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Synthesis and Profiling of a Diverse Collection of Azetidine-Based Scaffolds for the Development of CNS-Focused Lead-like Libraries

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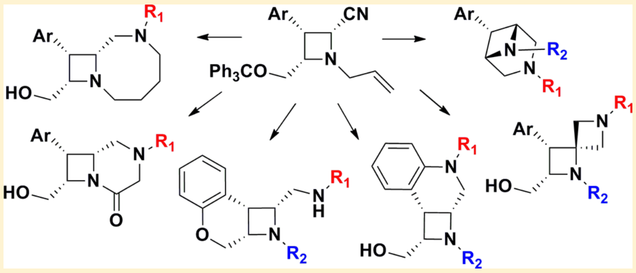
Ⓢ *Supporting Information*

ABSTRACT: The synthesis and diversification of a densely functionalized azetidine ring system to gain access to a wide variety of fused, bridged, and spirocyclic ring systems is described. The in vitro physicochemical and pharmacokinetic properties of representative library members are measured in order to evaluate the use of these scaffolds for the generation of lead-like molecules to be used in targeting the central nervous system. The solid-phase synthesis of a 1976-membered library of spirocyclic azetidines is also described.



■ INTRODUCTION

Diversity-oriented synthesis (DOS) has received considerable attention from both academic and industrial sectors over the past decade as a means to access new chemical space for probe and drug discovery.[1−3] Numerous DOS pathways have been reported which gain access to unique molecular frameworks;[4] however, a common perception associated with these compounds has been that they possess poor physicochemical properties.[5] While some DOS pathways have yielded compounds of high molecular weight and lipophilicity, the properties of DOS molecules are not inherently unfavorable to a drug discovery program. Simple descriptors such as MW, topological polar surface area (TPSA), LogP, LogD, rotatable bonds, and hydrogen bond donors/acceptors (HBD/HBA) can be readily calculated at the design stage, and filters may be applied to tailor the properties of prospective library members.[6] These parameters are especially important in the context of designing DOS libraries for CNS applications where the properties that facilitate blood-brain barrier (BBB) penetration are particularly stringent.[7] In this case, the collection and analysis of in vitro data such as solubility, protein binding, and permeability would be especially valuable in prioritizing synthetic pathways for full library production. Herein we describe the synthesis, physicochemical and pharmacokinetic (ADME) characterization, and profiling of several DOS scaffolds that have been optimized with these key CNS "drug-like" parameters in mind.[8]

Azetidine-based ring systems have had enormous application in medicinal chemistry in the form of β-lactams.[9] The use of the fully reduced form of this four-membered heterocycle in the context of drug discovery has been less common, however. This can be attributed in part to the apparent difficulty in accessing azetidines in their enantioenriched form.[10] Recently, Couty and co-workers demonstrated the convenient preparation of 2-cyanoazetidines from β-amino alcohols (Figure 1A).[11] We envisioned that expansion of this methodology would permit access to a number of highly functionalized azetidine-based scaffolds through the manipulation of the parent core system. In addition, having the ability to access all stereochemical permutations of each scaffold would provide the ability to study stereo/structure−activity relationships (SSAR)[12] in biological contexts.

In designing a template for library development, we chose to expand upon the previously described ephedrine-based scaffold.[11] This scaffold was especially compelling based on the observation that embedded within the backbone resides the phenethylamine structural motif (Figure 1B). This pharmacophoric element is common to a number of hormones, neurotransmitters, natural products, and drugs known to affect the central nervous system (CNS) and provides an excellent core scaffold which can be further derivatized. The incorporation of an aryl bromide and a pendant hydroxyl group will allow for downstream functional group pairing,[13] diversification, and immobilization onto solid support.[14]

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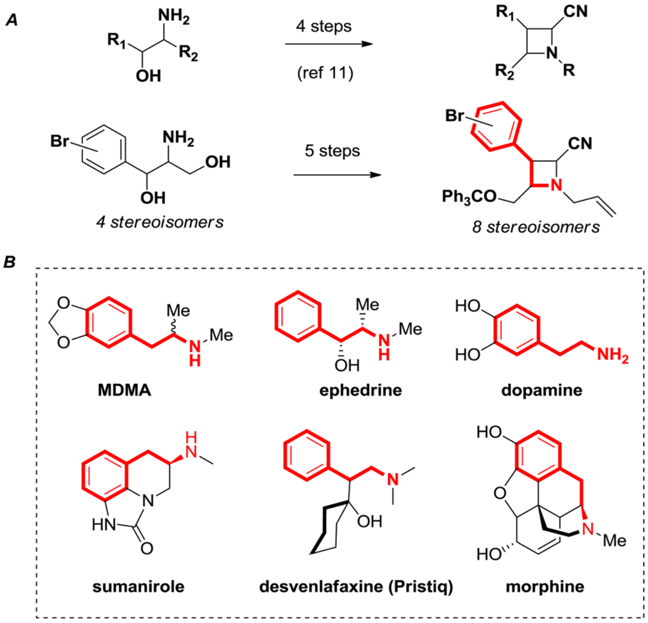


Figure 1. (A) Synthesis of 2-cyanoazetidines from *β*-amino alcohols and (B) representative CNS-active agents containing a phenylethylamine motif.

■ RESULTS AND DISCUSSION

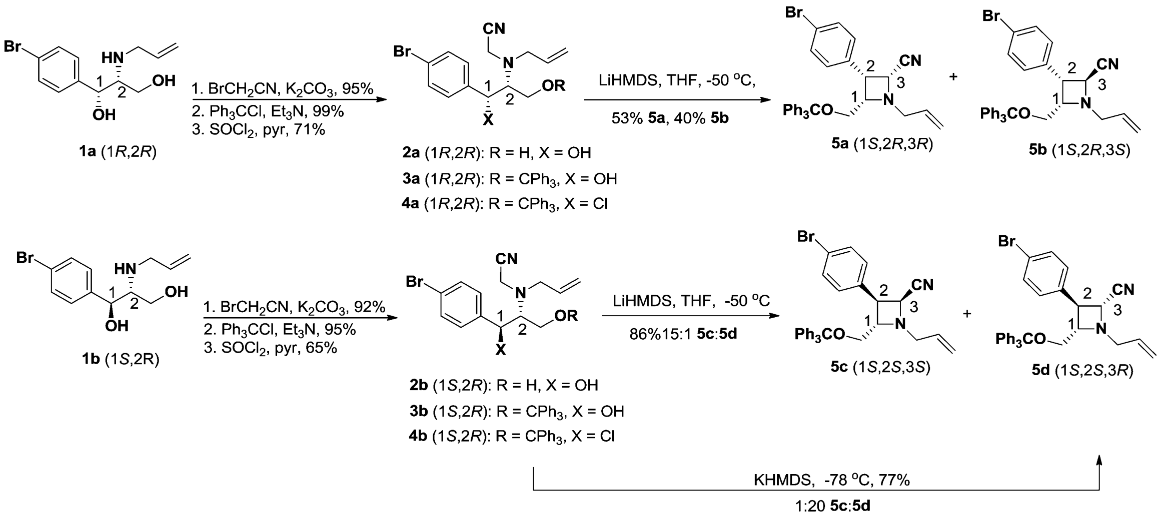
Synthesis of Azetidine-Based Scaffolds. The azetidine core systems required in the formation of the various library scaffolds were accessed from N-allyl amino diols **1a**[15] and **1b**[16] on multigram scale (20 g of **5a−d**) over four steps through adaptation of previously described conditions (Scheme 1).[11] The sequence included N-alkylation of a secondary amine with bromoacetonitrile (92−95%), protection of the primary alcohol as its trityl ether (95−99%), and formation of the benzylic chloride to arrive at compounds **4a** and **4b** (65−71%).[17] Treatment of chloride **4a** with lithium hexamethyldisilylazide (LiHMDS) at −50 °C provided a ca. 1.2:1 epimeric mixture of 2-cyanoazetidines **5a** and **5b**. The resulting products could be easily separated via flash chromatography on multigram scale to give 53% for **5a** and 40% for **5b**. The *anti*-configured linear template **4b** could selectively provide either **5c** or **5d** depending on the conditions employed. Treatment of **4b** with LiHMDS at −50 °C provided ca. 15:1 (**5c**/**5d**) ratio of product as a separable mixture. Alternatively, exposure of **4b** to KHMDS at −78 °C gave nearly exclusively **5d** in ca. 1:20 (**5c**/**5d**). This approach gave rise to multigram quantities of all eight stereoisomers of **5**.

Having developed a robust process for the synthesis of trisubstituted azetidines **5a−d**, we turned our attention to investigating key functional group pairing reactions for generating skeletal diversity. The sequence began with DIBAL reduction of the nitrile to the primary amine, which was immediately treated with *o*-nitrobenzenesulfonyl chloride to obtain **6a−d** in 71−91% yield over two steps (Scheme 2). This material could then be utilized to access three structurally unique molecular scaffolds. The first of these scaffolds (**8a** and **8d**) was inspired by recent work of Pinna and co-workers describing the synthesis and biological activity of several diazabicyclo [3.1.1] heptane ligands.[18] TFA-mediated trityl deprotection and subsequent mesylation of the pendant alcohol **7** gave an intermediate compound, which was heated in the presence of potassium carbonate to afford the *meso*-[3.1.1]-bridged bicyclic system in 91% yield for **8a** (from **7a**) and 86% yield for **8d** (from **7d**) over three steps.[19] Monoketopiperazine **10** could be readily accessed by removal of the allyl protecting group of **6a−d** followed by reaction of the resulting secondary amine functionalities with bromoacetyl chloride to afford **9a−d**. Removal of the trityl group provided **10a−d** in excellent yields.

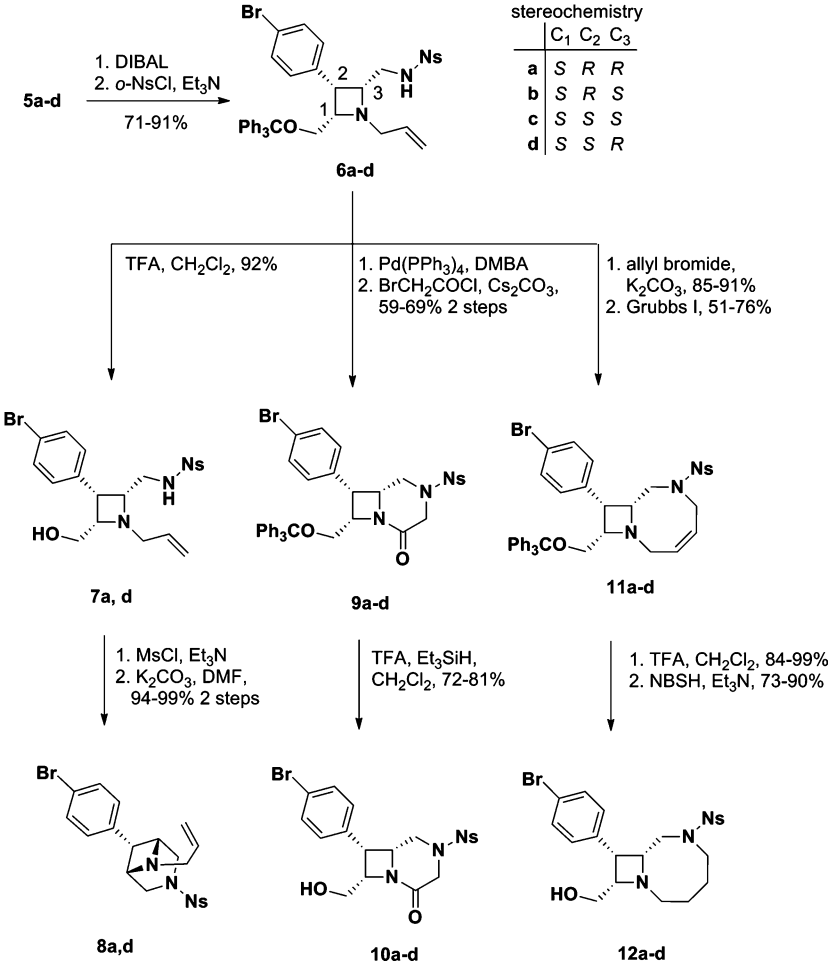
A third scaffold containing an azetidine-fused eight-membered ring could be readily derived from azetidine **6** through the use of ring-closing metathesis. The requisite material for this approach was obtained through the N-alkylation of **6a−d** with allyl bromide. This material was then treated with Grubbs first generation catalyst to effect the formation of the eight-membered ring system **11a−d** in 51−76% yield. Removal of the trityl protecting group and selective reduction of the olefin with *o*-nitrobenzenesulfonylhydrazide (NBSH)[20] yielded the final cores **12a−d** in 65−72% over two steps.[21]

Several papers highlighting the synthesis and physicochemical property analysis of spirocyclic oxetanes and spirocyclic azetidines for their potential use in drug discovery have recently been published by Carreira[22] and others.[23] In an attempt to

Scheme 1. Synthesis of Azetidine-Based Templates 5a−d



Scheme 2. Synthesis of Azetidine Scaffolds 8, 10, and 12



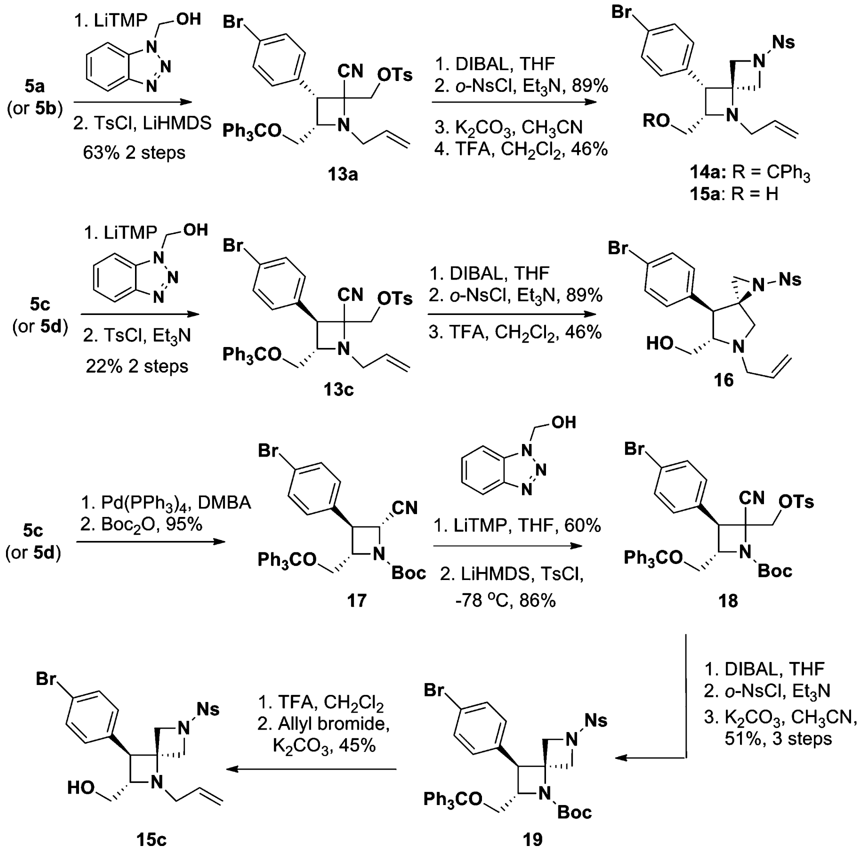
access compounds with similar property profiles, we turned our attention toward the formation of a novel spirocyclic azetidine scaffold derived from azetidine **5** (Scheme 3). The synthesis began with the metalation of aminonitrile **5a** (or **5b**) with lithium tetramethylpiperidide (LiTMP) at −78 °C in THF. The resulting anion could then be trapped with formaldehyde source benzotriazolylmethanol[24] to form a single compound. Treatment of this intermediate with tosyl chloride provided **13a**, which was then was reacted with a solution of DIBAL and immediately capped with *o*-nitrobenzenesulfonyl chloride. This material was treated with potassium carbonate to provide the spirocyclic intermediate **14** in 67% yield.[25] Removal of the trityl group with trifluoroacetic acid completed the synthesis of **15a**.[26]

Access to the *trans*-configured spirocyclic system (**15c**) was envisioned to be obtained through the same sequence of reactions that was used in the synthesis of **15a** (Scheme 3). Thus, alkylation of **5c** (or **5d**) furnished approximately a 1:1 mixture of α- and β-alcohols. Tosylation of the mixture provided **13c** in reasonable isolated yield. Treatment of **13c** with DIBAL appeared to immediately provide a cyclized product based on the observed loss of the pendant tosylate. Capping the resulting amine with *o*-nitrobenzenesulfonyl chloride and unmasking the primary alcohol with trifluoroacetic acid afforded a white solid, which upon recrystallization yielded X-ray quality crystals. Surprisingly, upon examination of the structural data, a [3.3.0] spirocycle was not observed but rather a [4.2.0] system (**16**).[25] Ring expansions of azetidine systems have been previously described to give substituted pyrroles through an intermediate 1-azoniabicyclo [2.1.0] pentane system;[27] however, to the best of our knowledge, this is the first example of a ring expansion followed by a spirocyclization to form a [4.2.0] ring system.

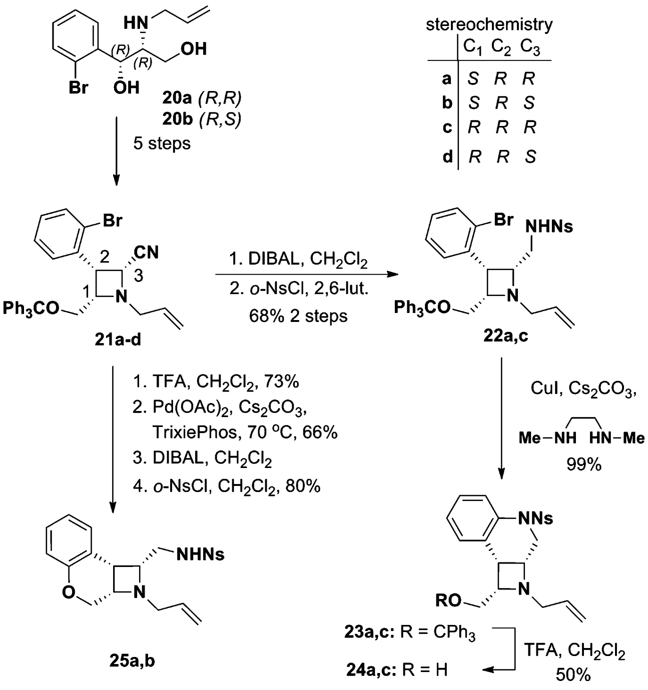
In an attempt to circumvent this rearrangement and provide the complementary *trans*-spirocyclic system **15c**, the nucleophilicity of the azetidine nitrogen was attenuated with a Boc protecting group. Access to this compound was achieved through the deprotection of the allyl group followed by treatment with Boc_2O. Further manipulation included alkylation and tosylation of **17** to provide compound **18**, which then underwent nitrile reduction with DIBAL and nosylation to form the precyclized product. Treatment of this substrate with potassium carbonate in acetonitrile afforded the *trans*-azetidine ring system **19** in 51% yield over three steps. Subsequent removal of the Boc and trityl groups followed by N-alkylation with allyl bromide provided **15c** in 45% yield.

Conversion of *o*-bromo amino diols **20a,b** to the corresponding *o*-bromonitrile azetidines **21a−d** allowed for facile access to a number of fused ring scaffolds (Scheme 4). The first compound in this series takes advantage of an intramolecular Buchwald/Hartwig cross-coupling reaction to access a tetrahydroquinoline core system.[28] DIBAL reduction of the nitrile group followed by nosylation of the resulting amine yielded **22a** and **22c** in 68 and 79% yield over two steps.

Scheme 3. Synthesis of Spirocyclic Azetidine Scaffold 15



Scheme 4. Synthesis of Scaffolds 24 and 25



Treatment of each of these intermediates with copper(I) iodide, cesium carbonate, and dimethylethane 1,2-diamine in toluene gave rise to the tricyclic system **23** in quantitative yield. Removal of the trityl protecting group provided the desired scaffolds **24a** and **24c**. Alternatively, removal of the trityl group in compounds **21a,b** allows for the pairing of the hydroxyl functionality through an O-arylation on the opposite side of the azetidine ring system.[29] Treating the resulting deprotected product with palladium acetate and cesium carbonate in the presence of a phosphine ligand gave the desired dihydrobenzopyran in 66 and 74% yield. Finally, reduction of the nitrile using DIBAL and nosyl protection afforded scaffolds **25a** and **25b**.

In Silico Analysis and In Vitro Compound Profiling. As our overall goal was to use the azetidine-based scaffolds to produce a diverse collection of compounds "pre-optimized" for CNS physicochemical and ADME requirements, we set out to validate our computational approach by collecting in vitro data on a representative set of library compounds. Early estimates of ADME properties can be useful to help guide the decision making process in how to populate a library collection with compounds having the highest likelihood of success in drug development. This property evaluation is critical when targeting the CNS due to penetration of the BBB (blood-brain barrier) which has been noted to have a narrow window of physicochemical boundaries for CNS-accessible chemical space.[30] A set of analogues representing various chemotypes (e.g., sulfonamide, amide, amine) was prepared to represent potential library members obtained from a full production (**26**–**32**, Figure 2). Full library production would focus only on those scaffolds which satisfied our CNS lead-like criteria and possessed no obvious metabolic or chemical instability.

In silico analysis of compounds **26**–**32** for MW, TPSA, HBD, cLogP, cLogD, and pK_a confirms that most compounds are well within the range of preferred properties for CNS compounds (Table 1) and compare well to marketed CNS drugs.[31] In addition, computed models of brain partitioning

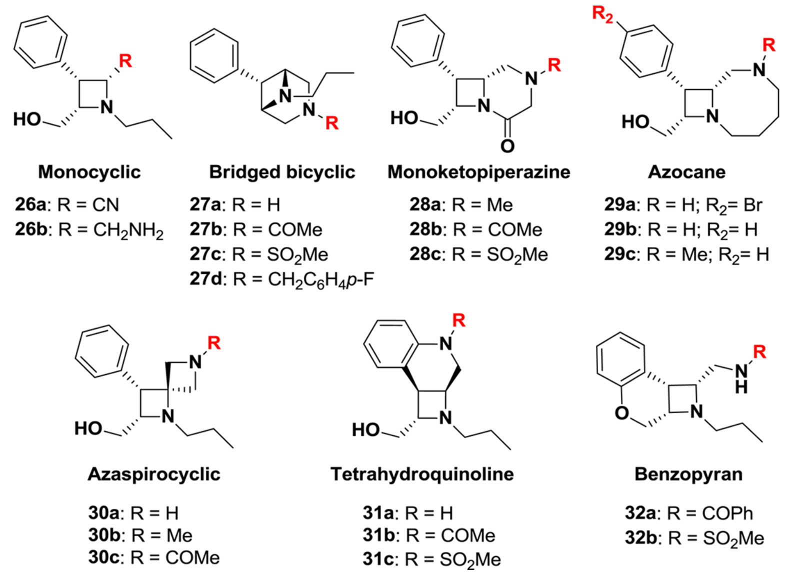


Figure 2. Representative library members synthesized for in vitro analysis.

Table 1. Calculated Physicochemical Properties[a]

cmpd	MW	TPSA	HBD	cLogP	cLogD	pK_a	Log BB	BBB cat	P-gp cat	CNS MPO
26a	230	47	1	2.26	0.93	3.9	0.31	+	no	5.83
26b	234	50	2	1.28	−0.41	9.5	0.09	+	no	4.75
27a	258	24	1	2.33	0.91	8.7	0.67	+	no	4.68
27b	258	24	0	2.33	0.91	7.1	0.67	+	no	5.20
27c	294	41	0	2.29	0.89	6.8	0.25	+	no	6.00
27d	324	7	0	4.05	3.90	7.9	0.82	+	no	3.32
28a	246	44	1	0.66	−0.30	5.4	−0.16	+	no	5.83
28b	274	61	1	0.59	0.59	−1.7	−0.23	−	no	5.83
28c	310	78	1	0.98	0.98	−2.0	−0.40	−	no	5.83
29a	325	36	2	2.28	0.57	9.8	0.34	+	no	4.40
29b	246	36	2	1.56	0.03	9.9	0.19	+	no	4.35
29c	260	27	1	1.87	0.79	9.0	0.40	+	no	4.68
30a	246	36	2	1.43	0.38	9.9	0.20	+	no	4.35
30b	260	27	1	1.42	1.06	9.4	0.37	+	no	4.48
30c	288	44	1	1.44	0.47	7.6	0.27	−	no	5.83
31a	232	36	2	1.68	0.81	8.8	0.24	+	no	4.90
31b	274	44	1	1.62	0.26	7.9	0.31	−	no	5.83
31c	310	61	1	1.76	0.16	7.3	0.50	+	no	5.83
32a	336	42	1	3.68	2.67	8.3	0.49	+	yes	5.55
32b	310	59	1	2.32	0.85	7.2	0.03	+	no	5.83

[a] Preferred physicochemical property ranges for increasing the potential for BBB penetration: MW <450, TPSA <70 Å, HBD 0−1, cLogP 2−4, cLogD 2−4.[31]

(log brain/blood, BBB category) and potential P-glycoprotein (P-gp) substrate status were utilized to assess the probability of reasonable brain exposures. The CNS multiparameter optimization (MPO) algorithm developed by Pfizer was also applied, and all but one compound (**21d**) displayed a high desirability score (≥4, using a scale of 0−6).[32] Of note, while maintaining properties in the desired CNS range and containing a common core structural motif, the azetidine-based compounds exhibit a high degree of structural diversity compared to existing CNS drugs as measured by Tanimoto coefficient (Tc) with a mean similarity less than 0.15 and a maximum similarity less than 0.26 (Figure 3).[33]

As shown in Table 2, several properties were measured in vitro for compounds **26**−**32**, including solubility, protein binding, stability, and permeability. Most compounds tested were found to be highly soluble (>400 μM) in water and phosphate buffered saline and displayed low to moderate protein binding in both mouse and human sera. This high proportion of free or unbound fraction of compound is an important attribute when considering diffusion into the CNS compartment.[34] Notably, almost all molecules exhibited excellent stability toward human and mouse plasma, liver microsomes, and hepatocytes, indicative of good pharmacokinetic properties (e.g., $T_{1/2}$).

The permeability of compounds **26**−**32** was evaluated using two distinct model systems: the BBB parallel artificial membrane permeability assay (BBB-PAMPA)[35] and Caco-2 cell lines. The BBB-PAMPA assay is used as a high-throughput method to predict passive BBB penetration of potential CNS drugs. Using this assay, most compounds displayed high

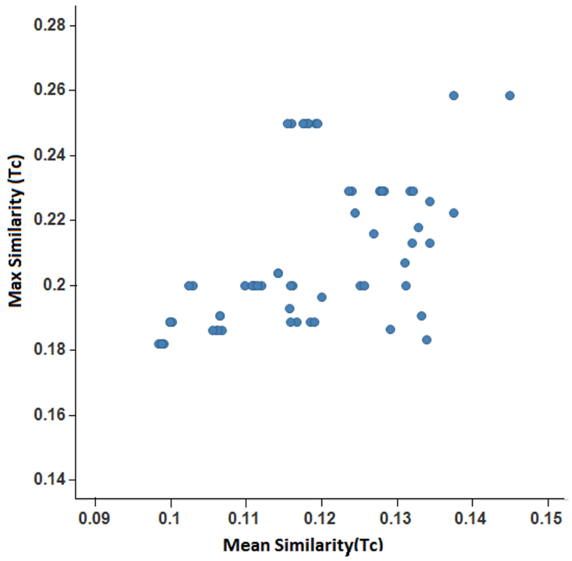


Figure 3. Multifusion similarity (MFS) map, ECFP_4 fingerprints (test set = azetidine scaffolds and derivatives ($n = 64$), reference set = CNS drugs ($n = 70$).

permeability values ($P_e \geq 10.0 \times 10^{-6}$ cm·s^{-1}) suggestive of effective diffusion across the endothelial cells in CNS blood vessels. Next, the permeability of each compound was evaluated using the cell-based Caco-2 system as a surrogate for permeability across the gut endothelium. Bidirectional analysis was conducted to evaluate the propensity of these compounds to act as substrates for efflux mechanisms expressed in Caco-2 (e.g., P-gp efflux transporter) as well as a measure of passive diffusion. Consistent with our results in the BBB-PAMPA assay, all compounds displayed high rates of permeation across the Caco-2 monolayer and displayed no directional bias indicative of active efflux.[36,37] The data suggest that most of these compounds should be highly permeable at the endothelial systems present in the gut (oral absorption) and at the blood-brain barrier.

Representative Solid-Phase Library Synthesis. The azetidine-based scaffolds described above have served as starting points for the production of over 20 000 CNS-focused compounds to date in our lab. Much like compounds **26–32**, the resulting library members retain the desired physicochemical properties for CNS-focused compounds (vide infra). As an example, we highlight below the synthesis of a 1976-membered library of spirocyclic azetidine compounds.

Starting from spirocyclic scaffold *des*-Br-**15** (Scheme 3), a virtual library was constructed using a master list of reagents, which included sulfonyl chlorides, isocyanates, acids, and aldehydes.[38] All possible building block combinations at R_1 (nosyl amine) and R_2 (allyl amine) were employed to yield a total of 9152 compounds per scaffold. The following CNS-focused property filters were then applied to yield a total of 3089 compounds: MW ≤450, ALogP −1 to 5, H-bond acceptors <7, H-bond donors ≤3, rotatable bonds ≤8, and TPSA ≤90. Using chemical similarity principles, maximizing diversity but retaining near neighbors for built-in SAR,[6] this set was further narrowed down to 494 compounds per stereoisomer (or 1976 compounds total). The same set of reagents was used for all four stereoisomers, thereby maintaining the ability to generate SSAR for each building block combination.

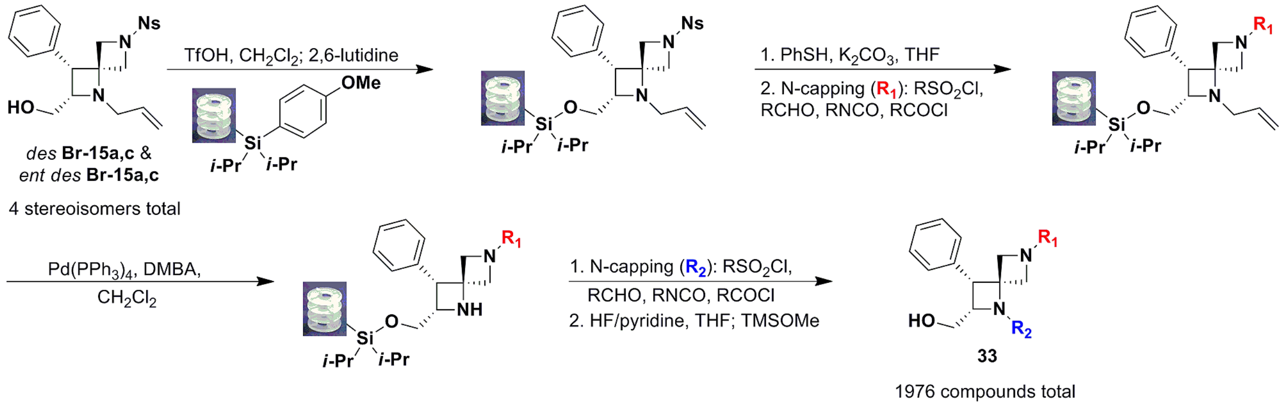
As shown in Scheme 5, all four stereoisomers of the spirocyclic scaffold were loaded onto SynPhase L-series Lanterns via activation of the silicon-fuctionalized Lanterns[14] with TfOH. Lanterns were equipped with radio frequency transponders to enable tracking and sorting of library members.

Table 2. In Vitro Compound Profiling Data[a]

	solubility (μM)		protein binding (% bound)		plasma stability (% remaining)		microsomal stability (% remaining)		hepatocytes (% remaining)			Caco-2	
cmpd	PBS	H_2O	mouse	human	mouse	human	mouse	human	mouse	human	BBB-PAMPA	A-B	B-A
26a	402	>500	65	65	110	109	62	88	59	54		67	49
26b	>500	>500	19	7	100	92	68	73	103	103	83	16	8
27a	>500	>500	35	49	103	102	79	94			4	30	22
27b	476	483	13	23	94	83	93	93	94	104	15	54	56
27c	470	490	39	31	102	113	72	86	67	72	31	66	54
27d	335	346	98	98	90	71	42	55			111	14	7
28a	>500				116	99	104	112				43	31
28b	>500		−9.2	−1.0	110	79	109	96				12	17
28c	>500		−2.3	−4.6	106	78	100	104				17	20
29a	485	388	46	24	94	97	98	96	99	104	14	14	32
29b	>500	491	9	8	94	99	89	86			6	2	8
29c	494	>500	5	1	78	82	97	96			9	14	21
30a	>500				108	106	93	95				3	12
30b	>500		−6.0	28	106	86	98	99				33	56
30c	>500		32	37	97	93	89	94				29	35
31a	>500	495	22	10	108	97	94	85			31	43	29
31b	489	496	20	18	98	106	64	88	71	32	14	48	51
31c	478	>500	50	45	107	101	34	69			35	56	64
32a	43		91	95	102	94	0	0				59	52
32b	453		37	37	105	97	63	73				66	57

[a] PBS and H_2O solubilities are based on a 24 h time point using dry powder; plasma protein binding is measured by rapid equilibrium dialysis (incubation at 37 °C for 5 h); plasma stability represents the % parent remaining at 5 h; microsome stability represents the % parent remaining at 1 h; hepatocyte stability represents the % parent remaining at 2 h; permeability is measured bidirectionally in the Caco-2 cell line, unit 10^{-6} cm·s^{-1}

Scheme 5. Solid-Phase Library Synthesis on SynPhase Lanterns



Following removal of the nosyl group, the first diversity site (R_1), an amine, was reacted with a total of 55 building blocks including isocyanates, sulfonyl chlorides, acids, and aldehydes.[39] The second diversity site (R_2) was then revealed via removal of the allyl group upon treatment with $Pd(PPh_3)_4$ in the presence of excess 1,3-dimethyl barbituric acid. The second azetidine nitrogen was capped with 41 building blocks including isocyanates, sulfonyl chlorides, acids, and aldehydes. This was followed by cleavage from the Lantern with HF/pyridine in THF to afford a total of 1976 products (**33**) with an average yield of 16 μmol (~8 mg).

All library products were analyzed by ultraperformance liquid chromatography, and compound purity was assessed by UV detection at 210 nm. The average purity of the library was 70%.[40] In general, most of the building block classes performed well with the exception of aldehydes in the first capping (R_1). Interestingly, the compounds were of high purity after the initial reductive alkylation; however, after carrying the tertiary amines through allyl deprotection and subsequent capping, low purities were observed.

In silico analysis of the spirocyclic azetidine library confirms that the physicochemical properties of the library members fall within the preferred range for CNS compounds (Table 3).[31]

Table 3. Calculated Physicochemical Properties

property	mean value	range
molecular weight	392	314−450
ALogP	2.06	−0.77−4.99
LogD	1.28	−0.93−4.65
TPSA	70.0	26.7−89.5
H-bond donors	1.15	1−2
H-bond acceptors	3.96	3−6
rotatable bonds	5.37	3−8
Fsp^3	0.47	0.25−0.72

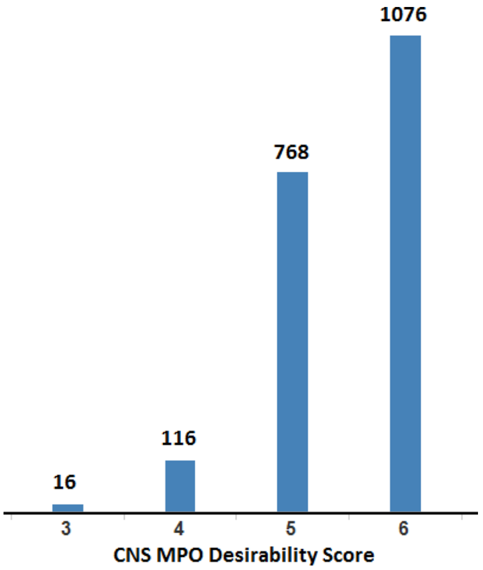


Figure 4. CNS MPO score for the spirocyclic azetidine library members (n = 1976) plotted from low to high CNS MPO score along the x-axis.

Moreover, application of the CNS MPO algorithm[34] showed that the majority of compounds displayed a desirability score ≥4 (Figure 4). In addition, much like other DOS compounds,[41] the structural complexity of the spirocyclic azetidine library is closer to that of natural products than typical commercial compounds as measured by the fraction of sp^3 centers (Fsp^3).[4c,42]

■ CONCLUSIONS

In summary, we have reported the synthesis of a collection of skeletally and stereochemically diverse azetidine-based scaffolds, including a focused set of 20 representative compounds and a 1976-membered library of spirocyclic azetidines. Analysis of the library members in silico indicated the compounds demonstrate ideal physicochemical properties for CNS application, and further analysis of a subset of compounds in vitro showed a very good ADME profile.

The importance of populating chemical libraries with preoptimized structures cannot be overstated in the successful and efficient growth of new chemical entities in drug and probe development.[43] By utilizing a data-driven approach for scaffold selection and focusing library production into this optimized chemical space, we hope to increase efficiency in downstream multiparametric optimization activities. These considerations are particularly acute when targeting the CNS due to the stringent physicochemical requirements for successful blood-brain barrier (BBB) penetration of small molecules. These results highlight the fact that through diligent examination of the scaffold properties one can apply a DOS approach to create a collection of structurally diverse compounds with good physicochemical properties for use in screening and follow up biological evaluation.

■ EXPERIMENTAL SECTION

General Methods. All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under vacuum (~0.5 mmHg) and purged with N_2 prior to use. All reagents and solvents were purchased from commercial vendors and used as received or synthesized according to the footnoted references. ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz and/or 500 MHz spectrometers. All chemical shifts are reported in parts per million (δ) referenced to residual nondeuterated solvent.[44] Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz; integration). Unless otherwise indicated, NMR data were collected at 25 °C. IR spectra were obtained with an FTIR spectrometer and are reported in cm^{-1}. Melting point experiments were performed on a Büchi M-560 melting point apparatus. Flash chromatography was performed using 40−60 μm silica gel (60 Å mesh) with the indicated solvent.

2-(Allyl((1*R*,2*R*)-1-(4-bromophenyl)-1,3-dihydroxypropan-2-yl)amino)acetonitrile 2a. To a solution of amino diol **1a**[15] (52.9 g, 185 mmol) in acetonitrile (1849 mL) was added potassium carbonate (38.3 g, 277 mmol) and 2-bromoacetonitrile (38.7 mL, 555 mmol). The resulting heterogeneous solution was heated to 85 °C and stirred for 3 h. Once the reaction was complete, the mixture was concentrated under reduced pressure and the residue was taken up in water and diethyl ether. The aqueous layer was extracted two additional times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel to provide pure product **2a** (59.5 g, 99%) as an oil: $[\alpha]_D^{20}$ −43.3 (*c* 1.45, $CHCl_3$); IR ν_{max} (film) 3419, 3080, 2912, 1642, 1592, 1486, 1419, 1070, 1010; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.80 (tt, *J* = 10.4, 6.7 Hz, 1H), 5.36 (d, *J* = 17.1 Hz, 1H), 5.30 (d, *J* = 10.1 Hz, 1H), 4.66 (d, *J* = 9.2 Hz, 1H), 3.91 (d, *J* = 17.3 Hz, 1H), 3.74 (d, *J* = 17.4 Hz, 1H), 3.72−3.66 (m, 1H), 3.61 (dd, *J* = 13.7, 5.8 Hz, 1H), 3.52 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.44 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.91−2.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 133.8, 131.6, 128.6, 122.0, 120.1, 116.9, 70.5, 69.0, 58.2, 54.7, 39.1; HRMS (ESI) calcd for $C_{14}H_{18}BrN_2O_2$ $[M + H]^+$ 325.0552, found 325.0551.

2-(Allyl((1*S*,2*S*)-1-(4-bromophenyl)-1,3-dihydroxypropan-2-yl)amino)acetonitrile *ent*-2a. Following the protocol above, 62 g of amino diol *ent*-**1a**[16] afforded 67 g (95%) of tertiary amine *ent*-**2a**: $[\alpha]_D^{20}$ +39.3 (*c* 0.99, $CHCl_3$).

2-(Allyl((1*R*,2*R*)-1-(4-bromophenyl)-1-hydroxy-3-(trityloxy) propan-2-yl)amino)acetonitrile 3a. To a solution of tertiary amine **2a** (59.5 g, 183 mmol) in CH_2Cl_2 (1830 mL) was added triethylamine (77 mL, 549 mmol), and the entire solution was cooled to 0 °C. Trityl chloride (77 g, 274 mmol) was then added, and the solution was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was quenched with aqueous saturated NH_4Cl solution, and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel to provide pure product **3a** (103 g, 99%) as a pale yellow oil: $[\alpha]_D^{20}$ −10.1 (*c* 1.94, $CHCl_3$); IR ν_{max} (film) 3060, 3022, 2878, 1594, 1489, 1448, 1071, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.22 (s, 15H), 7.08 (d, *J* = 8.4 Hz, 2H), 5.80−5.61 (m, 1H), 5.22 (d, *J* = 7.6 Hz, 1H), 5.20 (d, *J* = 14.2 Hz, 1H), 4.35 (d, *J* = 9.3 Hz, 1H), 3.85 (s, 1H), 3.65 (q, *J* = 17.0 Hz, 2H), 3.43 (dd, *J* = 13.9, 5.4 Hz 1H), 3.24 (dd, *J* = 10.9, 7.2 Hz, 1H), 3.16 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.09−2.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 139.9, 134.0, 131.5, 128.9, 128.4, 127.9, 127.2, 121.9, 119.8, 116.9, 87.8, 70.7, 67.8, 59.6, 54.0, 39.7; HRMS (ESI) calcd for $C_{33}H_{32}BrN_2O_2$ $[M + H]^+$ 567.1647, found 567.1646.

2-(Allyl((1*S*,2*S*)-1-(4-bromophenyl)-1-hydroxy-3-(trityloxy)-propan-2-yl)amino)acetonitrile *ent*-3a. Following the protocol above, 67 g of *ent*-**2a** afforded 116 g (99%) of trityl protected product *ent*-**3a**: $[\alpha]_D^{20}$ +4.6 (*c* 1.62, $CHCl_3$).

2-(Allyl((1*R*,2*R*)-1-(4-bromophenyl)-1-chloro-3-(trityloxy)-propan-2-yl)amino)acetonitrile 4a. To a solution of pyridine (43.2 mL, 536 mmol) in CH_2Cl_2 (950 mL) was added thionyl chloride (15.64 mL, 214 mmol) at room temperature. The above solution was then cooled to 0 °C and a solution of benzyl alcohol **3a** (60.8 g, 107 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 10 min and stirred for an additional 15 min at 0 °C (Note: If the solution is warmed or stirred for longer than 15 min, the product decomposes). The mixture was neutralized by the addition of a saturated aqueous solution of sodium bicarbonate and the aqueous layer extracted two additional times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel to provide pure product **4a** (44.6 g, 71%) as a white foam: $[\alpha]_D^{20}$ −47.9 (*c* 1.22, $CHCl_3$); IR ν_{max} (film) 3057, 3022, 2933, 2885, 1593, 1489, 1448, 1072; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 10.2 Hz, 2H), 7.39−7.23 (m, 15H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.72−5.56 (m, 1H), 5.26−5.10 (m, 3H), 3.68 (d, *J* = 17.4 Hz, 1H), 3.59 (d, *J* = 17.4 Hz, 1H), 3.50−3.35 (m, 2H), 3.32−3.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 138.2, 134.6, 131.6, 129.3, 128.5, 127.9, 127.2, 122.3, 118.9, 117.2, 87.5, 66.6, 62.8, 61.5, 55.1, 40.1; HRMS (ESI) calcd for $C_{33}H_{31}BrClN_2O$ $[M + H]^+$ 585.1308, found 585.1342. Anal. calcd/found for $C_{33}H_{30}BrClN_2O$: C, 67.64%/67.76%; H, 5.16%/5.44%; N, 4.78%/4.53%; Cl, 6.05%/6.43%; Br, 13.64%/12.13%.

2-(Allyl((1*S*,2*S*)-1-(4-bromophenyl)-1-chloro-3-(trityloxy)-propan-2-yl)amino)acetonitrile *ent*-4. Following the protocol above, 116 g of benzyl alcohol *ent*-**3a** afforded 69 g (58%) of chloride *ent*-**4a**: $[\alpha]_D^{20}$ +54.5 (*c* 0.96, $CHCl_3$).

2-(Allyl((1*S*,2*R*)-1-(4-bromophenyl)-1,3-dihydroxypropan-2-yl)amino)acetonitrile 2b. Following the protocol above, 50 g of amino diol **1b**[16] afforded 54.7 g (96%) of tertiary amine **2b**: $[\alpha]_D^{20}$ +2.1 (*c* 1.72, $CHCl_3$); IR ν_{max} (film) 3393, 2889, 1485, 1419, 1068, 1023, 1008; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 5.70 (ddt, *J* = 16.7, 10.0, 6.5 Hz, 1H), 5.33 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.24 (d, *J* = 10.1 Hz, 1H), 5.11 (s, 1H), 3.86−3.72 (m, 3H), 3.68 (d, *J* = 11.2 Hz, 1H), 3.49 (dd, *J* = 13.9, 6.4 Hz, 1H), 3.40 (dd, *J* = 13.9, 6.6 Hz, 1H), 3.01 (br s, 1H), 2.84 (dt, *J* = 5.8, 3.9 Hz, 1H), 2.38 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 133.8, 131.4, 127.3, 121.3, 119.5, 116.8, 71.9, 67.0, 57.9, 54.7, 38.8; HRMS (ESI) calcd for $C_{14}H_{18}BrN_2O_2$ $[M + H]^+$ 325.0552, found 325.0551.

2-(Allyl((1*R*,2*S*)-1-(4-bromophenyl)-1,3-dihydroxypropan-2-yl)amino)acetonitrile *ent*-2b. Following the protocol above, 50 g of amino diol *ent*-**1b**[16] afforded 55.7 g (98%) of tertiary amine *ent*-**2b**: $[\alpha]_D^{20}$ −2.7 (*c* 1.81, $CHCl_3$).

2-(Allyl((1*S*,2*R*)-1-(4-bromophenyl)-1-hydroxy-3-(trityloxy)-propan-2-yl)amino)acetonitrile 3b. Following the protocol above, 54 g of diol **2b** afforded 91 g (97%) of trityl protected product **3b**: $[\alpha]_D^{20}$ +7.2 (*c* 1.9, $CHCl_3$); IR ν_{max} (film) 3471, 3057, 1733, 1487, 1447, 1264; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.31 (m, 7H), 7.30−7.23 (m, 11H), 7.07 (d, *J* = 8.3 Hz, 2H), 5.71−5.54 (m, 1H), 5.23 (d, *J* = 17.6 Hz, 1H), 5.19 (d, *J* = 10.2 Hz, 1H), 4.96 (d, *J* = 4.0 Hz, 1H), 3.49 (q, *J* = 17.5 Hz, 2H), 3.36 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.30 (dd, *J* = 10.5, 5.4 Hz, 1H), 3.25−3.17 (m, 2H), 3.10 (q, *J* = 4.8 Hz, 1H), 3.03 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 143.1, 140.7, 134.2, 131.2, 128.5, 128.1, 127.9, 127.9, 127.6, 127.2, 126.6, 121.2, 119.3, 116.7, 87.6, 72.3, 65.9, 60.2, 54.8, 39.6; HRMS (ESI) calcd for $C_{33}H_{31}BrN_2NaO_2$ $[M + Na]^+$ 589.1467, found 589.1453.

2-(Allyl((1*R*,2*S*)-1-(4-bromophenyl)-1-hydroxy-3-(trityloxy)-propan-2-yl)amino)acetonitrile *ent*-3b. Following the protocol above, 55.7 g of diol *ent*-**2b** afforded 95 g (98%) of trityl protected product *ent*-**3b**: $[\alpha]_D^{20}$ −7.8 (*c* 1.5, $CHCl_3$).

2-(Allyl((1*S*,2*R*)-1-(4-bromophenyl)-1-chloro-3-(trityloxy)-propan-2-yl)amino)acetonitrile 4b. Following the protocol above, 91 g of benzyl alcohol **3b** afforded 62 g (66%) of chloride **4b**: $[\alpha]_D^{20}$ +27.7 (*c* 3.06, $CHCl_3$); IR ν_{max} (film) 3057, 2936, 2885, 1592, 1488, 1448, 1447; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.3 Hz, 5H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 5H), 7.26 (d, *J* = 7.2 Hz, 3H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.52−5.21 (m, 1H), 5.09−4.92 (m, 3H), 3.59−3.49 (m, 2H), 3.49−3.42 (m, 1H), 3.40 (s, 1H), 3.02 (dd, *J* = 14.1, 5.2 Hz, 1H), 2.89 (dd, *J* = 14.1, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.3, 137.9, 134.2, 131.4, 129.4, 128.6, 127.9, 127.9, 127.3, 122.2, 118.9, 116.9, 87.6, 66.9, 60.9, 60.4, 54.0, 39.9. Anal. calcd/found for C$_{33}$H$_{30}$BrClN$_2$O: C, 67.64%/67.57%; H, 5.16%/5.30%; N, 4.78%/4.70%; Cl, 6.05%/6.30%; Br, 13.64%/12.63%.

2-(Allyl((1*R*,2*S*)-1-(4-bromophenyl)-1-chloro-3-(trityloxy)propan-2-yl)amino)acetonitrile *ent*-3b. Following the protocol above, 95 g of benzyl alcohol *ent*-**3b** afforded 60.5 g (62%) of chloride *ent*-**4b**: $[\alpha]_D^{20}$ −36.8 (*c* 2.43, CHCl$_3$).

(2*S*,3*R*,4*R*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine 5a and (2*S*,3*R*,4*S*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine 5b. A solution of benzyl chloride **4a** (44.5 g, 76 mmol) in THF (1.1 L) was cooled to −50 °C. Lithium bis(trimethylsilyl)amide (1 M solution in THF, 114 mL, 114 mmol) was added dropwise over 15 min and the mixture was stirred for an additional hour at −50 °C. The reaction mixture was quenched with aqueous saturated NH$_4$Cl solution and the aqueous layer was extracted two times with CH$_2$Cl$_2$. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel to provide pure products **5a** (16.8 g, 40.3%) and **5b** (21.9 g, 53%) as a white solid and a white foam (93% combined yield).

(2*S*,3*R*,4*R*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine 5a. $[\alpha]_D^{20}$ = +29.6 (*c* 1.92, CHCl$_3$); IR $\nu_{\max}$ (film) 3057, 2866, 1488, 1448, 1264; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.23−7.14 (m, 9H), 7.14−7.11 (m, 6H), 5.74 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.22 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 4.08 (d, *J* = 7.9 Hz, 1H), 3.80 (t, *J* = 7.8 Hz, 1H), 3.67 (td, *J* = 7.9, 5.3 Hz, 1H), 3.31 (dd, *J* = 12.9, 6.2 Hz, 1H), 3.12 (dd, *J* = 12.9, 7.1 Hz, 1H), 3.04 (dd, *J* = 9.5, 5.3 Hz, 1H), 2.80 (dd, *J* = 9.4, 8.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.4, 133.3, 132.8, 131.4, 131.3, 128.3, 127.7, 126.9, 121.9, 119.6, 117.3, 86.4, 66.2, 61.2, 60.7, 54.4, 42.4; HRMS (ESI) calcd for C$_{33}$H$_{30}$BrN$_2$O [M + H]$^+$ 549.1542, found 549.1545.

(2*R*,3*S*,4*S*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine *ent*-5a. Following the protocol above, 47 g of chloride *ent*-**4a** afforded 17.6 g (40%) of *ent*-**5a**: $[\alpha]_D^{20}$ −50.0 (*c* 2.02, CHCl$_3$).

(2*S*,3*R*,4*S*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine 5b. $[\alpha]_D^{20}$ = +12.7 (*c* 1.37, CHCl$_3$); mp 129.5−133.5 °C IR $\nu_{\max}$ (film) 3057, 2862, 1488, 1448, 1264; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.22−7.09 (m, 17H), 5.71−5.53 (m, 1H), 5.24 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 4.18 (d, *J* = 2.2 Hz, 1H), 4.03 (dd, *J* = 13.0, 7.9 Hz, 1H), 3.79 (dd, *J* = 7.8, 2.3 Hz, 1H), 3.31 (qd, *J* = 13.7, 6.2 Hz, 2H), 2.99 (dd, *J* = 9.5, 5.1 Hz, 1H), 2.64 (t, *J* = 9.15 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.4, 135.1, 132.9, 131.5, 130.1, 128.3, 127.7, 126.9, 121.6, 118.9, 116.9, 86.5, 66.5, 61.5, 55.8, 55.6, 43.6; HRMS (ESI) calcd for C$_{33}$H$_{30}$BrN$_2$O [M + H]$^+$ 549.1542, found 549.1542.

(2*R*,3*S*,4*R*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine *ent*-5b. Following the protocol above, 47 g of chloride *ent*-**4b** afforded 20.3 g (46%) of *ent*-**5b**: $[\alpha]_D^{20}$ −11.3 (*c* 2.48, CHCl$_3$).

(2*S*,3*S*,4*S*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine 5c. A solution of benzyl chloride **4b** (62 g, 106 mmol) in THF (1058 mL) was cooled to −78 °C. Lithium bis(trimethylsilyl)amide (1 M solution in THF, 127 mL, 127 mmol) was added dropwise over 15 min and the mixture was stirred for an additional hour at −50 °C. The reaction mixture was quenched with aqueous saturated NH$_4$Cl solution and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel to provide **5c** (21.9 g, 53%) as a light orange foam: $[\alpha]_D^{20}$ +13.9 (*c* 1.62, CHCl$_3$); IR $\nu_{\max}$ (film) 3056, 3031, 2913, 2862, 2819, 1734, 1643, 1595, 1489, 1447; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 6H), 7.33−7.24 (m, 9H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.81−5.69 (m, 1H), 5.33 (d, *J* = 16.4 Hz, 1H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 3.85−3.75 (m, 2H), 3.52 (dd, *J* = 13.8, 5.0 Hz, 1H), 3.37−3.29 (m, 2H), 3.25 (dd, *J* = 10.2, 4.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.6, 134.5, 133.0, 131.7, 129.7, 128.5, 127.8, 127.1, 121.8, 118.9, 115.6, 86.9, 68.2, 65.7, 57.1, 55.4, 41.9; HRMS (ESI) calcd for C$_{33}$H$_{30}$BrN$_2$O [M + H]$^+$ 549.1541, found 549.1553.

(2*R*,3*R*,4*R*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine *ent*-5c. Following the protocol above, 108.6 g of chloride *ent*-**4c** afforded 87.6 g (81%) of *ent*-**5c**: $[\alpha]_D^{20}$ −12.6 (*c* 1.42, CHCl$_3$).

(2*S*,3*S*,4*R*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine 5d. A solution of benzyl chloride **4b** (45 g, 77 mmol) in THF (770 mL) was cooled to −78 °C. Potassium bis(trimethylsilyl)amide (1 M solution in THF, 115 mL, 115 mmol) was added dropwise over 15 min and the mixture was stirred for an additional hour at −78 °C. The reaction mixture was quenched with aqueous saturated NH$_4$Cl solution and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel to provide **5d** (35 g, 83%) as a light orange foam: $[\alpha]_D^{20}$ −20.3 (*c* 2.21, CHCl$_3$); IR $\nu_{\max}$ (film) 3057, 3031, 2913, 2864, 2810, 1643, 1595, 1489, 1447; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48 (d, *J* = 8.4, 2H), 7.42 (m, 5H), 7.36−7.25 (m, 11H), 7.10 (d, *J* = 8.3, 2H), 5.95−5.78 (m, 1H), 5.33 (d, *J* = 17.0, 1H), 5.24 (d, *J* = 10.2, 1H), 3.70 (t, *J* = 7.9, 1H), 3.61 (d, *J* = 8.2, 1H), 3.51 (dd, *J* = 5.7, 13.0, 1H), 3.44−3.33 (m, 2H), 3.32−3.22 (m, 1H), 3.16 (dd, *J* = 7.4, 13.1, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 143.6, 136.5, 132.6, 131.8, 128.7, 128.5, 127.8, 127.1, 121.5, 119.7, 119.1, 86.8, 69.0, 66.2, 60.4, 55.1, 44.4; HRMS (ESI) calcd for C$_{33}$H$_{30}$BrN$_2$O [M + H]$^+$ 549.1541, found 549.1544.

(2*R*,3*R*,4*S*)-1-Allyl-3-(4-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl) azetidine *ent*-5d. Following the protocol above, 30 g of chloride *ent*-**4d** afforded 23.7 g (84%) of *ent*-**5d**. $[\alpha]_D^{20}$ = +19.4 (*c* 1.78, CHCl$_3$) mp 110.9−111.6 °C.

***N*-(((2*S*,3*R*,4*R*)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzene sulfonamide 6a.** Nitrile azetidine **5a** (12.45 g, 22.66 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$ (227 mL) and subsequently cooled to 0 °C. DIBAL (24.2 mL, 136 mmol, 6.0 equiv) was added over 15 min and the reaction mixture was allowed to warm to room temperature and stirred for approximately 2 h. The mixture was quenched by the slow addition of MeOH (5.50 mL, 136 mmol, 6.0 equiv) until gas evolution ceased. Then a saturated solution of sodium potassium tartrate (Rochelle's salt) was added and the gel like solution was allowed to stir until two separate layers could be seen. The aqueous layer was then extracted two additional times with CH$_2$Cl$_2$. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure to provide the crude product, which was deemed pure enough for the next reaction.

A portion of the resulting amine (11.35 g, 20.50 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$ (205 mL) and cooled to 0 °C. 2,6-Lutidine (7.14 mL, 61.5 mmol, 3.0 equiv) was introduced followed by 2-nitrobenzene-1-sulfonyl chloride (5.15 g, 22.56 mmol, 1.1 equiv) in one portion. The solution was then allowed to warm to room temperature and stir for an additional 3 h. The reaction mixture was quenched with water and the aqueous layer was extracted two times with CH$_2$Cl$_2$. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel using hexanes/EtOAc to provide pure product **6a** (13.16 g, 87% 2-steps) as a pale yellow foam: $[\alpha]_D^{20}$ −32.4 (*c* 0.50, CHCl$_3$); IR $\nu_{\max}$ (film) 3332, 3056, 2872, 1537, 1348, 1167, 1070; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.88−7.79 (m, 1H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.22−7.16 (m, 6H), 7.16−7.11 (m, 4H), 7.09 (d, *J* = 2.0 Hz, 2H), 5.70 (dq, *J* = 6.6, 10.0 Hz, 1H), 5.20 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 4.91 (d, *J* = 4.2 Hz, 1H), 3.70−3.64 (m, 1H), 3.62 (dt, *J* = 6.4, 12.9 Hz, 1H), 3.57−3.42 (m, 1H), 3.28−3.15 (m, 2H), 3.15−2.98 (m, 2H), 2.88 (ddd, *J* = 6.4, 13.1 Hz, 20.4, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 147.5, 143.6, 135.2, 134.3, 133.4, 132.7, 132.6, 132.1, 130.8, 130.8, 128.3, 127.6, 126.8, 125.6, 120.9, 118.2, 86.2, 65.6, 65.4, 61.2, 60.9, 42.7, 42.2; HRMS (ESI) calcd for $C_{39}H_{37}BrN_3O_5S$ [M + H]$^+$ 738.1637, found 738.1633.

_N_-(((2_R_,3_S_,4_S_)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide _ent_-6a. Following the protocol above, 19.8 g of nitrile azetidine *ent*-**5a** afforded 23 g (87%) of *ent*-**6a**: $[\alpha]_D^{20}$ +33.1 (*c* 0.41, $CHCl_3$).

_N_-(((2_S_,3_R_,4_S_)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide 6b. Following the protocol above, 11.4 g of nitrile azetidine **5b** afforded 13.2 g (87%) of **6b**: $[\alpha]_D^{20}$ +62.4 (*c* 0.33, $CHCl_3$); IR ν_{max} (film) 3340, 3057, 2873, 1525, 1489, 1390, 1358, 1264; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.86 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.75−7.61 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.27−7.17 (m, 8H), 7.17 (s, 5H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.62−5.45 (m, 1H), 4.91 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 9.0 Hz, 1H), 4.07 (dt, *J* = 4.6, 11.2 Hz, 1H), 3.89 (d, *J* = 4.4 Hz, 1H), 3.73 (t, *J* = 8.1, 1H), 3.29 (d, *J* = 11.0 Hz, 1H), 3.20 (dtd, *J* = 5.0, 12.5, 17.3 Hz, 3H), 2.90 (ddd, *J* = 6.5, 12.4, 21.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 143.4, 135.9, 135.5, 133.4, 133.2, 132.5, 131.3, 130.9, 129.7, 128.5, 127.6, 126.9, 125.1, 120.4, 116.7, 87.1, 64.9, 64.1, 60.3, 52.8, 44.4, 40.1; HRMS (ESI) calcd for $C_{39}H_{37}BrN_3O_5S$ [M + H]$^+$ 738.1637, found 738.1626.

_N_-(((2_R_,3_S_,4_R_)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzene sulfonamide _ent_-6b. Following the protocol above, 20 g of nitrile azetidine *ent*-**5b** gave 25 g (93%) of *ent*-**6b**: $[\alpha]_D^{20}$ −52.1 (*c* 0.73, $CHCl_3$).

_N_-(((2_S_,3_S_,4_S_)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide 6c. Following the protocol above, 20 g of nitrile azetidine **5c** afforded 18 g (67%) of **6c**: $[\alpha]_D^{20}$ +56.2 (*c* 0.21, $CHCl_3$); IR ν_{max} (film) 3332, 3056, 2871, 1539, 1346, 1264, 1168; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.83 (t, *J* = 6.1 Hz, 1H), 7.74 (td, *J* = 1.2, 7.7 Hz, 1H), 7.69−7.60 (m, 1H), 7.44 (t, *J* = 8.9 Hz, 6H), 7.36−7.30 (m, 7H), 7.27 (dd, *J* = 2.9, 5.2 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.71 (ddd, *J* = 5.9, 10.9, 16.2 Hz, 1H), 5.10−4.97 (m, 2H), 4.94 (s, 1H), 3.97 (td, *J* = 4.7, 8.3 Hz, 1H), 3.85−3.73 (m, 1H), 3.52−3.45 (m, 1H), 3.45−3.32 (m, 3H), 3.19−3.02 (m, 2H), 2.75 (dt, *J* = 21.2, 47.3 Hz, 1H), 0.98 (dd, *J* = 7.5, 14.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 143.6, 137.0, 136.0, 133.4, 133.0, 132.6, 131.4, 130.7, 130.4, 128.7, 127.8, 127.1, 125.4, 120.9, 116.6, 87.2, 65.9, 64.2, 62.8, 52.8, 43.3, 41.4; HRMS (ESI) calcd for $C_{39}H_{37}BrN_3O_5S$ [M + H]$^+$ 738.1637, found 738.1642.

_N_-(((2_R_,3_R_,4_R_)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzene sulfonamide _ent_-6c. Following the protocol above, 20 g of nitrile azetidine *ent*-**5c** afforded 24 g (90%) of *ent*-**6c**: $[\alpha]_D^{20}$ −84.6 (*c* 0.45, $CHCl_3$).

_N_-(((2_S_,3_S_,4_R_)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide 6d. Following the protocol above, 20 g of nitrile azetidine **5d** afforded 23.5 g (88%) of **6d**: $[\alpha]_D^{20}$ −40.1 (*c* 0.81, $CHCl_3$); IR ν_{max} (film) 3332, 3056, 2869, 1533, 1489, 1447, 1394, 1357, 1264, 1166; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 1.9, 7.2 Hz, 1H), 7.85 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.74 (tt, *J* = 6.7, 13.1 Hz, 1H), 7.41 (t, *J* = 6.3 Hz, 5H), 7.31 (t, *J* = 7.5 Hz, 4H), 7.28−7.22 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.14 (s, 1H), 5.66 (td, *J* = 8.9, 17.5 Hz, 1H), 5.11 (d, *J* = 16.8 Hz, 1H), 4.83 (d, *J* = 9.6 Hz, 1H), 3.43 (dd, *J* = 5.5, 13.0 Hz, 1H), 3.34 (dd, *J* = 4.9, 9.7 Hz, 1H), 3.24 (t, *J* = 5.8 Hz, 3H), 3.18 (dd, *J* = 4.0, 9.7 Hz, 1H), 3.11−2.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 143.9, 138.7, 134.8, 133.4, 133.2, 132.4, 131.5, 131.1, 129.2, 128.6, 127.8, 126.9, 125.1, 120.6, 118.1, 86.8, 68.4, 68.0, 66.4, 60.4, 45.1, 41.2; HRMS (ESI) calcd for $C_{39}H_{37}BrN_3O_5S$ [M + H]$^+$ 738.1637, found 738.1635.

_N_-(((2_R_,3_R_,4_S_)-1-Allyl-3-(4-bromophenyl)-4-((trityloxy)methyl)azetidin-2-yl)methyl)-2-nitrobenzene sulfonamide _ent_-6d. Following the protocol above, 25 g of nitrile azetidine *ent*-**5d** afforded 31 g (93%) of *ent*-**6d.** $[\alpha]_D^{20}$ = +42.6 (*c* 0.71, $CHCl_3$).

_N_-(((2_S_,3_R_,4_R_)-1-Allyl-3-(4-bromophenyl)-4-(hydroxymethyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide 7a. Azetidine **6a** (14.1 g, 19.09 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (191 mL) and cooled to 0 °C. Trifluoroacetic acid (14.9 mL, 191 mmol, 10 equiv) was then added over approximately 10 min until the yellow color persisted. The mixture was neutralized by the addition of a saturated aqueous solution of sodium bicarbonate and the aqueous layer extracted 2 additional times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel using hexanes/EtOAc to provide the primary alcohol **7a** (8.74 g, 92%) as a foam: $[\alpha]_D^{20}$ −46.2 (*c* 0.59, $CHCl_3$); IR ν_{max} (film) 3335, 2873, 1538, 1346, 1166, 905; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.72 (td, *J* = 7.7, 1.5 Hz, 1H), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (m, 4H), 5.83 (m, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.17 (d, *J* = 10.1 Hz, 1H), 4.92 (s, 1H), 3.64 (s, 1H), 3.54 (s, 2H), 3.49−3.42 (m, 1H), 3.37 (m, 1H), 3.21 (s, 3H), 2.92 (t, *J* = 10.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 135.5, 133.8, 133.5, 132.7, 132.6, 132.2, 131.2, 130.9, 125.7, 121.4, 118.6, 67.3, 64.8, 61.4, 61.1, 42.8, 41.8; HRMS (ESI) calcd for $C_{20}H_{23}BrN_3O_5S$ [M + H]$^+$ 496.0542, found 496.0545.

_N_-(((2_R_,3_S_,4_S_)-1-Allyl-3-(4-bromophenyl)-4-(hydroxymethyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide _ent_-7a. Following the protocol above, 23 g of *ent*-**6a** azetidine afforded 14.6 g (94%) of azetidine *ent*-**7a**: $[\alpha]_D^{20}$ +42.5 (*c* 1.44, $CHCl_3$).

_N_-(((2_S_,3_S_,4_R_)-1-Allyl-3-(4-bromophenyl)-4-(hydroxymethyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide 7d. Following the protocol above, 23.5 g of azetidine **6d** afforded 14.6 g (92%) of azetidine **7d**: $[\alpha]_D^{20}$ −37.9 (*c* 0.49, $CHCl_3$); IR ν_{max} (film) 3320, 2872, 1537, 1342, 1162; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 1.6, 6.8 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79−7.62 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.97 (s, 1H), 5.69 (ddt, *J* = 6.7, 9.9, 16.8 Hz, 1H), 5.18 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 3.64 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.48 (d, *J* = 10.1 Hz, 1H), 3.34 (t, *J* = 7.7 Hz, 1H), 3.30−3.18 (m, 4H), 3.18−3.05 (m, 2H), 2.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 138.5, 134.1, 133.4, 132.9, 132.5, 131.2, 130.5, 129.0, 124.9, 120.2, 118.5, 70.0, 67.4, 62.1, 59.6, 45.5, 38.8; HRMS (ESI) calcd for $C_{20}H_{22}BrN_3O_5S$ [M + H]$^+$ 496.0542, found 496.0541.

_N_-(((2_R_,3_R_,4_S_)-1-Allyl-3-(4-bromophenyl)-4-(hydroxymethyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide _ent_-7d. Following the protocol above, 24 g of *ent*-**6d** azetidine gave 14 g (88%) of azetidine *ent*-**7d**: $[\alpha]_D^{20}$ +38.9 (*c* 0.28, $CHCl_3$).

6-Allyl-7-(4-bromophenyl)-3-(2-nitrophenylsulfonyl)-3,6-diazabicyclo[3.1.1] heptanes 8a. Nosyl amine **7a** (8.0 g, 16.1 mmol) was dissolved in CH_2Cl_2 (170 mL), and the reaction was subsequently cooled to 0 °C. Triethylamine (6.7 mL, 48.4 mmol) was added followed by the dropwise addition methanesulfonyl chloride (1.37 mL, 17.7 mmol). The solution was stirred for 30 min at 0 °C. The reaction mixture was quenched with water, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was deemed pure enough to continue without further purification.

The resulting sulfonate was dissolved in DMF (161 mL), and potassium carbonate (4.46 g, 32.2 mmol) was added in one portion. The reaction was heated to 65 °C for 3 h at which point the solvent was removed and the resulting residue was purified by chromatography over silica gel to provide 8.2 g of pure product **8a** (99%): IR ν_{max} (film) 2934, 1542, 1372, 1169, 578, 535; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (t, *J* = 7.7 Hz, 1H), 7.40 (dt, *J* = 17.0, 7.9 Hz, 3H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.1 Hz, 2H), 5.88−5.73 (m, 1H), 5.26 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 4.01 (d, *J* = 5.7 Hz, 2H), 3.90 (t, *J* = 5.9 Hz, 1H), 3.84 (d, *J* = 11.7 Hz, 2H), 3.48 (d, *J* = 11.7 Hz, 2H), 3.28 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 134.5, 133.8, 133.2, 131.1, 131.1, 130.4, 129.5, 127.5, 123.4, 120.0, 117.4, 59.6, 47.5, 40.2, 39.4; HRMS (ESI) calcd for $C_{20}H_{20}BrN_3O_4S$ [M + H]$^+$ 478.0436, found 478.0438.

6-Allyl-7-(4-bromophenyl)-3-(2-nitrophenylsulfonyl)-3,6-diazabicyclo[3.1.1]heptanes 8d. Nosyl amine **7d** (1.00 g, 2.02 mmol) was dissolved in CH_2Cl_2 (20 mL), and the reaction was subsequently cooled to 0 °C. Triethylamine (0.842 mL, 6.04 mmol) was added followed by the dropwise addition methanesulfonyl chloride (0.172 mL, 2.22 mmol). The solution was stirred for 30 min at 0 °C. The reaction mixture was quenched with water, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was deemed pure enough to continue without further purification.

The resulting sulfonate was dissolved in DMF (20 mL), and potassium carbonate (0.557 g, 4.03 mmol) was added in one portion. The reaction was heated to 65 °C for 1 h at which point the solvent was removed and the resulting residue was purified by chromatography over silica gel to provide pure product **8d** (0.902 g, 94%): IR ν_{max} (film) 2934, 1542, 1372, 1169, 578, 535; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, J = 1.6, 7.5 Hz, 1H), 7.82−7.73 (m, 2H), 7.70 (dd, J = 1.6, 7.5 Hz, 1H), 7.47 (s, 4H), 5.75 (ddd, J = 5.8, 10.9, 16.1 Hz, 1H), 5.14−5.06 (m, 2H), 3.88 (d, J = 11.0 Hz, 2H), 3.71 (s, 2H), 3.57 (d, J = 11.0 Hz, 2H), 3.06 (d, J = 5.8 Hz, 2H), 3.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 139.3, 133.9, 133.8, 131.5, 131.4, 131.2, 131.1, 129.4, 124.1, 120.5, 117.0, 62.1, 47.5, 45.6, 43.3; HRMS (ESI) calcd for $C_{20}H_{20}BrN_3O_4S$ $[M + H]^+$ 478.0436, found 478.0438.

(6*R*,7*R*,8*S*)-7-(4-Bromophenyl)-4-((2-nitrophenyl)sulfonyl)-8-((trityloxy)methyl)-1,4-diazabicyclo[4.2.0]octan-2-one 9a. To a solution of the nosylated amine **6a** (13.2 g, 17.9 mmol, 1.0 equiv) in EtOH (179 mL) at room temperature was added 1,3-dimethylbarbituric acid (3.92 g, 25.1 mmol, 1.4 equiv) followed by $Pd(PPh_3)_4$ (1.66 g, 1.43 mmol, 0.08 equiv). Upon completion of the reaction, the mixture was filtered through a silica gel plug, eluting with CH_2Cl_2/MeOH, and the filtrate was concentrated to provide the crude amine as a bright red, foamy solid.

The crude allyl-deprotected product was dissolved in acetonitrile (153 mL), and Cs_2CO_3 (74.0 g, 227 mmol, 10.0 equiv) was added and allowed to stir at room temperature for 30 min. Bromoacetyl chloride (1.89 mL, 22.7 mmol, 1.0 equiv) was then added and stirred until deemed complete via LC/MS analysis. The reaction was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude residue was partitioned in CH_2Cl_2 and water/brine. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel using hexanes/EtOAc, and again using CH_2Cl_2/EtOAc, which provided the pure product **9a** (6.96 g, 59% over two steps) as a white, foamy solid: $[\alpha]_D^{20}$ −73.0 (c 0.29, $CHCl_3$); IR ν_{max} (film) 3057, 1667, 1543, 1489, 1448, 1423, 1369, 1169; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.7, 1.5 Hz, 1H), 7.77−7.58 (m, 9H), 7.30 (d, J = 8.4 Hz, 2H), 7.23−7.12 (m, 9H), 7.06 (dd, J = 6.7, 3.0 Hz, 6H), 6.99 (d, J = 8.4 Hz, 2H), 5.13−5.01 (m, 1H), 5.00−4.88 (m, 1H), 4.18−3.98 (m, 3H), 3.73 (dd, J = 13.1, 4.8 Hz, 1H), 3.64 (d, J = 17.1 Hz, 1H), 3.40 (t, J = 10.0 Hz, 1H), 3.23 (dd, J = 12.9, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 148.1, 143.3, 134.3, 132.9, 132.2, 131.8, 131.4, 131.0, 128.6, 127.9, 127.2, 124.7, 121.9, 86.9, 66.1, 61.4, 57.4, 48.0, 45.4, 42.8; HRMS (ESI) calcd for $C_{38}H_{32}BrN_3NaO_6S$ $[M + Na]^+$ 760.1093, found 760.1097.

(6*S*,7*R*,8*S*)-7-(4-Bromophenyl)-4-((2-nitrophenyl)sulfonyl)-8-((trityloxy)methyl)-1,4-diazabicyclo[4.2.0]octan-2-one 9b. Following the protocol above, 7.3 g of **6b** afforded 5.02 g of **9b** (69% over two steps) as a white, foamy solid: $[\alpha]_D^{20}$ = +72.0 (c 0.25, $CHCl_3$); IR ν_{max} (film) 3057, 1668, 1543, 1490, 1448, 1415, 1370, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J = 7.5, 2.1 Hz, 1H), 7.72−7.54 (m, 3H), 7.31 (d, J = 8.4 Hz, 2H), 7.25−7.16 (m, 9H), 7.16−7.04 (m, 6H), 6.96 (d, J = 8.3 Hz, 2H), 5.33−5.21 (m, 1H), 4.90−4.78 (m, 1H), 4.37 (dd, J = 12.6, 4.8 Hz, 1H), 4.33 (d, J = 17.1 Hz, 1H), 3.98 (t, J = 8.6 Hz, 1H), 3.76 (d, J = 17.0 Hz, 1H), 3.38 (dd, J = 10.7, 5.1 Hz, 1H), 3.20−3.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 148.1, 143.4, 134.4, 134.2, 132.1, 131.6, 131.4, 131.3, 129.2, 128.6, 127.8, 127.1, 124.6, 121.2, 87.2, 66.4, 64.1, 61.7, 48.6, 48.4, 44.9; HRMS (ESI) calcd for $C_{38}H_{32}BrN_3NaO_6S$ $[M + Na]^+$ 760.1093, found 760.1095.

(6*S*,7*S*,8*S*)-7-(4-Bromophenyl)-4-((2-nitrophenyl)sulfonyl)-8-((trityloxy)methyl)-1,4-diazabicyclo[4.2.0]octan-2-one 9c. Following the protocol above, 7.35 g of **6c** afforded 4.51 g of **9c** (61% over 2 steps) as a white, foamy solid: $[\alpha]_D^{20}$ +68.6 (c 1.29; $CHCl_3$); IR ν_{max} (film) 3058, 1671, 1543, 1490, 1448, 1415, 1370, 1169; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02−7.91 (m, 1H), 7.70−7.52 (m, 3H), 7.52−7.36 (m, 8H), 7.36−7.18 (m, 9H), 7.03 (d, J = 8.4 Hz, 2H), 5.09 (ddd, J = 11.4, 8.2, 4.9 Hz, 1H), 4.75 (dd, J = 7.5, 3.6 Hz, 1H), 4.32 (d, J = 17.1 Hz, 1H), 3.98 (dd, J = 8.0, 4.6 Hz, 1H), 3.80−3.62 (m, 3H), 3.40 (dd, J = 10.6, 3.5 Hz, 1H), 2.61 (dd, J = 13.1, 11.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 148.0, 143.7, 134.39, 134.36, 132.3, 132.1, 131.7, 131.1, 129.4, 128.8, 128.1, 127.4, 124.7, 121.9, 87.2, 66.9, 64.3, 62.5, 48.7, 44.5, 42.9; HRMS (ESI) calcd for $C_{38}H_{32}BrN_3NaO_6S$ $[M + Na]^+$ 760.1093, found 760.1097.

(6*R*,7*S*,8*S*)-7-(4-Bromophenyl)-4-((2-nitrophenyl)sulfonyl)-8-((trityloxy)methyl)-1,4-diazabicyclo[4.2.0]octan-2-one 9d. Following the protocol above, 10.0 g of **6d** afforded 6.07 g of **9d** (61% over 2 steps) as a white, foamy solid: $[\alpha]_D^{20}$ −90.7 (c 0.38, $CHCl_3$); IR ν_{max} (film) 3058, 1673, 1544, 1490, 1448, 1419, 1370, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.4, 1.6 Hz, 1H), 7.84−7.68 (m, 3H), 7.45 (dd, J = 8.1, 1.8 Hz, 6H), 7.32 (d, J = 8.4 Hz, 2H), 7.30−7.14 (m, 9H), 6.83 (d, J = 8.4 Hz, 2H), 4.63 (ddd, J = 10.6, 6.6, 4.2 Hz, 1H), 4.49−4.39 (m, 1H), 4.35−4.23 (m, 2H), 4.18 (dd, J = 12.4, 4.1 Hz, 1H), 3.87 (d, J = 16.9 Hz, 1H), 3.52 (t, J = 6.8 Hz, 1H), 3.31 (ddd, J = 13.0, 11.6, 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 143.7, 137.3, 134.4, 132.1, 132.1, 131.7, 131.5, 128.8, 128.1, 127.4, 124.7, 121.7, 88.0, 72.2, 64.8, 59.4, 48.1, 47.2, 43.2; HRMS (ESI) calcd for $C_{38}H_{32}BrN_3NaO_6S$ $[M + Na]^+$ 760.1093, found 760.1085.

(6*R*,7*R*,8*S*)-7-(4-Bromophenyl)-8-(hydroxymethyl)-4-((2-nitrophenyl)sulfonyl)-1,4-diazabicyclo[4.2.0]octan-2-one 10a. To a solution of ketopiperazine **9a** in CH_2Cl_2 (92 mL) at room temperature was added trifluoroacetic acid (7.23 mL, 94 mmol, 10 equiv), followed by triethylsilane (1.5 mL, 9.4 mmol, 1.0 equiv). The reaction was stirred for 15 min, after which analysis of the reaction by LC/MS showed complete conversion of the starting material to the product. The reaction was quenched with MeOH, and then saturated aqueous $NaHCO_3$ solution until bubbling completely stopped. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel using CH_2Cl_2/MeOH as eluent, which provided the pure product **10a** (3.4 g, 73%) as a white, foamy solid: $[\alpha]_D^{20}$ −55.6 (c 0.30, $CHCl_3$); IR ν_{max} (film) 3361, 2936, 1644, 1541, 1358, 1166, 1034; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, J = 7.4, 1.7 Hz, 1H), 7.80−7.63 (m, 3H), 7.44 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 5.13−4.94 (m, 2H), 4.27 (d, J = 17.3 Hz, 1H), 4.07 (dd, J = 12.9, 9.7 Hz, 1H), 4.00 (t, J = 8.2 Hz, 1H), 3.84 (d, J = 17.3 Hz, 1H), 3.74 (dd, J = 13.1, 4.8 Hz, 1H), 3.42−3.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 148.0, 134.5, 132.3, 132.0, 131.8, 131.7, 131.4, 131.3, 124.8, 122.5, 70.5, 61.8, 60.7, 47.9, 44.8, 42.9; HRMS (ESI) calcd for $C_{19}H_{19}BrN_3O_6S$ $[M + H]^+$ 496.0178, found 496.0179.

(6*S*,7*R*,8*S*)-7-(4-Bromophenyl)-8-(hydroxymethyl)-4-((2-nitrophenyl)sulfonyl)-1,4-diazabicyclo[4.2.0]octan-2-one 10b. Following the protocol above, product **9b** (2.71 g, 81%) was obtained as a white powder: $[\alpha]_D^{20}$ +139.3 (c 0.26, DMSO); IR ν_{max} (film) 3419, 1667, 1548, 1362, 1171; ^1H NMR (300 MHz, DMSO-d_6) δ 8.14 (dd, J = 7.7, 1.4 Hz, 1H), 8.05 (dd, J = 7.8, 1.4 Hz, 1H), 7.95 (dt, J = 7.5, 1.5 Hz, 1H), 7.88 (dt, J = 7.5, 1.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 5.04−4.92 (m, 1H), 4.69−4.55 (m, 1H), 4.17−4.05 (m, 3H), 3.68 (d, J = 16.9 Hz, 1H), 3.43 (d, J = 4.6 Hz, 2H), 3.38−3.25 (obscured, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.0, 147.6, 135.4, 135.1, 132.6, 130.9, 130.5, 130.1, 129.5, 124.3, 119.8, 67.4, 63.3, 59.5, 48.2, 46.9, 43.6; HRMS (ESI) calcd for $C_{19}H_{19}BrN_3O_6S$ $[M + H]^+$ 496.0178, found 496.0170.

(6*S*,7*S*,8*S*)-7-(4-Bromophenyl)-8-(hydroxymethyl)-4-((2-nitrophenyl)sulfonyl)-1,4-diazabicyclo[4.2.0]octan-2-one 10c. Following the protocol above, product **10c** (4.18 g, 72%) was obtained as a white, foamy solid: $[\alpha]_D^{20}$ +132.2 (c 0.92, $CHCl_3$); IR ν_{max} (film) 3422, 2930, 1658, 1541, 1370, 1166; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 6.9, 1.5 Hz, 1H), 7.80−7.59 (m, 3H), 7.48 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 4.97 (ddd, J = 11.2, 8.7, 4.7 Hz, 1H), 4.78 (dd, J = 8.2, 4.5 Hz, 1H), 4.27 (d, J = 17.2 Hz, 1H), 4.08−3.92 (m, 2H), 3.85 (dd, J = 11.9, 5.0 Hz, 1H), 3.78−3.60 (m, 2H), 2.79 (br s, 1H), 2.64 (dd, J = 12.9, 11.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 148.0, 134.4, 134.0, 132.4, 132.3, 131.7, 131.3, 129.4, 124.7, 122.0, 69.0, 63.7, 62.6, 48.4, 44.6, 41.8; HRMS (ESI) calcd for $C_{19}H_{19}BrN_3O_6S$ [M + H]$^+$ 496.0178, found 496.0182.

(6*R*,7*S*,8*S*)-7-(4-Bromophenyl)-8-(hydroxymethyl)-4-((2-nitrophenyl)sulfonyl)-1,4-diazabicyclo[4.2.0]octan-2-one 10d. Following the protocol above, product **10d** (4.0 g, 73%) was obtained as a white, foamy solid: $[\alpha]_{\mathrm{D}}^{20}$ −104.5 (*c* 0.35, $CHCl_3$); IR ν_{max} (film) 3389, 2923, 1645, 1541, 1360, 1169; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.86−7.62 (m, 3H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.80−4.62 (m, 2H), 4.34−4.17 (m, 2H), 4.07 (dd, *J* = 12.8, 2.2 Hz, 1H), 3.85−3.67 (m, 2H), 3.56 (t, *J* = 7.5 Hz, 1H), 3.17 (dd, *J* = 12.7, 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 148.1, 136.1, 134.5, 132.4, 132.3, 131.5, 131.5, 128.8, 124.7, 122.1, 74.6, 65.5, 62.8, 48.1, 47.6, 44.1; HRMS (ESI) calcd for $C_{19}H_{19}BrN_3O_6S$ [M + H]$^+$ 496.0178, found 496.0183.

(8*R*,9*R*,10*S*,*Z*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)-sulfonyl)-10-((trityloxy)methyl)-1,6-diazabicyclo[6.2.0]dec-3-ene 11a. To a solution of the nosylated amine **6a** (16.5 g, 22.34 mmol, 1.0 equiv) in DMF (45 mL) at 0 °C were added potassium carbonate (4.63 g, 33.50 mmol, 1.5 equiv) and allyl bromide (2.08 mL, 24.57 mmol, 1.1 equiv). The reaction was stirred for 2 h, slowly warming to room temperature. Analysis of the reaction by LC/MS indicated complete disappearance of the starting material and the formation of a new product. The reaction mixture was quenched with water and extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography on silica gel using hexanes/EtOAc to obtain allylated compound (14.72 g, 85%): $[\alpha]_{\mathrm{D}}^{20}$ +24.9 (*c* 0.66, $CHCl_3$); IR ν_{max} (film) 3057, 2855, 1542, 1486, 1448, 1353, 1160, 1072; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.49 (m, 5H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.28−7.12 (m, 16H), 5.72−5.59 (m, 1H), 5.52−5.39 (m, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 4.82 (d, *J* = 17.1 Hz, 1H), 3.84 (dd, *J* = 16.1, 5.7 Hz, 1H), 3.76 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.60−3.53 (m, 2H), 3.48 (dd, *J* = 16.2, 6.6 Hz, 1H), 3.28−3.14 (m, 3H), 3.05 (dd, *J* = 9.2, 4.7 Hz, 1H), 2.96 (dd, *J* = 13.3, 7.2 Hz, 1H), 2.86 (dd, *J* = 9.0, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 143.8, 135.1, 133.4, 132.7, 132.6, 131.1, 128.4, 127.6, 126.7, 124.1, 120.7, 119.0, 117.8, 86.1, 66.6, 66.2, 60.8, 60.6, 51.6, 45.3, 44.2; HRMS (ESI) calcd for $C_{42}H_{41}BrN_3O_5S$ [M + H]$^+$ 778.1950, found 778.1948.

This material (16.06 g, 20.62 mmol, 1.0 equiv) was dissolved in benzene and degassed for 30 min. Grubbs catalyst I (4.24 g, 5.16 mmol, 0.25 equiv) was then added, and the reaction was stirred for 24 h at 50 °C, after which analysis of the reaction by LC/MS indicated complete disappearance of the starting material. The solvent was evaporated under reduced pressure and purified by flash chromatography on silica gel using hexanes/EtOAc, which provided **11a** (11.77 g, 76%) as a light brown foamy solid: $[\alpha]_{\mathrm{D}}^{20}$ +89.7 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3057, 3030, 2927, 2865, 1543, 1488, 1448, 1352, 1162, 1073; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.76−7.50 (m, 3H), 7.39−7.06 (m, 19H), 5.89−5.82 (m, 1H), 5.75−5.66 (m, 1H), 4.10 (dd, *J* = 15.2, 6.9 Hz, 1H), 3.98 (dd, *J* = 14.6, 9.2 Hz, 1H), 3.64−3.58 (m, 3H), 3.48 (dd, *J* = 15.3, 6.3 Hz, 1H), 3.26 (d, *J* = 13.8 Hz, 1H), 3.21−3.01 (m, 3H), 2.92 (dd, *J* = 9.2, 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 143.7, 134.8, 133.4, 133.0, 132.9, 132.1, 131.6, 131.1, 130.8, 128.5, 127.7, 126.9, 124.8, 124.1, 120.9, 86.5, 77.5, 77.0, 76.6, 67.0, 66.0, 61.9, 54.9, 49.5, 43.5, 43.2; HRMS (ESI) calcd for $C_{40}H_{37}BrN_3O_5S$ [M + H]$^+$ 750.1637, found 750.1639.

(8*S*,9*R*,10*S*,*Z*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)-sulfonyl)-10-((trityloxy)methyl)-1,6-diazabicyclo[6.2.0]dec-3-ene 11b. Following the protocol above, 22.0 g of nosyl amine **6b** afforded 20.99 g (91%) of the allylated product: $[\alpha]_{\mathrm{D}}^{20}$ +20.1 (*c* 0.26, $CHCl_3$); IR ν_{max} (film) 3058, 2916, 1542, 1489, 1448, 1353, 1162, 1071; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.1, 3.5 Hz, 3H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.26−7.17 (m, 9H), 7.14 (dd, *J* = 8.2, 5.4 Hz, 6H), 7.01 (d, *J* = 8.3 Hz, 2H), 5.72−5.43 (m, 2H), 5.17−5.05 (m, 2H), 4.99 (d, *J* = 18.1 Hz, 1H), 4.94 (d, *J* = 11.1 Hz, 1H), 4.05 (dd, *J* = 13.2, 6.0 Hz, 1H), 3.97−3.84 (m, 3H), 3.69−3.50 (m, 3H), 3.24 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.16 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.06 (dd, *J* = 14.5, 5.9 Hz, 1H), 2.86 (dd, *J* = 9.9, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 143.7, 137.0, 135.8, 133.6, 132.4, 131.7, 131.4, 131.1, 130.3, 128.7, 127.7, 127.0, 124.3, 120.5, 119.7, 116.5, 87.1, 64.8, 64.4, 60.8, 52.7, 51.1, 48.7, 43.3; HRMS (ESI) calcd for $C_{42}H_{41}BrN_3O_5S$ [M + H]$^+$ 778.1950, found 778.1936.

A portion of alllyl intermediate (5.0 g, 6.42 mmol, 1.0 equiv) was then reacted with Grubbs catalyst I (1.06 g, 1.28 mmol, 0.20 equiv) in the presence of styrene (2.94 mL, 25.7 mmol, 4.0 equiv) in DCE (321 mL) to provide **11b** (2.46 g, 51%) as a light brown foamy solid: $[\alpha]_{\mathrm{D}}^{20}$ +81.1 (*c* 0.26, $CHCl_3$); IR ν_{max} (film) 3031, 2920, 1541, 1488, 1448, 1345, 1161, 1071; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−7.95 (m, 1H), 7.73−7.53 (m, 3H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.25 (s, 15H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.12−5.84 (m, 2H), 4.11−3.85 (m, 4H), 3.84−3.63 (m, 2H), 3.51 (dd, *J* = 12.3, 8.5 Hz, 1H), 3.27 (dd, *J* = 8.1, 3.7 Hz, 1H), 3.14 (dd, *J* = 12.5, 6.4 Hz, 1H), 3.05 (dd, *J* = 9.6, 5.6 Hz, 1H), 2.72 (dd, *J* = 9.4, 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 143.8, 137.0, 133.7, 133.2, 131.8, 131.6, 131.3, 131.0, 130.5, 129.0, 128.6, 127.8, 127.0, 124.2, 120.7, 86.8, 68.2, 64.2, 62.1, 50.3, 46.1, 44.4, 42.7; HRMS (ESI) calcd for $C_{40}H_{37}BrN_3O_5S$ [M + H]$^+$ 750.1637, found 750.1627.

(8*S*,9*S*,10*S*,*Z*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)-sulfonyl)-10-((trityloxy)methyl)-1,6-diazabicyclo[6.2.0]dec-3-ene 11c. Following the protocol above, 22.0 g of nosyl amine **6b** afforded 20.99 g (91%) of the allylated product: $[\alpha]_{\mathrm{D}}^{20}$ −22.8 (*c* 0.11, $CHCl_3$); IR ν_{max} (film) 3060, 2890, 1541, 1488, 1447, 1352, 1160, 1070; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (td, *J* = 7.3, 1.4 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 8H), 7.38−7.18 (m, 11H), 5.72−5.54 (m, 1H), 5.54−5.38 (m, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.99−4.79 (m, 3H), 4.20 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.84 (dd, *J* = 16.1, 5.8 Hz, 1H), 3.63 (d, *J* = 3.1 Hz, 1H), 3.59−3.47 (m, 2H), 3.47−3.35 (m, 2H), 3.28 (dd, *J* = 15.1, 6.0 Hz, 1H), 3.20−3.04 (m, 2H), 2.96 (dd, *J* = 15.3, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 143.9, 139.3, 136.3, 133.4, 133.4, 132.9, 131.7, 131.6, 131.3, 131.1, 129.0, 128.0, 127.3, 124.2, 120.8, 119.1, 115.7, 87.4, 67.0, 65.5, 61.9, 52.1, 51.6, 47.3, 43.0; HRMS (ESI) calcd for $C_{42}H_{41}BrN_3O_5S$ [M + H]$^+$ 778.1950, found 778.1962.

This product (22.48 g, 28.90 mmol, 1.0 equiv) was then reacted with Grubbs catalyst I (5.94 g, 7.22 mmol, 0.25 equiv) in benzene (577 mL) to provide **11c** (13.10 g, 60.5%) as a light brown foamy solid: $[\alpha]_{\mathrm{D}}^{20}$ −6.54 (*c* 0.15, $CHCl_3$); IR ν_{max} (film) 3027, 2917, 1542, 1489, 1448, 1346, 1161, 1061; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.68−7.49 (m, 3H), 7.50−7.35 (m, 8H), 7.35−7.21 (m, 9H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.07−5.87 (m, 2H), 4.20−3.98 (m, 2H), 3.87 (dd, *J* = 13.1, 5.5 Hz, 1H), 3.73 (dd, *J* = 15.3, 6.2 Hz, 1H), 3.61 (t, *J* = 8.2 Hz, 1H), 3.52−3.38 (m, 2H), 3.38−3.26 (m, 2H), 3.09 (dt, *J* = 21.4, 11.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 144.0, 136.5, 133.5, 133.0, 131.7, 131.6, 131.4, 130.9, 130.0, 129.4, 128.8, 128.0, 127.2, 124.2, 120.7, 87.2, 66.6, 66.0, 65.3, 47.6, 46.3, 44.7, 41.8; HRMS (ESI) calcd for $C_{40}H_{37}BrN_3O_5S$ [M + H]$^+$ 750.1637, found 750.1641.

(8*R*,9*S*,10*S*,*Z*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)-sulfonyl)-10-((trityloxy)methyl)-1,6-diazabicyclo[6.2.0]dec-3-ene 11d. Following the protocol above, 23.4 g of nosyl amine **6d** afforded 22.42 g (91%) of the allylated product: $[\alpha]_{\mathrm{D}}^{20}$ −18.1 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3058, 2911, 2863, 1542, 1490, 1448, 1353, 1161, 1072; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 1H), 7.68−7.56 (m, 3H), 7.45−7.40 (m, 8H), 7.32−7.25 (m, 9H), 7.12 (d, *J* = 8.3 Hz, 2H), 5.87−5.73 (m, 1H), 5.57−5.44 (m, 1H), 5.20 (d, *J* = 17.1 Hz, 1H), 5.14−5.05 (m, 3H), 4.12 (dd, *J* = 16.4, 6.6 Hz, 1H), 3.97 (dd, *J* = 16.1, 6.0 Hz, 1H), 3.54 (d, *J* = 4.4, 2H), 3.42−3.08 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 144.4, 139.7, 135.3, 134.2, 133.7, 132.6, 131.9, 131.7, 131.4, 129.9, 129.1, 128.1, 127.3, 124.4, 120.7, 119.7, 118.4, 87.0, 69.7, 68.4, 67.0, 61.2, 51.5, 50.7, 44.0; HRMS (ESI) calcd for $C_{42}H_{41}BrN_3O_5S$ [M + H]$^+$ 778.1950, found 778.1960.

This product (22.3 g, 28.60 mmol, 1.0 equiv) was then reacted with Grubbs catalyst I (5.89 g, 7.16 mmol, 0.25 equiv) in benzene (573 mL) to provide product **11d** (16.43 g, 76%) as a light brown foamy solid: $[\alpha]_{\mathrm{D}}^{20}$ −22.5 (*c* 1.11, $CHCl_3$); IR ν_{max} (film) 3055, 3030, 2908, 2859, 1543, 1489, 1448, 1348, 1161, 1071; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.73−7.62 (m, 3H), 7.49−7.39 (m, 9H), 7.32−7.19 (m, 8H), 7.07 (d, *J* = 8.3 Hz, 2H), 5.90−5.81

(m, 1H), 5.69–5.54 (m, 1H), 4.44 (dd, *J* = 14.6, 7.9 Hz, 1H), 3.96 (dd, *J* = 14.6, 8.0 Hz, 1H), 3.86 (d, *J* = 13.9 Hz, 2H), 3.49–3.36 (m, 2H), 3.29–3.18 (m, 3H), 3.11 (dd, *J* = 13.5, 10.3 Hz, 1H), 2.97 (dd, *J* = 6.9, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.5, 144.3, 139.4, 133.7, 133.6, 132.0, 131.9, 131.2, 129.4, 129.0, 128.1, 127.4, 125.3, 124.5, 121.0, 87.0, 71.5, 70.6, 67.2, 59.4, 54.7, 44.8, 42.5; HRMS (ESI) calcd for $C_{40}H_{37}BrN_3O_5S$ [M + H]$^+$ 750.1637, found 750.1635.

((8*R*,9*R*,10*S*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)sulfonyl)-1,6-diazabicyclo[6.2.0] decan-10-yl) methanol 12a. Compound **11a** (10.0 g, 13.3 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$ (133 mL) and cooled to 0 °C. Trifluoroacetic acid (10.3 mL, 133 mmol, 10.0 equiv) was added dropwise, and the reaction was stirred for 1–2 h. Analysis of the reaction by LC/MS indicated complete disappearance of the starting material and the formation of a new product. The reaction mixture was quenched with a saturated solution of NaHCO$_3$ and extracted three times with EtOAc. The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting material was purified by chromatography on silica gel using hexanes/EtOAc to provide the primary alcohol (5.8 g, 86%).

To a solution of the alcohol described above (5 g, 9.84 mmol, 1.0 equiv) and triethylamine (5.5 mL, 39.3 mmol, 4.0 equiv) in dry THF (98 mL) was added 2-nitrobenzenesulfonylhydrazide (NBSH) (6.4 g, 29.5 mmol, 3.0 equiv), and the reaction was heated at 40 °C for 6 h. The reaction mixture was quenched with a saturated solution of NaHCO$_3$ and extracted three times with diethyl ether. The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography on silica gel using hexanes/EtOAc to provide pure **12a** (4.0 g, 80%): $[\alpha]_D^{20}$ +27.4 (*c* 0.255, CHCl$_3$); IR ν_{max} (film) 3380, 2937, 1541, 1372, 1340, 1160; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.77 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.68–7.51 (m, 3H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 3.83 (ddd, *J* = 14.5, 10.5, 4.7 Hz, 1H), 3.72–3.64 (m, 2H), 3.58–3.48 (m, 3H), 3.24 (d, *J* = 13.8 Hz, 1H), 3.12–2.99 (m, 2H), 2.91 (dd, *J* = 14.5, 9.7 Hz, 1H), 2.60–2.39 (br m, 1H), 1.97–1.75 (m, 3H), 1.63 (br m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.2, 133.3, 132.3, 131.6, 131.3, 130.2, 128.3, 124.1, 121.1, 68.2, 65.9, 60.9, 58.0, 55.1, 50.7, 42.1, 28.1, 25.4; HRMS (ESI) calcd for $C_{21}H_{25}BrN_3O_5S$ [M + H]$^+$ 510.0698, found 510.0705.

((8*S*,9*R*,10*S*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)sulfonyl)-1,6-diazabicyclo[6.2.0]decan-10-yl)methanol 12b. Following the protocol above, compound **11b** afforded 3.17 g of **7b** (73% over 2 steps) as a light yellow foamy solid: $[\alpha]_D^{20}$ +191.5 (*c* 0.26, CHCl$_3$); IR ν_{max} (film) 3388, 2927, 1541, 1372, 1340, 1160; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.90 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.71–7.56 (m, 3H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 4.23 (t, *J* = 8.4 Hz, 1H), 3.98–3.89 (m, 1H), 3.88–3.80 (m, 2H), 3.75 (dd, *J* = 12.3, 4.4 Hz, 1H), 3.62 (dd, *J* = 12.3, 4.4 Hz, 1H), 3.51 (t, *J* = 8.5 Hz, 1H), 3.25–3.10 (m, 1H), 3.03 (dd, *J* = 14.3, 9.9 Hz, 1H), 2.96–2.84 (m, 2H), 1.87 (br s, 3H), 1.62 (br s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.3, 135.9, 133.5, 133.2, 132.0, 131.8, 130.7, 129.6, 124.4, 121.0, 67.3, 65.8, 60.4, 55.6, 50.4, 49.4, 41.2, 28.1, 25.6; HRMS (ESI) calcd for $C_{21}H_{25}BrN_3O_5S$ [M + H]$^+$ 510.0698, found 510.0691.

((8*S*,9*S*,10*S*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)sulfonyl)-1,6-diazabicyclo[6.2.0]decan-10-yl)methanol 12c. Following the protocol above, **11c** afforded 7.60 g of **12c** (7.60 g, 76% over 2 steps) as a light yellow foamy solid: $[\alpha]_D^{20}$ +29.2 (*c* 0.205, CHCl$_3$); IR ν_{max} (film) 3387, 2931, 1541, 1371, 1342, 1160; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.67–7.49 (m, 3H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.11 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.93–3.61 (m, 5H), 3.15 (d, *J* = 14.0 Hz, 1H), 3.04 (ddd, *J* = 14.8, 7.5, 3.8 Hz, 1H), 2.97–2.80 (m, 2H), 2.74 (dd, *J* = 14.8, 10.4 Hz, 1H), 2.27 (br s, 1H), 1.95–1.69 (m, 3H), 1.69–1.49 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.2, 137.1, 133.4, 133.0, 131.8, 131.6, 130.4, 124.3, 120.8, 67.3, 65.2, 61.5, 50.8, 49.1, 47.8, 40.0, 27.5, 25.6; HRMS (ESI) calcd for $C_{21}H_{25}BrN_3O_5S$ [M + H]$^+$ 510.0698, found 510.0694.

((8*R*,9*S*,10*S*)-9-(4-Bromophenyl)-6-((2-nitrophenyl)sulfonyl)-1,6-diazabicyclo[6.2.0] decan-10-yl)methanol 12d. Following the protocol above, **11d** afforded 7.43 g of **12d** (7.43 g, 65% over 2 steps) as a light yellow foamy solid: $[\alpha]_D^{20}$ −112.9 (*c* 0.185, CHCl$_3$); IR ν_{max} (film) 3426, 2931, 1542, 1373, 1340, 1160; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.92 (dd, 6.6, *J* = 2.5 Hz, 1H), 7.76–7.56 (m, 3H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 3.87–3.76 (m, 2H), 3.67–3.58 (m, 2H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.36–3.26 (m, 1H), 3.18–3.16 (m, 2H), 2.97–2.89 (m, 2H), 2.64–2.60 (m, 2H), 2.05–1.92 (m, 2H), 1.74–1.59 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.6, 139.0, 133.8, 133.2, 132.1, 131.9, 131.0, 129.4, 128.7, 124.6, 121.2, 73.3, 67.5, 60.8, 56.3, 55.9, 50.6, 40.2, 28.4, 24.1; HRMS (ESI) calcd for $C_{21}H_{25}BrN_3O_5S$ [M + H]$^+$ 510.0698, found 510.0681.

(2*S*,3*S*,4*R*)-1-Allyl-2-(trityloxymethyl)-3-*para*-bromophenyl-4-cyano-4-(tosyloxymethyl)azetidine 13a. To a freshly prepared solution of LiTMP (0.4 M in THF, 270.0 mL, 109.0 mmol, 3.0 equiv) was added dropwise at −78 °C via addition funnel and over 30 to 40 min a solution of azetidine **5a** (20.0 g, 36.4 mmol, 1.0 equiv) in dry THF (100 mL). The mixture was stirred for 2 h at −78 °C, and then solid benzotriazomethanol (BTM) (10.9 g, 72.8 mmol, 2.0 equiv) was added in small portions every 15–20 min, over 1.5 h. The reaction mixture was allowed to warm to room temperature overnight and was quenched with a saturated solution of NH$_4$Cl. The aqueous layer was separated and extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO$_4$, filtered, and concentrated to afford a crude material that was quickly purified on silica gel using hexanes/EtOAc to afford the desired alcohol (15.7 g, 27.1 mmol, 74% yield) as a colorless foam. Only a single stereoisomer was obtained: $[\alpha]_D^{20}$ +56.9 (*c* 1.5, CHCl$_3$); mp 74.8–77.56 °C; IR ν_{max} (film) 3483, 2996, 2958, 1412, 1139, 1073, 944; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.24–7.18 (m, 9H), 7.18–7.12 (m, 6H), 5.74 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.20 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.05 (d, *J* = 10.1 Hz, 1H), 4.15–3.93 (m, 3H), 3.83 (d, *J* = 8.0 Hz, 1H), 3.52 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.31–3.14 (m, 2H), 2.98 (dd, *J* = 9.5, 7.7 Hz, 1H), 2.20 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.5, 134.3, 133.4, 131.3, 128.4, 127.9, 127.7, 126.9, 121.9, 118.4, 118.2, 86.6, 66.9, 64.6, 62.8, 61.1, 52.5, 45.0; HRMS (ESI) calcd for $C_{34}H_{32}BrN_2O_2$ [M + H]$^+$ 579.1647, found 579.1643.

A portion of the primary alcohol described above (3.5 g, 6.0 mmol, 1.0 equiv) was taken up in dry THF (60 mL) and cooled to −78 °C. LiHMDS (1.0 M in THF, 6.6 mL, 6.6 mmol, 1.1 equiv) was added dropwise via an addition funnel. After 40 min, a solution of *p*-toluenesulfonyl chloride (1.3 g, 6.6 mmol, 1.1 equiv) in dry THF (10 mL) was quickly syringed into the mixture, and the temperature was slowly raised to room temperature, allowing for complete conversion of the starting material. The reaction was quenched with saturated NH$_4$Cl solution, and the layers were separated. The organic phase was washed with brine, dried over MgSO$_4$, filtered, and concentrated. Purification on silica gel using hexanes/EtOAc afforded the sulfonate ester **13a** (3.8 g, 5.2 mmol, 85% yield): $[\alpha]_D^{20}$ +45.4 (*c* 1.7, CHCl$_3$); IR ν_{max} (film) 3056, 2930, 2870, 1489, 1369, 1177, 1074, 993; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.24–7.17 (m, 11H), 7.15–7.09 (m, 6H), 5.66 (ddt, *J* = 16.7, 10.0, 6.4 Hz, 1H), 5.06 (dd, *J* = 17.2, 1.3 Hz, 1H), 4.99 (d, *J* = 11.2 Hz, 1H), 4.42 (s, 2H), 4.01 (app td, *J* = 7.8, 5.5 Hz, 1H), 3.70 (d, *J* = 8.0 Hz, 1H), 3.39 (dd, *J* = 13.7, 6.8 Hz, 1H), 3.21 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.12 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.87 (dd, *J* = 9.5, 7.9 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.8, 143.4, 133.7, 132.4, 131.8, 131.4, 131.3, 130.1, 128.3, 128.1, 127.7, 126.9, 122.3, 118.8, 116.5, 86.6, 67.7, 64.4, 63.8, 61.2, 52.8, 46.0, 21.7; HRMS (ESI) calcd for $C_{41}H_{38}BrN_2O_4S$ [M + H]$^+$ 733.1736, found 733.1730.

(2*R*,3*R*,4*S*)-1-Allyl-2-(trityloxymethyl)-3-*para*-bromophenyl-4-cyano-4-(tosyloxymethyl)azetidine *ent*-13a. Following the above protocol, 8.3 g of *ent*-**5a** afforded 8.8 g of *ent*-**13a** (84%): $[\alpha]_D^{20}$ −39.8 (*c* 1.3, CHCl$_3$).

((2*S*,3*S*)-1-Allyl-3-(4-bromophenyl)-6-((2-nitrophenyl)sulfonyl)-1,6-diazaspiro[3.3]heptan-2-yl)methanol 14a. A 250 mL round-bottom flask was charged with a solution of nitrile **13a** (3.0 g, 4.1 mmol, 1.0 equiv) in dry CH$_2$Cl$_2$ (41 mL). At −78 °C, neat DIBAL (3.7 mL, 20.5 mmol, 5.0 equiv) was added dropwise to the mixture via syringe. The reaction was kept at this temperature until complete conversion of the starting material (30 to 45 min, LC/MS analysis). A careful addition of dry MeOH (5 mL) was done in order to quench the reaction mixture, followed by Rochelle's salt solution (50 mL). The mixture was stirred at room temperature overnight. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness and taken crude to the next step.

The primary amine was then dissolved in dry CH_2Cl_2 (41 mL), and triethylamine (1.1 mL, 8.2 mmol, 2.0 equiv) was quickly added to the mixture. At 0 °C, nosyl chloride (1.0 g, 4.5 mmol, 1.1 equiv) was added in one portion and the reaction was stirred for 3 h at room temperature, resulting in partial cyclization of the nosylated amine. The mixture was washed with saturated $NaHCO_3$ solution, and the phases were separated. After extraction of the aqueous phase with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated.

The nosylated material dissolved in acetonitrile (36 mL) and K_2CO_3 (1.5 g, 10.8 mmol, 3.0 equiv) was added, and the mixture was stirred at 50 °C until complete cyclization of the intermediate as judge by LC/MS analysis (8 h). Water was then added, and the mixture was extracted twice with EtOAc. The combined organic fractions were washed with brine and dried over $MgSO_4$. After filtration and removal of the solvents in vacuo, the crude was purified by chromatography on silica gel using hexanes/EtOAc to afford the spiroazetidine **14a** (2.1 g, 2.8 mmol, 68% yield over three steps) as a slightly yellow foam: $[\alpha]_D^{20}$ +58.2 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3026, 2870, 1544, 1488, 1368, 1169, 1073, 748; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.88 (m, 1H), 7.69–7.59 (m, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.20–7.14 (m, 9H), 7.13–7.08 (m, 6H), 7.06 (d, J = 8.4 Hz, 2H), 5.61 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.01 (d, J = 17.1 Hz, 1H), 4.80 (d, J = 8.6 Hz, 2H), 4.12 (d, J = 8.9 Hz, 1H), 3.92 (d, J = 9.3 Hz, 1H), 3.75 (d, J = 9.3 Hz, 1H), 3.70 (dd, J = 8.1, 4.7 Hz, 1H), 3.61 (d, J = 7.6 Hz, 1H), 3.27 (dd, J = 13.3, 6.7 Hz, 1H), 3.12 (dd, J = 13.3, 6.3 Hz, 1H), 2.99 (dd, J = 9.3, 4.8 Hz, 1H), 2.71 (app t, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 143.6, 134.9, 133.6, 131.7, 131.3, 131.2, 130.7, 129.6, 128.3, 127.6, 126.8, 124.1, 121.1, 117.9, 86.2, 64.7, 64.3, 61.1, 60.7, 57.8, 54.2, 49.9; HRMS (ESI) calcd for $C_{40}H_{37}BrN_3O_5S$ $[M + H]^+$ 750.1637, found 750.1654.

(2*R*,3*R*)-1-Allyl-2-(trityloxymethyl)-3-*para*-bromophenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *ent*-14a. Following the above protocol, 8.8 g of *ent*-**13a** afforded 6.5 g of *ent*-**14a** (72%): $[\alpha]_D^{20}$ −48.0 (*c* 1.8, $CHCl_3$).

(2*S*,3*S*)-1-Allyl-2-(hydroxymethyl)-3-*para*-bromophenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane 15a. A solution of spirocycle **14a** (4.3 g, 5.7 mmol, 1.0 equiv) in CH_2Cl_2 (55 mL) was added to a 250 mL round-bottom flask. At 0 °C, neat trifluoroacetic acid (6.3 mL, 86.0 mmol, 15.0 equiv) was slowly added via syringe and the mixture was stirred at this temperature for 1 h. MeOH (25 mL) was quickly added followed by a careful addition of K_2CO_3 (12.0 g, 86.0 mmol, 15.0 equiv). The cold bath was removed, and the reaction was left at room temperature for 1 h. The mixture was partitioned between water and CH_2Cl_2. The organic layer was washed one more time with water, dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using hexanes/EtOAc to afford **15a** (2.0 g, 3.9 mmol) with 69% yield: $[\alpha]_D^{20}$ +80.8 (*c* 1.2, $CHCl_3$); IR ν_{max} (film) 3383, 2948, 2870, 1544, 1488, 1369, 1169, 1128, 1011; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98–7.90 (m, 1H), 7.72–7.60 (m, 3H), 7.46 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 5.83 (ddt, J = 16.5, 10.0, 6.4 Hz, 1H), 5.21 (dd, J = 17.2, 1.5 Hz, 1H), 5.02 (dd, J = 10.1, 1.4 Hz, 1H), 4.79 (d, J = 8.9 Hz, 1H), 4.12 (d, J = 9.0 Hz, 1H), 3.99 (d, J = 9.4 Hz, 1H), 3.84 (d, J = 9.5 Hz, 1H), 3.61–3.51 (m, 2H), 3.45 (dd, J = 11.7, 4.8 Hz, 1H), 3.41 (dd, J = 14.5, 5.5 Hz, 2H), 3.25 (dd, J = 10.9, 5.1 Hz, 1H), 3.19 (dd, J = 13.7, 6.6 Hz, 1H), 1.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 135.5, 134.5, 133.7, 131.8, 131.5, 131.4, 131.1, 130.7, 124.1, 121.4, 118.0, 66.4, 64.0, 61.9, 60.5, 57.8, 54.2, 49.5; HRMS (ESI) calcd for $C_{21}H_{23}BrN_3O_5S$ $[M + H]^+$ 508.0542, found 508.0542.

(2*R*,3*R*)-1-Allyl-2-(hydroxymethyl)-3-*para*-bromophenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *ent*-15a. Following the protocol above, 3.3 g of *ent*-**15a** was obtained from 6.5 g of *ent*-**14a** (75% over 2 steps): $[\alpha]_D^{20}$ −65.9 (*c* 1.1, $CHCl_3$).

((3*R*,6*S*,7*R*)-5-Allyl-7-(4-bromophenyl)-1-((2-nitrophenyl)-sulfonyl)-1,5-diazaspiro [2.4]heptan-6-yl)methanol 16. Application of the cyclization sequence described above to **13c** as starting material (4.7 g, 8.6 mmol) led to the formation of spiropyrrolidino aziridine **16** (358 mg, 0.7 mmol) with 8.2% yield over five steps: $[\alpha]_D^{21}$ +50.5 (*c* 1.1, $CHCl_3$); mp 82.1–87.0 °C IR ν_{max} (film) 3343, 2921, 2865, 1542, 1367, 1333, 1164; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96–7.89 (m, 1H), 7.70–7.62 (m, 2H), 7.62–7.56 (m, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.90 (dddd, J = 15.3, 10.1, 7.7, 5.2 Hz, 1H), 5.29 (d, J = 16.2 Hz, 1H), 5.19 (d, J = 10.2 Hz, 1H), 3.78 (dd, J = 11.8, 2.6 Hz, 1H), 3.66–3.50 (m, 2H), 3.59 (d, J = 7.3 Hz, 1H), 3.36 (m, 2H), 3.10 (s, 1H), 3.03 (dd, J = 13.6, 7.8 Hz, 1H), 2.87 (d, J = 9.0 Hz, 1H), 2.54 (d, J = 9.6 Hz, 1H), 2.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 136.7, 134.2, 134.1, 132.7, 132.0, 131.5, 131.2, 130.8, 124.0, 121.2, 118.4, 72.5, 57.8, 56.6, 56.0, 55.7, 50.7, 42.6; HRMS (ESI) calcd for $C_{21}H_{23}BrN_3O_5S$ $[M + H]^+$ 508.0542, found 508.0551.

(2*S*,3*S*,4*R*)-1-*tert*-Butyloxycarbonyl-2-(trityloxymethyl)-3-*para*-bromo-phenyl-4-cyano azetidine 17. A 250 mL round-bottom flask was charged with a solution of *N*-allyl azetidine **5d** (4.7 g, 8.9 mmol) in 85 mL of CH_2Cl_2/EtOH = 1:2. *N*-Methyl barbituric acid (2.0 g, 12.8 mmol, 1.5 equiv) was added in one portion at room temperature, followed by $Pd(PPh_3)_4$ (0.5 g, 0.4 mmol, 0.05 equiv). The mixture was stirred at 40 °C for 72 h. The reaction was monitored by LC/MS and after completion, the solvents were removed in vacuo, and the crude residue was taken in CH_2Cl_2 (100 mL). The temperature was set to 0 °C, and Boc_2O (2.8 g, 12.8 mmol, 1.5 equiv) was added. The reaction was stirred at room temperature overnight and was monitored by LC/MS. After evaporation of the solvent, the crude was purified on silica gel (hexanes/EtOAc = 85:15) to afford *N*-Boc azetidine **17** (4.7 g, 7.7 mmol, 90% yield over two steps) as a colorless foam: $[\alpha]_D^{20}$ −18.7 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3056, 2926, 1710, 1367, 1149, 1074, 1010; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.34 (m, 8H), 7.28–7.12 (m, 9H), 7.00 (d, J = 8.4 Hz, 2H), 4.57 (d, J = 6.6 Hz, 1H), 4.15 (s, 1H), 3.95 (app t, J = 6.5 Hz, 1H), 3.56 (dd, J = 4.9, 10.4 Hz, 1H), 3.21 (dd, J = 2.8, 10.4 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 143.6, 136.3, 132.2, 128.6, 128.5, 127.9, 127.2, 122.1, 117.4, 86.9, 82.0, 67.3, 63.1, 51.8, 42.3, 28.2; HRMS (ESI) calcd for $C_{35}H_{33}BrN_2NaO_3$ $[M + Na]^+$ 631.1572, found 631.1574.

(2*R*,3*R*,4*S*)-1-*tert*-Butyloxycarbonyl-2-(trityloxymethyl)-3-*para*-bromo-phenyl-4-cyano azetidine *ent*-17. Following the general protocol described above, 40.0 g of *N*-allyl azetidine *ent*-**5d** afforded 42.5 g (96%) of azetidine *ent*-**17**: $[\alpha]_D^{20}$ +21.4 (*c* 1.2, $CHCl_3$).

(2*S*,3*R*)-1-*tert*-Butyloxycarbonyl-2-(trityloxymethyl)-3-*para*-bromophenyl)-4-cyano-4-(tosyloxymethyl) azetidine 18. To a freshly prepared solution of LDA in anhydrous THF (made at 0 °C using 10.0 mL, 70.2 mmol, 3.0 equiv of DIPA in 50 mL of THF and 43.0 mL, 69.9 mmol, 3.0 equiv of *n*-BuLi 1.6 M in hexanes) was added dropwise at −78 °C via addition funnel and over 30 to 40 min a solution of *N*-Boc azetidine (14.1 g, 23.1 mmol, 1.0 equiv) in 150 mL of dry THF. The mixture was stirred for 2 h at −78 °C, and then solid benzotriazomethanol (BTM) was added in small portions every 15–20 min, over 1.5 h. The reaction mixture was stirred overnight and allowed to reach room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (100 mL), and the aqueous layer was separated and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford a crude material that was purified on silica gel (hexanes/EtOAc = 75:25) to afford alcohol as a mixture of two inseparable diastereomers (10.5 g, 16.4 mmol, 71% yield, colorless foam).

A 500 mL round-bottom flask was charged with a solution of alcohol intermediate (10.5 g, 16.4 mmol, 1.0 equiv) in 135 mL dry THF. At −78 °C, LiHMDS (1.0 M in THF, 19.0 mL, 19.0 mmol, 1.2 equiv) was added dropwise via an addition funnel. After 40 min, a solution of *p*-toluenesulfonyl chloride (TsCl, 3.9 g, 20.5 mmol, 1.3 equiv) in 15 mL dry THF was quickly syringed into the mixture and the temperature was slowly raised to room temperature, allowing for complete conversion of the starting material. The reaction was quenched with saturated NH_4Cl solution, and the layers were separated. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification on silica gel (hexanes/EtOAc = 75:25) afforded the sulfonate ester **18** (11.4 g, 14.4 mmol, 88% yield). Due to its complexity, no NMR listing is provided for this compound. A copy of the ^1H NMR spectrum is provided in the Supporting Information. HRMS (ESI) calcd for $C_{43}H_{41}BrN_2NaO_6S$ $[M + Na]^+$ 815.1766, found 815.1767.

(2*R*,3*S*)-1-*tert*-Butyloxycarbonyl-2-(trityloxymethyl)-3-*para*-bromophenyl)-4-cyano-4-(tosyloxymethyl)azetidine *ent*-18. Following the protocol above, 12.6 g (92% yield) of *ent*-**18** was obtained from 11.1 g of *ent*-**17**.

(2*S*,3*R*)-1-*tert*-Butyloxycarbonyl-2-(trityloxymethyl)-3-*para*-bromophenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane 19. A 500 mL round-bottom flask was charged with a solution of nitrile **18** (11.3 g, 14.3 mmol, 1.0 equiv) in 140 mL dry CH_2Cl_2. At −78 °C, neat DIBAL (12.7 mL, 71.5 mmol, 5.0 equiv) was added dropwise to the mixture via syringe. The reaction was kept at this temperature until complete conversion of the starting material (30 to 45 min, LC/MS analysis). A careful addition of 100 mL dry MeOH was done in order to quench the reaction, followed by 100 mL of Rochelle's salt solution. The mixture was progressively brought to 50 °C and was stirred at this temperature overnight. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was then dissolved in 140 mL of dry CH_2Cl_2, and triethylamine (4.0 mL, 28.5 mmol, 2.0 equiv) was quickly added to the mixture. At 0 °C, nosyl chloride (3.47 g, 15.7 mmol, 1.1 equiv) was added in one portion, and the reaction was stirred overnight at room temperature, resulting in partial cyclization of the nosylated amine. The mixture was washed with saturated $NaHCO_3$ solution, and the phases were separated. After extraction of the aqueous phase with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. K_2CO_3 (4.0 g, 28.6 mmol, 2.0 equiv) was added to the crude material dissolved in acetonitrile (140 mL), and the mixture was stirred at 60 °C until complete cyclization of the intermediate (LC/MS, 3 h). Water was then added, and the mixture was extracted twice with EtOAc. The combined organic fractions were washed with brine and dried over $MgSO_4$. After filtration and removal of the solvents in vacuo, the crude was purified on silica gel (hexanes/EtOAc = 70:30) to afford the spiroazetidine **19** (5.9 g, 7.3 mmol, 51% yield over three steps) as a slightly yellow foam: $[\alpha]^{20}_{D}$ −35.9 (c 1.2, $CHCl_3$); IR ν_{max} (film) 3056, 3021, 2974, 2930, 2870, 1698, 1544, 1367, 1164, 1074; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.66 (s, 3H), 7.49−7.35 (m, 7H), 7.35−7.19 (m, 10H), 6.97 (d, J = 8.3 Hz, 2H), 4.92 (d, J = 8.8 Hz, 1H), 4.48 (br s, 1H), 4.18 (d, J = 8.9 Hz, 1H), 4.17 (br s, 1H), 3.81 (br s, 1H), 3.57 (br s, 1H), 3.49 (br d, J = 4.3 Hz, 2H), 3.15 (br d, J = 8.2 Hz, 1H), 1.57−1.21 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 148.2, 143.6, 135.7, 133.5, 132.1, 131.8, 129.7, 128.6, 127.9, 127.2, 124.2, 121.7, 86.9, 81.3, 64.0, 63.1, 61.5, 57.2, 47.1, 28.4; HRMS (ESI) calcd for $C_{42}H_{40}BrN_3NaO_7S$ $[M + Na]^+$ 832.1668, found 832.1669.

(2*R*,3*S*)-1-*tert*-Butyloxycarbonyl-2-(trityloxymethyl)-3-*para*-bromophenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *ent*-19. Following the above protocol, 2.1 g of *ent*-**19** was obtained from 3.3 g of *ent*-**18** (61% yield): $[\alpha]^{20}_{D}$ +39.1 (c 1.2, $CHCl_3$).

(2*S*,3*R*)-1-Allyl-2-(hydroxymethyl)-3-*para*-bromophenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane 15c. A solution of trityl ether **19** (5.9 g, 7.3 mmol, 1.0 equiv) in 73 mL of CH_2Cl_2 was added to a 250 mL round-bottom flask. At 0 °C, trifluoroacetic acid was slowly added via syringe and the mixture was stirred at this temperature for 1 h. The cold bath was then removed, and the reaction was left overnight at room temperature. Then, 36 mL of MeOH was quickly added followed by a careful addition of K_2CO_3 (30.2 g, 219.0 mmol, 30.0 equiv). After 1 h, the mixture was partitioned between water and CH_2Cl_2. The organic layer was washed one more time with water, dried over $MgSO_4$, filtered, and concentrated. The crude material was dissolved in acetonitrile (60 mL), and K_2CO_3 (1.5 g, 10.9 mmol, 1.5 equiv) was added, followed by allyl bromide (0.8 mL, 8.7 mmol, 1.2 equiv). The mixture was stirred at 80 °C using sealed tube conditions until complete disappearance of the starting material (3 h, monitored by LC/MS). The mixture was partitioned between water and EtOAc, and the organic layer was dried over $MgSO_4$, filtered, concentrated, and purified on silica gel (hexanes/EtOAc = 20:80) to afford *N*-allylated spiroazetidine **15c** as a colorless foam (1.9 g, 3.6 mmol, 50% yield over two steps): $[\alpha]^{20}_{D}$ +37.7 (c 1.3, $CHCl_3$); IR ν_{max} (film) 3396, 2922, 2848, 1543, 1370, 1171, 1010; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.5 Hz, 1H), 7.76−7.58 (m, 3H), 7.40 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 5.80 (ddt, J = 16.8, 10.0, 6.6 Hz, 1H), 5.22 (d, J = 17.1 Hz, 1H), 5.06 (d, J = 10.0 Hz, 1H), 4.34 (d, J = 9.3 Hz, 1H), 4.22 (d, J = 9.4 Hz, 1H), 4.12 (d, J = 9.4 Hz, 1H), 3.71−3.59 (m, 2H), 3.54 (d, J = 9.3 Hz, 1H), 3.51−3.42 (m, 2H), 3.39 (dd, J = 13.6, 6.6 Hz, 1H), 3.18 (dd, J = 13.4, 6.8 Hz 1H), 2.39 (br d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 134.9, 134.5, 133.8, 132.0, 131.7, 131.0, 130.8, 129.6, 124.2, 121.4, 118.7, 66.1, 64.8, 63.6, 61.2, 53.0, 52.9, 45.1; HRMS (ESI) calcd for $C_{21}H_{23}BrN_3O_5S$ $[M + H]^+$ 508.0542, found 508.0542.

(2*R*,3*S*)-1-Allyl-2-(hydroxymethyl)-3-*para*-bromophenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *ent*-15c. Following the above protocol, 2.4 g of *ent*-**15c** was obtained starting from 7.4 g of *ent*-**19** (52% over 2 steps): $[\alpha]^{20}_{D}$ −35.9 (c 1.0, $CHCl_3$).

(2*S*,3*R*,4*R*)-1-Allyl-3-(2-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl)azetidine 21a and (2*S*,3*R*,4*S*)-1-Allyl-3-(2-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl)azetidine 21b. Compound **20a** (41.6 g, 146 mmol, 1 equiv) was treated with trityl chloride (60.9 g, 218 mmol, 1.5 equiv) and triethylamine (60.9 mL, 437 mmol, 3.0 equiv) in CH_2Cl_2 (1450 mL). The reaction mixture was quenched with water extracts and dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The reaction provided, after purification, gave 70 g (91%) of trityl-**20a**: $[\alpha]^{20}_{D}$ −21.3 (c 1.9, $CHCl_3$); IR ν_{max} (film) 3060, 3021, 1489, 1460, 1448, 1281, 1071, 1031, 753; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.43 (m, 8H), 7.31 (dq, J = 6.8, 14.0 Hz, 10H), 7.15 (dd, J = 4.5, 10.7 Hz, 1H), 5.82 (ddt, J = 6.0, 10.5, 16.6 Hz, 1H), 5.12−4.98 (m, 2H), 4.89 (d, J = 3.3 Hz, 1H), 3.62−3.44 (m, 1H), 3.24 (m, 2H), 3.11−2.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 147.1, 143.9, 142.3, 136.6, 132.8, 128.8, 128.8, 128.3, 128.2, 128.0, 127.9, 127.4, 127.2, 126.7, 122.5, 116.2, 87.1, 70.9, 63.6, 61.5, 51.2; HRMS (ESI) calcd for $C_{31}H_{30}BrNO_2$ $[M + H]^+$ 528.1538, found 528.1543.

Nitrile-20a. The secondary amine (70 g, 132 mmol, 1 equiv) obtained above was treated with 2-bromoacetonitrile (27.7 g, 397 mmol, 3 equiv) and potassium carbonate (27.5 g, 199 mmol, 1.5 equiv) in acetonitrile (1325 mL). Solvent was removed in vacuo, and the resulting material was purified directly over silica gel to afford 67 g (89%) of pure product: $[\alpha]^{20}_{D}$ −39.8 (c 0.9, $CHCl_3$); IR ν_{max} (film) 3472, 3059, 2359, 2342, 1490, 1448, 1219, 1073, 1032, 772; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 7.8 Hz, 1H), 7.50−7.05 (m, 18H), 5.83−5.55 (m, 1H), 5.32−5.12 (m, 2H), 4.92 (d, J = 7.2 Hz, 1H), 3.86−3.69 (m, 2H), 3.68 (m, 1H), 3.44 (m, 2H), 3.30 (m, 2H), 3.14 (dd, J = 7.6, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.5, 134.5, 132.6, 129.3, 129.1, 128.6, 128.0, 127.9, 127.3, 123.2, 119.6, 87.9, 70.4, 67.6, 60.6, 54.5, 40.3; HRMS (ESI) calcd for $C_{33}H_{31}BrN_2O_2$ $[M + Na]^+$ 589.1467, found 589.1467

Chloride-20a. The resulting benzyl alcohol (nitrile-**20a**) (20 g, 35.2 mmol, 1 equiv) was treated with thionyl chloride (5.13 g, 70 mmol, 2 equiv) and pyridine (14.25 mL, 176 mmol, 5 equiv) in CH_2Cl_2 (352 mL). The reaction mixture was carefully quenched with aqueous sodium bicarbonate solution, and the extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The reaction provided, after purification, 15 g (73%) of chloride-**20a**: $[\alpha]^{20}_{D}$ −72.9 (c 1.8, $CHCl_3$); IR ν_{max} (film) 3060, 3022, 2882, 2359, 2342, 1490, 1468, 1448, 1219, 1154, 1072, 763, 747; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 1.4, 7.9 Hz, 1H), 7.56 (dd, J = 0.9, 8.0 Hz, 1H), 7.51−7.42 (m, 6H), 7.40−7.09 (m, 11H), 5.76 (d, J = 4.9 Hz, 1H), 5.44 (dddd, J = 5.5, 7.5, 9.7, 15.2 Hz, 1H), 5.25−5.02 (m, 2H), 3.80−3.57 (m, 2H), 3.57−3.31 (m, 4H), 3.14 (dd, J = 7.5, 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.1, 134.6, 132.7, 131.1, 129.8, 128.8, 128.1, 127.6, 127.3, 122.7, 119.0, 117.4, 87.7, 64.5, 62.6, 61.5, 55.8, 40.4; HRMS (ESI) calcd for $C_{33}H_{30}BrClN_2O$ [M + Na]$^+$ 607.1122, found 607.1122.

Chloride-**20a** (25 g, 43 mmol, 1 equiv) was treated with LiHMDS (55.5 mL, 55 mmol, 1.3 equiv) in THF (427 mL). The reaction mixture was quenched with aqueous saturated NH_4Cl solution, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The reaction provided, after purification, 11.5 g (49%) of **21a** and 11.5 g (49%) of **21b**.

21a: $[\alpha]_D^{20}$ +47.1 (*c* 1.5, $CHCl_3$); IR ν_{max} (film) 3057, 3021, 2866, 2359, 2342, 1489, 1472, 1448, 1220, 1073, 1024, 772, 749; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.61 (d, *J* = 8.0, 1H), 7.26 (m, 17H), 5.80 (ddt, *J* = 6.6, 10.0, 16.6 Hz, 1H), 5.28 (d, *J* = 16.6 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.65 (t, *J* = 8.1 Hz, 1H), 4.22 (d, *J* = 8.2 Hz, 1H), 3.77 (td, *J* = 5.5, 7.9 Hz, 1H), 3.36 (dd, *J* = 6.2, 13.0 Hz, 1H), 3.19 (dd, *J* = 7.1, 12.9 Hz, 1H), 3.06 (dd, *J* = 5.4, 9.7 Hz, 1H), 3.01−2.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 133.8, 133.1, 133.0, 131.0, 129.4, 128.7, 128.7, 127.9, 127.4 127.0, 126.0, 119.9, 117.5, 86.7, 77.6, 77.2, 76.8, 66.3, 61.7, 60.8, 54.5, 41.1; HRMS (ESI) calcd for $C_{33}H_{30}BrN_2O$ [M + H]$^+$ 549.1542, found 549.1548.

21b: $[\alpha]_D^{20}$ +7.9 (*c* 0.50, $CHCl_3$); IR ν_{max} (film) 3057, 2864, 1489, 1474, 1448, 1069, 1028; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 10.9, 7.9, 1.4 Hz, 2H), 7.25−7.17 (m, 15H), 7.17−7.09 (m, 2H), 5.70 (ddt, *J* = 10.2, 6.5, 6.1 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.44 (dd, *J* = 8.1, 3.5 Hz, 1H), 4.34 (d, *J* = 3.5 Hz, 1H), 4.13 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.48−3.27 (m, 2H), 2.97 (dd, *J* = 10.0, 5.4 Hz, 1H), 2.85 (dd, *J* = 10.0, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 135.7, 133.3, 133.0, 129.2, 128.7, 128.6, 127.8, 127.7, 127.0, 125.4, 118.9, 117.4, 87.0, 66.4, 62.2, 55.6, 55.0, 43.1; HRMS (ESI) calcd for $C_{33}H_{30}BrN_2O$ [M + H]$^+$ 549.1542, found 549.1537.

(2*S*,3*R*,4*R*)-1-Allyl-3-(2-bromophenyl)-4-carbonitrile-2-((trityloxy)methyl)azetidine 21c. Following the protocols described above for the formation of **21a** and **21b**, 25 g of trityl-**20b** gave 40.5 g (88%) of trityl protected product: $[\alpha]_D^{20}$ −23.2 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3465, 3065, 2882, 1496, 1443, 904; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.8 Hz, 1H), 7.31−7.24 (m, 4H), 7.24−7.09 (m, 12H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.99−6.89 (m, 1H), 5.91 (ddd, *J* = 16.1, 10.9, 5.8 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.14−5.02 (m, 2H), 4.13 (br s, 1H), 3.41 (dd, *J* = 14.4, 5.5 Hz, 1H), 3.30 (dd, *J* = 14.4, 6.1 Hz, 1H), 3.12 (dt, *J* = 7.0, 3.6 Hz, 1H), 2.99 (qd, *J* = 9.9, 5.3 Hz, 2H), 2.06 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 143.8, 139.9, 137.1, 132.6, 128.7, 128.6, 128.3, 128.2, 128.08, 128.00, 127.3, 127.2, 126.7, 121.7, 116.2, 87.4, 71.6, 62.6, 59.0, 49.8; HRMS (ESI) calcd for $C_{31}H_{30}BrNO_2$ [M + H]$^+$ 528.1558, found 528.1560.

The secondary amine (40 g) described above afforded 37 g (86%) of nitrile-**20b**: $[\alpha]_D^{20}$ −15.9 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3465, 3065, 2883, 1496, 1443, 904; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.1 Hz, 6H), 7.32−7.20 (m, 9H), 7.21−7.03 (m, 2H), 5.70 (dt, *J* = 17.0, 8.4 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 2H), 5.20 (d, *J* = 10.5 Hz, 1H), 3.76 (d, *J* = 17.2 Hz, 1H), 3.63 (d, *J* = 17.5 Hz, 1H), 3.54−3.40 (m, 3H), 3.30−3.17 (m, 2H), 2.91 (d, *J* = 4.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.7, 135.0, 132.9, 129.2, 128.8, 128.5, 128.1, 127.6, 127.3, 122.2, 119.1, 117.4, 87.9, 73.3, 64.5, 60.8, 55.3, 39.6; HRMS (ESI) calcd for $C_{33}H_{31}BrN_2O_2$ [M + Na]$^+$ 589.1467, found 589.1471.

The tertiary amine (18.5 g) described above afforded 12.5 g (65%) of chloride-**20b**: IR ν_{max} (film) 3065, 2913, 1491, 1443, 1065; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 6H), 7.26−7.10 (m, 9H), 7.04 (t, *J* = 7.3 Hz, 1H), 5.46 (d, *J* = 8.8 Hz, 1H), 5.28−5.09 (m, 1H), 4.94−4.77 (m, 2H), 3.69 (dd, *J* = 10.7, 2.0 Hz, 1H), 3.53 (dd, *J* = 10.6, 6.8 Hz, 1H), 3.44−3.36 (m, 1H), 3.34 (s, 2H), 3.18 (dd, *J* = 14.2, 5.0 Hz, 1H), 2.73 (dd, *J* = 14.2, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 139.0, 134.7, 132.8, 130.0, 129.8, 128.9, 128.1, 128.0, 127.4, 123.8, 118.7, 117.1, 87.9, 66.3, 60.4, 59.5, 54.1, 40.0; HRMS (ESI) calcd for $C_{33}H_{30}BrClN_2O$ [M + Na]$^+$ 607.1122, found 607.1108.

A solution of the above chloride-**20b** (17 g, 29.00 mmol, 1 equiv) in THF (290 mL) was cooled to −78 °C. To this mixture was added a cooled solution of LiHMDS (1 M in THF 43.5 mL, 43.5 mmol, 1.5 equiv) via cannula. The reaction mixture was stirred for 1 h and quenched with aqueous saturated NH_4Cl solution, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The reaction provided, after purification, 13 g (82%) of **21c** and 0.110 g (~1%) of **21d**.

21c: $[\alpha]_D^{20}$ −14.0 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3035, 2861, 1487, 1452, 1217; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 5H), 7.21 (m, 12H), 5.74 (m, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.15 (d, *J* = 10.1 Hz, 1H), 4.84 (d, *J* = 6.3 Hz, 1H), 3.95 (m, 2H), 3.54 (m, 1H), 3.32 (ddd, *J* = 6.2, 12.2, 18.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 135.7, 133.3, 133.1, 129.6, 129.5, 128.9, 128.2, 128.1, 127.8, 127.4, 119.2, 115.5, 87.3, 66.8, 66.4, 57.2, 56.0, 43.5; HRMS (ESI) calcd for $C_{33}H_{29}BrN_2NaO$ [M + Na]$^+$ 571.1361, found 571.1369.

21d: $[\alpha]_D^{20}$ +1.6 (*c* 0.63, $CHCl_3$); IR (cm^{-1}) 3057, 2866, 1489, 1473, 1447, 1072, 1025; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 8.2, 1.4 Hz, 6H), 7.38−7.21 (m, 11H), 7.21−7.11 (m, 1H), 5.92 (dddd, *J* = 15.8, 10.1, 7.4, 5.7 Hz, 1H), 5.35 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.25 (d, *J* = 10.1 Hz, 1H), 4.21 (t, *J* = 8.1 Hz, 1H), 3.66−3.52 (m, 3H), 3.41 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.33 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.21 (dd, *J* = 13.1, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 136.9, 133.5, 133.0, 129.3, 128.8, 128.7, 128.0, 127.7, 127.2, 124.8, 119.8, 119.5, 87.0, 68.2, 66.6, 60.6, 55.4, 44.2; HRMS (ESI) calcd for $C_{33}H_{29}BrN_2NaO$ [M + Na]$^+$ 571.1361, found 571.1350.

***N*-(((2*S*,3*R*,4*R*)-1-Allyl-3-(2-bromophenyl)-4-((trityloxy)-methyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide 22a.** Nitrile azetidine **21a** (13 g, 24 mmol, 1 equiv) was treated with diisobutylaluminium hydride (25 mL, 142 mmol, 6 equiv) in CH_2Cl_2 (240 mL). The reaction was quenched with MeOH (5.74 mL, 6 equiv). After aqueous extraction, the crude amine (13 g, 23.5 mmol) was treated with 2-nitrobenzene-1-sulfonyl chloride (5.4 g, 23.5 mmol, 1 equiv) and triethylamine (3.9 mL, 30.5 mmol, 1.3 equiv). The reaction mixture was quenched with aqueous saturated NH_4Cl solution, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The reaction, after purification, provided 11.7 g (68%) of pure product **22a**: $[\alpha]_D^{20}$ −27.4 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3058, 3021, 2930, 2860, 1540, 1448, 1348, 1169, 1072, 1023, 759; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 1.7, 7.4 Hz, 1H), 7.80 (dd, *J* = 1.7, 7.4 Hz, 1H), 7.70−7.60 (m, 2H), 7.58 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.54 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.21 (m, 15H), 7.00 (tdd, *J* = 4.5, 10.5, 14.9 Hz, 2H), 5.82−5.64 (m, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 9.5 Hz, 2H), 4.45 (t, *J* = 7.9 Hz, 1H), 3.70 (td, *J* = 5.4, 8.0 Hz, 1H), 3.60 (td, *J* = 5.6, 7.9 Hz, 1H), 3.35−3.19 (m, 2H), 3.18−3.05 (m, 2H), 3.00 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 143.9, 135.4, 134.8, 133.6, 133.4, 133.4, 132.9, 131.4, 130.9, 128.6, 128.4, 127.7, 126.9, 126.7, 126.3, 125.6, 118.4, 86.3, 65.8, 65.7, 61.5, 61.2, 43.3, 40.8; HRMS (ESI) calcd for $C_{39}H_{36}BrN_3O_5S$ [M + H]$^+$ 738.1637, found 738.1635.

***N*-(((2*R*,3*R*,4*R*)-1-Allyl-3-(2-bromophenyl)-4-((trityloxy)-methyl)azetidin-2-yl)methyl)-2-nitrobenzenesulfonamide 22c.** Following the above protocol, 5.2 g of nitrile azetidine **21c** afforded 5.5 g (79%) of nosyl amine **22c**: $[\alpha]_D^{20}$ −28.4 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3334, 3038, 2887, 1534, 1336, 1169; ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.1, 143.9, 137.1, 136.1, 133.8, 133.4, 133.0, 132.7, 131.1, 129.5, 128.9, 128.8, 128.0, 127.8, 127.2, 126.6, 125.4, 116.9, 87.2, 64.7, 64.6, 63.6, 52.9, 42.7, 42.4; HRMS (ESI) calcd for $C_{39}H_{36}BrN_3O_5S$ [M + H]$^+$ 738.1637, found 738.1614.

(1*S*,2a*R*,8b*R*)-2-Allyl-4-((2-nitrophenyl)sulfonyl)-1-((trityloxy)methyl)-1,2,2a,3,4,8b-hexahydroazeto[2,3-c]-quinolone 23a. To a solution of nosyl amine **22a** (11.7 g, 15.9 mmol, 1 equiv) in degassed toluene (160 mL) was added *N*,*N*-dimethyl-ethane-1,2-diamine (0.34 mL, 3.2 mmol, 0.2 equiv), cesium carbonate (7.7 g, 23.9 mmol, 1.5 equiv), and copper(I) iodide (0.3 g, 1.6 mmol, 0.1 equiv). The reaction was heated at 100 °C for 2 h. The reaction was then cooled, and the solution was then filtered through a pad of silica gel. The solvent was removed under vacuum to afford 10.4 g (99%) of the desired product **23a**: $[\alpha]_D^{20}$ −19.8, (*c* 1.46, $CHCl_3$); mp 96.1−100.7 °C; IR ν_{max} (film) 3060, 3022, 2871, 1542, 1489, 1448, 1369, 1219, 1165, 1068, 761; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.62−7.51 (m, 2H), 7.39−7.15 (m, 17H), 7.16−7.05 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 5.60 (ddt, *J* = 6.8, 9.8, 16.8 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 4.31 (dd, *J* = 2.1, 14.4 Hz, 1H), 3.77−3.58 (m, 3H), 3.17 (m, 2H), 3.08 (dd, *J* = 1.2, 14.4 Hz, 1H), 2.83 (dd, *J* = 4.2, 9.9 Hz, 1H), 2.64 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 138.2, 136.0, 135.1, 133.1, 132.2, 131.6, 131.0, 129.3, 128.9, 128.8, 128.5, 127.8, 127.1, 127.0, 125.5, 125.5, 124.1, 123.1, 117.9, 95.2, 87.1, 66.1, 64.1, 61.8, 59.6, 48.6, 34.4; HRMS (ESI) calcd for $C_{39}H_{35}N_3O_5S$ $[M + H]^+$ 658.2376, found 658.2371.

(1*R*,2a*R*,8b*R*)-2-Allyl-4-((2-nitrophenyl)sulfonyl)-1-((trityloxy)methyl)-1,2,2a,3,4,8b-hexahydroazeto[2,3-*c*]-quinolone 23c. Following the above protocol, 7.0 g of nosyl amine **22c** afforded 6.2 g (99%) of **23c**: $[\alpha]_D^{20}$ +24.1 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3010, 2891, 1539, 1365, 1209, 1156, 904; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.4 Hz, 1H), 7.69−7.54 (m, 3H), 7.43 (d, *J* = 7.4 Hz, 4H), 7.34−7.19 (m, 12H), 7.19−6.97 (m, 3H), 5.67 (dq, *J* = 11.3, 6.1 Hz, 1H), 5.04 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 9.3 Hz, 1H), 4.13 (dd, *J* = 13.8, 5.5 Hz, 1H), 4.08−3.97 (m, 1H), 3.57 (ddd, *J* = 15.0, 11.9, 4.3 Hz, 2H), 3.41−3.12 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 144.1, 137.3, 135.7, 135.4, 133.7, 131.9, 130.6, 129.5, 128.9, 128.0, 127.3, 126.4, 124.6, 123.9, 117.0, 87.2, 69.3, 65.1, 60.1, 52.6, 48.3, 35.5; HRMS (ESI) calcd for $C_{39}H_{35}N_3O_5S$ $[M + H]^+$ 658.2376, found 658.2368.

((1*S*,2a*R*,8b*R*)-2-Allyl-4-((2-nitrophenyl)sulfonyl)-1,2,2a,3,4,8b-hexahydroazeto[2,3-*c*]quinolin-1-yl)methanol 24a. Trityl alcohol **23a** (0.120 g, 0.162 mmol, 1 equiv) was treated with trifluoroacetic acid (0.10 mL, 1.30 mmol, 8 equiv) in CH_2Cl_2 (2 mL) at 0 °C and allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with a saturated sodium bicarbonate solution, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The reaction provided, after purification, 0.405 g (50%) of pure product **24a**: $[\alpha]_D^{20}$ +35.6 (*c* 1.7, $CHCl_3$); IR ν_{max} (film) 3417, 2922, 2857, 1541, 1498, 1350, 1161, 1130, 1027, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28−8.15 (m, 1H), 7.73 (m, 3H), 7.14−6.96 (m, 3H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.95 (ddt, *J* = 6.8, 10.1, 16.8 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 4.33 (dd, *J* = 1.9, 14.5 Hz, 1H), 3.72 (d, *J* = 7.2 Hz, 1H), 3.66−3.51 (m, 2H), 3.45−3.18 (m, 4H), 3.01 (d, *J* = 14.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 137.9, 137.1, 135.7, 133.8, 132.5, 131.1, 131.0, 130.1, 127.2, 126.2, 124.8, 122.9, 118.0, 67.8, 62.2, 61.3, 59.3, 48.6, 34.2; HRMS (ESI) calcd $C_{20}H_{21}N_3O_5S$ $[M + H]^+$ 416.1280, found 416.1281.

((1*R*,2a*R*,8b*R*)-2-Allyl-4-((2-nitrophenyl)sulfonyl)-1,2,2a,3,4,8b-hexahydroazeto[2,3-*c*]quinolin-1-yl)methanol 24c. Following the protocol above, 0.500 g of **23c** afforded 0.160 g (50%) of **24c**: $[\alpha]_D^{20}$ −28.0 (*c* 1.7, $CHCl_3$); IR ν_{max} (film) 3417, 2922, 2857, 1541, 1498, 1350, 1161, 1130, 1027, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 3.9 Hz, 2H), 7.74−7.63 (m, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.35−7.21 (m, 1H), 7.15 (s, 2H), 5.84 (qd, *J* = 11.6, 6.0 Hz, 1H), 5.31 (d, *J* = 16.7 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 4.39 (dd, *J* = 14.4, 5.0 Hz, 1H), 4.14 (s, 1H), 3.82−3.45 (m, 6H), 3.42−3.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 144.1, 137.6, 135.2, 134.1, 132.4, 130.2, 128.9, 128.0, 127.6, 126.6, 125.0, 123.1, 118.3, 72.5, 61.1, 60.4, 51.5, 47.1, 33.3; HRMS (ESI) calcd for $C_{20}H_{21}N_3O_5S$ $[M + H]^+$ 416.1280, found 416.1281.

(1*S*,2a*R*,8b*R*)-2-Allyl-2,2a,3,8b-tetrahydro-1*H*-chromeno[3,4-*b*]azete-1-carbonitrile 25a. To a solution of *o*-bromonitrile azetidine **21a** (500 mg, 0.91 mmol, 1.0 equiv) in CH_2Cl_2 (9.1 mL) at room temperature was added trifluoroacetic acid (0.5 mL, 6.5 mmol, 7.0 equiv) followed by triethylsilane (150 mL, 0.96 mmol, 1.05 equiv). The reaction was stirred for 15 min, after which analysis of the reaction by TLC and LC/MS showed that complete consumption of starting material had occurred. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by chromatography on silica gel using hexanes/EtOAc, which provided 204 mg (73%) of pure product that was used in the next reaction without further characterization.

To a flask containing palladium acetate (4.5 mg, 0.020 mmol, 0.03 equiv), 1,1′-binaphthyl-2-yl-di-*tert*-butylphosphine (12 mg, 0.030 mmol, 0.045 equiv), and cesium carbonate (325 mg, 0.995 mmol, 1.5 equiv) was added a solution of the pure alcohol from the previous step (204 mg, 0.684 mmol, 1.0 equiv) in toluene (2.2 mL) at room temperature. The reaction was heated to 55 °C and stirred for 16 h. Analysis of the reaction showed complete consumption of starting material and conversion to the desired product. The reaction was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated, and the resulting yellow residue was purified by chromatography on silica gel using hexanes/EtOAc, which provided the pure aryl ether: $[\alpha]_D^{20}$ +130.0 (*c* 0.24, $CHCl_3$); IR ν_{max} (film) 2975, 2894, 1491, 1463, 1333, 1259, 1225, 1201, 1093; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.20 (m, 1H), 7.09 (d, *J* = 8.1, 2.1 Hz, 1H), 7.03 (ddd, *J* = 7.4, 5.6, 1.2 Hz, 2H), 5.89 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.32 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.24 (d, *J* = 10.1 Hz, 1H), 4.22−4.10 (m, 2H), 3.83−3.67 (m, 2H), 3.62 (dd, *J* = 12.6, 1.3 Hz, 1H), 3.43−3.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 133.0, 130.7, 129.1, 122.2, 120.0, 119.7, 118.3, 117.0, 65.4, 62.2, 59.5, 55.8, 31.8; HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$ 227.1184, found 227.1178.

To a solution of the aryl ether (42 mg, 0.186 mmol, 1.0 equiv) in CH_2Cl_2 (1.9 mL) at 0 °C was added diisobutylaluminum hydride (0.198 mL, 1.11 mmol, 6.0 equiv). The reaction was stirred for 1 h, after which TLC showed complete consumption of starting material. The reaction was quenched with MeOH and stirred until bubbling stopped. Then a saturated solution of Rochelle's salt was added (25 mL), and the mixture was vigorously stirred for about 90 min until the aqueous and organic layers had clearly separated. The layers were then separated, and the aqueous layer was extracted once with CH_2Cl_2 (15 mL). The combined organic layers were dried, filtered, and concentrated in vacuo, and the crude material (32 mg, 75%) was used in the next step without further purification.

The crude residue was then redissolved in CH_2Cl_2 (1.4 mL) at 0 °C, and then triethylamine (39 mL, 0.28 mmol, 2.0 equiv) and 2-nitrobenzenesulfonyl chloride (32 mg, 0.15 mmol, 1.05 equiv) were added. The reaction was stirred until all starting material had been consumed (~60 min) as determined by LC/MS. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel using hexanes/EtOAc, which provided **25a** as a clear oil: $[\alpha]_D^{20}$ +46.5 (*c* 0.195, $CHCl_3$); IR ν_{max} (film) 3319, 2869, 1539, 1488, 1348, 1167; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 6.9, 1.8 Hz, 1H), 7.81 (dd, *J* = 7.8, 2.4, 1H), 7.75−7.57 (m, 2H), 7.15−6.94 (m, 2H), 6.94−6.78 (m, 2H), 5.86 (ddt, *J* = 17.0, 10.9, 6.8 Hz, 1H), 5.36 (br s, 1H), 5.27 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.16 (d, *J* = 10.0 Hz, 1H), 4.06 (d, *J* = 12.2 Hz, 1H), 3.78−3.59 (m, 3H), 3.53 (dd, *J* = 12.2, 1.3 Hz, 1H), 3.37 (dd, *J* = 12.7, 6.3 Hz, 1H), 3.24 (d, *J* = 12.7, 7.2 Hz, 1H), 2.87−2.70 (m, 1H), 2.70−2.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 148.1, 134.7, 133.7, 133.5, 132.8, 130.9, 130.1, 128.2, 125.4, 122.0, 121.2, 119.1, 118.4, 66.7, 65.2, 61.9, 60.3, 44.9, 31.0; HRMS (ESI) calcd for $C_{20}H_{22}N_3O_5S$ $[M + H]^+$ 416.1280, found 416.1278.

(1*S*,2a*R*,8b*R*)-2-Allyl-2,2a,3,8b-tetrahydro-1*H*-chromeno[3,4-*b*]azete-1-carbonitrile 25b. *o*-Bromonitrile azetidine **21b** (1.89 g, 3.44 mmol, 1.0 equiv) in CH_2Cl_2 (69 mL) was reacted with trifluoroacetic acid (2.65 mL, 34.4 mmol, 10 equiv). The reaction was stirred for 15 min, after which analysis of the reaction by TLC and LC/MS showed that complete consumption of starting material had occurred. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by chromatography on silica gel using hexanes/EtOAc, which provided 646 mg (61% yield) of pure product, and used in the next step without further characterization.

The intermediate alcohol (124 mg, 0.404 mmol, 1.0 equiv) was reacted with palladium acetate (3.90 mg, 0.017 mmol, 4.5 mol %), 1,1′-binaphthyl-2-yl-di-*tert*-butylphosphine (10.5 mg, 0.026 mmol, 6.5

mol %), and cesium carbonate (197 mg, 0.605 mmol, 1.5 equiv) in toluene (3.0 mL) at 55 °C for 16 h and then at 70 °C for 3 h. The filtrate was concentrated, and the resulting yellow residue was purified by chromatography on silica gel using hexanes/EtOAc, which provided the pure aryl ether (62 mg, 68% yield): $[\alpha]_D^{20}$ −125.9 (*c* 0.28, $CHCl_3$); IR ν_{max} (film) 2861, 2818, 1582, 1489, 1460, 1258, 1229, 1117; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 14.8, 7.5 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.05 (dd, *J* = 7.3, 6.0 Hz, 2H), 5.89 (ddt, *J* = 16.5, 10.3, 6.3 Hz, 1H), 5.42 (d, *J* = 17.1 Hz, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 4.33 (d, *J* = 12.8 Hz, 1H), 4.10 (d, *J* = 7.8 Hz, 1H), 3.98 (s,1H), 3.85 (d, *J* = 7.7 Hz, 1H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.49 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 133.2, 129.8, 129.0, 122.4, 122.0, 119.4, 118.4, 117.6, 65.6, 63.1, 57.6, 55.4, 34.3; HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$ 227.1184, found 227.1185.

The cyclized product (50 mg, 0.221 mmol, 1.0 equiv) was reacted with diisobutylaluminum hydride (0.28 mL, 1.571 mmol, 7.0 equiv) in CH_2Cl_2 (2.2 mL) at 0 °C. The reaction was stirred for 1 h, after which TLC showed complete consumption of starting material. The reaction was quenched with MeOH and stirred until bubbling stopped. Then a saturated solution of Rochelle's salt was added (25 mL), and the mixture was vigorously stirred for about 90 min until the aqueous and organic layers had clearly separated. The layers were then separated, and the aqueous layer was extracted once with CH_2Cl_2 (15 mL). The combined organic layers were dried, filtered, and concentrated in vacuo, and the crude material (51 mg, 99% yield) was used in the next step without further purification.

The crude residue was reacted with triethylamine (62 mL, 0.443 mmol, 2.0 equiv) and 2-nitrobenzenesulfonyl chloride (52 mg, 0.233 mmol, 1.05 equiv) in CH_2Cl_2 (4.4 mL) at 0 °C for ∼60 min. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel using hexanes/EtOAc, which provided, after purification, 23 mg (25% yield) of pure product **25b**: $[\alpha]_D^{20}$ −6.3 (*c* 0.51, $CHCl_3$); IR ν_{max} (film) 3077, 2914, 1536, 1487, 1346, 1163, 1114; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 5.6, 3.6 Hz, 1H), 7.86 (dd, *J* = 5.8, 3.4 Hz, 1H), 7.75 (dd, *J* = 5.8, 3.5 Hz, 2H), 7.23−7.13 (m, 1H), 6.95 (dd, *J* = 6.8, 1.7 Hz, 3H), 6.46 (s, 1H), 5.66 (ddd, *J* = 16.6, 11.1, 6.2 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 4.91 (d, *J* = 10.2 Hz, 1H), 4.58 (d, *J* = 13.0 Hz, 1H), 4.18 (d, *J* = 8.2 Hz, 1H), 3.66−3.53 (m, 2H), 3.53−3.38 (m, 2H), 3.32−3.09 (m, 3H), 3.00 (dd, *J* = 12.7, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 148.3, 134.8, 133.7, 133.5, 132.7, 131.3, 128.3, 127.2, 125.4, 122.7, 118.0, 117.8, 70.9, 66.2, 61.7, 52.5, 45.2, 33.2; HRMS (ESI) calcd for $C_{20}H_{22}N_3O_5S$ $[M + H]^+$ 416.1280, found 416.1266.

(2*R*,3*R*,4*S*)-4-(Carbonitrile)-3-phenyl-1-propylazetidine-2-hydroxymethyl 26a. To the solution of **5a** (5.00 g, 9.10 mmol) in isopropyl alcohol (91 mL) were added AIBN (0.299 g, 1.82 mmol) and tributylchlorostannane (0.368 mL, 1.37 mmol). The reaction mixture was heated to reflux (∼100 °C) and was allowed to stir of 5 min. After 5 min at reflux, a solution of sodium cyanotrihydroborate (0.86 g, 13.7 mmol) in isopropyl alcohol (20 mL) was added simultaneously with a solution of AIBN (0.600 g, 3.64 mmol) in 20 mL of isopropyl alcohol via two separate syringes over a 10 min period. The reaction was stirred for approximately 1 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was residue was purified over silica gel to obtain 3.50 g (82%) of the dehalogenated material: $[\alpha]_D^{20}$ +42.3 (*c* 0.17, $CHCl_3$); IR ν_{max} (film) 3056, 2866, 1490, 1448, 1264, 1063; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48−7.41 (m, 2H), 7.31−7.25 (m, *J* = 6.3, 9.6 Hz, 3H), 7.22−7.06 (m, *J* = 6.0, 7.9, 14H), 5.76 (ddt, *J* = 6.7, 10.1, 13.3 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 4.11−4.03 (m, 1H), 3.81 (t, *J* = 7.9 Hz, 1H), 3.63 (dd, *J* = 7.4, 13.5 Hz, 1H), 3.37 (dd, *J* = 5.9, 12.9 Hz, 1H), 3.11 (dd, *J* = 7.2, 12.9 Hz, 1H), 3.03 (dd, *J* = 5.9, 9.6 Hz, 1H), 2.89 (dd, *J* = 7.3, 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 134.3, 132.9, 129.8, 128.4, 128.2, 127.8, 127.6, 126.8, 119.4, 117.6, 86.5, 66.5, 62.1, 60.8, 54.7, 42.9; HRMS (ESI) calcd for $C_{33}H_{30}N_2O$ $[M + H]^+$ 471.2436, found 471.2448.

The dehalogenated intermediate (4.85 g, 10.31 mmol) was treated with trifluoroacetic acid (6.35 mL, 82.0 mmol, 8 equiv) in CH_2Cl_2 (103 mL) at 0 °C and allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with a saturated sodium bicarbonate solution, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The reaction provided, after purification, 1.90 g (81%) of pure product: $[\alpha]_D^{20}$ +187.2 (*c* 1.21, $CHCl_3$); IR ν_{max} (film) 3419, 2867, 1643, 1490, 1414, 1071, 1009; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 6.9, 1.5 Hz, 2H), 7.46−7.28 (m, 3H), 5.91 (dt, *J* = 17.0, 10.1, 6.6 Hz, 1H), 5.34 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.25 (d, *J* = 10.1 Hz, 1H), 4.14 (d, *J* = 8.1 Hz, 1H), 3.81 (t, *J* = 7.9 Hz, 1H), 3.62−3.44 (m, 2H), 3.45−3.28 (m, 2H), 3.21 (dd, *J* = 13.1, 6.9 Hz, 1H), 1.42 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 133.4, 129.8, 128.6, 128.3, 119.7, 117.6, 68.0, 62.0, 60.9, 54.3, 42.6; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ 229.1341, found 229.1333.

The primary alcohol described above (0.200 g, 0.876 mmol) was dissolved in methanol (9 mL). Ten percent palladium on carbon (20 mg) was added, and hydrogen gas was bubbled into the solution for 5 min. The reaction was then allowed to stir under an atmosphere of hydrogen (via balloon) for approximately 2 h. Once the reaction was complete, the mixture was filtered through Celite and then a short plug of silica gel. The solvent was removed under reduced pressure to provide 190 mg (94%) of **26a**: $[\alpha]_D^{20}$ +120.6 (*c* 1.07, $CHCl_3$); IR ν_{max} (film) 3190, 2958, 2918, 2873, 1455, 1249, 1049; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.1 Hz, 2H), 7.45−7.20 (m, 3H), 4.08 (d, *J* = 8.0 Hz, 1H), 3.82 (t, *J* = 7.7 Hz, 1H), 3.65−3.28 (m, 3H), 2.80−2.61 (m, 1H), 2.61−2.40 (m, 1H), 1.69−1.49 (m, 2H), 1.42 (br s, 1H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 129.9, 128.6, 128.3, 117.9, 68.2, 62.0, 60.7, 55.0, 42.4, 21.1, 11.9; HRMS (ESI) calcd for $C_{14}H_{19}N_2O$ $[M + H]^+$ 231.1497, found 231.1487.

((2*S*,3*R*,4*R*)-4-(Aminomethyl)-3-phenyl-1-propylazetidin-2-yl)methanol 26b. Nitrile azetidine **26a** (0.200 g, 0.868 mmol) was dissolved in CH_2Cl_2 (10 mL) and subsequently cooled to 0 °C. DIBAL (0.929 mL, 5.21 mmol) was added over 15 min, and the reaction mixture was allowed to warm to room temperature and stirred for approximately 2 h. The mixture was quenched by the slow addition of methanol (0.211 mL, 5.21 mmol) until gas evolution ceased. Then a saturated solution of sodium potassium tartrate (Rochelle's salt) was added, and the gel-like solution was allowed to stir until two separate layers could be seen. The aqueous layer was then extracted two additional times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product which was purified over silica gel (CH_2Cl_2/MeOH) to obtain 58 mg (67%) of **26a**: $[\alpha]_D^{20}$ +13.3 (*c* 0.63, $CHCl_3$); IR ν_{max} (film) 3363, 3030, 2958, 2931, 2872, 1541, 1493, 1455, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (t, *J* = 9.7 Hz, 2H), 7.35−7.03 (m, 4H), 3.64 (t, *J* = 8.0 Hz, 1H), 3.49 (d, *J* = 6.2, 2H), 3.35 (dd, *J* = 7.2, 13.3, 1H), 3.31−3.09 (m, 1H), 2.71 (dd, *J* = 9.3, 12.9 Hz, 1H), 2.65−2.53 (m, 1H), 2.59−2.35 (m, 2H), 1.52 (d, *J* = 8.4 Hz, 2H), 1.47 (s, 3H), 1.05−0.70 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 130.8, 128.4, 127.2, 76.5, 69.4, 67.5, 61.3, 42.1, 41.9, 22.3, 12.1; HRMS (ESI) calcd for $C_{14}H_{23}N_2O$ $[M + H]^+$ 235.1810, found 235.1808.

7-Phenyl-6-propyl-3,6-diazabicyclo[3.1.1]heptane 27a. Compound **8a** (0.416 g, 0.870 mmol) was dissolved in DMF (11 mL) followed by the addition of thiophenol (0.357 mL, 3.38 mmol) and potassium carbonate (0.721 g, 5.22 mmol) at room temperature and stirred overnight (Note: in some cases, the solution needed to be heated to 50 °C to drive the reaction to completion). The solvent was removed and the resulting residue slurried in EtOAc. The solution was acidified with 1 M HCl and the aqueous layer extracted with additional EtOAc. The resulting aqueous layer was basified with a 40% KOH solution until a pH >10 was achieved. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by silica gel chromatography to provide pure product (0.250 g, 98%) as an oil: mp 162.2−164.7 °C (decomp); IR ν_{max} (film) 2917, 2857, 1487, 1398, 1176, 1008, 916, 810; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.00 (dd, *J* = 8.4, 1.1 Hz, 2H), 5.86 (ddd, *J* = 16.2, 11.1, 6.0 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.14 (dd, *J* = 10.3, 1.6 Hz, 1H), 4.01 (t, *J* = 5.6 Hz, 1H), 3.87 (d, *J* = 5.6 Hz, 2H), 3.40 (d, *J* = 6.0 Hz, 2H), 3.35 (d, *J* = 13.5 Hz, 2H), 2.79 (d, *J* = 13.6 Hz, 2H), 1.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 134.4, 131.6, 126.9, 119.9, 116.9, 63.2, 48.3, 41.1, 38.8; HRMS (ESI) calcd for $C_{14}H_{18}BrN_2$ $[M + H]^+$ 293.0653, found 293.0655.

A solution of the above amine (0.150 g, 0.512 mmol) was dissolved in methanol (5 mL) at room temperature. Platinum oxide (12 mg, 0.48 mmol) was added, and hydrogen gas was bubbled into the solution for 5 min. The reaction was then allowed to stir under an atmosphere of hydrogen (via balloon) overnight (Note: the starting material must be free of sulfur impurities for reaction to proceed). Once the reaction was complete, the mixture was filtered through a plug of Celite and then silica gel. The solvent was removed under reduced pressure to provide in sufficient purity for the next step.

To a solution of the above product (0.151 g, 0.511 mmol) in isopropyl alcohol (5 mL) were added AIBN (0.021 g, 0.128 mmol) and tributylchlorostannane (0.28 mL, 0.102 mmol). The reaction mixture was heated to reflux (~100 °C) and was allowed to stir for 5 min. A solution of sodium cyanotrihydroborate (0.048 g, 0.767 mmol) in isopropyl alcohol (1 mL) was then added simultaneously with a solution of AIBN (0.042 g, 0.256 mmol) in isopropyl alcohol (1 mL) via two separate syringes over a 10 min period. The reaction was stirred for approximately 1 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was residue was purified over silica gel using CH_2Cl_2/MeOH to obtain 52 mg (47% over 2 steps) of **27a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.6, 2H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 5.93 (ddd, *J* = 5.9, 11.1, 16.4 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 4.16 (t, *J* = 5.6 Hz, 1H), 3.96 (d, *J* = 5.7 Hz, 2H), 3.48 (d, *J* = 5.9 Hz, 2H), 3.40 (d, *J* = 13.7 Hz, 2H), 2.88 (d, *J* = 13.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 128.8, 126.4, 125.4, 64.2, 47.0, 41.6, 38.9, 20.6, 12.1; HRMS (ESI) calcd for $C_{14}H_{21}N_2$ $[M + H]^+$ 217.1705, found 217.1698.

7-Phenyl-6-propyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-ethanone 27b. A solution of amine **27a** (0.90 mg, 416 mmol), triethylamine (0.218 mL, 1.25 mmol), and PyBOP (0.238 mg, 0.458 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added to acetic acid (0.026 mL, 0.458 mmol). The solution was warmed to room temperature and stirred for 5 h, and the solvent was removed. The residue was purified by silica gel chromatography to afford 0.025 g (24%) of **27b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 4.05 (d, *J* = 4.6 Hz, 2H), 4.02 (d, *J* = 2.1 Hz, 1H), 3.70 (dd, *J* = 8.1, 18.1 Hz, 2H), 3.58 (d, *J* = 14.2 Hz, 1H), 3.49 (d, *J* = 12.1 Hz, 1H), 2.65−2.38 (m, 2H), 1.77 (s, 3H), 1.59−1.40 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 136.4, 128.4, 126.3, 125.8, 60.2, 59.7, 46.5, 41.1, 38.3, 21.2, 20.9, 12.0; HRMS (ESI) calcd for $C_{16}H_{23}N_2O$ $[M + H]^+$ 259.1810, found 259.1812.

3-(Methylsulfonyl)-7-phenyl-6-propyl-3,6-diazabicyclo-[3.1.1]heptane 27c. To a solution of amine **27a** (52 mg, 0.240 mmol) and triethylamine (0.101 mL, 0.720 mmol) in CH_2Cl_2 (2.5 mL) was added methanesulfonyl chloride (0.028 mL, 0.361 mmol) at 0 °C. The reaction was allowed to stir for 1 h at 0 °C. Water was then added, and the resulting aqueous solution was extracted (3×) with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered, and rotoevaporated to dryness. The resulting oil was chromatographed over silica gel to obtain 50.3 mg (71%) of **27c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.6, 2H), 7.25 (dd, *J* = 5.1, 12.7, 1H), 7.06 (d, *J* = 7.7, 2H), 4.05 (s, 3H), 3.74 (d, *J* = 11.7, 2H), 3.26 (d, *J* = 11.7, 2H), 2.77−2.47 (m, 2H), 1.71 (s, 3H), 1.61−1.40 (m, 2H), 0.98 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.65, 128.84, 126.68, 126.16, 59.89, 46.34, 40.73, 39.16, 34.02, 21.21, 12.02; HRMS (ESI) calcd for $C_{15}H_{23}N_2O_2S$ $[M + H]^+$ 295.1480, found 295.1477.

3-(4-Fluorobenzyl)-7-phenyl-6-propyl-3,6-diazabicyclo-[3.1.1]heptane 27d. To a solution of amine **27a** (0.125 g, 0.462 mmol) in ethanol (2 mL) was added 4-bromobenzaldehyde (0.049 mL, 0.462 mmol), and the reaction mixture was stirred for 1 h. An additional 1.0 mL of ethanol was added followed by 1.4 mL of THF and sodium borohydride (0.035 g, 0.925 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with water (5 drops), diluted with CH_2Cl_2 (25 mL), and filtered. The filtrate was concentrated in vacuo, and the residue was extracted with diethyl ether. The combined organics were dried over $MgSO_4$, filtered, and rotoevaporated to get an oil. The compound was purified over silica gel to afford 0.060 mg (40%) of **27d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 6.9, 1H), 7.26 (d, *J* = 7.1, 0H), 7.05 (d, *J* = 7.5, 1H), 6.70 (t, *J* = 8.7, 1H), 6.36 (dd, *J* = 5.7, 8.3, 1H), 3.97 (s, 0H), 3.93 (s, 1H), 3.43 (s, 1H), 2.94 (d, *J* = 11.3, 1H), 2.78 (d, *J* = 11.2, 1H), 2.47 (s, 1H), 1.58−1.36 (m, 1H), 0.96 (t, *J* = 7.4, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 160.5, 139.8, 134.7, 129.0, 129.0, 128.0, 125.1, 124.6, 114.5, 114.4, 61.8, 58.2, 46.0, 44.6, 42.3, 20.4, 12.1; HRMS (ESI) calcd for $C_{21}H_{26}FN_2$ $[M + H]^+$ 325.2080, found 325.2091.

(6*R*,7*R*,8*S*)-8-(Hydroxymethyl)-4-methyl-7-phenyl-1,4-diazabicyclo[4.2.0]octan-2-one 28a. To the solution of **5a** (5.00 g, 9.10 mmol) in isopropyl alcohol (91 mL) were added AIBN (0.299 g, 1.82 mmol) and tributylchlorostannane (0.368 mL, 1.37 mmol). The reaction mixture was heated to reflux (~100 °C) and was allowed to stir for 5 min. After 5 min at reflux, a solution of sodium cyanotrihydroborate (0.86 g, 13.7 mmol) in isopropyl alcohol (20 mL) was added simultaneously with a solution of AIBN (0.600 g, 3.64 mmol) in 20 mL of isopropyl alcohol via two separate syringes over a 10 min period. The reaction was stirred for approximately 1 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was residue was purified over silica gel to afford 3.50 g (82%) of product: $[\alpha]_D^{20}$ +42.3 (*c* 0.17, $CHCl_3$); IR ν_{max} (film) 3056, 2866, 1490, 1448, 1264, 1063; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.41 (m, 2H), 7.31−7.25 (m, *J* = 6.3, 9.6 Hz, 3H), 7.22−7.06 (m, *J* = 6.0, 7.9, 14H), 5.76 (ddt, *J* = 6.7, 10.1, 13.3 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 4.11−4.03 (m, 1H), 3.81 (t, *J* = 7.9 Hz, 1H), 3.63 (dd, *J* = 7.4, 13.5 Hz, 1H), 3.37 (dd, *J* = 5.9, 12.9 Hz, 1H), 3.11 (dd, *J* = 7.2, 12.9 Hz, 1H), 3.03 (dd, *J* = 5.9, 9.6 Hz, 1H), 2.89 (dd, *J* = 7.3, 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 134.3, 132.9, 129.8, 128.4, 128.2, 127.8, 127.6, 126.8, 119.4, 117.6, 86.5, 66.5, 62.1, 60.8, 54.7, 42.9; HRMS (ESI) calcd for $C_{33}H_{30}N_2O$ $[M + H]^+$ 471.2436, found 471.2448.

The nitrile azetidine described above (3.5 g, 7.44 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (75 mL) and subsequently cooled to 0 °C. DIBAL (7.95 mL, 44.6 mmol, 6.0 equiv) was added over 15 min, and the reaction mixture was allowed to warm to room temperature and stirred for approximately 2 h. The mixture was quenched by the slow addition of MeOH (5.50 mL, 136 mmol, 6.0 equiv) until gas evolution ceased. Then a saturated solution of sodium potassium tartrate (Rochelle's salt) was added, and the gel-like solution was allowed to stir until two separate layers could be seen. The aqueous layer was then extracted two additional times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product (~3.53 g), which was deemed pure enough for the next reaction.

The resulting amine (3.5 g, 7.37 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (74 mL) and cooled to 0 °C. 2,6-Lutidine (2.59 mL, 22.1 mmol, 3.0 equiv) was introduced followed by 2-nitrobenzene-1-sulfonyl chloride (1.85 g, 8.11 mmol, 1.1 equiv) in one portion. The solution was then allowed to warm to room temperature and stirred for an additional 3 h. The reaction mixture was quenched with water, and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel using hexanes/EtOAc to provide the nosylated amine (2.91 g, 60% over 2 steps) as a pale yellow foam.

To a solution of the nosylated amine (1.00 g, 1.516 mmol) and 1,3-dimethyl barbaturic acid (0.355 g, 2.273 mmol) in EtOH (30 mL) was added palladium tetrakis (0.350 g, 0.303 mmol). The resulting orange solution was stirred for approximately 1 h at room temperature. The solution was then evaporated and taken up in acetonitrile. The resulting solid was filtered through Celite and taken on imediately as a crude solution.

Potassium carbonate (210 g, 15.2 mmol) was added to the orange solution obtained above and the mixture cooled to 0 °C. 2-Bromoacetyl chloride (0.380 mL, 4.55 mmol) was then added dropwise and the resulting mixture warmed to room temperature, and the solution was stirred for several hours. After the reaction was deemed complete (LC/MS analysis), the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and water after which the aqueous layer was extracted (3×) with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give an oily residue. The residue was purified by chromatography to obtain 88% of the fully protected monoketopiperazine *des*-Br-**9a**: $[\alpha]^{20}_{D}$ −135.8 (*c* 0.55, $CHCl_3$); IR ν_{max} (film) 3059, 3031, 2942, 1665, 1543, 1453, 1370; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.5, 1H), 7.72−7.66 (m, 1H), 7.63 (t, *J* = 7.0 Hz, 2H), 7.30−7.20 (m, 9H), 7.18−7.10 (m, 8H), 7.06−6.97 (m, 5H), 5.03−4.87 (m, 2H), 4.13−4.04 (m, 2H), 4.00 (dd, *J* = 4.7, 10.0 Hz, 1H), 3.72 (dd, *J* = 4.8, 13.0 Hz, 1H), 3.63 (d, *J* = 17.1 Hz, 1H), 3.50 (t, *J* = 9.9 Hz, 1H), 3.36−3.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 147.8, 143.2, 134.0, 133.8, 131.9, 131.7, 131.1, 129.3, 128.5, 128.4, 127.6, 127.6, 126.8, 124.4, 86.6, 77.2, 77.0, 76.7, 66.2, 61.4, 57.5, 47.7, 45.5, 42.8; HRMS (ESI) calcd $C_{38}H_{33}N_3O_6S$ $[M + Na]^+$ 682.1988, found 682.1982.

To a solution of the fully protected monoketopiperazine described above *des*-Br-**9a** (0.615 g, 0.932 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added trifluoroacetic acid (0.718 mL, 9.32 mmol). The resulting solution was then warmed to room temperature and stirred for approximately 1 h. A saturated sodium bicarbonate solution was added and stirred until bubbling ceased. The aqueous layer was extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain an oil. After filtering over a plug of silica gel, the detritylated product was taken forward to the next step.

The above product was dissolved in DMF (9 mL), and potassium carbonate (0.510 g, 3.69 mmol) was added and the mixture cooled to 0 °C. Thiophenol (0.303 mL, 2.95 mmol) was then added, and the reaction was heated to 50 °C and stirred for 2 h. After starting material was consumed, the DMF was rotoevaporated down and taken up in EtOAc. HCl (2 M) was then added until pH was approximately 1. The aqueous was washed with EtOAc, and the organics were discarded. The aqueous solution was basified with 40% KOH solution until pH >10. The solution was then extracted with CH_2Cl_2 (3×), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain a yellowish oil which, was imediately taken crude to the next step.

To a solution of the free amino alcohol (35 mg, 0.151 mmol), acetic acid (0.086 mL, 1.507 mmol), and formaldehyde (0.021 mL, 0.753 mmol) in MeOH (5 mL) was added sodium cyanoborohydride (0.047 g, 0.753 mmol) in portions at room temperature. The mixture was then heated to 60 °C and stirred for approximately 30 min. The solvent was evaporated, and to the resulting white solid was added saturated $NaHCO_3$ that was introduced until gas evolution ceased. At this point, a 1 M NaOH solution was added until pH >11, then the solution was extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness to give a cloudy oil. Purification over silica gel afforded 15 mg (42%) of **28a**: $[\alpha]^{20}_{D}$ −13.5 (*c* 1.71, $CHCl_3$); IR ν_{max} (film) 3057, 2944, 1641, 1489, 1447, 1409, 1216, 1071; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.33 (m, 3H), 7.23 (d, *J* = 6.1 Hz, 2H), 5.40−5.29 (m, 1H), 5.20 (t, *J* = 7.4 Hz, 1H), 4.23 (dd, *J* = 9.9, 13.0 Hz, 1H), 4.11 (t, *J* = 7.9 Hz, 1H), 3.75 (d, *J* = 16.4 Hz, 1H), 3.44 (dd, *J* = 2.6, 13.0 Hz, 1H), 3.35 (d, *J* = 16.5 Hz, 1H), 3.16 (dd, *J* = 4.8, 12.0 Hz, 1H), 2.93 (t, *J* = 11.8 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 132.0, 129.4, 128.9, 128.6, 71.0, 61.1, 60.0, 57.2, 54.6, 54.4, 45.4; HRMS (ESI) calcd $C_{14}H_{19}N_2O_2$ $[M + H]^+$ 247.1440, found 247.1443.

(6*R*,7*R*,8*S*)-7-Phenyl-8-((trityloxy)methyl)-1,4-diazabicyclo[4.2.0]octan-2-one 28b. To a solution of the fully protected monoketopiperazine *des*-Br-**9a** described in the synthesis of **28a** (0.580 g, 0.879 mmol) and potassium carbonate (0.607 g, 4.40 mmol) in DMF (10 mL) was added thiophenol (0.361 mL, 3.52 mmol) at 0 °C. The reaction was allowed to come to room temperature and stir for 2 h. Water was added and the solution extracted with diethyl ether (3×). The organics were combined and dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain an oil. This material was then purified over silica gel to yield 75% of trityl-protected free amine of *des*-Br **9a** scaffold: $[\alpha]^{20}_{D}$ −182.8 (*c* 0.42, $CHCl_3$); IR ν_{max} (film) 3306, 3057, 2944, 1641, 1489, 1447, 1409, 1216, 1071; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.22 (m, 7H), 7.23−7.14 (m, 8H), 7.09 (dd, *J* = 2.9, 6.6 Hz, 6H), 5.11−4.97 (m, 1H), 4.94−4.84 (m, 1H), 4.08 (dd, *J* = 4.7, 9.9 Hz, 1H), 4.02 (t, *J* = 7.4 Hz, 1H), 3.53 (t, *J* = 10.1 Hz, 1H), 3.43 (d, *J* = 9.3 Hz, 1H), 2.97 (dd, *J* = 10.7, 13.0 Hz, 1H), 2.74 (dd, *J* = 5.2, 13.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 143.5, 134.6, 129.6, 128.4, 128.2, 127.5, 127.3, 126.7, 86.3, 77.2, 77.0, 76.7, 66.2, 63.6, 57.5, 49.2, 47.2, 41.4; HRMS (ESI) calcd $C_{32}H_{30}N_2O_2$ $[M + Na]^+$ 497.2205, found 497.2201.

To a solution of the trityl-protected free amine scaffold obtained above (0.22 g, 0.46 mmol) in CH_2Cl_2 (9 mL) at 0 °C was added triethylamine (0.19 mL, 1.37 mmol) followed by acetyl chloride (0.051 mL, 0.683 mmol). The reaction was stirred for 30 min at which time water was added. The aqueous layer was and extracted with CH_2Cl_2 and dried over $MgSO_4$, filtered, and evaporated to obtain an oil. This material was used directly in the next step without purification.

The resulting oil was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. Trifluoroacetic acid (0.139 mL, 1.802 mmol) was then added, and the reaction was warmed to room temperature and stirred for 1 h. A saturated sodium bicarbonate solution was added and stirred until gas evolution ceased. The aqueous layer was then extracted with CH_2Cl_2 (3×), and the combined organics were dried over $MgSO_4$, filtered, and evaporated to obtain an oil. Purification by silica gel chromatography afforded 0.069 g (74%) of **28b**: $[\alpha]^{20}_{D}$ −67.1 (*c* 0.31, $CHCl_3$); IR ν_{max} (film) 3401, 2930, 1636, 1417; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49−7.31 (m, 3H), 7.31−7.21 (m, 2H), 5.18−5.04 (m, 1H), 4.94−4.77 (m, 1H), 4.46 (dd, *J* = 4.8, 13.1 Hz, 1H), 4.30−4.20 (m, *J* = 8.0, 20.3 Hz, 2H), 4.14−4.00 (m, 2H), 3.78 (d, *J* = 18.7 Hz, 1H), 3.64−3.50 (m, 1H), 3.41 (td, *J* = 2.7, 12.7 Hz, 1H), 3.08−2.96 (t, *J* = 12.7 Hz, 1H), 2.12 (s, 2H), 2.06 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 169.0, 164.7, 163.3, 132.7, 132.6, 129.5, 129.4, 128.6, 128.5, 128.2, 128.0, 70.6, 70.3, 61.3, 61.0, 60.8, 49.4, 45.9, 44.9, 43.3, 38.6, 21.5, 21.5; HRMS (ESI) calcd $C_{15}H_{18}N_2O_3$ $[M + Na]^+$ 297.1215, found 297.1217.

(6*R*,7*R*,8*S*)-8-(Hydroxymethyl)-4-(methylsulfonyl)-7-phenyl-1,4-diazabicyclo[4.2.0]octan-2-one 28c. To a solution of the trityl-protected free amine scaffold described above (0.170 g, 0.358 mmol) and triethylamine (0.150 mL, 1.075 mmol) in CH_2Cl_2 (3 mL) was added methanesulfonyl chloride (0.042 mL, 0.537 mmol) at 0 °C. The solution was allowed to warm to room temperature and stir for approximately 1 h. Water was then added, and the resulting aqueous layer was extracted with CH_2Cl_2 (3×). The combined organics were dried over $MgSO_4$, filtered, and evaporated. This material was run through a short plug of silica gel, concentrated, and taken directly to the next step in the sequence.

The resulting oil was then dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. Trifluoroacetic acid (0.139 mL, 1.80 mmol) was added, and the reaction was warmed to room temperature and stirred for 1 h. A saturated sodium bicarbonate solution was added and stirred until bubbles ceased. The aqueous layer was then extract with CH_2Cl_2 (3×), and the combined organics were dried over $MgSO_4$, filtered, and evaporated to obtain and oil. Purification by silica gel chromatography afforded 0.069 g (74%) of **28c**: $[\alpha]^{20}_{D}$ −34.5 (*c* 0.40, $CHCl_3$); IR ν_{max} (film) 3365, 3011, 2928, 1638, 1456, 1426, 1336, 1150; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (q, *J* = 6.5, 3H), 7.24 (m, 2H), 5.14 (t, *J* = 7.8 Hz, 1H), 5.12−4.98 (m, 1H), 4.54 (s, 1H), 4.30 (d, *J* = 14.6 Hz, 1H), 4.24 (dd, *J* = 12.6, 25.1 Hz, 2H), 4.04 (t, *J* = 8.1 Hz, 1H), 3.79 (d, *J* = 17.2 Hz, 1H), 3.64 (dd, *J* = 4.9, 12.5 Hz, 1H), 3.40 (t, *J* = 12.2 Hz, 1H), 3.27−3.13 (m, 1H), 2.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 132.6, 129.5, 128.7, 128.3, 70.7, 61.8, 60.75, 47.9, 45.3, 42.2, 37.2; HRMS (ESI) calcd $C_{14}H_{18}N_2O_4S$ $[M + H]^+$ 311.1066, found 311.1057.

((8*R*,9*R*,10*S*)-9-(4-Bromophenyl)-1,6-diazabicyclo[6.2.0]decan-10-yl)methanol 29a. Nosyl amine **12a** (0.700 g, 1.37 mmol) was dissolved in DMF (20 mL), and potassium carbonate (0.948 g, 6.86 mmol) was added followed by thiophenol (0.563 mL, 5.49

mmol). The reaction mixture was heated to 50 °C and stirred for 2 h. Once the reaction was complete, the solvent was removed in vacuo, at which time water and EtOAc were added to the remaining residue. HCl (2 M) was added to the biphasic mixture until the water layer maintained a pH of approximately 1. The organics were removed, and the remaining aqueous layer was extracted with EtOAc. The aqueous layer was then basified to pH >10 using a 40% KOH solution. The water was then extracted with EtOAc three times, and the combined organics were dried over $MgSO_4$, filtered, and rotoevaporated to dryness to afford **29a** (0.395 g, 89%): $[\alpha]_D^{20}$ −24.7 (c 0.59, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.6 Hz, 2H), 7.31−7.19 (m, 2H), 3.61 (t, J = 7.9 Hz, 1H), 3.58−3.48 (m, 2H), 3.47−3.38 (m, 2H), 3.07 (dd, J = 5.0, 12.1 Hz, 1H), 2.89 (d, J = 9.1 Hz, 1H), 2.75−2.57 (m, 2H), 2.30 (d, J = 14.3 Hz, 1H), 2.23 (t, J = 11.4 Hz, 1H), 1.82 (s, 4H), 1.56−1.43 (m, 1H), 1.41−1.30 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 132.3, 131.0, 120.7, 68.0, 67.1, 60.7, 60.0, 50.4, 48.6, 43.7, 29.2, 27.1; HRMS (ESI) calcd for $C_{15}H_{22}BrN_2O$ $[M + H]^+$ 325.0916, found 325.0902.

((8*R*,9*R*,10*S*)-9-Phenyl-1,6-diazabicyclo[6.2.0]decan-10-yl)-methanol 29b. To the solution of aryl bromide **29a** (0.395 g, 1.21 mmol) in isopropyl alcohol (12.1 mL) were added AIBN (0.050 g, 0.304 mmol) and tributylchlorostannane (0.066 mL, 0.243 mmol). The reaction mixture was then heated to reflux (∼110 °C) and was allowed to stir for 10 min. A solution of sodium cyanotrihydroborate (0.114 g, 1.822 mmol) in isopropyl alcohol (5 mL) was added contemporaneously with a solution of AIBN (0.100 mg) in isopropyl alcohol (5 mL) over a 15 min period. Upon completion of the reaction, the solvent was removed in vacuo and the remaining sludge taken up in EtOAc and water. HCl (2 M) was added to the biphasic mixture until the water layer maintained a pH of approximately 1. The organic layer was removed and the remaining aqueous layer extracted with EtOAc. The aqueous layer was then basified to pH >10 using a 40% KOH solution. The water layer was extracted with CH_2Cl_2 (3×), and the combined organics were dried over $MgSO_4$, filtered, and concentrated to dryness to afford **29b**: $[\alpha]_D^{20}$ −28.5 (c 0.34, $CHCl_3$); mp 100.9−105.2 °C; IR ν_{max} (film) 3306, 2921, 2845, 1454, 1034; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 6.1 Hz, 2H), 7.28 (t, J = 7.0 Hz, 2H), 7.24−7.18 (m, 1H), 3.62 (t, J = 7.9 Hz, 1H), 3.60−3.55 (m, 1H), 3.55−3.48 (m, 1H), 3.49−3.34 (m, 4H), 3.11−3.00 (m, 1H), 2.85 (d, J = 9.8 Hz, 1H), 2.74 (dd, J = 8.1, 14.1 Hz, 1H), 2.64 (t, J = 11.7 Hz, 1H), 2.40−2.14 (m, 2H), 1.93−1.55 (m, 6H), 1.55−1.40 (m, 2H), 1.40−1.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 130.8, 128.0, 126.7, 77.4, 68.1, 67.8, 60.9, 60.3, 50.4, 44.4, 29.1, 27.3; HRMS (ESI) calcd for $C_{15}H_{23}N_2O$ $[M + H]^+$ 247.1810, found 247.1814.

((8*R*,9*R*,10*S*)-6-Methyl-9-phenyl-1,6-diazabicyclo[6.2.0]-decan-10-yl)methanol 29c. To a solution of **29b** (0.070 g, 0.284 mmol), acetic acid (0.163 mL, 2.84 mmol), and formaldehyde (0.039 mL, 1.421 mmol) in MeOH (5 mL) was added $NaCNBH_3$ (0.089 g, 1.421 mmol) portion-wise at room temperature. The mixture was then heated to 60 °C and stirred for 30 min. The solvent was then evaporated, and to the resulting white solid was added a saturated solution of $NaHCO_3$ until gas evolution ceased. At this point, a 1 M NaOH solution was added until pH >11, then the solution was extracted with EtOAc (3×). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness to give a cloudy oil. The oil was taken up in chloroform and filtered though Celite and dried to obtain **29c** as a clear oil: $[\alpha]_D^{20}$ −0.73 (c 0.93, $CHCl_3$); IR ν_{max} (film) 3250, 2928, 2851, 1455, 1214, 750; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.26−7.16 (m, 1H), 3.64 (t, J = 8.2 Hz, 1H), 3.60−3.48 (m, 3H), 3.39 (dd, J = 7.2, 13.4 Hz, 1H), 3.04 (ddd, J = 2.9, 5.7, 12.0 Hz, 1H), 2.73−2.63 (m, 1H), 2.55 (dd, J = 8.7, 13.8 Hz, 1H), 2.43−2.35 (m, 1H), 2.33−2.26 (m, 1H), 2.21 (s, 3H), 2.10 (dd, J = 2.1, 13.8 Hz, 1H), 1.94−1.84 (m, 1H), 1.84−1.74 (m, 1H), 1.68 (s, 1H), 1.62−1.43 (m, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 130.8, 128.7, 127.6, 67.8, 64.9, 61.3, 59.9, 59.1, 57.1, 47.1, 44.4, 26.6, 25.0; HRMS (ESI) calcd for $C_{16}H_{25}N_2O$ $[M + H]^+$ 261.1967, found 261.1969.

Procedure for the Synthesis of Spiroazetidine Derivatives 30a−c. To a 50 mL round-bottom flask was added a solution of *des*-Br **14a** (**b** or **c**) (1.02 g, 1.52 mmol, 1 equiv) in dry DMF (15 mL). At 0 °C, K_2CO_3 (0.84 g, 6.07 mmol, 4 equiv) was added, followed by thiophenol (0.31 mL, 3.04 mmol, 2 equiv). After 1 h at 0 °C, water (15 mL) was added to the mixture and the crude was extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The material was then dissolved in MeOH (9 mL) and purged with argon for 10 min. Pd (10% on carbon, 32 mg, 0.20 equiv) was quickly added, and hydrogen gas was sparged for 1 h. The mixture was stirred overnight at room temperature under an atmosphere of hydrogen, carefully filtered through a pad of Celite, and concentrated. Purification over silica-supported *p*-TsOH using ammonia (2.0 M in MeOH) as the mobile phase afforded the desired secondary amine (439 mg, 0.90 mmol, 59.1% yield over two steps).

(2*S*,3*S*)-1-Propyl-2-hydroxymethyl-3-phenyl-1,6-diazaspiro-[3.3]heptane 30a. To a solution of the amine described above (138 mg, 0.28 mmol) in CH_2Cl_2 (5.5 mL) was added trifluoroacetic acid (0.32 mL, 4.24 mmol, 15 equiv) dropwise at 0 °C. Upon completion of the reaction, MeOH (3 mL) was added via syringe followed by addition of K_2CO_3 (0.59 g, 4.24 mmol, 15 equiv) and the mixture was stirred 30 min at room temperature. The crude reaction mixture was filtered through a pad of Celite and evaporated. Purification on silica gel (CH_2Cl_2/MeOH/2.0 M NH_3 in MeOH = 95:4.95:0.05) afforded amino alcohol **30a** (69 mg, 0.28 mmol, 99% yield) as a pale yellow foam: $[\alpha]_D^{20}$ +46.2 (c 0.9, MeOH); IR ν_{max} (film) 3382, 3204, 2965, 2874, 1668, 1182, 1132; ^1H NMR (300 MHz, CD_3OD) δ 7.33−7.24 (m, 6H), 4.74 (d, J = 11.8 Hz, 1H), 4.16 (d, J = 11.7 Hz, 1H), 3.98 (d, J = 12.1 Hz, 1H), 3.73 (d, J = 7.9 Hz, 2H), 3.56 (dd, J = 13.5, 6.0 Hz, 1H), 3.37 (dd, J = 11.3, 5.7 Hz, 1H), 3.25 (s, 1H), 3.20 (dd, J = 11.3, 6.2 Hz, 1H), 2.83 (app dt, J = 12.3, 7.7 Hz, 1H), 2.62 (app dt, J = 12.3, 7.0 Hz, 1H), 1.64−1.49 (m, 2H), 0.97 (app t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, MeOD) δ 136.8, 131.1, 129.7, 128.7, 68.4, 68.2, 63.0, 56.7, 54.3, 54.2, 51.2, 23.3, 12.3; HRMS (ESI) calcd for $C_{15}H_{23}N_2O$ $[M + H]^+$ 247.1810, found 247.1813.

(2*S*,3*S*)-1-Propyl-2-hydroxymethyl-3-phenyl-6-methyl-1,6-diazaspiro[3.3]heptane 30b. To a solution of amine described above (145 mg, 0.30 mmol) in CH_2Cl_2 (5.5 mL) was added at rt $MgSO_4$ (357 mg, 2.97 mmol, 10 equiv) followed by formaldehyde (37% in H_2O, 0.13 mL, 1.78 mmol, 6 equiv). After 15 min at room temperature, $NaBH(OAc)_3$ (755 mg, 3.56 mmol, 12 equiv) was added as a solid in one portion, and the mixture was stirred overnight at rt. Water (10 mL) was then added and the layers separated. The organic phase was dried over $MgSO_4$, filtered, concentrated, and the crude was submitted to TFA-mediated trityl removal as described for the preparation of **30a**. Compound **24b** was isolated after purification on silica gel (CH_2Cl_2/MeOH/2.0 M NH_3 in MeOH = 95:4.95:0.05) as a thick colorless oil (65 mg, 0.25 mmol, 84% yield over two steps): $[\alpha]_D^{20}$ +109.1 (c 0.8, $CHCl_3$); IR ν_{max} (film) 3367, 2960, 2873, 1673, 1199, 1132; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.35 (br d, J = 10.0 Hz, 1H), 3.81 (d, J = 9.6 Hz, 1H), 3.65 (d, J = 7.8 Hz, 2H), 3.60−3.54 (m, 1H), 3.51 (dd, J = 11.5, 4.3 Hz, 1H), 3.45 (d, J = 4.8 Hz, 1H), 3.38 (dd, J = 11.2, 7.2 Hz, 1H), 2.79 (app dt, J = 12.0, 7.8 Hz, 1H), 2.60−2.52 (m, 1H), 2.51 (s, 3H), 1.63−1.41 (m, 2H), 0.97 (app t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 129.6, 128.6, 127.5, 66.6, 64.5, 64.4, 62.3, 61.9, 53.3, 49.8, 43.6, 22.3, 11.8; HRMS (ESI) calcd for $C_{16}H_{25}N_2O$ $[M + H]^+$ 261.1967, found 261.1964.

(2*S*,3*S*)-1-Propyl-2-hydroxymethyl-3-phenyl-6-acetyl-1,6-diazaspiro[3.3]heptane 30c. To a solution of amine described above (155 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added NEt_3 (88 μL, 0.63 mmol, 2 equiv) followed by Ac_2O (36 μL, 0.38 mmol, 1.2 equiv). The mixture was stirred for 1 h at 0 °C and was then quenched with a saturated solution of aqueous NH_4Cl (5 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to afford a crude product that was submitted to the TFA-mediated trityl removal step without any further purification (see preparation of **30a**). Purification by silica gel chromatography (CH_2Cl_2/MeOH/2.0 M NH_3 in MeOH = 95:4.95:0.05) afforded compound **30c** as a colorless foam (73 mg, 0.25 mmol, 78% yield over two steps): $[\alpha]_D^{20}$ +126.2 (c 1.1, $CHCl_3$); IR ν_{max} (film) 3376, 2959, 2873, 1622, 1455, 1033, 906; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 7.33−7.16 (m, 5H), 4.75 (A)/4.68 (B) (d, J = 9.4 (A)/11.1 (B) Hz, 1H), 4.05 (A)/3.92 (B) (d, J = 9.4 (A)/10.3 (B) Hz, 1H), 3.90 (s, 1H), 3.82 (app q, J = 11.9 Hz, 1H), 3.52 (br s, 2H), 3.43 (br d, J = 9.5 Hz, 1H), 3.37−3.24 (m, 1H), 2.76−2.45 (m, 2H), 2.21 (A)/1.99 (B) (br s, 1H), 1.84 (A)/1.71 (B) (s, 3H), 1.59−1.37 (m, 2H), 0.95 (app t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, two rotamers) δ 170.5/170.2, 136.1/135.7, 129.4, 128.2, 127.2, 66.3/66.2, 64.3/64.1, 61.9, 60.5, 57.9/55.9, 53.6/53.3, 49.7, 21.9, 18.9/18.8, 11.9; HRMS (ESI) calcd for $C_{17}H_{25}N_2O_2$ [M + H]$^+$ 289.1916, found 289.1917.

((±)-2-Propyl-1,2,2a,3,4,8b-hexahydroazeto[2,3-*c*]quinolin-1-yl)methanol 31a. A solution of *des*-Ns (±)-**24c** (0.110 g, 0.478 mmol) was dissolved in methanol (5 mL) at room temperature. Platinum oxide (11 mg, 0.48 mmol) was added, and hydrogen gas was bubbled into the solution for 5 min. The reaction was then allowed to stir under an atmosphere of hydrogen (via balloon) overnight. Once the reaction was complete, the mixture was filtered through Celite and then a plug of silica gel. The solvent was removed under reduced pressure to provide 24 mg (22%) of (±)-**31a**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.16 (td, J = 1.5, 7.7 Hz, 1H), 7.04 (dd, J = 1.3, 7.5 Hz, 1H), 6.85 (td, J = 1.0, 7.5 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 4.87 (d, J = 6.9 Hz, 1H), 4.18−4.11 (m, 1H), 4.09 (s, 1H), 3.97 (dd, J = 2.0, 14.0 Hz, 1H), 3.82 (dd, J = 4.4, 14.0 Hz, 1H), 3.75 (s, 1H), 3.66 (d, J = 14.2 Hz, 1H), 3.39 (td, J = 5.4, 11.7 Hz, 1H), 3.20 (td, J = 5.2, 11.7 Hz, 1H), 3.07 (dd, J = 3.5, 14.3 Hz, 1H), 1.83−1.59 (m, 3H), 0.96 (t, J = 7.4 Hz, 4H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.1, 128.6, 128.6, 122.4, 121.0, 116.2, 75.3, 63.5, 59.7, 50.3, 40.5, 31.2, 18.3, 11.2; HRMS (ESI) calcd for $C_{14}H_{20}N_2O$ [M+]$^+$ 232.1654, found 232.1656.

1-((±)-1-(Hydroxymethyl)-2-propyl-1,2a,3,8b-tetrahydroazeto[2,3-*c*]quinolin-4(2*H*)-yl)ethanone 31b. A solution of acyl (±)-**24c** (0.094 g, 0.345 mmol) was dissolved in methanol (4 mL) at room temperature. Ten percent palladium on carbon (37 mg) was added, and hydrogen gas was bubbled into the solution for 5 min. The reaction was then allowed to stir under an atmosphere of hydrogen (via balloon) overnight. Once the reaction was complete, the mixture was filtered through a pad of Celite and then silica gel. The solvent was removed under reduced pressure to provide 91 mg (96%) of (±)-**31b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35−7.26 (m, 1H), 7.23−7.12 (m, 3H), 5.19 (s, 1H), 4.38 (s, 1H), 3.96 (s, 1H), 3.66 (d, J = 12.0 Hz, 1H), 3.55 (d, J = 11.7 Hz, 1H), 3.35 (s, 1H), 2.78 (s, 2H), 2.51 (s, 1H), 2.27 (s, 3H), 1.63−1.41 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 168.8, 139.9, 131.5, 128.9, 127.6, 126.2, 124.4, 72.9, 63.3, 60.5, 50.8, 40.3, 34.3, 23.2, 21.2, 11.6; HRMS (ESI) calcd for $C_{16}H_{23}N_2O_2$ [M+]$^+$ 275.1760, found 275.1749.

((±)-4-(Methylsulfonyl)-2-propyl-1,2,2a,3,4,8b-hexahydroazeto[2,3-*c*]quinolin-1-yl)methanol 31c. A solution of mesyl (±)-**24c** (0.115 g, 0.373 mmol) was dissolved in methanol (4 mL) at room temperature. Ten percent palladium on carbon (40 mg) was added, and hydrogen gas was bubbled into the solution for 5 min. The reaction was then allowed to stir under an atmosphere of hydrogen (via balloon) overnight. Once the reaction was complete, the mixture was filtered through Celite and then a plug of silica gel. The solvent was removed under reduced pressure to provide 44 mg (38%) of (±)-**31c**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, J = 8.2, 1H), 7.32−7.24 (m, 1H), 7.18−7.12 (m, 2H), 4.41 (dd, J = 3.7, 13.8 Hz, 1H), 4.15 (dt, J = 3.6, 7.6 Hz, 1H), 3.79−3.73 (t, 1H), 3.71 (dd, J = 3.3, 11.7, 1H), 3.61 (dd, J = 1.6, 11.7, 1H), 3.54−3.48 (m, 1H), 3.30 (dd, J = 3.7, 13.8 Hz, 1H), 3.12 (s, 3H), 2.94−2.82 (m, 2H), 2.68−2.56 (m, 1H), 1.55−1.38 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.9, 131.1, 128.9, 127.4, 125.2, 121.6, 71.2, 61.2, 60.9, 50.3, 46.2, 38.9, 33.6, 22.0, 11.9; HRMS (ESI) calcd for $C_{15}H_{22}N_2O_3S$ [M+]$^+$ 310.1429, found 310.1433.

Procedure for the Synthesis of Benzopyran Derivatives 32a and 32b. To a degassed solution of tetrahydrochrome derivative (see synthesis of **25a**) (285 mg, 1.26 mmol, 1.0 equiv) dissolved in MeOH (12.6 mL) was added palladium hydroxide (20 wt % on activated carbon, 18 mg, 0.126 mmol, 0.1 equiv). Hydrogen gas was bubbled through the reaction mixture for 5 min and then placed under a static H$_2$ atmosphere (balloon pressure) and stirred for 15 h, after which analysis of the reaction mixture by LC/MS showed that the reaction was complete. The mixture was diluted with CH$_2$Cl$_2$ and filtered through Celite. The filtrate was concentrated under reduced pressure, and the crude product (197 mg, 69% yield) was used in the next step without further purification: $[\alpha]^{20}_{\mathrm{D}}$ −161.0 (c 0.10, CHCl$_3$); IR $\nu_{\max}$ (film) 2971, 2953, 2930, 2900, 1582, 1489, 1460, 1259, 1225, 1202, 1116, 1004; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.28−7.22 (m, 1H), 7.09 (d, J = 6.8 Hz, 1H), 7.03 (t, J = 7.4 Hz, 2H), 4.15 (dd, J = 12.7, 1.5 Hz, 1H), 4.11 (d, J = 7.8 Hz, 1H), 3.77 (t, J = 7.8 Hz, 1H), 3.70−3.59 (m, 2H), 2.70 dt, J = 11.3, 7.7 Hz, 1H), 2.62 dt, J = 11.4, 7.6 Hz, 1H), 1.54 (q, J = 7.5 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.1, 130.7, 129.1, 122.2, 119.8, 118.4, 117.3, 65.6, 62.8, 59.3, 56.6, 31.7, 20.9, 11.8; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ [M + H]$^+$ 229.1341, found 229.1344.

The resulting *N*-propyl nitrile azetidine (197 mg, 0.863 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$ (8.6 mL) at 0 °C, and then diisobutylaluminum hydride (0.923 mL, 5.18 mmol, 6.0 equiv) was added, and the reaction was stirred for 2 h, after which analysis of the reaction by TLC showed that all starting material had been consumed. The reaction was quenched with MeOH (10 mL) until bubbling stopped, diluted with CH$_2$Cl$_2$, and then quenched further with a saturated solution of potassium sodium tartrate (∼100 mL). The mixture was stirred vigorously for about 1.5 h until bubbling stopped and the two layers had clearly formed. The layers were separated, and the aqueous layer was extracted further with CH$_2$Cl$_2$ (2 × 15 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure to provide the crude primary amine as a clear oil, which was used without further purification.

***N*-(((1*R*,2a*S*,8b*R*)-2-Propyl-2,2a,3,8b-tetrahydro-1*H*-chromeno[3,4-*b*]azet-1-yl) methyl)benzamide 32a.** To solution of the crude amine described above (50 mg, 0.215 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2.2 mL) at 0 °C were added diisopropylethylamine (111 mL, 0.646 mmol, 3.0 equiv), benzoic acid (39 mg, 0.323 mmol, 1.5 equiv), and PyBOP (146 mg, 0.280 mmol, 1.3 equiv). The solution was stirred for 15 h, after which LC/MS of the reaction showed that all starting material had been consumed. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel using hexanes/EtOAc to provide 42 mg of **32a** (58% yield) as a clear oil: $[\alpha]^{20}_{\mathrm{D}}$ −121.0 (c 0.14, CHCl$_3$); IR $\nu_{\max}$ (film) 3307, 2957, 2924, 2873, 1629, 1578, 1533, 1489, 1459, 1229; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.61 (d, J = 6.9 Hz, 2H), 7.50−7.31 (m, 3H), 7.05−6.94 (m, 2H), 6.94−6.85 (m, 1H), 6.79 (br s, 1H), 6.75 (d, J = 8.1 Hz, 1H), 4.18 (d, J = 12.0 Hz, 1H), 3.77 (br s, 1H), 3.63 (t, J = 5.4 Hz, 3H), 3.32−3.10 (m, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.61−1.32 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.4, 155.3, 134.3, 131.2, 130.2, 128.3, 128.0, 127.0, 122.3, 122.2, 118.0, 67.4, 64.2, 62.5, 59.5, 40.5, 31.1, 21.8, 12.0; HRMS (ESI) calcd for $C_{21}H_{25}N_2O_2$ [M + H]$^+$ 337.1916, found 337.1917.

***N*-(((1*R*,2a*S*,8b*R*)-2-Propyl-2,2a,3,8b-tetrahydro-1*H*-chromeno[3,4-*b*]azet-1-yl) methyl)methanesulfonamide 26b.** To solution of the crude amine described above (57 mg, 0.245 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2.5 mL) at 0 °C were added 2,6-lutidine (85 mL, 0.936 mmol, 3.0 equiv) and methanesulfonyl chloride (29 mL, 0.368 mmol, 1.5 equiv). The solution was stirred for 3 h, after which TLC of the reaction showed that all starting material had been consumed. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel using hexanes/EtOAc to provide 27 mg of **26b** (36% yield) as a colorless oil: $[\alpha]^{20}_{\mathrm{D}}$ −96.4 (c 0.29, CHCl$_3$); IR $\nu_{\max}$ (film) 3283, 2959, 2930, 2872, 1581, 1489, 1459, 1317, 1228, 1147; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.17 (t, J = 8.0 Hz, 1H), 7.08−6.90 (m, 3H), 4.51 (br s, 1H), 4.10 (d, J = 11.3 Hz, 1H), 3.77−3.54 (m, 4H), 2.98−2.85 (m, 1H), 2.74 (ddd, J = 12.9, 6.1, 3.9 Hz, 1H), 2.71−2.59 (m, 2H), 2.55 (s, 3H), 1.55−1.41 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.1, 130.1, 128.3, 122.1, 122.0, 118.4, 67.5, 64.6, 62.4, 59.9, 43.8, 39.7, 30.7, 21.7, 12.0; HRMS (ESI) calcd for $C_{15}H_{23}N_2O_3S$ [M + H]$^+$ 311.1429, found 311.1434.

(2*S*,3*S*)-1-Allyl-2-(hydroxymethyl)-3-phenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *des*-Br-15a. Scaffold *des*-Br-**15a** was prepared identical to **15a**: $[\alpha]^{21}_{\mathrm{D}}$ +61.1 (c 0.96, CHCl$_3$); IR $\nu_{\max}$ (film) 3387, 2952, 2874, 1544, 1370, 1356, 1169, 1031; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.95 (m, 1H), 7.66 (m, 3H), 7.31 (m, 5H), 5.84 (ddt, J =

6.3, 10.0, 16.4, 1H), 5.22 (d, *J* = 17.2, 1H), 5.02 (d, *J* = 10.1, 1H), 4.80 (d, *J* = 9.0, 1H), 4.14 (d, *J* = 8.9, 1H), 4.01 (d, *J* = 9.5, 1H), 3.92 (d, *J* = 9.4, 1H), 3.43 (m, 2H), 3.23 (m, 2H), 1.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.67, 136.11, 135.68, 134.01, 132.11, 131.94, 131.04, 129.73, 128.85, 127.80, 124.50, 118.24, 66.98, 64.40, 62.61, 61.21, 58.35, 54.67, 50.30; HRMS (ESI) calcd for $C_{21}H_{24}N_3O_5S$ [M + H]$^+$ 430.1437, found 430.1425.

(2*R*,3*R*)-1-Allyl-2-(hydroxymethyl)-3-phenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *ent-des*-Br-15a: $[\alpha]_D^{21}$ −69.3 (*c* 0.3, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{24}N_3O_5S$ [M + H]$^+$ 430.1437, found 430.1428. Spectral data were identical to those provided for enantiomer *des*-Br-**15a**.

(2*S*,3*R*)-1-Allyl-2-(hydroxymethyl)-3-phenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *des*-Br-15c. Scaffold *des*-Br-**15c** was prepared identical to **15c**: $[\alpha]_D^{21}$ +75.1 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3399, 2922, 2873, 1542, 1354, 1169, 1126, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8, 1H), 7.73−7.59 (m, 3H), 7.31−7.21 (m, 3H), 7.11 (d, *J* = 7.7, 2H), 5.79 (ddt, *J* = 6.5, 10.1, 16.6, 1H), 5.18 (d, *J* = 17.1, 1H), 4.98 (d, *J* = 10.1, 1H), 4.33 (d, *J* = 9.3, 1H), 4.18 (dd, *J* = 9.4, 20.5, 2H), 3.70−3.63 (m, 2H), 3.60−3.52 (m, 2H), 3.45 (br d, *J* = 11.4, 1H), 3.34 (dd, *J* = 6.4, 13.5, 1H), 3.21 (dd, *J* = 6.6, 13.5, 1H), 2.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.60, 136.10, 134.83, 134.09, 131.91, 130.87, 130.24, 128.95, 128.01, 127.44, 124.29, 118.44, 66.15, 65.14, 63.86, 61.53, 53.38, 53.01, 45.79; HRMS (ESI) calcd for $C_{21}H_{24}N_3O_5S$ [M + H]$^+$ 430.1437, found 430.1428.

(2*R*,3*S*)-1-Allyl-2-(hydroxymethyl)-3-phenyl-6-*ortho*-nosyl-1,6-diazaspiro[3.3]heptane *ent-des*-Br-15c: $[\alpha]_D^{21}$ −79.0 (*c* 0.38, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{24}N_3O_5S$ [M + H]$^+$ 430.1437, found 430.1431. Spectral data were identical to those provided for enantiomer *des*-Br-**15c**.

Solid-Phase Library Synthesis. Solid-phase library synthesis was conducted on silicon-functionalized polystyrene Lanterns (L-series)[14] equipped with radio frequency transponders for directed sorting and compound tracking. All reactions were conducted in heavy wall pressure vessels with agitation in an incubator shaker.

Scaffold Loading. To a flame-dried flask containing silicon-functionalized Lanterns[14] was added a freshly prepared solution of TfOH in anhydrous CH_2Cl_2 (9.0 equiv, 5 g of TfOH/100 mL of CH_2Cl_2). Each flask was shaken at rt for 10 min at which time the Lanterns had turned bright orange. The deep red TfOH solution was removed via cannula, and anhydrous 2,6-lutidine (12.0 equiv relative to Si) was added. Once the Lantern color had changed from orange to white, the appropriate stereoisomer of *des*-Br-**15** (1.2 equiv relative to Si) was added as a solution in anhydrous CH_2Cl_2 (0.4 mL/Lantern) and the reaction mixture was shaken at rt overnight. The loading mixture was removed and set aside (to recover any unreacted alcohol), and the Lanterns were washed with the following solvents for 30 min intervals: CH_2Cl_2, THF, 3:1 THF/IPA, 3:1 THF/H_2O, DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting. All four stereoisomers of *des*-Br-**15** were loaded via the same protocol.

Nosyl Removal. To a flask containing Lanterns was added THF (0.8 mL/Lantern) followed by thiophenol (20 equiv) and potassium carbonate (30 equiv). The Lanterns were shaken at rt overnight and then washed with the following solvents for 30 min intervals: DMF (two washes), THF/H_2O (3:1), THF/isopropyl alcohol (3:1), THF, and CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

N-Capping/Sulfonyl Chlorides. To each flask containing Lanterns was added CH_2Cl_2 (0.8 mL/Lantern) followed by 2,6-lutidine (30 equiv) and the desired sulfonyl chloride (15 equiv). The Lanterns were shaken at rt overnight and then washed with the following solvents for 30 min intervals: CH_2Cl_2, DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

N-Capping/Isocyanates. To each flask containing Lanterns was added CH_2Cl_2 (0.8 mL/Lantern) followed the desired isocyanate (15 equiv). The Lanterns were shaken at rt overnight and then washed with the following solvents for 30 min intervals: CH_2Cl_2, DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

N-Capping/Acids. To each flask containing lanterns was added CH_2Cl_2 (0.8 mL/Lantern) followed by triethylamine (30 equiv) and the desired acid (20 equiv). PyBOP (20 equiv) was added, and the Lanterns were shaken at rt overnight and then washed with the following solvents for 30 min intervals: CH_2Cl_2, DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting

N-Capping/Aromatic Aldehydes. To each flask containing Lanterns was added DMF with 2% AcOH (0.800 mL/Lantern) followed by the desired aldehyde (20 equiv). The reaction mixture was shaken at rt for 1 h, and then sodium triacetoxyborohydride (25 equiv) was added and shaking was continued. After 3 days, the reaction mixture was removed and the Lanterns were washed with the following solvents for 30 min intervals: DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

N-Capping/Aliphatic Aldehydes. To each flask containing lanterns was added THF/MeOH 4:1 with 2% AcOH (0.800 mL/Lantern) followed by the desired aldehyde (20 equiv). The reaction mixture was shaken at rt for 1 h then sodium cyanoborohydride (25 equiv) was added and shaking was continued. After 3 days, the reaction mixture was removed and the Lanterns were washed with the following solvents for 30 min intervals: DMF, 3:1 THF/H_2O, 3:1 THF/IPA, THF, CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

Allyl Removal. To a flask containing Lanterns was added EtOH (0.8 mL/Lantern) followed by $Pd(PPh_3)_4$ (2 equiv) and 1,3-dimethylbarbituric acid (15 equiv). The Lanterns were shaken at 40 °C for 4 days and then washed with the following solvents for 30 min intervals: DMF (two washes), THF/H_2O (3:1), THF/IPA (3:1), THF, and CH_2Cl_2. The Lanterns were then dried on a lyophilizer overnight prior to sorting.

Cleavage Protocol. To a 96-well plate containing Lanterns was added a 15% solution of HF/pyridine in stabilized THF (350 μL/Lantern). After 2 h, the cleavage solution was quenched with TMSOMe (700 μL/Lantern) and the contents of each well were transferred to a preweighed 1.4 mL tube. The Lanterns were washed with an additional 200 μL of stabilized THF (or THF/MeOH), and the solution was transferred to the same 1.4 mL tube. The samples were concentrated on a multisample solvent evaporation system overnight without heating. The recovered mass for each library member was determined on an automated weighing system.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds, LC/MS data for representative library members, Charts SI-1 and SI-2 which were cited in ref 41, Figure SI-1 which was cited in ref 41, and X-ray crystallographic information for select compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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