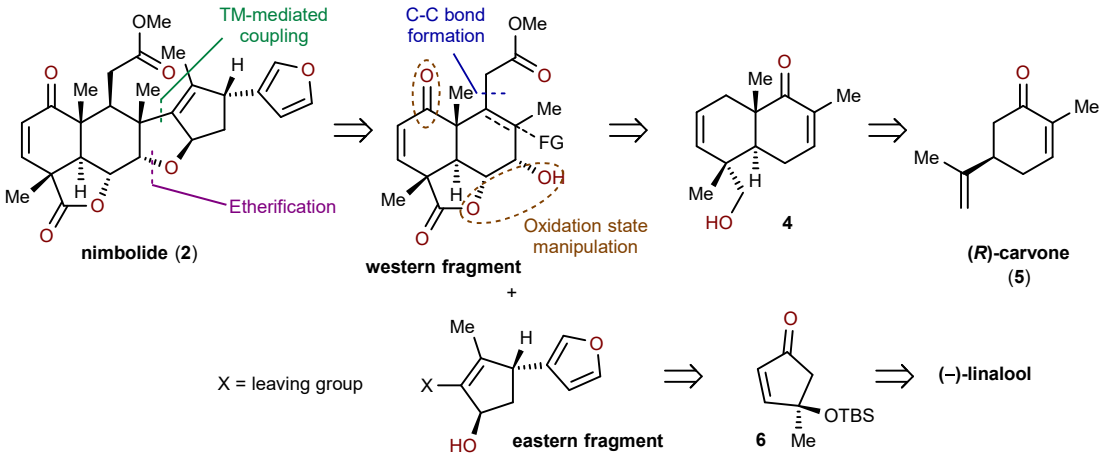
Figure 4. a) Nimbolide bioavailability after oral administration. b) Metabolic concentration of nimbolide.

The presented problems could be addressed more accurately through metabolic studies, aimed at the identification of the molecule's "soft spots" by analysis of secondary metabolites. These studies could be greatly helped by the development of a chemically flexible total synthesis. Such achievement would ensure a greater freedom of access to nimbolide analogues in comparison to any other strategy based on the use of the natural product itself as a starting point. Through an iterative approach between soft spots identification and more stable analogue synthesis, a virtuous cycle would be created, eventually leading to a compound with the ideal metabolic stability. The same strategy could be used to solve the (oral)bioavailability issues, thanks to the fine tuning of the desired pharmacokinetic and pharmacodynamic properties that a total synthesis enables.

For these reasons, we decided it would be worth pursuing the total synthesis of nimbolide.

2.1.2 General disconnection approach and state of the art

Our approach during the retrosynthetic analysis of nimbolide was guided by our desire to achieve a good synthetic efficiency. Following this concept, we proceeded to find disconnections in a convergent fashion. Previous studies towards the total synthesis of azadirachtin from the Nicolaou's group reported diastereoselective installation of the quaternary carbon of the tetrahydrofuran (D-ring) in a similar substrate, using a hydrodehalogenative radical cyclization between the sp^2-carbon and the B ring.[33] Taking inspiration from this, we envisioned a first disconnection between the same two carbon atoms through a (retro) transition metal-mediated coupling (scheme 1). A consequential (retro)etherification disconnection completes the simplification of the target structure,



Scheme 1. General retrosynthetic plan from nimbolide.

efficiently separating nimbolide into two halves, a western fragment and an eastern one. According to our strategy, the latter is a highly functionalized cyclopentenol with a vinyl leaving group necessary for the final cyclization. On the other side, the former possesses an appropriate functional handle to behave as the coupling counterpart, *id est* an olefin (for an intramolecular Heck reaction) or a carboxylic acid (for an intramolecular decarboxylative coupling). This approach would also be suitable for an alternative radical cyclization, similarly to the previously mentioned one, in case the transition metal-catalyzed step presented difficulties. Proceeding with the retrosynthetic analysis, the western fragment was reconducted to bicyclic intermediate **4** through adjustments of oxidation states and disconnection of the methyl ester side chain. **4** would finally derive from chiral pool member (*R*)-carvone (**5**) through diastereoselective construction of the A-ring. The identification of (*R*)-carvone as the ideal starting material was due to its natural abundancy, which would enable an easy access to enantioselective synthesis at low costs. The eastern fragment was eventually traced back to known compound **6**, previously reported by Maimone's group, and synthesizable in three steps from (–)-linalool (see the "Attempted syntheses" section for details).[34]

It is important to point out that in our strategy, while we were willing to modify and adapt most of the synthetic approach according to experimental feedback, the inclusion of bicyclic intermediate **4** was considered to be of crucial importance. In fact, we realized that the development of a quick, efficient, and stereoselective route to **4**, its epimer at the allylic quaternary carbon (**epi-4**), and corresponding analogues would be greatly beneficial not only towards the synthesis of nimbolide itself, but also to open the doors

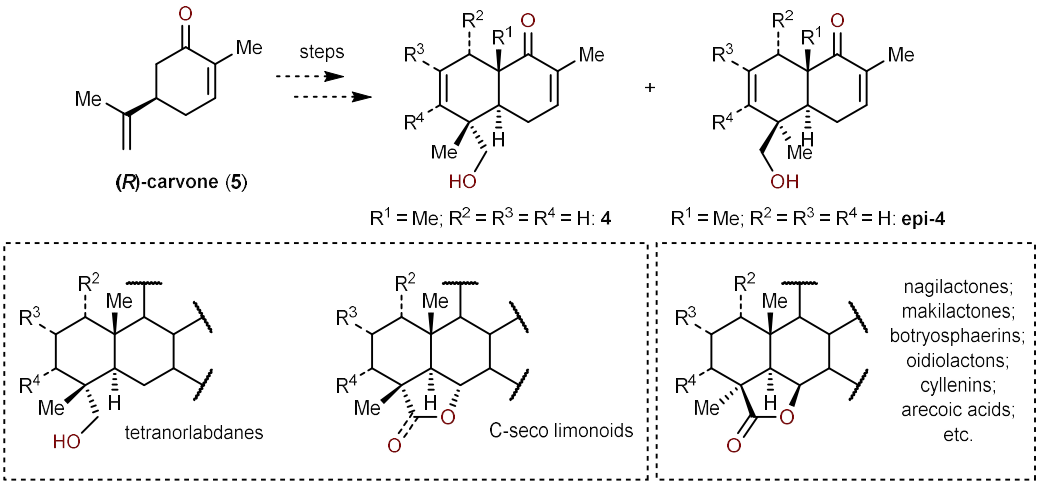
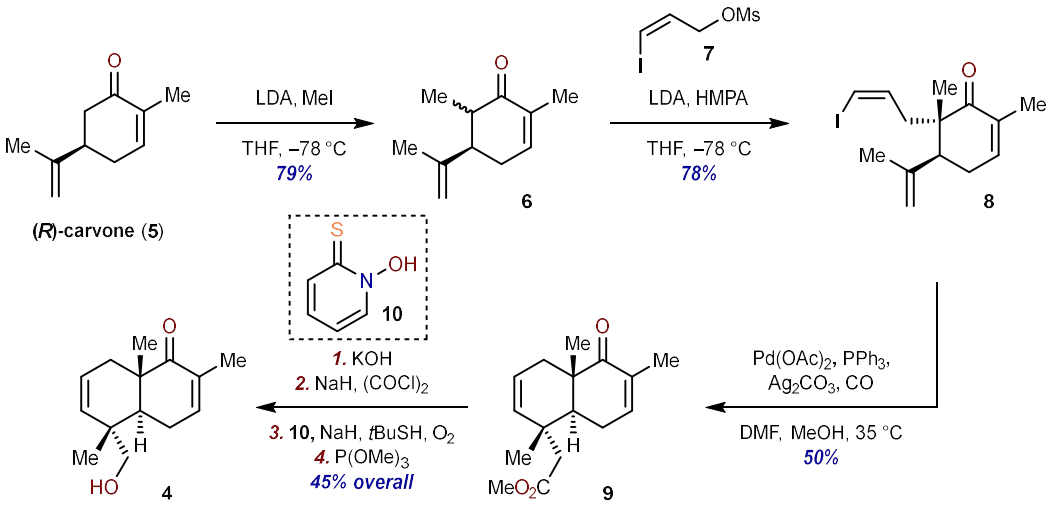


Figure 5. Potential access to families of natural products through **4** and **epi-4**.

to the main skeletal structure of entire families of natural products (figure 5). With appropriate modifications of the electrophiles used for the sequential derivatizations of carvone, over sixty possible target molecules were identified, showcasing the potential of this strategy. To the best of our knowledge, the key intermediate **4** has been



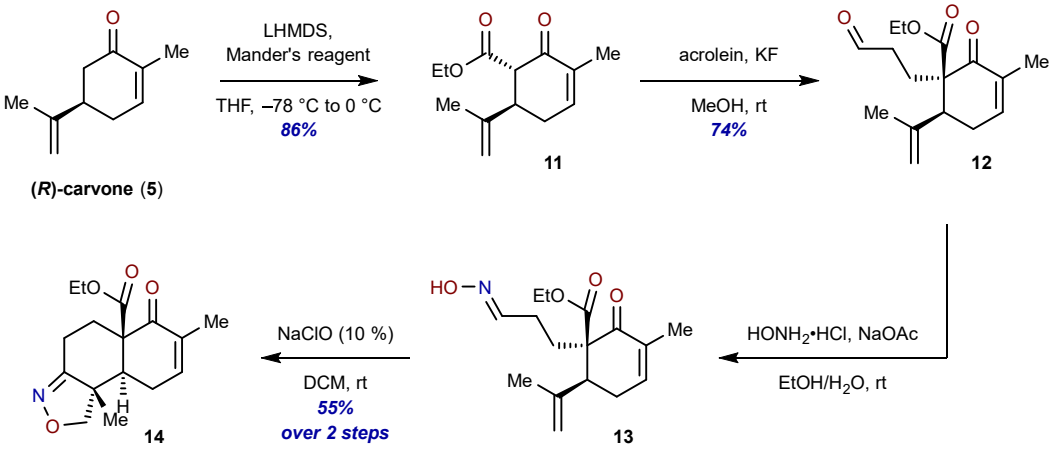
Scheme 2. Current reported synthetic pathway to bicycle **4**.

previously synthesized only once, in a seven-step sequence starting from (*R*)-carvone (scheme 2).[35]

The reported route involves initial methylation of (*R*)-carvone (**5**) through treatment with LDA and methyl iodide in THF. The transformation afforded **6** as a 3:1 mixture of diastereomers in 79% yield. Although the two epimers were separable by silica gel flash column chromatography, the following second kinetic deprotonation would erase the stereochemical information at that carbon. They were therefore treated together with 2 eq. of LDA in THF at -78 °C, followed by 1 eq. of HMPA at 0 °C, and then *cis*-3-iodo-2-propenyl methanesulfonate (**7**) to give a 78% yield of vinyl iodide **8** as a single stereoisomer. A series of conditions to perform subsequential intramolecular carbonylative Heck reaction were screened. After careful kinetic studies, the optimal combination required a specific order of addition of the reactants, with stoichiometric amounts of palladium(II) acetate involved. The desired diastereomer **9** was afforded in 50% yield, alongside 23% yield of its epimer at the allylic quaternary carbon (not shown). The final conversion to **4** was carried out in four steps following Barton's decarboxylation/hydroxylation procedure. Initial hydrolysis of methyl ester on **9** afforded the corresponding carboxylic acid, which was converted to the acyl chloride through treatment with sodium hydride and oxalyl chloride. Formation of the Barton's

ester and subsequent radical decarboxylation could be performed one pot in the presence of *N*-hydroxy-2-thiopyridinone (**10**), sodium hydride, *tert*-butylthiol, and oxygen. These conditions afforded the corresponding hydroperoxide, which was reduced with trimethylphosphite to give desired compound **4** in an excellent 45% yield over the four steps.

Other strategies have been reported in the literature to access compounds that could be converted to **4** or related analogues with short synthetic sequences. One example is given by the synthesis of **14** as an intermediate in the construction of the ABD tricyclic skeleton of melicarpinin B (scheme 3).[36] Carvone was kinetically acylated by treatment

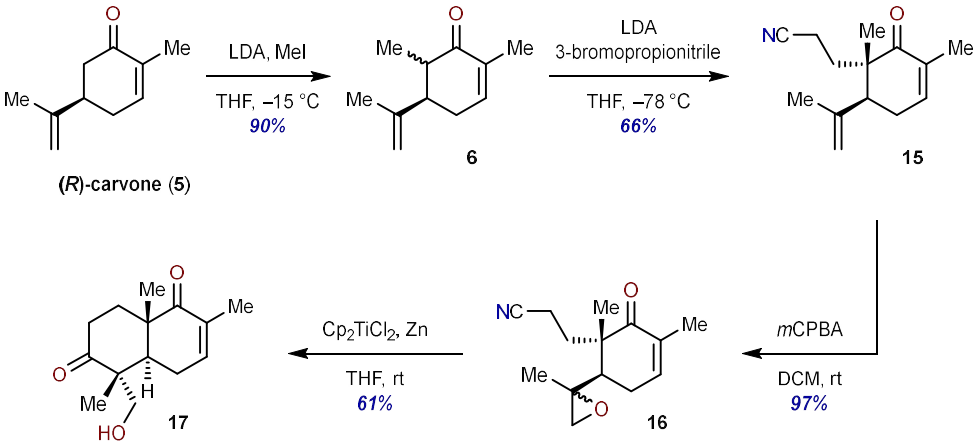


Scheme 3. Synthetic pathway from (*R*)-carvone to tricycle **14**.

with LiHMDS, and Mander's reagent (ethyl cyanoformate) to produce β-ketoester **11**. Second alkylation was performed through a Michael addition on acrolein, with optimized conditions involving the use of potassium fluoride as base and methanol as solvent. Aldehyde **12** was subsequently condensed with hydroxyl amine hydrochloride, giving oxime **13** as product. At this point, the key intramolecular nitrile-oxide cycloaddition (INOC) could be performed with conventional conditions. Subjecting the substrate to a 10 wt% NaClO/DCM mixture, resulted in a smooth INOC reaction, which afforded *trans*-decalin **14** as a single diastereoisomer in 55% yield over the two steps. Notably, other oxidants such as chloramine-T, *tert*-butyl hypochlorite and iodobenzene diacetate gave diminished yields or complex mixtures.

The last example is given by the synthesis of **17** as an intermediate in the total synthesis of pyripyropene A (scheme 4).[37] In this case carvone was alkylated with methyl iodide first, and subsequently with 3-bromoproprionitrile to afford **15** as a single isomer in 59% yield over the two steps. Epoxidation with *m*CPBA afforded **16**, which was subjected to

a titanocene-mediated radical cyclization. Diastereoisomer **17** was obtained in 61% yield as the major product, alongside a 20% of the epimer at the allylic quaternary carbon (not shown).



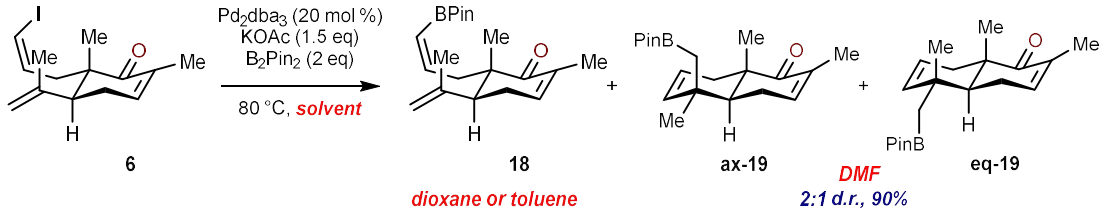
Scheme 4. Synthetic pathway to access bicycle **17** in four steps.

The three presented synthetic routes each showcase some strengths and weaknesses, which were taken into consideration during the planning of our approach. For example, the first one directly accesses the key bicyclic intermediate **4**, but it does not present an ideally efficient pathway. It involves the use of stoichiometric amounts of palladium for a relatively low diastereoselective outcome (2:1 d.r.) and requires the removal of an extra carbon shortly after its installation. The second and third routes present better diastereoselectivities, but they require further steps to access **4** from the reported intermediates, again not delivering the desired optimal synthetic efficiency. Eventually, taking inspiration from the first approach (scheme 2), we envisioned to construct bicyclic intermediate **4** in one step from vinyl iodide **8**, by modifying the intramolecular carbonylative Heck reaction into its borylative analogue. The installation of a boron-based functional handle on the product would enable an easy access not only to the desired alcohol, but also to possible other diversifications. Moreover, we reasoned that in the transformation the diastereoselctivity could be influenced by the use of an appropriate ligand, enhancing the d.r. above the reported 2:1 for both **4** and **epi-4**. With this final missing connection filled, we then started our synthetic campaign.

2.2 Results and discussion

2.2.1 Optimization of Heck reaction

The first problem that we faced was the development of the intramolecular borylative Heck reaction necessary to synthesize the bicyclic intermediate **4**, according to the strategy presented in the previous section. As mentioned, such a compound was considered to have a strategic importance because of its potential towards the total synthesis of nimbolide and several other natural products. Our efforts started with the synthesis of **6**, already reported in the literature, and easily accessible through a slightly modified procedure, through double alkylation of (*R*)-carvone with methyl iodide first, and with (*Z*)-3-bromo-1-iodopropene second.[35] The latter electrophile was synthesized through a three-step reported procedure starting from methyl propiolate (hydroiodination, LAH reduction, and Appel reaction).



Scheme 5. Preliminary results of the intramolecular borylative Heck reaction.

After a survey of the literature on typical borylative Heck conditions, preliminary experiments were run using palladium trisdibenzylideneacetone (20 mol %) as the catalyst, potassium acetate (1.5 eq) as the base and bispinacolato diboron (2 eq) as the boron source (scheme 5). The reactions were run in 1,4-Dioxane, toluene and DMF as solvents (0.1 M) at 80 °C until full conversion was observed by LCMS analysis (typically overnight). While dioxane and toluene predominantly afforded the non-cyclized Miyaura borylation product **18** , the use of DMF showcased an excellent yield of borylative cyclization. The diasteroselectivity was only modest, with a 2:1 ratio favoring the axially disposed boronate **ax-19** over the equatorially disposed **eq-19**. Subsequent screening of different conditions (precatalysts, ligands, and additives) showed interesting results, which are summarized in figure 6. When the same conditions found in the preliminary results were applied (plus the bidentate phosphine ligand, entry 1a), the reaction outcome selectively gave cyclopropanation product **20**. Such alternative reactivity was not completely unexpected, since it had been reported before.[35]

However, when a palladium(II) precatalyst was used under the same conditions (entry 1b), a 2:1 mixture of borylation to cyclopropanation products was observed.

The analysis of a batch of reactions that was showing inconsistent results (due to

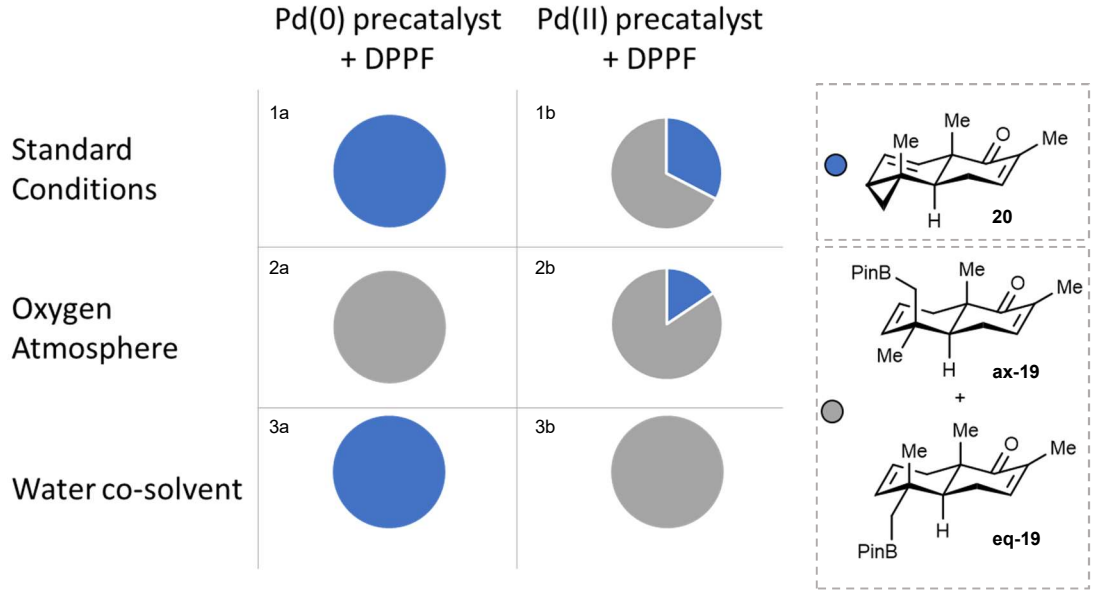
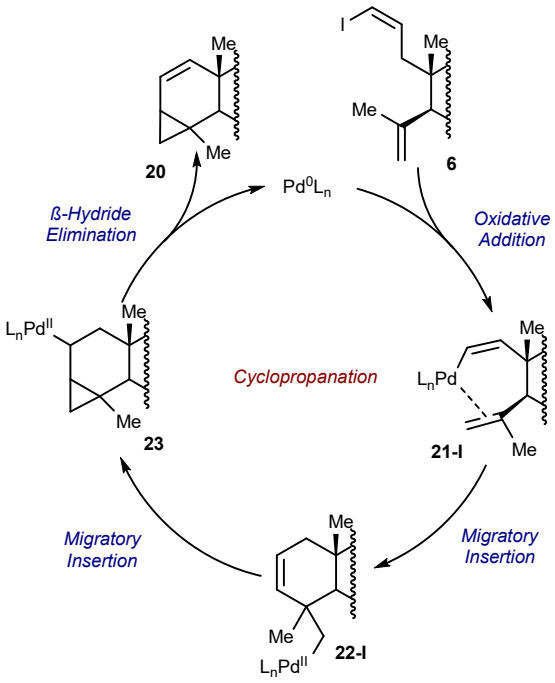


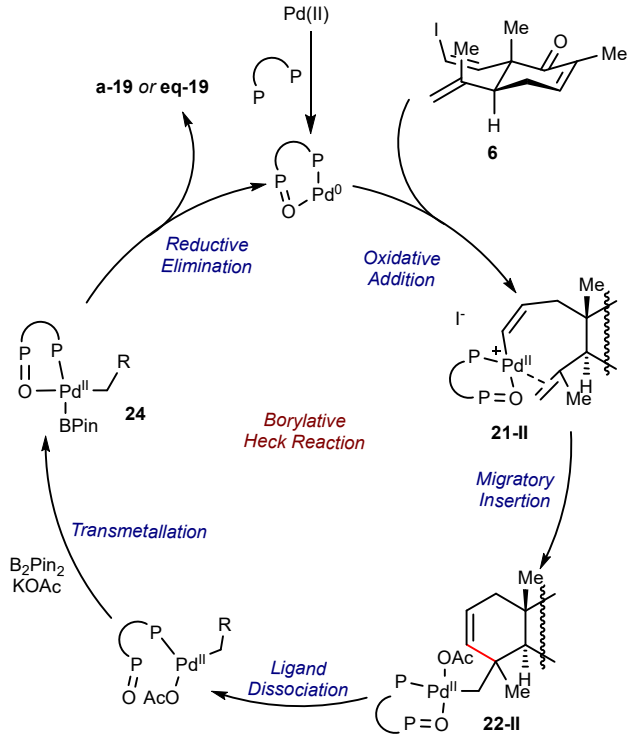
Figure 6. Summary of some different screened conditions, with product distribution between cyclopropanation and borylative cyclization.

imperfect de-gassing of the DMF) showed that the presence of oxygen in the reaction mixture significantly influenced the product distribution. The serendipitous discovery allowed us to observe a complete switch of selectivity of the products when an oxygen atmosphere was used with palladium(0) precatalyst (entry 2a). The effect on palladium(II) precatalyst-based reactions was not as strong, but increased the selectivity to 5:1 (**ax-19 + eq-19:20**), indicating a tendency to suppress cyclopropanation also in this case (entry 2b). Lastly, between the screened co-solvents, significant effects were observed when water was involved. Palladium(0)-based reactions afforded only cyclopropanation product **20** (entry 3a), while selective formation of the desired borylation product(s) was afforded with palladium(II) precatalysts (entry 3b). Despite this result might not be considered a big step forward with respect to the one initially obtained in the preliminary studies; it represented an important improvement. In fact, the discovery of conditions to completely suppress cyclopropanation in the presence of a phosphine ligand meant that we could move our efforts to the optimization of the diastereoselectivity through the screening of a variety of ligands.

The rationale of the different product outcomes according to the conditions employed is the involvement of two distinct catalytic cycles, supported by literature precedents.[35,38] A palladium(0) source can immediately undergo oxidative addition into vinyl iodide **6** (scheme 6), affording vinyl-palladium(II) species **21-I**, which undergoes migratory insertion to form β-quaternary alkyl-palladium(II) species **22-I**. At this point, because of the sterically hindered environment around palladium due to the bulky phosphine ligand, transmetallation with boron is unfavored in comparison to a secondary migratory insertion into the more accessible nearby olefin. This process efficiently forms alkyl-palladium(II) species **23**, which upon β-hydride elimination grants final product **20** and closes the cycle. When a palladium(II) precatalyst is used, the metal must be reduced to palladium(0) before entering the catalytic cycle (scheme 7). In the presence of phosphines, this happens with contingent oxidation to the phosphine-oxide. More specifically, when equimolar amounts of a palladium(II) salt and a bidentate phosphine ligand are used, a peculiar bis-phosphine-monoxide (BPMO) gets formed. Initial oxidative addition and migratory insertion are not influenced by this, forming **21-II** and **22-II**. However, the transmetallation step can now happen, since the hemi-liability of



Scheme 7. Cyclopropanation catalytic cycle.



Scheme 6. Borylation catalytic cycle.

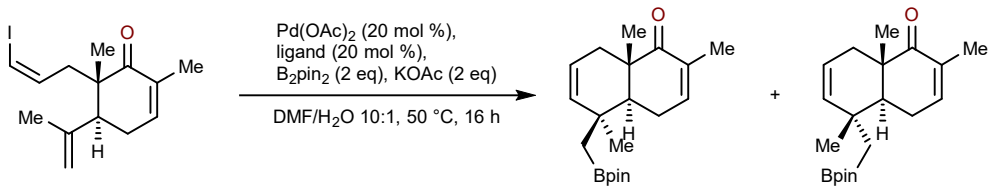
the BPMO opens a new coordination spot on the metal center, which drastically lowers the energetic barrier necessary for transmetallation. Intermediate **24** finally affords the desired borylated product(s) after reductive elimination. The presence of the BPMO ligand in the reaction was confirmed by ^{31}P NMR studies.

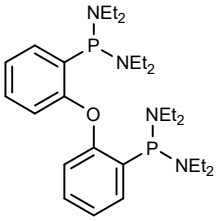
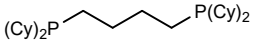
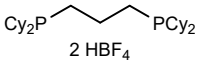
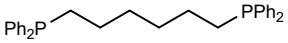
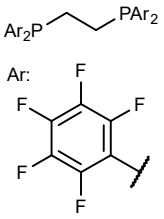
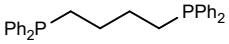
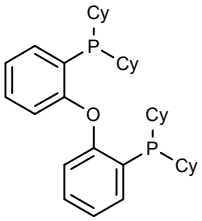
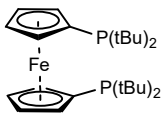
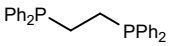
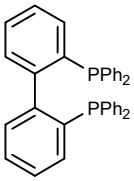
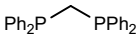
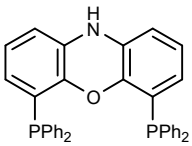
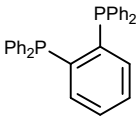
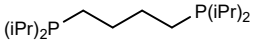
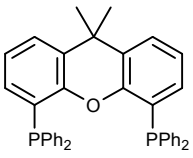
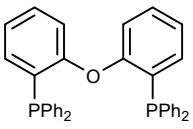
In this sense, the use of a chelating phosphine is of crucial importance because it guarantees a metal complex stability high enough to possibly catalyze the transformation in the ligand-controlled domain (for diastereoselectivity), while allowing enough lability to favor transmetallation. The same cannot be achieved with the use of a monodentate phosphine ligand since the easy dissociation of the phosphine-oxide would never allow to override the substrate-control.

Despite these considerations, the ligand screening campaign on vinyl iodide **6** showed a general difficulty in overcoming the innate substrate control as regards diastereoselectivity (table 1). The predominancy of the axially disposed product was noticed in almost all cases, with many of them being close to the 2:1 d.r. obtained when no ligand was used (entries 1, 3, 6, 7, 8, 14, 15, 16, and 17). Electron-rich phosphines enhanced the axial selectivity with effects from light (entries 2, 4, 8, and 9) to moderate (entry 5), with a peak of 4.8:1 d.r. when DTBPF (1,1'-bis(di-*tert*-butylphosphino)-ferrocene) was used. Equatorially disposed boronate predominance was observed only in one case (entry 11) with DPPB (1,4-bis(diphenylphosphino)butane) as a modest 1:1.5 ratio. This result was part of a screening sequence (entries 10-14) aimed at testing the effect of the alkyl chain length connecting the two phosphorus atoms on the outcome. The optimal length observed with DPPB suggests that the ligand bite angle may play an important role on the influence of diastereoselectivity.

To further understand the potential factors that are involved in the reaction, alternative vinyl iodides with different substituents were also tested under the same conditions. Such substrates could be easily synthesized simply by changing the electrophiles used in the double functionalization of carvone. Analogues bearing different substituents at the quaternary position (**25**, using Mander's reagent and (*Z*)-3-bromo-1-iodopropene) or at the allylic position (**26** and **27**, using methyl iodide and iodoacroleine, protecting with either acetic anhydride or TBSCl) were synthesized. Not surprisingly, these modifications provided different outcomes of the reaction when the same ligands presented before

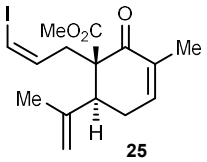
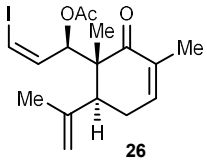
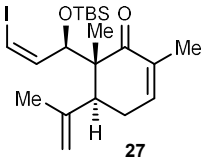
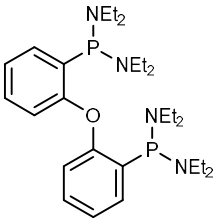
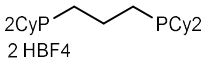
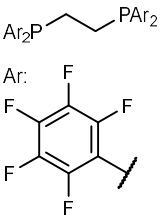
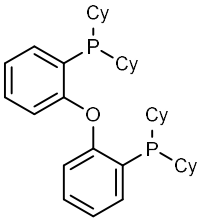
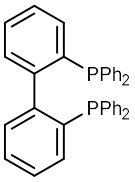
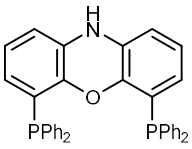
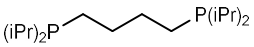
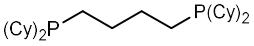
Table 1. Ligand screening on vinyl iodide **6**.



1		2.0 Ax:Eq	9		3.2 Ax:Eq
2		3.5 Ax:Eq	10		1.5 Ax:Eq
3		2.2 Ax:Eq	11		0.66 Ax:Eq
4		2.7 Ax:Eq	12		1.2 Ax:Eq
5		4.8 Ax:Eq	13		1.5 Ax:Eq
6		2.3 Ax:Eq	14		1.8 Ax:Eq
7		2.2 Ax:Eq	15		2.0 Ax:Eq
8		2.60 Ax:Eq	16		2.0 Ax:Eq
			17		2.0 Ax:Eq

were used (table 2). Although it is hasty to draw conclusions from the limited data obtained so far, some general tendencies can be noticed. For example, **25** gave exclusively the axial disposed product, with diastereomeric ratios averagely higher than

Table 2. Ligand screening on different substrates.

		 **25**	 **26**	 **27**
1		2.9 Ax:Eq	1.11 Ax:Eq	1.81 Ax:Eq
2		3.0 Ax:Eq	0.40 Ax:Eq	1.63 Ax:Eq
3		2.7 Ax:Eq	0.90 Ax:Eq	1.03 Ax:Eq
4		2.9 Ax:Eq	3.54 Ax:Eq	1.26 Ax:Eq
5		3.8 Ax:Eq	1.13 Ax:Eq	1.48 Ax:Eq
6		1.4 Ax:Eq	3.00 Ax:Eq	1.81 Ax:Eq
7		3.9 Ax:Eq	9.63 Ax:Eq	1.12 Ax:Eq
8		3.8 Ax:Eq	0.91 Ax:Eq	1.30 Ax:eq

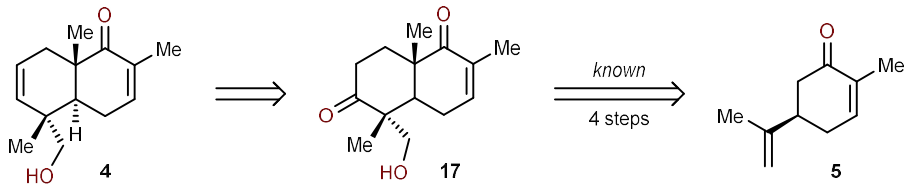
the ones afforded by **6**. Instead, the sterically hindering TBS protected alcohol **27** showed ratios closer to 1:1, but with little effect by the different ligands, and never affording the equatorial product as the major one. Finally, allylic acetate **26** was

observed to be the most versatile one, with both diastereomers achievable with moderate selectivity, including peaks of axial:equatorial 9.6:1 with DIPB (1,4-(bis-(di-*iso*-propylphosphino)butane, entry 7), and 1:2.5 with DCPP·HBF_4 (1,4-bis-(dicyclohexylphosphino)propane bis(tetrafluoroborate), entry 2). Further screenings are still ongoing in the group and will be reported in due course.

2.2.2 Attempted syntheses

Western Fragment

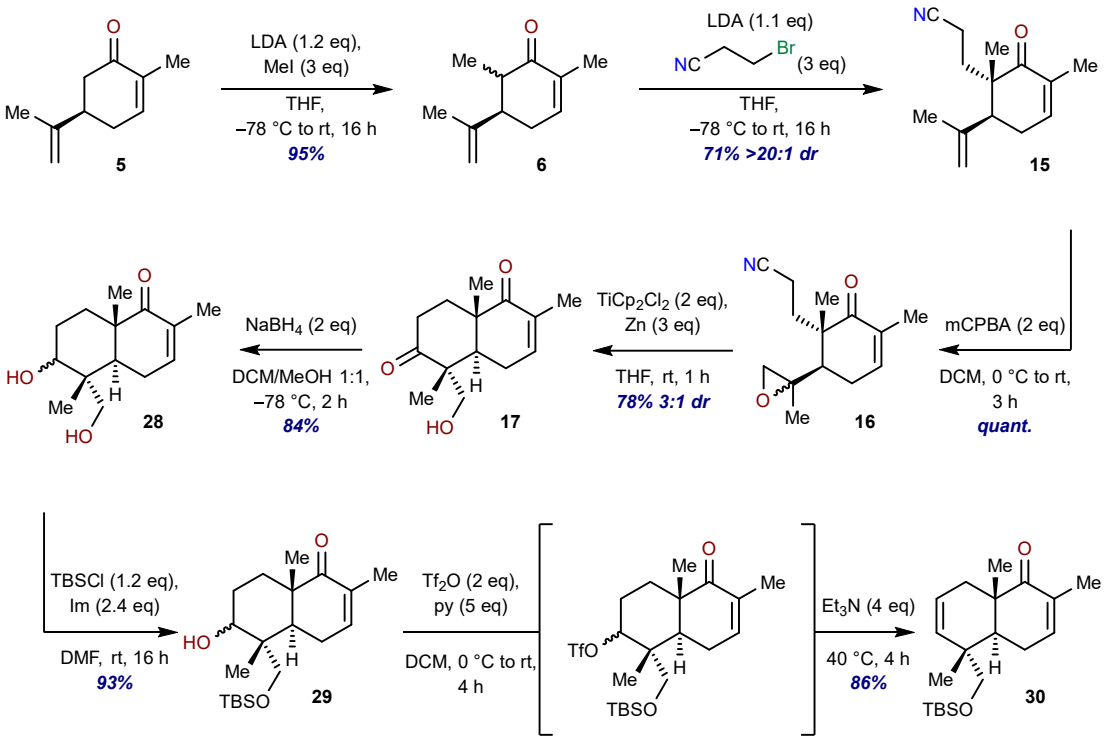
While developing the intramolecular borylative Heck reaction, we desired to start the exploration of the frontline towards the total synthesis of nimbolide. In order to do so, an alternative synthetic pathway that would intercept the same key intermediate **4** was necessary. As presented before (see "General disconnection approach and state of the art" section), it was reported in the literature that bicycle **17** could be synthesized in four steps from (*R*)-carvone. Tracing **4** back to **17** would complete the synthetic connection and guarantee a temporary substantial material throughput (scheme 8).



Scheme 8. Retrosynthetic plan to access key bicyclic intermediate **4** from (*R*)-carvone.

Reproduction of the four known steps proceeded smoothly (scheme 9): double alkylation of carvone with methyl iodide and 2-bromo propionitrile afforded **15** in 67% overall yield as a single detectable isomer. Quantitative epoxidation to **16** and titanocene-mediated radical cyclization afforded intermediate **17** as reported.

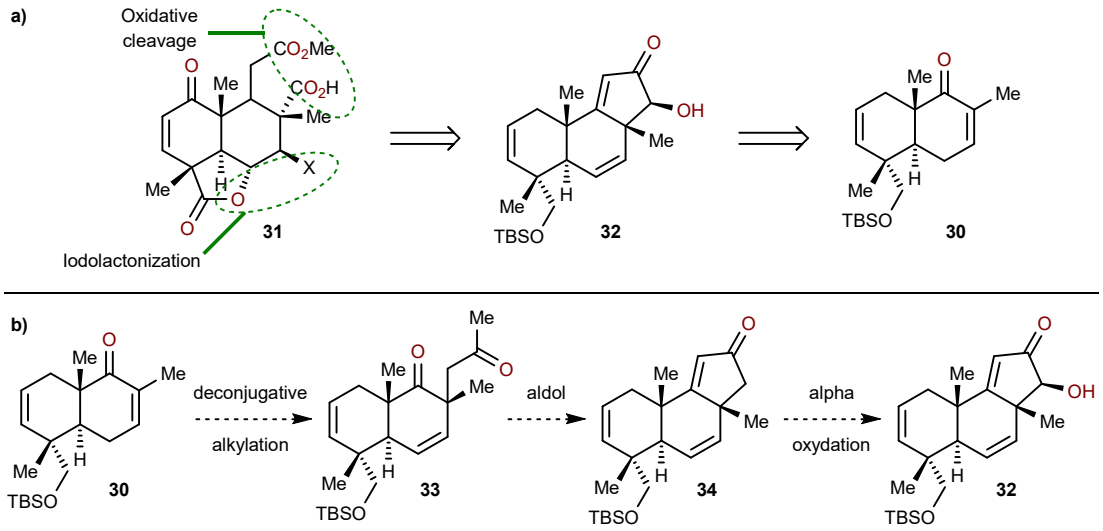
At this point, efforts to quickly convert the ketone functionality into the desired olefin through one-pot procedures (e.g.: Bamford-Stevens or Shapiro conditions) were unsuccessful, and a longer pathway was undertaken. Sodium borohydride in a 1:1 DCM:MeOH mixture at -78 °C selectively reduced the ketone over the enone, forming **28** as a single unassigned stereoisomer. Subsequent selective TBS protection of the primary alcohol under classic conditions afforded corresponding silyl ether **29**. A series of different conditions for elimination of the secondary alcohol were tried. Eventually,



Scheme 9. Synthetic pathway from (*R*)-carvone to bicycle intermediate **30**.

the most efficient one proved to be a one-pot sequence of triflation/elimination, to finally obtain **4**-TBS protected analogue **30**. Deprotection of the alcohol would formally complete the route to the interception point, but the protected version was considered more suitable for our initial studies. With this reliable route secured, we started our exploration of further derivatizations.

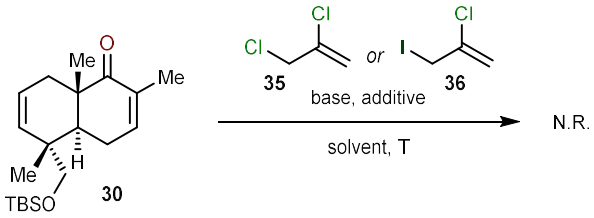
As mentioned previously, our general approach was based on a late-stage metal mediated coupling to form the D-ring. We reasoned that a carboxylic acid could be an



Scheme 10. a) Retrosynthetic plan from tricycle **31** to accessed bicycle **30**. b) Envisioned forward synthesis to **32**.

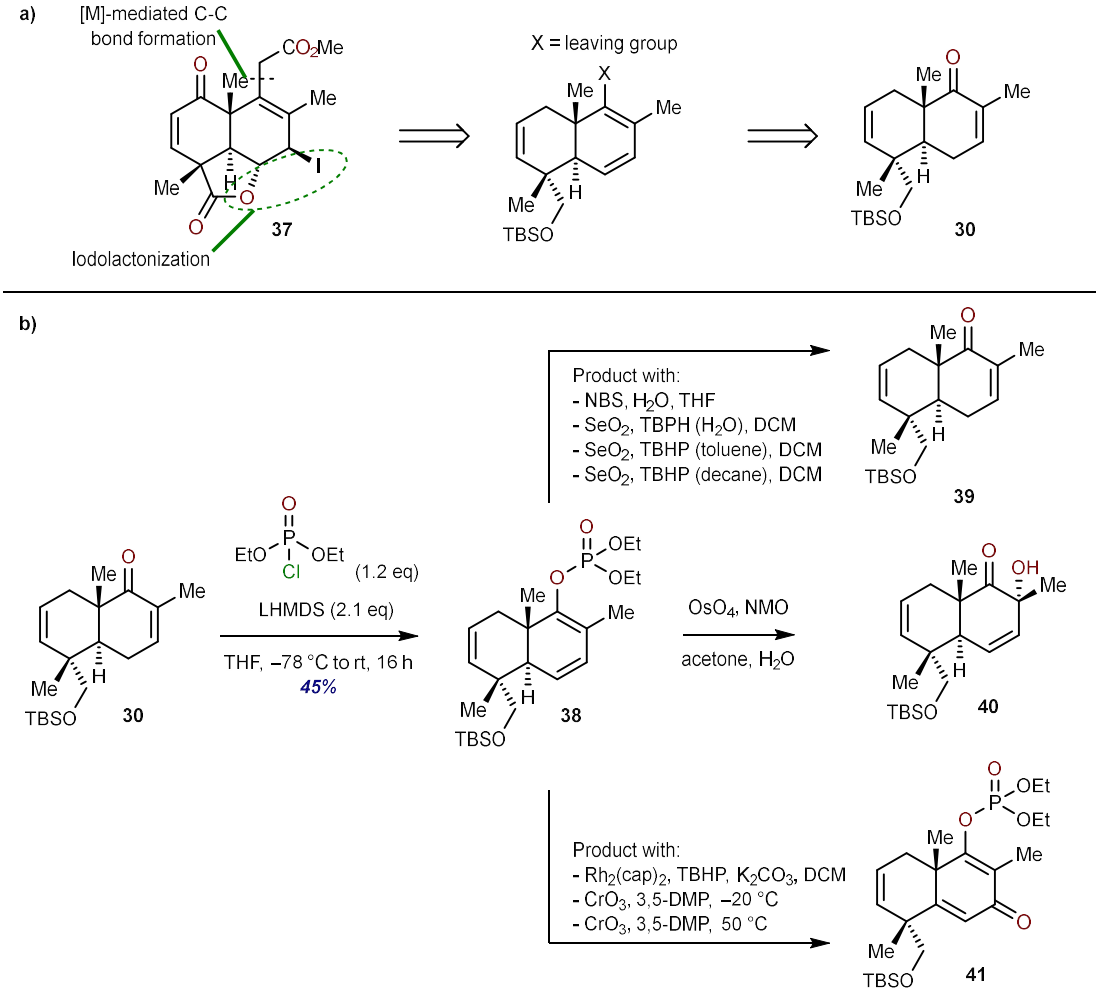
appropriate functional handle for this purpose, giving access to a decarboxylative coupling (scheme 10a). The stereochemistry at the newly formed quaternary center would be defined by the one of the adjacent ether. Simplification of **31** would be achieved considering the side ester and the carboxylic acid the result of an oxidative cleavage on one side and constructing the C ring through an iodolactonization on the other. Such disconnections bring to tricycle **32**, which could be linked to **30** in multiple ways. For example, a sequence involving alkyne addition/oxidative Rautenstrauch rearrangement (not shown) was tried, but it afforded messy results. An alternative was given by the possibility of performing a deconjugative alkylation on **30**, which would open the doors towards an intramolecular aldol condensation (scheme 10b) through **33**. Final α-hydroxylation of **34** would afford oxidative cleavage precursor **32**. Unfortunately, several attempts to perform the necessary deconjugative alkylation were unsuccessful (table 3). The reaction was tried with both 2,3-dichloropropene (**35**) and 2-chloro-3- iodopropene (**36**) as electrophiles. Screened bases included NaH, LDA, LHMDS, NHMDS and KHMDS. THF was the chosen solvent, alongside a combination of co-solvents as DMF and HMPA, varying the temperatures between -78 °C and 60 °C. In all cases starting material **30** was fully recovered and no conversion was ever noticed, independent of reaction times.

Table 3. Selected deconjugative alkylation attempts.



base	solvent	T (°C)
NaH	THF, HMPA	RT
NaH	THF, HMPA	60
NaH	THF, DMF	RT
NaH	THF, DMF	60
LDA	THF, HMPA	–78
LDA	THF, HMPA	0
LDA	THF	–78
LDA	THF	0
LHMDS	THF, HMPA	–78
LHMDS	THF	–78
NHMDS	THF, HMPA	–78
NHMDS	THF	–78
KHMDS	THF, HMPA	–78
KHMDS	THF	–78

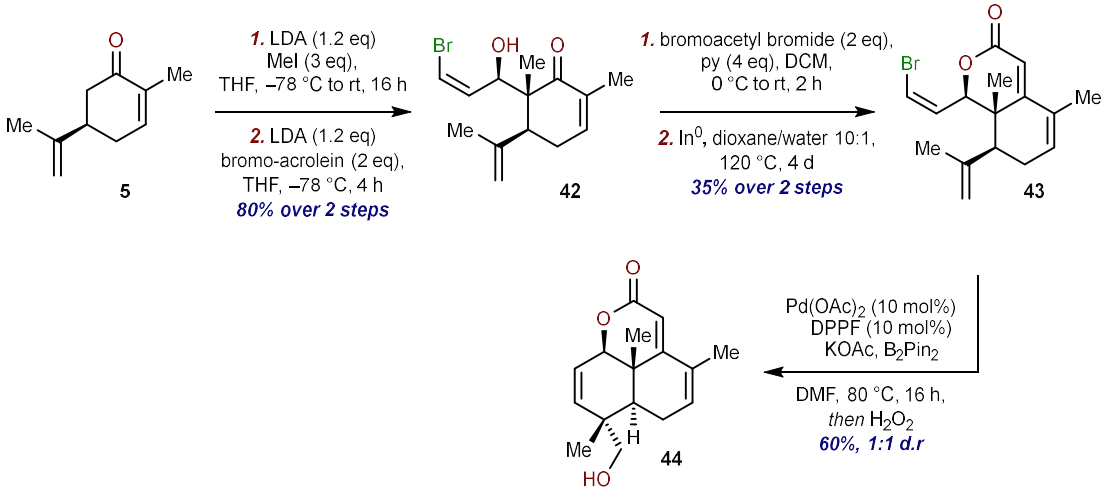
We decided to tackle the problem with a different approach, using an olefin as the late-stage metal mediated coupling partner instead of the carboxylic acid (scheme 11a). Such plan would give more flexibility on the approach to **37**. For example, a pathway involving the formation of a vinyl triflate as a precursor for the methyl ester chain installation was envisioned. A series of soft and hard enolization conditions were unsuccessful for this



Scheme 11. a) Retrosynthetic plan from **37** to accessed bicycle **30**. b) Formation of vinyl phosphate **38** and derivatizations performed.

transformation. Curiously, vinyl phosphate **38** could be generated in a moderate yield when LHDMS deprotonation was followed by quenching with diethylchlorophosphate (scheme 11b). Several attempts were made to derivatize intermediate **38** into other more advanced intermediates which could be beneficial for the total synthesis. Vinyl metal species were not formed under a variety of conditions, probably due to the great steric hindrance of the substrate, which prevents oxidative addition into the carbon-oxygen bond from happening. Oxidation conditions to introduce other useful functional handles only afforded undesired reactivity. Cleavage of the phosphate back to bicycle **30** was observed with NBS and Sharpless oxidation. Upjohn conditions afforded selective dihydroxylation of the most substituted olefin, giving α-hydroxy ketone **40**. Doyle and chromium trioxide mediated oxidations afforded β-phosphate dienone **41**, which was an interesting and unexpected product, although of little utility for our purpose.

During previous explorations of other possible strategies towards the western fragment, some interesting results were found (scheme 12). According to a different approach, the intramolecular borylative Heck reaction would be performed after the installation of the C-C connectivity as regards the methyl ester side chain on the B-ring. Alkylation of carvone with methyl iodide followed by aldol reaction with (*Z*)-bromoacroleine afforded **42** as a single isomer. Functionalization of the alcohol into an α-bromo ester disclosed the possibility of forming the desired C-C bond on the B-ring by taking advantage of the enone through an intramolecular Reformatsky condensation. Between the multitude of



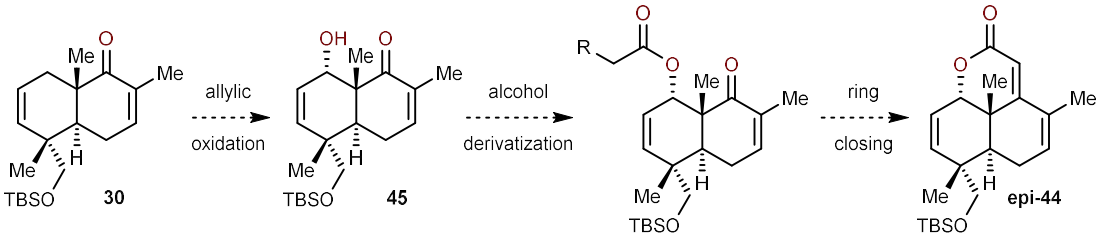
Scheme 12. A-ring last exploratory route towards the western fragment.

conditions tried, samarium diiodide proved to be the most efficient, although not sustainable on large scale because of operational complexity and costs. A solution was found through the use of indium(0) powder, which could affording moderate amounts of product **43** after several days, before stalling completely. Such interruption of the conversion is due to the tendency of the indium powder to conglomerate during the course of the reaction, even when vigorous stirring is applied. This phenomenon eventually kills the capacity of indium(0) to chemically interact with the substrate, causing incomplete conversion.

Subjecting dienone **43** to intramolecular borylative Heck conditions, followed by oxidation with hydrogen peroxide, afforded the desired product **44** in an unoptimized 60% yield and 1:1 diastereomeric ratio. Although promising, this pathway was put in a stand-by for multiple reasons. Firstly, this approach would not involve bicyclic intermediate **4** (or its analogue **30**), which was considered of fundamental importance for the reasons explained before. Secondly, both the Reformatsky and the Heck steps

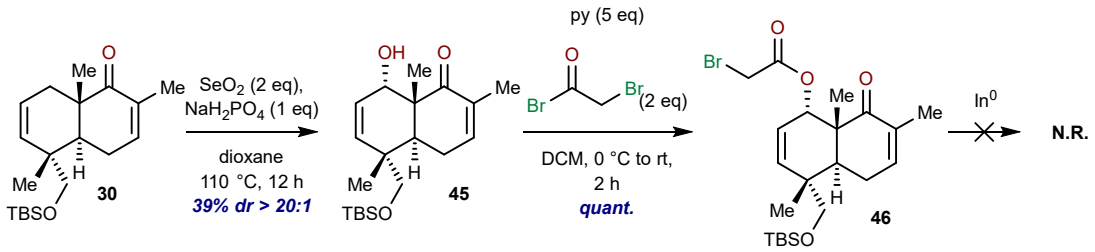
presented low efficiencies, which would strongly limit the material throughput necessary for the continuation of the synthesis.

However, considering the successful transformations carried out in this route, we attempted to apply an analogous strategy on **30** (scheme 13). The plan foresaw the



Scheme 13. Reformatsky-based strategy towards the western fragment.

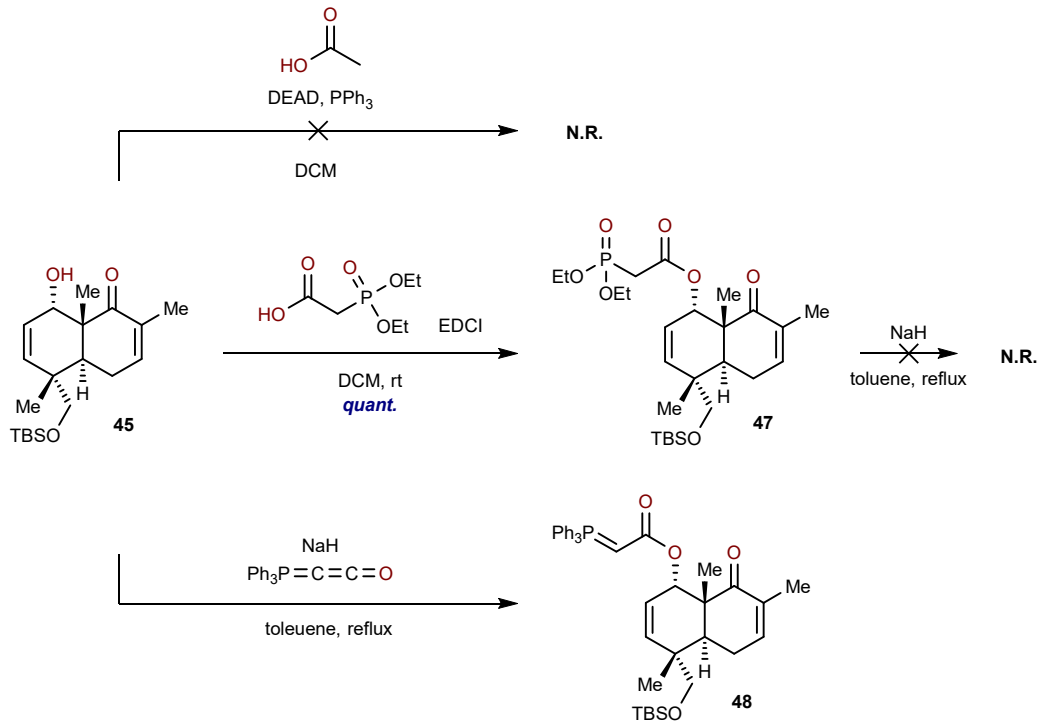
installation of an alcohol through allylic oxidation and its functionalization in a way that would allow to cyclize on the B-ring enone. Treatment with selenium dioxide in the presence of sodium phosphate monobasic indeed gave access to allylic alcohol **45** as a single diastereomer (scheme 14). Derivatization to the corresponding α-bromoester **46** proceeded smoothly, but the same indium-based Reformatsky conditions did not show



Scheme 14. Reformatsky-based strategy on **30**.

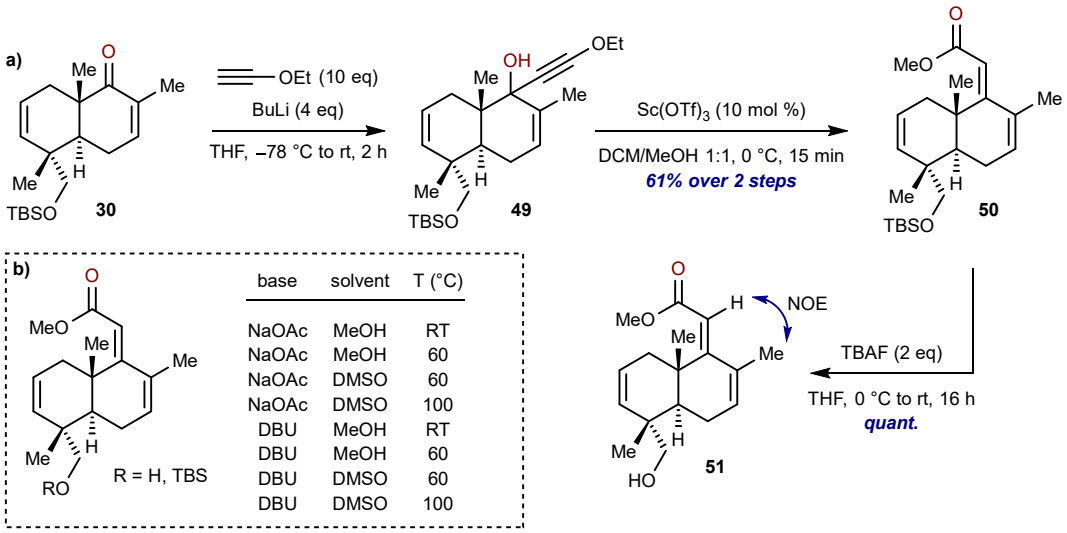
any conversion, even after several days. We reasoned the problem could be deriving from the opposite configuration of the alcohol obtained through allylic oxidation respect to the one obtained with aldol reaction (**45** vs **42**). To prove this, allylic alcohol **45** was subjected to several Mitsunobu conditions, all of which did not show any conversion, reasonably because of the steric hindrance of the nearby methyl group (scheme 15). As an alternative, phosphorous-ylide-based cyclizations were also tried, but without success: both intramolecular HWE and intramolecular Wittig did not show any productive transformation. The former was attempted on phosphonate **47**, obtained by coupling of allylic alcohol **45** with diethyl phosphonoacetic acid. The latter was attempted in a one-pot procedure using Bestmann's ylide on **45** with addition of sodium

hydride as the base. Both reactions stalled at the open chain stage, even after prolonged heating.



Scheme 13. Mitsunobu attempt and phosphorous-based cyclization attempts.

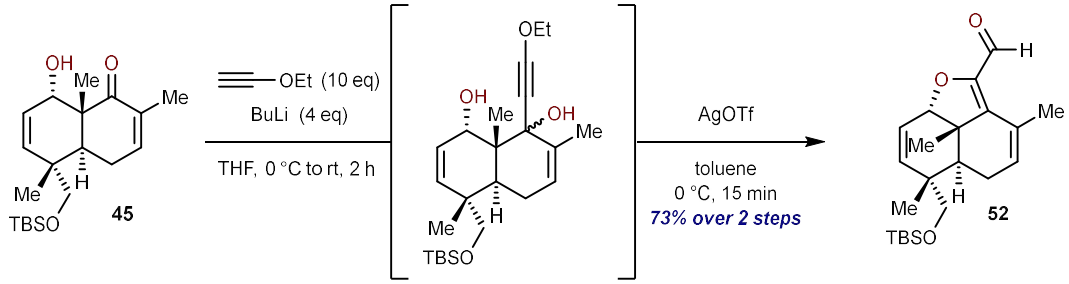
After these failed attempts, we envisioned to install the methyl ester chain through a Meyer-Schuester rearrangement (scheme 16a). Such sequence was initially performed on bicycle **30** through 1,2-addition of lithium ethoxy acetylide to afford tertiary alcohol **49**, followed by treatment with scandium(III) triflate in a DCM:MeOH 1:1 mixture at 0 °C for 15 min. The reaction afforded desired product **50** in 61% yield over the two steps as a single isomer, unambiguously assigned after TBS deprotection with TBAF through NOE



Scheme 14. a) Meyer-Schuester rearrangement on bicycle **30**. b) Examples of tried isomerization conditions.

correlation seen of **51**. Several conditions were tried to isomerize the compound to the endocyclic diene analogue, but none of them showcased conversion, and starting material was always recovered. For example, sodium acetate and DBU were tested as bases in either methanol or DMSO at various temperatures (scheme 16b).

The same reactivity pattern was also applied to allylic alcohol **45**. In this case the rearrangement did not showcase a classic Meyer-Schuester mechanism, but it afforded undesired tricycle **52** through a fast 5-endo-dig cyclization. A variety of acids were tested to see whether the reactivity could be changed after 1,2 addition, but **52** was obtained as the only product in all cases, including AgOTf, *p*TSA, $BF_3{\cdot}OEt_2$, $PhB(OH)_2$, $Sc(OTf)_3$, $In(OTf)_3$, and $VO(acac)_2$.



Scheme 15. Non-classic Meyer-Schuester rearrangement on substrate **45**.

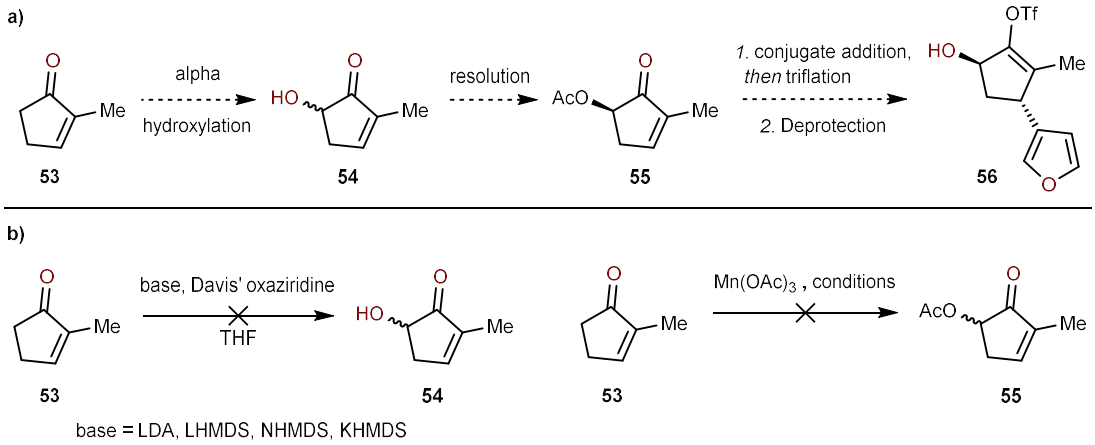
Possible solutions to these problems include performing the rearrangement on an alcohol-protected analogue of **52**, keeping in mind that sterically demanding groups prevent 1,2-addition from happening (as it was noticed in the case of TBS). Dienoate **50** is also a promising starting point for future explorations, considering the multiple activated positions for possible derivatizations. Synthetic studies towards the envisioned western fragment **37** are still ongoing in our group and will be reported in due course.

Eastern Fragment

As part of the general synthetic strategy (see "General disconnection approach and state of the art" section), the western fragment would eventually be connected to the eastern fragment. The approaches that were explored to synthesize the appropriate compound will be presented here.

The first explored pathway consisted in using 2-methyl cyclopentenone (**53**) as starting material (scheme 18a). According to the planned route, racemic α-hydroxylation would afford hydroxyketone **54**, which upon chemoenzymatic resolution with one of the

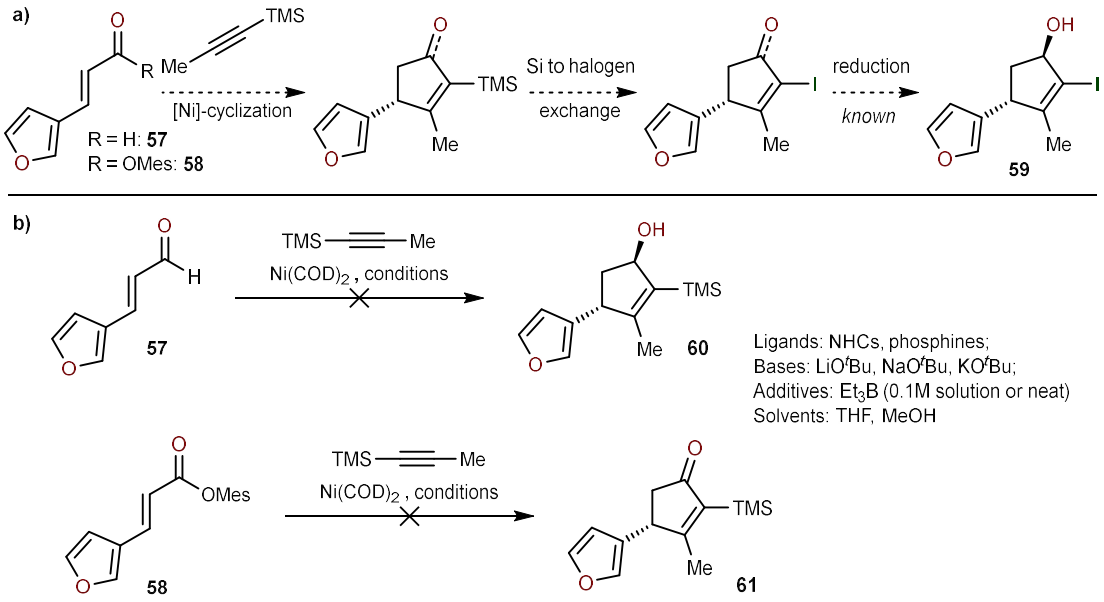
available methods[39] would afford the stereochemical pure acetate analogue **55**. Conjugate addition followed by *in situ* trapping of the enolate with a triflating agent would finally afford the desired target compound **56**.



Scheme 16. a) Envisioned synthetic pathway to eastern fragment. b) Failed α-functionalization reactions.

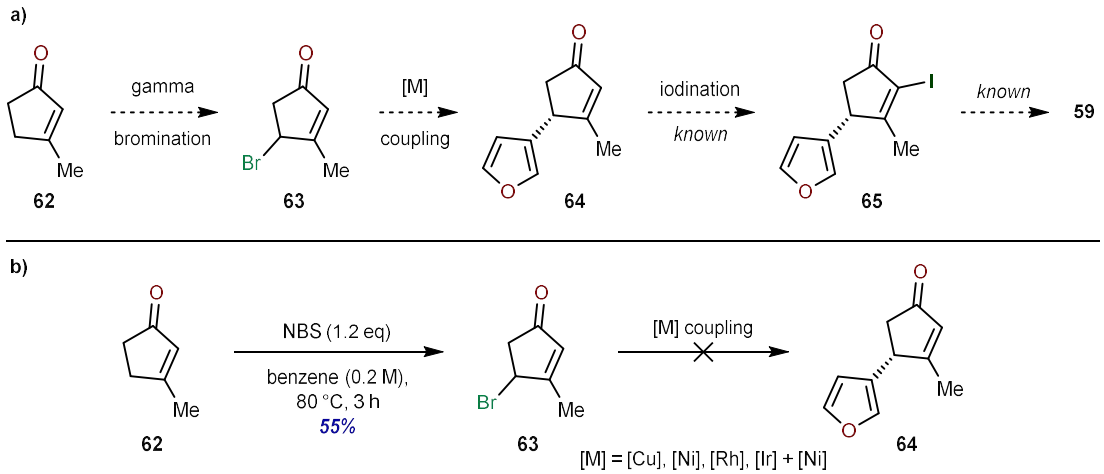
53 can be obtain either from commercial suppliers or through laboratory-scale synthesis between the many reported in the literature, from which the most reliable proved to be the one reported by Tsuji.[40] Classic α-hydroxylation conditions with Davis' oxaziridine were tried without success (scheme 18b). The cause was reasoned to be the instability of the intermediate cyclopentadiene enolate, formed after deprotonation. In fact, the consumption of the starting material mostly led to decomposition. As an alternative, α-acetoxylation conditions through the use of manganese(III) acetate were tried without success, in this case always recovering starting material.

A different approach based on nickel-mediated cyclization was considered (scheme 19a).[41] The transformation would couple an α,β-unsaturated aldehyde (**57**) or ester (**58**) with an alkyne. Silicon to halogen exchange would install the necessary leaving group at the vinyl position, lastly affording the target compound **59** in the case of the aldehyde, or after a diastereoselective CBS-reduction in the case of the ester.[42] The two versions of the same approach were tested. In the first one, aldehyde **57** was easily obtained in one step through a Horner-Wadsworth-Emmons reaction from the corresponding furan-carboxyaldehyde. In the second one, enoate **58** derived from a Knoevenagel condensation/decarboxylation sequence, followed by esterification of the corresponding acid. In both cases the reaction conditions afforded complex mixtures in which the desired products **60** and **61** could not be detected.



Scheme 17. a) Envisioned synthetic pathway through nickel cyclizations. b) Unsuccessful attempts.

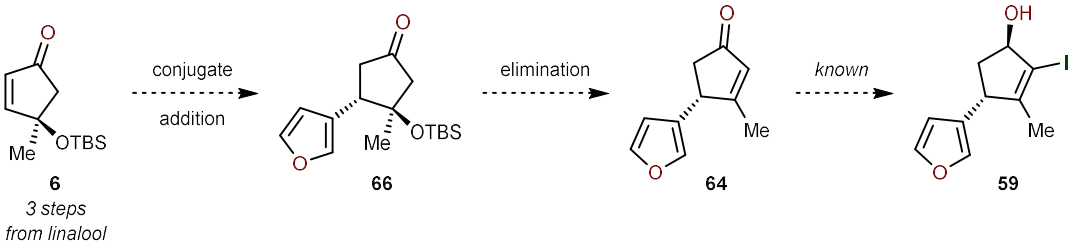
A third, complementary approach was elaborated starting from 3-methylcyclopentenone (**62**), a cheap and commercially available material (scheme 20 a). This synthetic pathway foresaw that γ-bromination would afford the corresponding allylic bromide **63**, which could be used for an enantioselective transition-metal mediated coupling to obtain **64**.[43] The rest of the sequence would be known using a Johnson iodination to get to **64** and the same CBS-reduction step mentioned before to the target compound.[42] NBS in refluxing benzene for 3 hours afforded the desired allylic bromide **63** in 55% yield (scheme 20b), with the rest of the mass being recovered starting material and bromination at the other activated positions (alpha to the carbonyl, and the allylic methyl group). Unfortunately, a series of coupling conditions were tried on



Scheme 18. a) Envisioned synthetic pathway through γ-bromination. b) Unsuccessful metal-mediated couplings.

the substrate, but none of them showed productive transformation towards our desired product **64**.

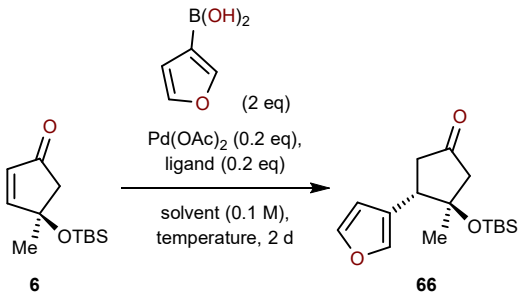
Finally, derivatization of enone **6** into our target molecule was considered. **6** has been previously reported by Maimone's group in three steps from linalool (ring-closing metathesis, TBS protection, and allylic oxidation),[34] making it an easily accessible and functionalizable enantiopure intermediate. In our plan, the steric hindrance of the silyl ether would force conjugate addition on the enone from one face selectively affording **66**. β-Elimination would restore the enone functionality on the molecule, intercepting known intermediate **64** once again.



Scheme 19. Envisioned synthetic pathway from Maimone's enone **6**.

6 was subjected to a variety of conditions in the attempt to achieve an optimal diastereoselective 1,4-addition of the furan moiety. For example, Hayashi conditions with 3-furylboronic acid only gave recovered starting material, and the same was noticed with analogous palladium-based transformations (table 4). No reactivity was observed when 2,2'-bipyridine was used as a ligand (entries 1 and 2), neither in water at 50 °C nor in a mixture of THF, acetic acid, and water at 80 °C. The same outcome was noticed when triphenylphosine was used as the ligand, in a mixture of toluene and chloroform at 80 °C.

Table 4. Selected examples of tried palladium-mediated conjugate addition conditions.

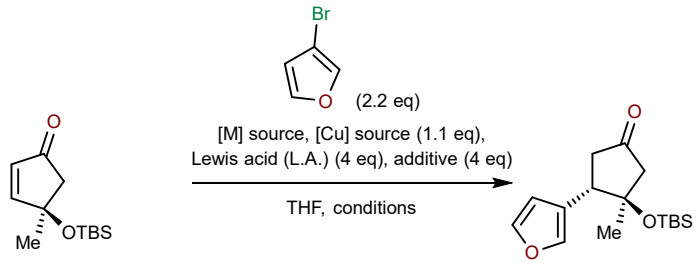


Entry	Ligand	Solvent	T	Outcome
1	2,2'-bpy	H_2O	50 °C	n.r.
2	2,2'-bpy	THF/AcOH/H_2O	80 °C	n.r.
3	PPh_3	toluene, $CHCl_3$	80 °C	n.r.

More classic copper-mediated conditions were tried afterwards (table 5). Initial screening using turbo-Grignard as 3-bromofuran metalation source proved to be unsuccessful (entries 1-3), with only decomposition observed. Finally, running the

reaction with *n*BuLi as the lithiating source (entry 4), CuI (with added DMS for solubility) as the cuprate precursor, and $BF_3{\cdot}OEt_2$ as the Lewis acid, afforded the desired product **66** in 64% yield, although with a modest 2:1 diastereomeric ratio. Switching to *tert*-butyllithium showed a cleaner lithiation process, and for this reason it was used in the

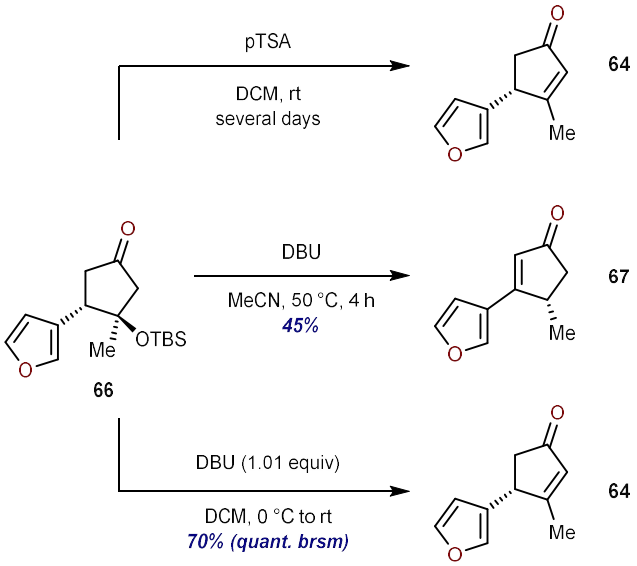
Table 5. Copper-mediated conjugate addition conditions.



Entry	[M] source	[Cu] source	Additive	L.A.	Conditions	Outcome
1	*i*PrMgCl•LiCl	CuBr•DMS	HMPA	TMSCl	–78 °C to 0 °C, 5 h	decomp.
2	*i*PrMgCl•LiCl	CuCl	HMPA	TMSCl	–78 °C to 0 °C, 5 h	decomp.
3	*i*PrMgCl•LiCl	CuI	DMS + HMPA	TMSCl	–78 °C to 0 °C, 5 h	decomp.
4	*n*BuLi	CuI	DMS	$BF_3{\cdot}OEt_2$	–78 °C to 0 °C, 5 h	64% (dr 2:1)
5	*t*BuLi	CuI	DMS	–	–78 °C, 6 h	n.r.
6	*t*BuLi	CuCN	–	TMSCl	–78 °C, 6 h	34% (dr >20:1)
7	*t*BuLi	CuCN	–	$BF_3{\cdot}OEt_2$	–78 °C, 2 h	35% (dr 5:1)
8	*t*BuLi	CuI	DMS	TMSCl	–50 °C to rt, 3 h	85% (dr >20:1)

other small scale test reactions. Experiments at lower temperature were run in the attempt to increase the diastereoselectivity. Exclusion of the Lewis acid from the reaction mixture (entry 5) prevented any conversion from happening. The use of copper(I) cyanide as cuprate precursor showcased formation of the product in scarce yields, although with excellent and moderate diastereoselectivity (entries 6 and 7), when TMSCl and $BF_3{\cdot}OEt_2$ were present, respectively. Ultimately, copper(I) iodide with DMS and TMSCl, and a gradual warming of the reaction mixture from -50 °C to room temperature over 3 h proved to be the conditions of choice, affording **66** in 85% yield and only one detectable diastereomer (entry 8). For larger scale reactions the use of *t*BuLi was avoided, and *n*BuLi could be used with only a small decrease in the final yield. It is worth saying that the presented outcomes are significantly influenced by the purity of **6**. For optimal results, the enone had to be carefully distilled under vacuum, since common silica gel column chromatography was unable to guarantee the same outcomes with good reproducibility. The role of TMSCl in the reaction may be considered trivial, participating as a mild Lewis acid, but it might also present some more complex interactions involved in the activation of the cuprate.[44]

After securing reliable conditions to **66**, the following elimination step was analyzed for optimization (scheme 22). During the first exploratory reactions, acidic conditions proved to be very sluggish, with no full conversion observed after several days at room temperature. Basic conditions provided much faster reactivity but afforded undesired isomer **67** when an excess of base was used or when the solution was heated. Such compound is the result of the initial desired elimination, followed by a 1,5-hydride shift upon enolization. Accurate control of the reaction conditions eventually allowed to afford desired enone **64**, using 1.0 eq of DBU at 0 °C for 30 minutes. Although full conversion was not achieved in this case, a prolonged reaction time caused gradual formation of the undesired isomerized product **67**, which was inseparable from the desired one, and was therefore preferentially avoided. Final optimization of the solvent



Scheme 20. Screening of β-elimination conditions.

showed that the use of DCM or diethylether must be preferred over other heavier solvents due to the volatility of **64**. This allowed to remove the solvent after workup without significant loss of product. For the same reason, during the purification process *via* silica gel column chromatography, a pentane:diethylether mixture was used as eluent. A distillation would be ideal, but prohibitive on the small scales at which the reaction was run.

The following two steps to the planned eastern fragment were reproduced according to the reported procedures, completing the synthetic pathway.

2.3 Conclusions

In conclusion, the lack of metabolic studies and the poor pharmacokinetics and pharmacodynamics of nimbolide could be addressed through the development of a chemically flexible total synthesis.

Two main fragments were identified in the attempt to achieve the best synthetic efficiency, a western and an eastern one.

The envisioned western fragment presents three fused cycles with the appropriate functional handles for a late-stage coupling with its counterpart. Initial studies towards a decarboxylative coupling were abandoned due to the difficulties in synthesizing the necessary starting material. A more chemically tractable tetrasubstituted olefin was chosen as its replacement, being able to act as a coupling partner in a Heck reaction or in a radical cyclization.

Efforts were made to develop a quick and stereoselective pathway towards the key bicyclic intermediate of the western fragment, which would guarantee access to the main skeleton of entire families of natural products. An intramolecular borylative Heck reaction was identified as the appropriate tool in this sense. Screening of a variety of conditions eventually afforded the desired results, although with still modest diastereoselectivities and on merely two substrates.

While optimization studies were ongoing, the development of an alternative route to intercept the same intermediate allowed us to start exploring the frontline with a good material throughput. Several approaches were undertaken, but none proved to be successful so far, although promising results were obtained.

The eastern fragment was successfully synthesized in four steps from previously known materials after careful optimization of a conjugate addition and subsequent elimination.

Studies on the further optimization of the intramolecular borylative Heck reaction and towards the total synthesis of nimbolide are still ongoing in the group and will be reported in due course.

2.3 Experimental section

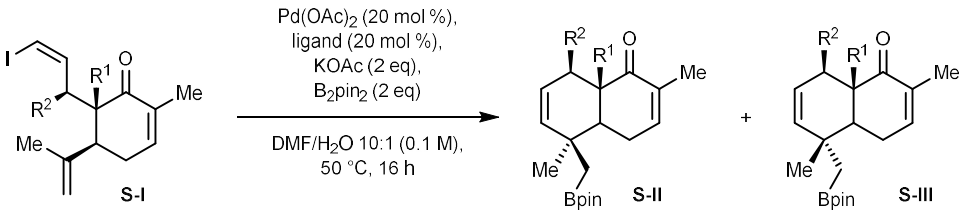
General Procedures

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, 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 SilicaFlash® 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) or residual methanol (δ = 3.31 ppm, ^1H; 49.00 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 by the University of Illinois Mass Spectrometry Laboratory. 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).

Abbreviations

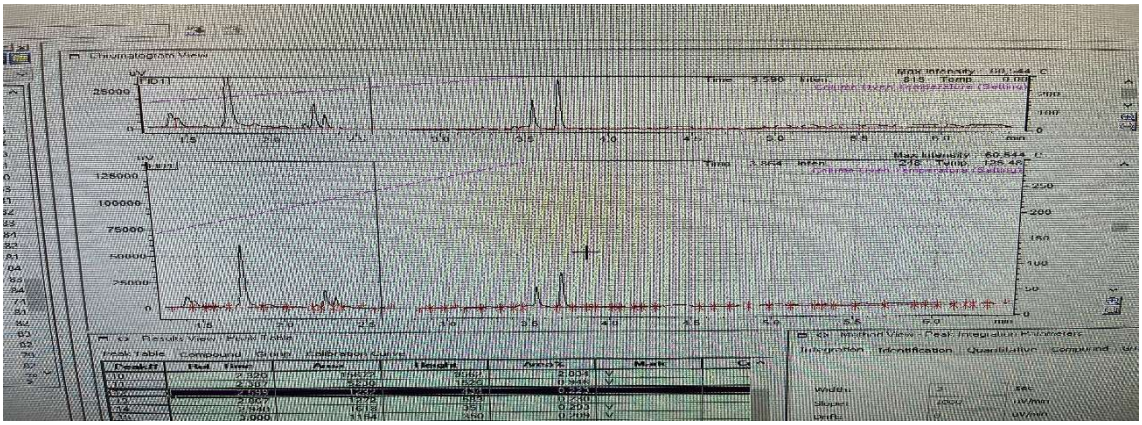
GC-MS = gas chromatography-mass spectrometry; DCM = Dichloromethane; DMF = *N*,*N*-Dimethylformamide; TBSCl = *tert*-butyldimethylsilyl chloride; THF = tetrahydrofuran; EDCI = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide.

Intramolecular Heck reaction optimization



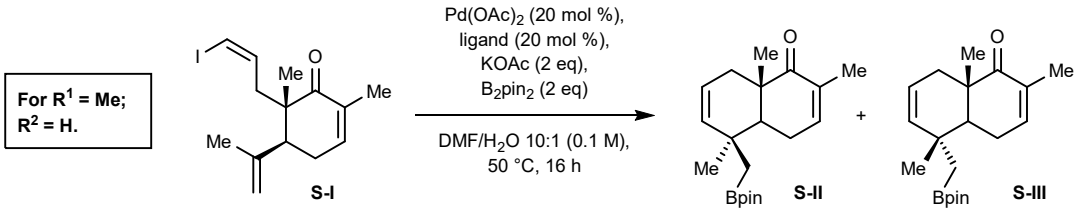
Inside of a glovebox, palladium acetate (3.2 mg, 13 µmol, 20 % mol), diphosphine ligand (13 µmol, 20 mol %), potassium acetate (8.8 mg, 0.13 mmol, 2 eq), and bispinacolato diboron (25.6 mg, 0.13 mmol, 2 eq) were weighted in an over dried vial equipped with a stir bar. A 0.1 M stock solution of vinyl iodide **S-I** in DMF was added (670 µL, 67 µmol, 1 eq, 0.1 M) followed by addition of water (24.1 mg, 24.1 µL, 1.34 mol, 20 eq). The vial was sealed, taken out of the glovebox, and placed in a heating block. The reaction mixture was stirred at 50 °C for 16 h. Afterwards, the mixture was cooled down to room temperature and filtered. The so obtained clear solution was analyzed on GC-MS for determination of the diastereomeric ratio **S-II**/**S-III**.

Typical GC-MS chromatogram



The first peak (minor) after 3.5 min is the equatorially disposed product **S-III**, while the second one (major) is the axially disposed product **S-II**. By performing the same analysis on all the reaction during the screening, the products distribution could be derived from the integration of the peaks.

Intramolecular borylative Heck reaction optimization tables



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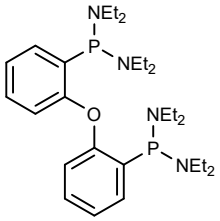
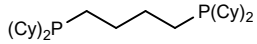
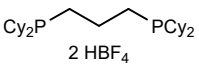
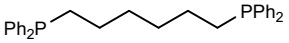
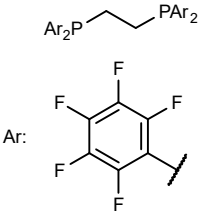
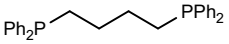
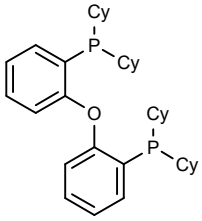
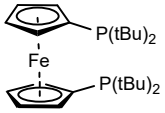
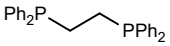
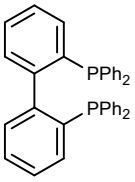
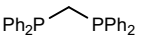
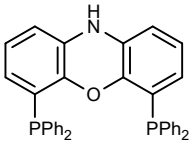
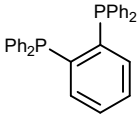
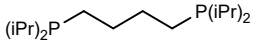
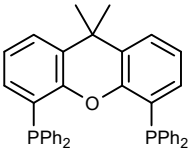
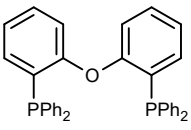
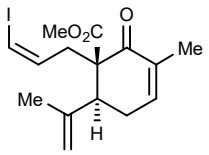
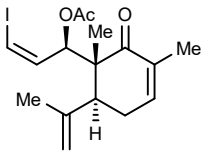
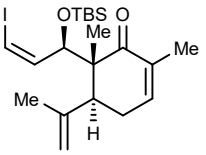
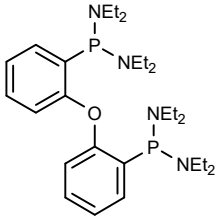
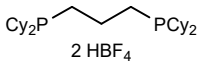
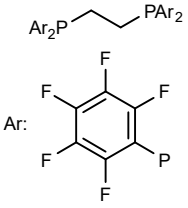
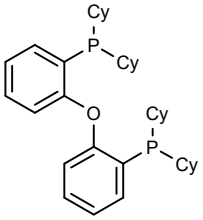
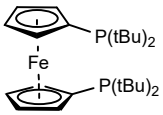
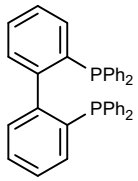
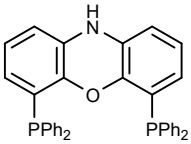
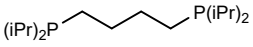
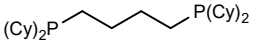
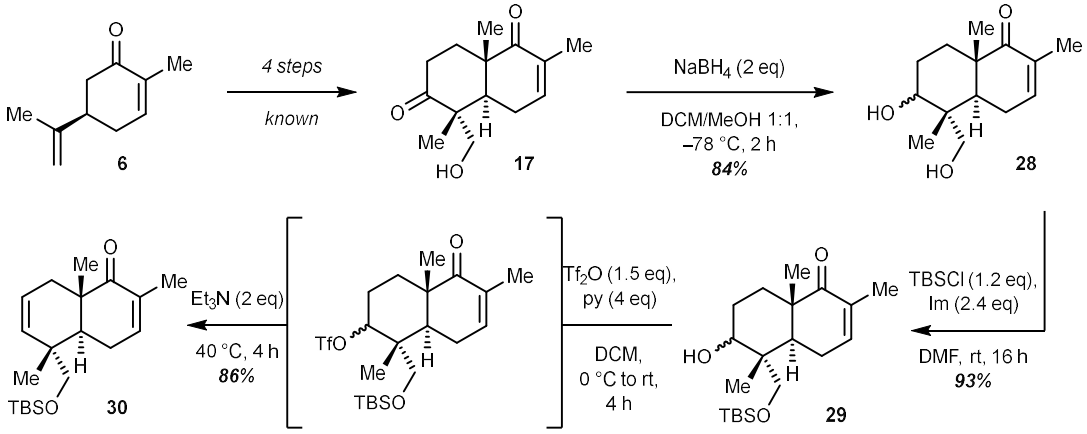
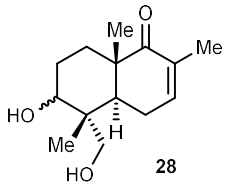
1		2.0 Ax:Eq	9		3.2 Ax:Eq
2		3.5 Ax:Eq	10		1.5 Ax:Eq
3		2.2 Ax:Eq	11		0.66 Ax:Eq
4		2.7 Ax:Eq	12		1.2 Ax:Eq
5		4.8 Ax:Eq	13		1.5 Ax:Eq
6		2.3 Ax:Eq	14		1.8 Ax:Eq
7		2.2 Ax:Eq	15		2.0 Ax:Eq
8		2.60 Ax:Eq	16		2.0 Ax:Eq
			17		2.0 Ax:Eq

Entry	Ligand	For R^1 = CO_2Me; R^2 = H.  d.r. (S-II:S-III)	For R^1 = Me; R^2 = OAc.  d.r. (S-II:S-III)	For R^1 = Me; R^2 = OTBS.  d.r. (S-II:S-III)
1		2.9 Ax:Eq	1.11 Ax:Eq	1.81 Ax:Eq
2		3.0 Ax:Eq	0.40 Ax:Eq	1.63 Ax:Eq
3		2.7 Ax:Eq	0.90 Ax:Eq	1.03 Ax:Eq
4		2.9 Ax:Eq	3.54 Ax:Eq	1.26 Ax:Eq
5		n.d.	0.64 Ax:Eq	2.34 Ax:Eq
6		3.8 Ax:Eq	1.13 Ax:Eq	1.48 Ax:Eq
7		1.4 Ax:Eq	3.00 Ax:Eq	1.81 Ax:Eq
8		3.9 Ax:Eq	9.63 Ax:Eq	1.12 Ax:Eq
9		3.8 Ax:Eq	0.91 Ax:Eq	1.30 Ax:eq

Synthesis of 30



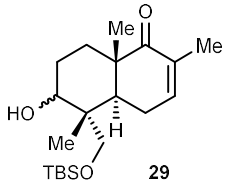


Compound 28

In a round bottom flask, compound **17** (8.6 g, 36 mmol, 1 eq) was dissolved in a 1:1 DCM:MeOH mixture (360 mL, 0.1 M). The solution was cooled to -78 °C in a dry ice/acetone bath, and sodium borohydride (2.8 g, 73 mmol, 2 eq) was added in one portion. After completion as monitored by TLC (*about 1.5 h*), 100 mL of acetone were added, and the reaction mixture was allowed to warm up to room temperature. After 30 min at that temperature, the volatiles were removed *via* rotary evaporation. The so obtained solids were redissolved in 200 mL of ethyl acetate and washed with sodium carbonate (10 wt% aq. sol., 100 mL). The organic phase was separated, and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were dried loaded on silica for column chromatography (SiO_2, 1:1 to 0:1 hexanes:EtOAc) to afford diol **28** (7.3 g, 31 mmol, 84% yield) as a white amorphous solid.

R_f : 0.27 (hexanes:EtOAc = 1:4, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (d, *J* = 5.9 Hz, 1H), 3.63 – 3.51 (m, 2H), 3.38 (d, *J* = 9.5 Hz, 1H), 2.37 – 2.29 (m, 1H), 2.13 – 2.04 (m, 1H), 1.99 – 1.83 (m, 2H), 1.70 (s, 6H), 1.16 – 0.99 (m, 6H).



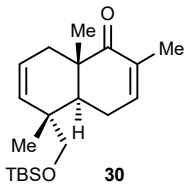
Compound 29

Diol **28** (5.6 g, 23 mmol, 1 eq) was dissolved in DMF (230 mL, 0.1 M), and the solution was cooled to 0 °C in an ice bath. Imidazole (3.8 g, 56 mmol, 2.4 eq) and TBSCl (4.2 g, 28 mmol, 1.2 eq) were added, and the mixture was allowed to warm up to room temperature while stirring. After 16 h, the

reaction mixture was quenched with sodium bicarbonate (sat. aq. sol., 100 mL) and diethyl ether (100 mL) was added. The organic phase was separated, and the water phase was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 3 x 50 mL), and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were dried loaded on silica for column chromatography (SiO_2, 20:1 to 4:1 hexanes:EtOAc) to afford alcohol **29** (7.7 g, 22 mmol, 93% yield) as a colorless oil which solidifies upon standing.

R_f : 0.43 (hexanes:EtOAc = 4:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (d, *J* = 5.9 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.36 (d, *J* = 9.5 Hz, 1H), 2.39 – 2.28 (m, 1H), 2.16 – 2.05 (m, 1H), 1.95 – 1.81 (m, 2H), 1.73 (s, 6H), 1.51 – 1.40 (m, 1H), 1.12 – 0.97 (m, 8H), 0.94 – 0.81 (m, 12H).



30

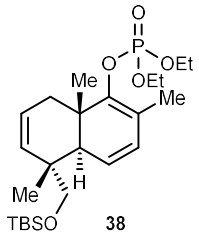
Compound 30

Alcohol **29** (2.2 g, 6.2 mmol, 1 eq) was dissolved in DCM (62 mL, 0.1 M), and the solution was cooled to 0 °C in an ice bath under inert atmosphere. Pyridine (2.0 g, 2.0 mL, 25 mmol, 4 eq) was added, followed by dropwise addition of triflic anhydride (2.6 g, 1.6 mL, 9.4 mmol, 1.5 eq) over 15 minutes. The reaction mixture was stirred at that temperature for 2 h, and then let to warm up to room temperature. At this point triethylamine (1.3 g, 1.7 mL, 12 mmol, 2 eq) was added and the mixture was stirred at 40 °C for 4 h. Afterwards, it was cooled down to room temperature and water was added (50 mL). The organic phase was separated, and the water phase was extracted with DCM (3 x 20 mL). The collected organic phases were washed with copper(II) sulfate (sat. aq. sol., 3 x 15 mL), sodium chloride (sat. aq. sol., 30 mL), and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were dried loaded on silica for column chromatography (SiO_2, 40:1 to 10:1 hexanes:EtOAc) to afford alkene **30** (1.8 g, 5.4 mmol, 86% yield) as a light-yellow oil.

R_f : 0.58 (hexanes:EtOAc = 10:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (s, 1H), 5.68 (s, 1H), 5.31 (s, 1H), 3.26 (q, *J* = 9.8 Hz, 2H), 2.37 (s, 2H), 2.23 (s, 2H), 2.04 (m, 1H), 1.76 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.85 (s, 9H), -0.01 (s, 6H).

Phosphate derivatizations

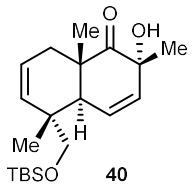


38

Compound 38

Enone **30** (2.5 g, 7.5 mmol, 1 eq) was dissolved in anhydrous THF (37.4 mL, 0.2 M) under inert atmosphere. The solution was cooled to -78 °C in a dry ice/acetone bath, and solid LHMDS (2.63 g, 15.7 mmol, 2.1 eq) was added. The mixture was stirred at 0 °C for 2 h and cooled back down to -78 °C before dropwise addition of diethyl chlorophosphate (1.55 g, 1.30 mL, 1.2 eq). The mixture was let to warm up to room temperature overnight, then it was quenched with ammonium chloride (sat. aq. sol., 50 mL). The organic phase was separated , and the water phase was extracted with diethyl ether (3 x 25 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 dried loaded on silica for column chromatography (SiO_2, 30:1 to 6:1 hexanes:EtOAc) to afford vinyl phosphate **38** (1.6 g, 3.4 mmol, 45% yield) as a light-yellow oil.

R_f : 0.44 (hexanes:EtOAc = 6:1, UV, $KMnO_4$)



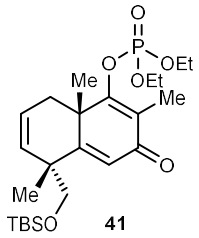
40

Compound 40

To a solution of vinyl phosphate **38** (20 mg, 42 µmol, 1 eq) in acetone (420 µL, 0.1 M) were added water (15 mg, 15 µL, 850 µmol, 20 eq), NMO (5.0 mg, 43 µmol, 1.01 eq), and osmium tetroxide (0.2 M in MeCN, 21 µL, 4 µmol, 10 mol %). The reaction was stirred at room temperature for 3 h, and then quenched with sodium thiosulfate (10 wt % aq. sol., 1 mL) and diluted with ethyl acetate. The organic phase was separated , and the water phase was extracted with ethyl acetate (3 x 1 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 3 mL), and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were analyzed through NMR, showing full conversion to hydroxy ketone **40**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.85 (dd, *J* = 10.2, 3.2 Hz, 1H), 5.66 (dddd, *J* = 15.4, 10.3, 6.0, 2.0 Hz, 1H), 5.38 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.40 – 3.23 (m, 3H), 2.72 (dd, *J* = 3.3, 1.9 Hz, 1H), 1.98 (dt, *J* = 17.6, 6.8 Hz, 1H), 1.46 (s, 3H), 1.32 – 1.22 (m, 3H), 1.03 (s, 3H), 0.90 – 0.74 (m, 9H), 0.06 – -0.10 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 217.0, 133.1, 131.2, 129.2, 123.6, 72.6, 71.5, 47.6, 44.1, 40.8, 32.2, 28.6, 26.0, 19.8, 18.5, 18.3, -5.2, -5.3.



41

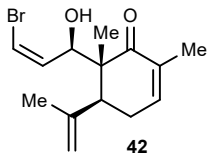
Compound 41

A vial equipped with a stirbar was charged with vinyl phosphate **38** (20 mg, 42 µmol, 1 eq), DCM (420 µL, 0.1 M), potassium carbonate (2.9 mg, 21 µmol, 50 mol %), and $Rh_2(cap)_4$ (0.28 mg, 0.4 µmol, 1 mol %). The flask was sealed, equipped with an air-filled balloon, and the mixture was heated to 40 °C in a heating block. To the mixture was added TBHP (70 wt % in H_2O, 27 mg, 29 µL, 210 µmol, 5 eq) in one portion *via* syringe to which the color of the solution immediately turned from light blue to deep red. After 1.5 hours, a second portion of $Rh_2(cap)_4$ (0.28 mg, 0.4 µmol, 1 mol %) was added, followed by a second portion of TBHP (70 wt % in H_2O, 27 mg, 29 µL, 210 µmol, 5 eq). After stirring for another 1.5 hours, the solution was filtered through a short plug of silica gel to remove the catalyst. The crude was concentrated in vacuo and analyzed with NMR to show clean conversion to dienone **41** (6 mg, 10 µmol, 30% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, *J* = 4.3 Hz, 1H), 5.85 – 5.76 (m, 1H), 5.57 (dd, *J* = 9.9, 2.9 Hz, 1H), 4.29 – 4.16 (m, 4H), 3.59 – 3.45 (m, 2H), 2.51 (ddd, *J* = 16.5, 9.4, 6.5 Hz, 1H), 2.22 – 2.10 (m, 1H), 1.95 (d, *J* = 2.1 Hz, 3H), 1.52 – 1.36 (m, 9H), 1.26 (d, *J* = 4.3 Hz, 3H), 0.83 (s, 9H), -0.01 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.1, 167.0, 166.9, 166.2, 133.1, 123.6, 122.9, 122.4, 71.3, 64.9, 64.9, 64.8, 43.3, 43.1, 32.4, 29.8, 26.4, 25.9, 25.3, 25.0, 18.3, 16.3, 9.4, -5.3.

Reformatsky pathway



42

Compound 42

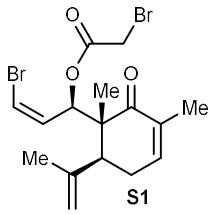
To a round bottom flask was added THF (50 mL), diisopropyl amine (2.2 mL, 1.25 eq.) and then *n*-BuLi (9.36 mL, 1.6 M in hexanes, 1.2 eq) at -78 °C. This was stirred at -78 °C for 15 minutes and then a solution of methyl carvone (2.00 g, 12.2 mmol, 1 eq) in THF (25 mL) was added dropwise. The reaction was stirred for an additional hour and then a solution of the previously prepared (*Z*)-bromo-acrolein was added at -100 °C (2.63 g, 1.6 eq in 25 mL THF). The reaction was quenched after stirring at -100 °C for 10 minutes by the addition of 25 mL of 1 M HCl with vigorous

stirring. The crude mixture was extracted with diethyl ether (3 x 50 mL) and then washed with brine and dried with magnesium sulfate. The organic layers were concentrated *in vacuo* and then purified by column chromatography (hexanes:EtOAc = 4:1) to afford product **42** as a pale-yellow oil (3.27 g, 10.9 mmol, 90% yield) that solidifies upon standing in the freezer.

R_f = 0.31 (hexanes:EtOAc = 4:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (m, 1H), 6.58 (dd, 1H), 6.31 (d, 1H), 4.89 (s, 1H), 4.81 (s, 1H) 2.97 (dd, 1H), 2.54 (m, 1H), 2.36 (m, 1H), 2.01 (m, 1H), 1.72 (s, 3H), 1.72 (s, 3H) 0.99 (s, 3H)

^{13}C NMR (130 MHz, $CDCl_3$) δ 204.3, 145.1, 143.4, 134.6, 134.4, 115.3, 110.8, 72.5, 52.5, 47.3, 29.4, 22.7, 16.3, 14.3.



S1

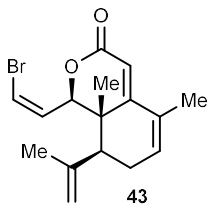
Compound S1

To a solution of starting material **42** (3.6 g, 12 mmol, 1 eq) in DCM (120 mL, 0.1 M) was added bromoacetyl bromide (3.6 g, 1.6 mL, 18 mmol, 1.5 eq) and pyridine (1.9 g, 1.9 mL, 24 mmol, 2 eq) at 0 °C. The reaction was allowed to stir at this temperature until complete (*judged by TLC, about 1 h*) and then quenched by the addition of 15 mL of 1 M HCl. The organic layer was separated, and the aqueous layer was extracted three times with DCM (3 x 50 mL). The combined organic layers were dried with magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (hexanes:EtOAc = 8:1 to 6:1) to provide the desired product **S1** as a pale-yellow oil (90%).

R_f = 0.33 (hexanes:EtOAc = 6:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (m, 1H) 6.57 (s, 1H), 6.55 (q, 1H), 4.90 (s, 1H), 4.79 (s, 1H), 3.8 (dd, 2H), 2.88 (t, 1H) 2.79 (m, 1H), 2.45 (m, 1H), 1.80 (q, 3H), 1.72 (d, 3H), 1.15 (s, 3H).

^{13}C NMR (130 MHz, $CDCl_3$) δ 200.7, 165.76, 144.6, 142.4, 134.6, 129.87, 115.8, 113.9, 51.5, 48.0, 29.1, 25.7, 21.7, 16.4, 14.8.



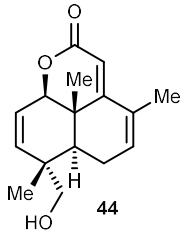
43

Compound 43

To a flame-dried 8 mL vial with a stir bar was added indium powder (611 mg, 5.32 mmol, 4 eq) in a nitrogen filled glovebox. The vial was capped and removed from the glovebox and then a solution of

starting material (430 mg, 1.33 mmol, 1 eq) in 1,4-dioxane (6 mL, 0.22 M) was added directly. The reaction was stirred at 110 °C for three days and monitored by TLC (hexanes:EtOAc). After completion, the reaction was quenched by the addition of water (10 mL). The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL) and then dried with magnesium sulfate and concentrated *in vacuo*. The crude product was further purified by column chromatography (hexanes:EtOAc = 4:1 to 2:1) to provide the desired product as an off-white solid (183 mg, 0.57 mmol, 43% yield).

R_f : 0.55 (hexanes:EtOAc = 2:1, UV, $KMnO_4$)



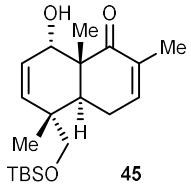
44

Compound 44

To a flame-dried 8 mL vial with a stir bar was added $Pd(OAc)_2$ (15.1 mg , 0.07 mmol, 10 mol %,), DPPF (37.3 mg, 0.07 mmol, 10 mol %), KOAc (66.0 mg, 1.0 mmol, 1.5 eq), and B_2Pin_2 (256 mg, 1.34 mmol, 2 eq), the vial was capped and removed from the glovebox. To this was added a solution of the starting material **43** (220 mg, 0.672 mmol, 1 eq) in DMF (6 mL, 0.1 M). The vial was then allowed to stir at 80 °C for 24 hours. The reaction was then cooled to 0 °C and H_2O_2 (206 µL, 6.7 mmol, 10 eq) was added dropwise at this temperature. The reaction was stirred for 4 hours and allowed to warm to room temperature over this time. The oxidation was quenched by the addition of sodium thiosulfate (sat. aq. sol., 1 mL) and stirred vigorously. The mixture was extracted with ethyl acetate (3 x 5 mL), washed with brine (15 mL), dried with magnesium sulfate, and concentrated i*n vacuo*. The crude product was purified by column chromatography (hexanes:EtOAc = 2:1 to 1:1) to provide the product as a pale white solid (101 mg, 0.41 mmol, 60% yield) as a 1:1 mixture of the two diastereomers.

Note: since the 1:1 mixture of the two diastereomer was not separated, reporting the NMR peaks challenging. The products were determined in combination with GC-MS and 2D NMRs.

Intramolecular HWE pathway



45

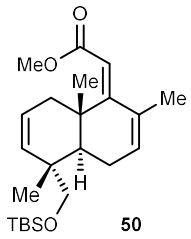
Compound 45

To a solution of alkene **30** (440 mg, 0.99 mmol, 1 eq) in 1,4-dioxane (9.9 mL, 0.1 M) was added NaH_2PO_4 (118 mg, 0.99 mmol, 1 eq), and selenium dioxide (219 mg, 1.97 mmol, 2 eq). The mixture was heated at 80 °C overnight, then cooled down to room temperature and filtered, rinsing with ethyl acetate. The crude materials were dried *in vacuo* and loaded on silica for column chromatography (SiO_2, 10:1 to 4:1 hexanes:EtOAc) to afford allylic alcohol **45** (130 mg, 0.37 mmol, 38% yield) as a light-yellow oil.

R_f : 0.38 (hexanes:EtOAc = 4:1, UV, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 – 6.74 (m, 1H), 5.93 (dd, *J* = 10.0, 6.1 Hz, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 4.37 (d, *J* = 6.1 Hz, 1H), 3.33 (s, 2H), 2.66 (dd, *J* = 11.6, 5.0 Hz, 1H), 2.52 – 2.34 (m, 3H), 1.78 (dt, *J* = 2.7, 1.3 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 6H), 0.88 (s, 9H), 0.13 – -0.08 (m, 6H).

Meyer-Schuester pathway



50

Compound 50

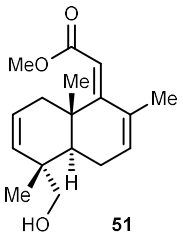
Step 1: A solution of enone **30** (700 mg, 2.09 mmol, 1 eq) in anhydrous THF (10.5 mL, 0.2 M) was cooled to -78 °C under inert atmosphere in a dry ice/acetone bath. In a separate flask, a solution of ethoxyacetylene (50 wt % in hexane, 2.0 mL, 20.9 mmol, 10 eq) in anhydrous THF (10.5 mL, 0.2 M) was cooled to -78 °C, and *n*BuLi (1.6 M in hexane, 5.23 mL, 8.37 mmol, 4 eq) was added dropwise. The mixture was stirred at that temperature for 30 min, after which it was cannulated into the allylic alcohol solution previously prepared. The so obtained solution was warmed to 0 °C and stirred at that temperature for 2 h. Afterwards, it was quenched with water (20 mL), and the organic phase was separated. The organic phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 20 mL), and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.*

Step 2: The so obtained material was redissolved in a DCM/MeOH 1:1 mixture (21 mL, 0.1 M), and the solution was cooled to 0 °C before addition of scandium triflate (103 mg, 0.21 mmol, 10 mol %) was added in one portion. The mixture was stirred for 15 minutes,

after which it was directly dry loaded on silica for column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 4:1) to afford dienoate **50** (502 mg, 1.29 mmol, 61% yield) as a light-yellow oil.

R_f : 0.23 (hexanes:EtOAc = 4:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.70 – 5.61 (m, 1H), 5.60 – 5.51 (m, 1H), 5.44 – 5.38 (m, 1H), 3.73 (s, 3H), 3.22 (s, 1H), 2.32 – 2.23 (m, 2H), 2.15 – 2.03 (m, 2H), 1.94 (dd, *J* = 10.8, 6.1 Hz, 1H), 1.87 – 1.80 (m, 4H), 1.04 (s, 3H), 0.95 (d, *J* = 10.8 Hz, 3H), 0.88 (d, *J* = 13.8 Hz, 9H), 0.01 (d, *J* = 14.1 Hz, 6H).

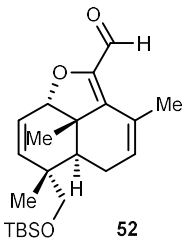


51

Compound 51

To a solution of dienoate **50** (5 mg, 0.01 mmol, 1 eq) in THF (100 µL, 0.1 M) cooled to 0 °C was added TBAF (1 M in THF, 70 µL, 0.07 mmol, 5 eq). The mixture was let to warm up to room temperature overnight, after which it was quenched with water (0.5 mL). The organic phase was separated, and the water phase was extracted with ethyl acetate (3 x 0.5 mL). The combined organic phases were washed with sodium chloride (sat. aq. sol., 1 mL), and thereafter dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Alcohol **51** (3 mg, 0.01 mmol, >99% yield) was obtained as a colorless oil pure enough for analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (t, *J* = 8.4 Hz, 1H), 5.85 (s, 1H), 5.64 (s, 1H), 5.36 (d, *J* = 10.1 Hz, 1H), 3.73 (s, 3H), 3.30 (d, *J* = 10.9 Hz, 1H), 3.17 (d, *J* = 10.7 Hz, 1H), 2.20 (s, 3H), 2.12 (dd, *J* = 16.4, 6.5 Hz, 1H), 1.85 (d, *J* = 2.2 Hz, 3H), 1.78 (d, *J* = 16.9 Hz, 1H), 1.25 (s, 5H), 1.07 (s, 3H), 0.93 (s, 3H).



52

Compound 52

Step 1: A solution of allylic alcohol **45** (2.49 g, 7.10 mmol, 1 eq) in anhydrous THF (35.5 mL, 0.2 M) was cooled to -78 °C under inert atmosphere in a dry ice/acetone bath. In a separate flask, a solution of ethoxyacetylene (50 wt % in hexane, 6.8 mL, 71 mmol, 10 eq) in anhydrous THF (35.5 mL, 0.2 M) was cooled to -78 °C, and *n*BuLi (1.6 M in hexane, 17.8 mL, 28.4 mmol, 4 eq) was added dropwise. The mixture was stirred at that temperature for 30 min, after which it was cannulated into the allylic alcohol solution previously

prepared. The so obtained solution was warmed to 0 °C and stirred at that temperature for 2 h. Afterwards, it was quenched with water (50 mL), and the organic phase was separated. The organic phase was extracted with ethyl acetate (3 x 20 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.*

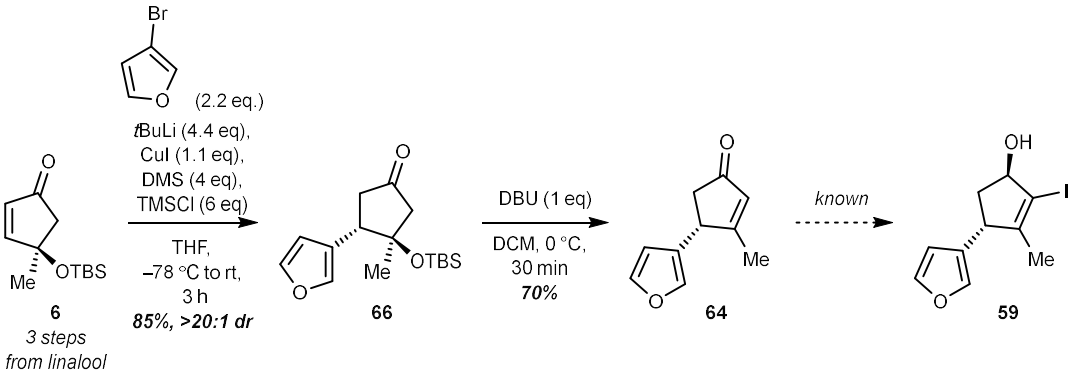
Step 2: The so obtained material was redissolved in anhydrous toluene (71 mL, 0.1 M), and the solution was cooled to 0 °C before addition of silver triflate (182 mg, 0.71 mmol, 10 mol %) was added in one portion. The mixture was stirred for 15 minutes, after which it was directly dry loaded on silica for column chromatography (SiO_2, 10:1 to 4:1 hexanes:EtOAc) to afford aldehyde **52** (1.94 g, 5.18 mmol, 73% yield) as a light-yellow oil.

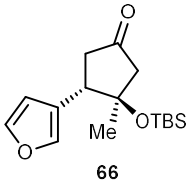
R_f : 0.62 (hexanes:EtOAc = 4:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 5.94 (d, *J* = 1.8 Hz, 2H), 5.78 – 5.71 (m, 1H), 4.56 (d, *J* = 1.7 Hz, 1H), 3.36 (d, *J* = 9.5 Hz, 1H), 3.27 (d, *J* = 9.5 Hz, 1H), 2.24 (ddq, *J* = 8.1, 3.9, 2.0 Hz, 2H), 2.09 (q, *J* = 1.9 Hz, 3H), 2.00 (dd, *J* = 9.9, 6.5 Hz, 1H), 1.33 – 1.22 (m, 3H), 0.93 (s, 3H), 0.86 (s, 9H), 0.01 (d, *J* = 1.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 145.3, 142.5, 140.0, 130.5, 126.9, 123.0, 82.2, 70.8, 46.4, 42.3, 39.0, 25.9, 25.4, 22.5, 20.9, 18.4, 17.7, -5.3.

Eastern fragment synthesis





Compound 66

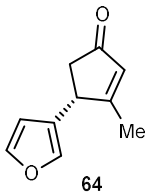
To a cooled (−78 °C) solution of β-bromofuran (273 mg, 1.86 mmol, 2.2 eq) in THF (3.71 mL, 0.5 M) was added *t*BuLi (1.6 M solution in heptane, 2.32 mL, 3.71 mmol, 4.4 eq). The solution was let to stir for 30 minutes. In a separate flask, Me_2S (220 mg, 261 µL, 3.53 mmol, 4 eq) was added to a suspension

of CuI (177 mg, 0.93 mmol, 1.1 eq) in THF (2.21 mL, 0.4 M) and the mixture was stirred until a clear solution formed. This solution was cannulated into the solution of the furyllithiate. The resulting solution was stirred for 15 minutes at −78 °C. TMSCl (576 mg, 673 µL, 5.30 mmol, 6 eq) was added to the cuprate. After 15 min at −78 °C a solution of enone **6** (200 mg, 0.88 mmol, 1 equiv.) in THF (883 µL, 1 M) was added dropwise to the former solution. The resulting suspension was let to warm up to rt over the course of 3 h. The reaction was quenched by the addition of a mixture of ammonium chloride (sat. aq. sol., 3 mL) and ammonium hydroxide (28 wt% aq. sol., 3 mL). After stirring for 20 minutes, the mixture was extracted with diethylether (3 × 5 mL). The combined organic layers were washed with sodium chloride (sat. aq. sol., 20 mL), dried over MgSO4, filtered and concentrated. The obtained residue was purified by flash column chromatography (SiO_2, hexanes:EtOAc = 40:1 to 10:1) to yield ketone **66** as a pale-yellow oil (221 mg, 0.75 mmol, 85% yield).

R_f : 0.59 (hexanes:EtOAc = 10:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 1.7 Hz, 1H), 7.33 (dt, *J* = 1.6, 0.7 Hz, 1H), 6.40 (dd, *J* = 1.9, 0.9 Hz, 1H), 3.08 (dd, *J* = 12.4, 7.8 Hz, 1H), 2.69 – 2.59 (m, 1H), 2.57 – 2.46 (m, 2H), 2.35 (d, *J* = 17.7 Hz, 1H), 1.44 (s, 3H), 0.80 (s, 9H), 0.06 (s, 3H), -0.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 215.9, 142.5, 140.4, 121.8, 111.4, 79.6, 54.9, 45.8, 43.1, 25.9, 25.2, 18.2, -2.4.



64

Compound 64

The substrate **66** (1.9 g, 6.5 mmol, 1 eq) was dissolved in DCM (32 mL, 0.2 M) and the solution was cooled to 0 °C. DBU (1.0 g, 1.0 mL, 6.8 mmol, 1.05 eq) was added dropwise and the reaction was stirred for 30 minutes at that temperature. Then, the mixture was quenched with ammonium chloride (sat. aq. sol., 30 mL). The organic phase was separated, and the water phase was extracted with DCM (3 x 10 mL), washed with sodium chloride (sat. aq. sol., 30 mL), dried over $MgSO_4$, and filtered. The solution was concentrated *in vacuo* at 30 °C and 600 mbar until most of the solvent was removed. The remaining crude material was purified with column chromatography using pentane:ether (4:1) as the eluent mixture, finally affording enone **64** as a pale-yellow oil (734 mg, 4.53 mmol, 70% yield).

R_f : 0.35 (hexanes:EtOAc = 4:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, *J* = 1.9 Hz, 1H), 7.37 (s, 1H), 6.18 (s, 1H), 6.07 (q, *J* = 1.6 Hz, 1H), 3.90 (d, *J* = 7.0 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.43 – 2.35 (m, 1H), 2.01 (s, 3H).

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