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Design and Synthesis of Conformationally Constrained Ligands for Grb2 SH2 Binding and Thermodynamic Evaluation and The Development of a Diversity Oriented Synthesis of 2-Arylpiperidines

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Design and Synthesis of Conformationally Constrained Ligands for Grb2 SH2 Binding and Thermodynamic Evaluation and The Development of a Diversity Oriented Synthesis of 2-Arylpiperidines

by

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Dedication

To my older brother Phil, whose incessant know-it-all-ism drove me to achieve at the highest level, and prepared me for the academic world.

Acknowledgements

I'd like to thank Professor Stephen F. Martin, for accepting me into his lab and always encouraging me to perform my best in lab, and in the classroom. I'd like to thank every member of lab 2, past and present, for always keeping our work environment fun and exciting. I'd like to thanks my current and former lab mates David Cramer, Caleb Hethcox, Daniel Klosowski, Lance Lepovits, And Zachary White, for teaching me how to act like I knew what I was doing. I'd also like to especially thank Ian Riddington, Steve Sorey, and Angela Spangenberg, for their help in characterizing compounds.

I must also thank my mother Lorraine, my father Bruce, and all my family members who encouraged and supported me along the way. Lastly, I thank Emma Dietrich, for standing by my side through the highs and lows of the past two years.

Abstract

Design and Synthesis of Conformationally Constrained Ligands for Grb2 SH2 Binding and Thermodynamic Evaluation and The Development of a Diversity Oriented Synthesis of 2-Arylpiperidines

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The University of Texas at Austin, 2016

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The ways in which torsional strain in the bound form of a ligand affects the energetics of protein binding are poorly understood. In order to study this feature of protein-ligand interactions, a conformationally constrained ligand for Grb2 SH2 containing a 1,1,2 trisubstituted cyclopropane was designed, and the synthesis of this ligand attempted.

Additionally, a novel iminium ion formation/cyclization cascade was applied to the synthesis of a library of 2-arylpiperidines with varying aryl group substitution, and nitrogen atom functionalization. This strategy should allow further access to chemical space already identified as containing potential therapeutics and tool compounds for biological interrogation.

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CHAPTER 1: CONFORMATIONALLY CONSTRAINED LIGANDS FOR GRB2-SH2

1.1 Introduction

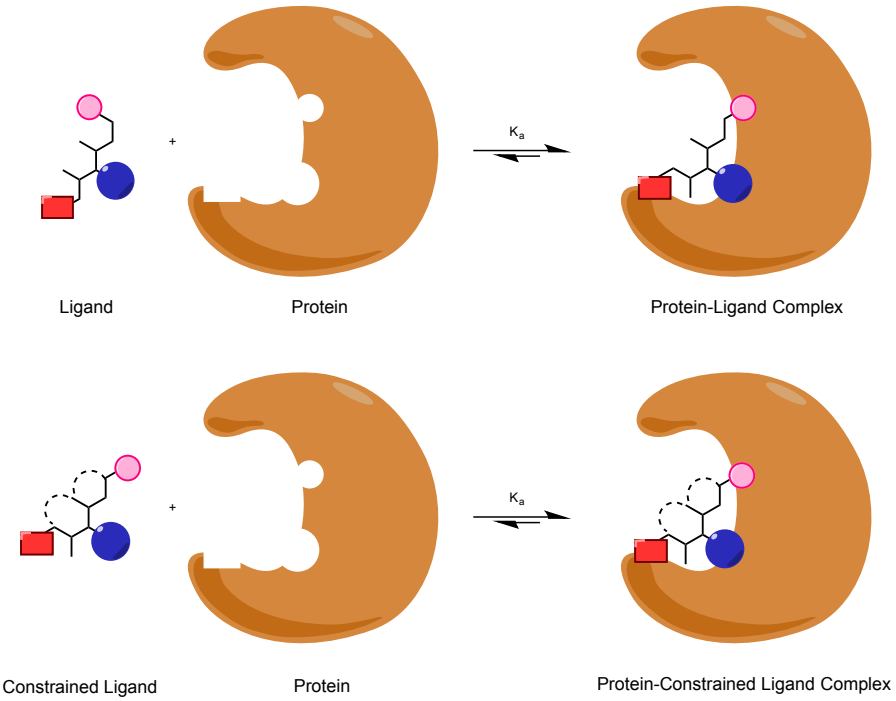
A major challenge in the process of drug discovery and development, as well as the study of molecular recognition in biological systems, is predicting and understanding how changes to the structural features of drug leads and small molecules will affect their relative binding affinities.[1-3] Addressing this challenge is non-trivial because the free energy of binding ($\Delta G°$) for an interaction frequently fails to correlate with enthalpy ($\Delta H°$) and/or entropy ($-T\Delta S°$) of binding, requiring in depth thermodynamic analysis in order to determine how changes in binding affinity (K_a) arise.[4] Unfortunately, progress in molecular recognition efforts have been hampered by the scarcity of published experiments where $\Delta H°$ and $-T\Delta S°$ are determined for a series of incrementally modified ligands.

Optimization of protein ligand interactions generally utilizes strategies that are believed to have predictable effects on both $\Delta H°$ and $\Delta S°$ of binding. For instance, maximization of non-covalent interactions between the ligand and the protein should increase binding enthalpy. Optimizing such interactions in practice, however, is very challenging because desolvating polar functionalities is enthalpically unfavorable. This penalty often outweighs the enthalpic benefit gained from increasing the strength of non-covalent interactions, leading to a precarious balancing act.[5] Polar interactions are also highly angle and distance dependent, further complicating the process of optimizing these interactions.[6] These challenges make clear that a qualitative understanding of the non-

covalent interactions at play in biomolecular recognition is not sufficient for prediction of the effects changes in structure will have on binding enthalpy.

Optimization of binding entropy is another approach to increasing binding affinity. Such strategies are frequently based on a qualitative understanding of the role entropy plays in protein-ligand interactions. One such approach involves the incorporation of conformational constraints into a ligand.[7,8] These constraints are typically installed with the intention of reducing the conformational entropy of the unbound ligand (Figure 1.1), thereby making $\Delta S°$ of binding more favorable.[9] However, conformational constraints frequently result in unanticipated, compensatory decreases in the $\Delta H°$ of binding. Additionally, there are examples of conformational constraints increasing $\Delta G°$ while having a *negative* impact on $\Delta S°$ of binding, illuminating deficiencies in our understanding of protein ligand interactions.[10]

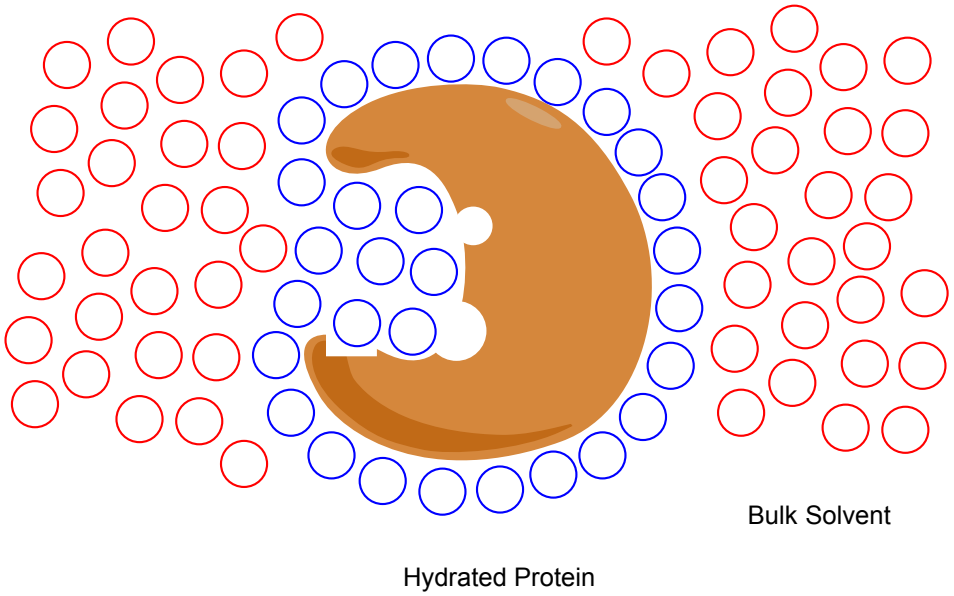
Figure 1.1: Comparison of K_a for flexible (top) and constrained (bottom) ligands. K_a is generally assumed to increase due to more favorable ΔS° of binding.



The favorability of binding entropy is also frequently enhanced *via* increasing the hydrophobic surface area buried upon binding. This strategy relies on our understanding of how solvent behaves when it hydrates the surface of a protein. When a protein is dissolved in water, the system is essentially made up of three parts. These are the bulk solvent, the solvent hydrating the surface of the protein, and the protein itself. The bulk solvent is believed to tumble freely through the system, which is entropically favorable. This high translational and rotational entropy is thought to be enthalpically unfavorable, as it limits the hydrogen bonding capabilities of bulk solvent due to the high distance and angle dependency of these interactions. The water molecules involved in hydrating the protein are thought to be far less mobile than the bulk solvent, in order to maintain the most favorable contacts possible with the proteins surface. While maintaining the ideal

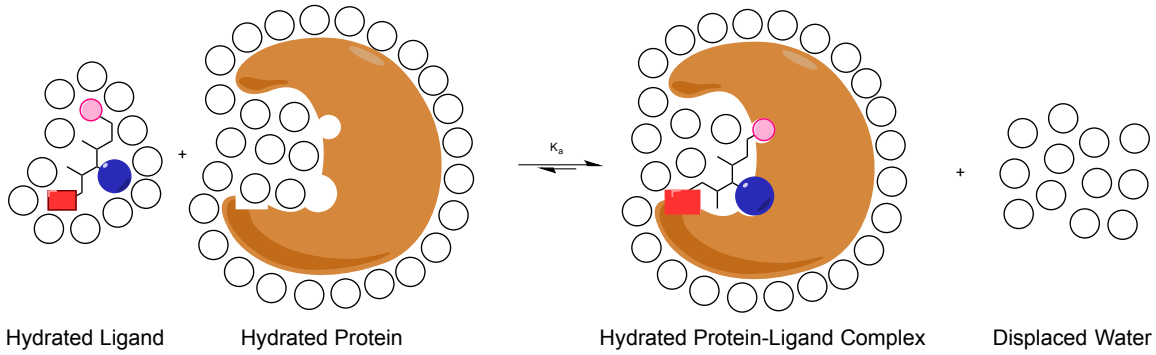
energetic contacts possible with the protein is enthalpically favorable, the "frozen" nature of these water molecules is thought to be entropically unfavorable (Figure 1.2)

Figure 1.2: A Dissolved Protein with Hydrating Water Molecules (Blue) and Bulk Solvent Molecules (Red)



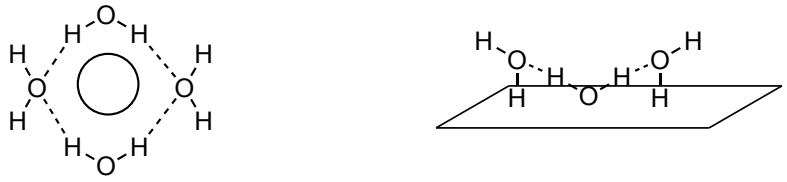
Now consider a binding event taking place between a protein and a small, hydrophobic molecule in aqueous solution (Figure 1.3). The protein and small molecule are initially both hydrated by "frozen" water molecules, which interact with the bulk solvent to keep each binding partner in solution. When these two molecules make contact in a binding event, hydrating water molecules are released into the bulk solvent to make room for new protein/ligand contact points, essentially "burying" the hydrophobic surfaces that were previously hydrated. Because bulk solvent molecules have greater entropy than molecules involved in hydration, this process is believed to be entropically favorable. Thus, by increasing the amount of hydrophobic surface area on a ligand, we can minimize entropic penalties paid upon binding to the protein.

Figure 1.3: A Protein-Ligand Binding Event in Aqueous Solution



While taking advantage of the hydrophobic effect for enhancing binding affinities seems simple, burying hydrophobic surface area is far from an ideal strategy for increasing binding affinities. First, there are strict limitations on the amount of hydrophobic surface area that can be added to a ligand before it's solubility in aqueous solution becomes too low to be useful for biological interrogation. Additionally, because desolvating hydrophobic groups is so energetically favorable, excessive greasiness can increase the promiscuity of ligands. Lastly, the behavior of water molecules involved in hydrophobic hydration changes depending on the contour of the surface being hydrated. For instance, when a small hydrophobic molecule is dissolved in water, the hydrating molecules form a "clathrate-like" structure around the solute. This arrangement allows the water molecules to make 100% of their potential hydrogen bonding contacts. When larger hydrophobic molecules are dissolved in water, such as a protein, the water molecules can satisfy a maximum of 75% of their potential hydrogen bonding contacts.[11] While this disruption of hydrogen bonding is not enthalpically favorable, there are entropic benefits that come from a slight increase in the rotational freedom of the hydrating water molecules (Figure 1.4).[12]

Figure 1.4: Comparison of Hydration of a Small Hydrophobic Solute and a Large Hydrophobic Solute (Represented Here as a Flat Surface)



enthalpically favorable entropically favorable

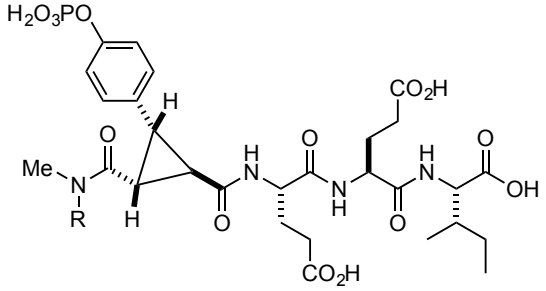
The common downfall of the above strategies is the inability to consistently overcome enthalpy-entropy compensation (*H*/*S* compensation), which refers to the tendency for favorable changes in $\Delta H°$ to be counteracted by unfavorable changes in $\Delta S°$, or vice versa. *H*/*S* compensation frequently plagues efforts to increase the K_a of a ligand in biomolecular recognition experiments.[13] The phenomenon is observed so frequently that it has been proposed to be a general feature of weak intermolecular interactions in aqueous media; however, experiments and statistical analyses have shown this not to be true.[14,15] While *H*/*S* compensation may not be a phenomenon intrinsically associated with biomolecular recognition, its presence in many such studies cannot be denied.[16-18]

1.1.1 1,2,3-TRISUBSTITUTED CYCLOPROPANES AS CONFORMATIONAL CONSTRAINTS

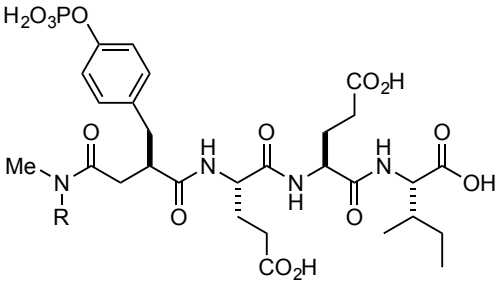
In 2002 the Martin group set out to establish whether 1,2,3-trisubstituted cyclopropane rings could serve as useful constraints for ligand preorganization.[19] The study compared a series of flexible ligands for the Src SH2 domain **1.1** and **1.2**, to constrained 1,2,3-trisubstituted cyclopropane analogs **1.3** and **1.4**. The thermodynamics of binding each ligand to Src SH2 were compared using isothermal titration calorimetry (ITC).

Isothermal titration calorimetry is a method by which a solution of one binding partner is titrated into a solution of another binding partner in small increments. The energy required to maintain constant temperature is measured and integrated against stoichiometry. The energy required to maintain constant temperature gives $\Delta H°$, and the slope of the line at the equivalence point gives the K_a. Knowing these two parameters allows us to calculate the $\Delta S°$ and $\Delta G°$ of binding as well.

Table 1.1: Constrained (left) and flexible (right) ligands studied by the Martin group in 2002.



1.1: R = H
1.2: R = Me



1.3: R = H
1.4: R = Me

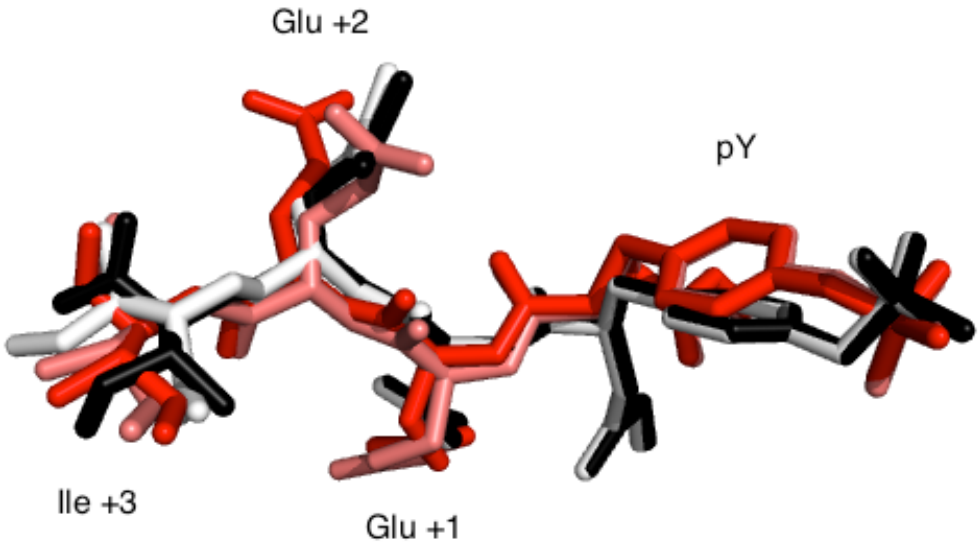
Compounds	K_a	$\Delta G°_{obs}$ (kcal mol^{-1})	$\Delta H°_{obs}$ (kcal mol^{-1})	$\Delta S°_{obs}$ (cal mol^{-1})
1.1	1.0 (±0.1) × 10^7	-9.55 ± 0.07	-5.91 ± 0.04	17 ± 1
1.3	1.7 (±0.6) × 10^7	-9.8 ± 0.2	-7.33 ± 0.03	8.3 ± 0.5
1.2	6.3 (±0.6) × 10^6	-9.26 ± 0.06	-5.01 ± 0.05	14.3 ± 0.4
1.4	1.4 (±0.1) × 10^7	-9.72 ± 0.06	-6.92 ± 0.09	9.4 ± 0.2

As is seen in Table 1.1, constrained ligands **1.1** and **1.2** enjoyed more favorable $\Delta S°$ of binding compared to flexible counterparts **1.3** and **1.4**, respectively. However, this favorable $\Delta\Delta S°$ was counteracted by an unfavorable $\Delta\Delta H°$ of binding for each

constrained ligand. This apparent *H*/*S* compensation resulted in almost no $\Delta\Delta G°$ between the constrained and flexible ligands.

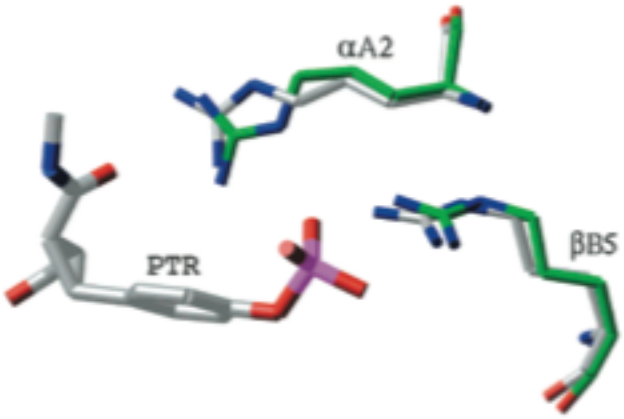
In order to gain insight as to what caused this unfavorable $\Delta\Delta H°$ the complex of Src SH2 with **1.1** (Src SH2–**1.1**) was studied with x-ray crystallography. Comparison of the crystal structure of Src SH2–**1.1** complex with the Src SH2–**1.3** complex revealed very few differences in the bound conformation of **1.1** and **1.3** (Figure 1.5).

Figure 1.5: Overlay of **1.1** (red and salmon) with the **1.3** (black and white) in the bound state. All conformations present in the asymmetric unit of each crystal structure are shown.



Although no significant differences were found in how ligand **1.1** and **1.3** bound to Src SH2, a significant difference in the structure of the SH2 domain was found in the two crystal structures. The pTyr residue of each ligand interacts with Arg residue αA2 in the binding pocket of Src SH2 (Figure 1.6).

Figure 1.6: Interactions of the pTyr (PTR) residue of **1.1** with Arg αA2. The conformation of Arg αA2 in the complex of Src SH2 with the native ligand is overlayed.



The conformation of Arg αA2 is significantly different in the complex of Src SH2–**1** and Src SH2–11-mer. The change in conformation of Arg αA2 results in a change in the hydrogen bonding network of the complex, breaking a hydrogen bond between Arg αA2 and the pTyr residue while creating a new hydrogen bond with a water molecule. Additionally, Arg αA2 is moved 0.5 Å further away from the aromatic face of the constrained pTyr residue, potentially disrupting a cation-π interaction between the guanidine of Arg αA2 and the aromatic ring of pTyr. The introduction of the cyclopropane ring appears to have given rise to torsional strain in the bound form of ligand **1.1**. The thermodynamic consequences of small internal strains in the bound state of a ligand, however, difficult to assess.

In order to determine if structural differences in the SH2 domain of the Src SH2–**1.1** and Src SH2–**1.3** complexes were the source of the *H*/*S* compensation observed with ligands **1.1** and **1.3**, Ward *et al*. carried out NMR experiments and molecular dynamics (MD) simulations.[21] The NMR experiments revealed downfield chemical shift

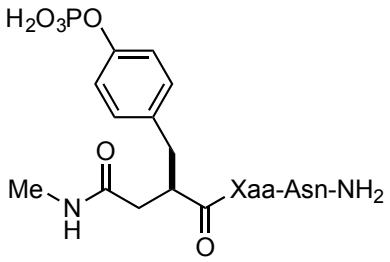
perturbations (CSPs), which arise from increased deshielding of a proton and reflect stronger hydrogen-bonding interactions, were observed for several residues in the complexes of **1.1** and **1.2** with Src SH2. These CSPs took place most frequently at the pTyr-binding pocket of the SH2 domain. Downfield CSPs are the result of increased deshielding of protons,[22] which indicate an increase in hydrogen bonding interactions. Downfield CSPs were present in both Src SH2–**1.1** and Src SH2–**1.2** complexes. While chemical shift perturbations reflect changes in hydrogen bonding that occur upon complex formation, chemical shift differences (CSDs) represent differences in the chemical shifts of different complexes. The CSDs linearly correlated with the $\Delta H°$ of binding for pYEEI, ligand **1.1**, and ligand **1.2** to Src SH2. The most enthalpically stable complex, Src SH2–pYEEI, had the largest CSDs, while the least enthalpically favorable complex, Src SH2–**1.1**, had the smallest CSDs. This correlation suggests that hydrogen bonding interactions at the pTyr-binding site have been compromised as a result of the constraint.

Binding interactions between Src SH2 and pTyr comprise more the 50% of $\Delta G°$ for binding ligands to Src SH2, classifying this region as a binding "hotspot."[23] It was determined that disturbances in the interaction of the pTyr residue with Src SH2 brought about by the installation of the cyclopropane ring are likely the source of *H*/*S* compensation. It is noteworthy that *the NMR studies revealed many differences in hydrogen bonding interactions that were not visible in the X-ray crystal structures of any complex with Src SH2*. This result is concerning because such detailed information is

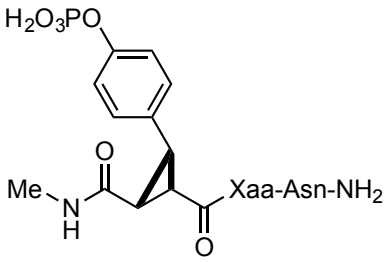
rarely available at the outset of rational ligand design campaigns, making the consequences of ligand modifications difficult to predict.

In order to further study the use of 1,2,3-trisubstituted cyclopropanes as conformational constraints in biomolecular recognition studies, flexible and constrained ligands of the general sequence Ac-pYXN-NH_2 (X = V, I, L, K, Q, or E) were prepared, and the thermodynamics of binding these ligands to Grb2 SH2 were obtained via ITC (Table 1.2).[24]

Table 1.2: Thermodynamic binding data for constrained and flexible analogs of Ac-pYXN-NH2.



1.5: Xaa = Val
1.6: Xaa = Ile
1.7: Xaa = Leu
1.8: Xaa = Gln
1.9: Xaa = Glu
1.10: Xaa = Lys



1.11: Xaa = Val
1.12: Xaa = Ile
1.13: Xaa = Leu
1.14: Xaa = Gln
1.15: Xaa = Glu
1.16: Xaa = Lys

Ligand	K_a (M^{-1})	ΔG° (kcal mol^{-1})	ΔH° (kcal mol^{-1})	ΔS° (cal mol^{-1})
1.5	$(4.5 \pm 0.12) \times 10^5$	-7.7 ± 0.02	-5.4 ± 0.14	7.9 ± 0.22
1.11	$(2.8 \pm 0.10) \times 10^6$	-8.8 ± 0.02	-7.9 ± 0.29	3.0 ± 0.30
1.6	$(4.0 \pm 0.15) \times 10^5$	-7.7 ± 0.02	-5.5 ± 0.20	7.4 ± 0.30
1.12	$(2.1 \pm 0.08) \times 10^6$	-8.6 ± 0.02	-8.3 ± 0.30	1.3 ± 0.30
1.7	$(1.7 \pm 0.06) \times 10^5$	-7.1 ± 0.02	-4.6 ± 0.17	8.6 ± 0.30
1.13	$(7.1 \pm 0.27) \times 10^5$	-8.0 ± 0.02	-6.0 ± 0.22	6.6 ± 0.30
1.8	$(5.6 \pm 0.15) \times 10^5$	-7.8 ± 0.02	-8.7 ± 0.23	-2.8 ± 0.22
1.14	$(1.2 \pm 0.06) \times 10^6$	-8.3 ± 0.01	-9.8 ± 0.20	-5.2 ± 0.18
1.9	$(3.0 \pm 0.08) \times 10^5$	-7.5 ± 0.02	-8.8 ± 0.23	-4.3 ± 0.22
1.15	$(3.6 \pm 0.10) \times 10^5$	-7.6 ± 0.02	-10.3 ± 0.27	-9.0 ± 0.22
1.10	$(9.8 \pm 0.23) \times 10^4$	-6.8 ± 0.02	-7.7 ± 0.20	-3.0 ± 0.21
1.16	$(5.5 \pm 0.15) \times 10^5$	-7.8 ± 0.02	-9.2 ± 0.24	-4.6 ± 0.22

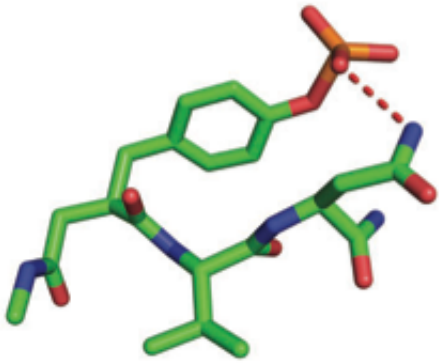
It was known at the outset of this study that the pTyr group of pYXN ligands bound to Grb2 SH2 in a fashion conformationally similar to Src SH2-pYEEI complexes. Surprisingly, in spite of this similarity, the $\Delta\Delta G°$, $\Delta\Delta H°$, and $\Delta\Delta S°$ for constraining pYXN ligands were very different from the results obtained with Src. Initially apparent is

the increase in binding affinity gained from constraining every pYXN ligand, which is reflected in the negative $\Delta\Delta G°$ values for each flexible/constrained pair. Even more surprising is the observation that in each case, negative $\Delta\Delta G°$ values result from a more negative $\Delta\Delta H°$ that *overcomes* less favorable $\Delta\Delta S°$ values. *These results were the first to demonstrate the increased K_as resulting from conformational constraints are not necessarily the result of more favorable binding entropy*.

Structural studies comparing flexible and constrained pYXN ligands showed that the ligands bound in a similar manner to one another. The constrained ligand of a given pair made more direct contacts with the domain, so there was a qualitative correlation between the total number of direct protein-ligand contacts and the relative $\Delta H°$ and $\Delta G°$ for each ligand pair. Conversely, the more flexible ligand of a pair made more single water-mediated contacts with the domain. Additionally, variations in binding enthalpies and entropies for the flexible and constrained ligands did not appear to arise from differences in either proton exchange or desolvation phenomena. There were no significant differences in the van der Waals contacts for a given flexible/constrained ligand pair. An analysis of crystallographic b-factors suggested that thermal motions in complexes of the constrained ligands were generally greater than those in the corresponding complexes of their flexible controls. If these motions in the solid state actually reflect more disorder, and hence more favorable configurational entropies, in the complexes of constrained ligands, one might anticipate that the binding entropies for their formation would be greater than those for their flexible counterparts; however, this prediction is inconsistent with our results.

Since structural analysis of the complexes of ligands **1.5**-**1.16** with Grb2 SH2 failed to explain the unexpected results of the experiment, focus was turned towards the solution state conformational dynamics of the unbound ligands.[25] Computations analyzing the solution state conformation of flexible ligand **1.5** and constrained ligand **1.11** actually predicted that flexible ligand **1.11** had *lower* entropy than its constrained counterpart. This is due to the dominant solution state conformation (35 mol%) of ligand **1.11** being macrocyclic in nature. As seen in Figure 1.7, the phosphate group of ligand **1.11** makes an intramolecular hydrogen bond with the amide moiety at the C-terminus of the molecule.

Figure 1.7: 35 mol% of Ligand 1.11 Exists in the Macrocyclic Conformation Below

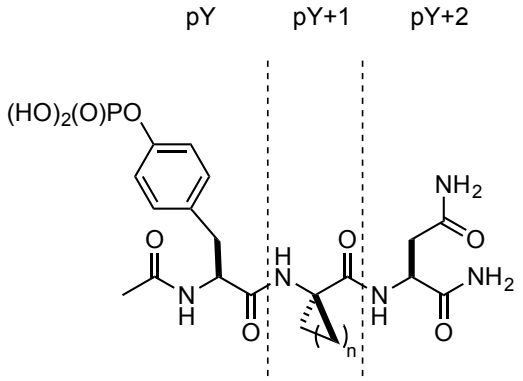


The cyclopropane in constrained ligand **1.5** prevents this interaction from occurring, thus *increasing* the solution state entropy of ligand **1.5** relative to its flexible counterpart. Thus, we have shown that *lowering the entropy of a ligand in any way that allows it to adopt its bound conformation can lead to a more favorable entropy of binding*.

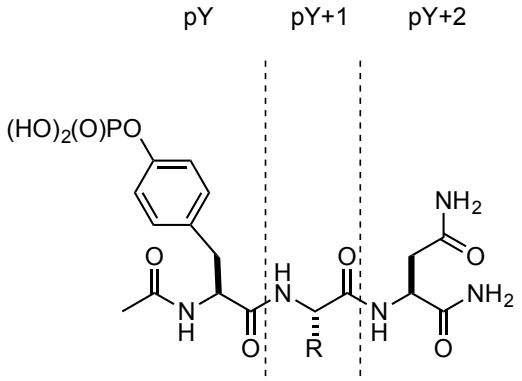
1.1.2 USING CONFORMATIONAL CONSTRAINTS TO EVALUATE THE EFFECTS OF INTERNAL STRAIN IN THE BOUND FORM OF A LIGAND

In 2013, the Martin group studied the effects increasing the length of an alkyl chain at the pY+1 residue of Ac-pYXN-NH_2 had on binding with Grb2 SH2.[17] It was already known that $\Delta G°$ of binding linearly correlated with cycloalkane size at the pY+1 region due to increasingly favorable $\Delta H°$ of binding.[17,26] Interestingly, no such trend was observed with the linear alkyl chain containing ligands **1.22**-**1.25** (Table 1.3).

Table 1.3: Thermodynamic Data for complex formation with Grb2 SH2.



1.17: n = 1
1.18: n = 2
1.19: n = 3
1.20: n = 4

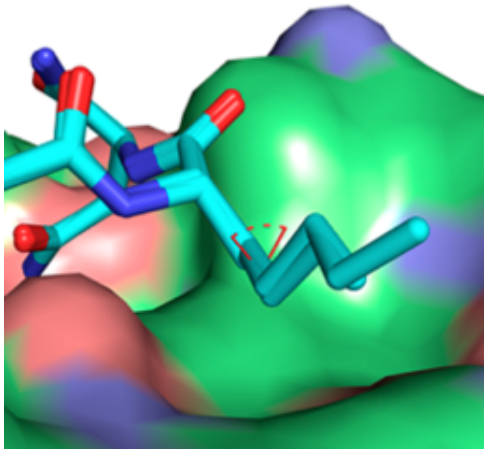


1.22: R = ethyl
1.23: R = *n*-propyl
1.24: R = *n*-butyl
1.25: R = *n*-pentyl

Ligand	K_a (× 10^5 M^{-1})	ΔG° (kcal mol^{-1})	ΔH° (kcal mol^{-1})	-TΔS° (kcal mol^{-1})
1.17	1.6 ± 0.1	-7.1 ± 0.1	-3.3 ± 0.3	-3.8 ± 0.1
1.22	8.6 ± 0.2	-8.1 ± 0.1	-6.8 ± 0.5	-1.3 ± 0.1
1.18	4.3 ± 0.4	-7.7 ± 0.1	-5.4 ± 0.3	-2.3 ± 0.2
1.23	7.6 ± 1.0	-8.0 ± 0.1	-6.7 ± 0.5	-1.3 ± 0.3
1.19	16.1 ± 1.1	-8.5 ± 0.1	-6.3 ± 0.4	-2.2 ± 0.2
1.24	8.4 ± 0.6	-8.1 ± 0.1	-7.3 ± 0.3	-0.8 ± 0.2
1.20	69.6 ± 12.0	-9.3 ± 0.1	-8.5 ± 0.4	-0.8 ± 0.4
1.25	7.8 ± 0.6	-8.0 ± 0.1	-7.2 ± 0.3	-0.8 ± 0.2

Unlike **1.17**-**1.20**, the addition of methylene groups in ligands **1.22**-**1.25** does not correlate with any thermodynamic parameter. Structural analysis of Grb2 SH2 complexes with compounds **1.22** through **1.25** revealed a gauche conformation along the $C_{ß}$-C_{γ} bond of the alkyl side chain in the bound form of ligands **1.23**-**1.25** (Figure 1.8). Presumably, this energetically unfavorable conformation present in the bound form of the ligand is having undesirable effects on the $\Delta\Delta G°$ of binding.

Figure 1.8: Structural Data for Grb2 SH2 complexes with **1.22**-**1.25**

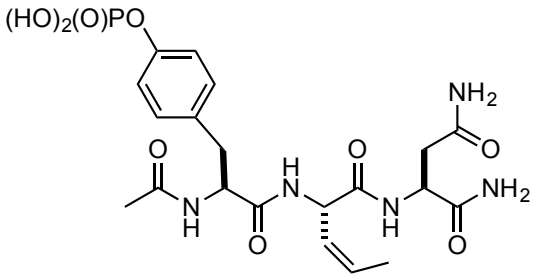


This observation presents a unique opportunity to test if relieving torsional strain in the bound form of a ligand will enhance binding affinity. This is an important question because ligands rarely bind to proteins in their lowest energy conformation.[27] Towards testing the effects of this torsional strain, ligand **1.26** was prepared (Figure 1.9a). This ligand contains a (*Z*)-propenyl side chain that was expected to remove torsional strain in the bound state while also removing a degree of rotational freedom prior to binding. Unfortunately, **1.26** bound with a thermodynamic signature that was identical to **1.23** within experimental error. Structural analysis of the Grb2 SH2–**1.26** complex revealed

that the side chain of **1.26** made fewer van der Waals (vdW) contacts to the protein than **1.23** (Figure 1.9b). This suggests the (*Z*)-propenyl side chain weakened the dispersive interactions between the ligand and Grb2 SH2.

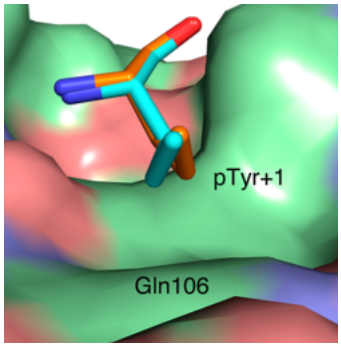
Figure 1.9: (a) Constrained ligand 1.26 and (b) overlay of **1.26** (dark grey) and **1.23** (light grey) bound to the Grb2 SH2 domain.

a)



1.26

b)

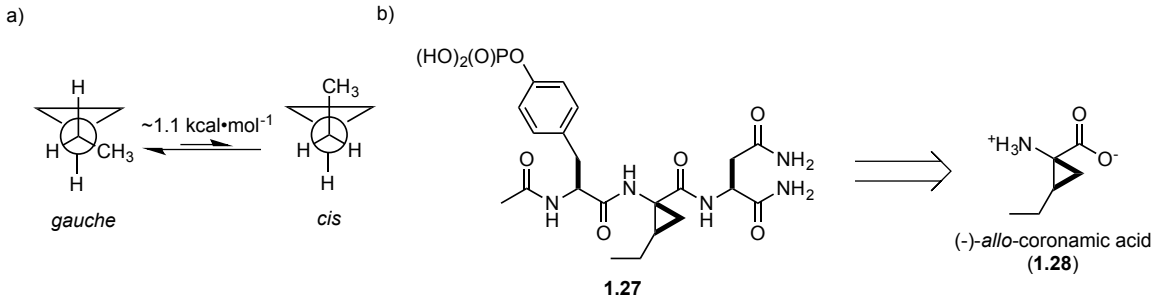


As the *Z*-alkene apparently had not been an effective mimic of the free *n*-propyl side chain, it was decided that using a more sophisticated preorganizational constraint would be necessary. We therefore set out to find functionalities that would stabilize the gauche conformation upon binding without decreasing the number of vdW contacts in the complex.

A unique solution to this quandary was found in ethylcyclopropane, which has been experimentally determined to exist in the *gauche* conformation under standard conditions (Figure 1.10a).[28,29] Thus, installation of a cyclopropane into the alkyl chain at the α carbon of **1.23** to give **1.27** seems to be a viable method for lowering the enthalpic penalty of the gauche conformation in the bound form. Preparation of **1.27** can be

accomplished through incorporation of (-)-*allo*-coronamic acid (Aca) into the ligand (Figure 1.10b).

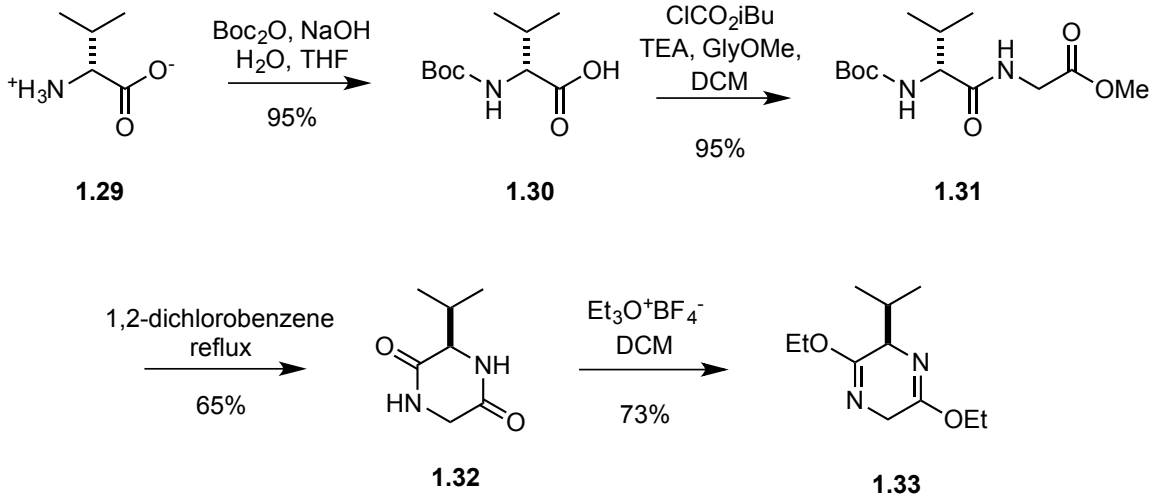
Figure 1.10: (a) Newman projection of gauche and cis ethyl cyclopropane. (b) Proposed compound **1.27** and required (-)-allo-coronamic acid (**1.28**)



1.2 Results and Discussion

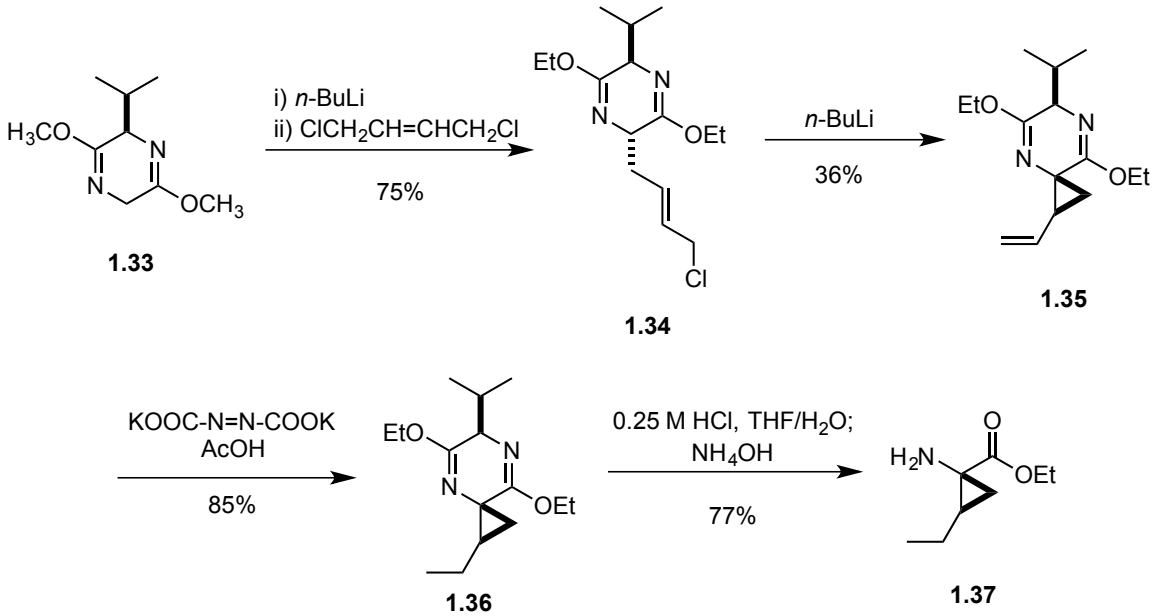
In 1991 Schöllkopf et al. reported the synthesis of (+)-allo-coronamic acid via chiral bislactim ether **1.33**.[30] While Schöllkopf's auxiliary is commercially available, the desired enantiomer is quite expensive. Thus, the chiral auxiliary was synthesized from D-valine (Scheme 1.1).[31] Protection of D-valine followed by coupling with glycine methyl ester provided **1.31** in near quantitative yield. Heating the protected dipeptide in 1,2-dichlorobenzene at 180 °C provided diketopiperazine **1.32** in 65% yield. Ethylation of **1.32** furnished Schollkopf's auxiliary (**1.33**) as a colorless liquid in 43% overall yield.

Scheme 1.1: Synthesis of Schöllkopf's auxiliary (**1.33**).

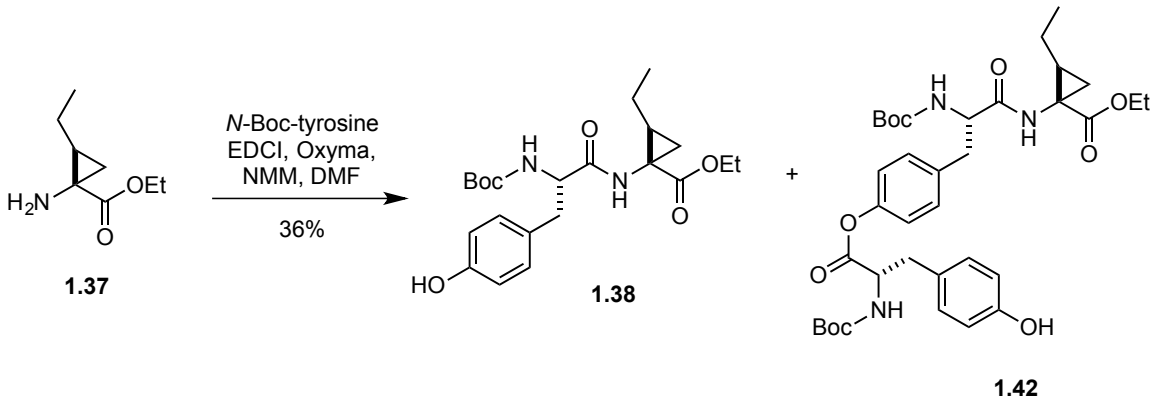


Alkylation of the glycine α-carbon of **1.33** with 1,4-dichlorobut-2-ene provided compound **1.34** in 75% yield. Upon addition of a second equivalent of *n*-BuLi, spirocycle **1.35** was formed via intramolecular S_N2' displacement of chloride ion as a separable mixture of diastereomers (dr = 4:1, determined by ^1H NMR). Many attempts were made to increase the dr of this cyclization reaction by changing the strength and steric bulk of the base, as well as using less coordinating solvents, but no increase in dr was observed. Hydrogenation of alkene **1.35** gave spirocycle **1.36**, which upon hydrolysis provided amino ester **1.37** in an overall 7% yield from D-valine (Scheme 1.2)

Scheme 1.2: Synthetic route to (-)-(2S, 3R)-allo-coronamic ethyl ester (**1.37**), analogous to that of Schöllkopf et al.



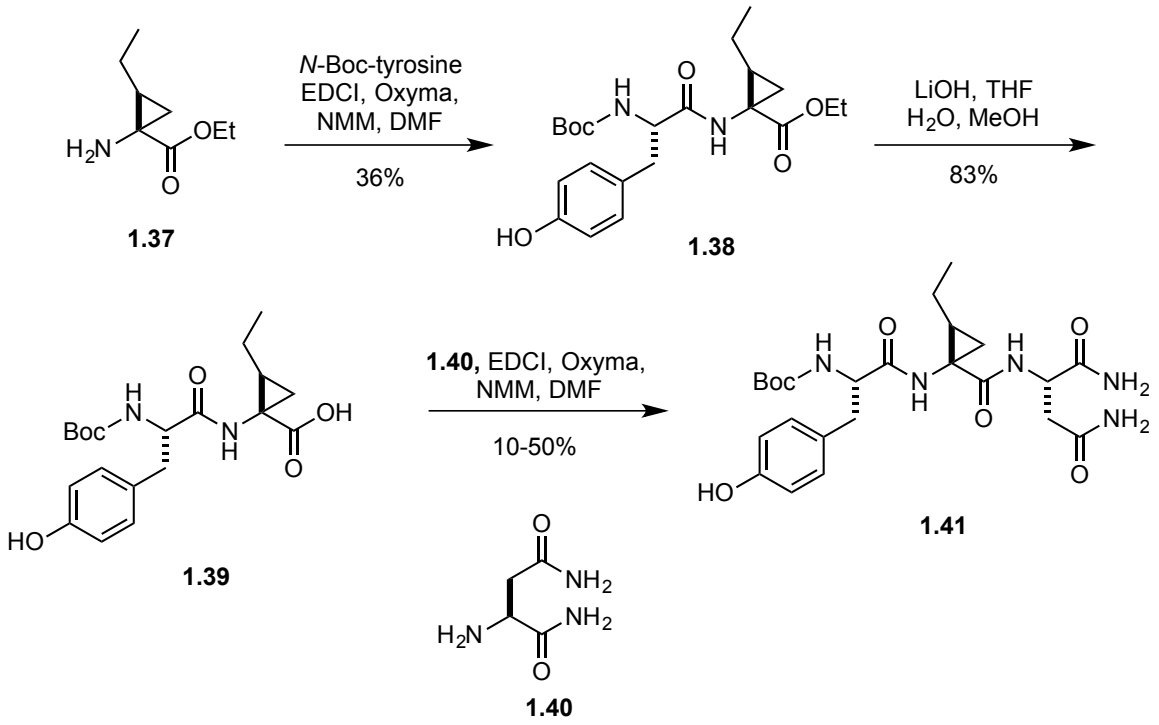
Amino ester **1.37** was then coupled to N-Boc-tyrosine to give protected dipeptide **1.38** in 36% yield. LC/MS data for coupling of *allo*-coronamic ethyl ester with *N*-Boc-tyrosine revealed a significant esterified byproduct (Equation 1.1).



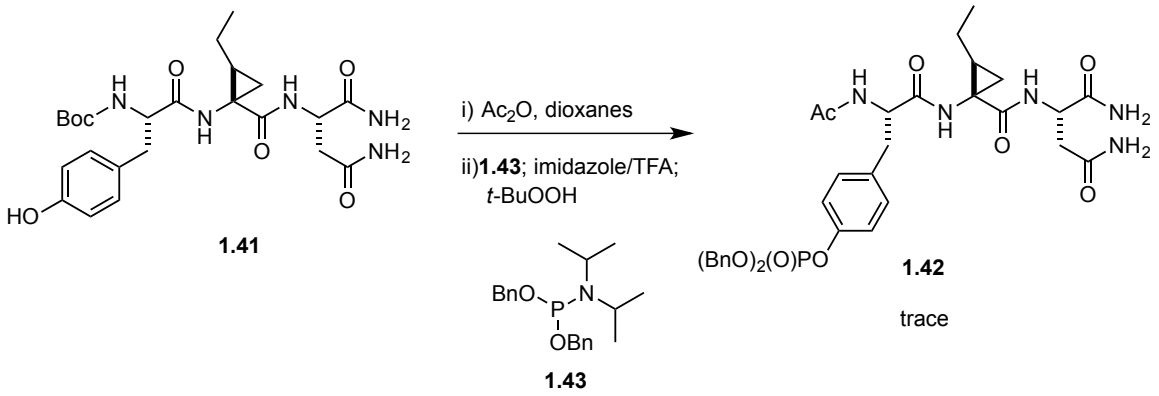
(1.1)

Saponification of ethyl ester **1.38** followed by coupling with asparagine amide gave tripeptide **1.40** in a combined 40% yield (Scheme 1.3)

Scheme 1.3: Initial attempt to synthesize ligand **1.27**.



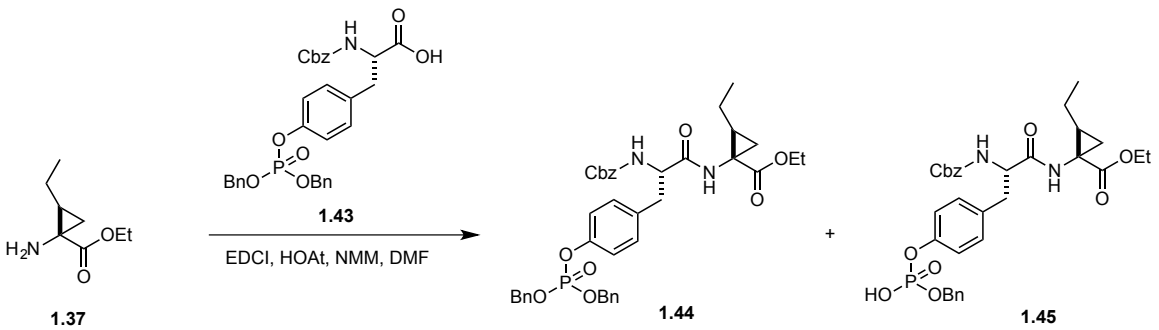
This tripeptide was deprotected and acetylated in 50% yield to give Ac-Tyr-Aca-Asn-NH_2, but purification of this compound was challenging due to the low solubility of the tripeptide in organic solvents. While LC/MS analysis showed attempts to phosphorylate this material without purification produced the desired product, the procedure used was too low yielding to isolate any useful amount of material.[32] (Equation 1.2)



(1.2)

Optimizing the phosphorylation reaction at this late stage of the synthesis was not practical due to low yields in the peptide coupling and deprotection steps, so the approach to ligand **1.27** was modified.

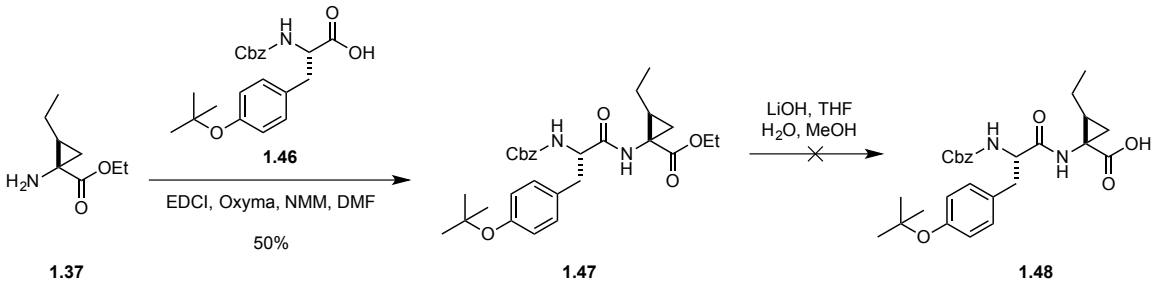
In order to stop the formation of esterified byproduct **1.42**, phosphorylated tyrosine **1.43** was used as the initial coupling partner. Unfortunately, peptide coupling additives such as HOBt, HOAt, and Oxyma deprotected the phosphate moiety, leading to low yields of desired compound **1.45** (Equation 1.3).



(1.3)

While it was possible to purify compound **44**, the phosphate moiety proved to be unstable under basic conditions, making saponification of the ethyl ester low yielding, so a *tert*-butyl ether was used to protect the tyrosine sidechain in the initial coupling step.

While the *tert*-butyl ether allowed coupling of compound **37** with tyrosine in 50% yield, the saponification of ethyl ether **45** was still sluggish and low yielding (Equation 1.4).



(1.4)

At this point it was decided the synthesis was not optimizable beyond the yields in Scheme 3, and the sequence would simply need to be performed on larger scale in order to access ligand **1.27**. However, constraints on reagent availability made producing more cyclopropane prohibitively time consuming, and the project was put on hold.

1.3 Summary

In summary, *allo*-coronamic acid was synthesized *via* a route reported by Schöllkopf *et al*.. Although the synthesis of *allo*-coronamic acid was initially thought to be the most complex portion of the synthesis of tripeptide **1.27**, we found peptide couplings involving this α,α-disubstituted amino acid to be very low yielding, due in part to side reactions that were encouraged by the steric bulk at the α carbon of **1.37**. Additionally, the liability of the dibenzyl phosphate group under peptide coupling conditions, combined with the large number of steps required to synthesize **1.27**, made the synthesis more impractical than initially thought. Efforts to synthesize ligand **1.27** are still ongoing in the Martin lab.

CHAPTER 2: PREPARING A LIBRARY OF 2-ARYL PIPERIDINES VIA IMINIUM ION CASCADE REACTIONS

2.1 Introduction

The preparation of large collections of organic compounds for biological screening campaigns has been a strategy on the forefront of drug discovery for decades. The strategy originally revolved around synthesizing a vast number of compounds by mixing and matching a few readily available building blocks in the hopes that one or more of the resulting compounds would display biological activity and lead the way to a new drug candidate. This technique did not lead to the number of new drug leads expected, likely because randomly generated libraries tend to lack the structural diversity necessary to efficiently probe chemical space.[33]

Newer approaches to library synthesis have revitalized this strategy, resulting in higher hit rates and more new lead compounds entering clinical trials per library created.[34] One such approach is biology-oriented synthesis (BIOS).[35] The primary factor separating BIOS from the synthesis of libraries comprised of random components is a focus on targeting libraries of compounds that are structurally similar to natural products. Because natural products are synthesized by binding to different enzymes in a series of chemical transformations, the subunits that make up natural products are frequently thought of as being biologically pre-validated. Thus, the BIOS strategy aims to guarantee that the regions of chemical space explored in a molecular library synthesis will at least be biologically relevant.

Another approach that has gained traction is diversity-oriented synthesis (DOS).[36] The primary goal of DOS is simply to maximize the complexity of the molecules in a library. Increasing "complexity" is generally achieved by increasing the level of saturation and the number of stereogenic centers in a molecule. Thus, the key to DOS is to use simple, readily available building blocks, which offer opportunities to increase complexity with simple inter- and intramolecular reactions down the line. Ideally, researchers avoid occupying "dense" chemical space, which plagued traditional combinatorial chemistry efforts, by pursuing strategies that access multiple different scaffolds.

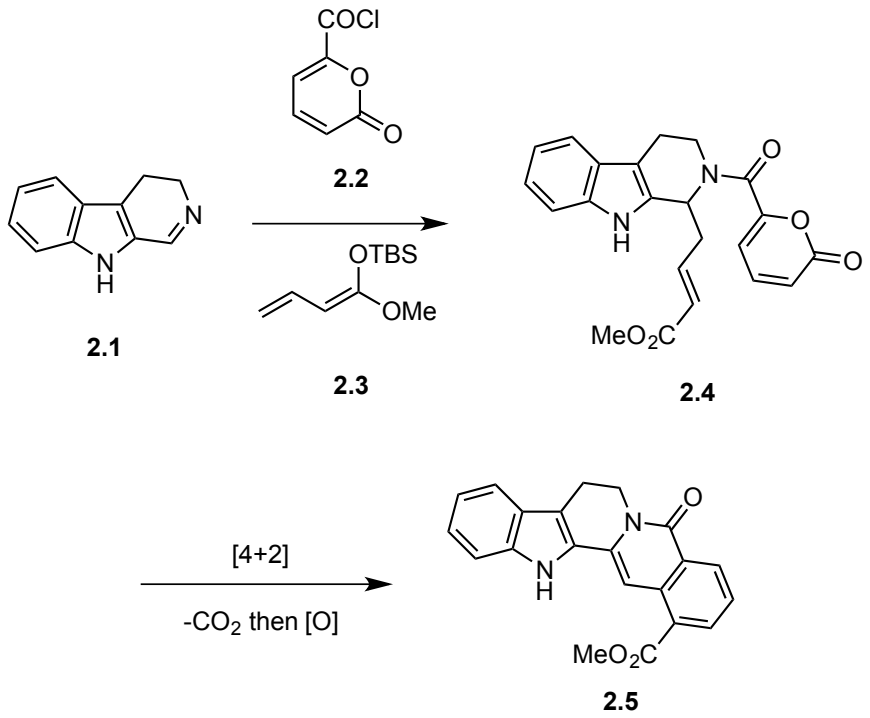
In order to establish structural complexity in only a few steps, diversity oriented synthesis frequently employs multi-component reactions (MCRs).[37-39] These reactions combine three or more components in a single step, which increases the level of complexity attainable in a single chemical transformation. By utilizing components with high functional group tolerance, we can create opportunities for further scaffold diversification after the MCR. Utilizing this strategy, MCRs allow quick access to collections of highly diverse scaffolds, each being derivatizable in unique ways.[40-42] Related to the MCR is the multi-component assembly process (MCAP). While an MCR constitutes a reaction with three or more reagents combined simultaneously to give one product, an MCAP uses three or more reagents in a specific sequence to form a new, higher complexity structure. [38,43,44] Together, the MCR and MCAP strategies represent the most efficient way to prepare molecular libraries.

The Martin group has had a longstanding interest in the synthesis of alkaloid natural products.[44] Through this interest, we have developed a multi-component assembly process that has allowed access to several related natural products. Extending this methodology from natural product synthesis to DOS has led to the synthesis of a variety of drug-like scaffolds that are highly diversifiable. Most notably, this methodology has lead to the synthesis of subtype selective sigma receptor ligands, which have shown significant promise as potential tool compounds that may be used to identify the sigma 2 receptor. By judicious manipulations of the MCAP methodology, we hope to thoroughly probe regions of chemical space that have been identified as regions of great promise for tool compounds for biological interrogation, and potential therapeutics.

2.1.1 Applications of MCAPs for Access to Alkaloid Natural Products

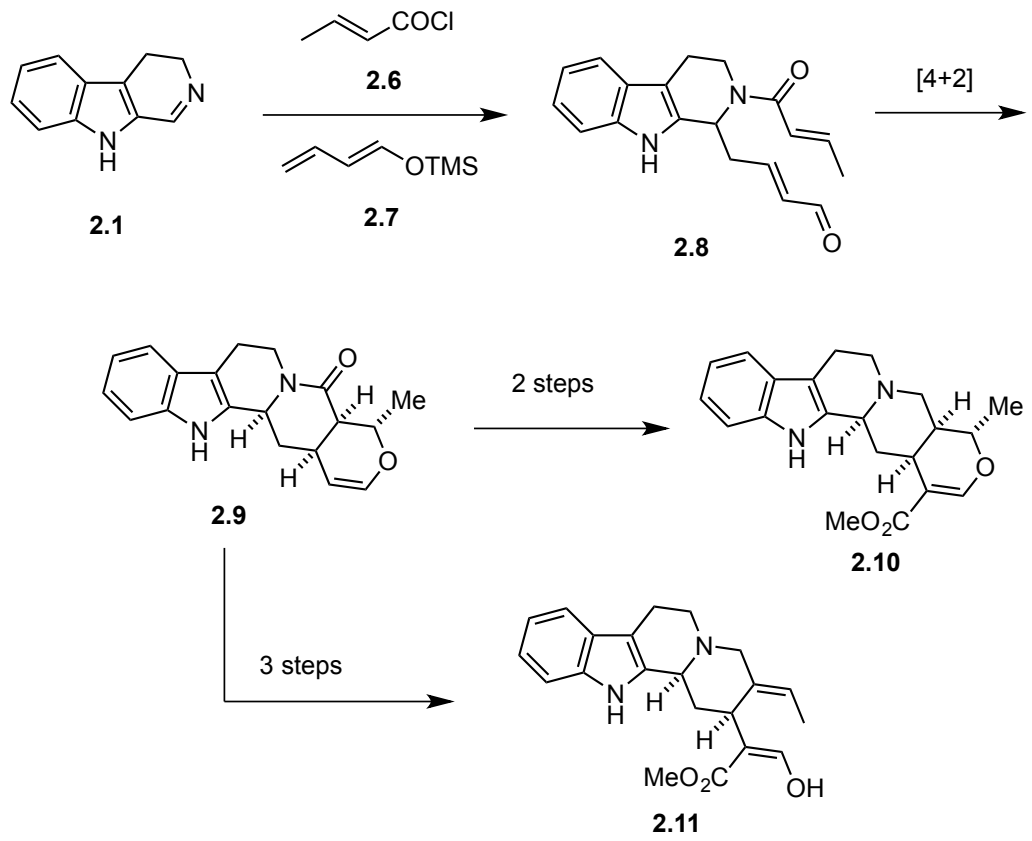
In the late 1980's, the Martin group utilized an MCAP as part of a unified strategy to access indole alkaloids of the yohimboid, heteroyohimboid, and corynantheoid classes.[45,46] In the synthesis of oxogambirtannine (**2.5**), known dihydro-β-carboline **2.1** was treated sequentially with acid chloride **2.2** and vinyl ketene acetal **2.3** in a three-component assembly process that provided intramolecular Diels-Alder substrate **2.4**. The Diels-Alder reaction was carried out in the presence of benzoquinone to promote oxidation after the spontaneous extrusion of CO_2 to yield oxogambirtannine (**53**) in only three steps (Scheme 2.1).

Scheme 2.1: The Martin group's total synthesis of oxogambirtannine (**2.5**)



The efficiency of this three-component assembly process was further exemplified for access to related indole alkaloids tetrahydroalstonine (**2.10**) and geissoschizine (**2.11**). This divergent synthesis utilized a similar three-component assembly process followed by an intramolecular hetero-Diels-Alder reaction to give common intermediate **2.9**, which was elaborated to tetrahydroalstonine (**2.10**) in two steps and geissoschizine (**2.11**) in three steps (Scheme 2.2).

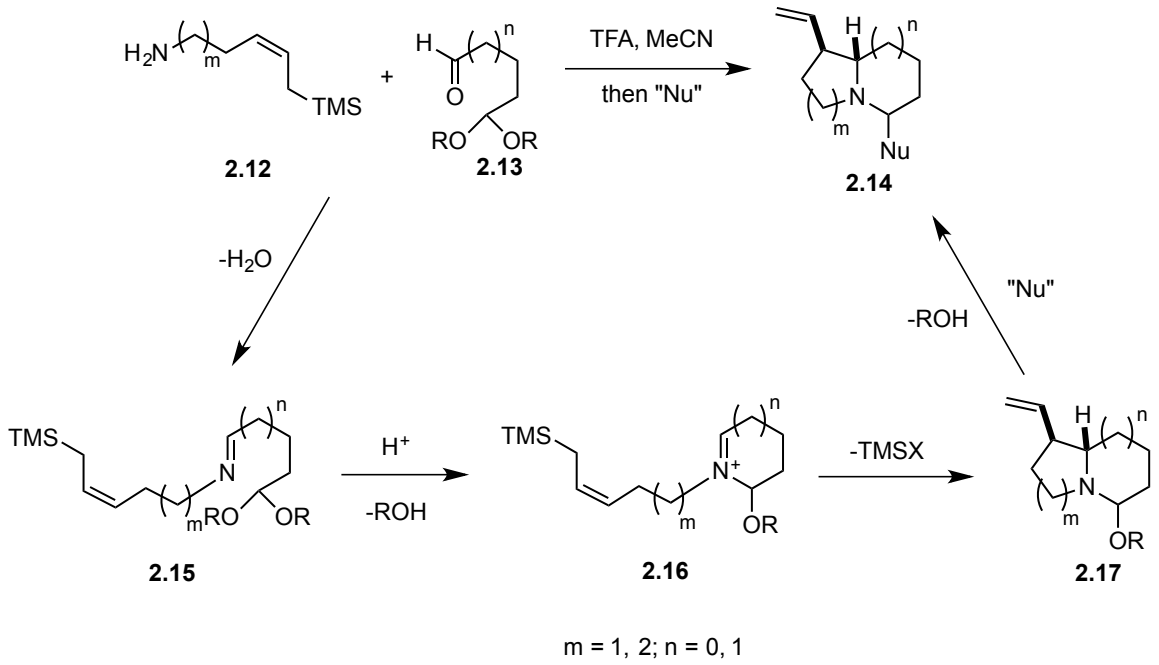
Scheme 2.2: The Martin group's total syntheses of tetrahydroalstonine (**2.10**) and geissoschizine (**2.11**).



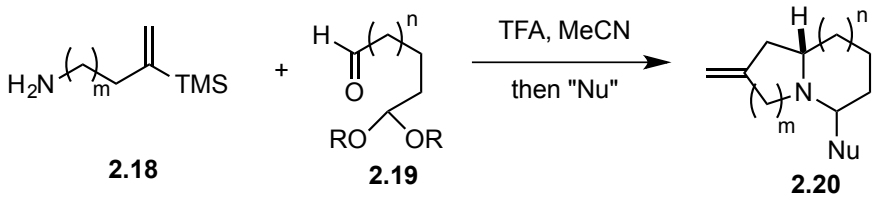
Recognizing the power of the three-component assembly process for quickly synthesizing alkaloid natural products, the Martin group became interested in probing the full scope of this strategy.[44,47-49] As a result of these efforts, the Martin group published a cascade iminium ion cyclization approach to the synthesis of quinolizidines, including natural products (±)-epilupinine and (-)-epimyrtine.[50] The sequence of reactions commenced with the condensation of amino allylsilane **2.12** with monoprotected dialdehyde **2.13** to generate imine **2.15**. Upon addition of acid, **2.15** cyclized to give iminium ion **2.16**, which underwent nucleophilic attack by the allylsilane moiety to give *N*,*O*-acetal **2.17**. Ionization of the alkoxy group in **2.17** would produce another iminium ion that could be

trapped by many different nucleophiles to provide a number of different fused bicyclic amines of the general type **2.14** (Scheme 2.3).

Scheme 2.3: Iminium ion cyclization cascade



A simple variation of the amino allylsilane from the linear analog **2.12** to the branched compound **2.15** offers additional entry points to these bicyclic systems of the general type **2.20** (Equation 2.1).

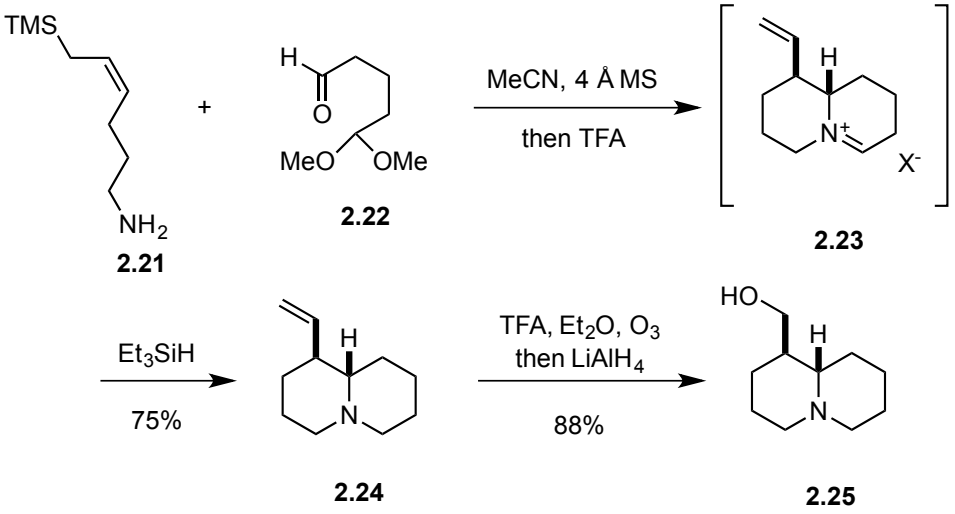


(2.1)

While the individual steps outlined in Scheme 6 were known, they had never been combined in a cascade such as the sequence here.[51,52] Thus, this work offered a

significantly higher increase in structural complexity in a single operation than any of the precedented reactions that made up its parts. The total syntheses of (±)-epilupinine (**2.25**) and (–)-epimyrtine (**2.24**) showcased the iminium ion cascade reactions by quickly accessing fused bicyclic amines. In the total synthesis of (±)-epilupinine (**2.25**), amino allylsilane **2.21** was condensed with the monoprotected dialdehyde **2.22**. The resulting imine was then treated with trifluoroacetic acid (TFA) without being isolated, initiating the two acid catalyzed cyclizations that generated the iminium ion **2.23**. Reduction of **2.23** with triethylsilane gave **2.24** as a single diastereomer in 75% yield from **2.21**. Ozonolysis of the trifluoroacetate salt of **2.24** followed by reduction of the intermediate ozonide provided (±)-epilupinine (**2.25)** in 88% yield (Scheme 2.4).

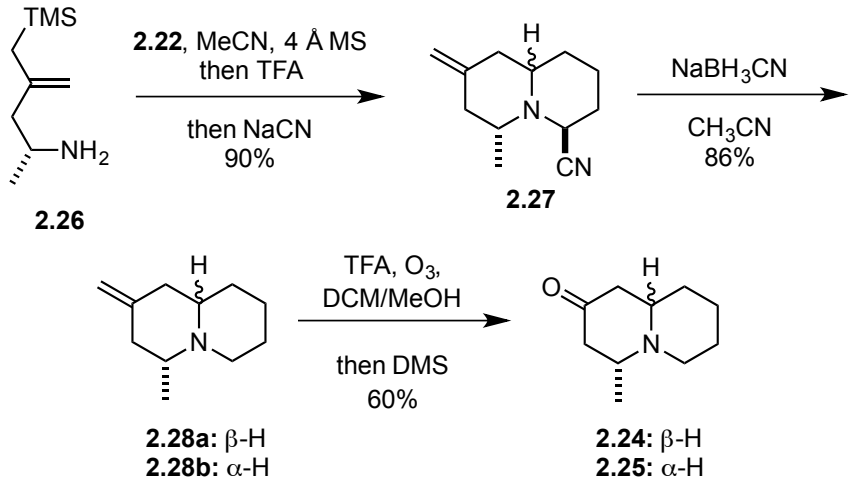
Scheme 2.4: Total Synthesis of (±)-Epilupinine (**2.25**)



The total synthesis of (–)-epimyrtine (**2.24**) also proceeded effectively utilizing the strategy outlined in Equation 4. The synthesis began with the condensation of chiral amino allylsilane **2.26** with aldehyde **2.22** to give an imine that was treated sequentially

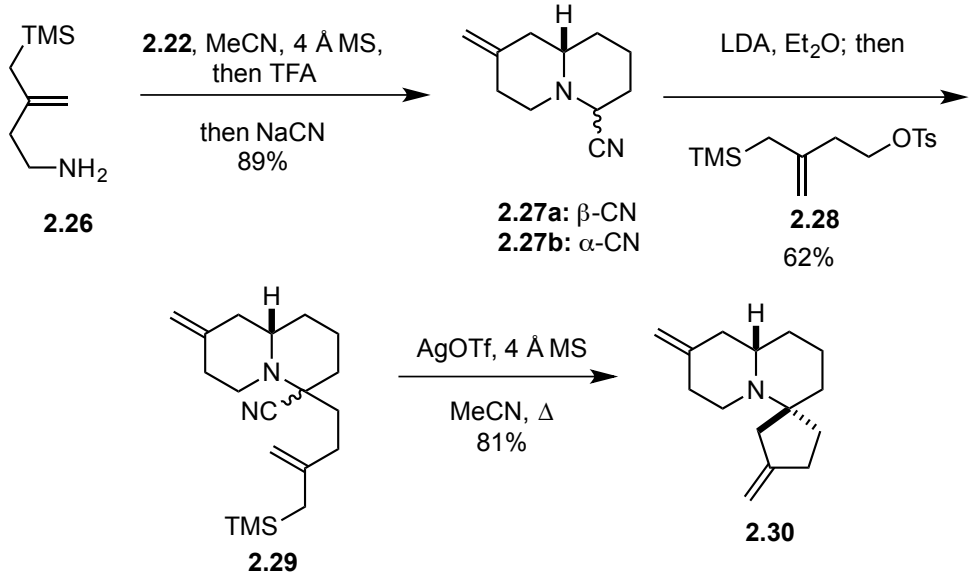
with trifluoroacetic acid and sodium cyanide to give quinolizidine **2.27** in 90% yield. Reduction of the aminonitrile moiety of **2.27** yielded an epimeric mixture (95:5) of quinolizidines **2.28a,b**. Ozonolysis of the trifluoroacetate salt of **2.28a,b** yielded an inseparable mixture (95:5) of (–)-epimyrtine (**2.24**) and (+)-myrtine (**2.25**) (Scheme 2.5).

Scheme 2.5: Total Synthesis of (–)-Epimyrtine (**2.24**)



The opportunity to trap iminium ions resulting from the collapse of the *N*,*O*-acetal in intermediates of the general type **2.17** presents an exciting opportunity to further build complexity into the scaffolds accessed via this iminium ion cascade. This concept was brought to fruition with the synthesis of spirocyclic tricycle **2.30**. Amino allylsilane **2.26** was condensed with aldehyde **2.22**, where upon trifluoroacetic acid and sodium cyanide were added sequentially to furnish an epimeric mixture (88:12) of amino nitriles **2.27a,b** in 89% yield. Quantitative deprotonation of **2.27a,b** followed by addition of tosylate **2.28** provided **2.29** in 62% yield. Finally, treatment of **2.29** with AgOTf formed an iminium ion, that was trapped by an intramolecular cyclization of the allylsilane to provide the spirocyclic tricycle **2.30** in 81% yield (Scheme 2.6).

Scheme 2.6: Use of Amino Nitrile to Access a Spirocyclic Tricycle



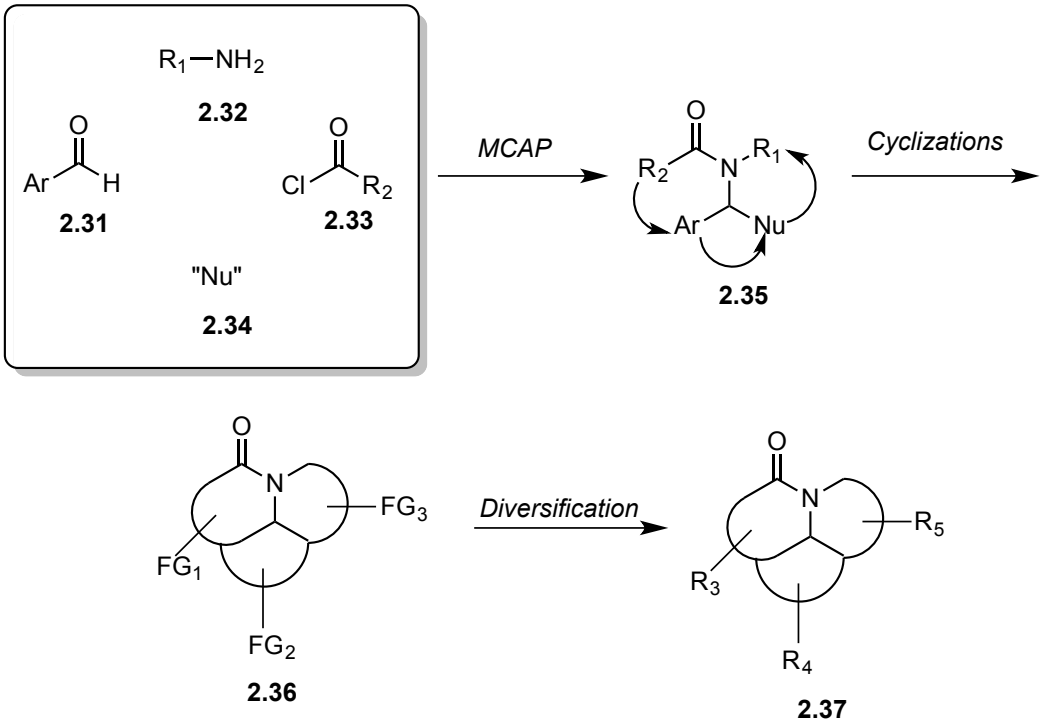
In summary, the Martin group's interest in the synthesis of natural products has lead to the discovery of several MCAPs and related reactions, each lending themselves to the preparation of a unique array of biologically pre-validated scaffolds. Most importantly, these syntheses demonstrate the impressive amount of molecular complexity attainable in a single, modular transformation *via* MCAP strategies.

2.1.2 Applications of MCAPs for the Synthesis of Molecular Libraries

The success of the MCAP methodology for accessing a series of structurally related natural products suggested the technique could be applied to the concise synthesis of a library of small molecules. Such a strategy would combine aspects of BIOS and DOS to generate multiple large collections of diverse compounds containing components of biologically pre-validated structures. In a four-component assembly process, we

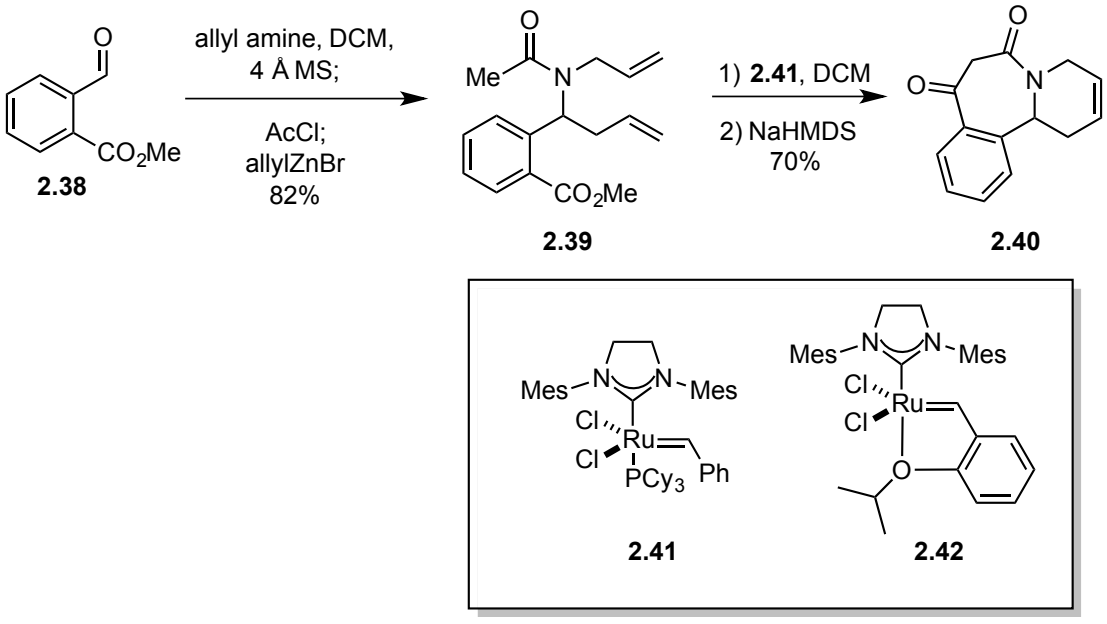
envisioned an aryl aldehyde **2.31** reacting first with an amine **2.32** to give an intermediate imine that then reacts with an acylating or alkylating agent **2.33** followed by a nucleophile **2.34** to provide aryl aminomethyl derivative **2.35**. It is important to note that the aryl aminomethyl motif accessed by this MCAP is very common in natural products and other medicinally relevant small molecules.[53] Including additional functional handles in the original four components of the MCAP allows **2.35** to undergo various intramolecular cyclization reactions to access even more complex scaffolds of the type **2.36**. Even further diversification of this variety of scaffolds via orthogonal functional handles that remain after the series of intramolecular cyclizations provides large collections of diverse compounds **2.37** (Scheme 2.7).

Scheme 2.7: General overview of the original Martin group MCAP strategy



Since the goal of this project was to quickly access diverse libraries of biologically pre-validated scaffolds, we turned our attention towards the application of this methodology to the synthesis of piperidine and homopiperdine ring systems, which are well represented subunits of both biologically active natural products and pharmaceutical agents.[39,54,55] The potential applications of this idea were demonstrated by condensing aryl aldehyde **2.38** with allylamine, followed by sequential treatment with acetyl chloride and allylzinc bromide to give the aryl aminomethyl moiety **2.39** in 82% yield. Ring closing metathesis of diene **2.39** with Grubb's II catalyst **2.41** and subsequent Dieckmann cyclization afforded benzazepine **2.40** in 70% yield (Scheme 2.8).

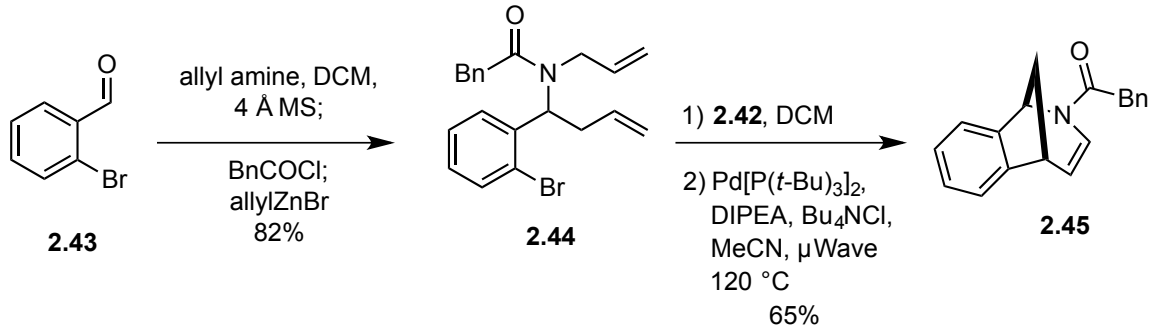
Scheme 2.8: MCAP/RCM/Dieckmann Cyclization Sequence



The versatility of the strategy was further demonstrated by showing how slight modifications of the MCAP reaction could allow access to totally different molecular

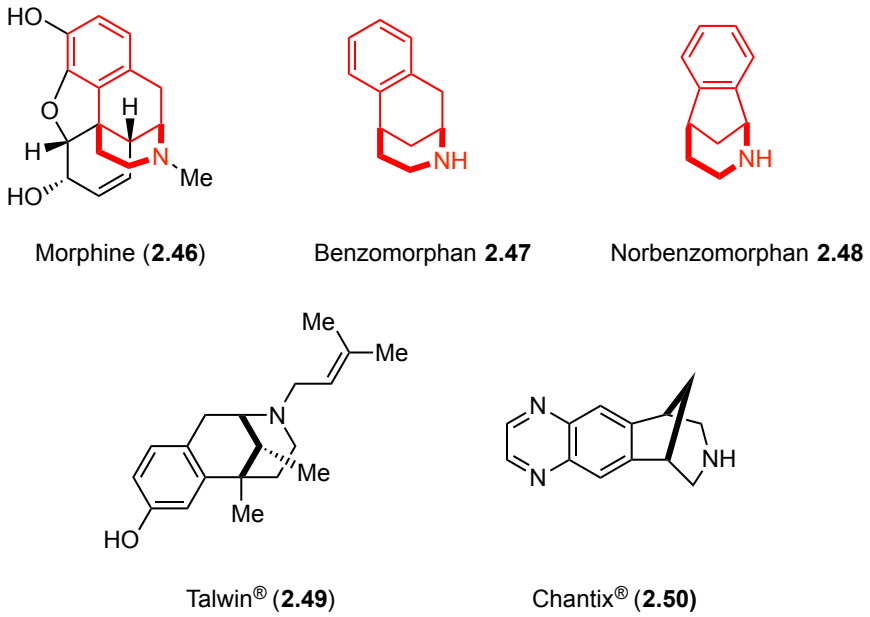
topographies. In this case, 2-bromobenzaldehyde (**2.43**) was condensed with allylamine, and the resultant imine was sequentially treated with phenylacetyl chloride and allylzinc bromide to give diene **2.44** in 85% yield. Ring closing metathesis with Hoveyda-Grubb's II **2.42** followed by an intramolecular Heck reaction afforded norbenzomorphan **2.45** in 65% yield (Scheme 2.9)

Scheme 2.9: MCAP/RCM/Intramolecular Heck Sequence



Compound **2.45** is a member of the norbenzomorphan structural family. The norbenzomorphan structure **2.48** was first synthesized in the 1960's and is related to benzomorphan (**2.47**), a structural subunit of morphine (**2.46**). Derivatives of norbenzomorphan have been found to have a wide range of therapeutically relevant activities, and structures closely related to norbenzomorphan **2.48** have been incorporated into the FDA approved psychoactive drugs Talwin® (**2.49**) and Chantix® (**2.50**) (Figure 2.1).[56,57]

Figure 2.1: The Norbenzomorphan Subunit and Related Structures Found in Morphine (**2.46**) and Psychoactive Drugs Talwin® (**2.49**) and Chantix® (**2.50**).

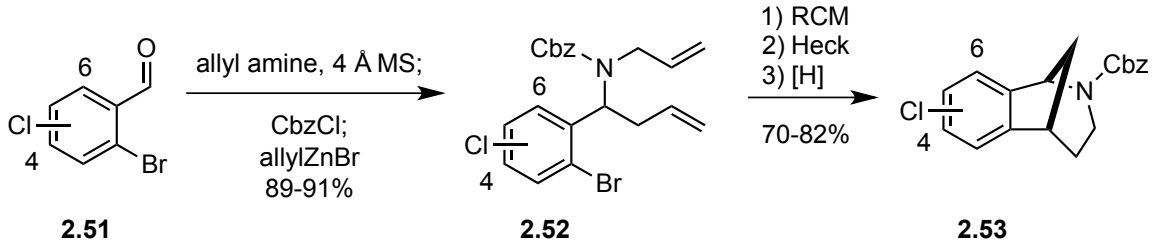


Morphine (**2.46**) Benzomorphan **2.47** Norbenzomorphan **2.48**

Talwin® (**2.49**) Chantix® (**2.50**)

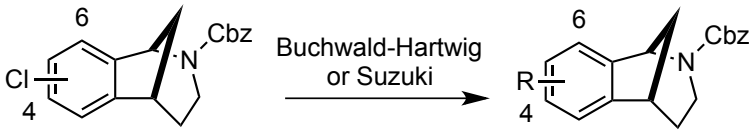
Considering the presence of the norbenzomorphan subunit and closely related chemical structures in biologically active compounds,[58,59] we decided to take advantage of the quick access to this chemical space that our MCAP offered by creating a library of derivatives based off the general structure **2.48**. The strategy proved to be quite useful, whereby 2,4-, 2,5-, and 2,6-dihalobenzaldehydes of the general type **2.51** were treated with allylamine, benzyl chloroformate, and allylzinc bromide to give dienes of the general type **2.52**. These dienes were cyclized by sequential ring closing metathesis and intramolecular Heck reactions, followed by reduction of the remaining double bond to give saturated norbenzomorphans of the general type **2.53** (Scheme 2.10).[56]

Scheme 2.10: Approach to a Diverse Library of Norbenzomorphans



2.51 **2.52** **2.53**

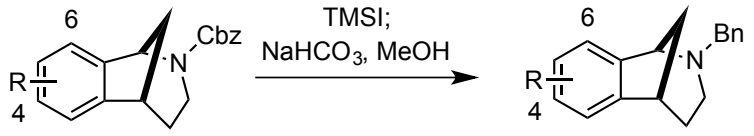
The norbenzomorphans **2.45** were then derivatized via cross-coupling the aryl chloride moiety with various amines and boronic acids to give substituted norbenzomorphans of the general type **2.55** (Equation 2.2).



2.54 **2.55**

R = aryl or amino (2.2)

Notably, norbenzomorphans **2.54** and **2.55** could be transformed to the tertiary benzylamine **2.56** in a single step *via* deprotection with TMSI, followed by treatment with base.[60] Quaternization was never observed when amines were benzylated by this method (Equation 2.3).



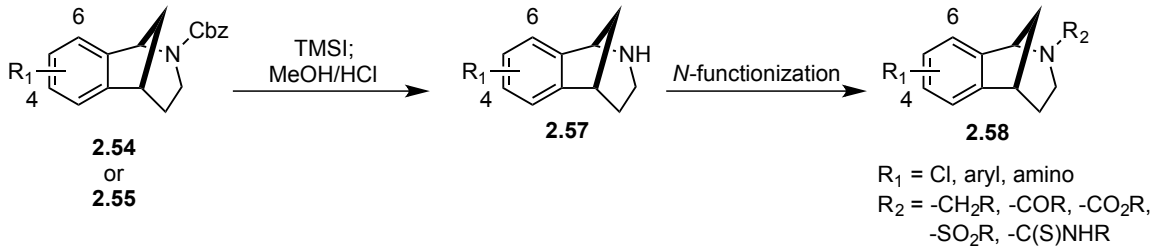
2.54
or
2.55

2.56

R = Cl, aryl, amino (2.3)

Treatment of norbenzomorphans of the general type **2.54** or **2.55** with TMSI followed by an acidic workup afforded secondary amines **2.57** that were derivatized into a variety of *N*-substituted norbenzomorphans of the general type **2.58** (Scheme 2.11).

Scheme 2.11: Amine Refunctionalization for the Assembly of a Library of Norbenzomorphans



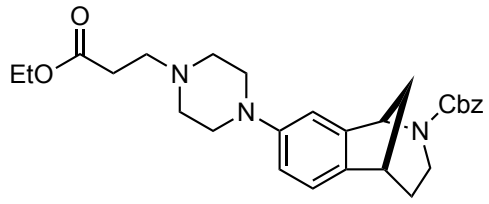
The NIH's Molecular Library Probe Production Center Network (MLPCN), the National Institute of Mental Health's (NIMH) Psychoactive Drug Screening Program (PDSP), and Eli Lilly's OPEN Innovation Drug Discovery (OIDD) Program, screened the initial library of 124 compounds for biological activity.[56] While several biologically active compounds were identified, the most interesting compounds were those with high affinity and subtype selectivity for sigma receptors,[61] an activity that has not previously been associated with norbenzomorphans.[57]

Sigma receptors are a distinct class of non-G protein-coupled receptor (GPCR) receptors that are involved in a variety of critical cellular processes, including regulation of ion channel concentration, stabilization of cell-surface receptors, and induction of apoptosis.[62] Two receptor subtypes, the sigma 1 receptor (Sig1R), and the sigma 2 receptor (Sig2R), have been identified. While Sig1R has been cloned, sequenced, and crystallized,[63] Sig2R has only been characterized by radioligand binding assays. In spite of this, Sig2R has been implicated in a number of disease states.[64,65] For example, Sig2R is overexpressed in cancer cells, making the protein an attractive target for cancer diagnostics and therapeutics. This interest is expanding into the realm of

chemotherapeutics because Sig2R agonists have been shown to induce cell death in a number of cancer cell lines.

While many compounds have high affinity for sigma receptors, there are not many tool compounds available that selectively target Sig2R over Sig1R. Such a compound is important for efforts to isolate, sequence, and eventually crystallize Sig2R. It is noteworthy then, that the further diversification of the original 124-member library of substituted norbenzomorphans yielded compound **2.59**, which displays a 574-fold preference for Sig2R over Sig1R (Figure 2.2).[57] Efforts to utilize the remarkable level of selectivity of compounds related to **2.59** as tools for the isolation and characterization of Sig2R are underway.

Figure 2.2: A Norbenzomorphan with High Selectivity for the Sigma 2 Receptor



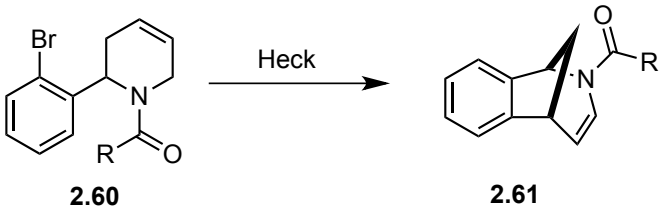
2.59

Sig1R K_i = 9294 nM
Sig2R K_i = 16.2 nM

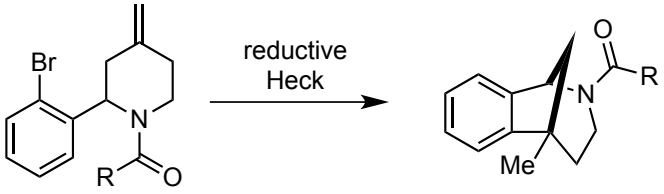
Sig1R K_i/Sig2R K_i = 574

The success of our library of norbenzomorphans made us eager to find related chemical spaces that MCAP methodology would allow us to access. For this reason, piperidines containing exocyclic double bonds of the general type **2.62** caught our interest. While an intramolecular Heck reaction using compounds of the general type **2.60** gives access to norbenzomorphans of the general type **2.61** (Equation 2.4), a reductive

intramolecular Heck reaction using compounds of the general type **2.62** would offer access to norbenzomorphans of the general type **2.63** (Equation 2.5).



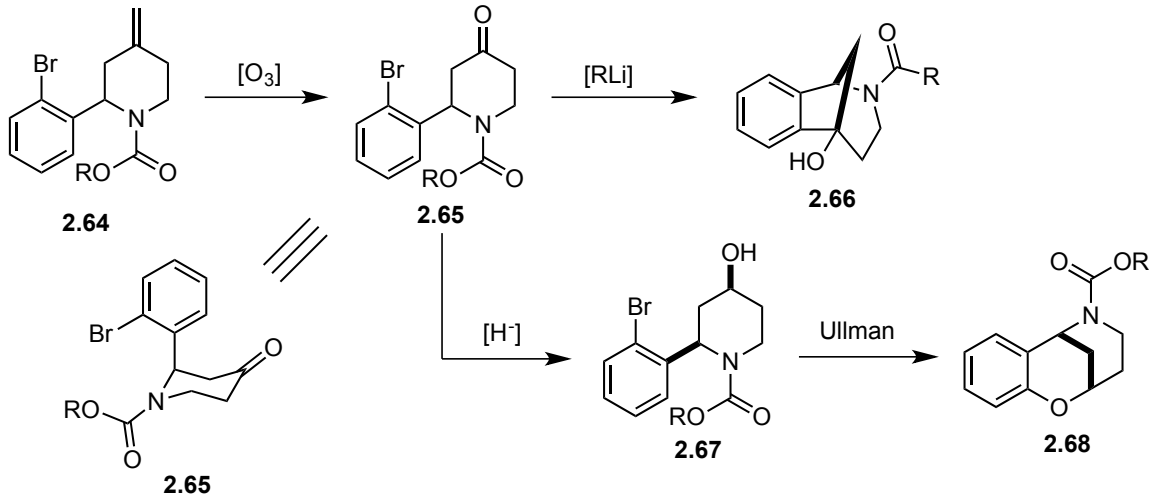
2.60 **2.61** (2.4)



2.62 **2.63** (2.5)

Not only does this approach incorporate a new quaternary center into the already biologically validated norbenzomorphan scaffold, but ozonolysis of the exocyclic double bond in compounds of the general type **2.64** could give ketones of the general type **2.65**, creating an opportunity to cyclize *via* lithium halogen exchange to give compounds **2.66**. Additionally, we believe the aryl ring in compounds **2.64** and **2.65** is preferentially oriented in the axial position on the piperidine ring in order to avoid $A^{1,3}$ strain resulting from interactions of the aryl group with the carbamate moiety. Thus, selective reduction from the least hindered face of ketones of the general type **2.65** should give alcohols *syn* to the aryl ring, allowing for an intramolecular Ullman reaction to give oxygenated benzomorphans of the general type **2.68** (Scheme 2.12).[66]

Scheme 2.12: Other Potential Scaffolds Accessible via Piperidines of the General Type **2.64**

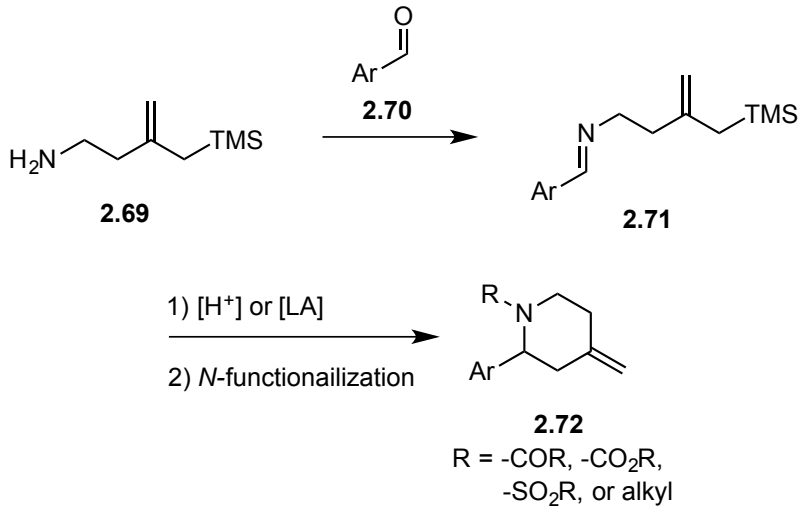


In addition to potentially allowing access to the scaffolds in Scheme 15, compounds of the general type **2.64** contain a piperidine ring, the most well represented nitrogen heterocycle in FDA approved pharmaceuticals.[67] With this in mind, as well as our hopes to access the scaffolds outlined in Schemes 12 and 14 in such a way that several derivatives of each can be easily prepared, we decided to find a method by which we could access an array of piperidines of the general subtype **2.64**.

Such a route would allow easy variation of the substitution on the aryl ring, as well as allowing easy manipulations of nitrogen atom functionality. We envisioned that by incorporating amine **2.69** into the MCAP procedure outlined in Scheme 9, we could access imines of the general type **2.71**. Formation of the iminium ion via protic or Lewis acids is known to initiate cyclization of the allylsilane to give 2-arylpiperidine **2.72** (Scheme 16). [50,51,68] While this cyclization is known, its potential application to DOS is yet to be explored, and with the aryl aminomethyl and piperidine subunits being so well

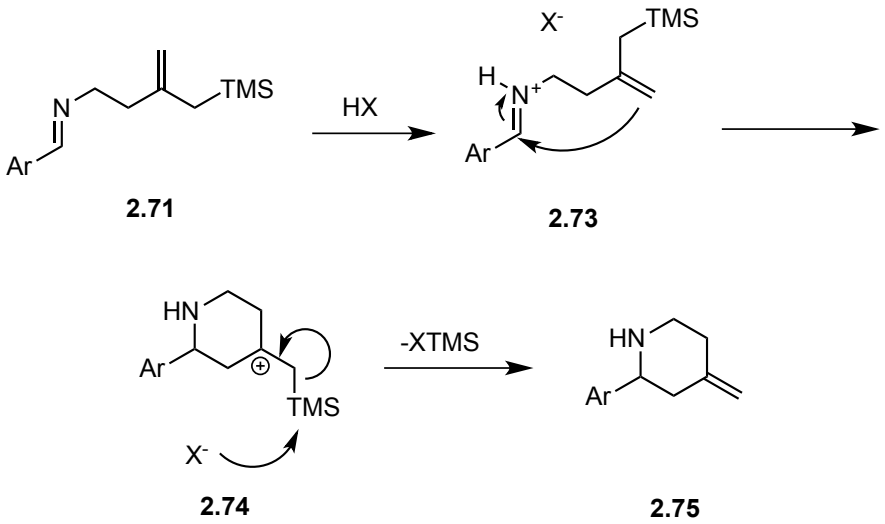
represented in pharmaceutical compounds and natural products, the creation of a library of compounds related to **2.72**, as well as their elaboration to more complex scaffolds, represent an opportunity to further explore promising chemical space.

Scheme 2.13: General Approach to Piperidines of the General Type **2.72**



Mechanistically, this cyclization is proposed to proceed by first forming the iminium ion **2.73**.[50,51] The allylsilane then adds into the iminium ion to give carbocation **2.74**. This intermediate undergoes elimination to provide the secondary amine **2.75** (Scheme 17).

Scheme 2.14: Mechanism of Iminium Ion Cyclization

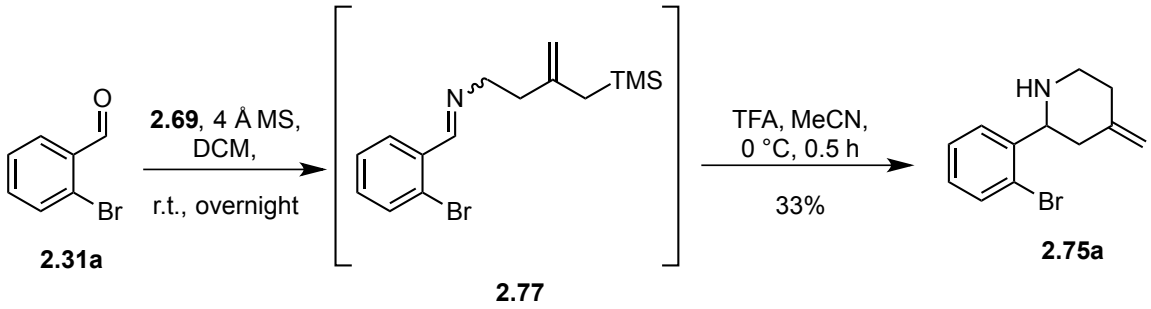


2.71 **2.73** **2.74** **2.75**

2.2 Results and Discussion

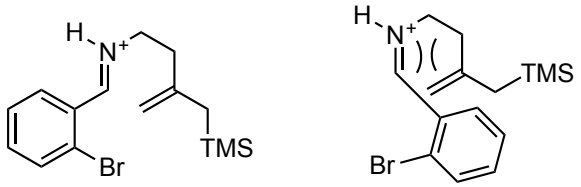
With the goal of creating a library of 2-arylpiperidines in mind, we first sought to establish a standard procedure by which all piperidines of the general type **2.72** would be synthesized. As part of an effort to synthesize compounds of the general type **2.68**, Dr. James Sahn had already established preliminary conditions for the cyclization of imine **2.77** to give 2-arylpiperidine **2.75a**. In this procedure 2-bromobenzaldehyde (**2.31a**) was condensed with amine **2.69** using 4 Å molecular sieves. The resultant imine was treated with one equivalent of trifluoroacetic acid (TFA) at 0 °C to give the 2-arylpiperidine in 34% yield (Scheme 2.15).

Scheme 2.15: Initial Procedure for the Synthesis of Compound **2.75a** via Iminium Ion Cyclization



While repeating Dr. Sahns work, it was found that intermediate imine **2.77** was being formed in roughly a 4:1 ratio of isomers, presumed to be the *trans* and *cis* isomers, respectively. We rationalized that the *cis* isomer would undergo cyclization less readily than the *trans* isomer because the transition state of the *cis* iminium ion would result in steric clash between the allylsilane moiety and the arene ring (Figure 8).

Figure 2.3: Comparison of the Transition States of the *trans* Isomer **2.73a** *cis* Isomer **2.73b** of Iminium Ion



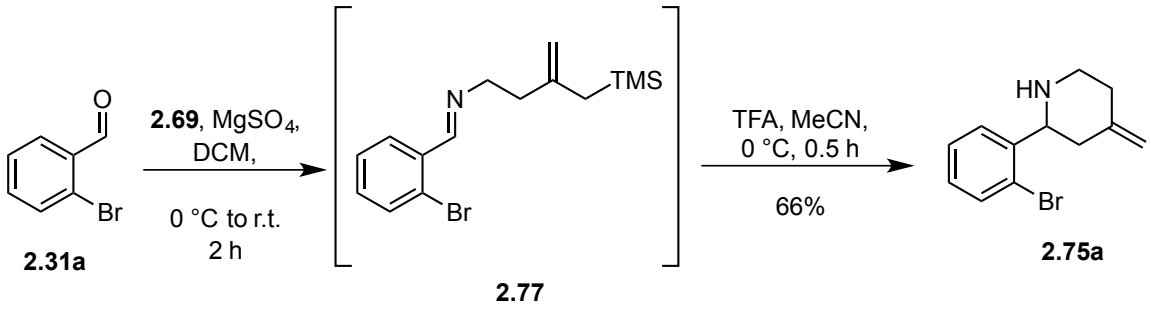
2.73a
trans imine

2.73b
cis imine

We found that cooling a solution of 2-bromobenzaldehyde (**2.31a**) in DCM to 0 °C and adding amine **2.69** dropwise in the presence of $MgSO_4$ before allowing the reaction to warm to room temperature, provided isomerically pure **2.77** after two hours. We then found that adding one equivalent of TFA to a solution of **2.77** in MeCN at 0 °C, followed by a basic workup and purification *via* flash column chromatography provided compound

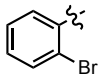
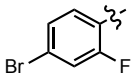
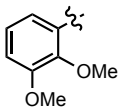
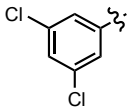
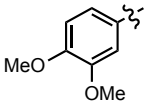
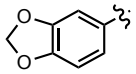
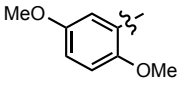
2.75a in 66% yield. This result suggests that the *trans* imine undergoes cyclization more readily than the *cis* imine, which aligns with our understanding of the mechanism of this reaction. These conditions were used as the standard procedure for this transformation, however, the imine was not typically isolated and characterized in subsequent experiments. No further efforts to optimize the cyclization reaction *via* changes in solvent, temperature, or proton source were made (Scheme 2.16).

Scheme 2.16: Optimized Procedure for the Synthesis of Compound **2.75a** *via* Iminium Ion Cyclization



This procedure was then applied to the synthesis of a series of 2-arylpiperidines **2.75a–h**. The yields were uniformly in the range of 50-70%, allowing us access to 100 mg quantities of each compound for further derivatization.

Table 2.1: 2-Arylpiperidines synthesized via Iminium Ion Cyclization Strategy

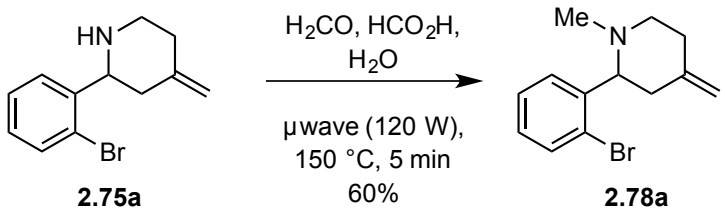
Entry	Aryl Group	Yield (%)*	Entry	Aryl Group	Yield (%)*
a		53	**e**		64
b		56	**f**		53
c		38	**g**		43
d		53	**h**		69

* Isolated yields of compounds >90% pure by ^{1}H NMR

With access to 2-arylpiperidines **2.75a–h** established, we set out to derivatize the compounds *via* a series of *N*-functionalizations. Ideally, we hoped to alkylate, tosylate, or acylate the amine in high yield and with minimal purification.

In preliminary experiments, we found that methylation of **2.75** could be carried out *via* reductive amination with formaldehyde and formic acid in water under

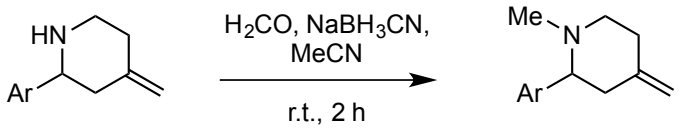
microwave heating in about 10 minutes. This procedure provided tertiary amine **2.78a** in 60% yield and greater than 90% purity by ^{1}H NMR (Equation 2.6).



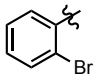
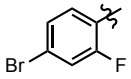
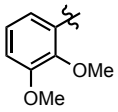
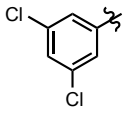
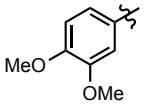
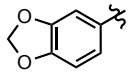
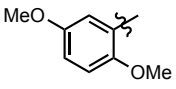
2.75a **2.78a** (2.6)

While this microwave procedure was convenient, the yield was significantly lower than we thought acceptable. Changing the reducing agent from formic acid to $NaBH_3CN$ and running the reaction at room temperature with no microwave heating provided tertiary amine **2.78a** in 80% yield after two hours. Having found conditions that provided compound **2.78a** in acceptable yields, we applied these conditions to the synthesis of compounds **2.78b–h**. The results of these experiments are outlined in Table 2.2.

Table 2.2: 2-Arylpiperidines Prepared *via* Reductive Alkylation of Compounds **2.75a–h**



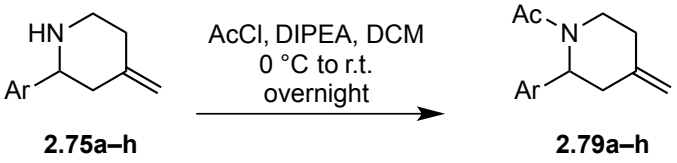
2.75a–h **2.78a–h**

Entry	Aryl Group	Yield (%)*	Entry	Aryl Group	Yield (%)*
a		88	**e**		74
b		66	**f**		59
c		94	**g**		94
d		94	**h**		92

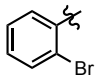
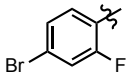
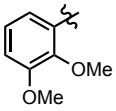
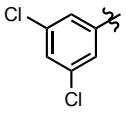
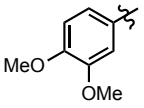
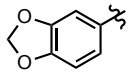
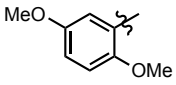
* Isolated yields of compounds >90% pure by ^{1}H NMR

Acylation was carried out by treating a solution of amine **2.75a** and diisopropylethylamine (DIPEA) with two equivalents of acetyl chloride (AcCl) at 0 °C, followed by stirring overnight at room temperature. Purification of the crude material by flash column chromatography afforded amide **2.79a** in 85% yield (Equation 11). The conditions were then applied to the synthesis of compounds **2.79b–h**, accordingly. These results are outlined in Table 2.3.

Table 2.3: Synthesis of N-Acylpiperidines *via* Acylation of Compounds **2.75a–h**



2.75a–h **2.79a–h**

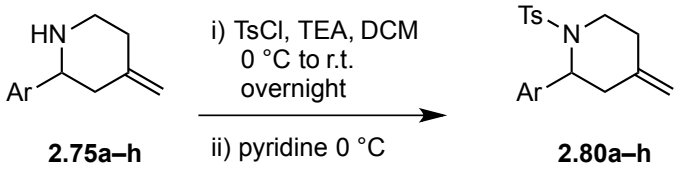
Entry	Aryl Group	Yield (%)*	Entry	Aryl Group	Yield (%)*
a		85	**e**		64
b		68	**f**		79
c		76	**g**		69
d		76	**h**		82

* Isolated yields of compounds >90% pure by ^{1}H NMR

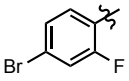
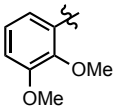
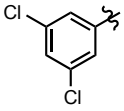
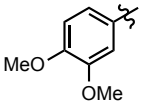
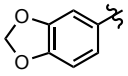
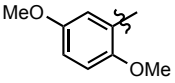
Finally, tosylation was accomplished by treating a solution of amine **2.75a** and triethylamine (TEA) in DCM with two equivalents of toluenesulfonyl chloride (TsCl) at 0 °C and then allowing this solution to warm to room temperature. Purification by flash column chromatography was avoided by adding 10 equivalents of pyridine in order to catalyze the hydrolysis of excess toluenesulfonyl chloride. Subsequent acid/base purification provided sulfonamide **2.79a** in 94% yield (Equation 12). With satisfactory *N*-

tosylation conditions established, we synthesized sulfonamides **2.80b–h**. The results of this effort are outlined in Table 2.4.

Table 2.4: Synthesis of Sulfonomides via Tosylation of Compounds **2.75a–h**



2.75a–h **2.80a–h**

Entry	Aryl Group	Yield (%)*	Entry	Aryl Group	Yield (%)*
a		94	**e**		65
b		60	**f**		76
c		60	**g**		32
d		60	**h**		83

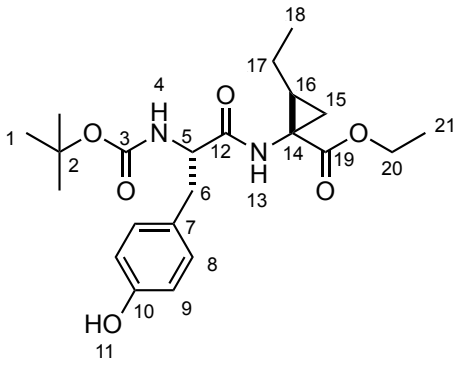
* Isolated yields of compounds >90% pure by ^{1}H NMR

2.3 Summary

In summary, we have developed a novel iminium ion formation and cyclization cascade of reactions and applied it to the synthesis of a library of highly diversifiable 2-aryl piperidines in good overall yield. The *N*-functionalization reactions were all easily carried out, thereby permitting the quick assembly of the library. It is noteworthy that the aryl aminomethyl subunit present in all of the compounds synthesized is a common structural motif found in biologically active small molecules,[53] and the reactions used to prepare each individual compound were metal-free and utilized inexpensive, common laboratory reagents. Additionally, while the 2-arylpiperidines synthesized already contain biologically relevant substructures, the use of 2-halobenzaldehydes of the general type **2.31a** also gives access to compounds that may prove to be valuable intermediates in the synthesis of new norbenzomorphan compounds (Equations 7 and 8, Scheme 15). This is particularly noteworthy given that the Martin lab has already shown the norbenzomorphan scaffold to have unusual biological activity in the context of the sigma receptors.[56,57]

CHAPTER 3: EXPERIMENTAL METHODS

General. Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.[63] Methanol, acetonitrile and dimethylformamide were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. Methylene chloride, diisopropylamine, triethylamine, and diisopropylethylamine were distilled from calcium hydride immediately prior to use. Pyridine was distilled from potassium hydroxide (KOH) and calcium hydride. All reagents were reagent grade and used without purification unless otherwise noted. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator at 25–30 °C. Chromatography was performed using forced flow (flash chromatography) and the indicated solvent system on Silicycle SiliaFlash F60 (40-63μ). Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent and are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent.

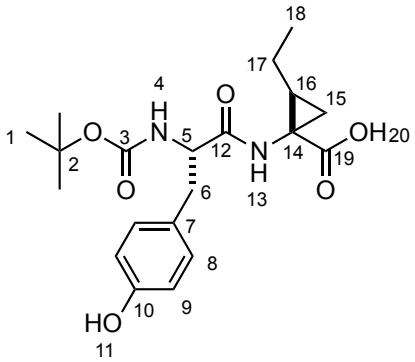


1.38

Ethyl (1*S*,2*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl) propanamido)-2-ethylcyclopropane-1-carboxylate (1.38). A solution of compound **1.37** (337 mg, 2.1 mmol), N-boc-tyrosine (603 mg, 2.1 mmol), EDCI•HCl (460 mg, 2.4 mmol), and Oxyma (611 mg, 4.3 mmol) in DMF (8.4 mL) was cooled to 0 °C and N-methylmorpholine (707 μL, 6.4 mmol) was added to the solution via syringe. The reaction stirred at room temperature until the starting material had been consumed (LC/MS). The reaction was concentrated and the resulting residue was dissolved in ethyl acetate (20 mL) and washed with 0.1 M HCl (3 x 10 mL) and saturated $NaHCO_3$ (3 x 10 mL). The organic solution was then dried over $MgSO_4$, and concentrated. The resulting residue was purified via flash column chromatography to yield 585 mg (67%) of **1.38**: ^{1}H NMR (400 MHz; CDCl3): δ 7.08 (d, *J* = 8.2 Hz, 2 H), 6.72 (d, *J* = 8.2 Hz, 2 H), 6.37 (br s, 1 H), 5.14 (br s, 1 H), 4.31-4.30 (q, 1 H), 4.13-4.08 (comp, 2 H), 3.01 (comp, 2 H), 1.70-1.66 (comp, 2 H), 1.46-1.44 (comp, 11 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.05-1.03 (m, 1 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 0.74 (dd, *J* = 6.7, 4.2 Hz, 1 H). ^{13}C-NMR (101 MHz): δ 173.0, 172.3, 155.8, 155.1, 130.7, 128.4, 115.6, 105.2, 61.5, 55.8, 37.8, 37.1, 30.1, 28.4,

22.8, 21.7, 14.3, 13.5. HRMS (ESI) *m/z* calcd for $C_{22\ H32}N_2O_6$ (M+Na)+, 443.2153; found, 443.2164

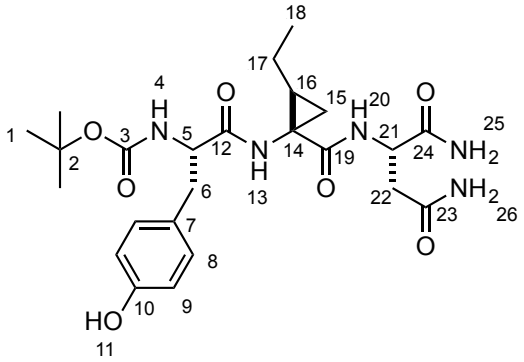
NMR Assignments. For **1.38**: ^{1}HNMR (400 MHz; CDCl3): δ 7.08 (d, *J* = 8.2 Hz, 2 H, C8-H), 6.72 (d, *J* = 8.2 Hz, 2 H, C9-H), 6.37 (br s, 1 H, N13-H), 5.14 (br s, 1 H, C11-H), 4.31 (q, 1 H, C5-H), 4.13-4.08 (comp, 2 H, C20-H), 3.01 (comp, 2 H, C6-H), 1.70-1.66 (comp, 2 H, C17-H), 1.46-1.44 (comp, 11 H, C1-H, C15-H), 1.20 (t, *J* = 7.1 Hz, 3 H, C21-H), 1.05-1.03 (m, 1 H, N4-H), 0.94 (t, *J* = 7.2 Hz, 3 H, C18-H), 0.74 (dd, *J* = 6.7, 4.2 Hz, 1 H, C16-H). ^{13}C-NMR (101 MHz): δ 173.0 (C19), 172.3 (C12), 155.8 (C10), 155.1 (C3), 130.7 (C8), 128.4 (C7), 115.6 (C9), 105.2 (C20), 61.5 (C2), 55.8 (C5), 37.8 (C21), 37.1 (C14), 30.1 (C6), 28.4 (C16), 22.8 (C1), 21.7 (C15), 14.3 (C18), 13.5 (C17).



1.39

(1*S*,2*S*)-1-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-2-ethylcyclopropane-1-carboxylic acid (1.39). To a solution of compound **1.38** (116 mg, 0.28 mmol) in 2:1:1 THF : water : methanol (0.55 mL) was added LiOH monohydrate (58 mg, 1.4 mmol). The resulting suspension was stirred at room temperature for 16 h before being diluted with water (5 mL) and washed

with ethyl acetate (5 mL). The aqueos solution was then acidified to a pH of ~2 with 0.1 M HCl and extracted with ethyl acetate (3 x 10 mL). The organic solution was dried over $MgSO_4$ and concentrated to yield 90 mg (83%) of compound **1.39** as a white solid. This material was used in the next step without further purification.



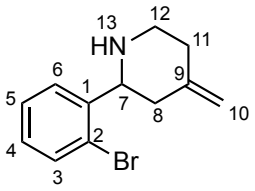
1.41

***tert*-Butyl ((*S*)-1-(((1*S*,2*S*)-1-(((*S*)-1,4-diamino-1,4-dioxobutan-2-yl)carbamoyl)-2-ethylcyclopropyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (1.41).** A solution of compound **1.39** (710 mg, 1.8 mmol), EDCI•HCl (382 mg, 2.0 mmol), Oxyma (515 mg, 3.6 mmol), and L-asparagine-amide (261 mg, 2.0 mmol) in DMF (1.8 mL) was cooled to 0 °C and N-methylmorpholine (995 μL, 9.1 mmol) was added via syringe. The reaction was stirred until the starting material was no longer present (TLC) and the solution was concentrated to give an orange residue which was purified via flash column chromatography to give 67 mg of compound **1.41** (7%) as a white solid. ^{1}H-NMR (400 MHz; CD_3OD): δ 7.07 (d, *J* = 8.4 Hz, 2 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 4.55 (t, *J* = 6.2 Hz, 1 H), 4.19 (t, *J* = 7.6 Hz, 1 H), 3.00-2.74 (comp, 4 H), 1.74-1.66 (m, 1 H), 1.41 (comp, 11 H), 0.92 (t, *J* = 7.3 Hz, 3 H), 0.67 (m, 1 H), 0.56 (dd, *J* = 7.2, 4.8 Hz, 1 H). ^{13}C NMR (126 MHz, CD_3OD) δ 175.8, 174.3, 174.2, 172.7, 156.8,

156.0, 130.0, 127.4, 114.8, 79.6, 56.5, 50.9, 39.0, 35.8, 28.4, 27.34, 20.9, 12.4. HRMS (ESI) *m/z* calcd for $C_{24}H_{35}N_5O_7$ (M+Na)+, 528.2429; found, 528.2434

NMR Assignments. For **1.41**: ^{1}H-NMR (400 MHz; CD_3OD): δ 7.07 (d, *J* = 8.4 Hz, 2 H, C8-H), 6.70 (d, *J* = 8.4 Hz, 2 H, C9-H), 4.55 (t, *J* = 6.2 Hz, 1 H, C5-H), 4.19 (t, *J* = 7.6 Hz, 1 H, C21-H), 3.00-2.74 (comp, 4 H, C6-H, C22-H), 1.74-1.66 (m, 1 H, C16-H), 1.41 (comp, 11 H, C1-H, C17-H), 0.92 (t, *J* = 7.3 Hz, 3 H, C18-H), 0.67 (m, 1 H, C15-H), 0.56 (dd, *J* = 7.2, 4.8 Hz, 1 H, C15-H). ^{13}C NMR (126 MHz, CD_3OD) δ 175.8 (C24), 174.3 (C23), 174.2 (C19), 172.7 (C12), 156.8 (C10), 156.0 (C3), 130.0 (C8), 127.4 (C7), 114.8 (C9), 79.6 (C2), 56.5 (C5), 50.9 (C21), 39.0 (C14), 35.8 (C6, C22), 28.4 (C16), 27.4 (C1), 20.9 (C15), 12.4 (C18).

Representative procedure for the synthesis of 2-arylpiperidines:

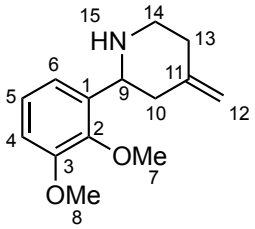


2.75

2-(2-Bromophenyl)-4-methylenepiperidine (2.75a). A solution of 2-bromobenzaldehyde (**2.31a**) (150 μL, 235 mg, 1.27 mmol) in dichloromethane (20 mL) containing $MgSO_4$ (2 g) was cooled to 0 °C, and 3-((trimethylsilyl)methyl)but-3-en-1-amine (**2.69**) **(**200 mg, 1.27 mmol) was added dropwise *via* syringe. The ice-bath was removed, and the reaction was stirred at room temperature for 2 h, at which point the $MgSO_4$ was removed by vacuum filtration, and the solvent removed under reduced pressure. The crude residue was dissolved in anhydrous acetonitrile (25 mL), and the

resulting solution was cooled to 0°C. Trifluoroacetic acid (100 μL, 145 mg, 1.27 mmol) was added to this solution dropwise *via* syringe, and the reaction stirred at 0 °C for 0.5 h, at which point a saturated solution of $NaHCO_3$ (5 mL) was added. This biphasic mixture was transferred to a separatory funnel with ethyl acetate (25 mL) and distilled water (10 mL) and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified *via* column chromatography, eluting with hexanes/ethyl acetate (2:1) to give 211 mg (53%) of compound **2.75a** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.53 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.31 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.11 (td, *J* = 8.0, 7.3, 1.8 Hz, 1 H), 4.78 – 4.75 (comp, 2 H), 3.99 (dd, *J* = 11.2, 2.8 Hz, 1 H), 3.31 – 3.23 (m, 1 H), 2.85 – 2.75 (m, 1 H), 2.52 (ddd, *J* = 12.9, 2.8, 0.9 Hz, 1 H), 2.34 – 2.25 (m, 2 H), 2.15 – 2.06 (m, 1 H), 1.77 (br s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 142.9, 132.8, 128.6, 127.80, 127.7, 123.3, 108.7, 61.3, 48.1, 41.9, 34.8. HRMS (ESI) *m/z* calcd for $C_{12\ H14}BrN$ (M+H)+, 252.0382; found, 252.0389

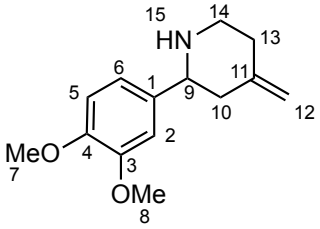
NMR assignments. For **2.75a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.8, 1.8 Hz, 1 H, C3-H), 7.53 (dd, *J* = 8.0, 1.3 Hz, 1 H, C6-H), 7.31 (td, *J* = 7.6, 1.3 Hz, 1 H, C4-H), 7.11 (td, *J* = 7.3, 1.8 Hz, 1 H, C5-H), 4.78 – 4.75 (comp, 2 H, C10-H_2), 3.99 (dd, *J* = 11.2, 2.8 Hz, 1 H, C7-H), 3.31 – 3.23 (m, 1 H, C12-H_{eq}), 2.85 – 2.75 (m, 1 H, C12-H_{ax}), 2.52 (ddd, *J* = 12.9, 2.8, 0.9 Hz, 1 H, C8-H_{eq}), 2.34 – 2.25 (comp, 2 H, C11-H_{eq} and C11-H_{ax}), 2.15 – 2.06 (m, 1 H, C8-H_{ax}), 1.77 (br s, 1 H, N15-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1 (C2), 142.9 (C1), 132.8 (C6), 128.6 (C5), 127.80 (C4), 127.7 (C3), 123.3 (C10), 108.7 (C9), 61.3 (C7), 48.1 (C12), 41.9 (C8), 34.8 (C11).



2.75b

2-(2,3-Dimethoxyphenyl)-4-methylenepiperidine (2.75b). Prepared in accord with the representative procedure to yield 84 mg (56%) of the title compound as a clear oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.02 (comp, 2 H), 6.83 (dd, *J* = 6.5, 3.1 Hz, 1 H), 4.77 – 4.68 (comp, 2 H), 3.97 (dd, *J* = 11.3, 2.9 Hz, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.30 – 3.21 (m, 1 H), 2.85 – 2.71 (m, 1 H), 2.45 – 2.37 (m, 1 H), 2.30 – 2.22 (comp, 3 H), 2.00 (br s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 146.8, 146.4, 137.7, 124.2, 118.8, 111.2, 108.2, 61.1, 56.5, 55.8, 48.2, 42.7, 35.2. HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NO_2$ (M+H)+, 234.1489; found, 234.1481

NMR assignments. For **2.75b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.02 (comp, 2 H, C6-H and C5-H), 6.83 (dd, *J* = 6.5, 3.1 Hz, 1 H, C4-H), 4.77 – 4.68 (comp, 2 H, C12-H_2), 3.97 (dd, *J* = 11.3, 2.9 Hz, 1 H, C9-H), 3.86 (s, 3 H, C7-H or C8-H), 3.84 (s, 3 H, C7-H, C8-H), 3.30 – 3.21 (m, 1 H, C14-H_{eq}), 2.85 – 2.71 (m, 1 H, C14-H_{ax}), 2.45 – 2.37 (m, 1 H, C10-H_{eq}), 2.30 – 2.22 (comp, 3 H, C10-H_{ax} and C13-H_{eq} and C13-H_{ax}), 2.00 (br s, 1 H, N15-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5 (C1), 146.8 (C2 or C3), 146.4 (C2 or C3), 137.7 (C5 or C6), 124.2 (C5 or C6), 118.8 (C4), 111.2 (C12), 108.2 (C11), 61.1 (C9), 56.5 (C7 or C8), 55.8 (C7 or C8), 48.2 (C14), 42.7 (C10), 35.2 (C13).

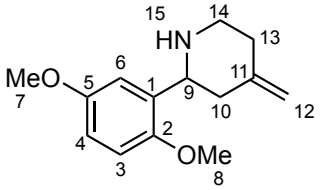


2.75c

2-(3,4-Dimethoxyphenyl)-4-methylenepiperidine (2.75c). Prepared in accord with the representative procedure to yield 57 mg (38%) of the title compound as an off white solid. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 2.0 Hz, 1 H), 6.89 (dd, *J* = 8.2, 2.0, 0.5 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 4.75 – 4.69 (comp, 2 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.53 (dd, *J* = 11.3, 2.9 Hz, 1 H), 3.29 – 3.21 (m, 1 H), 2.80 – 2.68 (m, 1 H), 2.38 (dd, *J* = 13.0, 2.9 Hz, 1 H), 2.30 – 2.21 (comp, 3 H), 1.97 (br s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 148.2, 146.6, 137.2, 118.6, 111.0, 109.7, 108.3, 62.9, 55.9, 55.9, 48.1, 44.0, 34.9. HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NO_2$ (M+H)+, 234.1489; found, 234.1492

NMR assignments. For **2.75c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 2.0 Hz, 1 H, C2-H), 6.89 (dd, *J* = 8.2, 2.0, 0.5 Hz, 1 H, C6-H), 6.81 (d, *J* = 8.2 Hz, 1 H, C5-H), 4.75 – 4.69 (comp, 2 H, C12-H_2), 3.89 (s, 3 H, C7-H or C8-H), 3.86 (s, 3 H, C7-H or C8-H), 3.53 (dd, *J* = 11.3, 2.9 Hz, 1 H, C9-H), 3.29 – 3.21 (m, 1 H, C14-H_{eq}), 2.80 – 2.68 (m, 1 H, C14-H_{eq}), 2.38 (dd, *J* = 13.0, 2.9 Hz, 1 H, C10-H_{eq}), 2.30 – 2.21 (comp, 3 H, C10-H_{ax} and C13-H_{eq} and C13-H_{ax}), 1.97 (br s, 1 H, N15-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0

(C1), 148.2 (C3 or C4), 146.6 (C3 or C4), 137.2 (C6), 118.6 (C2 or C5), 111.0 (C2 or C5), 109.7 (C12), 108.3 (C11), 62.9 (C9), 55.90 (C7 or C8), 55.88 (C7 or C8), 48.1 (C14), 44.0 (C10), 34.9 (C13).

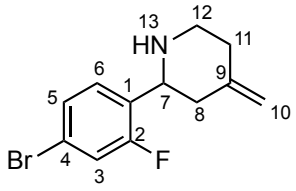


2.75d

2-(2,5-Dimethoxyphenyl)-4-methylenepiperidine (2.75d). Prepared in accord with the representative procedure to yield 79 mg (53%) of the title compound as an off white solid. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 3.0 Hz, 1 H), 6.79 (d, *J* = 8.8 Hz, 1 H), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1 H), 4.76 – 4.70 (comp, 2 H), 3.93 (dd, *J* = 11.3, 2.9 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.29 – 3.20 (m, 1 H), 2.82 – 2.70 (m, 1 H), 2.43 (dd, *J* = 12.9, 2.9 Hz, 1 H), 2.31 – 2.19 (comp, 4 H), 2.05 (br s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 150.8, 146.8, 133.2, 113.0, 112.4, 111.5, 108.2, 56.7, 55.9, 55.8, 48.0, 41.6, 35.2. HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NO_2$ (M+H)+, 234.1489; found, 234.2489

NMR assignments. For **2.75d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 3.0 Hz, 1 H, C6-H), 6.79 (d, *J* = 8.8 Hz, 1 H, C3-H), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1 H, C4-H), 4.76 – 4.70 (comp, 2 H, C12-H), 3.93 (dd, *J* = 11.3, 2.9 Hz, 1 H, C9-H), 3.79 (s, 3 H (C7-H or C8-H), 3.77 (s, 3 H, C7-H or C8-H), 3.29 – 3.20 (m, 1 H, C14-H_{eq}), 2.82 – 2.70 (m, 1 H, C14-H_{ax}), 2.43 (dd, *J* = 12.9, 2.9 Hz, 1 H, C10-H_{eq}), 2.31 – 2.19 (comp, 4 H, C10-H_{ax}

and C13-H_{eq} and C13-H_{ax}), 2.05 (br s, 1 H, N15-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (C2 or C5), 150.8 (C2 or C5), 146.8 (C1), 133.2 (C6), 113.0 (C4 or C3), 112.4 (C4 or C3), 111.5 (C12), 108.2 (C11), 56.7 (C9), 55.9 (C7 or C8), 55.8 (C7 or C8), 48.0 (C14), 41.6 (C10), 35.2 (C13).

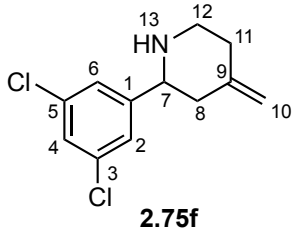


2.75e

2-(4-Bromo-2-fluorophenyl)-4-methylenepiperidine (2.75e). Prepared in accord with the representative procedure to yield 111 mg (64%) of the title compound as a white solid. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 1 H), 7.28 – 7.24 (m, 1 H), 7.19 (dd, *J* = 9.9, 1.9 Hz, 1 H), 4.77 – 4.71 (m, 2 H), 3.88 (dd, *J* = 11.3, 2.9 Hz, 1 H), 3.25 (ddd, *J* = 11.4, 4.6, 2.9 Hz, 1 H), 2.82 – 2.68 (m, 1 H), 2.40 (ddd, *J* = 13.0, 3.0, 1.1 Hz, 1 H), 2.31 – 2.21 (m, 2 H), 2.19 – 2.10 (m, 1 H), 1.76 (s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (d, *J* = 250.6 Hz), 145.7, 130.4 (d, *J* = 13.4 Hz), 128.9 (d, *J* = 5.6 Hz), 127.6 (d, *J* = 3.5 Hz), 120.7 (d, *J* = 9.9 Hz), 118.9 (d, *J* = 25.7 Hz), 108.9, 55.4 (d, *J* = 2.0 Hz), 48.0, 42.2, 34.9. HRMS (ESI) *m/z* calcd for $C_{12\ H13}$BrFN (M+H)+, 270.0288; found, 270.0297

NMR assignments. For **2.75e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 1 H, C6-H), 7.28 – 7.24 (m, 1 H, C5-H), 7.19 (dd, *J* = 9.9, 1.9 Hz, 1 H, C3-H), 4.77 – 4.71 (m, 2 H, C10-H_2), 3.88 (dd, *J* = 11.3, 2.9 Hz, 1 H, C7-H), 3.25 (ddd, *J* = 11.4, 4.6,

2.9 Hz, 1 H, C12-H_{eq}), 2.82 – 2.68 (m, 1 H, C12-H_{ax}), 2.40 (ddd, *J* = 13.0, 3.0, 1.1 Hz, 1 H, C8-H_{eq}), 2.31 – 2.21 (comp, 2 H, C11-H_{eq} and C11-H_{ax}), 2.19 – 2.10 (m, 1 H, C8-H_{ax}), 1.76 (s, 1 H, N13-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (d, *J* = 250.6 Hz, C2), 145.7 (C10), 130.4 (d, *J* = 13.4 Hz, C3), 128.9 (d, *J* = 5.6 Hz, C4), 127.6 (d, *J* = 3.5 Hz, C5), 120.7 (d, *J* = 9.9 Hz, C6), 118.9 (d, *J* = 25.7 Hz, C1), 108.9 (C9), 55.4 (d, *J* = 2.0 Hz, C7), 48.0 (C12), 42.2 (C8), 34.9 (C11).

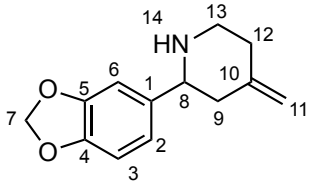


2.75f

2-(3,5-Dichlorophenyl)-4-methylenepiperidine (2.75f). Prepared in accord with the representative procedure to yield 82 mg (53%) of the title compound as a yellow oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (dd, *J* = 2.0, 0.5 Hz, 2 H), 7.23 (t, *J* = 1.9 Hz, 1 H), 4.74 (comp, 2 H), 3.53 (dd, *J* = 11.3, 2.9 Hz, 1 H), 3.30 – 3.20 (m, 1 H), 2.76 – 2.67 (m, 1 H), 2.37 (dd, *J* = 13.0, 3.0, 1.0 Hz, 1 H), 2.29 – 2.20 (comp, 2 H), 2.17 – 2.07 (m, 1 H), 1.79 (s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 145.6, 134.9, 127.4, 125.2, 109.0, 62.1, 47.8, 43.8, 34.7. HRMS (ESI) *m/z* calcd for $C_{12\,H13}Cl_2N$ (M+H)+, 242.0498; found, 242.0504

NMR assignments. For **2.75f:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (dd, *J* = 2.0, 0.5 Hz, 2 H, C6-H and C2-H), 7.23 (t, *J* = 1.9 Hz, 1 H, C4-H), 4.74 (comp, 2 H, C10-

H_2), 3.53 (dd, *J* = 11.3, 2.9 Hz, 1 H, C7-H), 3.30 – 3.20 (m, 1 H, C12-H_{eq}), 2.76 – 2.67 (m, 1 H, C12-H_{ax}), 2.37 (dd, *J* = 13.0, 3.0, 1.0 Hz, 1 H, C8-H_{eq}), 2.29 – 2.20 (comp, 2 H, C11-H_{eq} and C11-H_{ax}), 2.17 – 2.07 (m, 1 H, C8-H_{ax}), 1.79 (s, 1 H, N13-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, (C3 and C5) 145.6 (C1), 134.9 (C4), 127.4 (C6 and C2), 125.2 (C10), 109.0 (C9), 62.1 (C7), 47.8 (C12), 43.8 (C8), 34.7 (C11).

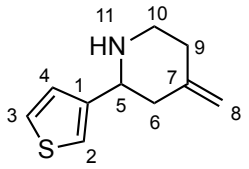


2.75g

2-(Benzo[1,3]dioxol-5-yl)-4-methylenepiperidine (2.75g). Prepared in accord with the representative procedure to yield 60 mg (43%) of the title compound as an amber oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 1.7 Hz, 1 H), 6.81 (dd, *J* = 7.9, 1.5 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 5.91 (s, 2 H), 4.71 (d, *J* = 10.0 Hz, 2 H), 3.48 (dd, *J* = 11.3, 2.9 Hz, 1 H), 3.28 – 3.20 (m, 1 H), 2.77 – 2.64 (m, 1 H), 2.34 (dd, *J* = 13.2, 3.1 Hz, 1 H), 2.27 – 2.15 (m, 3 H), 1.88 (br s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 146.6, 146.6, 138.6, 119.7, 108.3, 108.1, 107.1, 100.9, 62.9, 48.0, 44.0, 34.9. HRMS (ESI) *m/z* calcd for $C_{13\,H15}NO_2$ (M+H)+,218.1176; found, 218.1182.

NMR assignments. For **2.75g:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 1.7 Hz, 1 H, C6-H), 6.81 (dd, *J* = 7.9, 1.5 Hz, 1 H, C2-H), 6.73 (d, *J* = 8.0 Hz, 1 H, C3-H), 5.91 (s, 2 H, C7-H_2), 4.71 (d, *J* = 10.0 Hz, 2 H, C11-H_2), 3.48 (dd, *J* = 11.3, 2.9 Hz, 1 H, C8-

H), 3.28 – 3.20 (m, 1 H, C13-H_{eq}), 2.77 – 2.64 (m, 1 H, C13-H_{ax}), 2.34 (dd, *J* = 13.2, 3.1 Hz, 1 H, C9-H_{eq}), 2.27 – 2.15 (comp, 3 H, C9-H_{ax} and C12-H_{eq} and C12-H_{ax}), 1.88 (br s, 1 H, N14-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6 (C4), 146.60 (C5), 146.57 (C1), 138.6 (C2), 119.7 (C3), 108.3 (C6), 108.1 (C11), 107.1 (C10), 100.9 (C7), 62.9 (C8), 48.0 (C13), 44.0 (C9), 34.9 (C12).



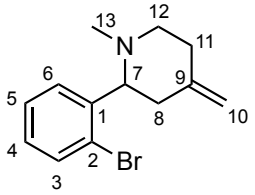
2.75h

4-Methylene-2-(thiophen-3-yl)piperidine (2.75h). Prepared in accord with the representative procedure to yield 79 mg (69%) of the title compound as a clear oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 5.0, 3.0 Hz, 1 H), 7.19 – 7.14 (m, 1 H), 7.09 (dd, *J* = 5.0, 1.3 Hz, 1 H), 4.77 – 4.68 (comp, 2 H), 3.71 (dd, *J* = 11.1, 3.0 Hz, 1 H), 3.23 (ddd, *J* = 11.5, 4.7, 2.7 Hz, 1 H), 2.73 (td, *J* = 11.3, 4.5 Hz, 1 H), 2.49 (ddd, *J* = 13.1, 3.1, 1.2 Hz, 1 H), 2.30 – 2.16 (comp, 3 H), 1.81 (s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 145.7, 126.3, 125.7, 120.2, 108.5, 58.4, 47.8, 43.3, 35.2. HRMS (ESI) *m/z* calcd for $C_{13\,H15}NO_2$ (M+H)+,180.0841; found, 180.0850.

NMR assignments. For **2.75h:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 5.0, 3.0 Hz, 1 H, C3-H), 7.19 – 7.14 (m, 1 H, C2-H), 7.09 (dd, *J* = 5.0, 1.3 Hz, 1 H, C4-H), 4.77 – 4.68 (comp, 2 H, C8-H_2), 3.71 (dd, *J* = 11.1, 3.0 Hz, 1 H, C5-H), 3.23 (ddd, *J* =

11.5, 4.7, 2.7 Hz, 1 H, C10-H_{eq}), 2.73 (td, *J* = 11.3, 4.5 Hz, 1 H, C10-H_{ax}), 2.49 (ddd, *J* = 13.1, 3.1, 1.2 Hz, 1 H, C6-H_{eq}), 2.30 – 2.16 (comp, 3 H, C6-H_{ax} and C9-H_{eq} and C9-H_{ax}), 1.81 (s, 1 H, N11-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3 (C1), 145.7 (C4), 126.3 (C3), 125.7 (C2), 120.2 (C8), 108.5 (C7), 58.4 (C5), 47.8 (C10), 43.3 (C6), 35.2 (C9).

Representative procedure for the methylation of 2-arylpiperidines:

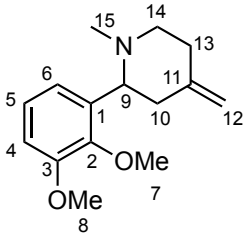


2.78a

2-(2-Bromophenyl)-1-methyl-4-methylenepiperidine (2.78a). A solution of **2.75a** (100 mg, 0.4 mmol) in acetonitrile (5 mL) was cooled to 0 °C, and formaldehyde (200 μL, 2.4 mmol, 37% aq. soln.) and $NaBH_3CN$ (50 mg, 0.8 mmol) were added sequentially. This suspension stirred for 2 h at room temperature before adding acetic acid (3 mL). The resulting solution stirred for 0.5 h open to air before being transferred to a separatory funnel with diethyl ether (30 mL) and 1 M HCl (15 mL). The layers were separated and the organic layer was washed with 1M HCl (3 x 15 mL). The combined aqueous layers were basified with 10 M NaOH until the pH was greater than 12 by pH paper. This aqueous solution was then washed with dichloromethane (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 94 mg (88%) of compound **2.78a** as a yellow solid. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.57 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.52 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.32 (dddd, *J* = 7.8, 7.3, 1.3, 0.5 Hz, 1 H), 7.09 (ddd, *J* = 8.0, 7.2, 1.8 Hz, 1 H), 4.76 – 4.67 (comp, 2 H), 3.46 (dd,

J = 11.4, 3.2 Hz, 1 H), 3.12 (ddd, *J* = 11.0, 4.9, 2.2 Hz, 1 H), 2.51 – 2.40 (m, 1 H), 2.40 – 2.19 (comp, 3 H), 2.18 – 2.09 (m, 1 H), 2.04 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 142.5, 132.7(, 128.9, 128.2, 127.8, 123.6, 108.1, 68.8, 57.8, 43.4, 42.6, 34.7. HRMS (ESI) *m/z* calcd for $C_{13\,H16}BrN$ (M+H)+, 266.0539; found, 266.0548

NMR assignments. For **2.78a**: ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.57 (dd, *J* = 7.8, 1.8 Hz, 1 H, C3-H), 7.52 (dd, *J* = 8.0, 1.2 Hz, 1 H, C6-H), 7.32 (dddd, *J* = 7.8, 7.3, 1.3, 0.5 Hz, 1 H, C4-H), 7.09 (ddd, *J* = 8.0, 7.2, 1.8 Hz, 1 H, C5-H), 4.76 – 4.67 (comp, 2 H, C10-H), 3.46 (dd, *J* = 11.4, 3.2 Hz, 1 H, C7-H), 3.12 (ddd, *J* = 11.0, 4.9, 2.2 Hz, 1 H, C12-H_{eq}), 2.51 – 2.40 (m, 1 H, C12-H_{ax}), 2.40 – 2.19 (comp, 3 H, C11-H_{eq} and C11-H_{ax} and C8-H_{eq}), 2.18 – 2.09 (m, 1 H, C8-H_{ax}), 2.04 (s, 3 H, C13-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5 (C2), 142.5 (C1), 132.7 (C6), 128.9 (C5), 128.2 (C4), 127.8 (C3), 123.6 (C10), 108.1 (C9), 68.8 (C7), 57.8 (C14), 43.4 (C15), 42.6 (C10), 34.7 (C13).

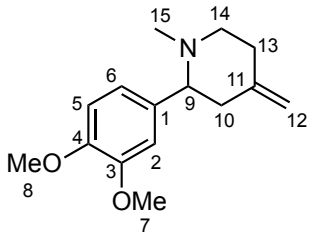


2.78b

2-(2,3-Dimethoxyphenyl)-1-methyl-4-methylenepiperidine (2.78b). Prepared in accord with the representative procedure to yield 14 mg (66%) of the title compound as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.04 (comp, 2 H), 6.80 (dd, *J* =

6.7, 2.9 Hz, 1 H), 4.71 (dq, *J* = 15.6, 1.9 Hz, 2 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.44 (dd, *J* = 10.3, 4.3 Hz, 1 H), 3.14 (ddd, *J* = 11.0, 4.8, 2.2 Hz, 1 H), 2.55 – 2.40 (m, 1 H), 2.33 – 2.18 (comp, 4 H), 2.05 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 146.7, 146.1, 137.3, 124.4, 119.5, 110.4, 107.8, 62.9, 60.8, 58.0, 55.6, 43.6, 43.3, 34.7. HRMS (ESI) *m/z* calcd for $C_{15}H_{21}NO_2$ (M+H)+, 248.1645; found, 248.1652

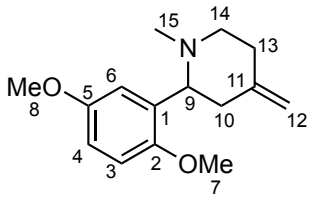
NMR assignments. For **2.78b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.04 (comp, 2 H, C6-H and C5-H), 6.80 (dd, *J* = 6.7, 2.9 Hz, 1 H, C4-H), 4.71 (dq, *J* = 15.6, 1.9 Hz, 2 H, C12-H), 3.86 (s, 3 H, C7-H or C8-H), 3.80 (s, 3 H, C7-H or C8-H), 3.44 (dd, *J* = 10.3, 4.3 Hz, 1 H, C9-H), 3.14 (ddd, *J* = 11.0, 4.8, 2.2 Hz, 1 H, C14-H_{eq}), 2.55 – 2.40 (m, 1 H, C14-H_{ax}), 2.33 – 2.18 (comp, 4 H, C10-H_2 and C13-H_2), 2.05 (s, 3 H, C15-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (C1), 146.7 (C2 or C3), 146.1 (C2 or C3), 137.3 (C5 or C6), 124.4 (C5 or C6), 119.5 (C4), 110.4 (C12), 107.8 (C11), 62.9 (C9), 60.8 (C7 or C8), 58.0 (C7 or C8), 55.6 (C15), 43.6 (C14), 43.3 (C10), 34.7 (C13).



2.78c

2-(3,4-Dimethoxyphenyl)-1-methyl-4-methylenepiperidine (2.78c). Prepared in accord with the representative procedure to yield 20 mg (94%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 1.7 Hz, 1 H), 6.85 – 6.78 (comp, 2 H), 4.74 – 4.63 (comp, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.15 – 3.04 (m, 1 H), 2.75 (dd, *J* = 11.1, 3.4 Hz, 1 H), 2.53 – 2.40 (m, 1 H), 2.40 – 2.24 (comp, 3 H), 2.13 (ddd, *J* = 12.8, 11.1, 2.9 Hz, 1 H), 2.02 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.1, 146.0, 136.3, 119.7, 110.8, 109.9, 107.9, 71.4, 57.9, 55.9, 55.9, 44.0, 43.7, 34.6. HRMS (ESI) *m/z* calcd for $C_{15}H_{21}NO_2$ (M+H)+, 248.1645; found, 248.1652

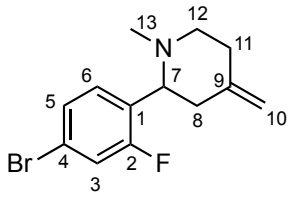
NMR assignements. For **2.78c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 1.7 Hz, 1 H, C2-H), 6.85 – 6.78 (comp, 2 H, C5-H and C6-H), 4.74 – 4.63 (comp, 2 H, C12-H), 3.90 (s, 3 H, C7-H_3 or C8-H_3), 3.87 (s, 3 H, C7-H_3 or C8-H_3), 3.15 – 3.04 (m, 1 H, C9-H), 2.75 (dd, *J* = 11.1, 3.4 Hz, 1 H, C14-H_{eq}), 2.53 – 2.40 (m, 1 H, C14-H_{ax}), 2.40 – 2.24 (comp, 3 H, C10-H_{eq} and C13-H_{eq} and C13-H_{ax}), 2.13 (ddd, *J* = 12.8, 11.1, 2.9 Hz, 1 H, C10-H_{ax}), 2.02 (s, 3 H, C15-H_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1 (C1), 148.1 (C3 or C4), 146.0 (C3 or C4), 136.3 (C6), 119.7 (C4 or C5), 110.8 (C4 or C5), 109.9 (C12), 107.9 (C11), 71.4 (C9), 57.9 (C7 or C8), 55.9 (C7 or C8), 55.9 (C15), 44.0 (C14), 43.7 (C10), 34.6 (C13).



2.78d

2-(2,5-Dimethoxyphenyl)-1-methyl-4-methylenepiperidine (2.78d). Prepared in accord with the representative procedure to yield 20 mg (94%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (br s, 1 H), 6.81 (d, *J* = 8.9 Hz, 1 H), 6.75 (dd, *J* = 8.9, 3.0 Hz, 1 H), 4.77 – 4.64 (comp, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.56 – 3.40 (m, 1 H), 3.14 (d, *J* = 11.1 Hz, 1 H), 2.61 – 2.41 (m, 1 H), 2.37 – 2.17 (comp, 4 H), 2.08 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 151.2, 146.2, 132.9, 113.0, 112.9, 112.3, 107.7, 62.6, 58.0, 56.3, 55.8, 43.3, 42.6, 34.7. HRMS (ESI) *m/z* calcd for $C_{15}H_{21}NO_2$ (M+H)+, 248.1645; found, 248.1651

NMR assignements. For **2.78d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (br s, 1 H, C6-H), 6.81 (d, *J* = 8.9 Hz, 1 H, C3-H), 6.75 (dd, *J* = 8.9, 3.0 Hz, 1 H, C4-H), 4.77 – 4.64 (comp, 2 H, C12-H), 3.79 (s, 3 H, C7-H_3 or C8-H_3), 3.78 (s, 3 H, C7-H_3 or C8-H_3), 3.56 – 3.40 (m, 1 H, C9-H), 3.14 (d, *J* = 11.1 Hz, 1 H, C14-H_{eq}), 2.61 – 2.41 (m, 1 H, C14-H_{ax}), 2.37 – 2.17 (comp, 4 H, C10-H_2, and C13-H_2), 2.08 (s, 3 H, C15-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (C2 or C5), 151.2 (C2 or C5), 146.2 (C1), 132.9 (C3 or C4), 113.0 (C3 or C4), 112.9 (C6), 112.3 (C12), 107.7 (C11), 62.6 (C9), 58.0 (C15), 56.3 (C7 or C8), 55.8 (C7 or C8), 43.3 (C14), 42.6 (C10), 34.7 (C13).

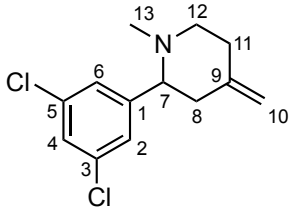


2.78e

2-(4-Bromo-2-fluorophenyl)-1-methyl-4-methylenepiperidine (2.78e). Prepared in accord with the representative procedure to yield 16 mg (74%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.9 Hz, 1 H), 7.29 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.21 (dd, *J* = 9.6, 1.9 Hz, 1 H), 4.72 (dt, *J* = 13.9, 1.9 Hz, 2 H), 3.25 (t, *J* = 7.3 Hz, 1 H), 3.09 (ddd, *J* = 11.2, 4.9, 2.3 Hz, 1 H), 2.44 (td, *J* = 12.7, 4.6 Hz, 1 H), 2.32 – 2.24 (comp, 3 H), 2.17 (ddd, *J* = 12.8, 11.1, 3.0 Hz, 1 H), 2.03 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (d, *J* = 250.3 Hz), 145.1, 129.9 (d, *J* = 5.1 Hz), 129.7 (d, *J* = 12.7 Hz), 127.8 (d, *J* = 3.7 Hz), 120.5 (d, *J* = 9.8 Hz), 119.0 (d, *J* = 26.1 Hz), 108.4, 62.2, 57.7, 43.5, 42.42, 34.6. HRMS (ESI) *m/z* calcd for $C_{13\ H15}$BrFN (M+H)+, 284.0445; found, 284.0452

NMR assignements. For **2.78e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.9 Hz, 1 H, C6-H), 7.29 (dd, *J* = 8.4, 2.0 Hz, 1 H, C5-H), 7.21 (dd, *J* = 9.6, 1.9 Hz, 1 H, C3-H), 4.72 (dt, *J* = 13.9, 1.9 Hz, 2 H, C10-H_2), 3.25 (t, *J* = 7.3 Hz, 1 H, C7-H), 3.09 (ddd, *J* = 11.2, 4.9, 2.3 Hz, 1 H, C12-H_{eq}), 2.44 (td, *J* = 12.7, 4.6 Hz, 1 H, C-12-H_{ax}), 2.32 – 2.24 (comp, 3 H, C8-H_{eq} and C11-H_{eq} and C11-H_{ax}), 2.17 (ddd, *J* = 12.8, 11.1, 3.0 Hz, 1 H, C8-H_{ax}), 2.03 (s, 3 H, C13-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (d, *J* = 250.3 Hz, C2), 145.1 (C10), 129.9 (d, *J* = 5.1 Hz, C4), 129.7 (d, *J* = 12.7 Hz, C1), 127.8 (d, *J* = 3.7

Hz, C5), 120.5 (d, *J* = 9.8 Hz, C6), 119.0 (d, *J* = 26.1 Hz, C3), 108.4 (C9), 62.2, (C7), 57.7 (C13), 43.5 (C12), 42.42 (C8), 34.6 (C11).

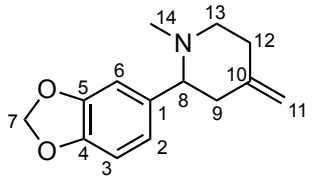


2.78f

2-(3,5-Dichlorophenyl)-1-methyl-4-methylenepiperidine (2.78f). Prepared in accord with the representative procedure to yield 12 mg (56%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 3 H), 4.71 (dq, *J* = 18.8, 1.8 Hz, 2 H), 3.08 (ddd, *J* = 11.1, 5.0, 2.3 Hz, 1 H), 2.77 (dd, *J* = 10.4, 4.1 Hz, 1 H), 2.44 (td, *J* = 12.9, 4.7 Hz, 1 H), 2.31 – 2.20 (comp, 3 H), 2.13 (ddd, *J* = 12.7, 11.1, 2.9 Hz, 1 H), 2.02 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.1, 135.0, 127.3, 125.9, 108.4, 70.6, 57.6, 44.0, 43.9, 34.9. HRMS (ESI) *m/z* calcd for $C_{13\ H15}Cl_2N$ (M+H)+, 256.0654; found, 256.0661

NMR assignements. For **2.78f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 3 H, C6-H and C2-H and C4-H), 4.71 (dq, *J* = 18.8, 1.8 Hz, 2 H, C10-H_2), 3.08 (ddd, *J* = 11.1, 5.0, 2.3 Hz, 1 H, C7-H), 2.77 (dd, *J* = 10.4, 4.1 Hz, 1 H, C12-H_{eq}), 2.44 (td, *J* = 12.9, 4.7 Hz, 1 H, C12-H_{ax}), 2.31 – 2.20 (comp, 3 H, C8-H_{eq} and C11-H_{eq} and C11-H_{ax}), 2.13 (ddd, *J* = 12.7, 11.1, 2.9 Hz, 1 H, C8-H_{ax}), 2.02 (s, 3 H, C13-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ

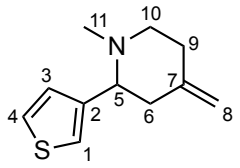
147.7 (C1), 145.1 (C3 and C5), 135.0 (C6 and C2), 127.3 (C4), 125.9 (C10), 108.4 (C9), 70.6 (C7), 57.6 (C13), 44.0 (C12), 43.9 (C8), 34.9 (C11).



2.78g

2-(Benzo[*d*][1,3]dioxol-5-yl)-1-methyl-4-methylenepiperidine (2.78g). Prepared in accord with the representative procedure to yield 20 mg (94%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.82 (m, 1 H), 6.79 – 6.70 (comp, 2 H), 5.94 (dd, *J* = 4.7, 1.5 Hz, 2 H), 4.68 (dq, *J* = 16.6, 1.9 Hz, 2 H), 3.08 (ddd, *J* = 11.1, 5.0, 2.3 Hz, 1 H), 2.72 (dd, *J* = 9.8, 4.7 Hz, 1 H), 2.52 – 2.37 (m, 1 H), 2.34 – 2.22 (comp, 3 H), 2.11 (ddd, *J* = 12.7, 11.1, 3.0 Hz, 1 H), 2.01 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 146.6, 146.1, 138.0, 120.6, 108.0, 107.8, 107.5, 100.9, 71.2, 57.8, 44.1, 43.7, 34.7. HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NO_2$ (M+H)+, 232.1332; found, 232.1336

NMR assignements. For **2.78g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.82 (m, 1 H, C6-H), 6.79 – 6.70 (comp, 2 H, C3-H and C2-H), 5.94 (dd, *J* = 4.7, 1.5 Hz, 2 H, C7-H_2), 4.68 (dq, *J* = 16.6, 1.9 Hz, 2 H, C11-H_2), 3.08 (ddd, *J* = 11.1, 5.0, 2.3 Hz, 1 H, C8-H), 2.72 (dd, *J* = 9.8, 4.7 Hz, 1 H, C13-H_{eq}), 2.52 – 2.37 (m, 1 H, C13-H_{ax}), 2.34 – 2.22 (comp, 3 H, C9-H_{eq} and C12-H_{eq} and C12-H_{ax}), 2.11 (ddd, *J* = 12.7, 11.1, 3.0 Hz, 1 H, C9-H_{ax}), 2.01 (s, 3 H, C14-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8 (C4), 146.6 (C5), 146.1 (C1), 138.0 (C2), 120.6 (C3), 108.0 (C6), 107.8 (C11), 107.5 (C10), 100.9 (C7), 71.2 (C8), 57.8 (C14), 44.1 (C13), 43.7 (C9), 34.7 (C12).

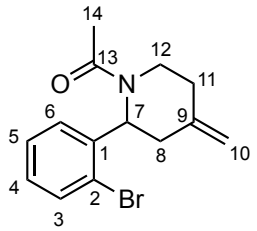


2.78h

1-Methyl-4-methylene-2-(thiophen-3-yl)piperidine (2.78h). Prepared in accord with the representative procedure to yield 20 mg (92%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 1 H), 7.14 – 7.08 (comp, 2 H), 4.70 (dq, *J* = 15.9, 1.9 Hz, 2 H), 3.11 – 2.98 (comp, 2 H), 2.54 – 2.36 (comp, 2 H), 2.36 – 2.23 (comp, 2 H), 2.14 (ddd, *J* = 12.4, 11.2, 3.1 Hz, 1 H), 2.04 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 144.8, 126.6, 125.7, 121.4, 108.0, 66.3, 57.6, 43.7, 43.1, 34.6. HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NS$ (M+H)+, 194.0998; found, 194.1001

NMR assignements. For **2.78h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3-7.25 (comp, 1 H, C1-H), 7.14 – 7.08 (comp, 2 H, C3-H and C4-H), 4.70 (dq, *J* = 15.9, 1.9 Hz, 2 H, C8-H_2), 3.11 – 2.98 (comp, 2 H, C5-H and C10-H_{eq}), 2.54 – 2.36 (comp, 2 H, C10-H_{ax} and C6-H_{eq}), 2.36 – 2.23 (comp, 2 H, C9-H_{eq} and C9-H_{ax}), 2.14 (ddd, *J* = 12.4, 11.2, 3.1 Hz, 1 H, C6-H_{ax}), 2.04 (s, 3 H, C11-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C2), 144.8 (C1), 126.6 (C3 or C4), 125.7 (C3 or C4), 121.4 (C8), 108.0 (C7), 66.3 (C5), 57.6 (C11), 43.7 (C10), 43.1 (C6), 34.6 (C9).

Representative procedure for the acylation of 2-arylpiperidines:

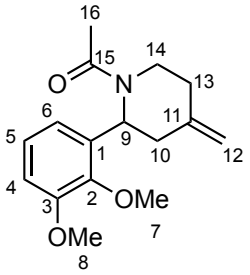


2.79a

1-(2-(2-Bromophenyl)-4-methylenepiperidin-1-yl)ethan-1-one (2.79a). A solution of compound **2.75a** (100 mg, 0.4 mmol) and triethylamine (121 mg, 167 μL, 1.2 mmol) in dichloromethane (5 mL) was cooled to 0 °C, and acetyl chloride (63 mg, 57 μL, 0.8 mmol) was added *via* syringe. The reaction was allowed to stir overnight at room temperature before adding 1 M HCl (5 mL) and stirring an additional 15 min. This biphasic mixture was then transferred to a separatory funnel with dichloromethane and 1 M HCl. The layers were separated and the aqueous layer was washed with dichloromethane (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified *via* column chromatography eluting with hexanes/ethyl acetate (4:1) to give 20 mg (85%) of compound **2.79z** as a yellow oil. ^{1}H NMR (500 MHz, Toluene-d_8, 100 °C) δ 7.39 – 7.27 (m, 1 H), 7.22 – 7.13 (m, 1 H), 6.96 – 6.90 (m, 1 H), 6.78 – 6.68 (m, 1 H), 5.39 (br s, 1 H), 4.68 (d, J = 7.2 Hz, 2 H), 4.12 (br s, 1 H), 3.23 – 3.05 (m, 1 H), 2.65 (dd, J = 14.5, 6.5 Hz, 1 H), 2.35 (dd, J = 14.4, 6.0 Hz, 1 H), 2.26 – 2.06 (comp, 2 H), 1.72 (s, 3 H). ^{1}H NMR (500 MHz, Toluene-d_8, 27 °C) δ 7.38-6.98 (rotamers, comp, 2 H), 6.95-6.81 (m, 1 H), 6.72-6.61 (m, 1 H), 6.19-5.65 and 5.34-4.86 (rotamers, br s, 1 H), 4.77-4.36 (rotamers, comp 3 H), 3.27-2.71 (rotamers, br s, 1 H), 2.56 (dd, J = 14.26, 6.64 Hz, 1 H),

2.40-1.83 (rotamers, comp, 3 H), 1.79-1.55 (br s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 171.5, 141.6, 140.8, 133.3, 129.0, 128.6, 128.1, 127.0, 121.7, 112.0, 59.0, 53.4, 42.9, 39.0, 37.9, 36.3, 33.3, 31.0, 21.8. HRMS (ESI) *m/z* calcd for $C_{14}H_{16}BrNO$ (M+Na)+, 316.0307; found, 316.0317

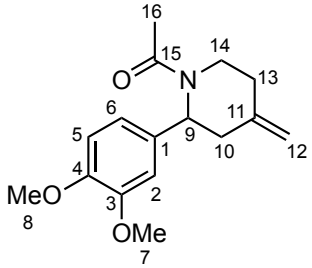
NMR assignments. For compound **2.79a:** ^{1}H NMR (500 MHz, Toluene-d_8, 100 °C) δ 7.39 – 7.27 (m, 1 H, C3-H), 7.22 – 7.13 (m, 1 H, C6-H), 6.96 – 6.90 (m, 1 H, C5-H), 6.78 – 6.68 (m, 1 H, C4-H), 5.39 (br s, 1 H, C7-H), 4.68 (d, J = 7.2 Hz, 2 H, C10-H_2), 4.12 (br s, 1 H, C12-H_{eq}), 3.23 – 3.05 (m, 1 H, C12-H_{ax}), 2.65 (dd, J = 14.5, 6.5 Hz, 1 H, C8-H_{eq}), 2.35 (dd, J = 14.4, 6.0 Hz, 1 H, C8-H_{ax}), 2.26 – 2.06 (comp, 2 H, C11-H_{eq} and C11-H_{ax}), 1.72 (s, 3 H, C14-H_3).



2.79b

1-(2-(2,3-Dimethoxyphenyl)-4-methylenepiperidin-1-yl)ethan-1-one (2.79b). Prepared in accord with the representative procedure to yield 16 mg (68%) of the title compound as a clear oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ

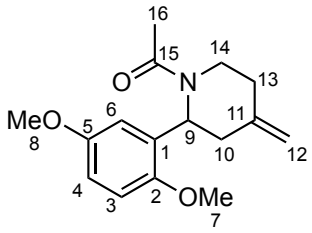
7.06-6.93 (comp, 2 H), 6.90-6.79 (comp, 2 H), 6.07-5.90 and 5.34-5.18 (rotamers, comp, 1 H), 4.95-4.80 (comp, 2 H), 4.62-4.45 and 3.77-3.62 (rotamers, comp, 1 H), 3.93-3.80 (comp, 6 H), 3.42-3.25 and 3.08-2.90 (rotamers, comp, 1 H), 2.80-2.62 (comp, 2 H), 2.46-2.32 (comp, 2 H), 2.20-2.07 (rotamers, comp, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 171.5, 169.6, 142.2, 141.6, 141.3, 140.8, 133.3, 129.0, 128.5, 128.1, 127.0, 123.8, 123.4, 121.7, 119.2, 112.0, 111.8, 111.6, 59.0, 53.5, 42.9, 38.9, 37.8, 36.3, 33.3, 31.0, 21.8. HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3$ (M+H)+, 276.1594; found, 276.1599



2.79c

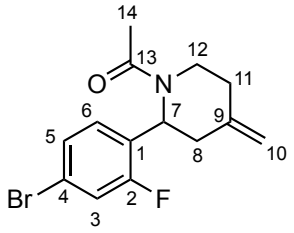
1-(2-(3,4-Dimethoxyphenyl)-4-methylenepiperidin-1-yl)ethan-1-one (2.79c). Prepared in accord with the representative procedure to yield 18 mg (76%) of the title compound as a clear oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02-6.67 (rotamers, comp, 3 H), 6.13-5.96 and 5.17-5.03 (rotamers, comp, 1 H), 5.00-4.79 (rotamers, comp, 2 H), 4.67-4.50 and 3.69-3.57 (rotamers, comp, 1 H), 3.91-3.75 (rotamers, comp, 6 H), 3.11-2.95 and 2.78-2.51 (rotamers, comp, 1 H), 2.93-2.81 (m, 1

H), 2.78-2.51 (rotamers, comp, 1 H), 2.39-2.22 (comp, 2 H), 2.21-2.15 (comp, 3 H). HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3$ (M+H)+, 276.1594; found, 276.1599



2.79d

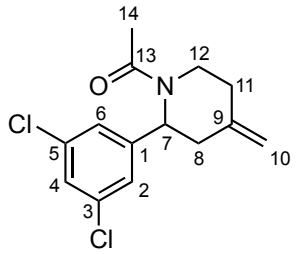
1-(2-(2,5-Dimethoxyphenyl)-4-methylenepiperidin-1-yl)ethan-1-one (2.79d). Prepared in accord with the representative procedure to yield 18 mg (76%) of the title compound as an off white solid. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-6.91 (rotamers, comp, 1 H), 6.85-6.68 (comp, 2 H), 6.05-5.89 and 5.34-5.22 (rotamers, comp, 1 H), 4.95-4.85 (comp, 2 H), 4.58-4.44 and 3.84-3.64 (rotamers, comp, 1 H), 3.84-3.64 (rotamers, comp, 6 H), 3.44-3.25 and 3.03-2.86 (rotamers, comp, 1 H), 2.78-2.61 (comp, 2 H), 2.46-2.31 (comp, 2 H), 2.17-2.07 (comp, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 170.6, 153.3, 150.8, 142.7, 130.6, 114.5, 112.3, 111.4, 111.2, 55.6, 53.4, 52.7, 37.9, 37.6, 32.7, 29.7, 21.5. HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3$ (M+Na)+, 298.1414; found, 298.1421



2.79e

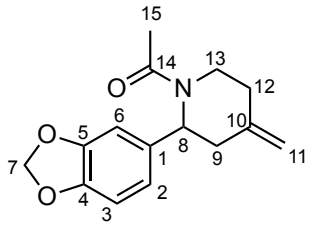
1-(2-(4-Bromo-2-fluorophenyl)-4-methylenepiperidin-1-yl)ethan-1-one

(2.79e). Prepared in accord with the representative procedure to yield 15 mg (64%) of the title compound as an off white solid. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (10:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32-7.14 (comp, 3 H), 6.08-5.92 and 5.33-5.16 (rotamers, br s, 1 H), 4.97-4.83 (comp, 2 H), 4.63-4.46 and 3.77-3.66 (rotamers, comp, 1 H), 3.30-3.10 and 2.95-2.81 (rotamers, comp, 1 H), 2.81-2.58 (comp, 2 H), 2.43-2.29 (comp, 2 H), 2.22-2.04 (rotamers, comp, 3 H). HRMS (ESI) *m/z* calcd for $C_{14}H_{15}BrFNO$ (M+H)+, 312.0394; found, 312.0400



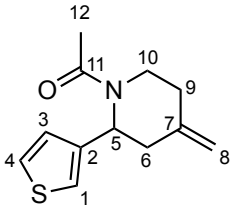
2.79f

1-(2-(3,5-Dichlorophenyl)-4-methylenepiperidin-1-yl)ethan-1-one (2.79f). Prepared in accord with the representative procedure to yield 19 mg (79%) of the title compound as an off white solid. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.06 (comp, 3 H), 6.06-5.95 and 5.11-5.01 (rotamers, comp, 1 H), 5.00-4.82 (comp, 2 H), 4.68-4.55 and 3.77-3.64 (rotamers, 1 H), 3.08-2.92 and 2.74-2.65 (rotamers, comp, 1 H) 2.89-2.77 (m, 1 H), 2.74-2.54 (m, 1 H), 2.35-2.11 (comp, 5 H). ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 169.6, 143.7, 140.7, 135.6, 135.0, 127.5, 127.2, 126.2, 125.1, 112.8, 50.1, 42.7, 38.2, 37.6, 35.5, 34.2, 32.8, 29.7, 21.8. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}BrFNO_2S$ (M+Na)+, 446.0196; found, 446.0201



2.79g

1-(2-(Benzo[*d*][1,3]dioxol-5-yl)-4-methylenepiperidin-1-yl)ethan-1-one (2.79g). Prepared in accord with the representative procedure to yield 16 mg (69%) of the title compound as a clear oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90-6.63 (comp, 3 H), 6.06-5.98 and 5.08-4.99 (rotamers, br s, 1 H), 5.96-5.85 (br s, 2 H), 4.98-4.77 (comp, 2 H), 4.65-4.49 and 3.71-3.54 (rotamers, comp, 1 H), 3.11-2.92 and 22.75-2.48 (rotamers, 1 H), 2.88-2.78 (m, 1 H), 2.75-2.48 (rotamers, comp, 1 H), 2.37-2.22 (comp, 2 H), 2.18-2.14 (br s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 141.8, 120.9, 112.1, 108.3, 107.9, 100.9, 50.3, 42.4, 37.9, 35.9, 34.4, 33.0, 29.7, 21.8. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NO_3$ (M+H)+, 260.1281; found, 260.1286

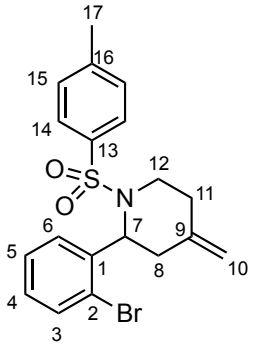


2.79h

1-(4-Methylene-2-(thiophen-3-yl)piperidin-1-yl)ethan-1-one (2.79h). Prepared in accord with the representative procedure to yield 20 mg (82%) of the title compound as a clear oil. The crude product was purified by flash column chromatography, eluting with hexanes/ethyl acetate (4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.16 and 7.14-7.06 (rotamers, comp, 2 H), 7.03-6.88 (m, 1 H), 6.17-6.00 and 5.21-5.10 (rotamers, 1 H), 4.99-4.81 (comp, 2 H), 4.63-4.53 and 3.69-3.57 (rotamers, comp, 1 H), 3.08-2.95 and 2.71-

2.51 (rotamers, comp, 1 H), 2.90-2.75 (m, 1 H), 2.71-2.51 (rotamers, comp 1 H), 2.34-2.09 (comp, 5 H). ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 169.4, 169.0, 142.1, 141.5, 141.3, 140.6, 127.7, 126.4, 125.4, 122.5, 122.1, 112.0, 54.4, 47.8, 42.5, 38.1, 38.0, 36.6, 34.6, 33.5, 29.7, 21.8, 21.6. HRMS (ESI) *m/z* calcd for $C_{12\ H15}$NOS (M+Na)+, 244.0767; found, 244.0774

Representative procedure for the tosylation of 2-arylpiperidines:

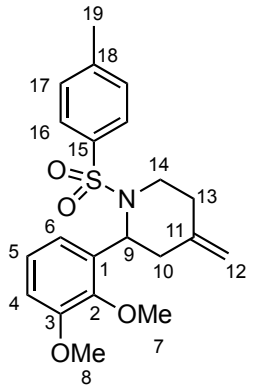


2.80a

2-(2-Bromophenyl)-4-methylene-1-tosylpiperidine (2.80a). A solution of compound **122** (100 mg, 0.4 mmol) and triethylamine (121 mg, 167 μL, 1.2 mmol) in dichloromethane (5 mL) was cooled to 0 °C, and toluenesulfonyl chloride (152 mg, 0.8 mmol) was added. The reaction was allowed to stir overnight at room temperature before cooling the solution back to 0 °C and adding pyridine (500 μL) and distilled water (500 μL) sequentially. The reaction stirred for an additional 30 minutes at room temperature before being transferred to a separatory funnel with dichloromethane (15 mL) and 1 M HCl (15 mL). The layers were separated and the aqueous layer was washed with

dichloromethane (3 x 20 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (3 x 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield 95 mg (94%) of compound **125** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.3, 2.5 Hz, 2 H), 7.47 (dq, *J* = 7.9, 1.4 Hz, 1 H), 7.34 (dq, *J* = 7.8, 1.7 Hz, 1 H), 7.21 – 7.08 (comp, 3 H), 7.04 (tdd, *J* = 7.7, 3.0, 1.7 Hz, 1 H), 5.34 (td, *J* = 6.0, 2.4 Hz, 1 H), 4.76 – 4.62 (comp, 2 H), 3.76 (dtd, *J* = 13.2, 5.4, 2.5 Hz, 1 H), 3.70 – 3.57 (m, 1 H), 2.64 (dd, *J* = 14.2, 6.3 Hz, 1H), 2.48 – 2.29 (comp, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 140.9, 139.8, 136.3, 132.9, 129.4, 128.6, 128.5, 127.3, 127.1, 122.3, 112.1, 57.9, 43.8, 38.3, 31.9, 21.5. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}BrFNO_2S$ (M+H)+, 406.0471; found, 406.0475

NMR Assignments. For **2.80a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.3, 2.5 Hz, 2 H, C14-H_2), 7.47 (dq, *J* = 7.9, 1.4 Hz, 1 H, C3-H), 7.34 (dq, *J* = 7.8, 1.7 Hz, 1 H, C6-H), 7.21 – 7.08 (comp, 3 H, C15-H_2 and C5-H), 7.04 (tdd, *J* = 7.7, 3.0, 1.7 Hz, 1 H, C4-H), 5.34 (td, *J* = 6.0, 2.4 Hz, 1 H, C7-H), 4.76 – 4.62 (comp, 2 H, C10-H), 3.76 (dtd, *J* = 13.2, 5.4, 2.5 Hz, 1 H, C12-H_{eq}), 3.70 – 3.57 (m, 1 H, C12-H_{ax}), 2.64 (dd, *J* = 14.2, 6.3 Hz, 1H, C8-H_{eq}), 2.48 – 2.29 (comp, 6 H, C8-H_{ax} and C11-H_{eq} and C11-H_{ax} and C17-H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (C2), 140.9 (C1), 139.8 (C13), 136.3 (C16), 132.9 (C4), 129.4 (C3), 128.6 (C6), 128.5 (C5), 127.3 (C14), 127.1 (C15), 122.3 (C10), 112.1 (C9), 57.9 (C7), 43.8 (C12), 38.3 (C8), 31.9 (C11), 21.5 (C17).

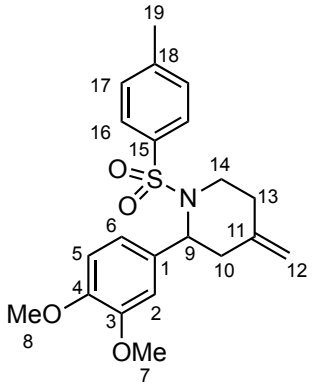


2.80b

2-(2,3-Dimethoxyphenyl)-4-methylene-1-tosylpiperidine (2.80b). Prepared in accord with the representative procedure to yield 20 mg (60%) of the title compound as a white solid. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.67 – 7.61 (comp, 2 H), 7.24 – 7.17 (comp, 2 H), 6.93 – 6.84 (comp, 2 H), 6.79 (dd, *J* = 7.7, 2.0 Hz, 1 H), 5.54 (dd, *J* = 6.7, 4.2 Hz, 1 H), 4.75 – 4.61 (comp, 2 H), 3.90 (s, 3 H), 3.87 – 3.77 (comp, 4 H), 3.51 – 3.40 (m, 1 H), 2.60 (dd, *J* = 14.0, 6.7 Hz, 1 H), 2.51 (dd, *J* = 14.0, 4.2 Hz, 1 H), 2.39 (s, 3 H), 2.33 – 2.24 (comp, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.6, 146.0, 142.9, 140.9, 137.4, 135.5, 129.3, 127.2, 123.2, 119.8, 111.5, 111.4, 60.6, 55.7, 53.4, 52.6, 43.0, 38.7, 32.2, 21.5. HRMS (ESI) *m/z* calcd for $C_{21}H_{25}NO_4S$ (M+Na)+, 410.1397; found, 410.1409

NMR Assignments. For **2.80b**: ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.67 – 7.61 (comp, 2 H, C16-H), 7.24 – 7.17 (comp, 2 H, C17-H), 6.93 – 6.84 (comp, 2 H, C4-H and C5-H), 6.79 (dd, *J* = 7.7, 2.0 Hz, 1 H, C6-H), 5.54 (dd, *J* = 6.7, 4.2 Hz, 1 H, C9-H), 4.75 – 4.61 (comp, 2 H, C12-H_2), 3.90 (s, 3 H, C7-H or C8-H), 3.87 – 3.77 (comp, 4 H, C7-H or C8-H; and C14-H_{eq}), 3.51 – 3.40 (m, 1 H, C14-H_{ax}), 2.60 (dd, *J* = 14.0, 6.7 Hz, 1 H, C10-H_{eq}), 2.51 (dd, *J* = 14.0, 4.2 Hz, 1 H, C10-H_{ax}), 2.39 (s, 3 H, C19-H_3), 2.33 – 2.24 (comp,

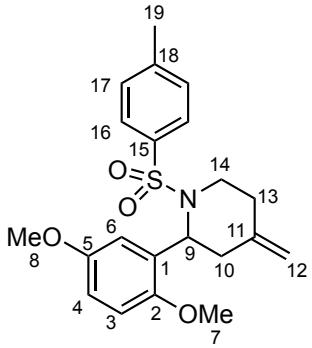
2 H, C13-H_{eq} and C13-H_{ax}). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.6 (C2), 146.0 (C3), 142.9 (C1), 140.9 (C6), 137.4 (C4), 135.5 (C5), 129.3 (C15), 127.2 (C18), 123.2 (C16), 119.8 (C17), 111.5 (C12), 111.4 (C11), 55.7 (C9), 53.4 (C7 or C8), 52.6 (C7 or C8), 43.0 (C14), 38.7 (C10), 32.2 (C13), 21.5 (C19).



2.80c

2-(3,4-Dimethoxyphenyl)-4-methylene-1-tosylpiperidine (2.80c). Prepared in accord with the representative procedure to yield 20 mg (60%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.72 (comp, 2 H), 7.30 – 7.21 (comp, 2 H), 6.92 (ddd, *J* = 8.3, 2.2, 0.9 Hz, 1 H), 6.86 (d, *J* = 2.1 Hz, 1 H), 6.75 (d, *J* = 8.3 Hz, 1 H), 5.26 (d, *J* = 6.3 Hz, 1 H), 4.86 – 4.80 (comp, 2 H), 3.84 (comp, 4 H), 3.74 (s, 3 H), 2.94 (ddd, *J* = 13.9, 12.0, 4.1 Hz, 1 H), 2.76 (d, *J* = 14.2 Hz, 1 H), 2.49 (ddd, *J* = 14.2, 6.3, 1.5 Hz, 1 H), 2.41 (s, 3 H), 2.23 – 2.06 (comp, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.7, 148.1, 143.1, 141.5, 138.5, 131.7, 129.7, 127.0, 120.1, 112.0, 111.2, 110.6, 55.8, 55.7, 55.3, 41.7, 36.1, 33.2, 21.5. HRMS (ESI) *m/z* calcd for $C_{21}H_{25}NO_4S$ (M+Na)+, 410.1397; found, 410.1403

NMR Assignments. For **2.80c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.72 (comp, 2 H, C16-H), 7.30 – 7.21 (comp, 2 H, C17-H), 6.92 (ddd, *J* = 8.3, 2.2, 0.9 Hz, 1 H, C6-H), 6.86 (d, *J* = 2.1 Hz, 1 H, C5-H), 6.75 (d, *J* = 8.3 Hz, 1 H, C2-H), 5.26 (d, *J* = 6.3 Hz, 1 H, C9-H), 4.86 – 4.80 (comp, 2 H, C12-H_2), 3.84 (comp, 4 H, C7-H_3 or C8-H_3; and C14-H_{eq}), 3.74 (s, 3 H, C7-H_3 or C8-H_3), 2.94 (ddd, *J* = 13.9, 12.0, 4.1 Hz, 1 H, C14-H_{ax}), 2.76 (d, *J* = 14.2 Hz, 1 H, C10-H_{eq}), 2.49 (ddd, *J* = 14.2, 6.3, 1.5 Hz, 1 H, C10-H_{ax}), 2.41 (s, 3 H, C19-H_3), 2.23 – 2.06 (comp, 2 H, C13-H_{eq} and C13-H_{ax}). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.7 (C2 or C5), 148.1 (C2 or C5), 143.1 (C1), 141.5 (C3 or C4), 138.5 (C3 or C4), 131.7 (C6), 129.7 (C15), 127.0 (C18), 120.1 (C16), 112.0 (C17), 111.2 (C12), 110.6 (C11), 55.8 (C7 or C8 or C9), 55.7 (C7 or C8 or C9), 55.3 (C7 or C8 or C9), 41.7 (C14), 36.1 (C10), 33.2 (C13), 21.5 (C19).

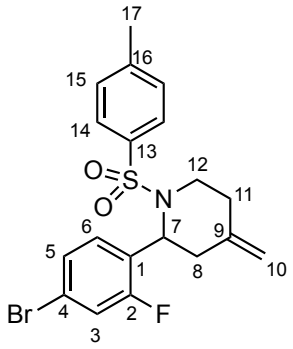


2.80d

2-(2,5-Dimethoxyphenyl)-4-methylene-1-tosylpiperidine (2.80d). Prepared in accord with the representative procedure to yield 20 mg (60%) of the title compound as a clear oil. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.61 – 7.56 (comp, 2 H), 7.22 – 7.15 (comp, 2 H),

6.95 – 6.91 (m, 1 H), 6.71 – 6.68 (comp, 2 H), 5.55 (dd, *J* = 6.4, 3.9 Hz, 1 H), 4.82 – 4.65 (comp, 2 H), 3.88 – 3.79 (m, 1 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 3.38 (ddd, *J* = 13.5, 10.9, 4.5 Hz, 1 H), 2.70 – 2.55 (comp, 2 H), 2.45 – 2.25 (comp, 5 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.9, 150.6, 142.6, 141.7, 137.9, 130.2, 129.2, 127.0, 114.9, 112.3, 111.4, 111.2, 55.6, 55.5, 51.9, 42.9, 37.9, 33.0, 21.4. HRMS (ESI) *m/z* calcd for $C_{21}H_{25}NO_4S$ (M+Na)+, 410.1397; found, 410.1410

NMR assignments: For **2.80d**: ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.61 – 7.56 (comp, 2 H, C14-H), 7.22 – 7.15 (comp, 2 H, C15-H), 6.95 – 6.91 (m, 1 H, C6-H), 6.71 – 6.68 (comp, 2 H, C3-H and C4-H), 5.55 (dd, *J* = 6.4, 3.9 Hz, 1 H, C9-H), 4.82 – 4.65 (comp, 2 H, C12-H_2), 3.88 – 3.79 (m, 1 H, C14-H_{eq}), 3.68 (s, 3 H, C7-H or C8-H), 3.66 (s, 3 H, C7-H or C8-H), 3.38 (ddd, *J* = 13.5, 10.9, 4.5 Hz, 1 H, C14-H_{ax}), 2.70 – 2.55 (comp, 2 H, C10-H_{eq} and C10-H_{ax}), 2.45 – 2.25 (comp, 5 H, C13-H_{eq} and C13-H_{ax} and C19-H_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.9 (C2), 150.6 (C5), 142.6 (C1), 141.7 (C4 or C3), 137.9 (C4 or C3), 130.2 (C6), 129.2 (C15), 127.0 (C18), 114.9 (C16), 112.3 (C17), 111.4 (C12), 111.2 (C11), 55.6 (C7 or C8), 55.5 (C7 or C8), 51.9 (C9), 42.9 (C14), 37.9 (C10), 33.0 (C13), 21.4 (C19).

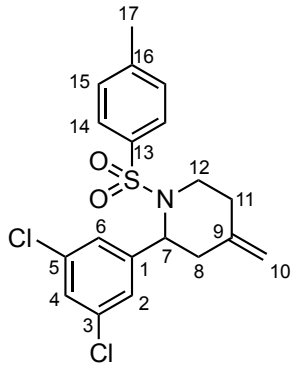


2.80e

2-(4-Bromo-2-fluorophenyl)-4-methylene-1-tosylpiperidine (2.80e). Prepared in accord with the representative procedure to yield 20 mg (65%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (comp, 2 H), 7.30 – 7.20 (comp, 3 H), 7.18 – 7.10 (comp, 2 H), 5.41 (t, *J* = 5.0 Hz, 1 H), 4.80 – 4.69 (comp, 2 H), 3.81 (dt, *J* = 13.5, 4.5 Hz, 1 H), 3.28 (ddd, *J* = 13.6, 9.7, 5.6 Hz, 1 H), 2.59 (d, *J* = 5.0 Hz, 2 H), 2.41 (s, 3 H), 2.32 – 2.22 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.7 (d, *J* = 252.0 Hz), 143.3, 140.4, 137.1, 130.1 (d, *J* = 4.5 Hz), 129.5, 127.0 (d, *J* = 17.6 Hz), 126.9 (d, *J* = 9.3 Hz), 121.4 (d, *J* = 9.8 Hz), 119.2 (d, *J* = 25.9 Hz), 112.1, 51.6, 42.9, 37.7, 32.6, 21.5. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}BrFNO_2S$ (M+Na)+, 446.0196; found, 446.0201

NMR assignments. For **2.80e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (comp, 2 H, C5-H and C6-H), 7.30 – 7.20 (comp, 3 H, C14-H and C3-H), 7.18 – 7.10 (comp, 2 H, C15), 5.41 (t, *J* = 5.0 Hz, 1 H, C9-H), 4.80 – 4.69 (comp, 2 H, C10-H_2), 3.81 (dt, *J* = 13.5, 4.5 Hz, 1 H, C12-H_{eq}), 3.28 (ddd, *J* = 13.6, 9.7, 5.6 Hz, 1 H, C12-H_{ax}), 2.59 (d, *J* = 5.0 Hz, 2 H, C8-H_{eq} and C8-H_{ax}), 2.41 (s, 3 H, C17-H_3), 2.32 – 2.22 (comp, 2 H, C11-H_{eq} and C11-H_{ax}). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.7 (d, *J* = 252.0 Hz, C2), 143.3 (C13),

140.4 (C16), 137.1 (C14), 130.1 (d, J = 4.5 Hz, C5), 129.5 (C15), 127.0 (d, J = 17.6 Hz, C1), 126.9 (d, J = 9.3 Hz, C4), 121.4 (d, J = 9.8 Hz, C6), 119.2 (d, J = 25.9 Hz, C3), 112.1 (C10), 51.6 (C7), 42.9 (C12), 37.7 (C8), 32.6 (C11), 21.5 (C17).

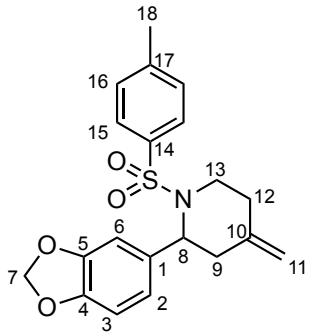


2.80f

2-(3,5-Dichlorophenyl)-4-methylene-1-tosylpiperidine (145). Prepared in accord with the representative procedure to yield 25 mg (76%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2 H), 7.32 – 7.27 (m, 2 H), 7.22 – 7.19 (m, 1 H), 7.19 – 7.15 (m, 2 H), 5.22 (d, J = 6.3 Hz, 1 H), 4.85 – 4.77 (m, 2 H), 3.96 – 3.87 (m, 1 H), 3.03 – 2.86 (m, 1 H), 2.66 (dd, J = 14.5, 2.2 Hz, 1 H), 2.43 (s, 4 H), 2.14 – 2.07 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 142.7, 139.9, 137.9, 135.0, 129.9, 127.4, 127.0, 126.2, 112.8, 55.2, 42.1, 36.0, 32.8, 21.5. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}Cl_2NO_2S$ (M+Na)+, 418.0406; found, 418.0414

NMR assignments. For **2.80f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (comp, 2 H, C14-H), 7.32 – 7.27 (comp, 2 H, C15-H), 7.22 – 7.19 (m, 1 H, C4-H), 7.19 – 7.15 (m, 2 H, C6 and C2-H), 5.22 (d, J = 6.3 Hz, 1 H, C7-H), 4.85 – 4.77 (m, 2 H, 10-H_2), 3.96 – 3.87 (m, 1 H, C12-H_{eq}), 3.03 – 2.86 (m, 1 H, C12-H_{ax}), 2.66 (dd, J = 14.5, 2.2 Hz,

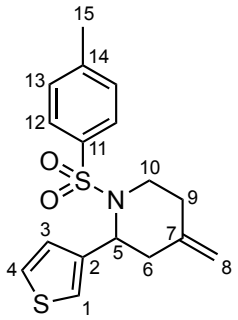
1 H, C8-H_{eq}), 2.43 (s, 4 H, C8-H_{ax} and C17-H_3), 2.14 – 2.07 (m, 2 H, C11-H_{eq} and C11-H_{ax}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C3 and C5), 142.7 (C1), 139.9 (C6 and C2), 137.9 (C4), 135.0 (C13), 129.9 (C16), 127.4 (C14), 127.0 (C15), 126.2 (C10), 112.8 (C9), 55.2 (C7), 42.1 (C12), 36.0 (C8), 32.8 (C11), 21.5 (C17).



2.80g

2-(Benzo[*d*][1,3]dioxol-5-yl)-4-methylene-1-tosylpiperidine (2.80g). Prepared in accord with the representative procedure to yield 11 mg (32%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (comp, 2 H), 7.26 (comp, 2 H), 6.88 (d, *J* = 1.9 Hz, 1 H), 6.86 – 6.82 (m, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 5.92 (d, *J* = 0.8 Hz, 2 H), 5.22 (d, *J* = 6.5 Hz, 1 H), 4.80 (comp, 2 H), 3.88 – 3.80 (m, 1 H), 2.98 (ddd, *J* = 14.0, 10.4, 5.7 Hz, 1 H), 2.71 – 2.64 (m, 1 H), 2.42 (comp, 4 H), 2.14 – 2.07 (comp, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 146.6, 143.2, 141.0, 138.3, 133.2, 129.7, 127.0, 121.2, 112.2, 108.4, 107.8, 101.0, 55.5, 41.7, 36.2, 32.9, 21.5. HRMS (ESI) *m/z* calcd for $C_{20}H_{21}NO_4S$ (M+Na)+, 394.1083; found, 394.1089

NMR assignments. For **2.80g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (comp, 2 H (C15-H), 7.26 (comp, 2 H, C15-H), 6.88 (d, *J* = 1.9 Hz, 1 H, C6-H), 6.86 – 6.82 (m, 1 H, C2-H), 6.70 (d, *J* = 8.0 Hz, 1 H, C3-H), 5.92 (d, *J* = 0.8 Hz, 2 H, C7-H_2), 5.22 (d, *J* = 6.5 Hz, 1 H, C8-H), 4.80 (comp, 2 H, C11-H_2), 3.88 – 3.80 (m, 1 H (C13-H_{eq}), 2.98 (ddd, *J* = 14.0, 10.4, 5.7 Hz, 1 H, C13-H_{ax}), 2.71 – 2.64 (m, 1 H, C9-H_{eq}), 2.42 (comp, 4 H, C9-H_{ax} and C18-H_3), 2.14 – 2.07 (comp, 2 H, C12-H_{eq} and C12-H_{ax}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (C5 or C4), 146.6 (C5 or C4), 143.2 (C1), 141.0 (C14), 138.3 (C17), 133.2 (C15), 129.7 (C16), 127.0 (C6), 121.2 (C2), 112.2 (C3), 108.4 (C11), 107.8 (C12), 101.0 (C7), 55.5 (C8), 41.7 (C13), 36.2 (C9), 32.9 (C12), 21.5 (C18).



2.80h

4-Methylene-2-(thiophen-3-yl)-1-tosylpiperidine (2.80h). Prepared in accord with the representative procedure to yield 31 mg (83%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.68 (comp, 2 H), 7.30 – 7.23 (comp, 2 H), 7.19 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.15 (dt, *J* = 2.9, 1.3 Hz, 1H), 6.97 (dd, *J* = 5.0, 1.4 Hz, 1H), 5.38 – 5.30 (m, 1 H), 4.87 – 4.76 (comp, 2 H), 3.90 – 3.79 (m, 1 H), 2.93 (ddd, *J* = 13.8,

11.1, 5.0 Hz, 1H), 2.69 – 2.60 (m, 1 H), 2.55 – 2.45 (m, 1 H), 2.41 (s, 3 H), 2.21 – 2.05 (comp, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 141.3, 140.4, 138.2, 129.7, 127.8, 127.0, 125.4, 123.0, 112.2, 52.8, 41.8, 37.1, 33.3, 21.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_2S_2$ (M+Na)+, 356.0749; found, 356.0755.

NMR assignments. For **2.80h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.68 (comp, 2 H, C12-H), 7.30 – 7.23 (comp, 2 H, C13-H), 7.19 (dd, *J* = 5.0, 3.0 Hz, 1H, C4-H), 7.15 (dt, *J* = 2.9, 1.3 Hz, 1H, C3-H), 6.97 (dd, *J* = 5.0, 1.4 Hz, 1H, C1-H), 5.38 – 5.30 (m, 1H, C5-H), 4.87 – 4.76 (comp, 2 H, C8-H_2), 3.90 – 3.79 (m, 1H, C10-H_{eq}), 2.93 (ddd, *J* = 13.8, 11.1, 5.0 Hz, 1H, C10-H_{ax}), 2.69 – 2.60 (m, 1H, C6-H_{eq}), 2.55 – 2.45 (m, 1H, C6-H_{ax}), 2.41 (s, 3 H, C15-H_3), 2.21 – 2.05 (comp, 2 H, C9-H_{eq} and C9-H_{ax}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (C11), 141.3 (C14), 140.4 (C2), 138.2 (C12), 129.7 (C13), 127.8 (C3), 127.0 (C1), 125.4 (C4), 123.0 (C8), 112.2 (C7), 52.8 (C5), 41.8 (C10), 37.1 (C6), 33.3 (C9), 21.5 (C15).

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