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Multicomponent, Mannich-type assembly process for generating novel, biologically-active 2-arylpiperidines and derivatives

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ABSTRACT

A multicomponent, Mannich-type assembly process commencing with commercially available bromobenzaldehydes was sequenced with [3+2] dipolar cycloaddition reactions involving nitrones and azomethine ylides to generate collections of fused, bicyclic scaffolds based on the 2-arylpiperidine subunit. Use of the 4-pentenoyl group, which served both as an activator in the Mannich-type reaction and a readily-cleaved amine protecting group, allowed sub-libraries to be prepared through piperidine N-functionalization and cross-coupling of the aryl bromide. A number of these derivatives displayed biological activities that had not previously been associated with this substructure. Methods were also developed that allowed rapid conversion of these scaffolds to novel, polycyclic dihydroquinazolin-2-ones, 2-imino-1,3-benzothiazinanes, dihydroisoquinolin-3-ones, and bridged tetrahydroquinolines.

1. Introduction

1.1. Methods for the discovery of novel, bioactive compounds

There is an ongoing need to discover new compounds that can modulate biological processes, both for use as probes to study cellular mechanisms and as drugs for treating disease. Perhaps the most well-known and utilized set of principles to guide drug discovery efforts toward identifying bioavailable compounds is outlined in Lipinski's 'rule of five'.[1] Related concepts include closer scrutiny of compounds and their topological polar surface area (PSA),[2] number of rotatable bonds,[3] and the degree of incorporation of sp^3 centers (Fsp^3).[4] Although these paradigms help steer the design of analogues of lead compounds with enhanced physicochemical and biological properties, the design and identification of truly novel bioactive compounds remains challenging.

Natural products, which frequently induce biological responses with a high degree of specificity, can be exploited to study the interactions of small molecules with biological receptors, and they have long served as a source of inspiration for drug design.[5] Indeed, approximately 50% of the small molecule drugs discovered during the past 30 years are natural products and compounds derived there from.[6] Consequently, the discovery and development of synthetic techniques to access these compounds and analogs that mimic their structural features represents a major undertaking in medicinal chemistry and chemical biology. Diversity-oriented synthesis (DOS) is one method, that is, progressively gaining popularity as a means of generating architecturally-complex, natural product-like structures rapidly whilst simultaneously exploring new regions of chemical space.[7] The combination of DOS approaches with the incorporation of so-called 'privileged substructures'—structural subunits, which elicit responses in a variety of biological receptors—is a promising method for the discovery of new structure–activity relationships.[8] One approach to small molecule discovery that implements such design principles is biology oriented synthesis (BIOS), which exploits core substructures of natural products as scaffolds for generating compound collections.[9]

1.2. Discovery of a new multicomponent assembly process

As part of our pursuit of the synthesis of biologically natural products, we developed a new Mannich-type multicomponent assembly process (MCAP) that allowed a remarkably concise synthesis of the pentacyclic indole alkaloid (±)-tetrahydroalstonine in only five steps from tryptamine.[10] It occurred to us at the time that the basic strategy embodied in this synthesis, which involves addition of a nucleophile to an acyliminium ion generated in situ by N-acylation of an imine followed by ring-forming and refunctionalization steps, might be developed into a powerful approach to natural products and polycyclic nitrogen heterocycles. For example, we have since exploited this concept in the synthesis of numerous

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natural products,[11,12] and we have applied it as a central strategic element to develop a novel DOS-type approach to generate libraries of 'unnatural product' libraries based around the arylaminomethyl core subunit, that is, common to many natural products and privileged substructures.[13]

During these investigations, we became intrigued by the structural features present in the fused bicyclic scaffolds **1** and **2** due to their adherence to Lipinski's rules, high sp^3 content and resemblance to a number of compounds with documented biological activities (Fig. 1). For example, the octahydro-1*H*-pyrrolo[3,2-*c*]pyridine scaffold present in **2** is represented in the CCR5 antagonist **3**[14] and the bradykinin receptor antagonist martinellic acid (**4**).[15] Moreover, the privileged 2-arylpiperidine substructure present in **1** and **2** can be found in the substance P antagonist **5**[16] and the neurokinin 1 receptor antagonist **6**.[17] Compound **1** itself displays activity as an activator of both the nuclear receptor DAF-12 (1% activation at 6.8 μM) and the mouse serotonin receptor 2A (19% activation at 7.6 μM).[18]

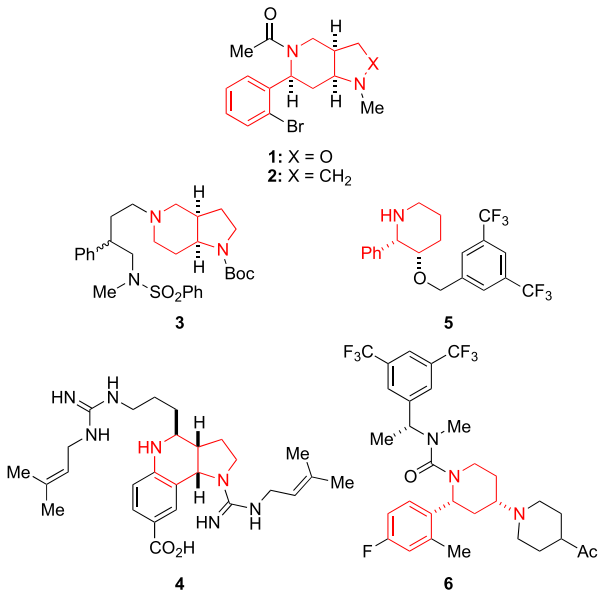


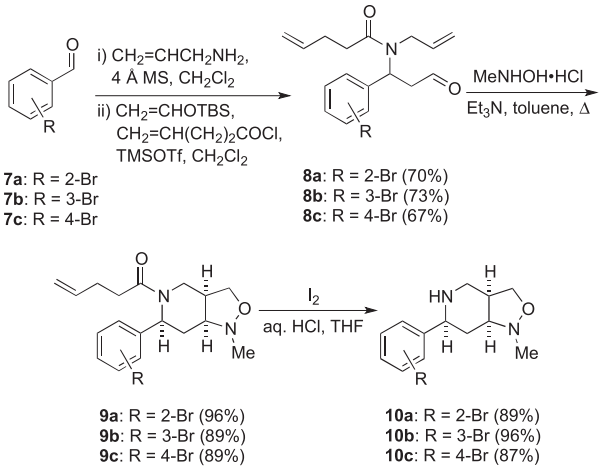
Fig. 1. MCAP-accessible fused bicyclic 2-arylpiperidine scaffolds **1** and **2** and structurally related, biologically active compounds.

Encouraged by this compelling precedent for the diverse biological activities associated with compounds closely related to **1** and **2**, we were motivated to create compound libraries based on these scaffolds for submission to the National Institutes of Health Molecular Libraries Small Molecule Repository (MLSMR) for screening against a large number of biological targets.[19] We now report the details of these studies.

2. Results and discussion

2.1. Assembly of core scaffolds for diversification

The regioisomeric aldehydes **8a**–**c** were prepared by a two-stage MCAP that commenced with condensation of the commercially available bromobenzaldehydes **7a**–**c** with allylamine, followed by subjecting the intermediate imines to an N-acylation with 4-pentenoyl chloride and a TMSOTf-catalyzed addition of vinyl TBS ether, a π-nucleophile (Scheme 1). Acid chlorides were found to be more effective activators than chloroformates in this process, and the pentenoyl group was chosen due to its robustness in subsequent reactions coupled with its ease of removal under mild conditions.[20] The aldehydes **8a**–**c** were then condensed with *N*-methylhydroxylamine to generate nitrones that underwent



Scheme 1. Preparation of octahydroisoxazolo[4,3-*c*]pyridine scaffolds via MCAP/nitrone cycloaddition sequences.

spontaneous dipolar cycloaddition under the reaction conditions to furnish the isoxazolidines **9a**–**c** as single diastereoisomers. The relative stereochemistry of these cycloadducts was confirmed by obtaining an X-ray crystal structure of compound **9a** (Fig. 2).

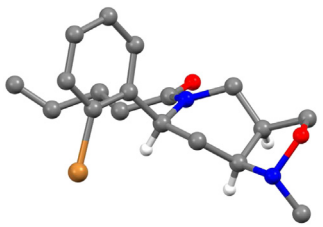


Fig. 2. X-ray crystal structure of **9a**; hydrogen atoms at all but stereogenic carbon atoms are omitted for clarity.

The *N*-pentenoyl side chains in compounds **9a**–**c** were then removed upon treatment with iodine in a mixture of THF and aqueous HCl to give the secondary amines **10a**–**c**. It was necessary to modify the known procedure[20] for cleaving this protecting group by conducting the reaction in the presence of aqueous acid to minimize deleterious formation of iodohydrin side-products. The amine **10c** exhibited inhibitory activity against Dengue virus 2, as indicated by an increase in viability of BHK-21 cells incubated with DENV-2 in a cytopathic effect assay (26% increase in cell viability at 10 μM).[21]

The aryl bromide moiety in compounds **9b**,**c** and **10b**,**c** served as an excellent functional group handle for introducing other substituents via cross-coupling reactions. For example, **9b** underwent facile cross-coupling with morpholine under Buchwald's conditions to give the aniline **12** (Scheme 2).[22] The corresponding etherification reaction with phenol was unsuccessful, because a side reaction involving Heck coupling of the aryl bromide with the carbon–carbon double bond in the pentenamide group outcompeted the desired etherification process. On the other hand, Ullmann-type copper-catalyzed cross coupling of **9b** with phenol furnished the diaryl ether **15**.[23] The pentenamide moieties in **12** and **15** were then cleaved using the modified deprotection procedure to give **13** and **16**, respectively.

Similar transformations were used to introduce various substituents onto **9c** (Scheme 3). In the event, Buchwald–Hartwig coupling of **9c** with piperidine gave **17**, whereas Ullmann coupling with imidazole gave **19**; deprotection of these intermediates by treatment with iodine in the presence of aqueous acid gave **18** and **20**, respectively. The pentenamide **17** demonstrated activity as an inhibitor (IC_{50}=52 μM) of the deubiquitinating enzyme RPN11.[24]

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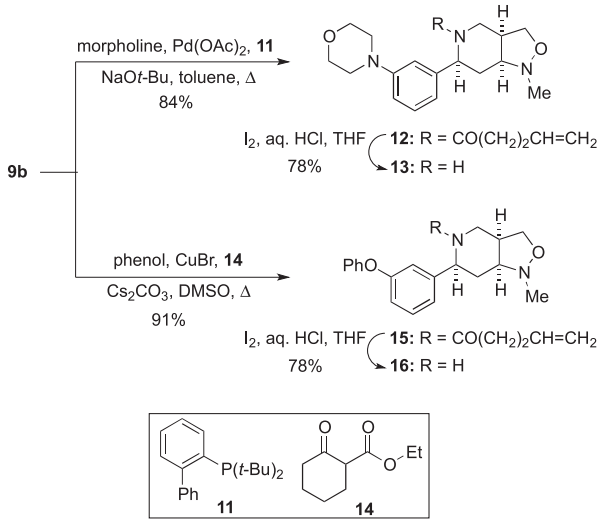
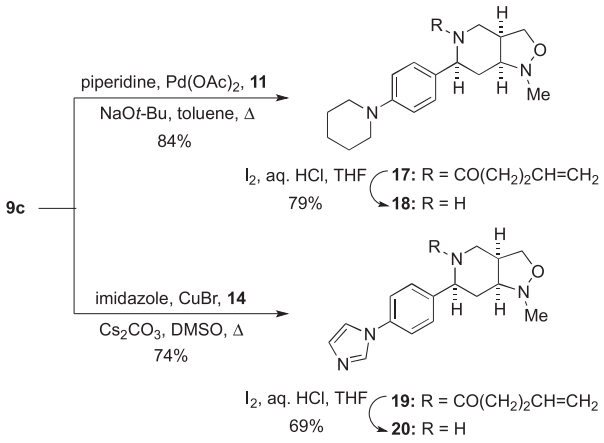
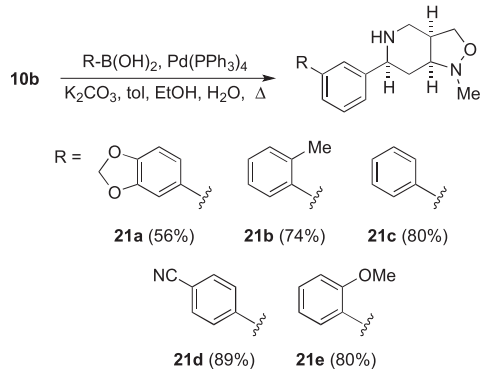


Scheme 2. Diversification of *m*-disubstituted benzenes via carbon–heteroatom cross-coupling processes.



Scheme 3. Diversification of *p*-disubstituted benzenes through *C*–*N* cross-coupling.

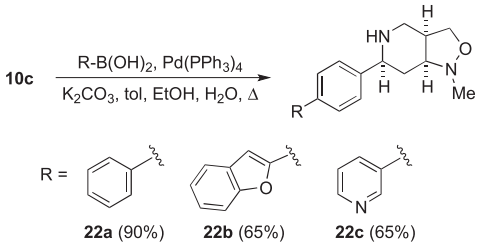
Compound **10b** was used as a substrate in Suzuki cross-coupling with phenylboronic acids to prepare the series of biaryls **21a**–**e**, which incorporate various substitution patterns of electron withdrawing and donating groups (Scheme 4).



Scheme 4. Synthesis of biphenyls through Suzuki cross-coupling of *m*-disubstituted substrate **10b**.

The isomeric 4-bromo compound **10c** underwent facile cross-coupling under the same conditions to afford the biaryls **22a**–**c** (Scheme 5).

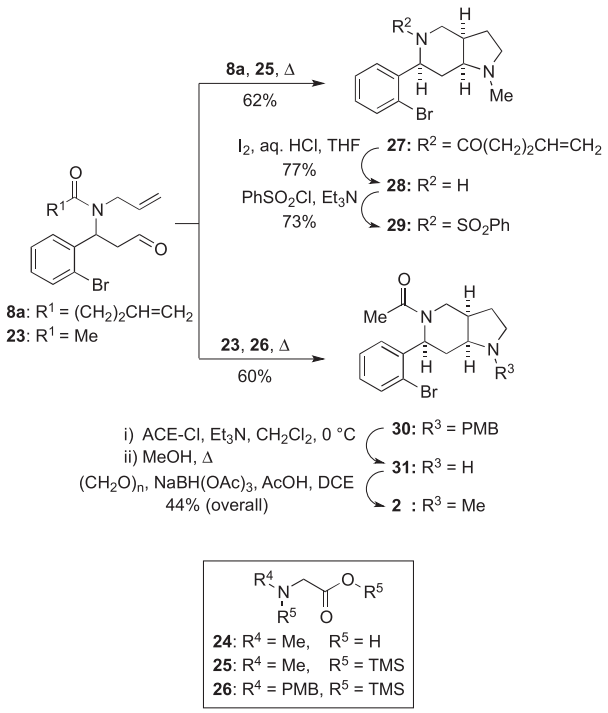
The biphenyl **22a** exhibited activity as an inhibitor of the orphan nuclear receptor NR0B1 (6% at 6.8 μM) and as an activator of the



Scheme 5. Synthesis of biaryls through Suzuki cross-coupling of *p*-disubstituted substrate **10c**.

nuclear receptor DAF-12 (11% at 6.8 μM).[25] The benzofuran **22b** was also active in a number of bioassays. For example, it was an inhibitor (IC_{50}=0.05 μM) of the LMP-1 inducible NF-κB pathway in the Epstein–Barr virus, as well as an inhibitor (IC_{50}=0.26 μM) of the zinc finger adapter protein Schnurri-3.[26] Preliminary attempts to perform cross-couplings of the substrate **10a** under similar conditions were unsuccessful, as the reaction stalled after very little conversion.

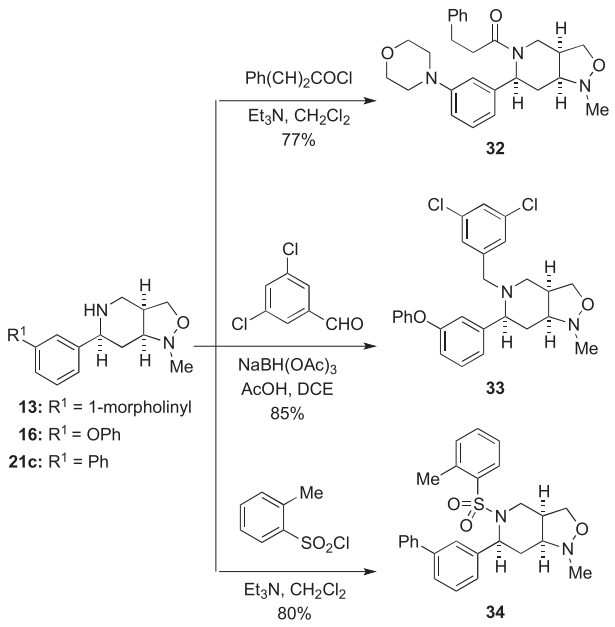
In order to generate a series of pyrrolidino-fused piperidines, we turned our attention to employing aldehydes **8a**–**c** as precursors of azomethine ylides. In the event, sarcosine (**24**) was heated with the aldehyde **8a** in toluene to furnish the pyrrolidine **27** (Scheme 6), but when this reaction was scaled up, formation of side products resulting from β-elimination of the amide moiety from the starting aldehyde became a significant problem. This difficulty was easily resolved by treating **8a** with the bis(trimethylsilyl)sarcosine derivative **25**, which was generated by reacting sarcosine with TMS-Cl and Et_3N, in toluene at room temperature. The putative oxazolidinone thus formed[27] was heated to generate an intermediate azomethine ylide that underwent subsequent cycloaddition to give **27** as a single diastereoisomer. This modified protocol proved more amenable to scale-up than the aforementioned reaction with sarcosine. Iodine-mediated pentenamide deprotection of **27** gave the secondary amine **28**, which underwent facile derivatization. For example, sulfonylation of **28** gave the benzenesulfonamide **29**. The diamine **28** demonstrated activity as a RAD52 inhibitor (IC_{50} of 4.6 μM) in an FRET-based high-throughput screen.[28]



Scheme 6. Synthesis and diversification of octahydro-1*H*-pyrrolo[3,2-*c*]pyridine scaffolds through azomethine ylide cycloadditions.

In a variant of the chemistry used to prepare **27**, the aldehyde **23**[12b,c] was allowed to react with the silylated reagent **26**, which was generated from *N*-(4-methoxybenzyl)glycine,[29] to give **30** via sequential azomethine ylide formation and cycloaddition. In order to determine the relative stereochemistry of the cycloadduct **30** and the viability of the PMB-protected amine as a precursor of analogs of **30**, the PMB group was removed by treatment with 1-chloroethyl chloroformate (ACE-Cl), followed by methanolysis of the intermediate carbamate to give the secondary amine **31**. Reductive methylation of **31** with paraformaldehyde, $NaBH(OAc)_3$, and acetic acid in 1,2-dichloroethane (DCE) delivered the tertiary amine **2**, which was identical with an authentic sample that had been previously prepared and structurally characterized by X-ray crystallography.[12b,c] Interestingly, the pyrrolidine **30** was shown to inhibit the Csn-mediated deconjugation of the Nedd8 protein from Cullin-ring ligases in a fluorescence polarization assay (160% activity at 12.5 μM).[30]

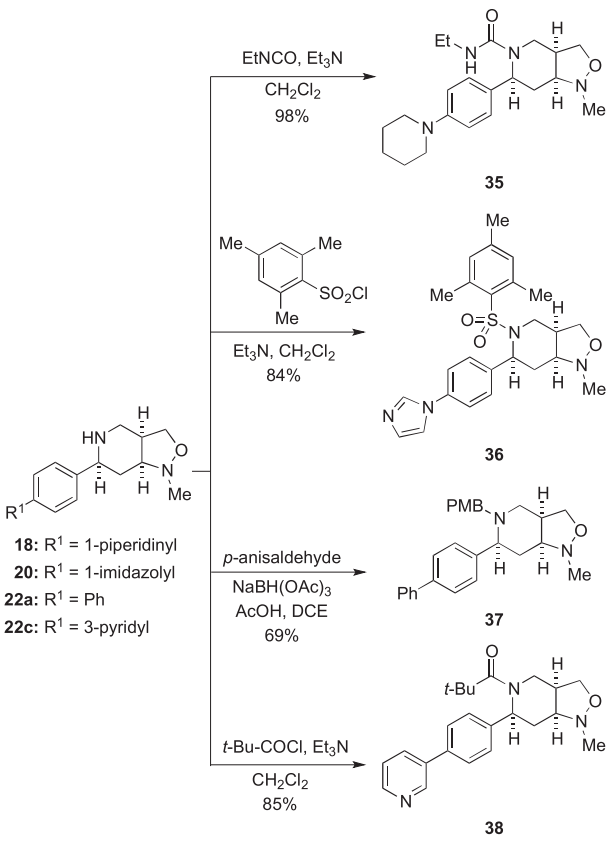
Small libraries of *N*-functionalized piperidines were then prepared from the cross-coupled products **13**, **16**, and **21c** (Scheme 7). For example, reaction of **13** with dihydrocinnamoyl chloride gave the amide **32**, whereas subjecting **16** to reductive alkylation by treatment with 3,5-dichlorobenzaldehyde and $NaBH(OAc)_3$ furnished the amine **33**, and sulfonylation of **21c** with 2-methylbenzenesulfonyl chloride provided the sulfonamide **34**. In biological testing, the amine **33** was found to be an inhibitor of the JMJD2A tudor domain (IC_{50}=89 μM) and an agonist of the mouse serotonin receptor 2A (15% activation at 7.6 μM).[31]



Scheme 7. Diversification of cycloadducts through piperidine N-functionalization.

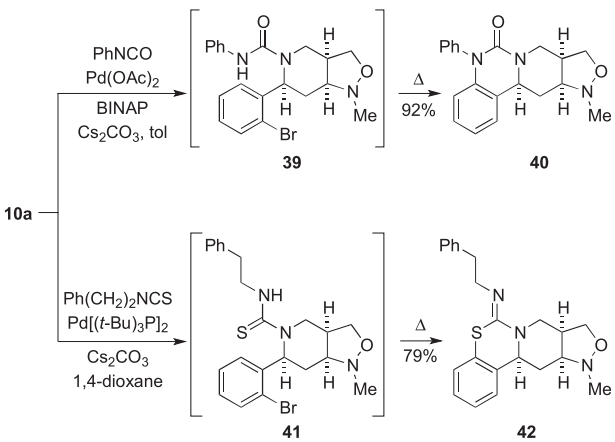
The *p*-disubstituted-2-arylpiperidines **18**, **20**, **22a**, and **22c** were also derivatized using similar methods (Scheme 8). For example, the urea **35** was obtained by reaction of **18** with ethyl isocyanate, and the sulfonamide **36** was prepared by treating **20** with mesitylenesulfonyl chloride. The 4-methoxybenzylamine **37**, which was prepared by reductive alkylation of **22a** using *p*-anisaldehyde and $NaBH(OAc)_3$, is an inhibitor (IC_{50}=11 μM) of Transforming Growth Factor beta (TGF-β).[32] Acylation of **22c** using pivaloyl chloride gave the amide **38**, which is an inhibitor (30% inhibition at 3 μM) of the human M1 muscarinic receptor.[33]

We next investigated opportunities for sequencing additional ring-forming reactions as a strategy for the facile construction of novel tri- and tetracyclic scaffolds. We began by examining



Scheme 8. Diversification of *p*-disubstituted benzenes through piperidine N-functionalization.

processes for tandem urea formation/cyclization commencing from the amine **10a** to give dihydroquinazolin-2-ones.[34] Our interest in dihydroquinazolin-2-ones arose following their identification in several biologically active compounds, including T-type calcium channel antagonists and anticonvulsants.[35] Accordingly, reaction of the piperidine **10a** with phenyl isocyanate and Cs_2CO_3 in toluene in the presence of $Pd(OAc)_2$ and (±)-BINAP at room temperature led to the rapid formation of the urea **39**. When this mixture was simply heated, the cyclized dihydroquinazoline-2-one **40** was produced in 92% yield (Scheme 9). $Pd(PPh_3)_4$ and $Pd(OAc)_2$/JohnPhos (**11**) were also examined as catalysts for this transformation, but the use of (±)-BINAP was critical to obtaining complete cyclization. We also discovered that it was essential to ensure complete formation of the intermediate urea prior to heating because otherwise mixtures of



Scheme 9. Diversification of (2-bromophenyl)piperidine **10a** through tandem urea and thiourea formation/cyclization processes.

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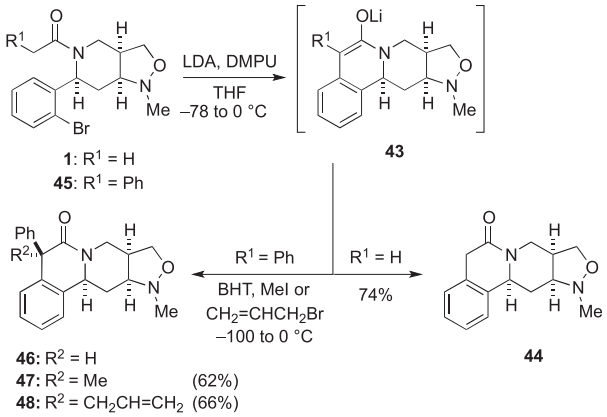
uncyclized **39** and the desired product **40** were obtained. This fact, along with the aforementioned unsuccessful attempts to couple **10a** under Suzuki conditions suggests that **10a** may poison some Pd catalysts. We were able to adapt this one-pot procedure to form cyclic isothioureas as illustrated by the conversion of **10a** to the 2-imino-1,3-benzothiazinane **42**,[36] although it was necessary to use $Pd[(t\text{-}Bu)_3P]_2$ instead of $Pd(PPh_3)_4$ or $Pd(OAc)_2$/(±)-BINAP as the catalyst to achieve complete cyclization of the intermediate thiourea **41**.

We also envisioned that 2-bromobenzyl amides, such as **1** might be amenable to enolate arylation to generate polycyclic dihydroisoquinolin-3-ones.[37] Indeed, treatment of **1** with excess LDA in the presence of DMPU, followed by an aqueous workup yielded the fused tetracycle **44** (Scheme 10). Presumably, this process occurs through concomitant formation of the amide lithium enolate and the benzyne through elimination of HBr from the arene, before cyclization of the enolate onto the benzyne and subsequent proton transfer to give the secondary enolate **43**.



Scheme 10. Generation of dihydroisoquinonlin-3-ones through a cascade base-mediated enolate arylation process.

We then extended this method to the phenylacetamide **45**, which was prepared in 84% yield by acylation of **10a** with phenylacetyl chloride and triethylamine. After subjecting **45** to the lithiation/benzyne formation/cyclization, we discovered that the intermediate enolate **43** could be protonated selectively from the less hindered face by quenching with 2,6-di-*tert*-butyl-4-methylphenol (BHT), a hindered proton source. Whilst this process gave crude **46** with high diastereoselectivity (dr>95:5, ^{1}H NMR), the product underwent rapid epimerization upon purification to give an isomeric mixture (~2:1). Motivated by the fact that several compounds bearing the 4,4-disubstituted dihydroisoquinolin-3-one substructure have been reported to show anticonvulsant and vasorelaxant properties,[35b,38] we questioned whether this initially high facial selectivity in the enolate quench could be exploited in alkylation reactions to create configurationally stable 4,4-disubstituted analogs.[39] In the event, addition of either methyl iodide or ally bromide to the solution of the enolate **43** generated from **45** at −100 °C led to **47** or **48**, respectively, with diastereocontrol of >95:5. X-ray crystallography of the methiodide salt derived from alkylation of the isoxazolidine nitrogen atom in **47** confirm the stereochemical outcome of the enolate alkylation (Fig. 3).

The isoxazolidine ring in nitrone cycloadducts, such as **1** masks a 1,3-amino alcohol functionality that can be revealed through reductive *N*–*O* bond cleavage (Scheme 11). However, it was necessary to exercise some care in order to avoid reductive debromination, which was a major side reaction under some conditions; however, use of zinc in aqueous HCl at 0 °C gave complete *N*–*O* bond cleavage without observable debromination.

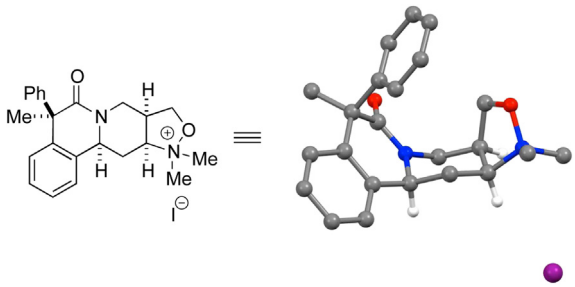
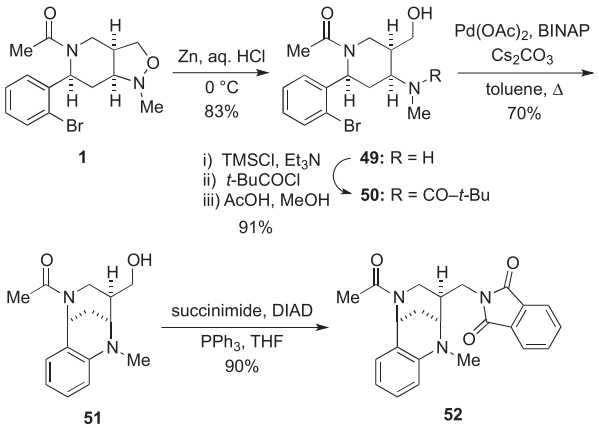


Fig. 3. X-ray crystal structure of the methiodide salt derived from **47** showing iodide ion (purple); hydrogen atoms at all but stereogenic carbon atoms are omitted for clarity.



Scheme 11. Isoxazolidine reductive ring-opening and subsequent diversification through acylation or intramolecular Buchwald–Hartwig coupling.

The densely-functionalized 2-arylpiperidine **49** could be *N*-acylated, although this transformation required use of a one-pot, three-stage process, in which the hydroxyl group was first protected as its TMS ether before sequential reaction with pivaloyl chloride and subsequent acid-catalyzed *O*-desilylation to give the pivalamide **50**. Alternatively, **49** could be subjected to a ring-forming process, in which the aminomethyl group was coupled with the aryl bromide moiety via an intramolecular Buchwald–Hartwig reaction to give the tetrahydroquinoline **51**. The pendant hydroxyl group in **51** was then exploited as a handle for further elaboration as exemplified by a Mitsunobu reaction to give **52**. The tetrahydroquinoline ring system in **51** is a well-recognized privileged substructure and is present in numerous compounds with a diverse range of activities, such as antiviral, antibiotic, and antithrombotic.[40] However, there are very few examples of bridged tetrahydroquinolines, such as **51**,[41] so the sequence of reactions in Scheme 11 holds some promise for the discovery of compounds having interesting biological activities.

3. Conclusions

In summary, we have utilized a 4-component, Mannich-type MCAP followed by [3+2] dipolar cycloadditions to create a number of novel pyrrolidino- and isoxazolidino-fused 2-arylpiperidines. Derivatives of these frameworks were prepared through a variety of aryl bromide cross-couplings and *N*-functionalizations. An enabling discovery was that the *N*-(4-pentenoyl) group was a competent activator in the MCAP protocol and a robust protecting group during carbon–heteroatom forming cross-coupling processes that could be readily cleaved to give amines on treatment with iodine in aqueous acid. A number of compounds prepared during these investigations have already been shown to exhibit promising biological activities. In particular, the range of activities exhibited by

the 1,4-disubstituted benzenes **10c**, **17**, **22a**, **22b**, **37**, and **38** suggests that this substructure may be worthy of further exploration by generating targeted sub-libraries.

A number of higher-order processes were developed that allowed the rapid diversification of scaffold **10a** in secondary ring-forming reactions that could be performed by judicious pairing of functional groups with the 2-bromoaryl moiety. For example, we developed novel tandem and sequential processes that involve urea or thiourea formation and cyclization, enolate cycloarylation, and alkylation, as well as reductive *N*–*O*-bond cleavage and intramolecular Buchwald–Hartwig coupling. We anticipate that these and related processes, which enable rapid generation of both skeletal and functional group diversity, will facilitate future efforts in DOS and targeted library synthesis. The synthesis and screening of compounds related to those presented herein is ongoing, and the results of these studies will be reported in due course.

4. Experimental

4.1. General

Unless otherwise noted, solvents and reagents were reagent-grade and used without further purification. Benzene, dichloromethane (CH_2Cl_2), triethylamine (Et_3N), 1,4-dioxane, diisopropylamine, and *N*,*N*′-dimethylpropylene urea (DMPU) were freshly distilled from CaH_2. Tetrahydrofuran (THF) was bubbled with argon to remove oxygen and dried by passage through two columns of activated neutral alumina. Toluene was bubbled with argon and passed through two columns of molecular sieves. DMSO for use in copper coupling reactions was distilled from CaH_2 and degassed by three freeze-thaw cycles prior to use. All solvents used for palladium-catalyzed cross-coupling reactions were degassed by sparging with nitrogen for 20 min prior to use. Reactions were performed under nitrogen or argon atmosphere in round-bottom flasks sealed under rubber septa with magnetic stirring, unless otherwise noted. Water sensitive reactions were performed with flame- or oven-dried glassware, stir-bars, and steel needles. Reaction temperatures are reported as the temperatures of the bath surrounding the vessel. Sensitive reagents and solvents were transferred using plastic or oven-dried glass syringes and steel needles using standard techniques. Nuclear magnetic resonance spectra were acquired in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ), downfield from trimethylsilane (TMS, δ=0.00 ppm) and are referenced to the residual solvent ($CDCl_3$, δ=7.26 ppm (^{1}H) and 77.16 ppm (^{13}C); DMSO-d_6, δ=2.50 ppm (^{1}H), and 39.5 ppm (^{13}C); benzene-d_6, δ=7.16 ppm (^{1}H), and 128.4 ppm (^{13}C)). The abbreviations s, d, t, q, m, and comp stand for the resonance multiplicities singlet, doublet, triplet, quartet, multiplet, and complex (overlapping multiplets of non-magnetically equivalent protons), respectively, whereas br stands for broad and app for apparent. Infra red (IR) spectra were recorded as films on sodium chloride plates and reported as wavenumbers (cm^{-1}). Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} silica gel plates eluting with solvents indicated, visualized by 254 nm UV lamp and stained with basic $KMnO_4$, acidic *p*-anisaldehyde or phosphomolybdic acid solutions. Flash chromatography was performed with ICN Silitech 32–63 D 60A silica gel according to the procedure of Still.[42]

4.2. General multicomponent assembly process (MCAP) procedure

Vinyl TBS ether was prepared according to the procedure of Kawakamie and co-workers.[43] 4-pentenoyl chloride was prepared according to the procedure of Rosenblum and co-workers and purified by fractional distillation under nitrogen prior to use.[44] Allylamine (1.9 g, 2.5 mL, 33 mmol), $MgSO_4$ (8.1 g, 67 mmol), and the appropriate bromobenzaldehyde **7a**–**c** (4.15 g, 22.4 mmol) were combined in CH_2Cl_2 (44 mL) and the mixture was stirred for 3–24 h. The mixture was filtered and the filtrate was concentrated in vacuo to give the allylimines, which were used without further purification. Vinyl TBS ether (10.6 g, 67 mmol) and CH_2Cl_2 (29 mL) were added and the solution was cooled to 0 °C, before dropwise addition of 4-pentenoyl chloride (2.9 g, 2.7 mL, 25 mmol). After 5 min, TMSOTf (0.50 g, 0.40 mL, 2.2 mmol) was added dropwise and the mixture was warmed to room temperature and stirred for 40 h. The mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (70 mL) and saturated aqueous $NaHCO_3$ (70 mL), and the mixture was stirred rapidly for 1 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate/hexanes/methanol (25:75:1→50:50:1→75:25:1) to give the desired aldehyde **8a**–**c**.

4.3. *N*-Allyl-*N*-(1-(2-bromophenyl)-3-oxopropyl)pent-4-enamide (8a)

Prepared according to the general MCAP procedure, starting from 2-bromobenzaldehyde (**7a**) (4.15 g, 22.4 mmol) to give 5.50 g (70%) of the aldehyde **8a** as a viscous, golden oil: ^{1}H NMR (600 MHz) (9:1 rotamer mixture, data given for the major rotamer): δ 9.76 (dd, *J*=2.7, 2.1 Hz, 1H), 7.64–7.58 (m, 1H), 7.37–7.30 (comp, 2H), 7.20 (ddd, *J*=8.1, 6.6, 2.4 Hz, 1H), 6.26 (dd, *J*=8.8, 6.3 Hz, 1H), 5.90–5.79 (m, 1H), 5.54–5.44 (m, 1H), 5.08–4.94 (comp, 4H), 3.72 (ddt, *J*=17.4, 5.1, 1.7 Hz, 1H), 3.64 (dd, *J*=17.4, 5.9 Hz, 1H), 3.18 (ddd, *J*=15.6, 8.8, 2.7 Hz, 1H), 2.99 (ddd, *J*=15.6, 6.3, 2.1 Hz, 1H), 2.48–2.34 (comp, 4H); ^{13}C NMR (150 MHz) (9:1 rotamer mixture, data given for the major rotamer): δ 199.6, 172.9, 137.4, 137.2, 133.9, 133.6, 129.8, 129.4, 127.6, 125.5, 117.2, 115.2, 53.2, 47.6, 46.4, 33.0, 29.2; IR (neat) 2979, 1723, 1643, 1470, 1415, 1025 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{17}H_{21}NO_2^{79}Br$ (M+1), 350.07502; found, 350.07504.

4.4. *N*-Allyl-*N*-(1-(3-bromophenyl)-3-oxopropyl)pent-4-enamide (8b)

Prepared according to the general MCAP procedure, starting from 3-bromobenzaldehyde (**7b**) (2.48 g, 13.4 mmol) with all other material amounts scaled accordingly, to give 3.44 g (73%) of the aldehyde **8b** as a viscous, golden oil: ^{1}H NMR (600 MHz, DMSO-d_6, 100 °C): δ 9.68–9.65 (m, 1H), 7.51–7.47 (m, 1H), 7.47–7.43 (m, 1H), 7.33–7.30 (m, 1H), 7.28 (app t, *J*=7.7 Hz, 1H), 5.94 (app br s, 1H), 5.88–5.79 (m, 1H), 5.65–5.57 (m, 1H), 5.10–4.97 (comp, 3H), 4.97–4.92 (m, 1H), 3.91 (dd, *J*=17.3, 3.6 Hz, 1H), 3.80–3.72 (m, 1H), 3.23 (dd, *J*=16.9, 6.6 Hz, 1H), 3.10 (dd, *J*=16.9, 6.6 Hz, 1H), 2.44 (app br s, 2H), 2.31 (app q, *J*=8.4 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K): δ 199.6, 192.9, 141.9, 2×137.2, 134.4, 2×129.8, 129.7, 126.0, 115.8, 114.2, 51.8, 46.3, 44.5, 31.8, 28.2; IR (neat) 3356, 3077, 2978, 2923, 1727, 1643, 1415, 1214, 917, 732; HRMS (ESI$^+$) *m*/*z* calculated for $C_{17}H_{20}NO_2^{79}BrNa$ (M+23), 372.05659; found, 372.05696.

4.5. *N*-Allyl-*N*-(1-(4-bromophenyl)-3-oxopropyl)pent-4-enamide (8c)

Prepared according to the general MCAP procedure, starting from 4-bromobenzaldehyde (**7c**) (3.21 g, 17.3 mmol) with all other material amounts scaled accordingly, to give 4.10 g (67%) of the aldehyde **8c** as a viscous, yellow oil: ^{1}H NMR (400 MHz) (5:1 rotamer mixture, data given for the major rotamer): δ 9.74–9.71 (m, 1H), 7.46 (d, *J*=8.3 Hz, 2H), 7.18 (d, *J*=8.3 Hz, 2H), 6.26 (app t, *J*=7.6 Hz, 1H), 5.90–5.75 (m, 1H), 5.60–5.49 (m, 1H), 5.16–4.94

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(comp, 4H), 3.80–3.71 (m, 1H), 3.66 (dd, J=17.8, 5.7 Hz, 1H), 3.14–3.03 (comp, 2H), 2.52–2.34 (comp, 4H); ^{13}C NMR (100 MHz): δ 199.4, 173.1, 137.5, 137.0, 133.9, 131.6, 129.5, 121.8, 117.3, 115.2, 51.3, 47.1, 45.3, 32.8, 29.0; IR (neat) 2978, 1724, 1643, 1409, 1009 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{17}H_{20}NO_2^{79}BrNa$ (M+23), 372.05696; found, 372.05688.

4.6. General nitrone condensation/cycloaddition procedure

N-Methylhydroxylamine hydrochloride (1.25 g, 15.0 mmol), aldehyde **8a**–**c** (3.50 g, 9.99 mmol), and Et_3N (3.0 g, 4.2 mL, 30 mmol) were combined in toluene (116 mL) and the mixture was heated under reflux for 90 min. After cooling to room temperature, water (60 mL) was added and the layers were separated. The aqueous layer was saturated with NaCl then extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by column chromatography eluting with ethyl acetate/hexanes/methanol (25:75:1→50:50:1→95:0:5) to afford the isoxazolidine **9a**–**c**.

4.7. 1-((3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-methyl tetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl)pent-4-en-1-one (9a)

Prepared according to the general nitrone condensation/cycloaddition procedure, starting from aldehyde **8a** (3.50 g, 9.99 mmol), to give 3.63 g (96%) of the isoxazolidine **9a** as a highly viscous, pale yellow gum that crystallized on standing: mp 70–71 °C; ^{1}H NMR (600 MHz) (3:1 rotamer mixture): δ 7.55 (dd, J=8.1, 1.1 Hz, 0.75H), 7.51 (d, J=7.7 Hz, 0.25H), 7.35–7.30 (m, 0.75H), 7.25 (dd, J=8.5, 1.7 Hz, 0.75H), 7.25–7.20 (m, 0.25H), 7.18–7.13 (m, 0.75H), 7.11 (dd, J=7.8, 1.2 Hz, 0.25H), 7.08–7.04 (m, 0.25H), 5.86–5.77 (m, 0.25H), 5.73–5.63 (m, 0.75H), 5.23 (dd, J=13.7, 4.8 Hz, 0.25H), 5.07–5.00 (comp, 1H), 5.00–4.92 (comp, 1H), 4.91–4.84 (comp, 1.5H), 4.20–4.10 (comp, 1H), 3.97 (dd, J=13.7, 5.4 Hz, 0.25H), 3.60–3.53 (comp, 1.25H), 3.07–2.88 (comp, 2.75H), 2.70 (s, 3H), 2.55–2.47 (m, 0.25H), 2.47–2.39 (m, 0.25H), 2.39–2.32 (m, 1.5H), 2.32–2.20 (comp, 1.5H), 2.16–2.07 (m, 0.75H), 1.86–1.77 (m, 0.75H), 1.77–1.67 (comp, 1H); ^{13}C NMR (150 MHz) (3:1 rotamer mixture): δ 173.2, 171.2, 142.7, 142.5, 137.4, 137.2, 133.2, 129.2, 128.7, 128.3, 127.9, 126.4, 125.3, 121.8, 121.1, 115.3, 115.1, 68.3, 68.0, 64.6, 55.7, 54.6, 43.9, 43.7, 42.8, 39.6, 33.3, 33.1, 32.6, 31.8, 29.0, 28.9; IR (neat) 2956, 2876, 1650, 1418, 1240, 1026, 915, 756 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{18}H_{24}N_2O_2^{79}Br$ (M+1), 379.10157; found, 379.10165.

4.8. 1-((3a*RS*,6*SR*,7a*SR*)-6-(3-Bromophenyl)-1-methyl tetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl)pent-4-en-1-one (9b)

Prepared according to the general nitrone condensation/cycloaddition procedure, starting from aldehyde **8b** (3.44 g, 9.82 mmol) with all other amounts scaled accordingly, to give 3.38 g (89%) of the isoxazolidine **9b** as a highly viscous, pale yellow gum: NMR (600 MHz, DMSO-d_6, 100 °C): δ 7.41 (s, 1H), 7.40–7.36 (m, 1H), 7.30–7.22 (comp, 2H), 5.77 (app br s, 1H), 5.04–4.86 (comp, 3H), 4.22 (app br s, 1H), 4.01 (app t, J=8.5, 1H), 3.44 (dd, J=8.5, 4.9, 1H), 3.14 (app br s, 1H), 2.98 (ddd, J=11.1, 9.0, 5.2 Hz, 1H), 2.90 (app br s, 1H), 2.57 (s, 3H), 2.45 (app br s, 1H), 2.27–2.12 (comp, 3H), 2.15 (app dt, J=13.8, 5.3 Hz, 1H), 1.74 (ddd, J=13.8, 12.0, 11.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K): δ 170.6, 146.4, 137.2, 129.9, 128.9, 127.6, 123.8, 121.2, 114.1, 66.9, 63.3, 53.0 (br), 42.2, 42.0 (br), 32.6, 31.7, 28.0 (one signal is believed to be undetectable due to peak broadening); IR (neat) 2956, 2882, 1643, 1472, 1416, 1238, 1070, 917, 754 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{18}H_{23}N_2O_2^{79}BrNa$ (M+23), 401.08396; found, 401.08351.

4.9. 1-((3a*RS*,6*SR*,7a*SR*)-6-(4-Bromophenyl)-1-methyl tetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl)pent-4-en-1-one (9c)

Prepared according to the general nitrone condensation/cycloaddition procedure, starting from aldehyde **8c** (3.34 g, 9.54 mmol) with all other material amounts scaled accordingly, to give 3.23 g (89%) of the isoxazolidine **9c** as a viscous, pale yellow gum: ^{1}H NMR (400 MHz) (11:9 rotamer mixture): δ 7.48 (d, J=8.2 Hz, 1.1H), 7.41 (d, J=8.2 Hz, 0.9H), 7.15–7.05 (comp, 2H), 5.89–5.75 (m, 0.45H), 5.75–5.62 (m, 0.55H), 5.09–4.83 (comp, 3H), 4.66 (dd, J=12.3, 5.5 Hz, 0.55H), 4.20–4.06 (comp, 1H), 3.97–3.86 (m, 0.45H), 3.58–3.50 (comp, 1H), 3.42 (t, J=12.8 Hz, 0.45H), 3.05–2.85 (comp, 2.55H), 2.67 (s, 3H), 2.56–1.80 (comp, 6H); ^{13}C NMR (150 MHz) (11:9 rotamer mixture): δ172.8, 171.2, 142.4, 137.2, 132.3, 131.6, 127.2, 126.7, 121.3, 120.6, 115.4, 115.2, 68.2, 64.6, 55.8, 53.7, 43.6, 43.2, 42.3, 39.2, 35.5, 33.4, 33.2, 32.9, 29.0; IR (neat) 2956, 1644, 1417, 1009 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{18}H_{23}N_2O_2^{79}BrNa$ (M+23), 401.08351; found, 401.08371.

4.10. General 4-pentenamide deprotection procedures

4.10.1. Procedure A. Iodine (1.05 g, 4.12 mmol) was added to a stirred solution of the 4-pentenamide (0.85 mmol) in THF (6.6 mL) and 1.5 M aqueous HCl (2.5 mL) at 0 °C. The stirred mixture was warmed to room temperature and after 45–60 min, saturated aqueous $Na_2S_2O_3$ was added until the solution became colorless. The mixture was then diluted with water (10 mL) and washed with ether (3×10 mL). The pH of the aqueous layer was adjusted to 12 by addition of 1 M aqueous NaOH and the solution was then saturated with NaCl and extracted with ethyl acetate or CH_2Cl_2 (3×10 mL). The combined CH_2Cl_3 extracts were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by flash column chromatography to give the desired amines.

4.10.2. Procedure B. Iodine (242 mg, 0.953 mmol) was added to a stirred solution of the 4-pentenamide (0.19 mmol) in THF (1.4 mL) and 3 M aqueous HCl (0.55 mL) at 0 °C and the mixture was warmed to room temperature. After 45–60 min, saturated aqueous $Na_2S_2O_3$ was added until the solution became colorless. The mixture was then diluted with 1 M aqueous HCl (10 mL) and washed with ether (3×10 mL). The pH of the aqueous layer was adjusted to 14 by addition of 1 M aqueous NaOH and the solution was then saturated with NaCl and extracted with $CHCl_3$ (4×10 mL). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by flash column chromatography to give the desired amines.

4.11. (3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-methyl octahydroisoxazolo[4,3-*c*]pyridine (10a)

Prepared according to the general 4-pentenamide deprotection procedure A, starting from amide **9a** (2.00 g, 5.27 mmol), with all other material amounts scaled accordingly. Purification by flash column chromatography eluting with ethyl acetate/methanol (100:1→90:10 along a gradient) gave 1.40 g (89%) of the amine **10a** as a brown solid: mp 106–108 °C (pale yellow needles from ethyl acetate/hexanes); ^{1}H NMR (400 MHz): δ 7.60–7.49 (comp, 2H), 7.34–7.27 (m, 1H), 7.11 (td, J=7.7, 1.6 Hz, 1H), 4.24 (dd, J=9.2, 7.2 Hz, 1H), 3.96 (dd, J=9.8, 2.2 Hz, 1H), 4.02–3.94 (m, 1H), 3.29 (d, J=12.5 Hz, 1H), 3.26–3.16 (comp, 2H), 3.07–2.95 (m, 1H), 2.68 (s, 3H), 2.12–2.02 (m, 1H), 1.68–1.50 (comp, 2H); ^{13}C NMR (100 MHz): δ 142.7, 132.7, 128.7, 2×127.9, 123.2, 68.0, 64.4, 57.7, 2×44.6, 37.8, 34.8; IR (neat) 3313, 2950, 2880, 1469, 1438, 1158, 1119, 1023, 755 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{13}H_{18}NO_2^{79}Br$ (M+1), 297.0602; found, 297.0597.

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4.12. (3a*RS*,6*SR*,7a*SR*)-6-(3-Bromophenyl)-1-methyl octahydroisoxazolo[4,3-*c*]pyridine (10b)

Prepared according to the general 4-pentenamide deprotection procedure A, starting from amide **9b** (1.00 g, 2.64 mmol), with all other material amounts scaled accordingly. Purification by flash column chromatography eluting with ethyl acetate/methanol (100:1→90:10 along a gradient) gave 0.753 g of the amine **10b** (96%) as a yellow gum: ^{1}H NMR (400 MHz): δ 7.53 (s, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.28 (d, J=7.8 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 4.23 (dd, J=9.0, 7.2 Hz, 1H), 3.96 (dd, J=9.0, 7.6 Hz, 1H), 3.58–3.48 (m, 1H), 3.29 (d, J=12.1 Hz, 1H), 3.22–3.10 (comp, 2H), 3.05–2.90 (m, 1H), 2.67 (s, 3H), 2.03–1.92 (m, 1H), 1.80–1.54 (comp, 2H); ^{13}C NMR (100 MHz): δ 144.6, 130.4, 130.1, 129.9, 125.3, 122.5, 67.9, 64.3, 58.9, 2×44.5, 37.7, 36.4; IR (neat) 3313, 2950, 2880, 2807, 1594, 1567, 1473, 1436, 1158, 1070, 996, 784, 698 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{13}H_{18}NO_2^{79}Br$ (M+1), 297.0602; found, 297.0597.

4.13. (3a*RS*,6*SR*,7a*SR*)-6-(4-Bromophenyl)-1-methyl octahydroisoxazolo[4,3-*c*]pyridine (10c)

Prepared according to the general 4-pentenamide deprotection procedure A, starting from amide **9c** (313 mg, 0.852 mmol). Purification by flash column chromatography eluting with ethyl acetate/methanol (100:1→90:10 along a gradient) gave 210 mg (87%) of the amine **10c** as a brown solid: mp 106–107 °C (white needles from ethyl acetate/hexanes); ^{1}H NMR (400 MHz): δ 7.44 (d, J=8.3 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 4.23 (app t, J=8.2 Hz, 1H), 3.96 (app t, J=8.2 Hz, 1H), 3.52 (dd, J=11.7, 2.0 Hz, 1H), 3.29 (d, J=12.7 Hz, 1H), 3.20–3.11 (comp, 2H), 3.04–2.93 (m, 1H), 2.66 (s, 3H), 2.00–1.91 (m, 1H), 1.80–1.54 (comp, 2H); ^{13}C NMR (75 MHz): δ 143.3, 131.5, 128.4, 121.0, 67.9, 64.3, 58.8, 2×44.5, 37.7, 36.5; IR (neat) 3322, 2950, 1487, 1071, 1010 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{13}H_{18}NO_2^{79}Br$ (M+1), 297.0602; found, 297.0605.

4.14. 1-((3a*RS*,6*SR*,7a*SR*)-Tetrahydro-1-methyl-6-(3-morpholinophenyl)isoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl) pent-4-en-1-one (12)

A solution of $Pd(OAc)_2$ (5.2 mg, 0.023 mmol) and (2-biphenyl)di-*tert*-butylphosphine (**11**) (6.4 mg, 0.021 mmol) in toluene (0.40 mL) was stirred at room temperature for 5 min, giving a clear brown solution. Morpholine (12 mg, 12 μL, 0.14 mmol) was added to a separate vial containing bromide **9b** (40.0 mg, 0.105 mmol) in toluene (0.225 mL, de-gassed by N_2 injection), followed by NaO^{t}Bu (13 mg, 0.137 mmol). An aliquot of the catalyst mixture (0.10 mL, 0.0053 mmol) was added, before purging the vial with N_2, sealing and heating under reflux for 20 h. The mixture was then cooled to room temperature and filtered through a plug of Celite, rinsing with toluene. The filtrate was evaporated under reduced pressure and purified by column chromatography, eluting with ethyl acetate/pentane (50:50→100:0) to afford 34.1 mg (84%) of the aniline **12** as a clear, colorless gum: ^{1}H NMR (400 MHz) (7:3 rotamer mixture): δ 7.28–7.15 (comp, 1H), 6.84–6.67 (comp, 3H), 5.92–5.76 (m, 0.3H), 5.76–5.60 (m, 0.7H), 5.10–4.80 (comp, 3H), 4.65 (dd, J=12.0, 4.4 Hz, 0.7H), 4.22–4.06 (comp, 1H), 3.95–3.77 (comp, 4.3H), 3.58–3.50 (comp, 1H), 3.43 (t, J=11.5 Hz, 0.3H), 3.22–3.06 (comp, 4H), 3.05–2.87 (comp, 2.7H), 2.67 (s, 3H), 2.58–1.84 (comp, 6H); ^{13}C NMR (100 MHz) (7:3 rotamer mixture): δ 173.1, 171.1, 151.9, 151.4, 144.5, 144.2, 137.4, 129.9, 129.3, 116.8, 116.4, 115.3, 115.0, 114.5, 114.3, 113.1, 111.7, 68.2, 67.8, 66.9, 66.8, 64.7, 64.5, 56.4, 54.2, 49.3, 49.1, 43.6, 43.2, 42.4, 39.3, 35.7, 33.5, 33.2, 32.8, 29.0; IR (neat) 2959, 2855, 1643, 1601, 1446, 1244, 1121, 918, 713 cm^{-1}; MS (ESI$^+$) m/z 408.22576 [$C_{22}H_{31}N_3O_3Na$ (M+Na) requires 408.22602].

4.15. (3a*RS*,6*SR*,7a*SR*)-1-Methyl-6-(3-morpholinophenyl) octahydroisoxazolo[4,3-*c*]pyridine (13)

Iodine (1.33 g, 5.25 mmol) was added to a stirred solution of amide **12** (405 mg, 1.05 mmol) in THF (8.1 mL) and 1.5 M aqueous HCl (3.0 mL) at room temperature, and the reaction was stirred for 45 min. After 45 min, saturated aqueous $Na_2S_2O_3$ (4.6 mL total) was added dropwise until the solution turned yellow, and 1 M NaOH was added dropwise until the pH of the solution reached 8. The mixture was then concentrated under reduced pressure, and the dry residue was triturated with methanol. The methanol extract was dry-loaded onto silica and purified by column chromatography, eluting with ethyl acetate/methanol (9:1→6:4) to afford 248 mg (78%) of the amine **13** as a brown gum: ^{1}H NMR (400 MHz): δ 7.23 (app t, J=7.9 Hz, 1H), 7.01–6.97 (m, 1H), 6.89–6.85 (m, 1H), 6.84–6.80 (m, 1H), 4.24–4.16 (m, 1H), 3.97–3.89 (m, 1H), 3.85 (app t, J=4.9 Hz, 4H), 3.67 (app d, J=11.9 Hz, 1H), 3.29–2.93 (comp, 9H), 2.66 (s, 3H), 2.08–1.97 (m, 1H), 1.81–1.70 (m, 1H); ^{13}C NMR (100 MHz): δ 151.6, 143.2, 129.4, 118.6, 115.0, 114.2, 68.0, 66.9, 64.3, 58.9, 49.3, 44.4, 43.9, 37.5, 34.8; IR (neat) 3322, 2955, 2855, 1602, 1448, 1244, 1121, 784, 730 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{17}H_{26}N_3O_2$ (M+1), 304.20195; found, 304.20203.

4.16. (3a*RS*,6*SR*,7a*SR*)-6-(3-Phenoxyphenyl)-5-(pent-4-enoyl)-1-methyloctahydroisoxazolo[4,3-*c*]pyridine (15)

Cs_2CO_3 (678 mg, 2.11 mmol), CuBr (77 mg, 0.54 mmol), ethyl 2-cyclohexanone-1-carboxylate (**14**) (191 mg, 1.12 mmol), and de-gassed DMSO (1 mL) were combined in a screw-capped vial and stirred at room temperature for 30 min. A solution of bromide **9b** (200 mg, 0.527 mmol) and phenol (198 mg, 0.53 mmol) in de-gassed DMSO (0.5 mL) was then added and the mixture was heated at 130 °C for 5 h. The mixture was cooled to room temperature, and then filtered through a pad of Celite, rinsing with toluene (30 mL), and water (30 mL). The layers of the filtrate were separated and the aqueous layer was extracted with toluene (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/hexanes/methanol (50:50:1→90:0:10) to afford 189 mg (91%) of the diaryl ether **15** as a pale yellow oil: ^{1}H NMR (400 MHz) (6:4 rotamer mixture) δ 7.38–7.17 (comp, 3H), 7.16–7.04 (comp, 1H), 7.02–6.80 (comp, 5H), 5.76–5.63 (m, 0.6H), 5.89–5.77 (m, 0.4H), 5.10–4.82 (comp, 3H), 4.65 (dd, J=12.3, 5.5 Hz, 0.6H), 4.20–4.05 (comp, 1H), 3.95–3.84 (m, 0.4H), 3.58–3.50 (comp, 1H), 3.39 (t, J=12.7 Hz, 0.4H), 3.05–2.85 (comp, 2.6H), 2.67 (s, 3H), 2.56–1.83 (comp, 6H); ^{13}C NMR (150 MHz) (6:4 rotamer mixture): δ 172.9, 171.2, 157.9, 157.5, 157.1, 156.8, 145.5, 145.3, 137.3, 130.6, 129.9, 129.7, 123.6, 123.2, 120.2, 119.5, 118.9, 117.7, 117.1, 115.5, 115.1, 68.3, 67.9, 64.7, 56.1, 53.8, 43.5, 43.2, 39.2, 35.5, 33.3, 32.9, 29.1; IR (neat) 2955, 2876, 1647, 1584, 1487, 1420, 1251, 695 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{24}H_{29}N_2O_3$ (M+1), 393.21727; found, 393.21714.

4.17. (3a*RS*,6*SR*,7a*SR*)-1-Methyl-6-(3-phenoxyphenyl) octahydroisoxazolo[4,3-*c*]pyridine (16)

Prepared according to the general 4-pentenamide deprotection procedure A, starting from amide **13** (72 mg, 0.18 mmol), with all other material amounts scaled accordingly. Purification by flash column chromatography eluting with ethyl acetate/methanol (19:1→9:1 along a gradient) gave 45 mg of the amine **16** (78%) as a yellow gum: ^{1}H NMR (400 MHz): δ 7.36–7.25 (comp, 3H), 7.14–7.06 (comp, 2H), 7.06–7.02 (m, 1H), 7.02–6.96 (m, 2H), 6.89 (ddd, J=8.2, 2.5, 1.0 Hz, 1H), 4.24–4.16 (m, 1H), 3.96–3.89 (m, 1H), 3.57 (app d, J=11.0 Hz, 1H), 3.26 (app d, J=12.5 Hz, 1H), 3.19–3.10 (comp, 2H), 3.03–2.92 (m, 1H), 2.65 (s, 3H), 2.09–1.93 (comp, 2H),

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1.71–1.57 (m, 1H); ^{13}C NMR (150 MHz): δ 157.3, 157.2, 145.9, 129.8, 129.7, 123.2, 121.5, 118.8, 117.9, 117.3, 67.9, 64.4, 58.9, 44.5, 44.3, 37.7, 36.1; IR (neat) 3307, 2950, 2880, 1582, 1488, 1439, 1248, 1215, 695 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{19}H_{23}N_2O_2$ (M+1), 311.17540; found, 311.17520.

4.18. 1-((3a*RS*,6*SR*,7a*SR*)-1-Methyl-6-(4-(piperidin-1-yl)phenyl)tetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl)pent-4-en-1-one (17)

A solution of $Pd(OAc)_2$ (47 mg, 0.21 mmol) and (2-biphenyl)di-*tert*-butylphosphine (**11**) (63 mg, 0.21 mmol) in toluene (4 mL) was stirred at room temperature for 20 min. This solution was then added to a mixture of piperidine (1.6 g, 1.9 mL, 19 mmol), NaO*t*-Bu (526 mg, 1.37 mmol), and bromide **9c** (794 mg, 2.09 mmol) in toluene (7.2 mL) and the resulting mixture was heated at 100 °C for 2.5 h. The mixture was cooled to room temperature and filtered through Celite, rinsing with methanol (5 mL). The combined filtrate and washings were concentrated under reduced pressure, and the residue was partitioned between ether (100 mL) and 1.5 M aqueous HCl (100 mL). The phases were separated and the aqueous layer was washed with ether (100 mL). 1 M aqueous NaOH was added to the aqueous layer to adjust the pH to 14 and the solution was saturated with NaCl. The aqueous layer was extracted with CH_2Cl_2 (6×50 mL) and the combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate/hexanes/methanol (25:75:1→90:0:10) to give 676 mg (84%) of the aniline **17**as a pale brown gum: ^{1}H NMR (400 MHz) (7:3 rotamer mixture): δ 7.18–7.10 (m, 0.6H), 7.06 (d, *J*=8.4 Hz, 1.4H), 6.90 (d, *J*=8.4 Hz, 2H), 5.90–5.75 (m, 0.3H), 5.75–5.62 (m, 0.7H), 5.10–4.83 (comp, 3H), 4.60 (dd, *J*=12.3, 5.7 Hz, 0.7H), 4.19–4.07 (comp, 1H), 3.91–3.81 (m, 1H), 3.58–3.52 (comp, 1H), 3.42 (t, *J*=12.1 Hz, 0.3H), 3.18–3.06 (comp, 4H), 3.03–2.86 (comp, 2.7H), 2.67 (s, 3H), 2.56–1.84 (comp, 6H), 1.78–1.64 (comp, 4H), 1.64–1.50 (comp, 2H); ^{13}C NMR (100 MHz) (7:3 rotamer mixture): δ 73.2, 151.5, 137.5, 133.6, 126.4, 125.7, 116.7, 115.2, 114.9, 68.3, 64.8, 55.8, 53.3, 50.5, 43.7, 42.5, 39.2, 35.8, 33.3, 32.9, 29.1, 25.8, 24.2; IR (neat) 2933, 1643, 1514, 1419, 1234 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{23}H_{34}N_3O_2$ (M+1), 384.2651; found, 384.2647.

4.19. 3a*RS*,6*SR*,7a*SR*)-1-Methyl-6-(4-(piperidin-1-yl) phenyl) octahydroisoxazolo[4,3-*c*]pyridine (18)

Prepared according to the general 4-pentenamide deprotection procedure B, starting from amide **17** (743 mg, 1.93 mmol). Purification by flash chromatography, eluting with CH_2Cl_2/methanol (100:1→95:5→90:10) gave 461 mg (79%) of the amine **18** as a brown gum: ^{1}H NMR (400 MHz): δ 7.23 (d, *J*=8.6 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 4.24–4.15 (m, 1H), 3.96–3.88 (m, 1H), 3.53 (app d, *J*=11.7 Hz, 1H), 3.22 (app d, *J*=12.9 Hz, 1H), 3.18–3.09 (comp, 6H), 3.03–2.90 (m, 1H), 2.66 (s, 3H), 2.30 (br s, 1H), 1.97 (app dd, *J*=12.7, 5.3 Hz, 1H), 1.75–1.64 (comp, 5H), 1.60–1.52 (comp, 2H); ^{13}C NMR (75 MHz): δ 151.9, 134.0, 127.7, 116.6, 68.2, 64.8, 58.6, 50.8, 44.8, 44.5, 37.8, 35.7, 26.1, 24.5; IR (neat) 3322, 2933, 1613, 1516, 1234 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{18}H_{28}N_3O$ (M+1), 302.2228; found, 302.2232.

4.20. 1-((3a*RS*,6*SR*,7a*SR*)-6-(4-(1*H*-Imidazol-1-yl)phenyl)-1-methyltetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl) pent-4-en-1-one (19)

A mixture of CuBr (190 mg, 1.32 mmol), ethyl 2-oxocyclohexanecarboxylate (**14**) (0.45 g, 0.42 mL, 2.6 mmol), and Cs_2CO_3 (1.72 g, 5.28 mmol) in DMSO (2.5 mL) was stirred at room temperature for 30 min. A solution of bromide **9c** (498 mg, 1.31 mmol) and imidazole (404 mg, 5.94 mmol) in DMSO (1.0 mL) was then added. The mixture was heated at 120 °C for 22 h and cooled to room temperature. The mixture was then filtered through Celite, rinsing with CH_2Cl_2 (5 mL). The combined filtrate and washings were partitioned between water (50 mL) and CH_2Cl_2 (50 mL) and the phases were separated. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/methanol (100:1→95:5) to give 357 mg (74%) of the *N*-phenylimidazole **19** as a brown gum: ^{1}H NMR (400 MHz) (11:9 rotamer mixture): δ 7.89–7.78 (comp, 1H), 7.44–7.16 (comp, 6H), 5.90–5.76 (m, 0.55H), 5.76–5.63 (m, 0.45H), 5.12–4.85 (comp, 3H), 4.77 (dd, *J*=12.1, 5.5 Hz, 0.45H), 4.25–4.09 (comp, 1H), 4.01–3.90 (m, 0.55H), 3.63–3.54 (comp, 1H), 3.49 (t, *J*=12.8 Hz, 0.55H), 3.10–2.90 (comp, 2.45H), 2.70 (s, 3H), 2.59–1.86 (comp, 6H); ^{13}C NMR (100 MHz) (11:9 rotamer mixture): δ 172.9, 171.4, 142.9, 142.7, 137.2, 136.7, 136.2, 135.5, 130.6, 130.3, 126.9, 126.5, 122.2, 121.9, 118.4, 118.2, 115.5, 115.2, 68.2, 67.9, 64.6, 64.4, 55.8, 53.8, 43.5, 43.3, 42.3, 39.3, 35.5, 35.1, 33.6, 33.3, 33.0, 29.0; IR (neat) 2956, 1640, 1522, 1428 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{21}H_{27}N_4O$ (M+1), 367.2134; found, 367.2134.

4.21. (3a*RS*,6*SR*,7a*SR*)-6-(4-(1*H*-Imidazol-1-yl)phenyl)-1-methyloctahydroisoxazolo[4,3-*c*]pyridine (20)

Prepared according to the general 4-pentenamide deprotection procedure B, starting from amide **19** (472 mg, 1.29 mmol), with all other material amounts scaled accordingly. Flash chromatography, eluting with CH_2Cl_2/methanol (100:1→95:5→80:20) gave 254 mg (69%) of the amine **20** as a brown gum: ^{1}H NMR (CD_3OD, 400 MHz): δ 8.12 (app s, 1H), 7.59–7.50 (comp, 5H), 7.14 (app s, 1H), 4.28–4.20 (m, 1H), 4.00–3.92 (m, 1H), 3.69 (app d, *J*=12.3 Hz, 1H), 3.44–3.35 (m, 1H), 3.34–3.26 (comp, 2H), 3.18 (app d, *J*=11.9 Hz, 1H), 3.13–3.01 (m, 1H), 2.66 (s, 3H), 2.03–1.94 (m, 1H), 1.55 (app q, *J*=12.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz): δ 144.6, 137.6, 136.9, 130.2, 129.4, 122.3, 119.7, 68.9, 65.4, 59.3, 44.9, 44.5, 38.4, 37.1; IR (neat) 3393, 2951, 1524, 1305 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{16}H_{21}N_4O$ (M+1), 285.1715; found, 285.1712.

4.22. General procedure for Suzuki cross-coupling

Bromide **10b** or **10c** (150 mg, 0.505 mmol), arylboronic acid (74 mg, 0.61 mmol), 2 M aqueous K_2CO_3 (0.25 mL, 0.50 mmol), and $Pd(PPh_3)_4$ (47 mg, 0.041 mmol) were combined in ethanol (2.5 mL) and toluene (2.5 mL). The mixture was heated under reflux for 14 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was partitioned between 1 M aqueous HCl (10 mL) and ether (10 mL). The phases were separated and the ether layer was extracted with 1 M aqueous HCl (10 mL). The pH of the combined aqueous layers was adjusted to 14 by addition of 4 M aqueous NaOH. The solution was then saturated with NaCl and extracted with CH_2Cl_2 (4×10 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by flash column chromatography to give the biaryl product **21a**–**e** or **22a**–**c**.

4.23. (3a*RS*,6*SR*,7a*SR*)-6-(3-(Benzo[*d*][1,3]dioxol-5-yl)phenyl)-1-methyloctahydroisoxazolo[4,3-*c*]pyridine (21a)

Prepared according to the general Suzuki coupling procedure from bromide **10b** (93 mg, 0.31 mmol) with all other material amounts scaled accordingly, to give 59 mg (56%) of the biaryl **21a** as a brown gum: ^{1}H NMR (400 MHz): δ 7.51 (s, 1H), 7.39 (d, *J*=7.3 Hz, 1H), 7.35 (app t, *J*=7.3 Hz, 1H), 7.28 (d, *J*=7.3 Hz, 1H), 7.06 (s, 1H), 7.05 (d, *J*=7.9 Hz, 1H), 6.86 (d, *J*=7.9 Hz, 1H), 5.98 (s, 2H), 4.23 (app t, *J*=8.0 Hz, 1H), 3.98 (app t, *J*=8.0 Hz, 1H), 3.60 (d, *J*=11.3 Hz, 1H), 3.29

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(d, *J*=12.7 Hz, 1H), 3.24–3.10 (comp, 2H), 3.04–2.90 (m, 1H), 2.66 (s, 3H), 2.11 (br s, 1H), 2.08–1.98 (m, 1H), 1.78–1.65 (m, 1H); ^{13}C NMR (100 MHz): δ 148.1, 147.1, 144.6, 141.1, 135.5, 128.9, 125.9, 2×125.3, 120.7, 108.5, 107.7, 101.1, 68.0, 64.5, 59.4, 2×44.6, 37.7, 36.3; IR (neat) 3324, 2951, 2884, 1603, 1476, 1230, 1039, 910, 793, 731 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{20}H_{23}N_2O_3$ (M+H), 339.17037; found, 339.17032.

4.24. (3a*RS*,6*SR*,7a*SR*)-6-(3-(2-Methylphenyl)phenyl)-octahydro-1-methylisoxazolo[4,3-*c*]pyridine (21b)

Prepared according to the general Suzuki coupling procedure from bromide **10b** (400 mg, 1.35 mmol) with all other material amounts scaled accordingly, to give 308 mg (74%) of the biaryl **21b** as a brown gum: ^{1}H NMR (400 MHz): δ 7.29–7.39 (comp, 3H), 7.28–7.19 (comp, 5H), 4.22 (dd, *J*=9.1, 7.1 Hz, 1H), 3.96 (dd, *J*=9.1, 7.4 Hz, 1H), 3.60 (dd, *J*=12.1, 1.8 Hz, 1H), 3.30 (d, *J*=12.5 Hz, 1H), 3.24–3.12 (comp, 2H), 3.04–2.90 (m, 1H), 2.67 (s, 3H), 2.25 (s, 3H), 2.09–1.99 (m, 1H), 1.76–1.62 (m, 1H), 1.60 (br s, 1H); ^{13}C NMR (100 MHz): δ 144.1, 142.2, 141.8, 135.3, 130.3, 129.8, 2×128.2, 127.6, 127.2, 125.7, 125.0, 68.0, 64.5, 59.4, 2×44.6, 37.7, 36.6, 20.5; IR (neat) 3320, 2949, 1476, 1437, 1157, 1117, 912, 760, 729 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{20}H_{25}N_2O$ (M+H), 309.19658; found, 309.19614.

4.25. (3a*RS*,6*SR*,7a*SR*)-6-(3-Phenylphenyl)-octahydro-1-methylisoxazolo[4,3-*c*]pyridine (21c)

Prepared according to the general Suzuki coupling procedure from bromide **10b** (400 mg, 1.35 mmol) with all other material amounts scaled accordingly, to give 327 mg (80%) of the biaryl **21c** as a brown gum: ^{1}H NMR (400 MHz): δ 7.64–7.55 (comp, 3H), 7.49 (d, *J*=7.3 Hz, 1H), 7.43 (app t, *J*=7.2, 2H), 7.38 (d, *J*=7.6 Hz, 1H), 7.36–7.30 (comp, 2H), 4.24 (dd, *J*=9.0, 7.0 Hz, 1H), 3.99 (dd, *J*=9.0, 7.4 Hz, 1H), 3.67–3.58 (m, 1H), 3.30 (d, *J*=12.9 Hz, 1H), 3.24–3.14 (comp, 2H), 3.05–2.93 (m, 1H), 2.68 (s, 3H), 2.10–2.00 (m, 1H), 1.88–1.50 (comp, 2H); ^{13}C NMR (100 MHz): δ 144.8, 141.5, 141.1, 128.9, 128.7, 127.3, 127.2, 126.2, 125.7, 125.6, 68.0, 64.5, 59.5, 2×44.6, 37.8, 36.4; IR (neat) 3323, 2951, 1599, 1478, 1437, 911, 760, 704 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{19}H_{23}N_2O$ (M+H), 295.1805; found, 295.1805.

4.26. (3a*RS*,6*SR*,7a*SR*)-6-(3-(4-Cyanophenyl)phenyl)-octahydro-1-methylisoxazolo[4,3-*c*]pyridine (21d)

Prepared according to the general Suzuki coupling procedure from bromide **10b** (400 mg, 1.35 mmol) with all other material amounts scaled accordingly, to give 377 mg (89%) of the biaryl **21d** as a brown glass: ^{1}H NMR (400 MHz): δ 7.72 (d, *J*=8.6 Hz, 2H), 7.68 (d, *J*=8.6 Hz, 2H), 7.60 (s, 1H), 7.48 (app dt, *J*=6.9, 1.9 Hz, 1H), 7.46–7.38 (comp, 2H), 4.25 (dd, *J*=9.0, 7.4 Hz, 1H), 3.99 (dd, *J*=9.0, 7.2 Hz, 1H), 3.62 (dd, *J*=12.2, 2.1, 1H), 3.32 (d, *J*=12.5 Hz, 1H), 3.26–3.14 (comp, 2H), 3.07–2.94 (m, 1H), 2.68 (s, 3H), 2.09–2.00 (m, 1H), 1.85–1.62 (comp, 2H); ^{13}C NMR (100 MHz): δ 145.6, 145.3, 139.4, 132.6, 129.3, 127.8, 127.2, 126.3, 125.6, 119.0, 110.9, 68.0, 64.4, 59.3, 44.6, 44.5, 37.7, 36.5; IR (neat) 3324, 2951, 2882, 2226, 1605, 1481, 1437, 913, 795, 732 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{20}H_{22}N_3O$ (M+H), 320.17618; found, 320.17574.

4.27. (3a*RS*,6*SR*,7a*SR*)-6-(3-(2-Methoxyphenyl)phenyl)-octahydro-1-methylisoxazolo[4,3-*c*]pyridine (21e)

Prepared according to the general Suzuki coupling procedure from bromide **10b** (400 mg, 1.35 mmol) with all other material amounts scaled accordingly, to give 354 mg (80%) of the biaryl **21e** as a brown gum: ^{1}H NMR (400 MHz): δ 7.49 (s, 1H), 7.44 (d, *J*=7.2 Hz, 1H), 7.40–7.27 (comp, 4H), 7.02 (td, *J*=7.4, 0.9 Hz, 1H), 6.97 (d, *J*=8.6 Hz, 1H), 4.22 (dd, *J*=8.9, 7.1 Hz, 1H), 3.96 (dd, *J*=8.9, 7.4 Hz, 1H), 3.80 (s, 3H), 3.64–3.55 (m, 1H), 3.29 (d, *J*=12.5 Hz, 1H), 3.24–3.10 (comp, 2H), 3.04–2.90 (m, 1H), 2.67 (s, 3H), 2.10–1.99 (m, 1H), 1.86–1.64 (comp, 2H); ^{13}C NMR (100 MHz): δ 156.4, 143.8, 138.7, 130.9, 130.6, 128.6, 128.0, 127.9, 125.2, 120.7, 111.1, 68.0, 64.6, 59.4, 55.5, 2×44.6, 37.7, 36.3; IR (neat) 3322, 2951, 1600, 1462, 1240, 1026, 911, 731 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{20}H_{25}N_2O_2$ (M+1), 325.19146; found, 325.19105.

4.28. (3a*RS*,6*SR*,7a*SR*)-6-(4-Phenylphenyl)-octahydro-1-methylisoxazolo[4,3-*c*]pyridine (22a)

Prepared according to the general Suzuki coupling procedure from bromide **10c** (150 mg, 0.505 mmol) to give 134 mg (90%) of the biaryl **22a** as a pale yellow solid: mp 150–152 °C (off-white crystals from $CHCl_3$); ^{1}H NMR (400 MHz): δ 7.84 (d, *J*=8.2 Hz, 2H), 7.55 (d, *J*=8.2 Hz, 2H), 7.47–7.39 (comp, 4H), 7.33 (t, *J*=7.4 Hz, 1H), 4.23 (app t, *J*=8.2 Hz, 1H), 3.99 (app t, *J*=8.2 Hz, 1H), 3.60 (d, *J*=11.6 Hz, 1H), 3.31 (d, *J*=12.3 Hz, 1H), 3.24–3.14 (comp, 2H), 3.05–2.92 (m, 1H), 2.68 (s, 3H), 2.09–1.93 (m, 1H), 1.78–1.64 (m, 1H), 1.57 (br s, 1H); ^{13}C NMR (100 MHz): δ 143.4, 140.9, 140.3, 128.8, 2×127.3, 127.2, 127.1, 68.1, 64.6, 59.2, 2×44.7, 37.8, 36.4; IR (neat) 3323, 2950, 2880, 1487, 1437 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{19}H_{23}N_2O$ (M+1), 295.1805; found, 295.1802.

4.29. (3a*RS*,6*SR*,7a*SR*)-6-(4-(Benzofuran-2-yl)phenyl)-1-methyloctahydroisoxazolo[4,3-*c*]pyridine (22b)

Prepared according to the general Suzuki coupling procedure from bromide **10c** (130 mg, 0.44 mmol) with all other amounts scaled accordingly, to give 96 mg (65%) of the biaryl **22b** as a white foam: ^{1}H NMR (400 MHz): δ 7.82 (d, *J*=8.2 Hz, 2H), 7.57 (dd, *J*=7.5, 1.2 Hz, 1H), 7.51 (dd, *J*=7.5, 0.8 Hz, 1H), 7.44 (d, *J*=8.2 Hz, 2H), 7.27 (app dt, *J*=7.5, 1.2 Hz, 1H), 7.22 (app dt, *J*=7.5, 0.8 Hz, 1H), 7.00 (s, 1H), 4.25 (app t, *J*=8.2 Hz, 1H), 3.99 (app t, *J*=8.2 Hz, 1H), 3.60 (app d, *J*=10.8 Hz, 1H), 3.31 (app d, *J*=12.5 Hz, 1H), 3.24–3.14 (comp, 2H), 3.05–2.94 (m, 1H), 2.68 (s, 3H), 2.02 (app dd, *J*=12.5, 5.7 Hz, 1H), 1.69 (app q, *J*=12.5 Hz, 1H); ^{13}C NMR (75 MHz): δ 155.8, 154.8, 144.6, 129.5, 129.2, 127.1, 125.1, 124.2, 122.9, 120.8, 111.1, 101.1, 68.0, 64.4, 59.1, 2×44.6, 37.7, 36.4; IR (neat) 3320, 2927, 1452, 1257 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{21}H_{23}N_2O_2$ (M+1), 335.17540; found, 335.17546 cm^{-1}.

4.30. (3a*RS*,6*SR*,7a*SR*)-1-Methyl-6-(4-(pyridin-3-yl) phenyl) octahydroisoxazolo[4,3-*c*]pyridine (22c)

Prepared according to the general Suzuki coupling procedure from bromide **10c** (130 mg, 0.44 mmol) with all other amounts scaled accordingly, to give 85 mg (65%) of the biaryl **22c** as an orange gum: ^{1}H NMR (400 MHz): δ 8.84 (d, *J*=2.4 Hz, 1H), 8.58 (dd, *J*=4.8, 1.4 Hz, 1H), 7.87 (app dt, *J*=7.9, 1.9 Hz, 1H), 7.55 (d, *J*=8.2 Hz, 2H), 7.47 (d, *J*=8.2 Hz, 2H), 7.35 (dd, *J*=7.9, 4.8 Hz, 1H), 4.25 (app t, *J*=8.2 Hz, 1H), 3.99 (app t, *J*=8.2 Hz, 1H), 3.63 (dd, *J*=11.8, 1.8 Hz, 1H), 3.32 (app d, *J*=12.1 Hz, 1H), 3.25–3.16 (comp, 2H), 3.07–2.95 (m, 1H), 2.68 (s, 3H), 2.09–1.90 (m, 1H), 1.94 (br s, 1H), 1.70 (app q, *J*=11.8 Hz, 1H); ^{13}C NMR (100 MHz): δ 148.6, 148.5, 144.5, 137.1, 137.1, 134.5, 127.7, 127.5, 123.8, 68.2, 64.7, 59.3, 2×44.8, 38.0, 36.6; IR (neat) 3342, 2952, 1474, 1435 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{18}H_{22}N_3O$ (M+1), 296.17574; found, 296.17597.

4.31. General procedure for the preparation of bis(-trimethylsilyl) amino acid derivatives

The *N*-alkylamino acid (sarcosine or *N*-(4-methoxybenzyl)glycine,[27] 13.3 mmol), Et_3N (5.4 g, 7.4 mL, 53 mmol), and TMSCl (4.3 g, 5.1 mL, 40 mmol) were combined in dry CH_2Cl_2 (27 mL). The

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resulting slurry was stirred for 20 h and then the volatile components were removed under reduced pressure. The residue was suspended in dry benzene (12 mL) and the solid was removed by Schlenk filtration under nitrogen. The filtrate was concentrated in vacuo to afford the crude *N*,*O*-bis(trimethylsilyl)amino acid **25** or **26**, which was used immediately without further purification.

4.32. 1-((3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-methyl tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-5(6*H*,7*H*,7a*H*)-yl)pent-4-en-1-one (27)

N,*O*-Bis(trimethylsilyl)sarcosine (**25**) (0.56 g, 2.4 mmol) and aldehyde **8a** (0.413 g, 1.18 mmol) were combined in dry toluene (4.6 mL) under nitrogen. After stirring for 1 h, the solution was heated at 135 °C for 20 h. The mixture was cooled to room temperature and then concentrated to dryness. The residue was purified by flash column chromatography eluting with CH_2Cl_2/methanol (100:1→90:10 along a gradient) to give 275 mg (62%) of the pyrrolidine **27** as a pale brown gum: ^{1}H NMR (2:1 rotamer mixture) (600 MHz): δ 7.54 (dd, *J*=8.0, 1.1 Hz, 0.7H), 7.50 (dd, *J*=7.7, 1.0 Hz, 0.3H), 7.33–7.28 (m, 0.7H), 7.26 (dd, *J*=7.7, 1.7 Hz, 0.7H), 7.23–7.19 (m, 0.3H), 7.16–7.10 (td, *J*=7.6, 1.7 Hz, 1H), 7.06–7.01 (m, 0.3H), 5.86–5.77 (m, 0.3H), 5.72–5.63 (m, 0.7H), 5.15 (dd, *J*=13.7, 4.7 Hz, 0.3H), 5.02 (dd, *J*=17.1, 1.5 Hz, 0.3H), 5.00–4.94 (comp, 1H), 4.92–4.84 (comp, 2.1H), 3.89 (dd, *J*=13.6, 5.3 Hz, 0.3H), 3.45–3.38 (m, 0.3H), 3.00–2.94 (comp, 1H), 2.90 (app t, *J*=12.6 Hz, 0.7H), 2.53–2.31 (comp, 7.2H), 2.31–2.18 (comp, 2.4H), 2.13–2.05 (m, 0.7H), 2.01–1.94 (comp, 1H), 1.79 (ddd, *J*=14.3, 8.1, 5.2 Hz, 0.7H), 1.60–1.45 (comp, 2H); ^{13}C NMR (150 MHz) (2:1 rotamer mixture): δ 173.1, 171.2, 143.5, 143.3, 137.6, 137.3, 2×133.0, 128.9, 128.6, 128.0, 127.8, 126.6, 125.5, 121.8, 121.1, 115.1, 114.9, 62.1, 61.9, 55.8, 55.7, 55.6, 54.9, 46.0, 42.0, 40.5, 40.2, 39.4, 38.6, 34.6, 33.4, 2×33.4, 32.7, 29.1, 29.0, 28.6, 28.3; IR (neat) 2936, 2782, 1649, 1417, 1238, 1024, 911, 755; HRMS (ESI$^+$) *m*/*z* calculated for $C_{19}H_{26}N_2O^{79}Br$ (M+1), 377.12230; found, 377.12228.

4.33. (3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-methyl octahydro-1*H*-pyrrolo[3,2-*c*]pyridine (28)

Prepared according to the general 4-pentenamide deprotection procedure B, starting with amide **27** (70 mg, 0.19 mmol). Purification by flash column chromatography eluting with CH_2Cl_2/methanol/Et_3N (100:1:1→90:10:1) gave 42 mg (77%) of the amine **28** as a pale yellow gum: ^{1}H NMR (400 MHz): δ 7.59 (dd, *J*=7.9, 1.7 Hz, 1H), 7.52 (dd, *J*=7.9, 0.9 Hz, 1H), 7.31 (td, *J*=7.9, 0.9 Hz, 1H), 7.10 (td, *J*=7.9, 1.7 Hz, 1H), 3.96 (dd, *J*=11.6, 2.4 Hz, 1H), 3.15–3.00 (comp, 3H), 2.93–2.84 (m, 1H), 2.74 (td, *J*=9.6, 4.1 Hz, 1H), 2.48–2.36 (m, 1H), 2.39 (s, 3H), 2.08–1.87 (comp, 3H), 1.31 (app q, *J*=11.6 Hz, 1H); ^{13}C NMR (75 MHz): δ 144.0, 132.8, 128.5, 128.0, 127.9, 123.1, 62.3, 57.1, 52.9, 47.1, 38.2, 37.5, 30.1, 26.3; IR (neat) 3392, 2936, 2787, 1468, 1440, 1022 cm^{-1}; HRMS (CI$^+$) *m*/*z* calculated for $C_{14}H_{20}N_2^{79}Br$ (M+1), 295.0810; found, 295.0804.

4.34. (3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-(4-methoxy benzyl)-5-(acetyl)octahydro-1*H*-pyrrolo[3,2-*c*]pyridine (30)

N,*O*-Bis(trimethylsilyl)-*N*-(4-methoxybenzyl) glycine (**26**) (224 mg, 0.66 mmol) was combined with aldehyde **23** (100 mg, 0.32 mmol) in toluene (3.3 mL). The mixture was stirred for 30 min at room temperature and then heated at 105 °C for a further 3 h. The mixture was cooled to room temperature and partitioned between water (10 mL) and toluene (10 mL). The phases were separated, and the toluene layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/methanol (100:1 then 95:5 then 90:10 along a gradual gradient) to give 86 mg (60%) of the amine **30** as a yellow gum: ^{1}H NMR (400 MHz) (2:1 rotamer mixture): δ 7.54–7.46 (comp, 1H), 7.33–7.08 (comp, 4.7H), 7.06–7.00 (m, 0.3H), 6.82 (d, *J*=8.5 Hz, 2H), 5.12 (dd, *J*=13.3, 4.8 Hz, 0.3H), 4.92–4.83 (comp, 1.4H), 3.89–3.73 (comp, 1.3H), 3.78 (s, 3H), 3.52–3.37 (comp, 1.3H), 2.94–2.83 (comp, 1.7H), 2.79–2.69 (m, 1H), 2.50–2.36 (m, 1H), 2.32–2.20 (comp, 2H), 2.11 (s, 0.9H), 1.97–1.87 (m, 1H), 1.72 (s, 2.1H), 1.55 (app q, *J*=13.0 Hz, 1H), 1.50–1.38 (m, 1H); ^{13}C NMR (100 MHz) (2:1 rotamer mixture): δ 171.3, 169.3, 158.8, 143.6, 143.1, 142.8, 133.1, 130.2, 128.9, 128.6, 128.0, 127.8, 126.2, 125.3, 121.8, 121.1, 113.7, 60.2, 59.9, 58.1, 57.7, 56.7, 55.3, 54.8, 52.9, 52.7, 47.0, 41.9, 39.1, 38.2, 34.5, 28.0, 22.4, 21.9; IR (neat) 2931, 1645, 1513, 1416, 1249 cm^{-1}; HRMS (CI$^+$) *m*/*z* calculated for $C_{23}H_{27}N_2O_2^{79}Br$ (M$^+$), 442.1256; found, 442.1252.

4.35. (3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-methyl-5-(acetyl) octahydro-1*H*-pyrrolo[3,2-*c*]pyridine (2)

1-Chloroethyl chloroformate (13 mg, 10 μL, 0.093 mmol) was added to a solution of amine **30** (20.7 mg, 0.0467 mmol) and Et_3N (47 mg, 0.047 mmol) in CH_2Cl_2 (0.2 mL) at 0 °C. After 15 min, the mixture was concentrated under reduced pressure. The residue was redissolved in methanol (5 mL) and the mixture was heated under reflux for 1 h, then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was passed through a plug of silica, eluting with (100:1→4:1 along a gradient) to give the crude intermediate amine **31** (7.8 mg). This was combined with acetic acid (1.5 mg, 0.0025 mmol), paraformaldehyde (8 mg, 0.3 mmol), and $NaBH(OAc)_3$ (31 mg, 0.15 mmol) in 1,2-dichloroethane (0.4 mL) and the mixture was stirred at room temperature for 30 h, then the mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash column chromatography, eluting with CH_2Cl_2/methanol (100:1→4:1 along a gradient) to give 6.8 mg (44% over two steps) of the amine **2** as a yellow gum. Spectroscopic data were identical to those obtained from a sample prepared previously.[12b,c]

4.36. General N-acylation or sulfonylation procedure

The amine substrate (0.091 mmol) was combined with Et_3N (28 mg, 0.28 mmol) and the required acid chloride or sulfonyl chloride (0.14 mmol) in CH_2Cl_2 (1.0 mL). After the reaction had reached completion (as judged by TLC) the mixture was concentrated under reduced pressure and the residue was suspended in ethyl acetate (2 mL). The mixture was then filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired amides or sulfonamides.

4.37. (3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-methyl-5-(phenylsulfonyl)octahydro-1*H*-pyrrolo[3,2-*c*]pyridine (29)

Prepared according to the general sulfonylation procedure from the amine **28** (27 mg, 0.091 mmol). Purification by flash column chromatography, eluting with CH_2Cl_2/methanol/Et_3N (100:1:1→90:10:1) gave 29 mg (73%) of the sulfonamide **29** as a yellow gum: ^{1}H NMR (400 MHz): δ 7.67 (d, *J*=7.8 Hz, 2H), 7.50 (t, *J*=7.5 Hz, 1H), 7.45 (d, *J*=7.9 Hz, 1H), 7.43–7.35 (m, 2H), 7.26 (dd, *J*=7.3, 1.4 Hz, 1H), 7.15 (t, *J*=7.3 Hz, 1H), 7.04 (td, *J*=7.9, 1.4 Hz, 1H), 5.03 (dd, *J*=13.0, 4.1 Hz, 1H), 4.05 (dd, *J*=14.4, 5.5 Hz, 1H), 3.37–3.28

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(m, 1H), 3.13–3.02 (m, 1H), 2.57–2.43 (m, 1H), 2.41 (s, 3H), 2.35–2.21 (comp, 3H), 2.00–1.88 (m, 1H), 1.86–1.65 (m, 1H), 1.58–1.44 (m, 1H); ^{13}C NMR (100 MHz): δ 142.1, 139.8, 132.8, 132.7, 129.0, 128.8, 128.0, 127.9, 127.4, 121.5, 62.5, 56.0, 55.5, 46.2, 39.9, 37.4, 33.4, 28.0; IR (neat) 2941, 2783, 1446, 1352, 1163 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{20}H_{24}N_2O_2S^{79}Br$ (M+1), 435.0738; found, 435.0736.

4.38. (3a*RS*,6*SR*,7a*SR*)-6-(3-Morpholinophenyl)-5-(3-phenylpropionyl)-1-methyloctahydroisoxazolo[4,3-*c*]pyridine (32)

Prepared according to the general acylation procedure from the amine **13** (24 mg, 0.077 mmol), with all other material amounts scaled accordingly. Purification by column chromatography, eluting with pentane/ethyl acetate/methanol (25:75:1→0:9:1) gave 26 mg (77%) of the amide **32** as a brown gum: ^{1}H NMR (400 MHz) (3:1 rotamer mixture): δ 7.33–7.14 (comp, 4.5H), 7.07–6.98 (comp, 1.5H), 6.72 (comp, 1.5H), 6.70–6.62 (comp, 1.5H), 5.03 (dd, *J*=12.7, 5.3 Hz, 0.25H), 4.94–4.85 (m, 0.75H), 4.38 (dd, *J*=12.5, 5.5 Hz, 0.75H), 4.17–4.07 (m, 0.75H), 4.08–4.00 (m, 0.25H), 3.89–3.80 (m, 4.25H), 3.52 (dd, *J*=9.0, 4.7 Hz, 0.75H), 3.47 (dd, *J*=8.6, 5.3 Hz, 0.25H), 3.36 (app t, *J*=13.0 Hz, 0.25H), 3.22–3.04 (comp, 4H), 3.20–2.78 (comp, 8.25H), 2.45 (dt, *J*=14.7, 9.0 Hz, 0.75H), 2.27 (ddd, *J*=14.7, 8.6, 5.7 Hz, 0.75H), 2.23–2.12 (m, 0.25H), 2.12–2.01 (m, 0.75H), 1.99–1.86 (m, 0.25H), 1.91–1.77 (m, 0.75H); ^{13}C NMR (100 MHz) (3:1 rotamer mixture): δ 173.3, 171.1, 152.0, 144.5, 141.1, 130.0, 129.4, 128.5, 128.4, 126.1, 116.9, 116.5, 114.5, 114.4, 113.4, 111.8, 68.2, 67.9, 66.9, 66.8, 64.6, 56.5, 54.3, 49.4, 49.1, 43.6, 43.3, 42.3, 39.3, 35.9, 35.4, 35.3, 31.7, 31.3; IR (neat) 2958, 2855, 1644, 1602, 1449, 1418, 1244, 1122, 753, 701 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{26}H_{34}N_3O_3$ (M+1), 436.25947; found, 436.25949.

4.39. (3a*RS*,6*SR*,7a*SR*)-6-(Biphenyl-3-yl)-1-methyl-5-(*o*-tolylsulfonyl)octahydroisoxazolo[4,3-*c*]pyridine (34)

Prepared according to the general sulfonylation procedure from the amine **21c** (20 mg, 0.067 mmol), with all other material amounts scaled accordingly. Purification by column chromatography eluting with pentane/ethyl acetate/methanol (75:25:1→50:50:1) gave 24 mg (80%) of the sulfonamide **34** as a colorless gum: ^{1}H NMR (400 MHz): δ 7.64 (dd, *J*=7.8, 1.0 Hz, 1H), 7.45–7.31 (comp, 5H), 7.27–7.22 (m, 1H), 7.16–7.07 (comp, 3H), 7.01–6.89 (comp, 3H), 4.82 (dd, *J*=12.4, 5.0 Hz, 1H), 4.27 (dd, *J*=14.0, 5.8 Hz, 1H), 4.23–4.14 (m, 1H), 3.52 (dd, *J*=9.0, 5.0 Hz, 1H), 3.40 (dd, *J*=14.0, 11.9 Hz, 1H), 3.26–3.14 (m, 1H), 3.15–3.00 (m, 1H), 2.69 (s, 3H), 2.39 (s, 3H), 2.21–2.11 (m, 1H), 2.02 (ddd, *J*=14.1, 12.5, 11.0 Hz, 1H); ^{13}C NMR (100 MHz): δ 141.6, 141.1, 140.7, 138.1, 137.3, 132.5, 132.0, 129.9, 2×128.7, 128.6, 127.3, 127.0, 126.2, 125.6, 125.1, 68.3, 64.6, 56.4, 43.5, 43.4, 43.1, 34.0, 20.1; IR (neat) 2954, 2852, 1602, 1489, 1448, 1263, 1247, 1122, 956, 785, 753 cm^{-1}; mass spectrum (CI$^+$) *m*/*z* calculated for $C_{26}H_{28}N_2O_3S$ (M$^+$), 448.1821; found, 448.1818.

4.40. (3a*RS*,6*SR*,7a*SR*)-5-(3,5-Dichlorobenzyl)-1-methyl-6-(3-phenoxyphenyl)octahydroisoxazolo[4,3-*c*]pyridine (33)

The amine **16** (21 mg, 0.065 mmol) was combined with 3,5-dichlorobenzaldehyde (68 mg, 0.39 mmol), acetic acid (5 mg, 0.08 mmol), and sodium triacetoxyborohydride (82 mg, 0.39 mmol) in 1,2-dichloroethane (1.4 mL) and the mixture was stirred for 19 h. Saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was stirred vigorously for 10 min. The mixture was filtered through Celite, rinsing with ethyl acetate (3 mL), and saturated $NaHCO_3$ (2 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (2×3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/pentane/methanol (50:50:5→100:0:5) to give 25 mg (85%) of the amine **33** as a colorless gum: ^{1}H NMR (400 MHz): δ 7.36–7.25 (comp, 3H), 7.20 (app d, *J*=1.7 Hz, 1H), 7.15–7.07 (comp, 4H), 7.06–7.03 (m, 1H), 6.98 (2H, d, *J*=7.8 Hz, 2H), 6.90 (ddd, *J*=8.0, 2.4, 0.8 Hz, 1H), 4.18–4.09 (m, 1H), 3.94–3.84 (m, 1H), 3.75 (d, *J*=14.1 Hz, 1H), 3.16 (dd, *J*=11.5, 2.35 Hz, 1H), 3.15–3.04 (m, 1H), 3.04–2.92 (comp, 2H), 2.80 (d, *J*=14.1 Hz, 1H), 2.62 (s, 3H), 2.33 (dd, *J*=13.3, 4.3 Hz, 1H), 2.02–1.93 (m, 1H), 1.92–1.79 (m, 1H); ^{13}C NMR (100 MHz): δ 157.7, 157.0, 145.5, 143.2, 134.8, 130.1, 129.8, 127.1, 126.5, 123.4, 122.2, 118.9, 118.0, 117.5, 68.1, 66.2, 63.8, 57.9, 50.6, 44.4, 38.5, 37.4; IR (neat) 2952, 2881, 2805, 1585, 1568, 2487, 1432, 1251, 1217, 797, 752 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{26}H_{27}^{35}Cl_2N_2O_2$ (M+1), 469.14441; found, 469.14419.

4.41. (3a*RS*,6*SR*,7a*SR*)-*N*-Ethyl-1-methyl-6-(4-(piperidin-1-yl)phenyl)hexahydroisoxazolo[4,3-*c*]pyridine-5(1*H*)-carboxamide (35)

Amine **18** (20.0 mg, 0.0664 mmol), Et_3N (6.8 mg, 0.067 mmol), and ethyl isocyanate (9.5 mg, 0.13 mmol) were combined in CH_2Cl_2 (0.5 mL). After 14 h, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with ethyl acetate/pentane/methanol (50:50:1→100:0:1) to give 24 mg (98%) of the urea **35** as an orange gum: ^{1}H NMR (400 MHz): δ 7.15 (d, *J*=8.7 Hz, 2H), 6.93 (d, *J*=8.7 Hz, 2H), 4.63 (dd, *J*=12.7, 5.5 Hz, 1H), 4.28 (dd, *J*=13.0, 4.4 Hz, 1H), 4.17–4.07 (comp, 2H), 3.52 (dd, *J*=8.9, 4.8 Hz, 1H), 3.20–3.13 (comp, 4H), 3.12–3.01 (comp, 3H), 3.01–2.80 (comp, 2H), 2.67 (s, 3H), 2.10–2.01 (m, 1H), 1.92–1.81 (m, 1H), 1.76–1.67 (comp, 4H), 1.63–1.54 (comp, 2H), 0.88 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 158.4, 151.8, 133.1, 126.0, 116.9, 68.4, 65.1, 55.6, 50.4, 43.7, 42.8, 40.2, 35.9, 35.5, 25.7, 24.2, 15.3; IR (neat) 3416, 2934, 1633, 1515, 1236 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{21}H_{33}N_4O_2$ (M+1), 373.2598; found, 373.2597.

4.42. (3a*RS*,6*SR*,7a*SR*)-6-(4-(1*H*-Imidazol-1-yl)phenyl)-5-(mesitylsulfonyl)-1-methyloctahydroisoxazolo[4,3-*c*] pyridine (36)

Prepared according to the general sulfonylation procedure from the amine **20** (19 mg, 0.067 mmol), with all other material amounts scaled accordingly. Purification by column chromatography eluting with pentane/ethyl acetate/methanol (75:25:1→50:50:1) gave 26 mg (84%) of the sulfonamide **36** as a colorless gum: ^{1}H NMR (400 MHz): δ 7.71 (s, 1H), 7.19 (s, 1H), 7.15 (s, 1H), 7.08 (d, *J*=8.7 Hz, 2H), 7.03 (d, *J*=8.7 Hz, 2H), 6.65 (s, 2H), 4.72 (dd, *J*=12.3, 4.8 Hz, 1H), 4.26 (dd, *J*=14.1, 5.7 Hz, 1H), 4.22–4.14 (m, 1H), 3.52 (dd, *J*=9.0, 4.8 Hz, 1H), 3.34 (dd, *J*=14.1, 12.1 Hz, 1H), 3.25–3.03 (comp, 2H), 2.69 (s, 3H), 2.45 (s, 6H), 2.19–2.08 (comp, 4H), 1.96 (ddd, *J*=14.1, 12.5, 10.8 Hz, 1H); ^{13}C NMR (75 MHz): δ 142.4, 140.9, 139.5, 136.2, 135.4, 133.5, 131.5, 130.4, 127.3, 120.9, 118.1, 68.3, 64.4, 55.6, 43.4, 43.2, 42.8, 34.0, 22.7, 20.7; IR (neat) 2956, 1523, 1307, 1153, 1057 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calculated for $C_{25}H_{31}N_4O_3S$ (M+1), 467.2109; found, 467.2111.

4.43. (3a*RS*,6*SR*,7a*SR*)-6-Biphenyl-4-yl)-5-(4-methoxy benzyl)-1-methyloctahydroisoxazolo[4,3-*c*]pyridine (37)

Amine **22a** (23 mg, 0.77 mmol) was combined with $NaBH(OAc)_3$ (100 mg, 0.47 mmol), acetic acid (4.6 mg, 0.77 mmol), and *p*-anisaldehyde (63 mg, 0.46 mmol) in DCE (1.5 mL) was stirred at room temperature for 16 h before addition of 1.5 M aqueous HCl (1 mL) and further stirring for 30 min. The mixture was then partitioned between ether (3 mL) and 1.5 M aqueous HCl (3 mL) and the phases were separated. The aqueous layer was washed with ether

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(2×3 mL). 4 M aqueous NaOH was added to the aqueous layer to adjust the pH to 14 and the solution was saturated with NaCl. The solution was then extracted with ethyl acetate (3×5 mL). The combined ethyl acetate extracts were dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography eluting with CH_2Cl_2/methanol (100:1 to 90:10 along a gradient), to give 22 mg (69%) of the amine **37**as a colorless gum: ^{1}H NMR (400 MHz): δ 7.61–7.53 (comp, 4H), 7.49 (d, J=7.8 Hz, 2H), 7.42 (app t, J=7.6 Hz, 2H), 7.32 (t, J=7.6 Hz, 1H), 7.17 (d, J=8.1 Hz, 2H), 6.82 (d, J=8.1 Hz, 2H), 4.11 (app t, J=7.9 Hz, 1H), 3.96 (app t, J=7.9 Hz, 1H), 3.82–3.73 (m, 1H), 3.78 (s, 3H), 3.22 (app dd, J=11.6, 2.8 Hz, 1H), 3.16–2.91 (comp, 3H), 2.78 (d, J=13.5 Hz, 1H), 2.63 (s, 3H), 2.33 (dd, J=12.9, 3.3 Hz, 1H), 2.04–1.86 (comp, 2H); ^{13}C NMR (100 MHz): δ 158.5, 143.2, 140.9, 140.1, 131.6, 129.3, 128.7, 127.9, 127.3, 127.1, 127.0, 113.6, 68.3, 66.1, 64.1, 58.0, 55.2, 50.1, 44.5, 38.7, 37.8; IR (neat) 2951, 1511, 1249, 1036 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{27}H_{30}N_2O_2Na$ (M+23), 437.21995; found, 437.21989.

4.44. (3a*RS*,6*SR*,7a*SR*)-1-Methyl-5-trimethylacetyl-6-(4-(pyridin-3-yl)phenyl)octahydroisoxazolo[4,3-*c*]pyridine (38)

Prepared according to the general acylation procedure from the amine **22c** (20 mg, 0.068 mmol), with all other material amounts scaled accordingly. Purification by column chromatography, eluting with pentane/ethyl acetate/methanol (25:75:1 →0:9:1) gave 22 mg (85%) of the amide **38** as a brown gum: ^{1}H NMR (400 MHz): δ 8.82 (d, J=1.7 Hz, 1H), 8.59–8.54 (m, 1H), 7.84 (app dt, J=7.8, 1.7 Hz, 1H), 7.51 (d, J=8.1 Hz, 2H), 7.34 (d, J=7.8, 4.9 Hz, 1H), 7.31 (d, J=8.1 Hz, 2H), 5.10–4.99 (m, 1H), 4.38–4.27 (m, 1H), 4.23–4.12 (m, 1H), 3.57 (dd, J=8.7, 4.2 Hz, 1H), 3.61–3.41 (m, 1H), 3.09–2.91 (comp, 2H), 2.70 (s, 3H), 2.27–2.15 (m, 1H), 1.93 (app q, J=12.7 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz): δ 177.0, 2×148.5, 144.5, 136.7, 136.5, 134.5, 127.8, 125.8, 123.8, 68.2, 64.6, 55.6, 2×43.8, 39.1, 34.2, 28.4; IR (neat) 2957, 1627, 1477, 1411, 1365 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{23}H_{29}N_3O_2Na$ (M+23), 402.21520; found, 402.21518.

4.45. (1*SR*,12*RS*,16*SR*)-15-Methyl-8-phenyl-14-oxa-8,10,15-triazatetracyclo[8.7.0.0^{2,7}.0^{12,16}]heptadeca-2(7),3,5-trien-9-one (40)

$Pd(OAc)_2$ (2.4 mg, 0.011 mmol) and (±)-BINAP (7.8 mg, 0.032 mmol) were combined in toluene (0.8 mL) and heated at 40 °C until all solid dissolved. The mixture was cooled to room temperature, then combined with amine **10a** (30 mg, 0.10 mmol) and Cs_2CO_3 (67 mg, 0.21 mmol) in a sealable tube. The mixture was cooled to 0 °C before dropwise addition of a solution of phenyl isocyanate (24 mg, 0.20 mmol) in toluene (0.2 mL). The mixture was warmed to room temperature and stirred for 30 min, before heating at 120 °C (sealed tube) for 13 h. The mixture was filtered through Celite and concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with ethyl acetate/methanol (100:1 →90:10 along a gradient) to give 31 mg (92%) of the dihydroquinazolin-2-one **40** as a yellow glass: ^{1}H NMR (400 MHz): δ 7.50 (t, J=7.6 Hz, 2H), 7.41 (t, J=7.6 Hz, 1H), 7.30–7.25 (m, 2H), 7.10 (dd, J=7.3, 1.6 Hz, 1H), 7.04 (td, J=8.0, 1.6 Hz, 1H), 6.98 (td, J=7.3, 1.1 Hz, 1H), 6.21 (dd, J=8.0, 1.1 Hz, 1H), 4.62 (dd, J=14.3, 2.0 Hz, 1H), 4.56 (dd, J=12.5, 2.3 Hz, 1H), 4.25 (app t, J=8.6 Hz, 1H), 3.78 (app t, J=8.6 Hz, 1H), 3.39–3.23 (comp, 2H), 3.13–3.02 (m, 1H), 2.69 (s, 3H), 2.29–2.18 (m, 1H), 1.99 (app q, J=12.5 Hz, 1H); ^{13}C NMR (75 MHz): δ 153.9, 139.1, 138.3, 2×129.8, 128.2, 128.1, 125.1, 122.3, 121.4, 115.1, 67.8, 64.1, 55.0, 44.3, 41.5, 38.5, 35.6; IR (neat) 2952, 1659, 1465, 1289, 1266 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{20}H_{22}N_3O_2$ (M+1), 336.1707; found, 336.1706.

4.46. (1*SR*,9*Z*,12*RS*,16*SR*)-15-Methyl-*N*-(2-phenylethyl)-14-oxa-8-thia-10,15-diazatetracyclo[8.7.0.02,7.012,16] heptadeca-2(7),3,5-trien-9-imine (42)

Amine **10a** (40 mg, 0.14 mmol), Cs_2CO_3 (92 mg, 0.28 mmol), Pd[(t-Bu)$_3$P]$_2$ (7.0 mg, 0.014 mmol), and phenethyl isothiocyanate (24 mg, 0.15 mmol) were combined in 1,4-dioxane (0.40 mL). The mixture was stirred at room temperature for 5 h and then heated under reflux for 11 h. The mixture was diluted with CH_2Cl_2 (3 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with $CHCl_3$/methanol (49:1) then CH_2Cl_2/methanol/Et_3N (95:5:1) to give 41 mg (79%) of the 2-imino-1,3-benzothiazinane **42** as a yellow gum: ^{1}H NMR (400 MHz): δ 7.36–7.16 (comp, 9H), 4.58–4.44 (m, 1H), 4.22–4.11 (comp, 2H), 3.66 (dt, J=13.2, 7.9 Hz, 1H), 3.58 (dt, J=13.2, 7.9 Hz, 1H), 3.57–3.51 (m, 1H), 3.12–2.94 (comp, 3H), 2.87 (t, J=7.9 Hz, 2H), 2.79 (s, 3H), 2.53–2.41 (m, 1H), 2.31–2.19 (m, 1H); ^{13}C NMR (75 MHz): δ 151.5, 140.7, 138.5, 132.2, 129.1, 128.3, 128.0, 127.1, 126.9, 126.0, 123.2, 68.6, 65.1, 54.1, 52.7, 43.9, 42.4, 41.0, 38.2, 27.6; IR (neat) 2857, 1613, 1443, 1380, 1240 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{22}H_{26}N_3OS$ (M+1), 380.1791; found, 380.1790.

4.47. (8a*RS*, 11a*SR*, 12a*SR*)-11-Methyl-8a9,11,11a, 12,12a-hexahydro-5*H*-isoxazolo[3′,4′:4,5]pyrido[2,1-*a*]isoquinolin-6-(8*H*)-one (44)

LDA was prepared by addition of n-butyllithium (2.4 M in hexanes, 1.24 mL, 3.0 mmol) to a solution of diisopropylamine (0.35 g, 0.48 mL, 3.4 mmol) in THF (6.0 mL) at 0 °C. After 30 min, the solution was warmed to room temperature. A portion of the LDA solution so obtained (0.41 M in THF/hexanes, 3.5 mL, 1.4 mmol) was added dropwise to a stirred solution of amide **1** (30 mg, 0.088 mmol) and DMPU (90 mg, 85 μL, 0.70 mmol) in THF (1 mL) at −78 °C. The solution was warmed to 0 °C and stirred for 1 h. Saturated aqueous NH_4Cl (1 mL) was added and the mixture was concentrated under reduced pressure to remove the THF. The residue was partitioned between water (10 mL) and CH_2Cl_2 (10 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/toluene/methanol (1:1:0 →9:0:1) to afford 18.6 mg (containing approximately 9% w/w DMPU, corrected yield=74%) of the lactam **44** as a pale yellow gum: ^{1}H NMR (400 MHz): δ 7.31–7.24 (comp, 2H), 7.20–7.14 (comp, 2H), 7.46 (app d, J=12.7, 1H), 4.40 (dd, J=13.9, 3.7 Hz, 1H), 4.30–4.21 (m, 1H), 3.72 (d, J=19.7 Hz, 1H), 3.63 (d, J=19.7 Hz, 1H), 3.59 (app t, J=8.2 Hz, 1H), 3.52–3.43 (m, 1H), 3.35–3.24 (m, 1H), 3.12–3.02 (m, 1H), 2.71 (s, 3H), 2.45–2.34 (m, 1H), 1.84–1.71 (m, 1H); ^{13}C NMR (150 MHz): δ 168.3, 134.0, 131.4, 127.8, 127.6, 126.9, 124.4, 67.9, 64.3, 56.5, 44.2, 39.8, 39.4, 36.4, 34.8; IR (neat) 2952, 2878, 1643, 1454, 1313, 1624, 760, 731; HRMS (ESI$^+$) m/z calculated for $C_{15}H_{19}N_2O_2$ (M+1), 259.14410; found, 259.14416.

4.48. 1-((3a*RS*,6*SR*,7a*SR*)-6-(2-Bromophenyl)-1-methyl tetrahydroisoxazolo[4,3-*c*]pyridin-5(1*H*,3*H*,6*H*)-yl)-2-phenyl ethanone (45)

Phenylacetyl chloride (64 mg, 55 μL, 0.41 mmol) was added dropwise to a solution of amine **10a** (100 mg, 0.336 mmol) and Et_3N (47 mg, 65 μL, 0.46 mmol) in CH_2Cl_2 (2 mL). After 1 h, the mixture was diluted with CH_2Cl_2 (10 mL) and partitioned with saturated aqueous $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate/hexanes (1:1 →3:1) to afford

117 mg (84%) of the amide **45** as a white foam: ^{1}H NMR (400 MHz) (2:1 rotamer mixture): δ 7.57 (d, J=8.0 Hz, 0.7H), 7.51 (d, J=7.8 Hz, 0.3H), 7.35–7.03 (comp, 7.7H), 7.00 (d, J=6.6 Hz, 0.3H), 5.24 (dd, J=13.5, 4.7 Hz, 0.3H), 5.04 (dd, J=12.5, 5.1 Hz, 0.7H), 5.01–4.93 (m, 0.7H), 4.20–4.08 (m, 0.7H), 4.05–3.92 (comp, 0.6H), 3.75 (s, 0.6H), 3.60–3.53 (m, 0.7H), 3.48–3.39 (comp, 0.6H), 3.36 (d, J=15.1 Hz, 0.7H), 3.28 (d, J=15.1 Hz, 0.7H), 3.10–2.82 (comp, 2.4H), 2.75–2.53 (m, 0.3H), 2.66 (s, 2H), 2.64 (s, 1H), 2.44–2.27 (comp, 1H), 1.77–1.57 (comp, 1H); ^{13}C NMR (100 MHz) (2:1 rotamer mixture): δ 171.8, 169.9, 142.5, 142.4, 134.6, 134.5, 133.4, 133.2, 129.4, 129.0, 128.8, 128.7, 128.5, 128.4, 127.8, 127.1, 126.8, 126.4, 125.3, 121.9, 121.1, 68.3, 67.9, 64.5, 55.8, 54.7, 44.3, 43.7, 43.5, 42.5, 42.1, 40.6, 39.9, 32.8, 31.8; IR (neat) 2955, 2874, 1646, 1414, 1026 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{22}H_{25}N_2O_2^{79}Br$ (M+1), 415.1016; found, 415.1016.

4.49. General procedure for the synthesis of dihydroisoquinoline-3-ones via one-pot enolate arylation/alkylation

LDA was prepared by addition of *n*-butyllithium (2.4 M in hexanes, 1.24 mL, 3.0 mmol) to a solution of diisopropylamine (0.35 g, 0.48 mL, 3.4 mmol) in THF (6.0 mL) at 0 °C. After 30 min, the solution was warmed to room temperature. A portion of the LDA solution so obtained (0.41 M in THF/hexanes, 3.5 mL, 1.4 mmol), was added dropwise to a solution of phenylacetamide **45** (100 mg, 0.241 mmol) and DMPU (0.37 g, 0.35 mL, 2.9 mmol) in THF (3 mL) at −78 °C. The solution was then warmed to 0 °C and stirred for 1 h. The mixture was then cooled to −100 °C, and a solution of alkyl halide (2.9 mmol) in THF (2 mL) was added dropwise. The mixture was warmed to −78 °C and held at this temperature for 20 min, before warming to 0 °C. Toluene (5 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was concentrated under reduced pressure to remove the THF. The residue was partitioned between water (5 mL) and toluene (5 mL), and the layers were separated. The toluene layer was washed with water (4×10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with pentane/ethyl acetate/methanol (25:75:1→0:100:1) to afford the desired 4,4-disubstituted dihydroisoquinolin-3-ones.

4.50. (1*SR*,8*RS*,12*RS*,16*SR*)-8,15-Dimethyl-8-phenyl-14-oxa-10,15-diazatetracyclo[8.7.0.0^{2,7}.0^{12,16}] heptadeca-2(7),3,5-trien-9-one (47)

Prepared according to the general enolate arylation/alkylation procedure using methyl iodide as the alkylating agent, to afford 52 mg (62%) of the dihydroisoquinolin-3-one **47** as a yellow gum: ^{1}H NMR (600 MHz): δ 7.36–7.30 (m, 2H), 7.25–7.14 (comp, 5H), 7.12 (d, J=7.3 Hz, 2H), 4.93 (d, J=13.9 Hz, 1H), 4.46 (dd, J=12.6, 1.8 Hz, 1H), 4.08–3.97 (m, 1H), 3.38–3.28 (m, 1H), 3.10–2.96 (comp, 3H), 2.67 (s, 3H), 2.24–2.13 (m, 1H), 2.01 (s, 3H), 1.48 (app q, J=12.6 Hz, 1H); ^{13}C NMR (75 MHz): δ 171.5, 145.7, 138.5, 133.1, 128.2, 128.0, 127.8, 127.0, 126.9, 126.8, 125.3, 67.2, 63.9, 57.4, 49.4, 44.3, 40.6, 38.0, 37.1, 26.6; IR (neat) 2937, 1644, 1444, 1260 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{22}H_{25}N_2O_2$ (M+1), 349.1916; found, 349.1915.

4.51. (1*SR*,8*RS*,12*RS*,16*SR*)-8-Allyl-15-methyl-8-phenyl-14-oxa-10,15-diazatetracyclo[8.7.0.0^{2,7}.0^{12,16}]heptadeca-2(7),3,5-trien-9-one (48)

Prepared according to the general enolate arylation/alkylation procedure using allyl bromide as the alkylating agent, to afford 60 mg (66%) of the dihydroisoquinolin-3-one **48** as a yellow gum: ^{1}H NMR (400 MHz): δ 7.36–7.27 (m, 2H), 7.26–7.12 (comp, 7H), 5.50–5.38 (m, 1H), 5.04 (dd, J=17.1, 1.5 Hz, 1H), 5.03–4.94 (m, 1H), 4.90 (dd, J=10.3, 1.5 Hz, 1H), 4.45 (dd, J=12.6, 2.2 Hz, 1H), 4.08–4.00 (m, 1H), 3.77 (dd, J=14.0, 6.8 Hz, 1H), 3.39–3.28 (m, 1H), 3.14–2.97 (comp, 3H), 2.88 (dd, J=14.0, 7.2 Hz, 1H), 2.58 (s, 3H), 2.26–2.16 (m, 1H), 1.47 (app q, J=12.6 Hz, 1H); ^{13}C NMR (75 MHz): δ 170.4, 145.0, 136.0, 134.4, 134.2, 129.0, 128.5, 127.8, 127.3, 127.2, 127.1, 125.4, 118.3, 67.4, 64.0, 57.4, 53.8, 44.5, 43.4, 40.6, 38.1, 37.9; IR (neat) 2953, 2680, 1643, 1443, 1243 cm^{-1}; HRMS (CI$^+$) m/z calculated for $C_{24}H_{26}N_2O_2$ (M+1), 374.1994; found, 374.1994.

4.52. 1-((2*SR*,4*SR*,5*RS*)-2-(2-Bromophenyl)-5-(hydroxymethyl)-4-(methylamino)piperidin-1-yl)ethanone (49)

Zinc dust (3.9 g, 59 mmol) was added at 0 °C to a stirred solution of isoxazolidine **1** (1.00 g, 2.95 mmol) in 10% aqueous HCl (45 mL). After 1 h, the mixture was filtered through Celite rinsing with 10% aqueous HCl (20 mL). The pH of the combined filtrate and rinsings was adjusted to 12 by the addition of 30% aqueous NH_4OH and the mixture was extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with CH_2Cl_2/methanol (100:1→1:1 along a gradient) to give 837 mg (83%) of the amino alcohol **49** as a clear, colorless gum: ^{1}H NMR (500 MHz, DMSO-d_6, 130 °C): δ 7.57–7.53 (m, 1H), 7.32 (dd, J=7.9, 1.2 Hz, 1H), 7.32–7.27 (m, 1H), 7.14 (ddd, J=7.9, 6.0, 2.7 Hz, 1H), 5.21 (app t, J=7.7 Hz, 1H), 4.16 (dd, J=13.7, 6.1 Hz, 1H), 3.59 (dd, J=11.0, 5.4 Hz, 1H), 3.55 (dd, J=11.0, 6.4 Hz, 1H), 3.03 (br s, 2H), 2.84 (ddd, J=9.1, 6.1, 3.3 Hz, 1H), 2.18–2.12 (comp, 2H), 2.16 (s, 3H), 1.95–1.90 (m, 1H), 1.94 (ddd, J=13.9, 8.8, 7.7 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 130 °C): δ 168.9, 142.5, 132.0, 127.6, 127.1, 126.0, 120.4, 59.9, 54.6, 54.5, 41.5, 39.2, 33.1, 31.0, 20.6; IR (neat) 3323, 2923, 1633, 1420, 1024 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{15}H_{22}N_2O_2^{79}Br$ (M+1), 341.0859; found, 341.0858.

4.53. *N*-((2*SR*,4*SR*,5*RS*)-1-Acetyl-2-(2-bromophenyl)-5-(hydroxymethyl)piperidin-4-yl)-*N*-methylpivalamide (50)

A solution of TMSCl (15 mg, 0.14 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise to a solution of amino alcohol **49** (40 mg, 0.12 mmol) and Et_3N (36 mg, 0.36 mmol) in CH_2Cl_2 (0.2 mL). After 30 min, the mixture was cooled to 0 °C and a solution of pivaloyl chloride (16 mg, 0.13 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise. After a further 30 min, the mixture was warmed to room temperature and stirred for 1 h. Methanol (0.79 g, 1.0 mL, 25 mmol) was added and after 1 h, the mixture was concentrated under reduced pressure. The residue was suspended in ethyl acetate (3 mL) and the insoluble salts were removed by filtration. The filtrate was concentrated under reduced pressure then dissolved in methanol/acetic acid (9:1, 5 mL) and concentrated under reduced pressure after 1 h. The residue was purified by flash column chromatography eluting with ethyl acetate/methanol (100:1→90:10) to give 45 mg (91%) of the amide **50** as a colorless gum: ^{1}H NMR (600 MHz, DMSO-d_6, 130 °C): δ 7.56 (dd, J=7.9, 1.1 Hz, 1H), 7.40–7.34 (m, 1H), 7.32 (dd, J=7.8, 1.8 Hz, 1H), 7.21–7.14 (m, 1H), 5.18 (dd, J=11.6, 6.3 Hz, 1H), 4.41–4.33 (m, 1H), 4.32 (dd, J=13.2, 6.2 Hz, 1H), 4.10 (br s, 1H), 3.51 (app t, J=13.2 Hz, 1H), 3.45 (d, J=5.3 Hz, 2H), 2.96 (s, 3H), 2.57–2.48 (m, 1H), 2.20–2.07 (comp, 2H), 1.91 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6, 130 °C): δ 176.2, 168.5, 142.0, 132.1, 127.9, 127.5, 125.6, 120.3, 58.5, 56.7, 52.4, 42.4, 39.0, 38.0, 32.9, 30.3, 27.5, 20.5; IR (neat) 3410, 2971, 1633, 1435 cm^{-1}; HRMS (ESI$^+$) m/z calculated for $C_{20}H_{30}N_2O_3^{79}Br$ (M+1), 425.1434; found, 425.1436.

4.54. 1-[(1*SR*,9*SR*,10*RS*)-10-(Hydroxymethyl)-8-methyl-8,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-12-yl] ethan-1-one (51)

$Pd(OAc)_2$ (6.0 mg, 0.027 mmol) and (±)-BINAP (20 mg, 0.032 mmol) were combined in toluene (5 mL) and heated at 40 °C

until all solid dissolved. The solution was cooled to room temperature over 10 min, then combined with amine **49** (92 mg, 0.27 mmol) and Cs_2CO_3 (177 mg, 0.543 mmol). The mixture was heated under reflux for 14 h, then cooled to room temperature, and filtered through Celite, rinsing with toluene (5 mL). The combined filtrate and rinsings were concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with $CHCl_3$/methanol (95:5) to afford 49 mg (70%) of the tetrahydroquinoline **51** as a pale yellow gum: ^{1}H NMR (600 MHz) (3:2 rotamer mixture): δ 7.22–7.15 (comp, 1.6H), 7.01 (dd, J=7.6, 1.5 Hz, 0.4H), 6.62–6.55 (comp, 2H), 5.91 (app br s, 0.6H), 4.93 (app br s, 0.4H), 4.36 (dd, J=13.3, 4.8 Hz, 0.4H), 3.83 (d, J=1.8 Hz, 0.4H), 3.72 (d, J=2.1 Hz, 0.6H), 3.66 (dd, J=10.4, 7.6 Hz, 0.6H), 3.60–3.49 (comp, 2H), 3.14 (s, 1.2H), 3.08 (s, 1.8H), 2.72 (br s, 1H), 2.69 (app t, J=12.8 Hz, 0.6H), 2.34 (s, 1.2H), 2.11 (app t, J=13.3 Hz, 0.4H), 2.05–1.81 (comp, 3H), 2.04 (s, 1.8H); ^{13}C NMR (150 MHz) (3:2 rotamer mixture): δ 168.7, 168.1, 146.5, 146.4, 129.9, 129.7, 129.2, 128.9, 120.5, 119.3, 115.6, 115.3, 109.7, 109.5, 62.7, 62.3, 54.4, 53.6, 46.6, 45.8, 45.7, 42.0, 40.0, 39.8, 36.4, 29.3, 28.4, 22.0, 22.0; IR (neat) 3392, 2931, 1614, 1503, 1436, 1045 cm^{-1}; HRMS (CI$^+$) m/z calculated for $C_{15}H_{20}N_2O_2$ ($M^{\bullet+}$), 260.1525; found, 260.1522.

4.55. 1-{[(1*RS*,9*RS*,10*SR*)-12-Acetyl-8-methyl-8,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-yl]methyl} pyrrolidine-2,5-dione (52)

DIAD (40 mg, 39 μL, 0.20 mmol) was added dropwise to a solution of alcohol **51** (21 mg, 0.081 mmol), triphenylphosphine (51 mg, 0.19 mmol), and succinimide (19 mg, 0.19 mmol) in THF (0.3 mL). The mixture was stirred at room temperature for 4 h, before concentration under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate/methanol (100:1→80:20 along a gradient) to give 25 mg (90%) of the succinimide **52** as a yellow gum: ^{1}H NMR (400 MHz) (1:1 rotamer mixture): δ 7.25–7.16 (comp, 1.5H), 7.01 (dd, J=7.6, 1.6 Hz, 0.5H), 6.67–6.61 (comp, 2H), 5.88 (app br s, 0.5H), 4.90 (app br s, 0.5H), 4.21 (dd, J=13.5, 4.9 Hz, 0.5H), 3.69 (dd, J=13.5, 4.1 Hz, 0.5H), 3.66–3.59 (comp, 1H), 3.59–3.54 (comp, 1H), 3.41 (dd, J=13.4, 9.0 Hz, 0.5H), 3.31 (dd, J=13.2, 4.9 Hz, 0.5H), 3.16 (s, 1.5H), 3.13 (s, 1.5H), 2.85 (app t, J=13.2 Hz, 0.5H), 2.75 (s, 2H), 2.72 (s, 2H), 2.31 (s, 1.5H), 2.29 (app t, J=13.4 Hz, 0.5H), 2.16–2.03 (comp, 1H), 1.99 (s, 1.5H), 1.98–1.94 (comp, 1H), 1.94–1.83 (comp, 1H); ^{13}C NMR (100 MHz) (1:1 rotamer mixture): δ 177.4, 177.3, 168.5, 167.8, 146.6, 146.3, 130.0, 129.8, 129.3, 129.0, 120.7, 119.5, 116.3, 116.0, 110.5, 110.4, 57.0, 56.9, 51.5, 45.3, 43.7, 43.1, 42.4, 41.2, 40.9, 40.6, 37.4, 29.6, 28.4, 28.2, 22.2, 21.9; IR (neat) 2935, 1696, 1633, 1432, 1175 cm^{-1}; HRMS (CI$^+$) m/z calculated for $C_{19}H_{23}N_3O_3$ ($M^{\bullet+}$), 341.1739; found, 341.1737.

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