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Synthesis of Enantiomerically Pure 5-Substituted-Piperazine-2-Acetic Acid Esters as Intermediates for Library Production

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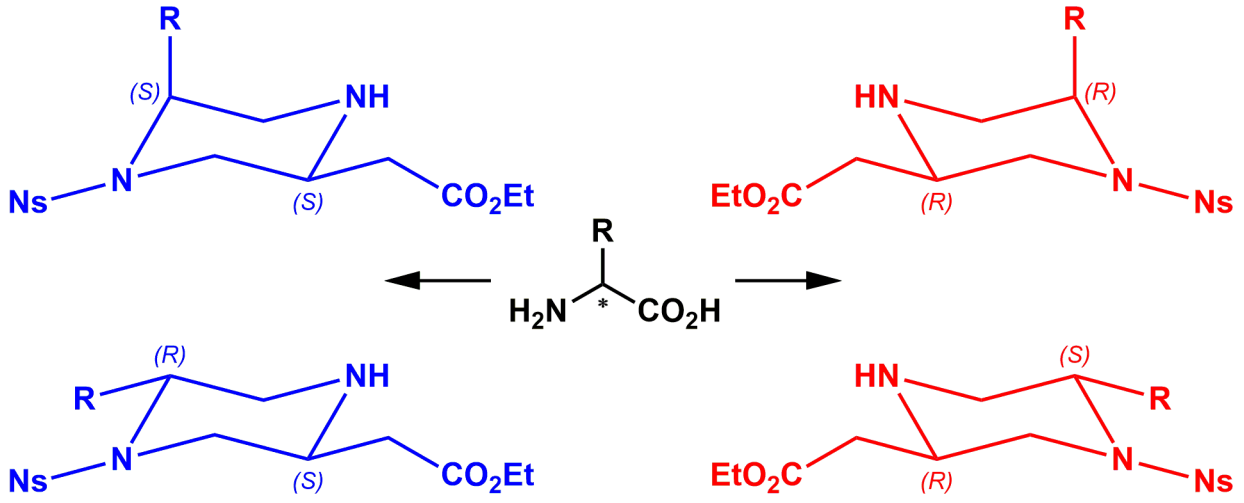
Abstract

The piperazine heterocycle is housed within a large number of FDA-approved drugs and biological probe compounds. Structurally however, these compounds are mostly confined to substitutions on the two ring nitrogen atoms rationalizing the expansion of piperazine chemical diversity through carbon substitutions. Based on the concept of systematic chemical diversity, a divergent six-step synthesis was developed in which chiral amino acids were transformed, with high diastereoselectivity, into either *cis* or *trans* 5-substituted-piperazine-2-acetic acid esters that could be chromatographically rendered diastereomerically homogenous. Starting from 6 commercially available amino acids or their respective amino alcohols, (both antipodes), a complete set of 24 protected chiral 2,5-disubstituted piperazines was obtained, as single stereoisomers in multi-gram quantities. These diverse and versatile piperazines can be functionalized on either nitrogen atom, allowing them to be used as starting materials for parallel library synthesis and as intermediates for the targeted production of more complex C-substituted piperazine compounds.



Introduction

One of the most critically important steps in early stage small-molecule drug discovery is the assembly of compounds for screening against disease-implicated biological targets. Compound collections ("libraries") are assembled for the purpose of presenting, to the target, a variety of substances with different chemical structures in the expectation that some of them will act as ligands to engage the target in a specific manner. Once such a substance is identified, rational manipulation of its structure can eventually produce derivatives that are capable of eliciting a beneficial disease-ameliorating clinical effect. Therefore, the composition of a screening collection used in the earliest part of the drug discovery process is critical for downstream clinical success and thus constitutes a major intellectual challenge.

For most biological targets, little to no information is initially available to guide a rational approach. Under this scenario, the prevailing notion is that the screening of compound libraries constructed based on chemical diversity will provide the most probable access to ligands that can serve as suitable starting points for lead generation.[1,2]

Chemical diversity takes many forms, among them fsp^3, defined as the fraction of carbon atoms in a compound that are sp^3 hybridized. Structural elements bearing sp^3 hybridized carbons impart 3-dimensional (3D) character to a molecule. As compared with 2D structural elements in compound libraries that are primarily composed of sp^2 hybridized carbons, the incorporation of 3D character in library design introduces both structural complexity and expanded opportunities for diversity. A single stereocenter introduces the presence of enantiomers that require either resolution or enantioselective synthesis, along with structure proof, if the racemic version of the compound emerges as a substance of interest. If more than one stereocenter is incorporated then diastereomers are obtained which must be separated and individually characterized, often a non-trivial endeavor. Each diastereomer, in turn, has two antipodes, creating another layer of complexity in the library design. Having multiple stereocenters offers the opportunity to create cohorts of stereoisomers where the same substituent groups are posed in different orientations in both relative and absolute space. The different substituent orientations can be incrementally varied in a controlled, systematic manner either by structural alteration or by conformational biasing. If such a cohort, upon presentation to a biochemical target, affords a specific ligand then the internally constructed stereochemical matrix will immediately reveal which structural characteristics are important for engagement with the target. We denote this kind of library design as systematic chemical diversity (SCD).

Our goal is to demonstrate the value of SCD through the design and production of libraries composed of complete matrices of different regioisomers and all the stereoisomers of diversifiable compounds bearing multiple stereocenters. The architecture of such a matrix is schematically represented in Figure 1. A core structural motif with multiple saturated carbons can bear

substituents in several relative regioisomeric orientations. From optically pure starting materials, each regioisomer can be synthetically produced as a pair of optically active diastereomers if the stereochemistry of the starting material is preserved and the formation of the second stereocenter can be rendered non-selective (shown as pairs of compounds on the horizontal axis). Alternatively, if the formation of the second stereocenter is so selective as to afford insufficient quantities of one diastereomer, an alternative route can be devised to reverse the stereochemical outcome such that practical quantities of both diastereomers can be obtained.[3] In either case, the separation of diastereomers affords its constituent individual absolute stereoisomers. For any given pair of substituents, represented by the red and blue spheres, there will be twelve possible stereoisomers.

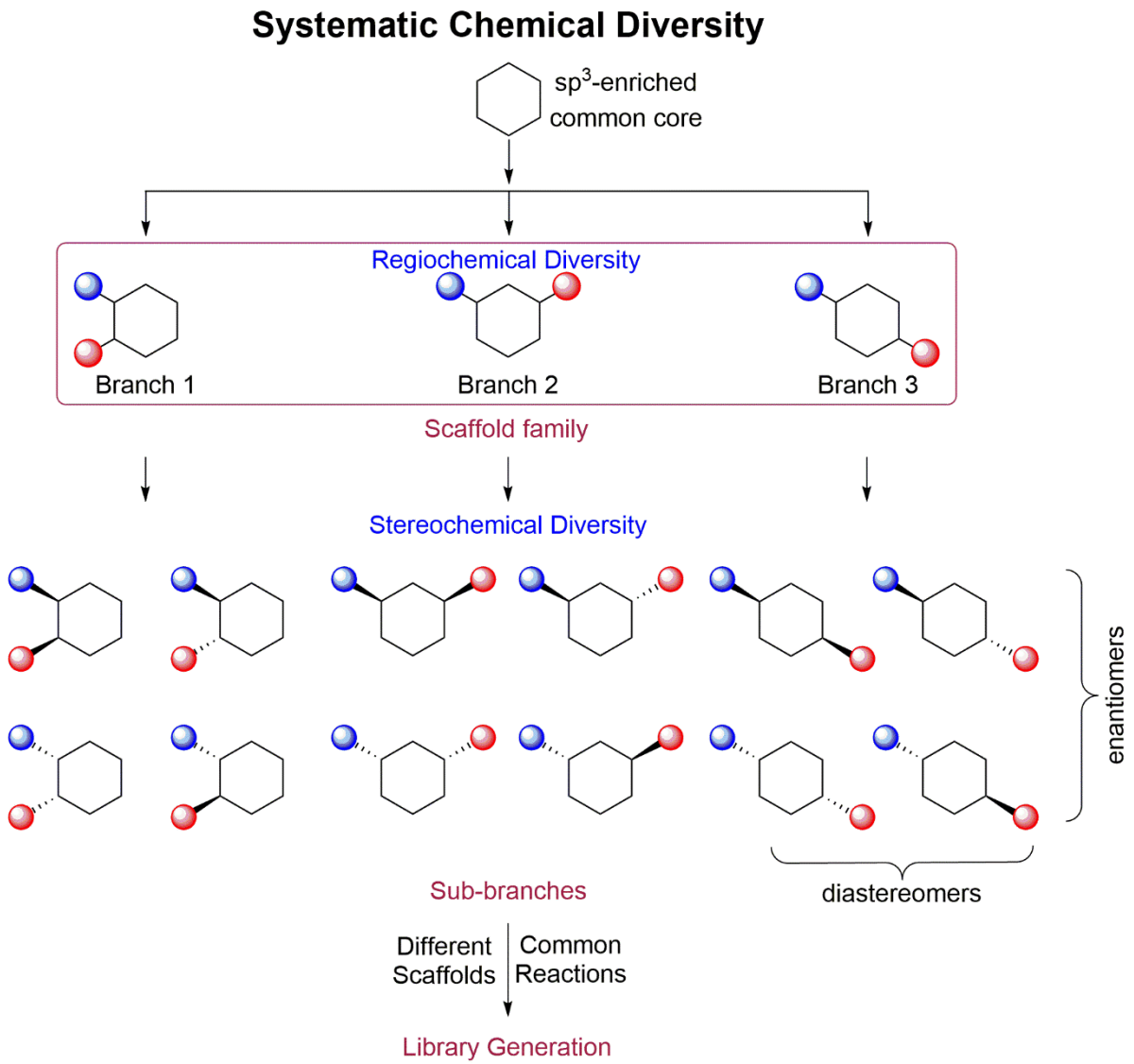


Figure 1. Systematic Chemical Diversity

The piperazine structural motif was chosen to demonstrate the above described design strategy. Piperazine may be considered as a “privileged” heterocyclic moiety given that it is ubiquitous in

both FDA approved clinical agents and numerous other biologically active materials.[4,5] However, within this large cohort of compounds, the structural diversity of piperazines is predominantly limited to N_1 and N_4 substitutions, eliminating access to a wide chemical space of exploration provided by *C* substitutions. Using SCD as a guiding concept, we envisioned the generation of the piperazine based "scaffold family" shown in Figure 2. The regioisomeric family branches of the depicted piperazine-2-acetic acids are denoted by their substitution patterns as 2,3-, 2,5- and 2,6-. The syntheses of the 2,3- and 2,6- family branches have been previously disclosed.[6,7] This report describes the preparation of the remaining 2,5- family branch.

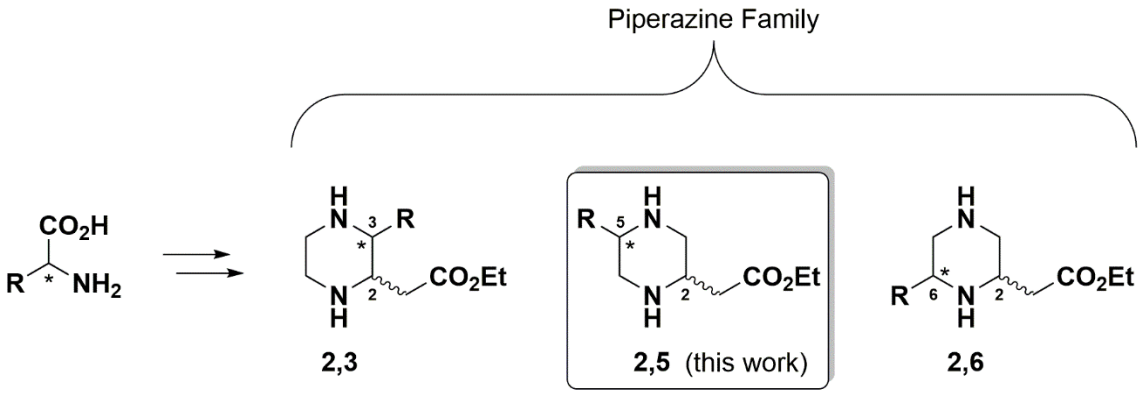


Figure 2. Familial relationship of piperazine scaffolds

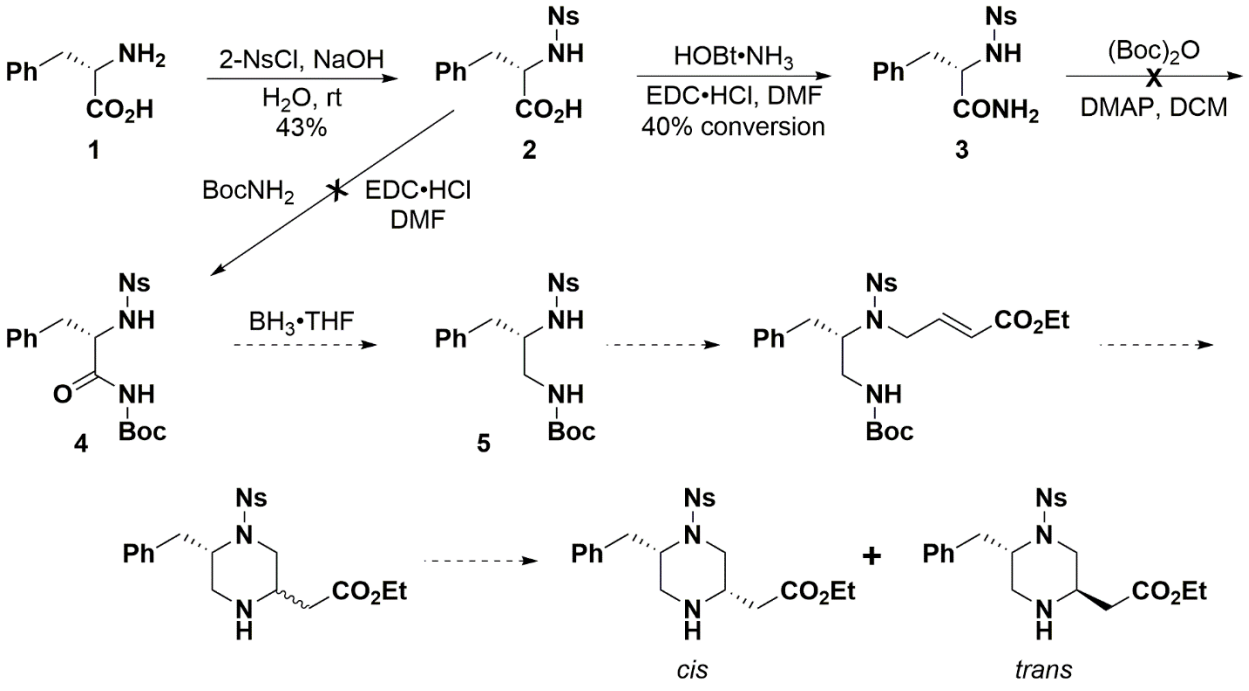
Discussion

The scaffold family depicted in Figure 2 was designed to generate 3D diversity for library production in a combinatorial fashion. Within this family, each atom of the piperazine scaffold can be functionalized to achieve maximum coverage of chemical space. The ring carbons contribute both side chain diversity and absolute stereochemical orientation of their covalently bonded substituents. The inclusion of substituents at two carbon atoms introduces diastereodiversity. The ring nitrogen atoms serve three purposes; they afford sites for further introduction of substituents, they modulate the basicity of the fragment and they influence its conformational orientation by affording alternative states of nitrogen hybridization when diversified with covalently bonded groups. The reported methodology in this work enables the production of multigram quantities of the scaffolds under ordinary laboratory conditions, such quantities being essential for compound library production by parallel synthesis.

Reports of the specific preparation of 2,5-disubstituted piperazines are relatively uncommon. The synthesis is traditionally carried out from an unsymmetrically substituted 1,2-diamine to which a bridging moiety of 3 carbons or more is attached. The preparation of 2,5-disubstituted oxo-piperazines which can serve as precursors for piperazines is the most commonly reported synthetic strategy.[8-14] In all the referenced studies, a fully saturated 2,5-disubstituted piperazine can only be obtained by subsequent reduction of the corresponding oxo-piperazine. Several methods have been reported that directly afford limited sets of chiral 2,5-disubstituted piperazines.[15] A small set of *cis* chiral 2,5-disubstituted piperazines using tosyl aziridine chemistry was described, but with the nitrogen atoms were substituted with methyl and toluenesulfonyl

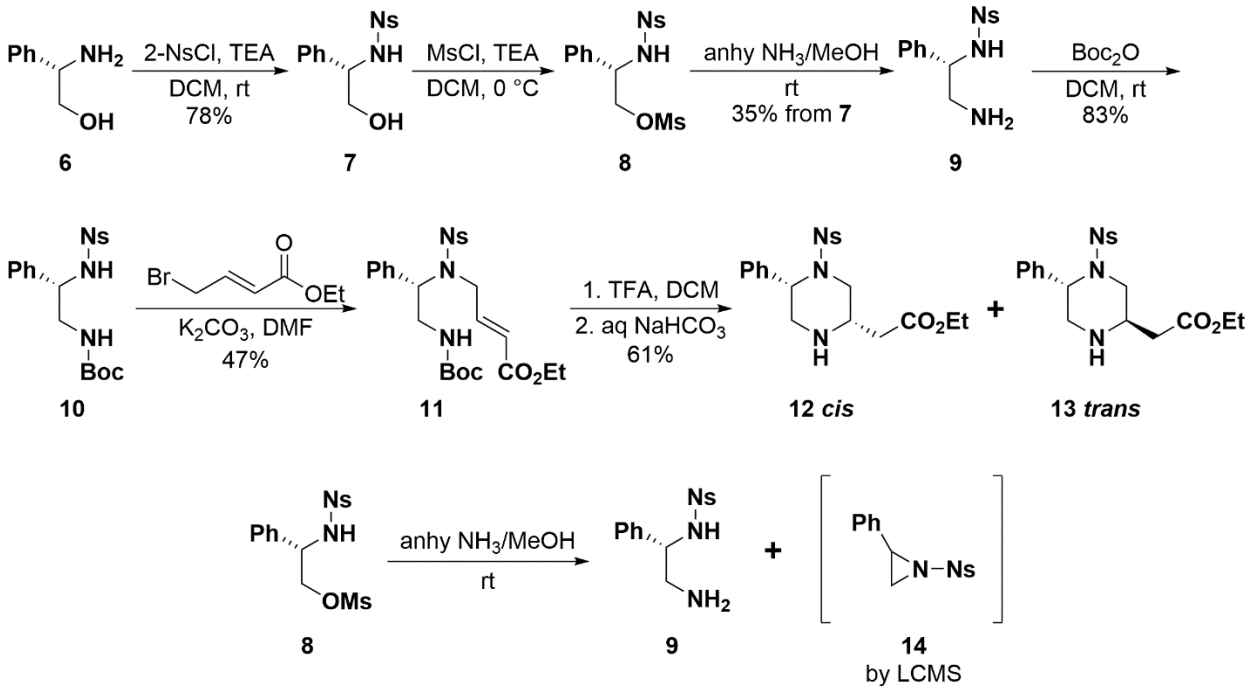
groups.[16,17] As such, the products are not orthogonally accessible to substitution limiting their potential for library production. Furthermore, no *trans* 2,5-disubstituted products are reported. Another report describes the preparation of a small set of orthogonally protected *trans* 2,5-disubstituted piperazines in fair yield on solid support.[18] None of the above studies provide a route to all the stereoisomers of a given 2,5-disubstituted piperazine.

Our goal was to prepare all the stereoisomers of the 2,5-disubstituted piperazine branch on multigram scale, having both nitrogen atoms readily available for diversification. We initially focused on the precedent set in our own previous work on the preparation of the 2,6-disubstituted piperazine family branch (see reference 6). The strategy is shown in Scheme 1 using (*S*)-phenylalanine **1** as an exemplar. It was envisioned that the orthogonally protected vicinal diamine **5** would be regioselectively alkylated on the 2-nosyl protected nitrogen with ethyl 4-bromocrotonate. Following Boc deprotection, an intramolecular aza-Michael addition would ensue to furnish the desired piperazine products. If the key intramolecular aza-Micheal reaction was relatively non-diastereoselctive, then both diastereomers could be obtained from a single reaction and chromatographically separated to yield the individual stereoisomers. Similar to our previous routes, the key intermediate **5** could be prepared in several steps from an amino acid by an imide reduction approach. Accordingly, treatment of (*S*)-Phe **1** with 2-NO_2-benzenesulfonyl chloride under basic aqueous conditions afforded **2**[19,20] which was exposed to HOBt•NH_3 under amide forming conditions to afford the crude amide **3** (40% by LCMS). Unfortunately, no conditions were found that would append the Boc group onto the amide nitrogen. Similarly, we were unable to identify conditions to prepare **4** directly from **2** by reaction with Boc-amine. The inability to reach **5** via imide **4** prompted a reformulation of the synthetic strategy away from one centered on amino acid derived imide reduction to a strategy using amino alcohols as starting materials for the synthesis.



Scheme 1. First approach to 5-substituted 2-piperazine acetic acid esters

Starting from (*S*)-phenylglycinol **6**, the second approach to the orthogonally protected diamine **10** is depicted in Scheme 2. (*S*)-Phenylglycinol was converted to its *N*-nosylated derivative **7** by exposure to NsCl in the presence of TEA.[21] The *N*-nosylated amino alcohol **7** was activated by reaction with MsCl/TEA to afford the corresponding mesylate **8**. Rather than employing the traditional 2-step protocol of azide displacement followed by Staudinger reduction[22,23], which would entail the removal of large amounts of the byproduct TPP-oxide when the reaction was scaled up, we explored the feasibility of direct mesylate displacement with ammonia. Exposure of **8** to a solution of anhydrous ammonia in MeOH (7M) gave, by LCMS, the monoprotected diamine **9** as a major product. Instead of isolating **9**, the reaction was evaporated to a residue and treated with Boc_2O/DCM to give the orthogonally protected diamine **10**. The yield of **10** from the *N*-nosylated alcohol **7** was modest (35%). The bis-protected diamine **10** was advanced through the synthesis along the lines previously established in our earlier 2,6-disubstituted piperazine studies. Regioselective alkylation with ethyl 4-bromocrotonate occurred exclusively at the *N*-nosyl position to afford the cyclization precursor **11**. Treatment of **11** with TFA unmasked the Boc protected nitrogen which effected an intramolecular aza-Michael addition to afford a 5:1 mixture of **12** ***cis*** and **13** ***trans*** in 61% combined yield.



Scheme 2. Second approach to 5-substituted 2-piperazine acetic acid esters

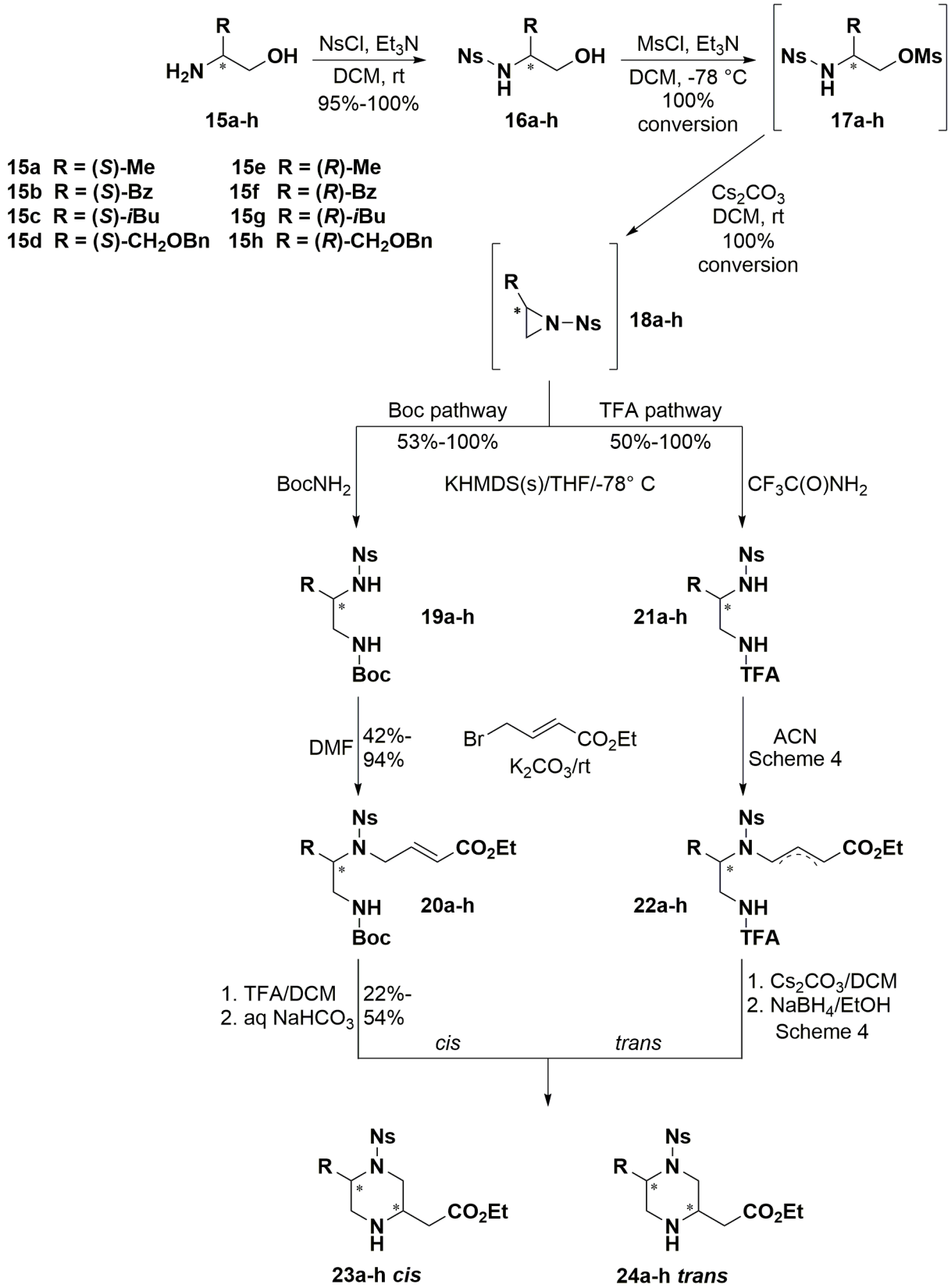
The overall yield of this approach was deemed unsatisfactory and in searching for a better alternative, the ammonia displacement reaction offered a clue. Closer examination of ammonia displacement reaction by LCMS revealed the formation of the *N*-nosyl aziridine **14** as a major constituent of the product mixture. The aziridine presumably arises from deprotonation of the *N*-nosyl group by ammonia followed by intramolecular mesylate displacement.[24-36] Alkyl substituted *N*-nosyl aziridines are known to react with nucleophiles to give regioselective ring opened

products.[37,38] Therefore, we rationalized that aziridine generation followed by introduction of the second nitrogen in protected form would directly lead to orthogonally protected diamines analogous to **10**. Fortunately, a prior example of such a transformation[39] had been reported, encouraging us to investigate this strategy (Scheme 3).

Amino alcohols **15a-h** were converted to their *N*-nosylated derivatives **16a-h** by exposure to NsCl/TEA in DCM at rt.[40-44] The crude products were treated with MsCl/TEA in DCM to give the mesylated intermediates **17a-h** by LCMS. Mesylates **17a-h** were isolated in crude form by extractive workup and immediately advanced without further characterization. Treatment with Cs_2CO_3 in DCM effectively generated the *N*-nosyl aziridines **18a-h** by LCMS, which were isolated as crude solutions given the instability of the *N*-nosyl aziridine in neat form.[45]

Introduction of the second nitrogen in Boc protected form was initially pursued (Scheme 3, Boc pathway). Treatment of aziridines **18a-h** with the preformed potassium salt of $BocNH_2$ in THF at −78°C directly afforded the regiospecifically ring opened, orthogonally protected diamines **19a-h**. KHMDS/THF was markedly superior to a range of other bases (NaH, KO*t*-Bu, K_2CO_3, NaOTMS) and solvents (DMF, DMSO, ACN, dioxane) in this reaction. The use of solid KHMDS, as opposed to commercially available solutions of this reagent, was critical in rendering the execution of this transformation manageable on multi-decagram (50g) scale. Using solid KHMDS reduced the volume of the reactions such that they could be carried out in a conventional laboratory fume hood.

Orthogonally protected diamines **19a-h** were regioselectively alkylated with ethyl 4-bromocrotonate to obtain the cyclization precursors **20a-h**. Nitrogen unmasking with TFA/DCM followed by bicarbonate neutralization gave a mixture of the piperazines **23a-h *cis*/24a-h *trans*** (dr *cis*/*trans* = 3.3-23:1). The optically active diastereomers were separated by normal phase column chromatography to provide the individual scaffolds **23a-h *cis*** and **24a-h *trans***. While the success of the synthetic sequence was gratifying, the substantial stereoselectivities rendered in the cyclization posed a challenge for us. Given that our objective was to obtain multigram quantities of *both* diastereomers for library production, we required a means toward generating the minor *trans* diastereomer in sufficient quantities. In the previously reported 2,6-piperazine work the dr upon aza-Michael cyclization was ~3:1, which furnished enough of the minor diastereomer to serve as a feedstock in combinatorial library synthesis. Using the above described route, a dr of ≥5:1 in most cases would not enable us to obtain enough of the minor *trans* diastereomer to meet our goals. Attempts to alter the *cis*/*trans* ratio to afford more *trans* isomer using stronger bases (K_2CO_3, NaO*t*-Bu, KHMDS) or prolonged (40 °C, 1 week) exposure of the products to Cs_2CO_3, which might promote a retro-Michael mediated equilibration, did not significantly affect the dr.



Boc pathway	Major	dr = 3.3-23:1	Minor
TFA pathway	Minor	dr = 1:15-20	Major

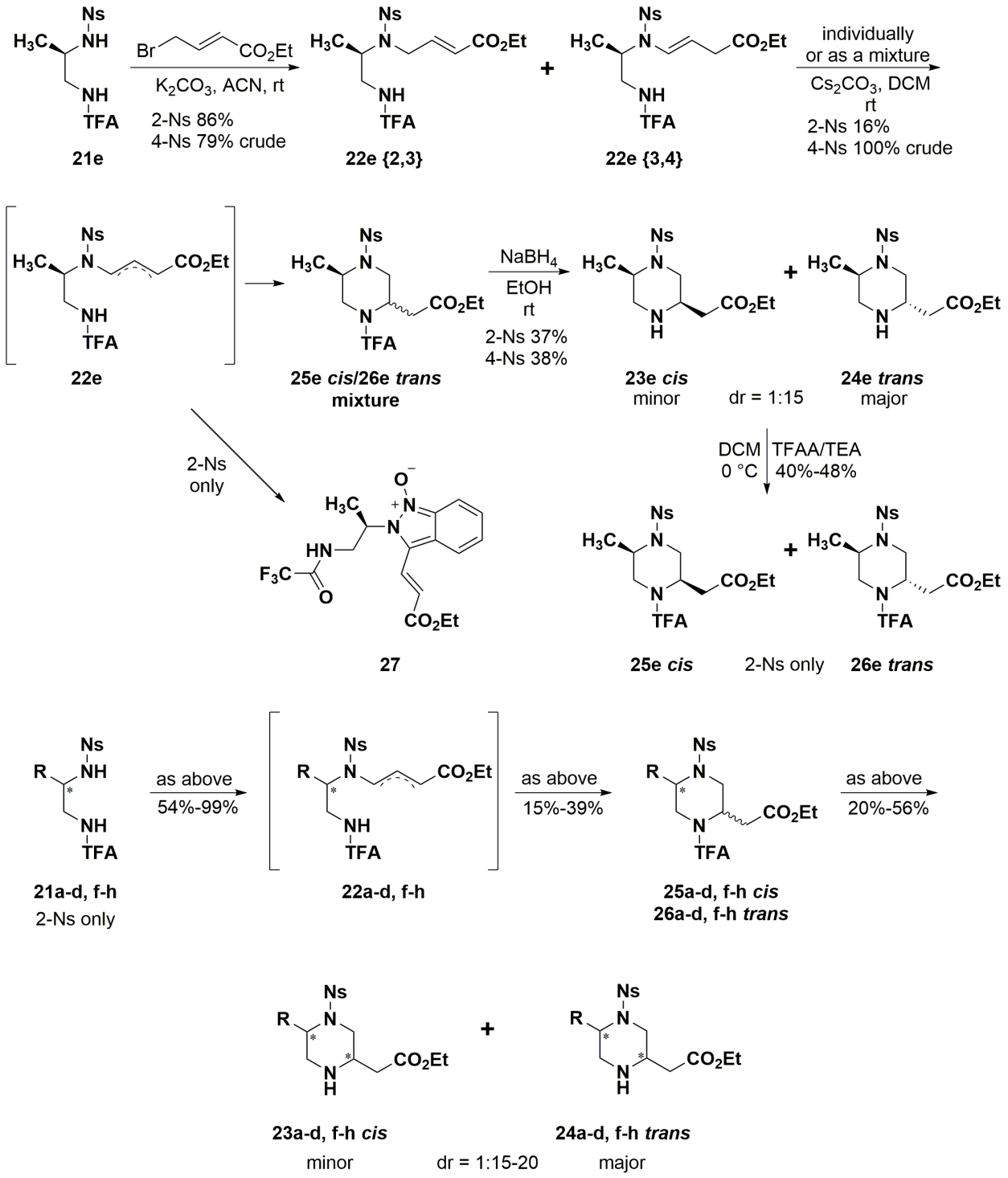
Scheme 3. General synthetic scheme for 5-alkyl-substituted piperazine-2-acetic acid esters.

We resorted to an alternative mode of aza-Micheal reactivity for piperazine formation in hopes of providing more of the *trans* isomer. We surmised that having a substituted nucleophilic nitrogen would increase the steric demand of the aza-Michael donor, which might alter the diastereoselectivity of the cyclization. Instead of unmasking the nucleophilic nitrogen under acidic conditions and effecting the intramolecular aza-Michael addition of the primary amino group to the acrylate, a base promoted anionic cyclization of a carbamate was pursued (Scheme 4).

Initially, the base promoted cyclization of the *N*-Boc precursor **20e** was attempted. Treatment of **20e** with strong base (NaH, KO*t*-Bu) afforded only migration of the 2-Ns aryl group from *N* to *C* (see below for a discussion of this rearrangement). Using weaker bases (Cs_2CO_3) led only to recovered starting material. Reasoning that the *N*-Boc proton was not acidic enough to be preferentially removed, the trifluoroacetamide (TFA) *N*-protecting group was employed, which would both lower the pK_a of its attached *N* atom and could be selectively removed by reduction with $NaBH_4$[46] in the presence of the ethyl ester.

The base promoted strategy is shown in detail using the (*R*)-Ala case. Aziridine **18e** was used to alkylate the potassium salt of $CF_3C(O)NH_2$, affording the differentially substituted diamine **21e** (Scheme 3). Literature precedent indicated that alkylation of **21e** should occur on the nosyl substituted nitrogen instead of the TFA substituted nitrogen given the difference in pK_a between the two acidic protons (Bordwell pK_a in DMSO for $CF_3C(O)NH_2$ = 17.2, $PhSO_2NH_2$ = 16.1; see also references).[47,48] Alkylation of **21e** with ethyl 4-bromocrotonate proceeded much more cleanly in ACN than in DMF, although the reaction was noticeably slower (48h instead of 16h). The reaction afforded a mixture of two products. A sample of the mixture was separated by pTLC and each product was individually characterized by ^{1}H NMR and LCMS. These were determined to be the olefin isomers **22e {2,3}** and **22e {3,4}** in an approximately 1.5:1 ratio. Each alkylation product was individually advanced through the base promoted cyclization reaction. A limited survey of bases and solvents revealed that Cs_2CO_3 was the best choice, but more importantly the reaction had to be carried out in a non-polar solvent, either DCM or DCE, in order to minimize the formation of the Smiles rearrangement product **27** (see the SI for the mechanism of this reaction).[49-55] Higher polarity solvents such as DMF or ACN gave no cyclization product, instead exclusively yielding **27**. Even in DCM, yields of piperazines **25e *cis*/26e *trans*** never exceeded 40%. The rearrangement product **27**, samples of which were isolated for characterization but which was not isolated for determination of yield, was easily separated from the desired piperazines **25e *cis*/26e *trans*** by normal phase chromatography. Removal of the TFA group was accomplished by reduction with $NaBH_4$ in absolute EtOH, affording the individual piperazine scaffolds **23e *cis*** and **24e *trans*** after chromatography. Gratifyingly, structural analysis by 1D ^{1}H NMR and X-ray confirmed that the major product of the anionic cyclization was indeed the desired *trans* isomer. Once the viability of the above sequence was established the purified 2-nosyl-TFA disubstituted amines **21a-h** were converted to the target piperazine scaffolds **24a-h *trans*** directly from the mixture of acrylates **22a-h** without purification of the intermediates. In general, the amounts of **23a-h *cis*** piperazine scaffolds obtained from the TFA pathway were sufficiently small that their isolation was not carried out.

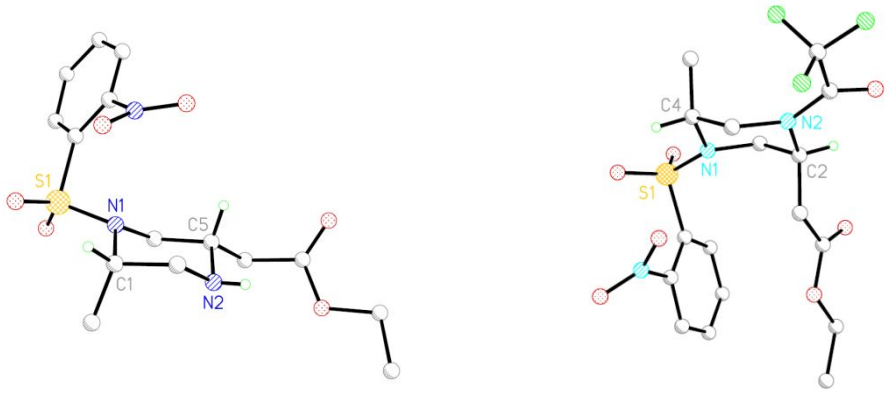
Although the quantities of **24e *trans*** produced by the above-described synthesis were sufficient to meet the immediate needs for library production purposes, there was room for improvement in the overall yield of the sequence. Recognizing that the most problematic part of the sequence depicted in Scheme 4 was the propensity for Ns migration from *N* to *C* with loss of SO_2 during the base promoted cyclization, several other electron deficient arylsulfonyl amine protecting groups were employed. To that end the synthesis was modified by using either 4-CF_3, 2,4-diF and 4-nosyl in place of 2-Ns on small scale in the case of the alanine derived diamine **21e**, with all other steps being carried out as depicted in Scheme 4. In the case of 4-CF_3-phenylsulfonyl, olefin isomerization took place during the alkylation using ethyl 4-bromocrotonate (3:1 {2,3}:{3,4}), while the cyclization using Cs_2CO_3/DCM provided improved cyclization yield to 25%. The problematic step was the removal of 4-CF_3 phenylsulfonyl group using Mg/MeOH on our parallel[56] chemistry platform for further N_4-diversification. In the case of 2,4-diF-phenylsulfonyl no olefin isomerization was observed during the alkylation using ethyl 4-bromocrotonate. However, the Cs_2CO_3/ACN cyclization was very slow and afforded only minor quantities of cyclized product along with isomerized {3,4} olefin but no observable {2,3} olefin (by ^{1}H NMR). In the case of 4-nosyl substitution, the amount of olefin isomerization was reduced to nearly zero (by crude NMR) and the propensity of the 4-nosyl group to migrate from *N* to *C* during the cyclization was not observed albeit on a smaller scale than performed for the 2-Ns routes. The overall yield of cyclized products from **21e** was improved from 7% to 30% mostly due to the improved outcome of the cyclization reaction. The reduction in solubility of earlier intermediates in 4-Ns case led to handling problems on larger scales (50g alaninol). The synthetic sequence was best carried out without purification of any intermediates between **21e** and **24e**. At this point, it was decided to move forward with 2-Ns protecting group because of the demonstrated ease of handling at larger scale as well the need to immediately obtain sufficient quantities of *trans* scaffolds to advance our library generation efforts. The investigation of other sulfonamides that suppress isomerization and rearrangement that can be scaled is warranted.



Scheme 4. TFA pathway detail

Remarkably, the dr of cyclization was reversed for the TFA pathway, now affording in the case of (*R*)-Ala, **24e *trans*** with high selectivity (dr *cis*/*trans* = <1:20). Each major product from the individual pathways using (*S*)-Ala was crystallized; the N_1 unprotected **23a *cis*** crystallized whereas **24a *trans*** had to be converted back to its TFA precursor **26a *trans*** to obtain crystals for

X-ray crystallography (Figure 3). The X-ray structures confirmed that the major product from the Boc pathway was *cis* while the major product from the TFA pathway was *trans.*



23a *cis* (from Boc pathway) **26a *trans*** (from TFA pathway)

Figure 3. X-ray structures of the (*S*)-Ala derived major products from Boc pathway and TFA pathway.

Consideration of the possible transition states for the two cyclizations provides a rationale for the different outcomes (Figure 4). Due to resonance stabilization, the *N-S* bond of the sulfonamide has considerable double bond character introducing $A_{(1,3)}$ strain with groups on the adjacent carbon atoms. In a chair-like transition state there is an unfavorable steric interaction between groups in the pseudoequitorial position of C_5 influencing the larger group to be disposed in a pseudoaxial position in all cases. Thus, we postulate that TS1 is the favored arrangement for the Boc pathway cyclization whereby the acrylate is equatorial leading to the observed *cis* isomer as the major product. For the TFA pathway the C_5 substituent remains pseudoaxial. However, in TS4 the pseudo-equatorial orientation for the acrylate leads to a steric clash between it and the trifluoroacetyl substituent on the incipient N_1 nitrogen. This causes the acrylate to rotate into the pseudo-axial position (TS3) and leads to the observed *trans* isomer as the major product. Therefore, through controlling the identity of the nucleophile we were able to achieve complementary diastereoselective aza-Michael reactions.

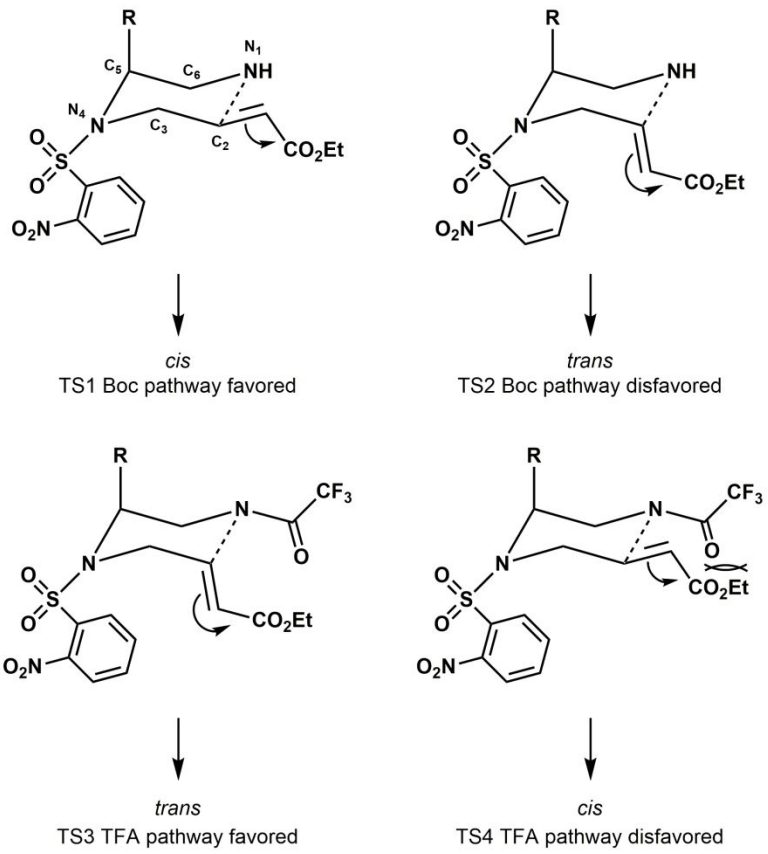
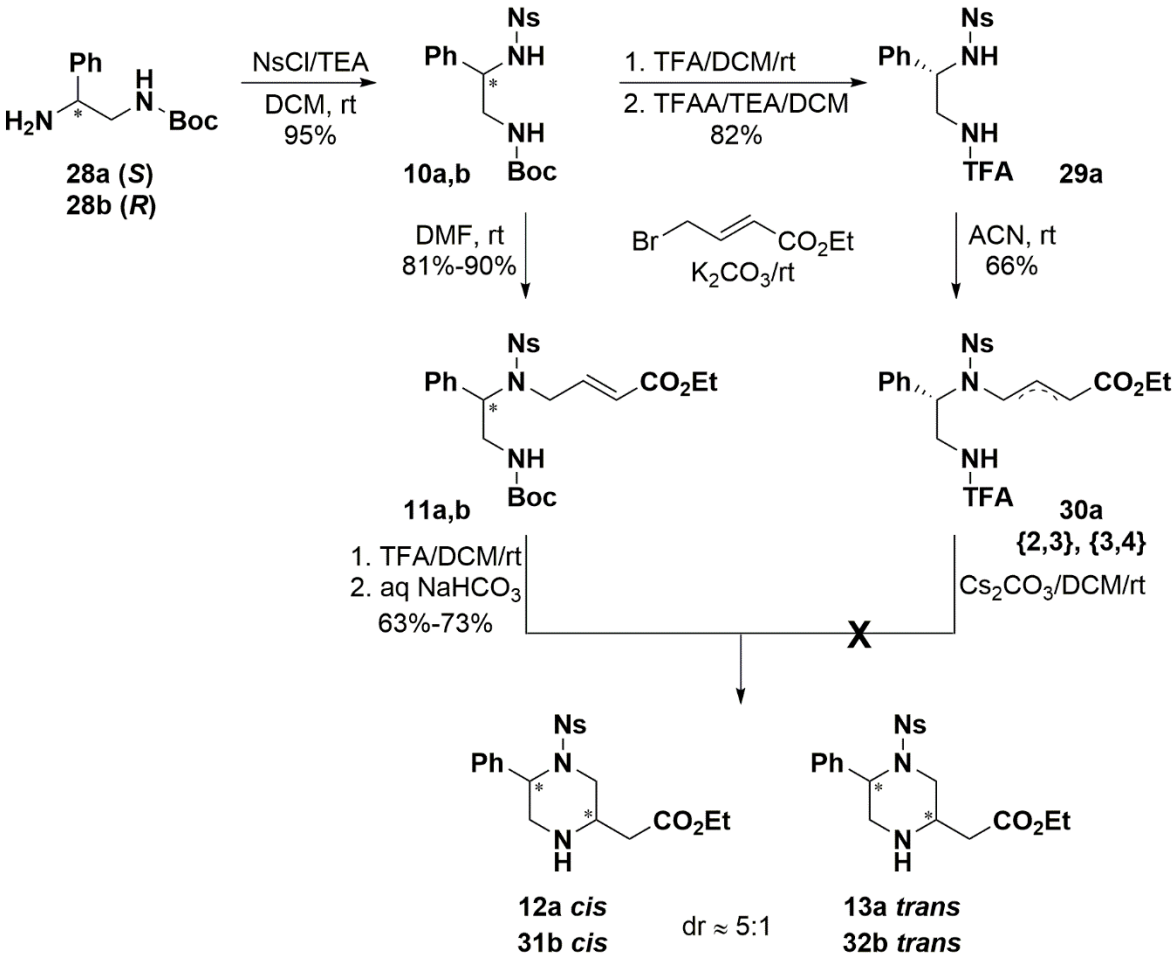


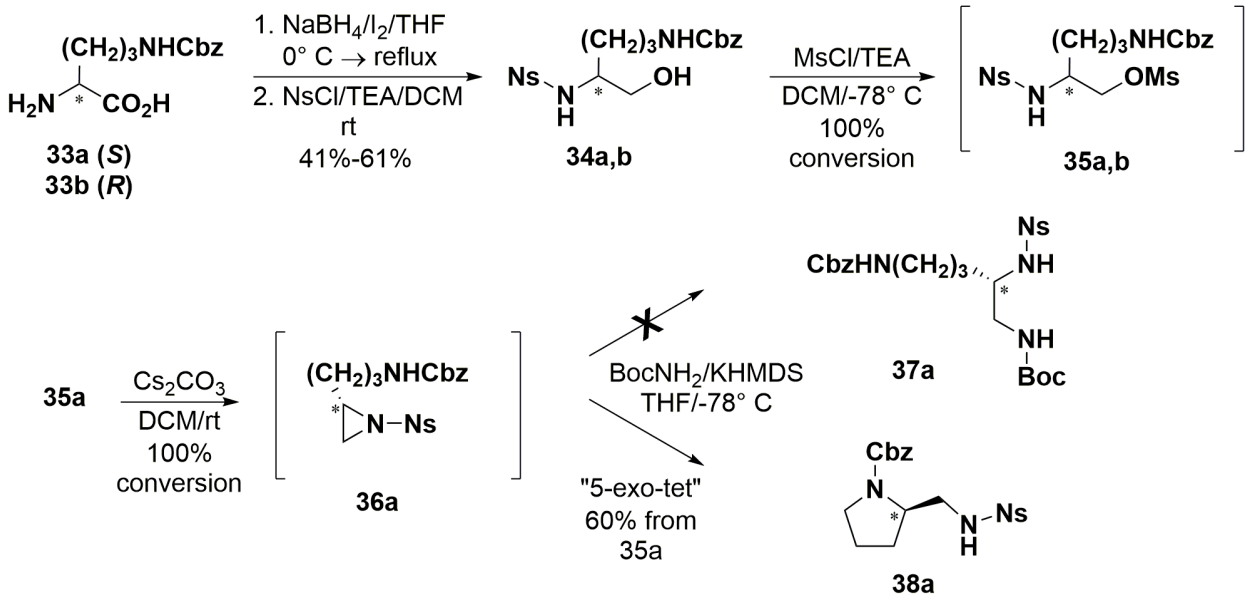
Figure 4. Proposed alternative transition states for cyclization of (*S*) configured diamine acrylates **20a-d**, **22a-d, 11a, 42a** and **44a.**

An exception to the synthesis depicted in Scheme 3 was the case of phenylglycine (Scheme 5). The route shown in Scheme 3 was not employed in this case due to concerns about possible non-selectivity in the aziridine ring opening.[57] The requisite monoprotected diamine precursors **28a** and **28b** were obtained commercially and nosylated as described above to give orthogonally protected diamines **10a/b** suitable for use in the Boc pathway. Compound **29a**, suitable for the TFA pathway, was obtained from **10a** by Boc removal and reaction of the unmasked nitrogen with TFAA/TEA. All three intermediates were alkylated with ethyl 4-bromocrotonate as described above to give **11a,b** and the isomeric mixture **30a**. Treatment of **11a,b** with TFA followed by neutralization afforded the piperazines **12a *cis***, **31b *cis***, **13a *trans*** and **32b *trans***. By contrast, treatment of **30a** with Cs_2CO_3 in DCM gave no evidence of the analogous mixture of piperazines obtained from the TFA route employed in Scheme 4. Instead two non-cyclized products were obtained. Proton NMR of the two products showed the phenyl moiety in one and the nosyl moiety in the other, suggesting that **30a** had undergone an unexpected bond scission. This result was not studied any further.



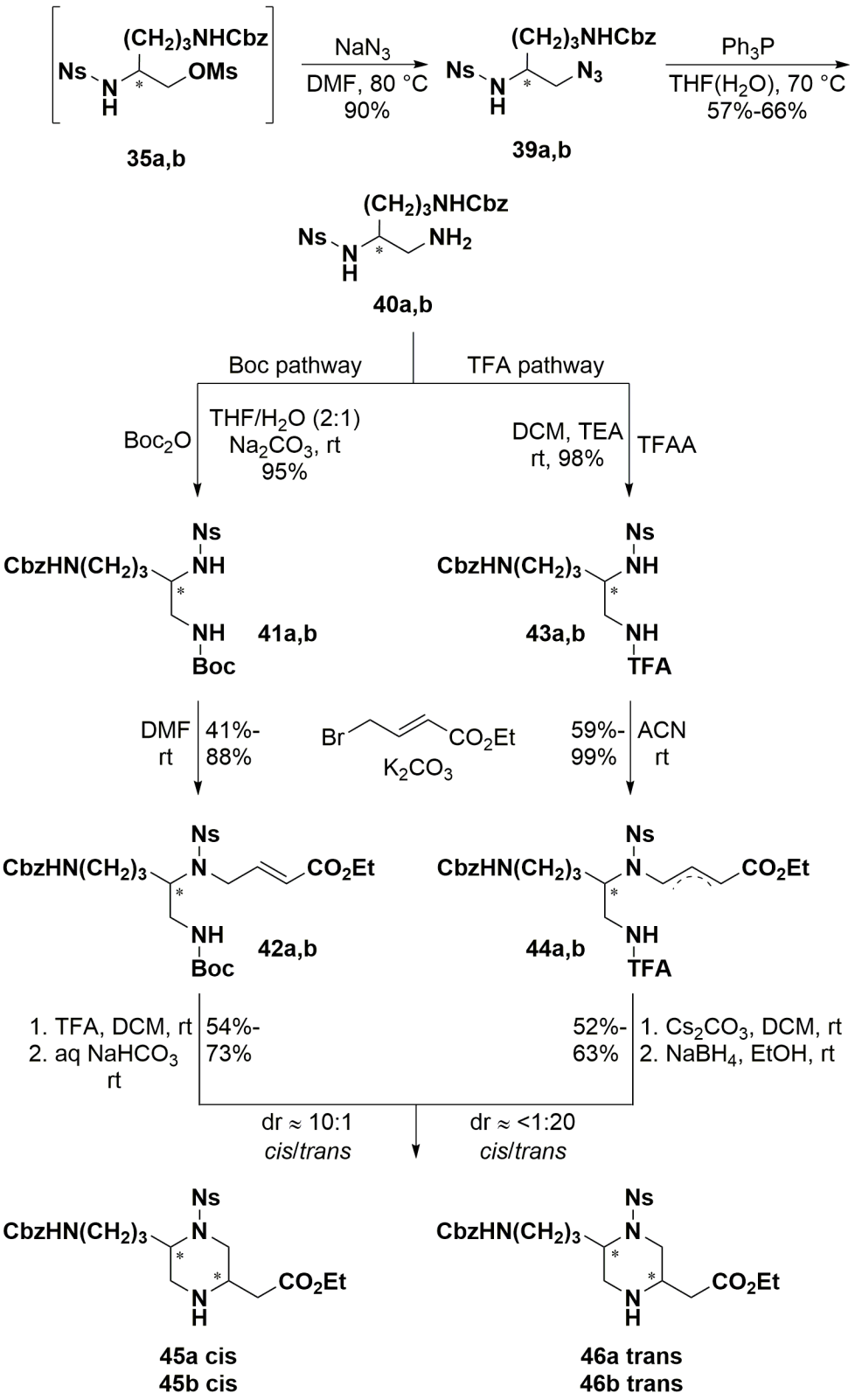
Scheme 5. Synthesis of phenylglycine derived scaffolds.

Another exception to the synthesis depicted in Scheme 3 is the case of ornithine (Scheme 6). *N*-nosylated amino alcohols **34a/b** were prepared from commercially available (*S*) and (*R*) N_5-Cbz Orn **33a/b** by reduction with $NaBH_4/I_2$ followed by nosylation of the derived amino alcohols (not shown). **34a/b** were converted to their corresponding mesylates **35a,b** as described in Scheme 3. Exposure of mesylate **35a** to Cs_2CO_3 led, by LCMS, to the formation of the aziridine **36a**. Treatment of aziridine **36a** with $BocNH_2$/KHMDS afforded, not the desired orthogonally protected acyclic diamine product **37a** but instead pyrrolidine **38a**. Pyrrolidine **38a** would likely arise from deprotonation of the *N*-Cbz group by the potassium salt of $BocNH_2$ followed by cyclization via a Baldwin favored "5-exo-tet" aziridine ring-opening mechanism.[58] In order to specifically determine whether the aziridine **36a** is formed as an intermediate in this transformation, and thus provide further evidence of our structural assignment of **38a**, the aziridine forming reaction was carried out in CD_2Cl_2 and followed by NMR. The aziridine **36a** was observed.



Scheme 6. Unsuccessful synthesis of piperazine scaffolds derived from N_5-Cbz ornithine.

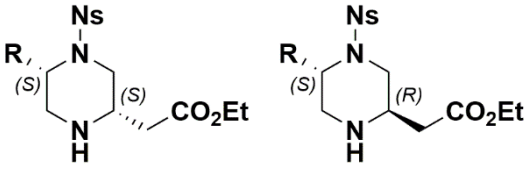
We turned to previously known conditions for the preparation of the ornithine derived piperazine scaffolds (Scheme 7). Mesylates **35a/b** were converted to *N*-nosyl amino azides **39a,b** by reaction with NaN_3 in DMF. Staudinger reduction afforded the corresponding monoprotected diamines **40a,b**. These were converted to the orthogonally tris-protected triamines **41a,b** which were alkylated on the nosyl protected nitrogen to give the cyclization precursors **42a,b**. Removal of the Boc group with TFA was followed by neutralization as described above to give the piperazine scaffolds **45a *cis***, **45b *cis***, **46a *trans*** and **46b *trans*** with a dr (10:1 *cis*/*trans*), very similar to what was obtained in Scheme 3.



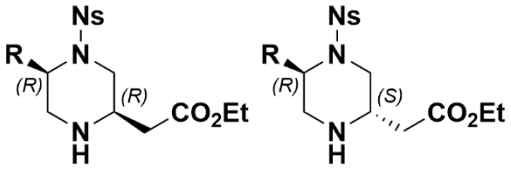
Scheme 7. Synthesis of piperazine scaffolds derived from N_5-Cbz ornithine.

In order to obtain larger quantities of the minor diastereomers of the Boc pathway, **46a,b *trans***, the base promoted TFA cyclization pathway was carried out. Triamines **40a,b** were treated with TFAA/TEA to obtain the Cbz-nosyl-TFA tris-protected triamines **43a,b**. Alkylation with 4-bromo-(*E*)-2-butenylate again proceeded exclusively on the nosyl protected nitrogen to afford the cyclization precursors **44a,b** as mixtures of olefin isomers. Cyclization of **44a,b** under basic conditions afforded the same piperazine products **45a,b** and **46a,b** with the expected reversal in dr.

Table 1 shows the piperazine scaffolds obtained from each amino alcohol and from each synthetic pathway.



cis/*trans* derived from (*S*) amino alcohols



cis/*trans* derived from (*R*) amino alcohols

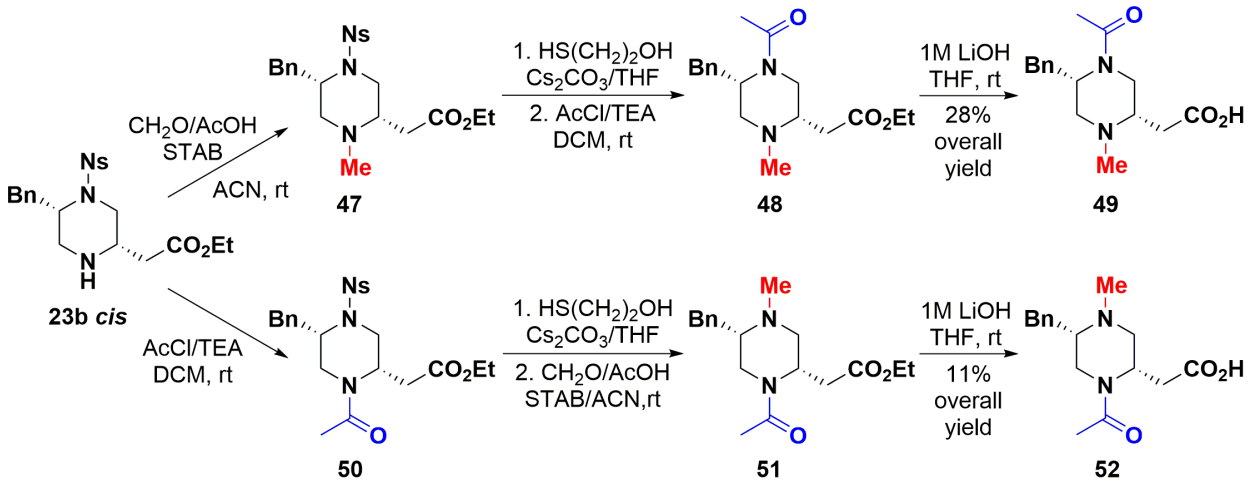
Entry	R	Route	dr *cis*/*trans*	Amount produced (g)(*cis*)	Amount Produced (g)(*trans*)	er (%:%)
1	(*S*)-CH_3 23a *cis*	Scheme 3 Boc	4.2:1	17.4†	4.1†	>99.8:0.2
2	(*S*)-CH_3 24a *trans*	Scheme 4 TFA	1:15	0.23	3.5	>99.8:0.2
3	(*R*)-CH_3 23e *cis*	Scheme 3 Boc	4.3:1	11.6†	2.7†	>99.8:0.2
4	(*R*)-CH_3 24e *trans*	Scheme 4 TFA	1:15	0.3	4.6	>99.8:0.2
5	(*S*)-CH_2Ph 23b *cis*	Scheme 3 Boc	4:1	8.0	2.0	>99.8:0.2
6	(*S*)-CH_2Ph 24b *trans*	Scheme 4 TFA	<1:20	--	5.5	>99.8:0.2
7	(*R*)-CH_2Ph 23f *cis*	Scheme 3 Boc	7.5:1	9.0	1.2	>99.8:0.2
8	(*R*)-CH_2Ph 24f *trans*	Scheme 4 TFA	<1:20	--	4.6	>99.8:0.2
9	(*S*)-*i*Bu 23c *cis*	Scheme 3 Boc	23:1	7.0	0.3	>99.8:0.2
10	(*S*)-*i*Bu 24c *trans*	Scheme 4 TFA	<1:20	--	3.5	99.2:0.8
11	(*R*)-*i*Bu 23g *cis*	Scheme 3 Boc	20:1	12.0	0.6	99.6:0.4
12	(*R*)-*i*Bu 24g *trans*	Scheme 4 TFA	<1:20	--	3.4	98.8:1.2
13	(*S*)-$CH_2OBz^{\#}$ 23d *cis*	Scheme 3 Boc	3.3:1	4.0	1.2	99.6:0.4
14	(*S*)-$CH_2OBz^{\#}$ 24d *trans*	Scheme 4 TFA	<1:20	--	1.0	99.2:0.8
15	(*R*)-$CH_2OBz^{\#}$ 23h *cis*	Scheme 3 Boc	4.7:1	5.2	1.1	99.4:0.6
16	(*R*)-$CH_2OBz^{\#}$ 24h *trans*	Scheme 4 TFA	<1:20	--	1.4	99.7:0.3
17	(*S*)-Ph 12a *cis* 13a *trans*	Scheme 5 Boc	4.8:1	3.8	0.8	>99.8:0.2 >99.8:0.2
18	(*R*)-Ph 31b *cis* 32b *trans*	Scheme 5 Boc	5.4:1	9.7	1.8	>99.8:0.2 >99.8:0.2

19	**(*S*)-(CH$_2$)$_3$-*N*HCbz 45a *cis***	**Scheme 7 Boc**	10:1	0.5	0.05	>99.8:0.2
20	**(*S*)-(CH$_2$)$_3$-*N*HCbz 46a *trans***	**Scheme 7 TFA**	<1:20	--	0.1	99.3:0.7
21	**(*R*)-(CH$_2$)$_3$-*N*HCbz 45b *cis***	**Scheme 7 Boc**	8:1	0.4	0.05	99.8:0.2
22	**(*R*)-(CH$_2$)$_3$-*N*HCbz 46b *trans***	**Scheme 7 TFA**	<1:20	--	0.12	99.4:0.6

Table 1. Scaffolds synthesized by stereochemistry and route. dr was determined either by isolation of the minor diastereomer or by TLC/crude ^{1}H analysis. <20:1 = no minor diastereomer detected by TLC/^{1}H NMR and none isolated by chromatography. †the sum of two runs. $^{\#}$the stereochemical designation for Ser-*O*-benzyl ether inverts from (*S*) to (*R*) when the amino acid is converted to its corresponding amino alcohol and then to the piperazine. Thus, (*S*)-Ser-*O*-benzyl ether gives (*R*)-serinol-*O*-benzyl ether and **(*R*)-23h *cis*** and **(*R*)-24h *trans*** as shown in the structures above and vice versa. All other amino acids retain their stereochemical designation.

The use of these piperazine scaffolds, in combination with their related regio- and stereoisomers, as a demonstration of our SCD strategy depends upon the successful diversification of both of their nitrogen atoms by parallel synthesis. As described above, the modulation of the chemical properties and the basicity of the derived diversified fragments can be effected by covalent attachment of various functional groups. But just as importantly, the judicious choice of diversification elements offers the possibility of creating conformational diversity by changing the hybridization state of the nitrogen atoms. Appending a series of functional groups ranging, for example, from acetyl through methanesulfonyl to methyl changes the bonding geometry on each nitrogen from trigonal planar through shallow pyramidal to fully tetrahedral. In doing so the library design enables the compounds to pose the same ring substituent groups in different orientations by conformational biasing, thus creating an enhanced coverage of chemical space.

Scheme 8 depicts two synthetic sequences that produce final products which illustrate the concepts described above using acetyl (for sp^2 hybridization) and methyl (for sp^3 hybridization) as the diversity elements. Starting with scaffold **23b** the alternative pathways, which employ the same chemistry suitable for parallel synthesis but in different orders, leads to the isomeric fragments **49** and **52**. The N_1 and N_4 atoms are present in alternating hybridization states and the site of the basic atom is transposed from one region of the molecule to the other. The implications of these structural modifications will be examined in greater depth in connection with the production of libraries derived from complete stereochemical matrices of these piperazine scaffolds.



Scheme 8. Orthogonal diversification of **23b *cis***.

Conclusion

In this report we describe the successful completion of a branch of 5-substituted piperazine-2-acetic acid esters, inspired by the concept of systematic chemical diversity. The piperazines produced in this study are poised for generating libraries of enantiomerically pure drug-like piperazine compounds through parallel combinatorial synthesis. The key sequence centered on the generation of chiral *N*-nosyl aziridines that could be efficiently converted to orthogonally bis-protected chiral 1,2-diamines which in short order could be taken forward to the title compounds.

During our previous syntheses of the 2,3 and 2,6 piperazine branches, we capitalized on the modest stereoselectivity in forming the second stereocenter to generate both *cis* and *trans* piperazines in one pot (see references 6 and 7). Scaling these reactions and efficient chromatographic separation led to multigram quantities of each diastereomer with ~ 50% fewer reactions needed to complete these series. In contrast to those studies, our initial 2,5-piperazine pathway was highly diasteroselective favoring the *cis* diastereomer. This prompted the development of a divergent pathway from a common intermediate leading mostly to the *trans* 2,5-disubstituted piperazine.

Analogous to natural product total synthesis, systematic chemical diversity is predicated on achieving a specific predefined outcome. While in total synthesis the natural product serves as the end goal, SCD requires complete sets of regio- and stereoisomeric products in suitable quantities for downstream diversification. However, unlike total synthesis the disparate structures required by SCD may render a single chemical pathway unsuitable toward achieving success. Indeed, it was our initial plan that all three branches could be synthesized using a common pathway; however, it became clear early in our studies that a single pathway could not accommodate the steric and electronic features intrinsic to each scaffold branch. This led to the development of three unique synthetic plans to complete the scaffold family depicted in Figure 5.

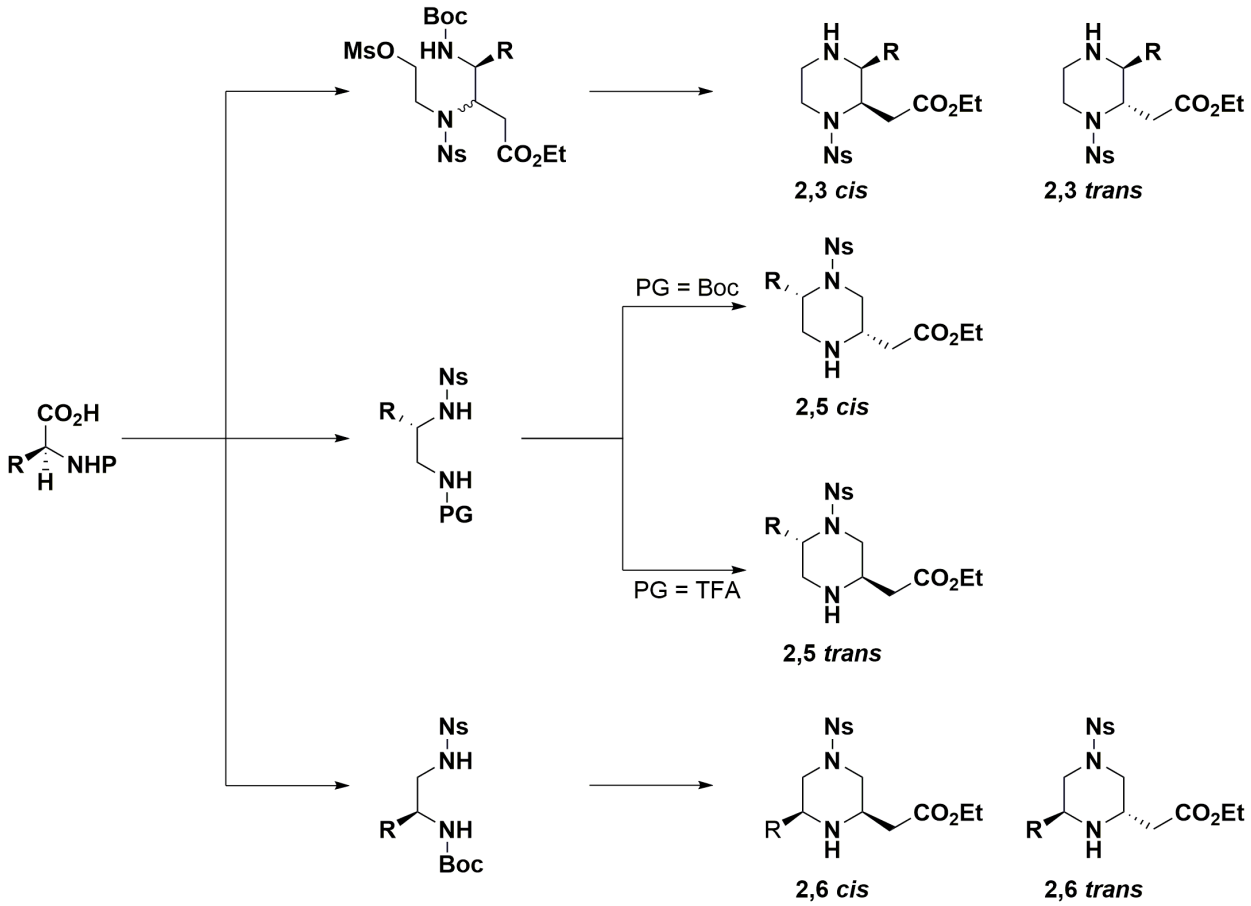


Figure 5. Summary of the disubstituted piperazine-2-acetic acid ester scaffold family synthesis pathways.

Guided by the concept of systematic chemical diversity, the work described here completes the third and final branch of the piperazine scaffold family. The deployment of the complete set of piperazine stereoisomers to generate libraries for fragment-based drug discovery (FBDD) and DNA-encoded libraries for biological discovery is currently underway and will be reported in due course.

Experimental

With the exception of Scheme 4, “Ns” refers exclusively to 2-Ns.

General Methods. All starting materials and reagents were purchased from commercial sources and used without further purification. Solvents were purchased as either anhydrous grade products in sealed containers or reagent grade and used as received. All reactions were carried out in dry glassware under a nitrogen atmosphere using standard disposable or gastight syringes, disposable or stainless steel needles, cannula, and septa. Stirring was achieved with magnetic stir bars or with an overhead mechanical stirrer. Flash column chromatography was performed with SiO_2 (230-400 mesh) or by using an automated chromatography instrument with an appropriately sized column. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (E. Merck). Non-UV active compounds were visualized on TLC using one of the following stains:

$KMnO_4$, ninhydrin, *p*-anisaldehyde, PMA, 2,4-DNP or bromocresol green. ^1H and ^{13}C NMR spectra were recorded on an instrument operating at either 600MHz or 800MHz, and 150MHz or 200MHz respectively. IR spectra were obtained neat on an FT-IR instrument and are expressed in cm^{-1}. LCMS data were collected using an HPLC instrument coupled to a low resolution mass spectrometer with single quadrupole ionization operating in either positive or negative ion mode. The analytical method utilized a C_{18} column (2.1 × 50 mm, 1.8 μm) eluting with a linear gradient of 95%/5% water/CH_3CN (modified with 0.05% formic acid; T = 0 min flow = 0.35 mL/min) to 95%/5% CH_3CN/water (T = 3.5 min flow = 0.5 mL/min) then 95%/5% CH_3CN/water to T = 5min (0.5 mL/min). Peak detection was done at 254 nm and 230 nm for UV active compounds. For non-UV active compounds total ion count was used. High-resolution mass spectrometry (HRMS) spectra were obtained on a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer equipped with a HESI source and using lock masses for correction. Samples were introduced into the HRMS via reversed phase HPLC on an Accucore Vanquish C18+ column (2.1 × 100 mm, 1.5 μm) eluting with a linear gradient of 95%/5% water/acetonitrile (modified with 0.1% formic acid) to 10%/90% water/acetonitrile over 8 min. Chiral HPLC analysis of piperazines was carried out on an instrument with automated 6-column array (Daicel ChiralPak I-series, IA through IF, 4.6 × 150 mm, 5 μm). Racemates were screened using a heptane (A)/ethanol (B) gradient (flow = 1 mL/min) as follows: T = 0 min (%A/%B) 95/5, T = 1 min 95/5, T = 11 min 10/90 (linear gradient), T = 13 min 10/90, T = 13.1min 95/5, T = 15min 95/5. Racemates that gave unsatisfactory resolution of enantiomers were rescreened using the above gradient with *i*PrOH instead of EtOH. Additional editing of the gradient or the use of an isocratic mobile phase to optimize separation was carried out as needed. Chiral materials were analyzed using optimized conditions and their traces were compared to the racemic traces for determination of enantiomeric ratio (er).

To determine our limit of detection (LOD) by chiral HPLC, 5 μL aliquots of 2 mg/mL stocks (10 ng injections) of purified protected scaffolds were subjected to chiral HPLC analysis to resolve and quantify enantiomers and determine enantiomeric ratios. Scouting solvent conditions across six 4.6 mm x 150 mm chiral columns (ChiralPak IA-IE) identified chromatographic conditions for every compound that successfully effected baseline resolution of the enantiomers of the racemic products. Absorbance at 254 nm (nosyl or benzyl) was used to detect and quantify the amount of scaffold. Serial dilutions of the 2 mg/mL stocks established that our LOD is approximately 0.02 ng/injection, or 0.2% of the total material loaded under these conditions. Therefore the limit of our detection of enantiomeric ratio is ≥99.8:0.2. All chiral traces of the scaffolds are included in the Supplementary Information.

Automated preparative reverse-phase HPLC purification was performed using a Mass Directed Fractionation (MDF) system with UV-DAD detection and a single quadrupole mass spectrometer. The instrument used a C_{18} column (21.2 mm i.d. × 150 mm, 5 μm, w/19 mm × 10 mm guard column). The crude product was dissolved in methanol and purified utilizing an elution of water (modified with 0.05% formic acid) and methanol, with a linear gradient increasing from 5% to 100% methanol over 15 m at a flow rate of 20 mL/min. Purification was carried out by mass trigger only.

All NMR chemical shifts are quoted on the δ scale and were referenced to residual non-deuterated solvent as an internal standard. Signal multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, b = broad, quar = quartet, quin = quintet, m = multiplet, v = very; abbreviations are combined, *e.g.* vbs = very broad singlet. The NMRs of products isolated as unseparated mixtures of diastereomers are included for reference only.

Scheme 1

((2-nitrophenyl)sulfonyl)-(*S*)-phenylalanine (2). (*S*)-Phenylalanine **1** (1.0 g, 6.05 mmol, 1.0 equiv) was dissolved in a solution of NaOH (363 mg, 9.0 mmol, 1.5 equiv) in water (10 mL) at 0 °C. Nosyl chloride (2.01 g, 9.05 mmol, 1.5 equiv) was added slowly to the solution, which slowly becomes homogenous. The resultant mixture was stirred at rt for 3 h and was monitored by TLC (10% MeOH in DCM) and LCMS. The reaction mixture was extracted with EtOAc to provide the title compound as an off-white solid (mp 92 – 96 °C, 900 mg, 43% yield). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.28 – 7.19 (m, 3H), 7.15 – 7.14 (m, 2H), 6.00 (d, *J* = 8.4 Hz, 1H), 4.50 (dt, J_t = 7.7 Hz, J_d = 5.3 Hz, 1H), 3.24 (½ABX, *J* = 14.1, 7.5 Hz, 1H), 3.08 (½ABX, *J* = 14.1, 7.5 Hz, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.0, 147.3, 134.5, 134.0, 133.6, 133.1, 130.3, 129.3, 128.7, 127.6, 125.7, 57.6, 38.7. IR: 3324 (broad), 3096, 2940, 1723, 1536, 1497, 1415, 1347, 1163, 1101, 1058, 1015. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}N_2O_6S$ 351.0651; Found 351.0669.

Preparation of HOBt•NH_3: Solid HOBt•H_2O was dissolved in methanolic ammonia (7N). The solution was evaporated to afford a white solid in quantitative yield. The solid was used as a source of NH_3 in the next reaction.

(*S*)-2-((2-nitrophenyl)sulfonamido)-3-phenylpropanamide (3). A 25 mL round bottom flask with stir bar was charged with a solution of **2** (100 mg, 0.28 mmol, 1.0 eq) in dry DMF (5 mL). EDC•HCl (165 mg, 0.85 mmol, 3 eq) and HOBt•NH_3 (345 mg, 2.28 mmol, 8 eq) were added. The reaction was stirred at rt for 48 h with monitoring by LCMS. LCMS indicated ≈40% conversion to product. The reaction was quenched with water (5 mL) and with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (80 mg, white viscous oil, 80% crude yield).

Scheme 2

(*S*)-*N*-(2-hydroxy-1-phenylethyl)-2-nitrobenzenesulfonamide (7). Using the method described to prepare compound **16e** using (*S*)-2-amino-2-phenylethan-1-ol **6** as the starting material, the title compound was obtained (5.5 g, white solid, mp 124 – 127 °C, 78% yield). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.76 (dt, J_t = 8.9 Hz, J_d = 1.3 Hz, 2H), 7.59 (dt, J_t = 7.8 Hz, J_d = 1.4 Hz, 1H), 7.46 (dt, J_t = 7.7, J_d = 1.3 Hz, 1H), 7.17 – 7.14 (m, 5H), 6.27 (d, *J* = 8.3 Hz, 1H), 4.68 (ddd, *J* = 8.4, 6.1, 4.4 Hz, 1H), 3.91 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.84 (dd, *J* = 11.4, 6.1 Hz, 1H), 1.90 (vbs, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 147.4, 137.0, 134.3, 133.1, 132.5, 130.8, 128.6, 128.2, 125.0, 66.2, 60.4, 60.4. IR: 3695, 3679, 3662, 3333 (broad), 2937, 2865, 2843, 1535, 1412,

1357, 1332, 1161, 1126, 1057, 1032, 1017. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{15}N_2O_5S$ 323.0702; Found 323.0697.

(*S*)-2-((2-nitrophenyl)sulfonamido)-2-phenylethyl methanesulfonate (8). Using the method described to prepare compound **17e** using compound **7** as the starting material, the title compound was obtained (200 mg, off-white semi-solid, 64% yield).

(*S*)-*N*-(2-amino-1-phenylethyl)-2-nitrobenzenesulfonamide (9). A 10 mL microwave vial was charged with a solution of 8 (200 mg, 0.5 mmol) in methanolic anhydrous ammonia (7M nominal, 0.35 mL, 2.5 mmol, 5 equiv) and stirred at rt for 2h. The reaction was monitored by TLC (5% MeOH/DCM) and LCMS, which showed complete disappearance of sm. All volatiles were removed and the residue partitioned between DCM and 2M HCl. The aqueous layer was basified to pH 8 with sat aq $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound (viscous brown oil, 60 mg, 38% yield).

***tert*-Butyl (*S*)-(2-((2-nitrophenyl)sulfonamido)-2-phenylethyl)carbamate (10).** A 25 mL round bottom flask was charged with a solution of (*S*)-N-(2-amino-1-phenylethyl)-2-nitrobenzenesulfonamide 9 (50 mg, 0.15 mmol, 1 equiv) in DCM (2 mL). Boc_2O (37 mg, 0.17 mmol, 1.1 equiv) was added. The homogeneous reaction mixture was stirred at rt for 16h and monitored by LCMS (negative ion mode). Water (2 mL) was added and extracted three times with DCM. The combined DCM layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography using an EtOAc/hexane gradient (20% to 100% EtOAc/hex) to provide the title compound as a white viscous oil (55 mg, 83% yield). This product was identical to compound **10a** obtained from compound **28a** in Scheme 5. See Scheme 5 for complete characterization.

Ethyl (*S,E*)-4-((*N*-(2-((*tert*-butoxycarbonyl)amino)-1-phenylethyl)-2-nitrophenyl)sulfonamido)but-2-enoate (11). Using the method described to prepare compound **20e** using compound **10** as the starting material, the title compound was obtained (30 mg, yellow semi-solid, 48% yield). This product was identical to compound **11a** obtained from compound **10a** in Scheme 5. See Scheme 5 for complete characterization.

Ethyl 2-((2*S*,5*S*)-4-((2-nitrophenyl)sulfonyl)-5-phenylpiperazin-2-yl)acetate (12 *cis*) and **ethyl 2-((2*R*,5*S*)-4-((2-nitrophenyl)sulfonyl)-5-phenylpiperazin-2-yl)acetate (13 *trans*).** Using the method described to prepare compounds **23e *cis*/24e *trans*** (Scheme 3), the mixture of the title compounds was obtained using compound **11** as the starting material (15 mg, tan oil, 61% yield). See Scheme 5 for the separation of the two diastereomers and for complete characterization data.

Scheme 3 (Boc pathway, intermediates 16a-h, 17a-h, 18a-h, 19a-h, 20a-h, 23 a-h *cis*)

(*R*)-*N*-(1-hydroxypropan-2-yl)-2-nitrobenzenesulfonamide (16e). A 2000 mL 3-necked round bottom flask was fitted with a mechanical stirrer, nitrogen inlet and glass stopper. The flask was charged with (*R*)-2-aminopropan-1-ol (**15e**, 49 g, 650 mmol) followed by dry DCM (500 mL). The

mixture was stirred until dissolution was complete. With stirring, the reaction solution was cooled to 0° C and charged with TEA (99.7 mL, 715 mmol, 1.1 equiv). Solid 2-nitrophenyl sulfonyl chloride (NsCl, 143 g, 644 mmol, 0.99 equiv) was added in portions. The ice bath was removed and the reaction stirred at rt for 18h. Analysis was performed by TLC (50% EtOAc/hex) and LCMS. DCM (300 mL) and ice water (250 mL) were added with stirring. The aqueous layer was drawn off by siphon and replaced with brine (200 mL) solution. After stirring, the aqueous was drawn off by siphon and again replaced with brine (200 mL). After stirring, the brine was drawn off by siphon and the organic layer was recovered by siphon. The organic layer was dried over $MgSO_4$, filtered and evaporated by continuous feed to give an off-white semisolid (161 g, 95% crude yield), which was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (dd, 1H, J = 9.2, 2.0 Hz), 7.90 (dd, 1H, J = 9.2, 2.0 Hz), 7.78 - 7.76 (m, 2H), 5.60 (bd, J = 6.9 Hz, 1H), 3.63 (bdt, J_t = 6.5 Hz, J_d = 3.4 Hz, 2H), 3.53 (bquart, J = 4.0 Hz, 1H), 2.24 (t, 1H, J = 5.5 Hz), 1.15 (d, J = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.8, 134.5, 133.6, 133.0, 130.9, 125.4, 66.2, 17.7. IR: 3532, 3331, 3098, 2975, 2936, 2881, 1537, 1413, 1359, 1339, 1165, 1125, 1058. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{13}N_2O_5S$ 261.0545; Found 261.0541.

The following additional intermediates were prepared using the method described above for compound **16e**.

(*S*)-*N*-(1-hydroxypropan-2-yl)-2-nitrobenzenesulfonamide **(16a)**. 86 g, off-white semisolid, 100% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) Identical to **16e** except for δ 2.24 (t, J = 5.5 Hz, 1H) which appears as δ 2.02 – 2.01 (bm, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.9, 134.5, 133.6, 132.9, 130.9, 125.4, 66.2, 52.5, 17.8. IR: 3346 (broad), 1538, 1440, 1411, 1360, 1340, 1266, 1165, 1124, 1086, 1058, 1024. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{13}N_2O_5S$ 261.0545; Found 261.0540.

(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-2-nitrobenzenesulfonamide **(16b)**. 59 g, light brown oil, 96% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.0, 2.2 Hz, 1H), 7.72 (dd, J = 6.3, 2.1 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.04 – 6.99 (m, 5H), 3.80 – 3.75 (m, 1H), 3.73 (dd, J = 11.3, 4.3 Hz, 1H), 3.67 (dd, J = 11.2, 4.9 Hz, 1H), 2.93 (dd, J = 14.0, 5.9 Hz, 1H), 2.75 (dd, J = 14.0, 8.8 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.1, 136.9, 134.2, 133.3, 133.1, 130.4, 129.2, 128.4, 126.7, 125.5, 64.8, 58.6, 37.8. IR: 3545, 3264, 1536, 1427, 1356, 1324, 1158. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O_5S$ 337.0858; Found 337.0854.

(*S*)-*N*-(1-hydroxy-4-methylpentan-2-yl)-2-nitrobenzenesulfonamide **(16c)**. 66 g, light brown oil, 98% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (dt, J_d = 9.3 hz, J_d = 4.0 Hz, 1H), 7.82 (dt, J_d = 9.3 Hz, J_t = 3.7 Hz, 1H), 7.75 – 7.70 (m, 2H), 5.70 (vbs, 1H), 3.55 – 3.50 (m, 2H), 3.48 – 3.45 (m, 1H), 2.79 (vbs, 1H), 1.52 (hept, J = 6.5 Hz, 1H), 1.37 – 1.27 (m, 2H), 0.78 (d, J = 6.7 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.6, 134.6, 133.7, 133.0, 130.6, 125.3, 65.0, 55.0, 40.8, 24.3, 22.8, 21.8. IR: 3336, 2955, 2870, 1538, 1412, 1360, 1338, 1164, 1060. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{19}N_2O_5S$ 303.1015; Found 303.1008.

(*S*)-*N*-(1-(benzyloxy)-3-hydroxypropan-2-yl)-2-nitrobenzenesulfonamide **(16d)**. 21 g, off-white semisolid, 99% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **16h** with the addition of δ 6.06

(d, *J* = 7.0 Hz, 1H), 2.22 (t, *J* = 5.7 Hz, 1H). The singlet signal at δ 4.33 appears as δ 4.38 (½AB, *J* = 11.7 Hz, 1H), 4.35 (½AB, *J* = 11.7 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.6, 137.2, 134.6, 133.4, 132.9, 130.6, 128.5, 128.0, 127.8, 125.5, 73.5, 70.1, 63.2, 55.6. IR: 3343, 2942, 1538, 1496, 1453, 1412, 1344, 1164, 1058, 1020. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O_6S$ 367.0964; Found 367.0958.

(*R*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-4-nitrobenzenesulfonamide **(16f)**. 67.8 g, light brown oil, 98% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **16b** with the addition of δ 5.83 (d, *J* = 7.3 Hz), 2.52 (vbs, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.2, 136.7, 134.2, 133.2, 133.1, 130.5, 129.1, 128.4, 126.7, 125.6, 64.9, 58.6, 37.8. IR: 3569, 3321, 1534, 1451, 1427, 1367, 1338, 1160, 1041. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O_5S$ 337.0858; Found 337.0857.

(*R*)-*N*-(1-hydroxy-4-methylpentan-2-yl)-4-nitrobenzenesulfonamide **(16g)**. 70 g, light brown oil, 95% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **16c**. ^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$) δ 147.6, 134.6, 133.7, 133.0, 130.6, 125.3, 64.9, 55.0, 40.8, 24.3, 22.8, 21.8. IR: 3336, 2955, 1538, 1413, 1337, 1164, 1060. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{19}N_2O_5S$ 303.1015; found 303.1008.

(*R*)-*N*-(1-(benzyloxy)-3-hydroxypropan-2-yl)-2-nitrobenzenesulfonamide **(16h)**. 20.6 g, light brown oil, 97% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.66/7.63 (two overlapping quart, $J_{apparent}$ = 1.4 Hz, 2H), 7.31 – 7.26 (m, 3H), 7.17 – 7.15 (m, 2H), 4.33 (s, 2H), 3.73 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.67 (m, 2H), 3.57 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.48 (dd, *J* = 9.8, 4.5 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.6, 137.3, 134.4, 133.5, 132.9, 130.6, 128.4, 127.9, 127.8, 125.4, 73.4, 69.8, 62.9, 55.7. IR: 3329, 2868, 1537, 1411, 1345, 1166, 1059. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O_6S$ 367.0964; found 367.0957.

(*R*)-2-((2-nitrophenyl)sulfonamido)propyl methanesulfonate (17e). A 1000mL round bottom flask was equipped with a magnetic stirrer, rubber septum and nitrogen inlet. The flask was charged with a solution of **16e** (15 g, 57.6 mmol, 1 equiv) in dry DCM (200 mL). The flask was cooled to −78 °C. TEA (8.84 mL, 63.5 mmol, 1.10 equiv) was added by syringe, followed by MsCl (4.91 mL, 63.5 mmol, 1.10 equiv). The reaction was stirred at −78° C for 1h. Complete conversion to the mesylate was confirmed by TLC (50% EtOAc/hex) and LCMS. The cold reaction was poured into a separatory funnel followed by water (100 mL). The layers were separated and the organic washed once with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give the title compound as an off white solid (19 g, 97% crude yield). The title compound was immediately used without further purification or characterization. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{10}H_{15}N_2O_7S_2$ 339.0; Found 339.0.

The following additional mesylates were prepared using the method described for **17e**. In all cases TLC (50% EtOAc/hex) and LCMS data indicated 100% conversion of alcohols **16a-d**, **f-h** to their corresponding mesylates. The crude products were immediately used without further characterization and under the assumption of quantitative conversion. Melting points were not obtained.

(*S*)-2-((2-nitrophenyl)sulfonamido)propyl methanesulfonate (17a). 108 g, off-white solid, 96% crude yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{10}H_{15}N_2O_7S_2$ 339.0; Found 339.0.

(*S*)-2-((2-nitrophenyl)sulfonamido)-3-phenylpropyl methanesulfonate (17b). 61 g, off-white solid, 95% crude yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{16}H_{19}N_2O_7S_2$ 415.1; Found 415.0.

(*S*)-4-methyl-2-((2-nitrophenyl)sulfonamido)pentyl methanesulfonate (17c). 80 g, white solid, 99% crude yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{13}H_{21}N_2O_7S_2$ 381.1; Found 381.1.

(*S*)-3-(benzyloxy)-2-((2-nitrophenyl)sulfonamido)propyl methanesulfonate (17d). 30 g, off-white solid, 99% crude yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{17}H_{21}N_2O_8S_2$ 445.1; Found 445.0.

(*R*)-2-((2-nitrophenyl)sulfonamido)-3-phenylpropyl methanesulfonate (17f). 64 g, off-white solid, 94% crude yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{16}H_{19}N_2O_7S_2$415.1; Found 415.1.

(*R*)-4-methyl-2-((2-nitrophenyl)sulfonamido)pentyl methanesulfonate (17g). 80 g, white solid, 99% crude yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{13}H_{21}N_2O_7S_2$ 381.1; Found 381.1.

(*R*)-3-(benzyloxy)-2-((2-nitrophenyl)sulfonamido)propyl methanesulfonate (17h). 23 g, off-white solid, 90% crude yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{17}H_{21}N_2O_8S_2$ 445.1; Found 445.1.

(*R*)-2-methyl-1-((2-nitrophenyl)sulfonyl)aziridine (18e). A dry 1000 mL round bottom flask was equipped with a magnetic stirrer, rubber septum and nitrogen inlet. The flask was charged with a solution of crude **17e** (19 g, 56 mmol, 1.0 equiv) in anhydrous DCM (100 mL). The flask was cooled to 0 °C and solid Cs_2CO_3 (20 g, 62 mmol, 1.1 equiv) was added in 2 portions. The ice bath was removed and the reaction stirred at rt for 18h. Analysis was performed by TLC (50% EtOAc/hex) and LCMS. Water (50 mL) was added to the reaction mixture and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and partially concentrated *in vacuo* to provide the crude aziridine as a yellow solution. (**Caution**: Do not remove all of the solvent since the concentrated aziridine will begin to polymerize upon standing. The volume of the crude product was approximately 30 mL). The resulting crude product was diluted with dry THF (30 mL) and used without any further purification or characterization. LCMS *m/z*: Calcd for $[M + H]^+$ $C_9H_{11}N_2O_4S$ 243.0; Found 243.1.

The following additional aziridine intermediates were prepared using the method described for 18e. In all cases TLC (50% EtOAc/hex) and LCMS data indicated 100% conversion of mesylates **17a-d**, **f-h** to their corresponding aziridines. The crude products, all yellow oils diluted with 1:1 THF/DCM, were used without further characterization and under the assumption of complete conversion of starting mesylate.

(*S*)-2-methyl-1-((2-nitrophenyl)sulfonyl)aziridine (18a). LCMS *m/z*: Calcd for $[M + H]^+$ $C_9H_{11}N_2O_4S$ 243.0; Found 243.0.

(*S*)-2-benzyl-1-((2-nitrophenyl)sulfonyl)aziridine (18b). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{15}H_{15}N_2O_4S$ 319.1; Found 319.1.

(*S*)-2-isobutyl-1-((2-nitrophenyl)sulfonyl)aziridine (18c). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{12}H_{17}N_2O_4S$ 285.1; Found 285.1.

(*S*)-2-((benzyloxy)methyl)-1-((2-nitrophenyl)sulfonyl)aziridine (18d). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{16}H_{17}N_2O_5S$ 349.1; Found 349.0.

(*R*)-2-benzyl-1-((2-nitrophenyl)sulfonyl)aziridine (18f). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{15}H_{15}N_2O_4S$ 319.1; Found 319.0.

(*R*)-2-isobutyl-1-((2-nitrophenyl)sulfonyl)aziridine (18g). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{12}H_{16}N_2O_4S$ 285.1; Found 285.1.

(*R*)-2-((benzyloxy)methyl)-1-((2-nitrophenyl)sulfonyl)aziridine (18h). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{16}H_{17}N_2O_5S$ 349.1; Found 349.0.

***tert*-Butyl (*R*)-(2-((2-nitrophenyl)sulfonamido)propyl)carbamate (19e)**: A 1000 mL flask was equipped with magnetic stirrer, rubber septum and nitrogen inlet. The flask was charged with solid KHMDS (33.5 g, 168 mmol, 3 equiv) followed by anhydrous THF (200 mL). The resultant slurry was cooled to −78 °C and a solution of NH_2Boc (20 g, 168 mmol, 3.0 equiv) in THF (50 mL) was added dropwise to the reaction mixture. The resultant turbid solution was stirred −78 °C for 30 m. After 30 m the dry ice bath was removed and a solution of aziridine **18e** (13.6 g, 56 mmol, 1 equiv) in THF/DCM (1:1, 60 mL total) was added dropwise over 30m. The resultant dark brown/black solution was stirred at rt for 18 h. Analysis was performed by TLC (50% EtOAc/hex) and LCMS. After completion of the reaction, water (200 mL) and EtOAc (200 mL) were added with stirring. The aqueous layer was drawn off by siphon and replaced with brine (100 mL). After stirring, the brine layer was drawn off by siphon and the organic layer was recovered by siphon. The organic was dried over $MgSO_4$, filtered and evaporated using continuous feed to afford the title compound as a yellowish brown oil (18.5 g, 92% crude yield) which was used without any further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (dt, J_d = 4.6 Hz, J_t = 2.0 Hz, 1H), 7.87 (dt, J_d = 4.4 Hz, J_t = 2.1 Hz, 1H), 7.77 – 7.74 (m, 2H), 5.59 (bd, J = 7.2 Hz, 1H), 4.94 (t, J = 6.4 Hz, 1H), 3.63 (bhex, J = 4.3 Hz, 1H), 3.30 – 3.27 (m, 1H), 3.06 (bquart, J = 6.9 Hz, 1H), 1.42 (s, 9H), 1.10 (d, J = 6.7 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.3, 147.9, 134.5, 133.6, 132.9, 130.8, 125.4, 79.7, 51.3, 46.0, 28.3, 19.0. IR: 3343, 2976, 2929, 1689, 1538, 1420, 1364, 1272, 1248, 1162, 1120. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{22}N_3O_6S$ 360.1229; Found 360.1223. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_9H_{14}N_3O_4S$ 260.0705; Found 260.0701 (base peak).

The following additional intermediates were prepared using the method described for **19e**. In all cases TLC (50% EtOAc/hex) and LCMS data indicated 100% conversion of aziridines **18a-d**, **f-h** to their corresponding orthogonally bis-protected diamines.

tert-Butyl (*S*)-(2-((2-nitrophenyl)sulfonamido)propyl)carbamate **(19a)**. 113 g, brown semi-solid, 100% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **19e**. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.3, 147.9, 134.6, 133.6, 132.9, 130.8, 125.4, 79.8, 51.3, 46.0, 28.3, 19.0. IR: 3339, 2977, 2931, 2359,

1693, 1539, 1421, 1365, 1248, 1164, 1121, 1060. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_9H_{14}N_3O_4S$ 260.0705; Found 260.0700.

tert-Butyl (*S*)-(2-((2-nitrophenyl)sulfonamido)-3-phenylpropyl)carbamate **(19b)**. 50 g, viscous black oil, 63% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 – 7.90 (m, 1H), 7.75 – 7.74 (m, 1H), 7.65 – 7.60 (m, 2H), 7.01 (bs, 5H), 5.74 (bd, *J* = 6.8 Hz, 1H), 5.03 (bt, *J* = 6.5 Hz, 1H), 3.82 (bquart, *J* = 3.1 Hz, 1H), 3.44 – 3.40 (m, 1H), 3.25 (dt, *J* = 13.7, 6.7 Hz, 1H), 2.89 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.68 (dd, *J* = 14.1, 9.0 Hz, 1H), 1.45 (s, 9H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.4, 147.2, 136.4, 134.4, 133.1, 133.0, 130.4, 129.1, 128.4, 126.8, 125.5, 79.8, 57.3, 45.1, 39.1, 28.4. IR: 3349, 2977, 2931, 1691, 1536, 1363, 1161, 1087. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{15}H_{18}N_3O_4S$ 336.1018; Found 336.1015.

tert-Butyl (*S*)-(4-methyl-2-((2-nitrophenyl)sulfonamido)pentyl)carbamate (**19c**). 73.5 g, dark brown viscous oil, 84% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 – 8.10 (m, 1H), 7.89 – 7.81 (m, 1H), 7.78 – 7.67 (m, 2H), 5.62 (d, *J* = 8.1 Hz, 1H), 4.94 (d, *J* = 6.4 Hz, 1H), 3.58 (pd, *J* = 7.1, 3.9 Hz, 1H), 3.32 – 3.18 (m, 1H), 3.06 (dt, *J* = 13.4, 6.3 Hz, 1H), 1.63 – 1.48 (m, 1H), 1.45 (s, 5H), 1.40 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 2H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.6, 156.2, 147.8, 134.8, 133.5, 132.9, 130.6, 125.3, 79.6, 79.5, 53.6, 44.9, 42.1, 28.32, 28.25, 24.3, 22.8, 21.9. IR: 3337, 2963, 1691, 1533, 1364, 1272, 1160, 1125. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{28}N_3O_6S$ 402.1699; Found 402.1693. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{12}H_{20}N_3O_4S$ 302.1175; Found 302.1168 (base peak).

tert-Butyl (*R*)-(3-(benzyloxy)-2-((2-nitrophenyl)sulfonamido)propyl)carbamate (**19d**). 25 g, dark brown viscous oil, 69% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.70 – 7.63 (two overlapping quartets, 2H), 7.34 – 7.29 (m, 4H), 7.16 (dd, *J* = 7.5, 2.2 Hz, 2H), 6.05 (d, *J* = 7.3 Hz, 1H), 4.96 (t, *J* = 6.2 Hz, 1H), 4.36 (½AB, *J* = 12.0 Hz, 1H), 4.33 (½AB, *J* = 12.0 Hz, 1H), 3.72 (bpent, *J* = 7.1 Hz, 1H), 3.46 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.41 – 3.35 (m, 2H), 3.24 (dt, *J* = 14.4, 6.2 Hz, 1H), 1.43 (s, 9H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.3, 147.6, 137.2, 134.5, 133.3, 132.8, 130.7, 128.4, 127.9, 127.8, 125.4, 79.7, 73.5, 70.1, 54.6, 42.5, 28.3. IR: 3353, 3164, 2971, 2874, 1686, 1537, 1454, 1434, 1389, 1366, 1293, 1161. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{28}N_3O_7S$ 466.1648; Found 466.1645. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{16}H_{20}N_3O_5S$ 366.1124; Found 366.1120 (base peak).

tert-Butyl (*R*)-(2-((2-nitrophenyl)sulfonamido)-3-phenylpropyl)carbamate (**19f**). 46.2 g, viscous black oil, 53% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **19b**. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.4, 147.1, 136.5, 134.4, 133.1, 133.0, 130.4, 129.1, 128.4, 126.8, 125.5, 79.7, 57.4, 45.1, 39.1, 28.4. IR: 3346, 2977, 2929, 1691, 1536, 1454, 1417, 1362, 1248, 1160, 1087. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{26}N_3O_6S$ 436.1542; Found 436.1544. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{15}H_{18}N_3O_4S$ 336.1018; Found 336.1018 (base peak).

tert-Butyl (*R*)-(4-methyl-2-((2-nitrophenyl)sulfonamido)pentyl)carbamate (**19g**). 76 g, dark brown viscous oil, 85% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **19c**. ^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$) δ 156.2, 147.7, 134.7, 133.6, 132.9, 130.6, 125.4, 79.5, 53.6, 44.9, 42.1, 28.3, 24.3, 22.8, 21.9. IR: 3338, 3293, 1691, 1533, 1446, 1423, 1364, 1336, 1166, 1125. HRMS (ESI-TOF) *m/z*: $[M + H + Na]^+$ Calcd for $C_{17}H_{27}N_3NaO_6S$ 424.1518; Found 424.1511. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{12}H_{20}N_3O_4S$ 302.1175; Found 302.1168 (base peak).

tert-Butyl (*S*)-(3-(benzyloxy)-2-((2-nitrophenyl)sulfonamido)propyl)carbamate (**19h**). 24.7 g, black viscous oil, 95% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **19d**. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.3, 147.6, 137.2, 134.5, 133.4, 132.8, 130.7, 128.4, 127.9, 127.8, 125.4, 79.7, 73.4, 70.0, 54.6, 42.5, 28.3. IR: 3353, 3166, 2972, 2915, 1686, 1536, 1365, 1341, 1292, 1275, 1259, 1161, 1122, 1096. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{28}N_3O_7S$ 466.1648; Found 466.1647. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{16}H_{20}N_3O_5S$ 366.1124; Found 366.1120 (base peak).

Ethyl (*R*,*E*)-4-((*N*-(1-((*tert*-butoxycarbonyl)amino)propan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (20e): A 1000 mL round bottom flask was equipped with a magnetic stirrer, a nitrogen inlet and a rubber septum. The flask was charged with a solution of **19e** (18.1 g, 50.5 mmol, 1.0 equiv) in anhydrous DMF (100 mL). Anhydrous K_2CO_3 (10.5 g, 75 mmol, 1.5 equiv) was added followed by ethyl *(E)*-4-bromobut-2-enoate (80% purity, 14.2 g, 60 mmol, 1.2 equiv not discounted for purity). The mixture was stirred at rt for 16 h. Analysis was performed using TLC (50% EtOAc/hex, same R_f, $KMnO_4$ stains the product not the SM) and LCMS. EtOAc (200 mL) and ice water (100 mL) were added to the reaction vessel and stirring was continued until all solids had dissolved. The aq phase was drawn from the flask by siphon and discarded. The organic was washed three more times with brine (3 x 50 mL), with the aq washings being drawn from the flask and discarded. The organic was drawn from the flask, dried over $MgSO_4$, filtered and evaporated to an oil. The crude product was chromatographed over silica gel using a hexane/EtOAc gradient (20% to 100% EtOAc/hexane) to afford the title compound as a yellow oil (21 g, 89% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.6, 1.1 Hz, 1H), 7.73 – 7.67 (m, 3H), 6.82 (dt, J_d = 15.7 Hz, J_t = 5.9 Hz, 1H), 5.98 (dt, J_d = 15.7 Hz, J_t = 1.7 Hz, 1H), 4.83 (vbt, J = 6.1 Hz, 1H), 4.24 – 4.10 (m, 4H), 4.07 (dd, J = 17.0, 5.4 Hz, 1H), 3.20 (t, J = 7.2 Hz, 2H), 1.40 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.5, 155.7, 147.8, 144.2, 133.9, 133.8, 131.9, 131.7, 124.4, 123.6, 79.6, 60.6, 54.3, 44.1, 43.3, 28.3, 17.1, 14.2. IR: 3408 (broad), 2978, 1702, 1542, 1455, 1367, 1268, 1155, 1124, 1024. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{30}N_3O_8S$ 472.1754; Found 472.1749. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1220 (base peak).

The following additional intermediates were prepared using the method described for **20e** with the exception that the crude product was partially purified by solid phase extraction as follows: load crude onto silica gel column, elute with 10% EtOAc/hex until *(E)*-4-bromobut-2-enoate is no longer detected in the eluent, then switch to 100% EtOAc until all the product is recovered.

Ethyl (*S,E*)-4-((*N*-(1-((*tert*-butoxycarbonyl)amino)propan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (**20a**). 140 g, yellow-brown semi-solid, 94% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **20e**. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.1, 165.5, 155.7, 147.8, 144.2, 133.9, 133.7, 131.9, 131.7, 124.4, 123.6, 79.6, 60.6, 60.4, 54.3, 44.1, 43.3, 28.3, 21.0, 17.1, 14.2. IR: 2985, 2923, 1714 (broad), 1544, 1458, 1368, 1275, 1260, 1173, 1040. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1219.

Ethyl (*S,E*)-4-((*N*-(1-((*tert*-butoxycarbonyl)amino)-3-phenylpropan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (**20b**). 30 g, brown oil, 64% yield. ^{1}H NMR (600 MHz,

$CDCl_3$) δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.23 (t, *J* = 7.0 Hz, 2H), 7.19 – 7.14 (m, 3H), 6.86 (dt, *J* = 15.9, 6.2 Hz, 1H), 6.04 (d, *J* = 15.7 Hz, 1H), 4.78 (bt, *J* = 5.9 Hz, 1H), 4.29 – 4.16 (m, 6H), 3.32 (vbquart, *J* = 10.2 Hz, 1H), 3.18 (bm, 1H), 3.01 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.71 (dd, *J* = 13.8, 9.2 Hz, 1H), 1.37 (s, 9H), 1.29 (q, *J* = 7.1 Hz, 6H). ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 165.5, 155.7, 147.7, 144.1, 136.9, 133.7, 131.9, 131.6, 129.1, 128.7, 126.9, 124.4, 123.9, 79.5, 60.6, 60.0, 44.8, 41.1, 38.8, 28.3, 14.2. IR: 3408, 2978, 1701, 1541, 1366, 1255, 1159, 1036. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{34}N_3O_8S$ 548.2067; Found 548.2068. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{21}H_{26}N_3O_6S$ 448.1542; Found 448.1538 (base peak).

Ethyl (*S,E*)-4-((*N*-(1-((*tert*-butoxycarbonyl)amino)-4-methylpentan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (**20c**). 65 g, brown oil, 77% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.74 – 7.69 (m, two overlapping quarts, 2H), 7.65 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.87 (dt, J_d = 15.7 Hz, J_t = 6.2 Hz, 1H), 6.00 (dt, J_d = 15.5 Hz, J_t = 1.6 Hz, 1H), 4.88 (bt, *J* = 5.5 Hz, 1H), 4.22 – 4.11 (m, 4H), 4.05 – 4.01 (m, 1H), 3.98 – 3.93 (m, 1H), 3.24 (dt, *J* = 14.5, 5.6 Hz, 1H), 3.13 (dt, J_t = 6.1 Hz, J_d = 3.4 Hz, 1H), 1.61 (hep, *J* = 6.6 Hz, 1H), 1.34 (s, 9H), 1.27 (t overlapping m, J_t = 7.2 Hz, 6H), 0.83 (two overlapping d, *J* = 6.5 Hz, 6H). ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 165.5, 155.6, 147.8, 144.6, 133.8, 133.7, 131.9, 131.7, 124.3, 123.6, 79.4, 60.6, 56.7, 44.5, 42.1, 40.5, 28.3, 24.5, 22.5, 22.3, 14.2. IR: 2958, 1708, 1542, 1509, 1366, 1265, 1156, 1037. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{36}N_3O_8S$ 514.2223; Found 514.2216. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{18}H_{28}N_3O_6S$ 414.1699; found 414.1690 (base peak).

Ethyl (*R,E*)-4-((*N*-(1-(benzyloxy)-3-((*tert*-butoxycarbonyl)amino)propan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (**20d**). 17 g, brown oil, 42% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.28 (m, 3H), 7.21 – 7.20 (m, 2H), 6.83 (dt, J_d = 15.8 Hz, J_t = 6.0 Hz, 1H), 5.93 (dt, J_d = 15.7 Hz, J_d = 1.7 Hz, 1H), 4.91 (vbt, *J* = 5.7 Hz, 1H), 4.35 (quart, *J* = 10.8 Hz, 2H), 4.24 – 4.15 (ABX overlapping with quart, 4H), 3.57 (bt, *J* = 5.2 Hz, 2H), 3.36 – 3.29 (m, 2H), 1.40 (s, 9H), 1.31 – 1.21 (m, 6H). ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 165.6, 155.8, 147.9, 144.4, 137.2, 133.5, 131.6, 131.5, 128.4, 128.0, 127.9, 124.1, 123.3, 79.7, 73.4, 69.3, 60.5, 57.8, 45.4, 39.9, 28.3, 14.2. IR: 2918, 1708, 1541, 1366, 1265, 1158, 1027. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{36}N_3O_9S$ 578.2172; Found 578.2172. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{22}H_{28}N_3O_7S$ 478.1648; Found 478.1644 (base peak).

Ethyl (*R,E*)-4-((*N*-(1-((*tert*-butoxycarbonyl)amino)-3-phenylpropan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (**20f**). 33 g, light brown oil, 57% yield. ^1H NMR (600 MHz, $CDCl_3$) identical to **20b**. ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 165.5, 155.7, 147.7, 144.1, 136.9, 133.7, 131.9, 131.6, 129.1, 128.7, 128.4, 126.9, 124.4, 123.9, 79.5, 60.6, 60.0, 44.8, 41.1, 38.9, 28.3, 14.2. IR: 3411, 2977, 2925, 1707, 1541, 1366, 1266, 1159, 1037. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{34}N_3O_8S$ 548.2067; Found 548.2070. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{21}H_{26}N_3O_6S$ 448.1542; Found 448.1538 (base peak).

Ethyl (*R,E*)-4-((*N*-(1-((*tert*-butoxycarbonyl)amino)-4-methylpentan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (**20g**). 90 g, brown oil, 83% yield. ^1H NMR (600 MHz,

$CDCl_3$) identical to **20c**. ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 165.5, 155.6, 147.8, 144.6, 133.8, 133.6, 131.9, 131.7, 124.3, 123.6, 79.4, 60.6, 56.7, 44.5, 42.1, 40.4, 28.3, 24.5, 22.5, 22.3, 14.3. IR: 3411, 2958, 1708, 1542, 1366, 1156, 1037. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{36}N_3O_8S$ 514.2223; Found 514.2220. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{18}H_{28}N_3O_6S$ 414.1699; Found 414.1693 (base peak).

Ethyl (*S,E*)-4-((*N*-(1-(benzyloxy)-3-((*tert*-butoxycarbonyl)amino)propan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (**20h**). 19 g, brown oil, 59% yield. ^1H NMR (600 MHz, $CDCl_3$) identical to **20d**. ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 165.6, 155.8, 147.9, 144.4, 137.2, 133.6, 131.6, 131.5, 128.4, 128.0, 127.9, 124.1, 123.3, 79.6, 73.4, 69.3, 60.5, 57.8, 45.4, 39.9, 28.3, 14.2. IR: 2981, 2916, 1708, 1542, 1366, 1274, 1261, 1158, 1028. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{36}N_3O_9S$ 578.2172; Found 578.2174. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{22}H_{28}N_3O_7S$ 478.1648; Found 478.1646 (base peak).

Ethyl 2-((2*R*,5*R*)-5-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23e *cis*) and **ethyl 2-((2*S*,5*R*)-5-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24e *trans*):** A 500 mL round bottom flask was equipped with a magnetic stir bar and nitrogen inlet. The flask was charged with a solution of **20e** (36 g, 76.4 mmol) in dry DCM (200 mL). TFA (50 mL) was added and the solution was stirred at rt for 1.5 h. LCMS confirmed disappearance of the substrate. Toluene (50 mL) was added and the solution concentrated *in vacuo* to a residue. Toluene (50 mL) was again added, swirled to effect re-dissolution and the solution again concentrated *in vacuo* to a residue. The residue was dissolved in DCM (300 mL) and, with stirring, was cooled in a cold tap water bath. The solution was treated with sat aq $NaHCO_3$ (50 mL). After 10 m, the two phase mixture was partitioned. The organic was washed with brine, dried over $MgSO_4$, filtered and concentrated to an oil. The oil was chromatographed over silica gel using a hexane/EtOAc gradient (30% to 100% EtOAc/hexane) to afford the two title compounds.

(–)-23e *cis*: 8.92 g, light brown oil, 31% yield. ^1H NMR (800 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.65 (dd, *J* = 6.7, 1.8 Hz, 1H), 4.14 (dquar, *J* = 7.1, 0.8 Hz, 2H), 4.08 – 4.05 (m, 1H), 3.55 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.03 – 2.95 (m, 3H), 2.79 (dd, *J* = 12.1, 1.6 Hz, 1H), 2.43 (½ABX, *J* = 16.2, 4.0 Hz, 1H), 2.35 (½ABX, *J* = 16.2, 7.9 Hz, 1H), 2.07 (vbs, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 6.7 Hz, 3H). ^{13}C {^1H} NMR (201 MHz, $CDCl_3$) δ 171.3, 147.8, 133.8, 133.5, 131.9, 130.9, 124.4, 60.8, 51.9, 50.4, 49.0, 45.2, 37.9, 15.2, 14.2. IR: 3345 (broad), 2360, 1724, 1541, 1441, 1370, 1336, 1158, 1025. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ –1.07 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1215.

24e *trans*: 2.25 g, brown oil, 8% yield. ^1H NMR (800 MHz, $CDCl_3$) identical to **24e *trans*** derived as the major cyclization product derived from compound **22e** (see Scheme 4 for full characterization). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1213.

The following additional *cis* disubstituted piperazine scaffolds **23a-d, f-h *cis*** were prepared using the method described above for **23e *cis***. A lesser amount of *trans* disubstituted scaffold **24a *trans*** was also obtained.

(+)-Ethyl 2-((2*S*,5*S*)-5-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23a *cis*). The title compound was prepared using the method for preparation of compound **23e** using compound **20a** as the starting material (13.95 g, light brown oil, 37% yield). ^{1}H NMR (800 MHz, $CDCl_3$) was identical to **23e *cis***. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 171.3, 147.8, 133.8, 133.5, 131.9, 130.9, 124.4, 60.8, 51.9, 50.4, 49.0, 45.2, 37.9, 15.2, 14.2. IR: 3337, 2904, 2359, 1724, 1540, 1440, 1370, 1347, 1296, 1255, 1156, 1127, 1060, 1025. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ +1.37 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1213.

Ethyl 2-((2*R*,5*S*)-5-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24a *trans*). Using the method for preparation of compound **23e**, the title compound was obtained from compound **20a** as the minor product (4.20 g, light brown oil, 11% yield). ^{1}H NMR (800 MHz, $CDCl_3$) identical to **24a *trans*** derived as the major cyclization product from compound **22a** (See Scheme 4 for full characterization). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1217.

(+)-Ethyl 2-((2*S*,5*S*)-5-benzyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23b *cis*). 8 g, brown oil, 43% yield (**24b *trans***, 2 g, brown oil, 11% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.67 – 7.59 (m, 3H), 7.21 – 7.13 (m, 4H), 7.12 (t, *J* = 2.1 Hz, 1H), 4.16 (quar, *J* = 7.1 Hz, 2H), 4.08 (bt, *J* = 4.7 Hz, 1H), 3.70 (dt, *J* = 12.8, 1.7 Hz, 1H), 3.25 (dd, *J* = 13.2, 9.5 Hz, 1H), 3.14 – 3.10 (m, 1H), 3.08 – 3.04 (m, 1H), 2.94 – 2.90 (m, 1H), 2.86 (½ABX, *J* = 12.3, 1.6 Hz, 1H), 2.83 (½ABX, *J* = 12.3, 3.4 Hz, 1H), 2.48 (½ABX, *J* = 16.2, 4.0 Hz, 1H), 2.41 (½ABX, *J* = 16.2, 8.2 Hz, 1H), 2.13 (vbs, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.4, 147.6, 138.2, 133.9, 133.5, 132.0, 130.8, 129.4, 128.5, 126.6, 124.4, 60.8, 55.5, 52.1, 46.9, 46.1, 37.9, 35.1, 14.2. IR: 3679, 3341, 2980, 2864, 2843, 1724, 1540, 1454, 1369, 1347, 1161, 1126, 1057. Chiral analysis on ChiralPak IC (heptane/EtOH). $[\alpha]_D^{25}$ +3.32 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3O_6S$ 448.1542; Found 448.1538.

(+)-Ethyl 2-((2*S*,5*S*)-5-isobutyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23c *cis*). 7 g, brown oil, 22% yield (**24c *trans***, 0.3 g, 1% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.56 (dd, *J* = 7.5, 1.6 Hz, 1H), 4.05 (quar, *J* = 7.1 Hz, 2H), 3.86 (bdt, J_t = 6.8 Hz, J_d = 2.3 Hz, 1H), 3.59 (d, *J* = 10.8 Hz, 1H), 2.91 – 2.77 (m, 4H), 2.35 (½ABX, *J* = 16.4, 3.9 Hz,1H), 2.26 (½ABX, *J* = 16.3, 4.9 Hz, 1H), 2.03 (vbs, 1H), 1.67 – 1.63 (m, 1H), 1.47 – 1.36 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H), 0.77 (d, *J* = 6.3 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.2, 147.7, 134.0, 133.6, 131.9, 130.8, 124.2, 60.7, 51.8, 51.6, 47.9, 45.7, 37.8, 37.7, 24.8, 22.9, 22.2, 14.1. IR: 2955, 2869, 1724, 1542, 1369, 1351, 1297, 1158, 1073, 1025. Chiral analysis on ChiralPak IC (heptane/*i*-PrOH). $[\alpha]_D^{25}$ +3.21 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{28}N_3O_6S$ 414.1699; Found 414.1679.

(–)-Ethyl 2-((2*S*,5*R*)-5-((benzyloxy)methyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23d *cis*). 4 g, brown oil**,** 36% yield (**24d *trans***, 1.3 g, 11.5% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (dt, *J* = 7.1, 1.3 Hz, 1H), 7.61 – 7.55 (m, 3H), 7.33 – 7.27 (m, 3H), 7.22 (d, *J* = 6.9 Hz, 2H), 4.45 (½AB, *J* = 11.9 Hz, 1H), 4.38 (½AB, *J* = 11.8 Hz, 1H), 4.14 (quar, *J* = 7.1 Hz, 2H), 4.07

(bquart, *J* = 5.7 Hz, 1H), 3.77 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.71 – 3.68 (m, 2H), 3.14 (dd, *J* = 12.4, 1.5 Hz, 1H), 3.04 (octet, *J* = 3.9 Hz, 1H), 2.97 – 2.91 (m, 2H), 2.40 (½ABX, *J* = 16.2, 4.2 Hz, 1H), 2.30 (½ABX, *J* = 16.2, 8.4 Hz, 1H), 2.13 (vbs, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.2, 147.6, 137.9, 134.0, 133.3, 131.7, 131.2, 128.4, 127.7, 124.2, 73.2, 67.7, 60.8, 52.4, 51.9, 46.6, 46.3, 37.9, 14.2. IR: 2986, 2855, 1725, 1541, 1453, 1369, 1349, 1275, 1260, 1163, 1127, 1027. Chiral analysis on ChiralPak IC (heptane/EtOH). $[\alpha]_D^{25}$ –4.25 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3O_7S$ 478.1648; found 478.1656.

(–)-Ethyl 2-((2*R*,5*R*)-5-benzyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23f *cis*). 9 g, brown oil, 34% yield (**24f *trans***, 1.2 g, 4.5% yield). ^{1}H NMR (600 MHz, $CDCl_3$) identical to **23b *cis***. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.4, 147.6, 138.2, 133.9, 133.4, 131.9, 130.8, 129.4, 128.5, 126.6, 124.4, 60.8, 55.5, 52.1, 46.9, 46.1, 37.9, 35.1, 14.2. Chiral analysis on ChiralPak IC (heptane/EtOH). IR: 3341, 2980, 1724, 1540, 1454, 1368, 1347, 1286, 1160, 1125, 1056. $[\alpha]_D^{25}$ –3.31 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3O_6S$ 448.1542; found 448.1540.

(–)-Ethyl 2-((2*R*,5*R*)-5-isobutyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23g *cis*). 12 g, brown oil, 21% yield (**24g *trans***, 0.6 g, 1% yield). ^{1}H NMR (600 MHz, $CDCl_3$) identical to **23c *cis***. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.2, 147.7, 134.0, 133.6, 131.8, 130.8, 124.2, 60.7, 51.8, 51.6, 47.9, 45.74, 37.8, 37.7, 24.8, 22.9, 22.2, 14.1. IR: 2955, 2869, 1725, 1542, 1465, 1369, 1351, 1297, 1158, 1073, 1026. Chiral analysis on ChiralPak IC (heptane/*i*-PrOH). $[\alpha]_D^{25}$ –6.04 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{28}N_3O_6S$ 414.1699; Found 414.1675.

(+)-Ethyl 2-((2*R*,5*S*)-5-((benzyloxy)methyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23h *cis*). 5 g, brown oil, 40% yield (**24h *trans***, 1 g, 8% yield). ^{1}H NMR (600 MHz, $CDCl_3$) identical to **23d *cis***. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.2, 147.6, 137.9, 134.0, 133.3, 131.7, 131.2, 128.4, 127.7, 124.2, 73.2, 67.7, 60.8, 52.4, 51.9, 46.6, 46.3, 37.9, 14.2. IR: 2851, 1725, 1540, 1453, 1370, 1349, 1276, 1261, 1164, 1128, 1097, 1027. Chiral analysis on ChiralPak IC (heptane/EtOH). $[\alpha]_D^{25}$ +3.61 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3O_7S$ 478.1648; Found 478.1656.

Scheme 3 (TFA pathway, compounds 21a-h)

(*R*)-2,2,2-trifluoro-*N*-(2-((2-nitrophenyl)sulfonamido)propyl)acetamide (21e): A 2000 mL 3-neck flask was equipped with a mechanical stirrer, rubber septum and nitrogen inlet. The flask was charged with solid KHMDS (117 g, 586 mmol, 2.0 equiv) followed by anhydrous THF (500 mL). The resultant slurry was cooled to –78 °C. A solution of $CF_3C(O)NH_2$ (66.3 g, 586 mmol, 2.0 equiv) in THF (100 mL) was added dropwise to the reaction mixture. The finely divided off-white suspension was stirred at –78 °C for 30 m. The dry ice bath was removed and a solution of **18e** (71 g, 293 mmol, 1.0 equiv) in THF/DCM (100 mL) was added dropwise over 30 m. The resultant orange solution stirred at rt for 18h during which it turned a dark yellow-brown. Analysis was performed by TLC (2:1 EtOAc/hex) and LCMS. After completion of the reaction water (300 mL) and EtOAc (300 mL) were added. After stirring the aqueous layer was drawn off by siphon and

replaced with brine (200 mL). After stirring the brine layer was drawn off by siphon and the organic layer was recovered. The organic layer was dried over $MgSO_4$, filtered and evaporated by continuous feed to a yellowish brown oil (100 g, 96% crude yield) which was used without any further purification. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.17 (dd, J = 5.9, 3.3 Hz, 1H), 7.90 (dd, J = 6.0, 3.3 Hz, 1H), 7.82 – 7.79 (m, 2H), 7.17 (vbs, 1H), 5.54 (d, J = 7.7 Hz, 1H), 3.72 – 3.70 (m, 1H), 3.63 (ddd, J = 14.0, 6.6, 3.7 Hz, 1H), 3.26 (ddd, J = 14.1, 9.0, 5.3 Hz, 1H), 1.16 (d, J = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.1, 158.0, 157.8, 157.6, J_{quar} = 37.3 Hz), 147.8, 134.1, 133.6, 133.2, 131.1, 125.5, (117.9, 116.4, 115.0, 113.6, J_{quar} = 287.7 Hz), 50.1, 47.1, 46.1, 45.2, 18.9, 17.2. IR: 3333 (broad), 1711, 1424, 1360, 1210, 1164, 1122, 1060, 1039. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{13}F_3N_3O_5S$ 356.0528; Found, 356.0520.

The following additional orthogonally protected diamines **21b-d, f-h** were prepared using the method described above for **21e**.

(*S*)-2,2,2-trifluoro-*N*-(2-((2-nitrophenyl)sulfonamido)propyl)acetamide (21a). 113 g, light yellow semi-solid, 100% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **21e**. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.1, 157.9, 157.7, 157.5, J_{quar} = 37.3 Hz), 147.9, 134.1, 133.5, 133.2, 131.1, (117.9, 116.4, 115.0, 113.6, J_{quar} = 287.6 Hz), 50.1, 45.3, 18.9. IR: 3336 (broad), 1709, 1537, 1422, 1358, 1209, 1157, 1120, 1060, 1040. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{13}F_3N_3O_5S$ 356.0528; Found 356.0525.

(*S*)-2,2,2-trifluoro-*N*-(2-((2-nitrophenyl)sulfonamido)-3-phenylpropyl)acetamide (21b). 66 g, yellow semi-solid, 99% yield. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.7, 1.5 Hz, 1H), 7.73 (dd, J = 7.8, 1.3 Hz, 1H), 7.62 (td, J = 7.7, 1.4 Hz, 1H), 7.58 (td, J = 7.6, 1.3 Hz, 1H), 7.48 (bt, J = 5.4 Hz, 1H), 7.01 (d, J = 7.1 Hz, 2H), 6.95 – 6.90 (m, 3H), 6.01 (d, J = 7.8 Hz, 1H), 3.98 (bdt, J_t = 9.0 Hz, J_d = 4.2 Hz, 1H), 3.76 (ddd, J = 14.0, 6.3, 3.6 Hz, 1H), 3.36 (ddd, J = 14.4, 9.0, 5.8 Hz, 1H), 2.93 (dd, J = 14.3, 4.5 Hz, 1H), 2.68 (dd, J = 14.2, 10.2 Hz, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.3, 158.1, 157.9, 157.8, J_{quar} = 37.2 Hz), 146.9, 135.9, 133.9, 133.28, 133.25, 130.4, 129.1, 128.3, 127.0, 125.5, (118.0, 116.5, 115.1, 113.7, J_{quar} = 287.6 Hz), 56.5, 44.8, 38.8. IR: 3337 (broad), 2359, 1712, 1537, 1497, 1421, 1358, 1210, 1161, 1089, 1038. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}F_3N_3O_5S$ 432.0841; Found 432.0840.

(*S*)-2,2,2-trifluoro-*N*-(4-methyl-2-((2-nitrophenyl)sulfonamido)pentyl)acetamide (21c). 81 g, yellow-brown semi-solid, 98% yield. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.16 (dd, J = 5.0, 2.8 Hz, 1H), 7.89 (dd, J = 4.6, 2.8 Hz, 1H), 7.80 – 7.78 (m, 2H), 7.39 (bt, J = 5.8 Hz, 1H), 5.72 (d, J = 7.9 Hz, 1H), 3.68 – 3.66 (m, 1H), 3.61 (ddd, J = 14.0, 6.2, 3.6 Hz, 1H), 3.26 (ddd, J = 14.1, 8.6, 5.7 Hz, 1H), 1.43 (octet, J = 6.5 Hz, 1H), 1.34 (qdd, J = 14.2, 8.4, 5.8 Hz, 2H), 0.78 (d, J = 6.6 Hz, 3H), 0.61 (d, J = 6.6 Hz, 3H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.2, 158.0, 157.8, 157.6, J_{quar} = 37.2 Hz), 147.6, 134.0, 133.9, 133.1, 130.8, 125.4, (117.9, 116.5, 115.1, 113.6, J_{quar} = 287.5 Hz), 52.5, 44.5, 42.0, 24.3, 22.6, 21.6. IR: 3705, 3679, 3334 (broad), 2965, 2866, 1710, 1537, 1421, 1360, 1345, 1209, 1158, 1058, 1032, 1014. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{19}F_3N_3O_5S$ 398.0998; Found 398.0992.

(*S*)-*N*-(3-(benzyloxy)-2-((2-nitrophenyl)sulfonamido)propyl)-2,2,2-trifluoroacetamide (21d). 23 g, brown semi-solid, 96% yield. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.11 (dd, J = 7.8, 1.3 Hz, 1H), 7.74 (dd, J = 7.9, 1.4 Hz, 1H), 7.71 (dquar, J_{quart} = 7.7 Hz, J_d = 1.2 Hz, 1H), 7.66 (dquar, J_{quart} =

7.7 Hz, J_d = 1.1 Hz, 1H), 7.33 – 7.31 (m, 3H), 7.28 (bt, *J* = 5.5 Hz, 1H), 7.17 (dd, *J* = 6.7, 2.8 Hz, 2H), 6.17 (d, *J* = 7.9 Hz, 1H), 4.37 (½AB, *J* = 11.4Hz, 1H), 4.35 (½AB, *J* = 11.4 Hz, 1H), 3.83 (bhex, *J* = 4.0 Hz, 1H), 3.68 (ddd, *J* = 14.0, 6.9, 4.2 Hz, 1H), 3.51 (½ABX, *J* = 9.8, 4.8 Hz, 1H), 3.44 (½ABX, *J* = 9.8, 4.8 Hz, 1H), 3.38 (ddd, *J* = 14.0, 7.6, 4.8 Hz, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.0, 157.9, 157.7, 157.5, J_{quar} = 37.4 Hz), 147.5, 136.7, 133.8, 133.7, 133.1, 130.7, 128.5, 128.1, 128.0, 125.5, (117.8, 116.4, 115.0, 113.5, J_{quar} = 287.6 Hz), 73.7, 70.1, 53.3, 42.1. IR: 3336, 2970, 2810, 1713, 1538, 1418, 1356, 1210, 1164, 1122, 1026. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{19}F_3N_3O_6S$ 462.0947; Found 462.0946.

(*R*)-2,2,2-trifluoro-*N*-(2-((2-nitrophenyl)sulfonamido)-3-phenylpropyl)acetamide (21f). 61 g, yellow semi-solid, 90% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **21b** except that δ 7.48 (bt, *J* = 5.4 Hz, 1H) is shifted to δ 7.53 (bt, *J* = 5.6 Hz, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.3, 158.1, 158.0, 157.8, J_{quar} = 37.4 Hz), 146.8, 135.9, 134.1, 133.90, 133.88, 133.3, 133.2, 130.3, 129.1, 128.9, 128.3, 127.0, 125.5, (118.0, 116.6, 115.1, 113.7, J_{quar} = 287.4 Hz), 56.5, 44.8, 38.8. IR: 3337, 2889, 2849, 2835, 2360, 1711, 1537, 1496, 1421, 1357, 1211, 1158, 1089, 1037, 1024. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}F_3N_3O_5S$ 432.0841; Found 432.0840.

(*R*)-2,2,2-trifluoro-*N*-(4-methyl-2-((2-nitrophenyl)sulfonamido)pentyl)acetamide (21g). 41 g, yellow-brown semi-solid, 50% yield (some loss due to aziridine polymerization during handling). ^{1}H NMR (800 MHz, $CDCl_3$) identical to **21c**. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.2, 158.0, 157.8, 157.6, J_{quar} = 37.2 Hz), 147.6, 134.0, 133.9, 133.1, 130.8, 125.4, (117.9, 116.5, 115.1, 113.6, J_{quar} = 287.5 Hz), 52.5, 44.6, 42.0, 24.3, 22.6, 21.6. IR: 3695, 3679, 3335 (broad), 2965, 2870, 1711, 1538, 1421, 1361, 1345, 1208, 1160, 1125, 1060, 1032, 1013. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{19}F_3N_3O_5S$ 398.0998; Found 398.0996.

(*R*)-*N*-(3-(benzyloxy)-2-((2-nitrophenyl)sulfonamido)propyl)-2,2,2-trifluoroacetamide (21h). 30 g, brown semi-solid, 96% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **21d** except that δ 7.28 (bt, *J* = 5.5 Hz, 1H) is shifted to δ 7.18 (bt, *J* = 5.4 Hz, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.0, 157.8, 157.6, 157.5, J_{quar} = 37.3 Hz), 147.6, 136.7, 133.8, 133.7, 133.1, 130.7, 128.5, 128.2, 128.03, 128.02, 125.6, (117.8, 116.4, 114.9, 113.5, J_{quar} = 287.6 Hz), 73.8, 70.2, 53.2, 42.1. IR: 3338 (broad), 3093, 2868, 2359, 1716, 1538, 1417, 1358, 1210, 1164, 1122, 1059. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{19}F_3N_3O_6S$ 462.0947; Found 462.0946.

Scheme 4 (compounds 22a-h, 25e *cis*, 26e *trans*, 25a-d, f-h *cis*, 26a-d, f-h *trans*, 24a-h *trans*, 27)

Ethyl (*R,E*)-4-((2-nitro-*N*-(1-(2,2,2-trifluoroacetamido)propan-2-yl)phenyl)sulfonamido)but-2-enoate (22e {2,3}) and **ethyl (*R,E*)-4-((2-nitro-*N*-(1-(2,2,2-trifluoroacetamido)propan-2-yl)phenyl)sulfonamido)but-3-enoate (22e {3,4})**. A 2000mL 3-necked round bottom flask was equipped with a mechanical stirrer, a nitrogen inlet and a rubber septum. The flask was charged with a solution of compound **21e** (99 g, 279 mmol, 1 equiv) in anhy ACN (500 mL). Anhy K_2CO_3 (58 g, 418 mmol, 1.5 equiv) was added followed by ethyl *(E)*-4-bromobut-2-enoate (80% purity, 80.6 g, 334 mmol, 1.2 equiv not discounted for purity). The mixture was stirred at rt for 48h. Analysis was performed using TLC (2:2:1 hex/DCM/EtOAc) and LCMS. EtOAc (500 mL) and ice water (100 mL) were added to the reaction vessel and stirring was continued until all solids had dissolved. The aq phase was drawn from the flask by siphon and discarded. The organic was

washed with brine (3 x 50 mL) with the aqueous washings being drawn from the flask by siphon and discarded. The organic was drawn from the flask, dried over $MgSO_4$, filtered and evaporated to an oil. The crude product was chromatographed over silica gel with all fractions containing the desired mixture being collected (20% to 100% EtOAc/hex). The mixture of the title compounds was obtained as a yellow oil (112 g, 86% yield).

A portion of the mixture obtained from the above procedure was chromatographed by pTLC (2:2:1 hex:DCM:EtOAc) to give samples of the individual components **22e {2,3}** and **22e {3,4}** for characterization in a ratio ≈ 1.5:1.

Ethyl (*R*,*E*)-4-((2-nitro-*N*-(1-(2,2,2-trifluoroacetamido)propan-2-yl)phenyl)sulfonamido)but-2-enoate **(22e {2,3})**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 – 8.05 (m, 1H), 7.79 – 7.71 (m, 3H), 7.04 (vbt, J = 5.6 Hz, 1H), 6.75 (dt, J_d = 15.8 Hz, J_t = 6.2 Hz, 1H), 5.96 (dt, J_d = 15.8 Hz, J_t = 1.6 Hz, 1H), 4.30 – 4.23 (m, 1H), 4.22 – 4.06 (m, 4H), 3.51 (ddd, J = 14.5, 10.7, 6.4 Hz, 1H), 3.38 – 3.33 (m, 1H), 1.32 – 1.25 (m, 7H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 165.2, (157.8, 157.5, 157.4, 157.2, J_{quar} = 37.7 Hz), 156.5, 147.7, 143.2, 134.3, 133.2, 132.2, 131.9, 124.6, 124.2, (117.4, 116.3, 114.9, 113.4, J_{quar} = 287.8 Hz), 96.1, 60.8, 53.1, 44.0, 42.3, 29.7, 17.1, 14.1. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{21}F_3N_3O_7S$ 468.1052; Found 468.1036.

Ethyl (*R*,*E*)-4-((2-nitro-*N*-(1-(2,2,2-trifluoroacetamido)propan-2-yl)phenyl)sulfonamido)but-3-enoate **(22e {3,4})**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.7, 1.5 Hz, 1H), 7.78 – 7.70 (m, 5H), 7.02 (s, 1H), 6.08 (dt, J_d = 13.9 Hz, J_t = 1.3 Hz, 1H), 5.69 (dt, J_d = 13.9 Hz, J_t = 7.4 Hz, 1H), 4.43 – 4.40 (m, 1.5H), 4.19 – 4.14 (quart overlapping m, J_{quar} = 7.1 Hz, 3.5H), 3.57 (dd, J = 10.7, 6.2 Hz, 1.15H), 3.40 (dt, J_d = 14.2 Hz, J_t = 4.4 Hz, 1.5H), 3.28 (dd, J = 13.3, 10.2 Hz, 0.85H), 3.15 (dt, J_d = 7.5 Hz, J_t = 1.3 Hz, 2H), 3.03 (dd, J = 13.1, 5.9 Hz, 0.5H), 1.34 – 1.26 (m, 10H), ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 171.2, 170.9, (158.0, 157.7, 157.6, 157.4, J_{quar} = 37.2 Hz), 147.9, 147.7, 147.6, 134.21, 134.20, 134.14, 134.12, 133.4, 133.14, 133.13, 132.30, 132.29, 132.21, 132.20, 132.01, 131.99, 131.11, 131.09, 125.65, 125.63, 125.3, 124.41, 124.37, 123.9, 122.1, (116.4, 116.3, 115.0, 114.9, J_{quar} = 287.7 Hz), 96.1, 61.5, 61.2, 53.7, 53.4, 50.1, 50.0, 45.3, 42.9, 42.1, 35.4, 33.4, 29.7, 19.04, 18.96, 16.6, 14.9, 14.16, 14.05. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{21}F_3N_3O_7S$ 468.1052; Found 468.1047.

The following additional mixtures of acrylate regioisomers were prepared using the method described above. The regioisomeric mixtures were used immediately after solid phase extraction without further characterization beyond LCMS. Solid phase extraction was carried out as follows: the crude product was loaded onto a silica gel column and eluted with 10% EtOAc/hex until *(E)*-4-bromobut-2-enoate was no longer detected in the eluent, then the mobile phase was switched to 100% EtOAc until all the product was recovered.

Ethyl (*S*,*E*)-4-((2-nitro-*N*-(1-(2,2,2-trifluoroacetamido)propan-2-yl)phenyl)sulfonamido)but-2-enoate/but-3-enoate (22a {2,3}/22a {3,4}). 140 g, yellow semi-solid, 94% yield. LCMS *m/z*: Calcd for [M + H]$^+$ $C_{17}H_{21}F_3N_3O_7S$ 468.1; Found 468.1.

Ethyl (*S*,*E*)-4-((2-nitro-*N*-(1-phenyl-3-(2,2,2-trifluoroacetamido)propan-2-yl)phenyl)sulfonamido)but-2-enoate/but-3-enoate (22b {2,3}/22b {3,4}). 83 g, yellow semi-solid, 99% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{23}H_{25}F_3N_3O_7S$ 544.1; Found 544.1.

Ethyl (*S*,*E*)-4-((*N*-(4-methyl-1-(2,2,2-trifluoroacetamido)pentan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate/but-3-enoate (22c {2,3}/22c {3,4}). 68 g, yellow-brown semi-solid, 66%. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{20}H_{27}F_3N_3O_7S$ 510.2; Found 510.1.

Ethyl (*S*,*E*)-4-((*N*-(1-(benzyloxy)-2-(2,2,2-trifluoroacetamido)ethyl)-2-nitrophenyl)sulfonamido)but-2-enoate/but-3-enoate (22d {2,3}/22d {3,4}). 20.5 g, yellow semi-solid, 72% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{24}H_{27}F_3N_3O_8S$ 574.2; Found 574.2.

Ethyl (*R*,*E*)-4-((2-nitro-*N*-(1-phenyl-3-(2,2,2-trifluoroacetamido)propan-2-yl)phenyl)sulfonamido)but-2-enoate/but-3-enoate (22f {2,3}/22f {3,4}). 70 g, yellow semi-solid, 91% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{23}H_{25}F_3N_3O_7S$ 544.1; found 544.1.

Ethyl (*R*,*E*)-4-((*N*-(4-methyl-1-(2,2,2-trifluoroacetamido)pentan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate/but-3-enoate (22g {2,3}/22g {3,4}). 48 g, yellow-brown semi-solid, 94% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{20}H_{27}F_3N_3O_7S$ 510.2; Found 510.1.

Ethyl (*R*,*E*)-4-((*N*-(1-(benzyloxy)-3-(2,2,2-trifluoroacetamido)propan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate/but-3-enoate (22h {2,3}/22h {3,4}). 20 g, yellow semi-solid, 54% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{24}H_{27}F_3N_3O_8S$ 574.2; Found 574.1.

Ethyl 2-((5*R*)-5-methyl-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25e *cis*/26e *trans*): A 2000mL 3-necked round bottom flask was equipped with a mechanical stirrer, rubber septum and nitrogen inlet. The flask was charged with a solution of a mixture of **22e {2,3}/22e {3,4}** (112 g, 240 mmol, 1.0 equiv) in dry DCM (500 mL). The flask was cooled to 0 °C and solid Cs_2CO_3 (93.6 g, 288 mmol, 1.2 equiv) was added in one portion. The ice bath was removed and the reaction stirred at rt for 18h. Analysis was performed by TLC (2:2:1 hex/DCM/EtOAc) and LCMS. Water (300 mL) was added and stirring was continued until all solids had dissolved. The aq phase was drawn from the flask by siphon and discarded. The organic was washed three more times with brine (3 x 100 mL) with the aq washings being drawn from the flask and discarded. The organic was drawn from the flask, dried over $MgSO_4$, filtered and evaporated to an oil. The crude product was chromatographed over silica gel using a hexane/EtOAc gradient (20% to 100% EtOAc/hexane), collecting all fractions containing the desired mixture, to afford the mixture of title compounds as a yellow oil (18 g, 16% yield).

Samples of the individual compounds **25e *cis*** and **26e *trans*** were obtained from **23e *cis*** and **24e *trans*** (preparation described below) respectively.

Ethyl 2-((*2R,5R*)-5-methyl-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25e *cis*). A 25 mL round bottom flask was equipped with a magnetic stirrer and nitrogen inlet. The flask was charged with a solution of **23e *cis*** (20 mg, 0.05 mmol, 1 equiv) in dry DCM (2 mL). TEA (15 μL, 1.5 equiv) and TFAA (12 μL, 1.5 equiv) were added and reaction was

stirred at rt for 3 h. The reaction was monitored by TLC (EtOAc) and LCMS. After completion of the reaction, the mixture was poured into brine (5 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product (30 mg, yellow semi-solid) was subjected to silica gel column chromatography (5%-100% EtOAc/hex) to afford the title compound as an off-white semisolid (10 mg, 40% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.8, 1.4 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.53 (dd, J = 7.8, 1.3 Hz, 1H), 4.34 – 4.31 (m, 1.75H), 4.16 (dt, J = 11.7, 6.1 Hz, 1.25H), 4.07 – 4.01 (quar overlapping m, J_{quar} = 7.2 Hz, 3H), 3.78 (dd, J = 14.9, 6.2 Hz, 1.4H), 3.40 (dd, J = 15.4, 10.8 Hz, 1.25H), 3.17 (dd, J = 15.1, 10.9 Hz, 1H), 2.55 (½ABX, J = 16.1, 7.4 Hz, 1.4H), 2.45 (½ABX, J = 16.1, 4.5 Hz, 1.2H), 2.27 (t, J = 7.5 Hz, 0.7H), 1.28 (quar, J = 6.8 Hz, 5H). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}F_3N_3O_7S$ 468.1052; Found 468.1050.

Ethyl 2-((*2S,5R*)-5-methyl-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (26e *trans*). Using the method described above for preparation of **25e *cis***, the title compound was obtained using compound **24e *trans*** as the starting material (12 mg, off-white semi-solid, 48% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (dt, J_d = 7.7 Hz, J_t = 1.2 Hz, 1H), 7.78 – 7.72 (m, 3H), 5.05 (bt, J = 9.2 Hz, 0.6H), 4.51 (bt, J = 5.1 Hz, 0.4H), 4.41 – 4.28 (m, 1.7H), 4.21 – 3.99 (m, 3H), 3.81 – 3.74 (m, 1.7H), 3.69 – 3.66 (m, 0.7H), 3.53 (ddd, J = 14.2, 5.9, 3.6 Hz, 1H), 3.33 (dd, J = 13.8, 3.9 Hz, 0.4H), 2.91 (dd, J = 16.6, 9.7 Hz, 0.4H), 2.62 (½ABX, J = 15.8, 8.5 Hz, 1H), 2.50 – 2.45 (m, 1H), 1.29 – 1.12 (m, 10H). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}F_3N_3O_7S$ 468.1052; Found 468.1048.

Preparation of 26a *trans* for X-ray crystallography. A DCM solution of compound **26a *trans***, obtained using the procedure to prepare **26e *trans*** from compound **24a** as the starting material, was transferred to a 2 mL screw top vial and evaporated to a residue, then layered with hexane (1 mL) and clamped in a 60 °C bath. DCM was added dropwise with swirling by syringe until dissolution was complete. The vial, with a screw cap loosely fitted, was placed at the back of a fume hood for 5d, affording crystals suitable for X-ray analysis.

The following additional mixtures of piperazine diastereomers were prepared using the method described above. The diastereomeric mixtures were used immediately after chromatography without further characterization.

Ethyl 2-((5*S*)-5-methyl-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25a *cis*/26a *trans*). 12.5 g, yellow semi-solid, 19% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{17}H_{21}F_3N_3O_7S$ 468.1; Found 468.0.

Ethyl 2-((5*S*)-5-benzyl-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25b *cis*/26b *trans*). 24 g, yellow-semi-solid, 29% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{23}H_{25}F_3N_3O_7S$ 544.1; Found 544.1.

Ethyl 2-((5*S*)-5-isobutyl-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25c *cis*/26c *trans*). 20 g, yellow semi-solid, 29% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{20}H_{27}F_3N_3O_7S$ 510.2; Found 510.2.

Ethyl 2-((5*S*)-5-((benzyloxy)methyl)-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25d *cis*/26d *trans*). 4.5 g, yellow semi-solid, 22% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{24}H_{27}F_3N_3O_8S$ 574.2; Found 574.1.

Ethyl 2-((5*R*)-5-benzyl-4-((4-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25f *cis*/26f *trans*). 20 g, yellow semi-solid, 24% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{23}H_{25}F_3N_3O_7S$ 544.1; Found 544.1.

Ethyl 2-((5*R*)-5-isobutyl-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25g *cis*/26g *trans*). 19 g, yellow semi-solid, 39% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{20}H_{27}F_3N_3O_7S$ 510.2; Found 510.1.

Ethyl 2-((5*R*)-5-((benzyloxy)methyl)-4-((2-nitrophenyl)sulfonyl)-1-(2,2,2-trifluoroacetyl)piperazin-2-yl)acetate (25h *cis*/26h *trans*). 3 g, yellow semi-solid, 15% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{24}H_{27}F_3N_3O_8S$ 574.2; Found 574.2.

Ethyl 2-((2*R*,5*R*)-5-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (23e *cis*) and **(–)-Ethyl 2-((2*S*,5*R*)-5-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24e *trans*).** A 250 mL round bottom flask was equipped with a magnetic stirrer, rubber septum and nitrogen inlet. The flask was charged with a solution of **25e *cis*/26e *trans*** (18 g, 38.5 mmol, 1.0 equiv) in abs EtOH (100 mL). Solid $NaBH_4$ (1.75 g, 46.2 mmol, 1.2 equiv) was added in several portions. The reaction mixture was stirred at rt for 2h. Analysis was performed using TLC (EtOAc) and LCMS. After completion, the reaction was quenched with sat aq NH_4Cl and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to provide the mixture of diastereomeric title compounds (19 g crude). The crude product was chromatographed (50% to 100% EtOAc/hexane) to provide the title compounds and **23e *cis*** and **24e *trans***.

23e *cis*: 650 mg, light brown oil, 4.6% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **23e *cis*** derived as the major cyclization product from compound **20e** (See Scheme 3 for full characterization). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1222.

(–)-24e trans: 4.6 g, white semi-solid, 32% yield (7% yield from **21e (2-Ns)**. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.6, 1.2 Hz, 1H), 7.73 – 7.67 (m, 3H), 4.11 (dquart, J_{quart} = 7.2 Hz, J_d = 3.5 Hz, 2H), 3.97 (bpent, J = 3.5 Hz, 1H), 3.62 (dd, J = 13.2, 3.5 Hz, 1H), 3.42 – 3.40 (m, 1H), 3.34 (dd, J = 13.1, 3.4 Hz, 1H), 3.24 (dd, J = 12.6, 3.9 Hz, 1H), 2.69 (dd, J = 16.4, 8.5 Hz, 1H), 2.58 (dd, J = 12.6, 3.3 Hz, 1H), 2.43 (dd, J = 16.4, 5.5 Hz, 1H), 2.10 (vbs, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 171.9, 147.8, 133.9, 133.5, 131.8, 130.8, 124.3, 60.6, 50.3, 48.9, 45.7, 45.5, 34.5, 15.3, 14.2. IR: 2980, 2865, 1728, 1542, 1454, 1369, 1281, 1213, 1145, 1097, 1052, 1032, 1018. Chiral analysis on ChiralPak IC (20% EtOH/heptane isocratic, 30 m run). $[\alpha]_D^{25}$ –5.10 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1211.

(–)-Ethyl 2-((2*R*,5*R*)-5-methyl-4-((4-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24e *trans*, 4-Ns). 78 mg, brown oil, 30% yield from **21e (4-Ns)**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 4.16 (quar, J = 7.2 Hz, 1H), 3.84 (bdt, J_t = 6.8 Hz, J_d = 3.2 Hz, 1H), 3.49 (dd, J = 12.4, 3.4 Hz, 1H), 3.44 (dt, J_t = 8.9 Hz, J_d = 3.6 Hz, 1H), 3.29 (dd, J = 12.4, 3.7 Hz, 1H), 3.15 (dd, J = 12.5, 3.8 Hz, 1H), 2.70 (dd, J = 16.4, 8.2 Hz, 1H), 2.60 (dd, J = 12.6, 3.7 Hz, 1H), 2.52 (dd, J = 16.4, 5.7 Hz, 1H), 1.27 (t, J = 7.2 Hz, 2H), 1.15 (d, J = 6.7 Hz, 2H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 171.7, 150.0, 146.0, 128.3, 124.4, 60.8, 50.4, 49.0, 46.6, 45.6, 34.7, 14.9, 14.2. IR: 2932, 2360, 2341, 1723, 1605, 1529, 1448, 1349, 1309, 1161, 1014. $[\alpha]_D^{25}$ –1.42 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1214.

The following additional *trans* disubstituted piperazine scaffolds were prepared using the method described above. The *cis* isomers were generally not collected.

(+)-Ethyl 2-((2*R*,5*S*)-5-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24a *trans*, 2-Ns). 3.5 g, white-semisolid, 35% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **24e *trans***. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 171.9, 147.8, 133.9, 133.5, 131.8, 130.8, 124.3, 60.6, 50.3, 48.9, 45.7, 45.5, 34.5, 15.3, 14.2. IR: 2985, 1726, 1542, 1372, 1275, 1260, 1161. Chiral analysis on ChiralPak IC (20% EtOH/heptane isocratic, 30 m run). $[\alpha]_D^{25}$ +5.40 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3O_6S$ 372.1229; Found 372.1213.

(+)-Ethyl 2-((2*R*,5*S*)-5-benzyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24b *trans*). 5.5 g, off-white semi-solid, 30% yield. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.9, 1.3 Hz, 1H), 7.68 – 7.62 (m, 3H), 7.18 (dd, J = 8.1, 6.8 Hz, 2H), 7.15 – 7.10 (m, 3H), 4.14 – 4.08 (m, 3H), 3.75 (dd, J = 13.6, 3.7 Hz, 1H), 3.62 (dt, J_d = 13.4 Hz, J_t = 1.4 Hz, 1H), 3.50 (vbquin, J = 3.5 Hz, 1H), 3.21 (dd, J = 13.3, 9.6 Hz, 1H), 3.15 (dd, J = 12.6, 4.0 Hz, 1H), 2.87 (dd, J = 13.3, 5.7 Hz, 1H), 2.81 (dd, J = 16.5, 8.9 Hz, 1H), 2.64 (dd, J = 12.6, 1.8 Hz, 1H), 2.41 (dd, J = 16.5, 5.3 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 172.1, 147.5, 137.9, 133.9, 133.3, 131.8, 131.0, 129.4, 128.4, 126.6, 124.48, 124.47, 60.5, 55.9, 48.5, 45.2, 40.6, 35.0, 33.9, 14.2. IR: 3354 (broad), 2928, 2888, 2850, 2359, 1725, 1541, 1440, 1369, 1334, 1162, 1127, 1038, 1027. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ +4.93 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3O_6S$ 448.1542; Found 448.1538.

(+)-Ethyl 2-((2*R*,5*S*)-5-isobutyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24c *trans*). 3.5 g, yellow semi-solid, 22% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **24g *trans***. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 172.0, 147.6, 134.0, 133.5, 131.7, 131.3, 124.5, 60.5, 52.2, 48.4, 44.9, 41.6, 37.5, 33.9, 25.0, 23.2, 22.0, 14.2. IR: 2955, 2870, 1726, 1541, 1466, 1439, 1368, 1341, 1162, 1126, 1059, 1028. Chiral analysis on ChiralPak IC (heptane/EtOH). $[\alpha]_D^{25}$ +8.87 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{28}N_3O_6S$ 414.1699; found 414.1674.

(–)-Ethyl 2-((2*R*,5*R*)-5-((benzyloxy)methyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24d *trans*). 1.0 g, off-white semi-solid, 20% yield. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.8, 1.0 Hz, 1H), 7.56 – 7.51 (m, 3H), 7.29 – 7.24 (m, 3H), 7.15 (dd, J = 6.9, 1.8 Hz, 2H), 4.36 (½AB, J = 11.8 Hz, 1H), 4.30 (½AB, J = 11.9 Hz, 1H), 4.11 – 4.03 (dquar overlapping m, 3H), 3.70 (dquar, J_{quar} = 7.0 Hz, J_d = 3.4 Hz, 2H), 3.54 (½ABX, J = 13.6, 8.1 Hz, 1H), 3.52 (½ABX, J = 13.6,

10.3 Hz, 1H), 3.39 – 3.37 (bm, 1H), 3.24 (dd, *J* = 12.9, 4.4 Hz, 1H), 2.83 (dd, *J* = 13.0, 1.7 Hz, 1H), 2.76 (dd, *J* = 16.5, 8.5 Hz, 1H), 2.38 (dd, *J* = 16.5, 5.8 Hz, 1H), 2.00 (vbs, 1H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 172.0, 147.5, 137.8, 133.8, 133.3, 131.6, 131.3, 128.4, 127.7, 124.1, 73.2, 67.8, 60.5, 52.8, 48.2, 45.5, 40.1, 33.8, 14.2. IR: 3363 (broad), 2936, 2864, 1719, 1541, 1454, 1367, 1164, 1123, 1058, 1032. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ –7.55 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3O_7S$ 478.1648; Found 478.1636.

(–)-Ethyl 2-((2S,5R)-5-benzyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24f *trans*). 4.6 g, off-white semi-solid, 29% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **24b *trans*.** ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 172.1, 147.5, 137.9, 133.9, 133.3, 131.8, 129.3, 128.5, 126.6, 124.5, 60.5, 55.9, 48.5, 45.2, 40.6, 35.0, 33.9, 14.2. IR: 3311 (broad), 2850, 2360, 2341, 1723, 1541, 1495, 1439, 1368, 1334, 1162, 1127, 1037, 1027. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ –5.62 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3O_6S$ 448.1542; Found 448.1538.

(–)-Ethyl 2-((2S,5R)-5-isobutyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24g *trans*). 3.4 g, yellow-semi-solid, 22% yield. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.73 – 7.67 (m, 3H), 4.09 (dquar, J_{quar} = 7.2 Hz, J_d = 3.5 Hz, 2H), 3.88 (vbt, *J* = 4.5 Hz, 1H), 3.56 (½ABX, *J* = 13.7, 3.6 Hz, 1H), 3.49 (½ABX, *J* = 13.6, 3.4 Hz, 1H), 3.40 (vbquar, *J* = 3.5 Hz, 1H), 3.26 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.74 (dd, *J* = 16.4, 8.7 Hz, 1H), 2.66 (dd, *J* = 12.8, 1.9 Hz, 1H), 2.35 (dd, *J* = 16.5, 5.6 Hz, 1H), 1.86 (ddd, *J* = 13.5, 9.3, 5.6 Hz, 1H), 1.43 (dt, J_d = 13.8 Hz, J_t = 6.6 Hz, 1H), 1.27 – 1.21 (m overlapping t, J_t = 7.1 Hz, 4H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 172.0, 147.6, 133.9, 133.5, 131.7, 131.3, 124.4, 60.5, 52.2, 48.4, 44.9, 41.6, 37.4, 34.0, 25.0, 23.2, 22.0, 14.2. IR: 3705, 3679, 2965, 2865, 2843, 1723, 1541, 1454, 1369, 1331, 1160, 1056, 1032, 1017. Chiral analysis on ChiralPak IC (heptane/EtOH). $[\alpha]_D^{25}$ –9.11 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{28}N_3O_6S$ 414.1699; Found 414.1680.

(+)-Ethyl 2-((2S,5S)-5-((benzyloxy)methyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (24h *trans*). 1.4 g, off-white-semisolid, 56% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **24d *trans***. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.9, 147.6, 137.8, 133.9, 133.2, 131.5, 131.4, 128.4, 127.7, 124.1, 73.2, 67.9, 60.5, 52.7, 48.3, 45.5, 40.1, 33.7, 14.2. IR: 2934, 1723, 1540, 1453, 1368, 1351, 1164, 1126, 1095, 1025. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ +7.17 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3O_7S$ 478.1648; Found 478.1651.

(*R,E*)-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-(1-(2,2,2-trifluoroacetamido)propan-2-yl)-2*H*-indazole 1-oxide (27). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.85 (dt, J_d = 8.6 Hz, J_t = 1.1 Hz, 1H), 7.69 (d, *J* = 15.7 Hz, 1H), 7.64 (dt, J_d = 8.7 Hz, J_t = 1.0 Hz, 1H), 7.38 (ddd, *J* = 8.8, 6.7, 1.0 Hz, 1H), 7.33 (ddd, *J* = 8.5, 6.7, 1.0 Hz, 1H), 6.58 (d, *J* = 15.7 Hz, 1H), 5.43 (vbs, 1H), 4.41 (dt, J_d = 15.1 Hz, J_t = 7.8 Hz, 1H), 4.33 (dquar, J_{quar} = 7.1 Hz, J_d = 1.3 Hz, 2H), 3.79 (dt, J_d = 14.4 Hz, J_t = 3.7 Hz, 1H), 1.81 (d, *J* = 7.1 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.4, (158.3, 158.1, 157.9, 157.7, J_{quar} = 37.7 Hz), 130.6, 128.0, 127.0, 126.8, 120.3, 120.1, 118.2, (117.9, 117.2, 116.4, 115.0, J_{quar} = 287.6 Hz), 113.6, 113.1, 77.2, 77.0, 76.9, 61.1,

56.0, 29.7, 14.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}F_3N_3O_4$ 386.1328; Found 386.1336.

Scheme 5 (compounds 10a-b, 11a-b, 12a *cis*, 13a *trans*, 29a, 30a, 31b *cis*, 32b *trans*)

***tert*-Butyl (*S*)-(2-((2-nitrophenyl)sulfonamido)-2-phenylethyl)carbamate (10a).** Using the method described for the preparation of compound **16e** the title compound was obtained using compound **28a** as the starting material. 10 g, colorless viscous oil, 95% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.53 (dt, J_t = 7.8 Hz, J_d = 1.0 Hz, 1H), 7.39 (dt, J_t = 7.7 Hz, J_d = 1.2 Hz, 1H), 7.13 – 7.08 (m, 5H), 5.05 (bt, *J* = 6.5 Hz, 1H), 4.70 (vbquart, *J* = 6.8 Hz, 1H), 3.46 (dt, *J* = 14.8, 5.4 Hz, 1H), 3.39 (ddd, *J* = 14.7, 9.0, 6.1 Hz, 1H), 1.44 (s, 9H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.7, 147.3, 137.6, 134.3, 133.0, 132.4, 130.7, 128.5, 128.0, 126.7, 124.8, 80.1, 59.6, 46.1, 28.3. IR: 3447, 3260, 2981, 1690, 1538, 1501, 1363, 1334, 1280, 1156, 1127. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{14}H_{16}N_3O_4S$ 322.0862; Found 322.0833.

***tert*-Butyl (*R*)-(2-((2-nitrophenyl)sulfonamido)-2-phenylethyl)carbamate (10b).** Using the method described for the preparation of compound **16e** the title compound was obtained using compound **28b** as the starting material. 19 g, colorless oil, 95% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **10a**. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.7, 147.3, 137.6, 134.3, 133.0, 132.4, 130.7, 128.5, 128.0, 126.7, 124.8, 80.1, 59.6, 46.0, 28.3. IR: 3447, 3256, 2982, 1691, 1538, 1500, 1363, 1334, 1279, 1259, 1158, 1127. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{14}H_{16}N_3O_4S$ 322.0862; Found 322.0833.

Ethyl (*S,E*)-4-((*N*-(2-((*tert*-butoxycarbonyl)amino)-1-phenylethyl)-2-nitrophenyl)sulfonamido)but-2-enoate (11a). Using the method described for the preparation of compound **20e** the title compound was obtained using compound **10a** as the starting material. 10.3 g, light brown viscous oil, 81% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.9 Hz, 1H), 7.73 (dt, J_t = 7.6 Hz, J_d = 1.1 Hz, 1H), 7.66 (dt, J_t = 7.0 Hz, J_d = 1.5 Hz, 2H), 7.31 – 7.26 (m, 5H), 6.52 (dt, J_d = 15.8 Hz, J_t = 6.1 Hz, 1H), 5.72 (dt, *J* = 15.7, 1.7 Hz, 1H), 5.21 (t, *J* = 7.8 Hz, 1H), 4.91 (vbt, *J* = 6.0 Hz, 1H), 4.13 – 4.06 (m, 3H), 3.99 – 3.95 (m, 1H), 3.73 (bpent, *J* = 7.9 Hz, 2H), 1.36 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.4, 155.6, 147.9, 143.5, 135.4, 133.92, 133.85, 132.0, 131.3, 128.9, 128.8, 128.3, 124.2, 123.4, 79.7, 60.4, 60.1, 45.7, 40.8, 28.3, 14.2. IR: 3411, 2979, 2914, 1715, 1705, 1519, 1364, 1344, 1304, 1281, 1152, 1123. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{32}N_3O_8S$ 534.1910; Found 534.1908. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{20}H_{24}N_3O_6S$ 434.1386; Found 434.1381 (base peak).

Ethyl (*R,E*)-4-((*N*-(2-((*tert*-butoxycarbonyl)amino)-1-phenylethyl)-2-nitrophenyl)sulfonamido)but-2-enoate (11b). Using the method described for the preparation of compounds **20e** the title compound was obtained using compound **10b** as the starting material. 22.7 g, light brown viscous oil, 90% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **11a**. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.4, 155.6, 147.9, 143.5, 135.4, 133.9, 132.0, 131.3, 128.9, 128.8, 128.3, 124.2, 123.4, 79.6, 60.4, 60.1, 45.7, 40.8, 28.3, 14.2. IR: 3412, 2982, 2918, 1717, 1706, 1519, 1364, 1341, 1304, 1280, 1152, 1122. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{32}N_3O_8S$

534.1910; Found 534.1910. HRMS (ESI-TOF) *m/z*: [M + H - Boc]$^+$ Calcd for $C_{20}H_{24}N_3O_6S$ 434.1386; Found 434.1379 (base peak).

(+)-Ethyl 2-((2*S*,5*S*)-4-((2-nitrophenyl)sulfonyl)-5-phenylpiperazin-2-yl)acetate (12a *cis*) and **(+)-Ethyl 2-((2*R*,5*S*)-4-((2-nitrophenyl)sulfonyl)-5-phenylpiperazin-2-yl)acetate (13a *trans*)**. Using the method described for the preparation of compounds **23e *cis*/24e *trans*** from compounds **20e** the title compounds were obtained using compound **11a** as the starting material.

(+)-12a *cis*: 3.8 g, off-white viscous oil, 55% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.70 – 7.61 (m, 3H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 5.15 (d, *J* = 3.1 Hz, 1H), 4.11 (quart, *J* = 7.1 Hz, 2H), 3.83 (dd, *J* = 13.5, 2.7 Hz, 1H), 3.59 (dd, *J* = 13.0, 1.4 Hz, 1H), 3.29 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.13 – 3.08 (m, 1H), 3.00 (dd, *J* = 13.5, 11.1 Hz, 1H), 2.37 (½ABX, *J* = 16.3, 4.6 Hz, 1H), 2.27 (½ABX, *J* = 16.3, 8.2 Hz, 1H), 1.94 (vbs, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.2, 147.7, 137.7, 134.1, 133.6, 131.9, 130.8, 128.7, 127.39, 127.37, 124.3, 60.8, 55.5, 51.7, 48.7, 46.8, 37.9, 14.1. IR: 3347, 3099, 2976, 2914, 1718, 1542, 1376, 1348, 1240, 1166. Chiral analysis on ChiralPak IC (heptane/EtOH). $[\alpha]_D^{25}$ +4.02 (*c* 5.0, $CHCl_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{24}N_3O_6S$ 434.1386; Found 434.1378.

(+)-13a *trans*: 0.8 g, off-white oil, 11% yield. ^{1}H NMR (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.21 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.12 – 7.09 (m, 1H), 7.05 (dt, J_t = 5.5 Hz, J_d = 1.3 Hz, 2H), 4.61 (dd, *J* = 7.5, 3.9 Hz, 1H), 4.16 (dquar, J_{quar} = 7.1 Hz, J_d = 3.2 Hz, 2H), 3.81 (dd, *J* = 12.7, 3.3 Hz, 1H), 3.40 (apparent dpent, J_{pent} = 4.9 Hz, J_d = 1.5 Hz, 1H), 3.26 (dd, *J* = 13.1, 4.0 Hz, 1H), 3.20 (ddd, *J* = 13.1, 11.2, 7.2 Hz, 2H), 2.56 (½ABX, *J* = 16.3, 8.3 Hz, 1H), 2.52 ((½ABX, *J* = 16.3, 4.9 Hz, 1H), 2.07 (vbs, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.6, 147.4, 136.7, 134.1, 133.0, 131.5, 130.6, 128.7, 128.0, 127.9, 124.1, 60.7, 60.3, 50.4, 48.9, 48.7, 36.9, 14.2. IR: 2981, 1723, 1539, 1447, 1367, 1336, 1160, 1125. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ +2.96 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{24}N_3O_6S$ 434.1386; Found 434.1379.

(–)-Ethyl 2-((2*R*,5*R*)-4-((2-nitrophenyl)sulfonyl)-5-phenylpiperazin-2-yl)acetate (31b *cis*) and **(–)-Ethyl 2-((2*S*,5*R*)-4-((2-nitrophenyl)sulfonyl)-5-phenylpiperazin-2-yl)acetate (32b *trans*).** Using the method described for the preparation of compounds **23e *cis*/24e *trans*** the title compounds were obtained using compound **11b** as the starting material.

(–)-31b *cis*: 9.7 g, off-white viscous oil, 62% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **12a *cis*.** ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.1, 147.7, 137.7, 134.1, 133.6, 133.0, 132.0, 130.8, 128.7, 127.4, 127.40, 127.37, 124.2, 60.8, 55.5, 51.7, 48.7, 46.8, 38.0, 14.1. IR: 3347, 3097, 2976, 2914, 2841, 1719, 1541, 1377, 1348, 1240, 1166. Chiral analysis on ChiralPak IC (heptane/EtOH). $[\alpha]_D^{25}$ –3.03 (*c* 5.0, $CHCl_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{24}N_3O_6S$ 434.1386; Found 434.1379.

(–)-32b *trans*: 1.8 g, off-white viscous oil, 11% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **13a *trans*.** ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.6, 147.4, 136.7, 134.1, 133.0, 131.5, 130.6, 128.6, 128.0, 127.9, 124.1, 60.7, 60.3, 50.3, 48.8, 48.7, 36.8, 14.2. IR: 2929, 1723, 1539, 1446, 1366, 1342, 1300, 1246, 1161, 1125, 1027. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ –5.19 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{24}N_3O_6S$ 434.1386; Found 434.1379.

(*S*)-2,2,2-trifluoro-*N*-(2-((2-nitrophenyl)sulfonamido)-2-phenylethyl)acetamide (29a). A 250mL round bottom flask was equipped with a magnetic stirrer, nitrogen inlet and rubber septum. The flask was charged with a solution of **10a** (7.5 g, 17.8 mmol, 1 equiv) in anhydrous DCM (100 mL). The reaction mixture was cooled to 0 °C. TFA (3.4 mL, 44.5 mmol, 2.5 equiv) was added dropwise. The resultant light brown solution was stirred at rt for 3 h. The reaction was monitored using TLC (2% MeOH/DCM) and LCMS. After completion, toluene (20 mL) was added and all volatiles were removed *in vacuo*. The crude was redissolved and flushed with toluene two more times to afford a yellow semi-solid (5.8 g, 99% yield). The yellow semi-solid was carried to the next step without further purification. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{16}H_{15}F_3N_3O_5S$ 418.1; Found 418.1.

A 250 mL round bottom flask was equipped with magnetic stirrer, nitrogen inlet and rubber septum. The flask was charged with a solution of the product of the reaction described above (5.7 g, 17.7 mmol, 1.0 equiv) in anhydrous DCM (100 mL). TEA (4.08 mL, 21.3 mmol, 1.2 equiv) was added. The reaction mixture was cooled to 0 °C. TFAA (2.75 mL, 19.5 mmol, 1.1 equiv) was added dropwise. After addition of the reagent, the reaction mixture was stirred at rt for 3h and monitored by TLC (2% MeOH/DCM) and LCMS. Sat. $NaHCO_3$ solution (30 mL) was added and the reaction was extracted with DCM (3 x 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a yellow semi-solid (7.0 g). The crude product was purified by normal phase column chromatography (0% to 100% EtOAc/hex) to provide **29a** as light yellow viscous oil (6.1 g, 82% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.63 (td, *J* = 7.7, 1.3 Hz, 1H), 7.55 (dt, J_t = 7.8 Hz, J_d = 1.3 Hz, 1H), 7.19 – 7.13 (m, 6H), 6.33 (d, *J* = 9.0 Hz, 1H), 4.76 (dt, J_t = 9.6 Hz, J_d = 4.4 Hz, 1H), 3.83 (ddd, *J* = 14.2, 7.0, 4.4 Hz, 1H), 3.56 (ddd, *J* = 14.6, 10.1, 5.1 Hz, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.2, 158.0, 157.8, 157.6, J_{quar} = 37.6 Hz), 147.3, 136.4, 133.7, 133.6, 132.8, 131.0, 129.0, 128.7, 126.3, 125.1, (117.8, 116.4, 115.0, 113.6, J_{quar} = 287.6 Hz), 58.3, 44.9. IR: 3331, 1710, 1537, 1456, 1420, 1356, 1210, 1157, 1060, 1021. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}F_3N_3O_5S$ 418.0685; Found 418.0682.

Ethyl (*S,E*)-4-((2-nitro-*N*-(1-phenyl-2-(2,2,2-trifluoroacetamido)ethyl)phenyl)sulfonamido)but-2-enoate and **ethyl (*S,E*)-4-((2-nitro-*N*-(1-phenyl-2-(2,2,2-trifluoroacetamido)ethyl)phenyl)sulfonamido)but-3-enoate (30a {2,3}/30a {3,4})**. Using the method described to prepare compound **20e**, the mixture of the title compounds was obtained using compound **29a** as the starting material (5.1 g, 66% yield). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{22}H_{23}F_3N_3O_7S$ 530.1; Found 530.1.

Scheme 6 (compounds 34a-b, 35a-b, 36a, 38a)

Benzyl (*S*)-(5-hydroxy-4-((2-nitrophenyl)sulfonamido)pentyl)carbamate (34a). A 250 mL round bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with (*S*)-ornithine (5g, 18.8 mmol, 1.0 equiv). Dry THF (50 mL) was added and the mixture was stirred until dissolution was complete. The solution was cooled to 0 °C. Solid $NaBH_4$ (1.78 g, 46.9 mmol, 2.5 equiv) was added in portions and the resultant suspension was stirred at 0 °C for 5 min. A solution of I_2 (4.77 g, 18.8 mmol, 1.0 equiv) in THF (50 ml) was slowly added resulting in the evolution of gaseous hydrogen. After hydrogen evolution had ceased, the reaction was refluxed for 18 h. Complete consumption of *S*-ornithine was confirmed using LC/MS. The reaction was cooled to rt and water (10 mL) was added. The THF was removed *in vacuo* and 20% aq KOH (10 mL) was added. The resulting solution was extracted with 10% MeOH in DCM (MeOH required to dissolve all solids; 3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colorless, viscous liquid which was used for the next step without further purification or characterization.

Using the method described to prepare compound **16e**, the title compound was obtained. 3.5 g, off-white oil, 61% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (bd, *J* = 7.2 Hz, 1H), 7.81 (bd, *J* = 7.2 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.38 – 7.31 (m, 5H), 5.86 (bd, *J* = 7.3 Hz, 1H), 5.07 (s, 2H), 5.00 (bt, *J* = 5.5 Hz, 1H), 3.51 (vbt, *J* = 6.1 Hz, 3H), 3.16 – 3.07 (bm, 2H), 2.66 (bt, *J* = 5.6 Hz, 1H), 1.58 – 1.43 (m, 4H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.7, 147.6, 136.6, 134.6, 133.5, 132.9, 130.6, 128.6, 128.1, 128.0, 125.3, 66.7, 64.5, 56.3, 40.5, 28.8, 26.1. IR: 3418, 2943, 1694, 1533, 1440, 1414, 1363, 1338, 1247, 1161, 1126, 1060, 1040. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}N_3O_7S$ 438.1335; Found 438.1315.

Benzyl (*R*)-(5-hydroxy-4-((2-nitrophenyl)sulfonamido)pentyl)carbamate (34b). Using the method described for the preparation of compound **34a**, the title compound was obtained using (*R*)-ornithine as the starting material. 1.6 g, off-white oil, 41% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **34a** with the exception that δ 2.66 (bt, *J* = 5.6 Hz, 1H) is replaced by a very broad signal that rises just above the baseline. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.6, 147.7, 136.5, 134.7, 133.5, 132.9, 130.7, 128.6, 128.2, 128.1, 125.3, 66.7, 64.6, 56.3, 40.5, 28.8, 26.1. IR: 3336, 2940, 1692, 1535, 1440, 1413, 1338, 1246, 1163, 1124, 1059, 1038. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}N_3O_7S$ 438.1335; Found 438.1311.

(*S*)-5-(((benzyloxy)carbonyl)amino)-2-((2-nitrophenyl)sulfonamido)pentyl methanesulfonate (35a). Using the method described for the preparation of compound **17e** and using compound **34a** as the starting material the title compound was obtained. 6.4 g, off-white viscous oil, 99% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{20}H_{26}N_3O_9S_2$ 516.1; Found 516.0.

(*R*)-5-(((benzyloxy)carbonyl)amino)-2-((2-nitrophenyl)sulfonamido)pentyl methanesulfonate (35b). Using the method described for the preparation of compound **17e** and using compound **34b** as the starting material the title compound was obtained. 2.7 g, white viscous oil, 99% yield. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{20}H_{26}N_3O_9S_2$ 516.1; Found 516.0.

Benzyl (*S*)-(3-(1-((2-nitrophenyl)sulfonyl)aziridin-2-yl)propyl)carbamate (36a). Using the method described for the preparation of compound **18e**, the title compound was obtained using 35a as

the starting material. The crude aziridine was not rendered free of solvent but was handled as a solution in 1:1 DCM/THF. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{19}H_{22}N_3O_6S$ 420.1; Found 420.1.

Benzyl (*R*)-2-(((2-nitrophenyl)sulfonamido)methyl)pyrrolidine-1-carboxylate (38a). Using the method described for the preparation of compound **19e**, the title compound was obtained using 36a as the starting material (2.02 g, yellow oil, 60% yield from 35a). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (dt, *J* = 6.0, 3.7 Hz, 1H), 7.80 (dquar, *J* = 7.8, 3.8 Hz, 1H), 7.70 (dquar, *J* = 7.6, 4.0 Hz, 2H), 7.42 – 7.30 (m, 5H), 5.77 – 5.58 (m, 1H), 5.16 – 5.08 (m, 2H), 4.05 – 3.94 (m, 1H), 3.47 (dt, *J* = 10.8, 6.9 Hz, 1H), 3.40 – 3.28 (m, 1H), 3.23 (dt, *J* = 12.1, 5.6 Hz, 1H), 3.07 (dd, *J* = 13.0, 7.2 Hz, 1H), 2.09 – 1.96 (m, 1H), 1.91 (dquar, *J* = 12.8, 6.5 Hz, 1H), 1.83 (dtd, *J* = 14.5, 8.8, 7.3, 4.0 Hz, 2H), 1.57 – 1.45 (m, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.1, 148.0, 147.8, 136.5, 133.7, 133.6, 132.7, 130.9, 130.6, 128.6, 128.5, 128.1, 128.1, 127.9, 127.9, 125.2, 67.4, 67.1, 57.3, 50.1, 47.3, 43.9, 31.0, 29.0, 23.8, 22.9, 22.8. IR: 2949, 2880, 2359, 2340, 1685, 1538, 1413, 1358, 1264, 1234, 1164, 1104. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{22}N_3O_6S$ 420.1229; Found 420.1221.

Scheme 7 (compounds 39a-b, 40a-b, 41a-b, 42a-b, 43a-b, 44a-b, 45a *cis*, 45b *cis*, 46a *trans*, 46b *trans*

Benzyl (*S*)-(5-azido-4-((2-nitrophenyl)sulfonamido)pentyl)carbamate (39a). A 250 mL round bottom flask was equipped with a magnetic stir bar and a nitrogen inlet. The flask was charged with a solution of mesylate 35a (1.89 g, 3.67 mmol, 1.0 equiv) in dry DMF (40 mL). Solid NaN_3 (0.24 g, 3.67 mmol, 1.0 equiv) was added and the reaction was stirred overnight at 80 °C. Analysis by LCMS confirmed complete conversion. The reaction was partitioned between EtOAc (100 mL) and brine (50 mL). The organic was washed with brine (2 x 50mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound as a yellow oil which was used without further purification. 1.60 g, 90% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.87 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.74 – 7.70 (two overlapping quar, 2H), 7.39 – 7.32 (m, 5H), 5.70 (d, *J* = 8.4 Hz, 1H), 5.10 (bd, *J* = 11.0 Hz, 2H), 4.91 (t, *J* = 5.9 Hz, 1H), 3.63 (vbquar, *J* = 4.3 Hz, 1H), 3.32 (bdquar, *J* = 12.5, 5.1 Hz, 2H), 3.16 (bdquar, *J* = 12.7, 6.9 Hz, 2H), 1.59 – 1.48 (bm, 5H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.5, 147.6, 136.6, 134.8, 133.7, 133.0, 130.4, 128.6, 128.2, 128.1, 125.5, 66.7, 55.2, 54.3, 40.3, 29.8, 26.1. IR: 3329, 2929, 2101, 1701, 1538, 1440, 1419, 1342, 1243, 1165, 1124, 1060, 1038. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{23}N_6O_6S$ 463.1400; Found 463.1394.

Benzyl (*R*)-(5-azido-4-((2-nitrophenyl)sulfonamido)pentyl)carbamate (39b). Using the method described above for preparation of compound **39a** the title compound was obtained using mesylate 35b as starting material. 1.53 g, yellow oil, 90% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ identical to **39a**. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 156.6, 147.6, 136.6, 134.7, 133.7, 133.1, 130.4, 128.6, 128.1, 128.0, 125.4, 66.6, 55.2, 54.3, 47.0, 40.3, 29.8, 26.0. IR: 3335, 2937, 2100, 1697, 1536, 1441, 1418, 1339, 1244, 1163, 1123, 1069, 1026. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{23}N_6O_6S$ 463.1400; Found 463.1389.

Benzyl (*S*)-(5-amino-4-((2-nitrophenyl)sulfonamido)pentyl)carbamate (40a). A 250 mL round bottom flask was equipped with a magnetic stir bar and a nitrogen inlet. The flask was charged with a solution of **39a** (1.6 g, 3.46 mmol, 1.0 equiv) and PPh_3 (1.09 g, 4.15 mmol, 1.2 equiv) in THF:H_2O (9:1; 50 mL). The solution was heated at 70 °C for 1 h. LCMS analysis confirmed complete conversion. The reaction was cooled to rt and all volatiles were removed *in vacuo*. The resulting crude mixture was purified by chromatography (10:1 DCM: MeOH) to give the title compound as a colorless oil. 1.0 g, 66% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 – 8.03 (m, 1H), 7.91 – 7.81 (m, 1H), 7.81 – 7.66 (m, 2H), 7.42 – 7.29 (m, 5H), 5.10 (s, 2H), 5.01 (s, 1H), 3.15 (dd, *J* = 12.8, 5.3 Hz, 3H), 2.87 (dt, *J* = 8.1, 4.8 Hz, 1H), 2.84 – 2.77 (m, 1H), 2.64 (vbs disappearing into the baseline, 2H), 1.60 – 1.58 (m, 1H), 1.55 – 1.40 (m, 2H), 1.34 – 1.19 (m, 1H). IR: 3311, 2931, 1696, 1535, 1453, 1439, 1363, 1333, 1243, 1160, 1124, 1061, 1026. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{25}N_4O_6S$ 437.1495; Found 437.1484.

Benzyl (*R*)-(5-amino-4-((2-nitrophenyl)sulfonamido)pentyl)carbamate (40b). Using the method described above for the preparation of compound **40a**, the title compound was obtained using **39b** as the starting material (0.82 g, off-white oil, 57% yield). ^{1}H NMR (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 – 8.09 (m, 1H), 7.76 – 7.74 (m, 1H), 7.67 – 7.62 (m, 2H), 7.35 – 7.29 (m, 5H), 5.17 (vbt, *J* = 5.9 Hz, 1H), 5.05 (s, 2H), 3.37 (vbquar, *J* = 5.7 Hz, 1H), 3.18 (vbs, 2H), 3.10 – 3.03 (m, 2H), 2.65 – 2.62 (bm, 2H), 1.46 – 1.38 (m, 4H). IR: 3306, 2931, 1696, 1536, 1454, 1439, 1334, 1257, 1160, 1124, 1061, 1037. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{25}N_4O_6S$ 437.1495; Found 437.1485.

Benzyl *tert*-butyl (2-((2-nitrophenyl)sulfonamido)pentane-1,5-diyl)(*S*)-dicarbamate (41a). A 250 mL round bottom flask was equipped with a magnetic stir bar and a nitrogen inlet. The flask was charged with a solution of compound **40a** (1.0 g, 2.29 mmol, 1.0 equiv) in a mixture of THF/H_2O (2:1; 75 mL). Solid Na_2CO_3 (0.73 g, 6.87 mmol, 3.0 equiv) was added followed by Boc_2O (1.00 g, 4.58 mmol, 2.0 equiv). The reaction was stirred at rt for 18h. The THF was removed *in vacuo* and the remaining aqueous was extracted with EtOAc (150 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound as an off-white viscous oil (1.47 g, 120% crude yield). The crude product was used without further purification. (product 80% pure due to residual Boc anhydride). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.1 Hz, 1H), 7.75 (dd, *J* = 7.4, 4.6 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.34 – 7.30 (m, 5H), 5.98 (d, *J* = 6.7 Hz, 1H), 5.10 – 5.07 (m, 1H), 5.05 (s, 3H), 3.52 (quart, *J* = 6.9 Hz, 1H), 3.20 (dt, *J* = 14.6, 5.1 Hz, 1H), 3.07 – 3.05 (m, 3H), 1.52 – 1.41 (m, 2H), 1.44 – 1.29 (m overlapping s, 12H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.6, 156.3, 147.6, 136.7, 134.5, 133.6, 132.9, 130.6, 129.2, 128.5, 128.1, 128.0, 125.2, 79.6, 66.5, 55.0, 44.3, 40.4, 29.8, 28.3, 25.8. IR: 3338, 2934, 1701 (broad), 1541, 1457, 1370, 1307, 1246, 1211, 1165, 1115, 1067. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{33}N_4O_8S$ 537.2019; Found 537.2017. HRMS (ESI-TOF) *m/z*: $[M + H - Boc]^+$ Calcd for $C_{19}H_{25}N_4O_6S)^+$ 437.1495; Found 437.1489 (base peak).

Benzyl *tert*-butyl (2-((2-nitrophenyl)sulfonamido)pentane-1,5-diyl)(*R*)-dicarbamate (41b). Using the method described above for preparation of compound **41a**, the title compound was obtained using **40b** as the starting material. 1.2 g, light brown oil, 95% crude yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ identical to **41a** except for δ 5.98 (d, *J* = 6.7 Hz, 1H) is shifted to δ 5.80 (d, *J* = 7.1

Hz, 1H); δ 5.10 – 5.07 (m, 1H) is shifted to δ 4.96 (quart, *J* = 5.9 Hz, 2H); δ 5.05 (s, 3H) is shifted to δ 5.03 (s, 2H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.5, 156.3, 147.7, 136.6, 134.6, 133.5, 133.0, 130.6, 128.5, 128.11, 128.08, 125.3, 79.7, 66.6, 55.1, 44.3, 40.4, 29.9, 28.3, 25.8. IR: 3335, 2931, 1690 (broad), 1535, 1453, 1364, 1246, 1161, 1122, 1060. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{33}N_4O_8S$ 537.2019; Found 537.2001. HRMS (ESI-TOF) *m/z*: [M + H - Boc]$^+$ Calcd for $C_{19}H_{25}N_4O_6S$ 437.1495; Found 437.1488 (base peak).

Ethyl (*S*,*E*)-4-((*N*-(13,13-dimethyl-3,11-dioxo-1-phenyl-2,12-dioxa-4,10-diazatetradecan-8-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (42a). Using the method described for the preparation of compound **20e**, the title compound was obtained using **41a** as the starting material. 180 mg, light brown oil, 88% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 – 7.9 (bm, 1H), 7.67 – 7.63 bm, 2H), 7.58 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.34 – 7.28 (m, 5H), 6.83 (dt, *J* = 16.0, 6.3 Hz, 1H), 5.97 (bd, *J* = 15.7 Hz, 1H), 5.08 – 5.05 (bm, 3H), 4.90 (t, *J* = 6.2 Hz, 1H), 4.17 – 4.08 (bm, 3H), 4.00 (dd, *J* = 17.0, 6.1 Hz, 1H), 3.93 (vbs, 1H), 3.19 – 3.07 (m, 4H), 1.55 – 1.42 (m, 4H), 1.33 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 156.5, 155.7, 147.7, 144.3, 136.7, 133.9, 133.5, 132.0, 131.5, 128.5, 128.09, 128.06, 124.3, 123.8, 79.5, 66.5, 60.7, 58.2, 44.4, 42.2, 40.3, 28.3, 28.2, 26.5, 14.2. IR: 3390 (broad), 2982, 1714, 1659, 1445, 1368, 1275, 1174, 1096, 1035. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{30}H_{41}N_4O_{10}S$ 649.2543; Found 649.2540. HRMS (ESI-TOF) *m/z*: [M + H - Boc]$^+$ Calcd for $C_{25}H_{33}N_4O_8S$ 549.2019; found 549.2012 (base peak).

Ethyl (*R*,*E*)-4-((*N*-(13,13-dimethyl-3,11-dioxo-1-phenyl-2,12-dioxa-4,10-diazatetradecan-8-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (42b). Using the method described for the preparation of compound **20e**, the title compound was obtained using compound **41b** as the starting material. 650 mg, light brown oil, 41% yield. ^1H NMR (600 MHz, $CDCl_3$) identical to **42a** except that δ 5.08 – 5.05 (bm, 3H), 4.90 (t, *J* = 6.2 Hz, 1H) has been replaced by δ 5.10 (b½AB, *J* = 12.3 Hz, 1H), 5.08 (b½AB, *J* = 12.3 Hz, 1H), 4.90 (bt, *J* = 6.1 Hz, 1H), 4.85 (bt, *J* = 6.2 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.5, 156.5, 155.7, 147.7, 144.2, 136.6, 133.8, 133.7, 132.0, 131.6, 128.5, 128.1, 124.3, 123.8, 79.6, 66.6, 60.7, 58.2, 44.5, 42.2, 40.3, 28.3, 28.2, 26.6, 14.2. IR: 3350, 2931, 1701 (broad), 1660, 1541, 1453, 1366, 1247, 1160, 1037. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{30}H_{41}N_4O_{10}S$ 649.2543; Found 649.2540. HRMS (ESI-TOF) *m/z*: [M + H - Boc]$^+$ Calcd for $C_{25}H_{33}N_4O_8S$ 549.2019; Found 549.2014 (base peak).

Benzyl (*S*)-(4-((2-nitrophenyl)sulfonamido)-5-(2,2,2-trifluoroacetamido)pentyl)carbamate (43a). A 250 mL round bottom flask was equipped with a magnetic stirrer and nitrogen inlet. The flask was charged with a solution of **40a** (3 g, 6.87 mmol, 1.0 equiv) in dry DCM (50 mL). TEA (1.98 mL, 1.5 equiv) and TFAA (1.45 mL, 1.5 equiv) were added and the reaction mixture was stirred at rt for 3 h. The reaction was monitored by TLC (50% EtOAc/hex) and LCMS. After completion of the reaction, the solution was poured into brine (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The yellow semi-solid crude product was subjected to flash chromatography (50% EtOAc/hex) to obtain the title compound as an off-white semisolid (3.65 g, 99% yield). ^1H NMR (800 MHz, $CDCl_3$) δ 8.14 (bd, *J* = 7.4 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.40 – 7.34 (m, 4H), 7.16 (vbs, 1H), 5.63 (bd, *J* = 7.0 Hz, 1H), 5.09 (½AB, *J* = 12.2 Hz, 1H), 5.06 (½AB,

J = 12.3 Hz, 1H), 4.76 (vbs, 1H), 3.67 (vbs, 1H), 3.56 – 3.54 (m, 1H), 3.30 (bdt, J_d = 13.3 Hz, J_t = 6.7 Hz, 1H), 3.12 – 3.09 (m, 1H), 3.04 (dq, J_d = 12.6 Hz, J_t = 6.8 Hz, 1H), 1.60 (bt, *J* = 8.4 Hz, 1H), 1.47 (bq, *J* = 8.7 Hz, 2H), 1.40 – 1.30 (m, 1H). ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (157.9, 157.7, 157.5, 156.6, J_{quar} = 37.4 Hz), 147.7, 136.4, 134.0, 133.8, 133.2, 130.7, 128.6, 128.3, 128.1, 125.5, (117.8, 116.4, 115.0, 112.5, J_{quar} = 287.8 Hz), 66.8, 53.8, 44.2, 39.9, 29.8, 29.7, 26.0. IR: 3328 (broad), 2947, 1700, 1538, 1441, 1362, 1252, 1210, 1160, 1060, 1019. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{24}F_3N_4O_7S$ 533.1318; Found 533.1318.

Benzyl (*R*)-(4-((2-nitrophenyl)sulfonamido)-5-(2,2,2-trifluoroacetamido)pentyl)carbamate (43b). Using the method described above for the preparation of **43a**, the title compound was obtained using compound **40b** as the starting material. 1.8 g, white semi-solid, 98% yield. ^{1}H NMR (800 MHz, $CDCl_3$) identical to **43a** except for δ 5.63 (bd, *J* = 7.0 Hz, 1H) is shifted to δ 5.94 (bd, *J* = 7.7 Hz, 1H), δ 1.93 (vbm, 1H) which is not present in **43a**. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ (158.0, 157.8, 157.6, 156.6, J_{quar} = 37.4 Hz), 147.6, 136.5, 133.93, 133.87, 133.1, 130.7, 128.6, 128.2, 128.0, 125.3, (117.9, 116.5, 115.0, 113.6, J_{quar} = 287.4 Hz), 66.7, 53.8, 44.1, 40.1, 29.7, 25.9. IR: 3333 (broad), 2938, 1700, 1537, 1453, 1441, 1361, 1251, 1210, 1160, 1058, 1016. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{24}F_3N_4O_7S$ 533.1318; Found 533.1311.

Ethyl (*S*,*E*)-4-((*N*-(5-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroacetamido)pentan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (44a). Using the method described for the preparation of compound **20e**, the title compound was obtained as a mixture of {2,3} and {3,4} olefin regioisomers. 2.5 g, 59% yield. LCMS *m/z*: Calcd for [M + H]$^+$ $C_{27}H_{32}F_3N_4O_9S$ 645.2; Found 645.2.

Ethyl (*S*,*E*)-4-((*N*-(5-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroacetamido)pentan-2-yl)-2-nitrophenyl)sulfonamido)but-2-enoate (44b). Using the method described for the preparation of compound **20e**, the title compound was obtained as a mixture of {2,3} and {3,4} olefin regioisomers. 2.6 g, 99% yield. LCMS *m/z*: Calcd for [M + H]$^+$ $C_{27}H_{32}F_3N_4O_9S$ 645.2; Found 645.1.

(+)-Ethyl 2-((*2S,5S*)-5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (45a *cis*). Using the method described for the preparation of compound **23e *cis*** (Scheme 3, Boc route) the title compound was obtained using **42a** as the starting material. 500 mg, light brown viscous oil, 54% yield (**46a *trans***, 50 mg, 5.3% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 6.4, 4.2 Hz, 1H), 7.65 (dd, *J* = 6.9, 2.5 Hz, 2H), 7.60 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.38 – 7.31 (bd overlapping m, J_d = 3.7 Hz, 4H), 5.09 (s, 2H), 4.93 (vbd, *J* = 6.2 Hz, 1H), 4.13 (quar, *J* = 7.1 Hz, 2H), 3.86 (vbquar, *J* = 7.3 Hz, 1H), 3.65 (d, *J* = 11.1 Hz, 1H), 3.18 (bhept, *J* = 7.2 Hz, 2H), 2.92 – 285 (m, 4H), 2.40 (dd, *J* = 16.4, 3.7 Hz, 1H), 2.30 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.16 (vbs, 1H), 1.75 (vbhept, *J* = 7.8 Hz, 2H), 1.47 (bpent, *J* = 7.3 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.3, 156.4, 147.7, 136.7, 134.0, 133.6, 131.9, 130.8, 128.5, 128.09, 128.08, 124.3, 66.6, 60.8, 53.4, 51.6, 47.9, 45.7, 40.6, 37.8, 26.6, 25.9, 14.2. IR: 3337, 2926, 1711, 1670 (shoulder), 1541, 1453, 1370, 1348, 1244, 1163, 1059, 1025. Chiral analysis on ChiralPak IC (40% EtOH/heptane, isocratic). $[\alpha]_D^{25}$ +2.41 (*c* 5.0, $CHCl_3$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{33}N_4O_8S$ 549.2019; Found 549.2010.

(+)-Ethyl 2-((*2R,5S*)-5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (46a *trans*). Using the method described for the preparation of **24e *trans*** (Scheme 4) the title compound was obtained using **44a** as the starting material. 110 mg, tan viscous oil, 63% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (bt, J = 4.5 Hz, 1H), 7.64 (bm, 3H), 7.39 – 7.33 (m, 5H), 5.08 (bs, 2H), 4.84 (vbs, 1H), 4.07 (dquar, J_{quar} = 8.0 Hz, J_d = 3.5 Hz, 2H), 3.84 (bd, J = 6.0 Hz, 1H), 3.49 (bd, J = 2.8 Hz, 2H), 3.39 (dt, J_t = 5.7 Hz, J_d = 2.4 Hz, 1H), 3.26 (dd, J = 12.8, 4.0 Hz, 1H), 3.13 – 3.10 (m, 2H), 2.69 – 2.64 (m, 2H), 2.31 (dd, J = 16.5, 5.8 Hz, 1H), 2.01 (vbs, 2H), 1.82 – 1.80 (m, 1H), 1.65 – 1.62 (m, 1H), 1.41 – 1.35 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.9, 156.3, 147.5, 136.6, 133.7, 133.6, 131.8, 131.0, 128.6, 128.2, 128.1, 124.4, 66.6, 60.5, 53.7, 48.2, 44.6, 41.6, 40.7, 33.9, 26.7, 25.8, 14.2. IR: 2937, 2359, 1713, 1542, 1454, 1369, 1215, 1163, 1023. Chiral analysis on ChiralPak ID (heptane/EtOH). $[\alpha]_D^{25}$ +3.98 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{33}N_4O_8S$ 549.2019; Found 549.2011.

(–)-Ethyl 2-((*2R,5R*)-5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (45b *cis*). Using the method described for the preparation of compound **23e** (Scheme 3, Boc route) the title compound was obtained using **42b** as the starting material. 400 mg, light brown viscous oil, 72.5% yield (**46b *trans***, 47 mg, 8.5% yield). ^{1}H NMR (600 MHz, $CDCl_3$) identical to **45a *cis***. ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.3, 156.4, 147.7, 136.7, 134.03, 133.6, 131.9, 130.8, 128.5, 128.1, 128.1, 124.3, 66.6, 60.8, 53.3, 51.6, 47.9, 45.7, 40.6, 37.7, 26.6, 25.9, 14.2. IR: 3336, 2931, 1711, 1677 (shoulder), 1540, 1453, 1370, 1348, 1244, 1163, 1059, 1025. Chiral analysis on ChiralPak IC (40% EtOH/heptane isocratic). $[\alpha]_D^{25}$ –1.93 (*c* 5.0, $CHCl_3$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{33}N_4O_8S$ 549.2019; Found 549.2008.

(–)-Ethyl 2-((*2S,5R*)-5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (46b *trans*). Using the method described for the preparation of **24e *trans*** (Scheme 4) the title compound was obtained using **44b** as the starting material. 90 mg, light brown viscous oil, 52% yield. ^{1}H NMR (600 MHz, $CDCl_3$) identical to **46a *trans*** except that δ 4.84 (vbs, 1H) is shifted to δ 4.79 (vbs, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.9, 156.3, 147.5, 136.6, 133.8, 133.6, 131.8, 131.0, 128.6, 128.2, 128.1, 124.4, 66.6, 60.5, 53.8, 49.7, 48.2, 44.7, 41.7, 40.7, 33.9, 32.2, 29.7, 27.7, 26.7, 25.8, 14.2. IR: 2936, 2865, 1716, 1541, 1454, 1370, 1248, 1164, 1056, 1033, 1018. Chiral analysis on ChiralPak ID (heptane/EtOH). $[\alpha]_D^{25}$ –2.85 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{33}N_4O_8S$ 549.2019; Found 549.2010.

Scheme 8 (compounds 47, 48, 49, 50, 51, 52)

The process described below demonstrates the orthogonal diversification of the piperazine scaffolds using synthetic sequences suitable for parallel synthesis. No reaction optimization was performed and some intermediates were characterized by LCMS only. MDF purified final products were characterized by HRMS, ^{1}H and ^{13}C NMR.

Ethyl 2-((*2S*,*5S*)-5-benzyl-1-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (47). A solution of compound **23b** (200 mg, 0.447 mmol, 1.0 equiv) in dry ACN (5 mL) was treated with AcOH (64 μL, 1.12 mmol, 2.5 equiv) followed by 37% aq HCHO (0.201 mL, 2.68 mmol, 6 equiv) at rt. The solution was stirred at rt for 10 m and then treated with sodium triacetoxyborohydride (STAB, 284 mg, 1.34 mmol, 3 equiv). The reaction was stirred at rt for 16 h. LCMS confirmed complete methylation. Satd aq $NaHCO_3$ (5 mL) was slowly added. The mixture was partitioned between EtOAc and satd aq $NaHCO_3$. The aq was extracted once with EtOAc. The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, filtered and evaporated. The crude product (yellow-green oil, 212 mg, 103% yield) was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.67 – 7.60 (m, 3H), 7.25 – 7.14 (m, 5H), 4.20 (quar, *J* = 7.1 Hz, 2H), 4.12 – 4.11 (m, 1H), 3.75 (dd, *J* = 13.4, 2.5 Hz, 1H), 3.40 (dt, J_t = 10.8 Hz, J_d = 2.5 Hz, 1H), 3.23 (dt, J_t = 9.5 Hz, J_d = 3.4 Hz, 1H), 2.93 (dd, *J* = 13.0, 5.8 Hz, 1H), 2.62 (dt, J_t = 12.0 Hz, J_d = 3.0 Hz, 2H), 2.43 – 2.39 (m, 2H), 2.25 (dd, *J* = 11.8, *3*.0 Hz, 1H), 2.22 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.0, 147.6, 138.3, 133.9, 133.4, 131.9, 130.8, 129.4, 128.5, 126.6, 124.4, 60.8, 59.3, 56.9, 55.9, 45.5, 42.7, 36.7, 35.9, 14.2. IR: 2957, 2800, 1728, 1541, 1453, 1367, 1347, 1297, 1265, 1158, 1124, 1090, 1061, 1034. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{22}H_{28}N_3O_6S$ 462.2; Found 462.2.

(–)-Ethyl 2-((*2S*,*5S*)-4-acetyl-5-benzyl-1-methylpiperazin-2-yl)acetate (48). A solution of compound **47** (212 mg crude, 0.447 mmol based on 100% conversion of **23b**, 1.0 equiv) in dry THF (3 mL) was treated with 2-mercaptoethanol (94 μL, 1.34 mmol, 3.0 equiv) at rt. Cs_2CO_3 (218 mg, 0.67 mmol, 1.5 equiv) was added. The reaction was stirred at rt for 16 h. LCMS confirmed complete deprotection. The reaction was partitioned between water and EtOAc. The organic layer was dried over anhy $MgSO_4$, filtered and evaporated to a residue. The crude product was purified by normal phase chromatography (5% CH_3OH/DCM) to afford the deprotected intermediate (88 mg). The compound was taken forward to the next step without further purification or characterization. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{16}H_{25}N_2O_2$ 277.2; Found 277.2.

A 0° C solution of the compound from the above reaction (88 mg, 0.317 mmol) in dry DCM (3 mL) was treated with TEA (66 μL, 0.476 mmol, 1.5 equiv) followed by AcCl (27 μL, 0.380 mmol, 1.2 equiv). The solution was stirred at rt for 2 h. LCMS confirmed complete acylation. The reaction mixture was partitioned between DCM and sat aq $NaHCO_3$. The organic layer was washed with brine, dried over anhy Na_2SO_4, filtered and evaporated to a residue. The crude product was purified by chromatography (5% CH_3OH/DCM) to afford **48** as a pale yellow oil (64 mg). ^{1}H NMR (600 MHz, $CDCl_3$, ~1:1 mixture of rotamers) δ 7.32 – 7.20 (m, 4H), 7.15 – 7.13 (m, 1H), 4.81 – 4.78 (m, 0.5H), 4.50 (dd, *J* = 13.5, 2.9 Hz, 0.5H), 4.19 (two overlapping quar, *J* = 7.1 Hz, 2H), 3.87 (m, 0.5H), 3.67 (dd, *J* = 12.9, 1.6 Hz, 0.5H), 3.26 (dt, J_t = 6.5 Hz, J_d = 2.5 Hz, 0.5H), 3.10 (ddd, *J* = 12.8, 9.0, 3.2 Hz, 1H), 3.01 (dd, *J* = 13.5, 6.7 Hz, 0.5H), 2.96 (dd, *J* = 13.2, 11.1 Hz, 0.5H), 2.82 (dd, *J* = 12.9, 5.9 Hz, 0.5H), 2.77 (dd, *J* = 11.7, 1.6 Hz, 0.5H), 2.72 (dd, *J* = 14.5, 2.9 Hz, 0.5H, 2.68 – 2.59 (m, 1H), 2.43 (dd, J = 15.3, 6.1 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.26 (s, 1.5H), 2.23 (s, 1.5H), 2.06 (s, 1.5H), 1.69 (s, 1.5H), 1.30 (two overlapping t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.4, 171.3, 169.3, 168.9, 138.8, 138.5, 129.4, 129.2, 128.7, 128.4, 126.8, 126.3, 60.8, 60.7, 59.8, 59.4, 58.6, 56.6, 56.4, 50.0, 46.7, 42.82, 42.76, 41.2, 37.3, 36.7, 36.5, 35.4, 21.6, 20.7, 14.3, 14.25. IR: 2978, 2855, 2794, 1730, 1642, 1495, 1421, 1369, 1299,

1253, 1177, 1087, 1065, 1030. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ –1.45 (*c* 5.0, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{27}N_2O_3$ 319.2022; Found 319.2024.

2-((*2S,5S*)-4-Acetyl-5-benzyl-1-methylpiperazin-2-yl)acetic acid (49). A solution of compound **48** (64 mg, 0.201 mmol, 1.0 equiv) in H_2O/THF (4 mL, 3:1) was treated with LiOH monohydrate (25.3 mg, 0.603 mmol, 3.0 equiv). The solution was stirred at rt for 16 h. LCMS confirmed complete ester hydrolysis. The reaction mixture was treated with aq HCl (1M, 900 µL). All volatiles were removed. The crude product was purified by automated preparative reverse-phase MDF HPLC. The appropriate fractions were pooled and evaporated to afford **49** as a clear, colorless oil (37 mg, 28% yield from **23b**). ^{1}H NMR (800 MHz, CD_3OD, ~1.3:1 mixture of rotamers) δ 7.32 – 7.20 (m, 5H), 4.98 (bquar, *J* = 7.3 Hz, 0.5H), 4.61 (dd, *J* = 11.4, 3.9 Hz, 0.5H), 4.28 (vbquar, *J* = 5.0 Hz, 0.5H), 3.93 (dd, *J* = 11.5, 2.7 Hz, 0.5H), 3.58 (t, *J* = 12.0 Hz, 0.5H), 3.31 (t, *J* = 12.3 Hz, 1H), 3.20 (t, *J* = 12.8 Hz, 0.5H), 3.16 (d, *J* = 12.4 Hz, 0.5H), 3.08 (dd, *J* = 13.8, 7.9 Hz, 0.5H), 3.04 – 2.98 (m, 1H), 2.93 – 2.92 (m, 1H), 2.88 – 2.81 (m, 0.5H), 2.76 – 2.69 (m, 2H), 2.65 (s, 1.5H), 2.63 (s, 1.5H), 2.03 (s, 1.5H), 1.54 (s, 1.5H). ^{13}C {^{1}H} NMR (201 MHz, CD_3OD) δ 170.7, 170.2, 137.7, 137.5, 129.0, 128.9, 128.4, 128.2, 126.7, 126.3, 60.2, 60.1, 57.5, 55.6, 55.3, 49.0, 44.5, 41.0, 39.2, 35.6, 34.7, 19.8, 19.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{23}N_2O_3$ 291.1709; Found 291.1704.

Ethyl 2-((*2S,5S*)-1-acetyl-5-benzyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)acetate (50). A 0 °C solution of compound **23b** (200 mg, 0.447 mmol) in dry DCM (5 mL) was treated with TEA (93 µL, 0.670 mmol, 1.5 equiv) followed by AcCl (38 µL, 0.536 mmol, 1.2 equiv). The solution was stirred at rt for 3 h. LCMS confirmed complete acylation. The reaction mixture was partitioned between DCM and satd aq $NaHCO_3$. The organic layer was washed with brine, dried over anhyd $MgSO_4$, filtered and evaporated to a residue. The crude product (yellow-green oil, 253 mg, 116% crude yield) was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (vbs, 1H), 7.71 – 7.58 (vbs overlapping doublet and m, 3H), 7.28 – 7.14 (bm, 5H), 4.47 – 4.40 (vbm, 2.5H), 4.23 – 4.11 (vbm, 5H), 3.51 (vbd, *J* = 9.8 Hz, 1H), 3.18 – 3.07 (vbm, 3H), 2.89 (dd, *J* = 13.7, 8.5 Hz, 3H), 2.34 (dd, *J* = 16.0, 8.3 Hz, 1H), 2.23 – 2.19 (vbm, 1H), 1.86 (bs, 3H), 1.26 (two overlapping bt, *J* = 7.5 Hz, 6H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.3, 169.8, 147.8, 135.8, 134.2, 132.1, 130.7, 129.4, 128.8, 127.2, 124.1, 60.8, 56.6, 47.5, 43.6, 40.1, 35.2, 29.7, 21.4, 14.1. IR: 2981, 1725, 1645, 1541, 1421, 1370, 1275, 1163, 1125, 1061, 1028. LCMS *m/z*: Calcd for $[M + H]^+$ $C_{23}H_{28}N_3O_7S)^+$ 490.2; Found 490.2.

(+)-Ethyl 2-((*2S,5S*)-1-acetyl-5-benzyl-4-methylpiperazin-2-yl)acetate (51). A solution of compound **50** (219 mg, 0.447 mmol, 1.0 equiv based on 100% yield of the previous step) in dry THF (5 mL) was treated with 2-mercaptoethanol (94 µL, 1.34 mmol, 3.0 equiv) at rt. Cs_2CO_3 (291 mg, 0.894 mmol, 2.0 equiv) was added. The reaction was stirred at rt for 16 h. LCMS confirmed complete deprotection. The reaction was partitioned between water and EtOAc. The organic layer was dried over anhyd $MgSO_4$, filtered and evaporated to a residue. The crude product was purified by normal-phase chromatography (5% CH_3OH/DCM) to afford a pale yellow oil (110 mg). LCMS *m/z*: Calcd for $[M + H]^+$ $C_{17}H_{25}N_2O_3$ 305.2; Found 305.2.

A solution of the product from the above reaction (110 mg, 0.361 mmol, 1.0 equiv) in ACN (5 mL) was treated with AcOH (52 μL, 0.903 mmol, 2.5 equiv) followed by 37% aq HCHO (0.161 mL, 2.15 mmol, 6.0 equiv) at rt. The solution was stirred at rt for 10 m and then treated with STAB (230 mg, 1.08 mmol, 3.0 equiv). The reaction was stirred at rt for 16 h. LCMS confirmed complete methylation. At the end of this time, satd aq $NaHCO_3$ was slowly added. The mixture was partitioned between EtOAc and satd aq $NaHCO_3$. The aqueous layer was extracted once with EtOAc. The combined organic layers were washed with brine, dried over anhyd $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (5% acetone/ DCM) to afford a pale yellow oil (40 mg). This sample was then purified further by pTLC (20% acetone/DCM) to afford **51** as a pale yellow oil (28 mg). ^{1}H NMR (600 MHz, $CDCl_3$, ~1:1 mixture of rotamers) δ 7.32 (t, *J* = 7.5 Hz, 1H), 7.28 – 7.18 (m, 4H), 4.98 (vbs, 0.5H), 4.27 – 4.24 (m, 1H), 4.15 – 4.08 (two overlapping quar, 2H), 3.22 (ddd, J = 13.8, 7.0, 3.7 Hz, 1H), 3.07 (dd, *J* = 14.1, 4.0 Hz, 0.5H), 2.93 – 2.83 (m, 1H), 2.83 – 2.76 (m, 1H), 2.58 (ddd, J = 18.9, 14.4, 7.4 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.37 (s, 1.5H), 2.35 (s, 1.5H), 2.30 (dd, J = 12.1, 4.0 Hz, 0.5H), 2.15 (bm,1H), 2.10 (s, 1.5H), 1.75 (s, 1.5H), 1.24 (two overlapping t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.4, 171.4, 168.9, 168.8, 138.0, 137.9, 129.2, 129.0, 128.7, 128.5, 126.7, 126.4, 64.4, 63.6, 60.8, 60.5, 59.5, 58.7, 50.9, 46.3, 45.5, 43.2, 43.0, 41.2, 37.6, 37.4, 35.6, 34.6, 21.22, 21.18, 14.2. IR: 2985, 2790, 1727, 1646, 1423, 1373, 1275, 1260, 1172, 1065, 1031. Chiral analysis on ChiralPak IA (heptane/EtOH). $[\alpha]_D^{25}$ +1.80 (*c* 2.8, EtOH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{27}N_2O_3$ 319.2022; Found 319.2026.

2-((*2S,5S*)-1-acetyl-5-benzyl-4-methylpiperazin-2-yl)acetic acid (52). A solution of compound **51** (28 mg, 0.094 mmol, 1.0 equiv) in H_2O/THF (2 mL, 3:1) was treated with LiOH monohydrate (12.0 mg, 0.283 mmol, 3.0 equiv). The solution was stirred at rt for 16 h. LCMS confirmed complete ester hydrolysis. The reaction mixture was treated with aq HCl (1M, 500 μL). All volatiles were removed. The crude product was purified by automated preparative reverse-phase MDF. The appropriate fractions were pooled and evaporated to afford **52** as a clear, colorless oil (14 mg, 11% yield from **23b**). ^{1}H NMR (800 MHz, CD_3OD, ~1.2:1 mixture of rotamers) δ 7.36 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.24 (m, 4H), 4.96 (vbd, *J* = 6.5 Hz, 0.5H), 4.45 (vbq, *J* = 5.8 Hz, 0.5H), 4.26 (dd, *J* = 14.1, 2.6 Hz, 0.5H), 3.41 (dd, *J* = 13.7, 2.6 Hz, 0.5H), 3.35 (t overlapping CD_3OD), 3.17 (d, *J* = 12.4 Hz, 0.5H), 3.14 – 3.11 (m, 1H), 2.91 – 2.82 (m, 2H), 2.69 (dd, *J* = 12.4, 3.8 Hz, 0.5H), 2.63 (dd, *J* = 14.2, 11.2 Hz, 0.5H), 2.59 – 2.55 (two singlets overlapping m, 6H), 2.46 (bt, *J* = 10.3 Hz, 0.5H), 2.14 (s, 1.5H), 1.78 (s, 1.5H). ^{13}C {^{1}H} NMR (201 MHz, CD_3OD) δ 170.3, 170.0, 137.2, 128.93, 128.87, 128.5, 128.3, 126.6, 126.4, 64.1, 64.0, 58.5, 57.6, 50.7, 45.6, 45.4, 41.5, 41.3, 40.0, 36.2, 35.9, 19.63, 19.60. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{23}N_2O_3$ 291.1709; Found 291.1706.

Associated Content

Mechanism of formation and spectral data for compound **27.** X-ray structures for compounds **23a *cis*** and **26a *trans***. ^{1}H and ^{13}C {^{1}H} NMR spectral data for all isolated compounds. Chiral analytical data for all piperazine scaffolds shown in Table 1 as well as for compounds **48** and **51**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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