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Spiropiperidine Sultam and Lactam Templates: Diastereoselective Overman Rearrangement and Metathesis followed by NH Arylation

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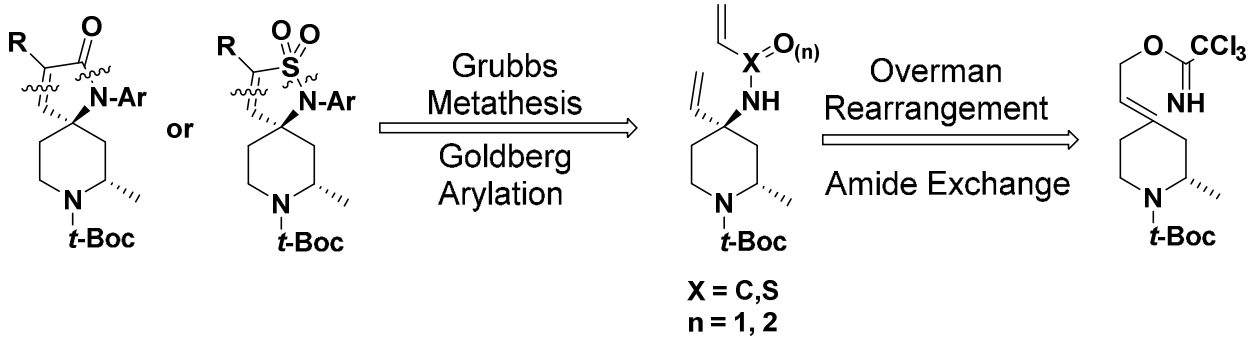
ABSTRACT

We report the diastereoselective synthesis of novel spiropiperidine templates for use in SAR studies of β-secretase (BACE) inhibitors and also as versatile ligands for other receptor types. The overall synthetic approach stems from chiral starting material benzyl (S)-2-methyl-4-

oxopiperidine-1-carboxylate and employs an Overman rearrangement to control the stereochemistry at the quaternary center. This process is followed by a Grubbs metathesis to close a 5-membered "top" ring to form an α,β-unsaturated lactam or an α,β-unsaturated sultam. We also demonstrate that this chemistry can accommodate additional substituents on the lactam/sultam ring and allows late stage sequential functionalization of the amine and amide nitrogens to rapidly produce diverse analogs.

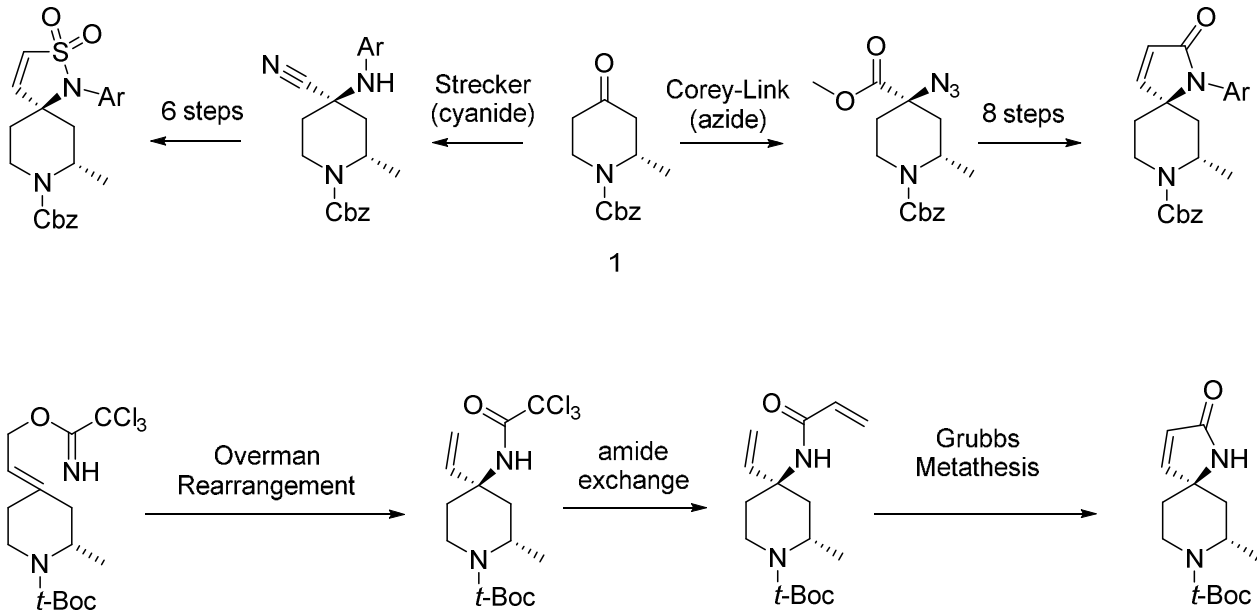


Introduction

We and others have reported the use of spiropiperidine ring systems as scaffolds for SAR studies on a multitude of protein receptors and enzymes including the aspartic acid protease β-secretase (BACE).[1] BACE inhibitors are a potentially disease modifying treatment for Alzheimer's disease (AD).[2] We were intrigued by the spiropiperidine template due to its rigidly defined binding orientation, good permeability and opportunities to explore several regions of a binding pocket. The spiropiperidine based ring system also offered a novel chemotype relative to the more common amidine based BACE inhibitors[3] and a potential differentiation if safety issues were identified for this chemical matter. Spiropiperidine based ring systems also possess an efficient ligand scaffold with a high fraction of Csp3 centers capable of spanning a large binding pocket.[4]

We previously described syntheses of this core template with the key transformation being the creation of the quaternary center through either a trichloromethyl anion addition from a Cbz piperidin-4-one[5] or from a Strecker based approach (Scheme 1).[1a] In each of those cases the quaternary center was later formed by addition of either, sodium azide ("Corey-Link") or, in the case of the Strecker synthesis, cyanide ion. We felt the synthesis would benefit from a new method that would avoid these two reagents. In the present study we describe an alternative means of forming the chiral spirocyclic center using the Overman rearrangement[6] of an allylic alcohol followed by a tandem Hoveyda-Grubbs metathesis[7] to construct the spirocyclic pyrrolidinone with good diastereoselectivity as controlled by a remote chiral center. This combination of technology has been used recently but not in the preparation of spirocyclic piperidine systems.[8]

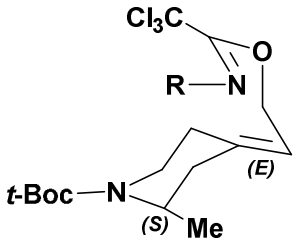
Scheme 1. Syntheses of Lactam and Sultam Templates. Overman-Grubbs process.

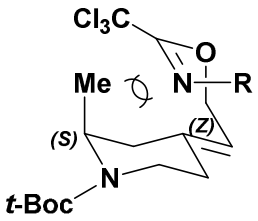


In the synthesis of the spiro-lactams and sultams from piperidine template **1**, we sought to enable an intramolecular addition of the nitrogen functionality to the face opposite the C-2

methyl established on a chiral piperidine precursor that contained all the necessary atoms for ring formation. Earlier efforts indicated that formation of the spiro-center by introduction of carbon nucleophiles was only moderately selective in the presumably thermodynamically controlled Strecker reaction,[9] and the likely kinetically controlled trichloromethyl anion addition and Corey-Link inversion.[10] The moderate selectivity of the Corey-Link process on our substrate was particularly surprising.[5] However, the selectivity was improved by increasing the size of the carbon nucleophile to further bias the approach toward the face of the ketone opposite the stereogenic methyl group. This was then followed by the inversion of the quaternary center by aniline in a Jocic process.[11] Alternatively, the "aza-Claisen" process described by Overman and adapted to our system should selectively deliver the nitrogen to the face of the olefin opposite the stereogenic methyl to afford the desired diastereomer.[6] In such a case, transition states leading to the undesired diastereomer place the trichloromethyl imidate in close proximity to the axial methyl, which we anticipated would be disfavored despite the high temperatures often reported for these reactions (Figure 1). In related series, NMR evidence at ambient temperature indicates that substituents at C-2 usually favor an axial position due to the presence of the neighboring *t*-Boc group which we anticipated should enhance its effect in the transition state.[12]

Figure 1. Proposed Overman Rearrangement Transition States





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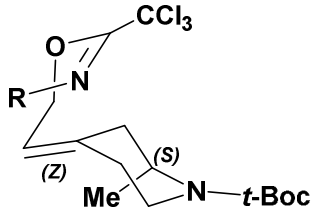
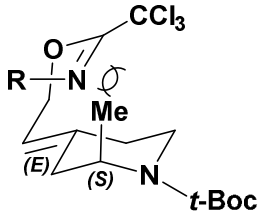
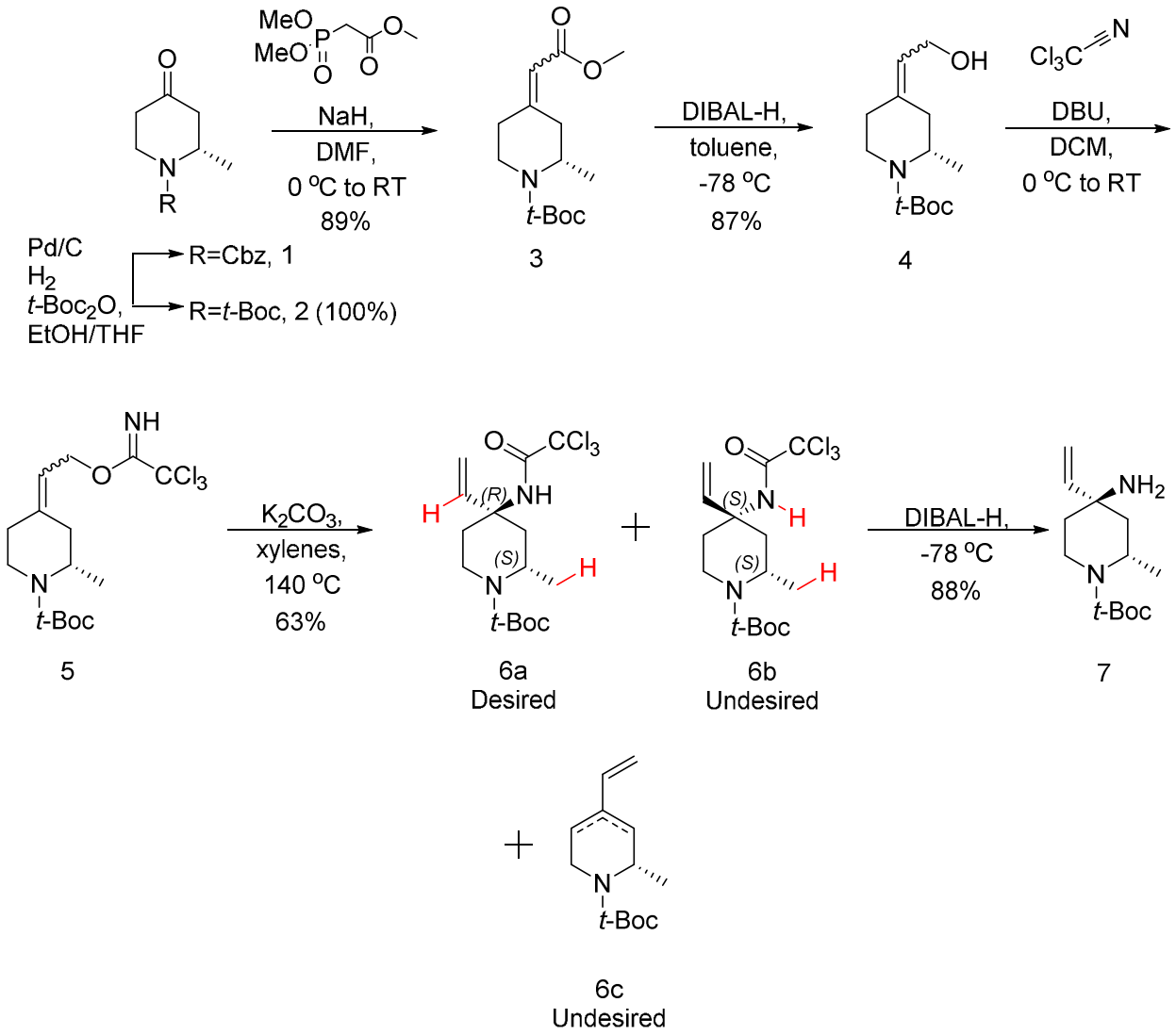




Results and Discussion

To begin the study, we had large supplies of chiral resolved **1** but we chose to replace the Cbz protecting group with *t*-Boc (Scheme 2).[13] Initial exploration had demonstrated that the Cbz protecting group on our bulk supply of ketone was incompatible with subsequent ester reduction conditions later in the sequence. In addition, we found that the *t*-Boc protecting group afforded crystalline intermediates, which provided opportunities to improve the d.r. at several points in the sequence. The desired protecting group was installed through catalytic hydrogenolysis of **1** in the presence of *t*-Boc anhydride. A Horner-Wadsworth-Emmons reaction[14] applied to **2** generated an inconsequential 1:1 mixture of *Z:E* isomers of the desired α,β-unsaturated ester **3** in high yield. Reduction of the ester with DIBAL-H efficiently provided the desired allylic alcohol **4**, also as a 1:1 mixture. Alcohol **4** was then treated with trichloroacetonitrile to afford isomeric trichloro-imidates **5**.

Scheme 2. Overman Process for the Synthesis of Allylic Amine **7**



We initially investigated a Pd(II) mediated rearrangement of **5** under mild conditions.[15] When **5** was treated with $PdCl_2$ in the presence of base, we observed rapid formation of undesired allylic amide **6b** as a minor product. However, the majority of the material isolated was comprised of dienes 6c from this and other similar reactions under catalysis. We explored other palladium catalysts and reaction conditions to prevent this result, but found that reaction to the undesired 2(S),4(S) configuration predominated ultimately leading to mixtures of 6b and 6c.[16] Presumably, the palladium catalyst complexes the less hindered face of the allylic imidate and

drives the rearrangement to occur on the more hindered side of the olefin to afford **6b** or the degradation products **6c**.

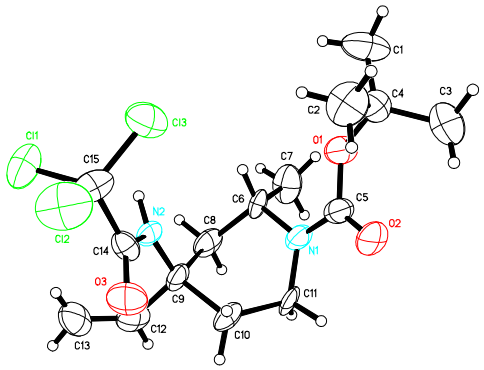
We then explored an uncatalyzed thermal transformation. Trichloro-imidate **5** was heated in xylenes at 140 ^{o}C in the presence of potassium carbonate to induce the Overman rearrangement.[17] ^{1}H-NMR analysis of the reaction mixture was consistent with a 4:1 mixture of trichloroacetamide diastereomers. We observed that inclusion of base prevented decomposition of the products. When the *Z* and *E* isomers of **5** were separately subjected to the Overman conditions we observed no difference in the rate of the reaction or the ratio of the products. Both isomers yielded a ~4:1 mixture of diastereomers after 48 h under the above conditions. Examination of models revealed that *Z* and *E* isomers of **5** favor approach from the face opposite the axial methyl (Figure 1). Trituration of the crude reaction mixture with ether effected crystallization of major diastereomer **6a** in 63% yield. NOE analysis of **6a** showed a strong interaction between the methine proton of the vinyl group and the piperidine methyl (H's labeled in red in Scheme 2), which is consistent with the desired *trans* arrangement of the amide and C-2 methyl. Single crystal X-ray analysis confirmed this conclusion (Figure 2). The undesired diastereomer, **6b**, was isolated via column chromatography of the crystallization filtrate. NOE analysis of **6b** showed an interaction between the trichloroacetamide NH and the piperidine methyl (H's also labeled in red in Scheme 2).

In an effort to reduce the reaction time on increased scale, we studied the rearrangement under continuous flow conditions. The role of temperature (160-225^{o}C), concentration (0.02 M – 0.5 M), equivalents of base (0 – 2.0 eq.), time (30-45 min.) and solvents (iPrOH, NMP, toluene) were investigated. Significant improvement in the time needed for the transformation was achieved and eventually 325g of **6a** was obtained from the reaction in toluene at 180 ^{o}C, for

45min. using 0.025 equiv. triethylamine, with a substrate concentration of 0.25M as a 3:1 mixture of **6a/b**. We observed that the increase in temperature, even for a shorter duration than the batch process, resulted in a slight decrease in diastereoselectivity. However, the pure diastereomer was obtained in a similar yield after trituration with ether.

After some experimentation, we found that the trichloroacetyl was efficiently removed with DIBAL-H at –78 ^{o}C to provide amine **7** in 88% yield. Overall, the diastereoselectivity of the Overman process was found to be reasonable at the required reaction temperature and we were gratified that significant amounts of purified material could be obtained by this approach.

Figure 2. Single crystal x-ray of *trans*-trichloroacetamide **6a.**

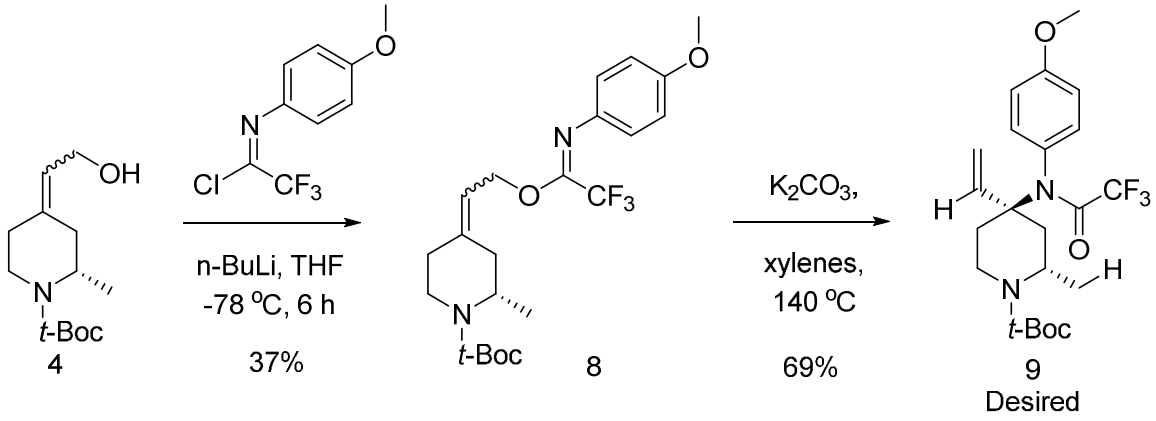


6a

We did examine additional approaches to improve the selectivity of the rearrangement based on the likely transition state. Steric effects from a removable group on nitrogen would destabilize the undesired transition state enhancing the desired product. We prepared the *N*-*p*-methoxyphenyl (*N*-PMP) trifluoroacetimidate **8** from the commercially available trifluoro-*N*-(4-methoxyphenyl)acetimidoyl chloride as described by Berkowitz *et. al*, using our piperidine substrate, **4**.[15b] (Scheme 3). When **8** was subjected to the thermal rearrangement, an improved 7:1 diastereomeric mixture of the corresponding desired *trans*-diastereomer was indeed observed by

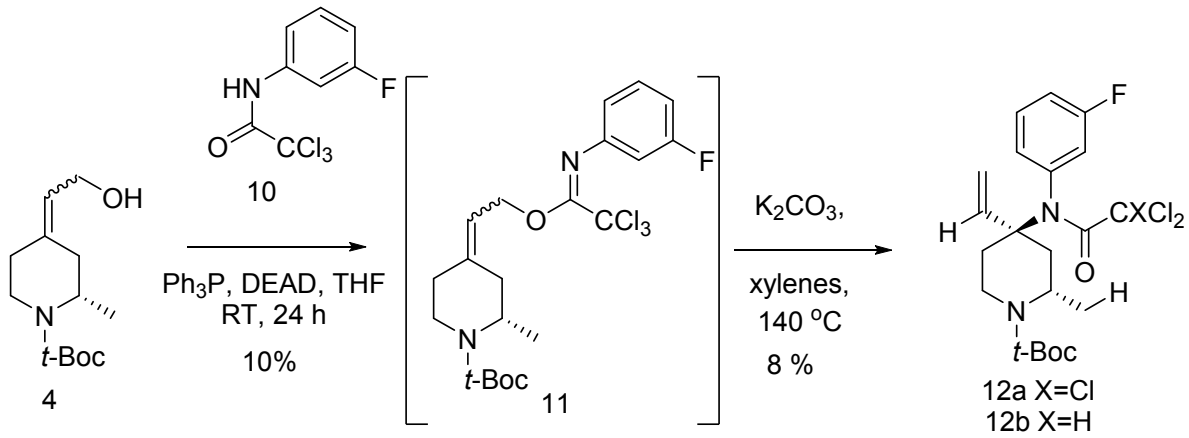
NMR. This indicates that the size of the imidate substituent does influence the *cis/trans* ratio. Unfortunately, selective removal of the PMP group in high yield was problematic. For instance, when ceric ammonium nitrate was used to remove the PMP group, the *t*-Boc protecting group also was cleaved due to the pH of the reaction. Variation of equivalents or use of any other reagents proved to be unsuccessful in cleaving the PMP group.

Scheme 3. Overman Process for the Synthesis of Allylic Amine **9**



We then attempted the Overman rearrangement with one of our key aromatic substituents, 3-fluorophenyl aniline. (Scheme 4) Imidate **11** was made in low yield via dehydration of the trichloroacetylamide **10** and alcohol **4** with triphenyl phosphine and DEAD.

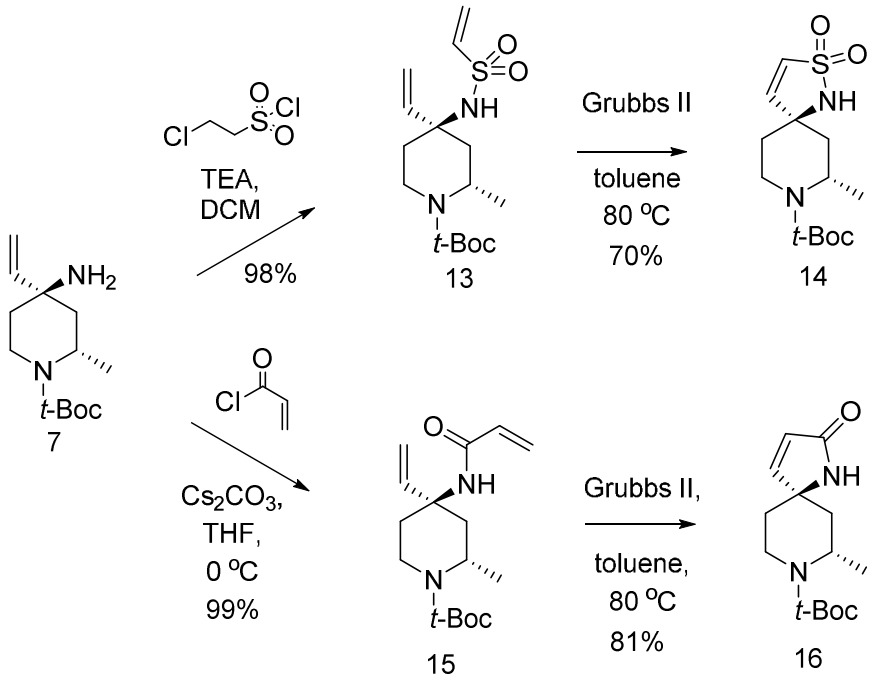
Scheme 4. Overman Process for the Synthesis of Allylic 3-Fluoroaniline **12**



Thermal rearrangement of **11** was very slow at high temperature. After 48 h the reaction was stopped and the products isolated through careful chromatography. Interestingly none of the desired product **12a** was found but we obtained a low yield of the related dichloroacetamide **12b** accompanied by a significant amount of the undesired diene adduct. Clearly the overall rearrangement process in this case was more complex than expected. We believe that the electron deficiency of the new imidate contributed to the slow rate and elimination side reaction. In addition, it is possible that at high temperature a radical process was initiated that lead to a halogen transfer reaction of the desired **12a** to form **12b** with chlorination of the solvent or other species. Although further improvement in selectivity was not possible, we were pleased that we had a sequence that provided highly purified template on scale, after crystallization, from a process with acceptable diastereoselectivity that has allowed a broad SAR investigation. We moved to the completion of the lactam synthesis and postponed the incorporation of the aromatic functionality to the end of the route.

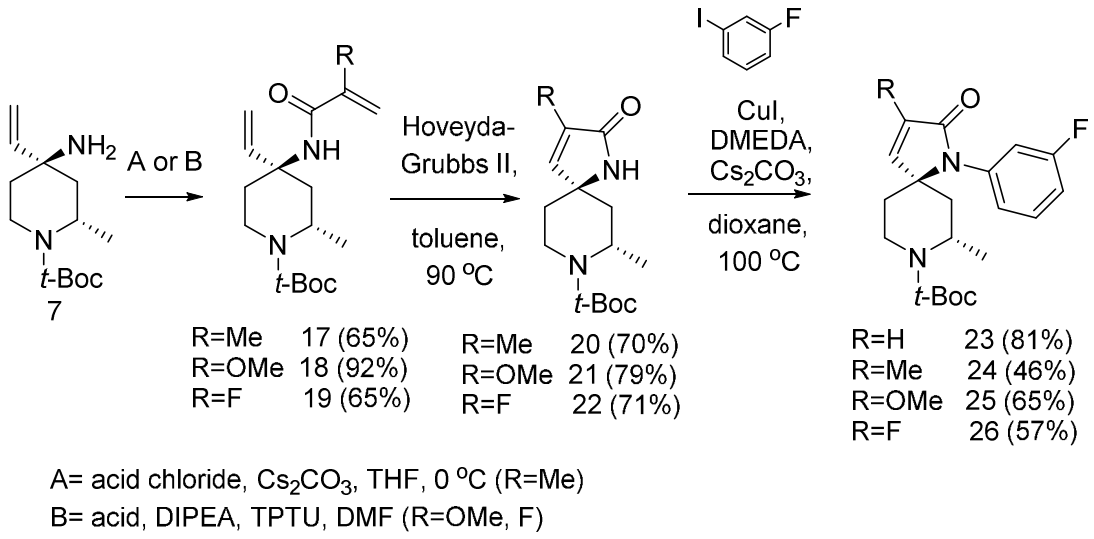
We were able convert the allylic amine **7** to a range of spirocyclic lactams and sultams (Scheme 5). The sultam synthesis was initiated by sulfonylating the free amine **7** with chloroethanesulfonyl chloride in the presence of triethylamine to afford di-olefin **13** directly. The lactam synthesis stemmed from the acylation of amine **7** with acryloyl chloride to afford the di-olefin **15**. Ring closing-metathesis using the second generation Grubbs catalyst furnished the sultam **14** and lactam **16** in the respective syntheses in good yields.[18]

Scheme 5. Grubbs Process for the Synthesis of Sultam **14** and Lactam **16**.



This approach also allowed for introduction of substituents at the 3-position of the lactam or sultam (Scheme 6). The amine **7** was acylated with an acid chloride, as in the case of α-Me **17**, or via amide coupling using an α-substituted acid, as in the case of α-methoxy **18** and α-fluoro **19.** With these more hindered olefins, we employed the Hoveyda-Grubbs second generation catalyst[19] for the ring closing metatheses to furnish lactams **20-22**. As we had done in the previous paper, [5a] these N-H lactams were subsequently arylated via the Goldberg reaction with excess diamine ligand using copper (I) iodide and *m*-iodofluorobenzene, as well as other aryl halides to generate lactams **23-26**.[20]

Scheme 6. Hoveyda-Grubbs Process for the Synthesis of α-Substituted Lactams.

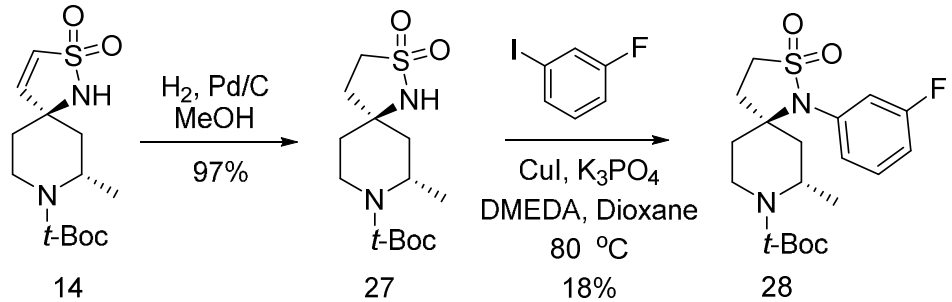


A= acid chloride, Cs_2CO_3, THF, 0 °C (R=Me)
B= acid, DIPEA, TPTU, DMF (R=OMe, F)

We also made several unsuccessful attempts at the direct arylation of sultam **14** using palladium or copper chemistry. When palladium was used, Heck addition of the aryl group to the carbon alpha to the sulfonamide was observed. When copper-based systems were used, no reaction was observed and starting material was recovered.

We shifted our attention to arylating **27** (Scheme 7). This saturated sultam was obtained in high yield via catalytic hydrogenation of **14**. Goldberg arylation of **27** provided the desired *m*-fluorophenyl sultam **28** in moderate yield but allowed us access to a novel spiropiperidine class for SAR investigation.

Scheme 7. Arylation of Saturated Sultam.



14 27 28

Conclusion

In summary, we have developed a new, more convergent synthesis of spiro-sultams and lactams based on an Overman-Grubbs tandem process that allows access to these novel structures. The new route enabled SAR exploration in both series of BACE inhibitors around each nitrogen substituent as well as the lactam or sultam ring substituents. The route avoids the use of toxic reagents such as cyanide or azide and allows for rapid functionalization of the spiro-lactam alpha to the carbonyl, and for variation of the *N*-aryl group late in the synthesis of the sultam and lactam. Also, the crystallization that afforded **6a**, followed by a series of stereospecific transformations allowed for the preparation of spirosultam **14** and spirolactam **16** as a single diastereomer, thus eliminating the potential need to use prep-HPLC for stereoisomer separation. Arylation of the lactams **16** and **20-22** and saturated sultam **27** has already proven quite useful as a tool to expand SAR. A discussion of the spiropiperidine lactam and sultam SAR that resulted from this work will be presented in the near future.

Experimental Section

General Methods. Solvents and reagents were of reagent grade, anhydrous (unless otherwise noted) and were used as supplied by the manufacturer. All reactions were run under a N_2 atmosphere. Organic extracts were routinely dried over anhydrous Na_2SO_4. Concentration refers to rotary evaporation under reduced pressure. Chromatography refers to flash chromatography using disposable RediSepR_f 4 to 330 g silica columns or Biotage disposable columns on a CombiFlash Companion or Biotage Horizon automatic purification system.

NMR Analysis. $CDCl_3$ (99.9%) was purchased in sealed ampules from Cambridge Isotopes. Yields reported are isolated yields unless otherwise noted. NMR spectra were recorded on a

Bruker AMX 400 and Varian XL 300 MHz NMR spectrometer (for ^{1}H and ^{13}C).The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, b = broad, at = apparent triplet, ad = apparent doublet. Optical rotations were obtained using a JASCO P-2000 polarimeter and the sample solutions were prepared using MeOH as the solvent. High resolution mass spectra were recorded on an Agilent-Masshunter spectrometer using ESI ionization (electrospray positive) and time of flight (TOF) mass analyzer.

(*S*)-*tert*-Butyl 2-methyl-4-oxopiperidine-1-carboxylate 2: Into a Parr Shaker flask was added Pd/C (50% wet, 1.05 g), EtOH (40 mL, absolute), THF (40 mL) and (*S*)-benzyl 2-methyl-4-oxopiperidine-1-carboxylate[1] (5.0 g, 20 mmol). To the resulting suspension was added di-tert-butyl dicarbonate (4.85 g, 22 mmol). The flask was placed in a Parr Shaker hydrogenation equipment under a H_2 atmosphere. The solution was first saturated with H_2, and then an internal pressure of 15 PSI was set. The resulting heterogeneous solution was shaken at rt until complete consumption of starting material was observed. The reaction mixture was then filtered through a Celite pad and the pad was washed with EtOH (3x). The combined filtrates were concentrated under reduced pressure to afford (*S*)-*tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate (4.26 g, 20 mmol, 99%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (br. s., 1 H), 4.16 (ddd, *J*=13.6, 6.7, 2.7 Hz, 1 H), 3.25 (ddd, *J*=13.8, 11.2, 3.9 Hz, 1 H), 2.61 (dd, *J*=14.6, 6.8 Hz, 1 H), 2.35 - 2.44 (m, 1 H), 2.23 - 2.31 (m, 1 H), 2.18 (dt, *J*=14.6, 2.1 Hz, 1 H), 1.39 - 1.46 (m, 9 H), 1.11 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 154.4, 80.3, 47.9, 46.6, 40.6, 38.2 - 38.4, 28.3 - 28.5, 18.9 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{11}H_{19}NNaO_3$ 236.1257; found, 236.1266; $[\alpha]_D^{25}$: +25.5 (*c* = 0.10g/100mL; MeOH).

(*S*)-*tert*-Butyl 4-(2-methoxy-2-oxoethylidene)-2-methylpiperidine-1-carboxylate 3: A three neck round bottomed flask was charged with sodium hydride (0.975 g, 24.4 mmol, 60% in mineral oil). The sodium hydride was washed with hexanes (2x50 mL) and then suspended in DMF (35 mL). The mixture was then cooled to 0 ^{o}C. Methyl 2-(dimethoxyphosphoryl)acetate (3.38 mL, 23.4 mmol) was added in a dropwise manner to the reaction mixture. The mixture was then held at 0 ^{o}C for 20 min with a vigorous stirring. A solution of (*S*)-*tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate (4.00 g, 18.8 mmol) in DMF (10 mL) was added to the reaction mixture in a dropwise manner. The resulting solution was then allowed to reach rt and stir for 16 h. The reaction mixture was diluted with Et_2O (250 mL). Then the mixture was washed with H_2O (500 mL), then the resulting aqueous layer was back extracted with Et_2O (3x). The organic layers were combined and washed with H_2O (4x), brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford (*S*)-*tert*-butyl 4-(2-methoxy-2-oxoethylidene)-2-methylpiperidine-1-carboxylate (4.35 g, 16.1 mmol, 86%) as an oil and a 1:1 mixture of *Z:E* isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (s, 1H), 5.65 (s, 1H), 4.54-4.35 (m, 2H), 4.10 – 3.87 (m, 2H), 3.63 (d, *J* = 3.0 Hz, 6H), 3.60 – 3.47 (m, 2H), 2.98 – 2.83 (m, 2H), 2.48 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.24 – 2.09 (m, 4H), 2.01 (ddd, *J* = 13.5, 3.0, 1.3 Hz, 1H), 1.40 (s, 18H), 1.01 (dd, *J* = 6.9, 3.6 Hz, 6H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.72, 166.5, 156.8, 156.7, 154.6, 116.5, 116.3, 79.7, 79.7, 50.9, 50.97, 41.5, 36.4, 34.4, 29.4, 28.5, 28.5, 17.3, 16.8 ppm. HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{14}H_{23}NNaO_4$; 292.1519; found, 292.1518; $[\alpha]_D^{25}$: +29.7 (*c* = 0.30g/100mL; MeOH).

(*S*)-*tert*-Butyl-4-(2-hydroxyethylidene)-2-methylpiperidine-1-carboxylate 4: To a toluene solution (530 mL) of (*S*)-*tert*-butyl 4-(2-methoxy-2-oxoethylidene)-2-methylpiperidine-1-

carboxylate (21.3 g, 79.1 mmol) at -78 °C, was added DIBAl-H (132 mL, 198 mmol, 1.5 M in toluene) in a dropwise manner. The mixture was stirred at -78 °C until complete consumption of starting material. MeOH (4.0 mL) was then added to the reaction mixture and the resulting solution was allowed to slowly warm up to rt. H_2O (250 mL) was added and the resulting solution was allowed to stir at rt for 2 h. The precipitate was removed by Celite filtration. The Celite plug was washed with EtOAc (3x). The filtrate was concentrated under reduced pressure and purified by flash column chromatography, using a gradient of EtOAc in heptanes (0 to 100%), to afford (*S*)-*tert*-butyl-4-(2-hydroxyethylidene)-2-methylpiperidine-1-carboxylate (16.6 g, 68.8 mmol, 87%) as an oil and a 1:1 mixture of *Z:E* isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (t, *J*=7.0 Hz, 1 H), 5.41 (t, *J*=7.0 Hz, 1 H), 4.45 (br. s., 1 H), 4.36 (br. s., 1 H), 4.12 (d, *J*=7.0 Hz, 2 H), 4.08 (dd, *J*=7.0, 3.9 Hz, 2 H), 3.90 - 4.00 (m, 2 H), 2.74 - 2.86 (m, 2 H), 2.29 - 2.47 (m, 4 H), 2.15 - 2.05 (m, 3 H), 1.98 - 1.88 (m, 3 H), 1.40 (s, 18 H), 0.98 (t, *J*=7.2 Hz, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 137.1, 136.7, 124.6, 124.6, 79.5, 79.5, 58.5, 40.6, 35.7, 35.6, 28.5, 28.1, 16.7, 16.5 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{13}H_{23}NO_3Na$ 264.157; found 264.1568.; $[\alpha]_D^{26}$: +42.9 (*c* = 0.20g/100mL; MeOH).

***tert*-Butyl (2*S*, 4*R*)-2-methyl-4-(2,2,2-trichloroacetamido)-4-vinylpiperidine-1-carboxylate 6a:** Trichloroacetonitrile (10.3 mL, 103 mmol) was added to a DCM (475 mL) solution of (*S*)-*tert*-butyl-4-(2-hydroxyethylidene)-2-methylpiperidine-1-carboxylate (16.6 g, 68.8 mmol) and DBU (2.17mL, 13.8mmol) at 0 °C. The resulting solution was allowed to warm slowly to rt. After 2 h, the reaction mixture was concentrated under reduced pressure to yield an oily residue. This residue was purified by flash column chromatography, eluting with EtOAc and heptanes, to

afford the intermediate *tert*-butyl (*S*)-2-methyl-4-(2-(2,2,2-trichloro-1-iminoethoxy)ethylidene)piperidine-1-carboxylate (23.2 g, 60.5 mmol, 88%) as an oily residue.

To a xylenes (2.0 L) solution of (*S*)-2-methyl-4-(2-(2,2,2-trichloro-1-iminoethoxy)ethylidene)piperidine-1-carboxylate (23.2 g, 60.5 mmol) was added K_2CO_3 (72.1 g, 520 mmol) and the resulting heterogeneous solution was treated at 140 ^oC for 72 h. Then the reaction mixture was cooled down to rt and filtered through Celite. The Celite plug was washed with xylenes (3x) and the combined filtrates were concentrated under reduced pressure to yield a yellow solid. Trituration of the organic crude with Et_2O (50 mL) afforded *tert*-butyl (2*S*,4*R*)-2-methyl-4-(2,2,2-trichloroacetamido)-4-vinylpiperidine-1-carboxylate (14.6 g, 38.2 mmol, 63%) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 1H), 5.99 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.30 – 5.13 (m, 2H), 4.14 (h, *J* = 6.6 Hz, 1H), 3.93 (ddd, *J* = 14.2, 6.2, 2.6 Hz, 1H), 2.98 (ddd, *J* = 14.2, 11.6, 4.5 Hz, 1H), 2.32 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.10 (dt, *J* = 14.0, 3.6 Hz, 1H), 1.91 – 1.74 (m, 2H), 1.38 (s, 9H), 1.11 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 154.5, 139.5, 115.0, 92.9, 79.8, 56.2, 45.8, 38.4, 35.2, 34.6, 28.5, 18.5 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{15}H_{23}Cl_3N_2NaO_3$; 407.0666; found 407.067; $[\alpha]_D^{23}$: +31.8 (*c* = 0.25g/100mL; MeOH).

***tert*-Butyl (2*S*,4*S*)-2-methyl-4-(2,2,2-trichloroacetamido)-4-vinylpiperidine-1-carboxylate 6b**: The undesired amide from the Overman rearrangement reaction was isolated via column chromatography from the crystallization filtrate. The filtrate was concentrated under reduced pressure and purified by flash column chromatography, using a gradient of EtOAc in heptanes (0 to 100%), to afford *tert*-butyl (2*S*,4*S*)-2-methyl-4-(2,2,2-trichloroacetamido)-4-vinylpiperidine-1-carboxylate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 5.79 (dd, *J* = 17.3, 10.7

Hz, 1H), 5.17 – 5.03 (m, 2H), 4.41 – 4.27 (m, 1H), 3.95 (ddd, *J* = 14.2, 4.7, 2.6 Hz, 1H), 2.94 (td, *J* = 13.7, 2.5 Hz, 1H), 2.26 (dq, *J* = 14.3, 2.6 Hz, 1H), 2.13 (dt, *J* = 14.8, 2.3 Hz, 1H), 1.80 (dd, *J* = 14.7, 6.7 Hz, 1H), 1.61 (td, *J* = 13.7, 4.7 Hz, 1H), 1.39 (s, 9H), 1.22 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 154.5, 140.6, 113.6, 93.1, 79.8, 56.4, 44.9, 37.9, 34.3, 33.4, 28.4, 17.5 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{15}H_{23}Cl_3N_2NaO_3$ 407.0666; found 407.065; $[\alpha]_D^{25}$: +37.9 (*c* = 0.20g/100mL).

***tert*-Butyl (2*S*,4*R*)-4-amino-2-methyl-4-vinylpiperidine-1-carboxylate 7:** A 500 mL round bottomed flask. was charged with *tert*-butyl (2*S,*4*R*)-2-methyl-4-(2,2,2-trichloroacetamido)-4-vinylpiperidine-1-carboxylate (16.26 g, 42.16 mmol) and DCM (324 mL). The resulting solution was cooled down to -78 ^{o}C, and then DIBAl-H (42.2 mL, 63.2 mmol, 1.5 M in toluene) was added to the reaction mixture solution in a dropwise manner. The resulting solution was stirred at -78 ^{o}C for 1 h. After that time, the reaction mixture was then diluted with brine (250 mL, aq.) and EtOAc (500 mL). The resulting heterogeneous solution was allowed to warm up slowly to rt. and stirred at rt for 3h. Solids formed were filtered through Celite and the Celite pad was washed with EtOAc (5x). The filtrates were combined and the layers were separated. Aqueous layer was extracted with EtOAc (3x). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a clear oily residue. Flash column chromatography of the organic crude, using a solvent system of 1% of a (20% NH_4OH in MeOH solution) in 99% EtOAc to 10% of a (20% NH_4OH in MeOH solution) in 90% EtOAc, afforded *tert*-butyl (2*S*,4*R*)-4-amino-2-methyl-4-vinylpiperidine-1-carboxylate (9.71 g, 40.4 mmol, 96%) as a clear oily residue. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.11 (d, *J* = 17.6 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.26 (pd, *J* = 6.8, 3.8 Hz, 1H), 3.91 – 3.77 (m, 1H), 2.92

(ddd, J = 13.9, 12.4, 3.1 Hz, 1H), 1.84 (ddt, J = 13.5, 4.7, 2.1 Hz, 1H), 1.66 – 1.51 (m, 2H), 1.39 (s, 10H), 1.07 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 145.7, 111.9, 79.3, 50.8, 46.4, 43.5, 37.3, 36.7, 28.5, 18.4 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{13}H_{24}N_2NaO_2$ 263.173; found 263.1719; $[\alpha]_D^{27}$: +16.7 (c = 0.23g/100mL; MeOH).

***tert*-Butyl (2*S*,4*R*)-2-methyl-4-(2,2,2-trifluoro-N-(4-methoxyphenyl)acetamido)-4-vinylpiperidine-1-carboxylate 9:** To a solution of (*S*)-*tert*-butyl-4-(2-hydroxyethylidene)-2-methylpiperidine-1-carboxylate (0.806 g, 3.34 mmol) in THF (23.9 mL, anhydrous) at -78 ^{o}C was added *n*-butyllithium (1.60 mL, 4.01 mmol, 2.5 M in hexanes) in a dropwise manner. After 40 min. at -78 ^{o}C, a THF (5 mL, anhydrous) solution of 2,2,2-trifluoro-N-(4-methoxyphenyl)acetimidoyl chloride (1.19 g, 5.01 mmol) was added in a dropwise manner. The resulting reaction mixture was stirred at -78 ^{o}C under N_2, for 5.5 h. The reaction mixture was quenched with ammonium chloride (aqueous, saturated, 100 mL) and organics were then extracted with ethyl acetate (3x). Combined organics were then washed with brine (1x), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield an oily residue. This residue was purified by flash column chromatography, eluting with ethyl acetate and heptanes, to afford the intermediate *tert*-butyl (*S*,*Z*)-2-methyl-4-(2-(2,2,2-trifluoro-1-((4-methoxyphenyl)imino)ethoxy)ethylidene)piperidine-1-carboxylate (0.54 g, 1.22 mmol, 37%) as an oily residue.

To a xylenes (500 mL) solution of *tert*-butyl (*S*,*Z*)-2-methyl-4-(2-(2,2,2-trifluoro-1-((4-methoxyphenyl)imino)ethoxy)ethylidene)piperidine-1-carboxylate (0.54 g, 1.22 mmol) was added K_2CO_3 (1.47 g, 10.5 mmol) and the resulting heterogeneous solution was treated at 135 ^{o}C for 48 h. Then the reaction mixture was cooled down to rt and filtered through Celite. The Celite

plug was washed with xylenes (3x) and the combined filtrates were concentrated under reduced pressure to yield a yellow solid. This solid was purified by flash column chromatography, eluting with ethyl acetate and heptanes, to afford *tert*-butyl (2*S*,4*R*)-2-methyl-4-(2,2,2-trifluoro-N-(4-methoxyphenyl)acetamido)-4-vinylpiperidine-1-carboxylate (0.37 g, 0.84 mmol, 69%) as a clear oily residue. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.01 (m, 2H), 6.93 – 6.81 (m, 2H), 6.58 (ddd, *J* = 17.8, 10.8, 0.8 Hz, 1H), 5.43 – 5.23 (m, 2H), 4.42 – 4.24 (m, 1H), 3.90-3.81 (m, 4H), 2.89 (ddd, *J* = 13.9, 12.5, 2.7 Hz, 1H), 2.50 (dt, *J* = 13.7, 2.6 Hz, 1H), 2.02 – 1.85 (m, 2H), 1.45-1.35 (m, 10H), 1.13 (d, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 156.8, 154.4, 139.8, 132.1, 131.8, 128.3, 127.1, 115.7, 114.7, 113.7, 113.6, 79.6, 63.6, 55.4, 46.3, 39.1, 35.6, 33.4, 28.4, 18.2 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{22}H_{29}F_3N_2NaO_4$ 465.1971; found 465.1972; $[\alpha]_D^{23}$: +45.2 (*c* = 0.37g/100mL; MeOH).

2,2,2-trichloro-N-(3-fluorophenyl)acetamide 10: To a solution of *m*-fluoroaniline (5.0 g, 45.0 mmol) in THF (118 mL) was added DMAP (6.87 g, 56.2 mmol) and 2,2,2-trichloroacetyl chloride (8.59 g, 47.2 mmol) at 0 ^{o}C. The resulting white heterogeneous solution was left stirring at rt over 16 h. The reaction mixture was poured on ice water (300 mL) and organics were then extracted with ethyl acetate (3 x). Combined organic layers were then washed with brine (1 x), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield an oily residue. Flash column chromatography of the organic crude oily residue, using a gradient of EtOAc in heptanes (0 to 15 %) afforded 2,2,2-trichloro-N-(3-fluorophenyl)acetamide **10** (11.3 g, 43.9 mmol, 98%) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.52 (dt, J = 10.4, 2.3 Hz, 1H), 7.36 (td, J = 8.2, 6.2 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.95 (tdd, J = 8.3, 2.5, 0.9 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.2 – 187.2 (m), 187.6 – 186.2 (m),

168.0 – 166.0 (m), 164.2, 161.7, 159.2, 138.7 – 136.4 (m), 130.5 (d, J = 9.5 Hz), 115.7 (d, J = 3.2 Hz), 112.9 (d, J = 21.4 Hz), 107.9 (d, J = 26.9 Hz) ppm; HRMS (ESI-TOF) m/z: [MH] + Calcd for $C_8H_5Cl_3FNO$; 256.4719; found 256.4722.

tert*-butyl *(2S,4R)*-4-(2,2-dichloro-N-(3-fluorophenyl)acetamido)-2-methyl-4-vinylpiperidine-1-carboxylate 12b*: To a chilled (ice-water) solution of 2,2,2-trichloro-*N*-(3-fluorophenyl)acetamide 10 (1.0 g, 4.14 mmol), *tert*-butyl (*S*)-4-(2-hydroxyethylidene)-2-methylpiperidine-1-carboxylate 4 (1.06g, 4.14mmol), Triphenylphosphine (1.20 g, 4.56 mmol) in THF (8mL) was added Diethyl azodicarboxylate (0.718 mL, 4.56 mmol) in a drop wise manner. The resulting solution was stirred at 0 ^oC for 30 min. and allowed to reach rt over 16 h. The reaction mixture was concentrated under reduced pressure to yield an orange oily residue. This residue was purified by flash column chromatography, eluting with ethyl acetate and heptanes, to afford the intermediate *tert*-butyl (*S*,*Z*)-2-methyl-4-(2-(2,2,2-trichloro-1-((3-fluorophenyl)imino)ethoxy)ethylidene)piperidine-1-carboxylate (0.18 g, 0.37 mmol, 9 %) as an oily residue that was used as is for the next step reaction.

To a xylenes (12 mL) solution of *tert*-butyl (*S*,*Z*)-2-methyl-4-(2-(2,2,2-trichloro-1-((3-fluorophenyl)imino)ethoxy)ethylidene)piperidine-1-carboxylate (0.18 g, 0.37 mmol) was added K_2CO_3 (0.44 g, 3.1 mmol) and the resulting heterogeneous solution was treated at 140 ^oC for 48 h. Then the reaction mixture was cooled down to rt and filtered through Celite. The Celite plug was washed with xylenes (3 x) and the combined filtrates were concentrated under reduced pressure to yield a yellow solid. This solid was purified by flash column chromatography, eluting with ethyl acetate and heptanes, to afford *tert*-butyl (2*S*,4*R*)-4-(2,2-dichloro-N-(3-fluorophenyl)acetamido)-2-methyl-4-vinylpiperidine-1-carboxylate **12b** (0.014 g, 0.031 mmol,

8%) as a clear oily residue. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.39 (m, 1H), 7.25 – 7.18 (m, 1H), 7.07 – 6.91 (m, 2H), 6.61 (ddd, J = 17.2, 10.8, 5.9 Hz, 1H), 5.47 (s, 1H), 5.42 – 5.25 (m, 2H), 4.40 – 4.26 (m, 1H), 3.96 – 3.81 (m, 1H), 3.00 – 2.86 (m, 1H), 2.66 – 2.48 (m, 1H), 2.08 – 1.87 (m, 2H), 1.52 – 1.35 (m, 10H), 1.14 (d, J = 7.1, 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 154.4, 139.8, 132.1 (d, *J* = 1.7 Hz), 131.8 (d, *J* = 1.4 Hz), 128.3 (d, *J* = 1.5 Hz), 115.7, 113.7, 113.6, 79.6, 63.6, 55.4, 46.3, 39.1, 35.6, 33.4, 28.4, 18.3ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{21}H_{27}Cl_2FN_2NaO_3$ 467.1236; found, 467.1265; $[\alpha]_D^{23}$: +16.6 (c = 0.26g/100mL; MeOH).

***tert*-Butyl (2*S*, 4*R*)-2-methyl-4-vinyl-4-(vinylsulfonamido)piperidine-1-carboxylate 13:** To an oven dried round bottomed flask. was added *tert*-butyl (2S, 4R)-4-amino-2-methyl-4-vinylpiperidine-1-carboxylate (3.00 g, 12.5 mmol), DCM (60mL) and triethylamine (8.70 mL, 62.4 mmol). The resulting solution was cooled down to 0 ^{o}C for 10 min. Then 2-chloroethanesulfonyl chloride (2.72 mL, 25.0 mmol) was added in a dropwise manner over a period of 5 m. The reaction mixture was allowed to reach rt slowly and it was stirred at rt until complete consumption of starting material. The reaction mixture was then diluted with H_2O (200 mL). Organics were extracted with DCM (2x) dried over Na_2SO_4, filtered and concentrated to yield a yellow oil. Flash column chromatography of the organic crude, using a gradient of MeOH in DCM (0 to 5%) afforded *tert*-butyl (2S, 4R)-2-methyl-4-vinyl-4-(vinylsulfonamido)piperidine-1-carboxylate (4.03 g, 12.2 mmol, 98%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, *J*=16.5, 9.9 Hz, 1 H), 6.15 (d, *J*=16.4 Hz, 1 H), 5.96(dd, *J*=17.8, 10.8 Hz, 1 H), 5.81 (d, *J*=9.8 Hz, 1 H), 5.37 - 5.30 (m, 2 H), 4.39 - 4.29 (m, 2 H), 3.97 - 3.89 (m, 1 H), 2.95 (ddd, *J*=14.0, 12.3, 3.2 Hz, 1 H), 2.25 -2.18 (m, 1 H), 2.07 (dd, *J*=13.5, 6.5 Hz, 1 H),

1.93 - 1.77 (m, 2 H), 1.45 (s, 9 H), 1.13 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 140.6, 139.2, 124.9, 116.5, 79.7, 57.4, 46.1, 41.1, 35.9, 34.9, 28.4, 18.2 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{15}H_{26}N_2NaO_4S$ 353.1505; found 353.1509; $[\alpha]_D^{25}$: +6.0 (*c* = 0.20g/100mL; MeOH).

***tert*-Butyl (5*R*, 7*S*)-7-methyl-2-thia-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 2,2-dioxide 14:** To an oven dried round bottomed flask equipped with a stir bar, was added tert-butyl (2S, 4R)-2-methyl-4-vinyl-4-(vinylsulfonamido)piperidine-1-carboxylate (4.0 g, 12.2 mmol) and toluene (90 mL). The resulting solution was sparged with N_2 for 5min. and the purged with vacuum. The vial was refilled with N_2 and this procedure was repeated two more times. To the resulting solution Grubbs' 2nd generation catalyst was added (0.518 g, 0.610 mmol). The resulting solution was heated to 80 ^{o}C for 24 h. The reaction mixture was then concentrated under reduced pressure to yield a black solid. Flash column chromatography of the organic crude, using a gradient of EtOAc in heptanes (0 to 100%) afforded *tert*-butyl (5*R,* 7*S*)-7-methyl-2-thia-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 2,2-dioxide (2.6 g, 8.6 mmol, 70%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J*=6.7 Hz, 1 H), 6.69 (d, *J*=6.5 Hz, 1 H), 4.64 (s, 1 H), 4.38 - 4.28 (m, 1 H), 3.99 (dt, *J*=14.4, 4.4 Hz, 1 H), 3.13 - 3.03 (m, 1 H), 2.01 (dd, *J*=13.7, 6.5 Hz, 1 H), 1.93 - 1.88 (m, 2 H), 1.76 (dd, *J*=13.7, 5.3 Hz, 1 H), 1.49 - 1.44 (m, 9 H), 1.22 (d, *J*=6.9 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 143.7, 127.4, 80.3, 62.9, 46.2, 41.0, 36.2, 36.0, 28.4, 19.0 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{13}H_{22}N_2NaO_4S$ 325.1192; found 325.1191; $[\alpha]_D^{26}$: +23.0 (*c* = 0.19g/100mL; MeOH).

***tert*-Butyl (2*S*, 4*R*)-4-acrylamido-2-methyl-4-vinylpiperidine-1-carboxylate 15:** A 35 mL round bottomed flask was charged with *tert*-butyl (2S,4R)-4-amino-2-methyl-4-vinylpiperidine-1-carboxylate (44.8 mg, 0.186 mmol), THF (3 mL) and Cs_2CO_3 (90.9 mg, 0.279 mmol). The resulting solution was cooled down to 0 ^oC, followed by addition of acryloyl chloride (19.1 mg, 0.205 mmol). After stirring at 0 ^oC for 2h., the reaction was quenched with NH_4Cl (aq., sat'd) and water. Organics were then extracted with EtOAc (2x), dried over Na_2SO_4, filtered and concentrated to yield a clear oil. Flash column chromatography of the organic crude, using a gradient of EtOAc in heptanes (0 to 70%) afforded *tert*-butyl (2S,4R)-4-acrylamido-2-methyl-4-vinylpiperidine-1-carboxylate (39 mg, 0.186 mmol, 99%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (dd, *J*=16.8, 1.4 Hz, 1 H), 6.16 – 5.97 (m, 2 H), 5.59 (dd, *J*=10.3, 1.5 Hz, 1 H), 5.43 (br. s., 1 H), 5.21 (d, *J*=5.9 Hz, 1H), 5.17 (s, 1 H), 4.23 - 4.13 (m, 1 H), 3.97 - 3.89 (m, 1 H), 3.02 (ddd, *J*=14.1, 11.7, 4.5 Hz, 1 H), 2.37 (dd, *J*=13.7, 6.5 Hz, 1 H), 2.12 (dt, *J*=13.8, 3.0 Hz, 1 H), 1.91 - 1.80 (m, 2 H), 1.44 (s, 9 H), 1.15 (d, *J*=6.9 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 154.8, 141.2, 131.3, 126.4, 113.8, 79.5, 54.9, 46.0, 39.0, 35.5, 34.8, 28.5, 18.6 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{16}H_{26}N_2NaO_3$ 317.1836; found 317.1836; $[\alpha]_D^{25}$: +41.4 (*c* = 0.2g/100mL; MeOH).

***tert*-Butyl (5*R*, 7*S*)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 16:** To an oven dried round bottomed flask equipped with a stir bar, was added *tert*-butyl (2S,4R)-4-acrylamido-2-methyl-4-vinylpiperidine-1-carboxylate (36 mg, 0.12 mmol) and toluene (5 mL). The resulting solution was sparged with N_2 for 5 min. and the purged with vacuum. The vial was refilled with N_2 and this procedure was repeated two more times. To the resulting solution Grubbs' 2nd generation catalyst was added (5 mg, 0.006 mmol). The resulting solution was

heated to 80 °C for 24 h. The reaction mixture was then concentrated under reduced pressure to yield a black solid. Flash column chromatography of the organic crude, using a gradient of EtOAc in heptanes (0 to 100%) afforded *tert*-butyl (5*R,* 7*S*)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate (23 mg, 0.085 mmol, 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J*=5.9, 1.8 Hz, 1 H), 6.76 (br. s., 1 H), 6.04 (dd, *J*=5.9, 1.6 Hz, 1 H), 4.45 (td, *J*=6.8, 3.4 Hz, 1 H), 4.12 - 4.04 (m, 1 H), 3.02 (ddd, *J*=14.2, 12.4, 3.5 Hz, 1 H), 2.02 (dd, *J*=13.6, 6.6 Hz, 1 H), 1.85 (td, *J*=12.9, 5.2 Hz, 1 H), 1.76 - 1.69 (m, 1 H), 1.58 (ddd, *J*=13.7, 3.4, 1.8 Hz, 1 H), 1.46 (s, 9 H), 1.24 (d, *J*=1.0 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 154.4, 152.8, 126.2, 80.0, 62.4, 46.1, 39.5, 36.5, 34.8, 28.4, 18.7 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{14}H_{22}N_2NaO_3$289.1523; found 289.1522; $[\alpha]_D^{27}$: +39.1 (*c* = 0.15g/100mL; MeOH).

***tert*-Butyl (2*S*,4*R*)-4-methacrylamido-2-methyl-4-vinylpiperidine-1-carboxylate 17:** Methylacryloyl chloride (23 μL, 0.23 mmol) was added, drop-wise, to a cooled (0 °C, ice bath) mixture of *tert*-butyl (2S,4R)-4-amino-2-methyl-4-vinylpiperidine-1-carboxylate (51 mg, 0.21 mmol) and cesium carbonate (90.9 mg, 0.32 mmol) in THF (3 mL), under nitrogen. The mixture was stirred at 0°C for 90 min, then the ice bath was removed and the mixture stirred at room temperature for 18 h. The reaction was quenched with NH_4Cl (aq., sat'd, 3 mL) and water (5 ml). Organics were extracted with EtOAc (2x), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to an oil. Purification via silica gel chromatography (Gradient: 0% to 100% ethyl acetate in heptane) afforded *tert*-butyl (2S,4R)-4-methacrylamido-2-methyl-4-vinylpiperidine-1-carboxylate as white foam (42 mg, 0.14 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, *J*=17.6, 10.9 Hz, 1 H) 5.66 (s, 1 H) 5.61 - 5.58 (m, 1 H) 5.29 (quin, *J*=1.5 Hz, 1 H) 5.20 (d, *J*=5.9

Hz, 1 H) 5.17 (s, 1 H) 4.17 (sxt, *J*=6.6 Hz, 1 H) 4.00 – 3.91 (m, 1 H) 3.04 (ddd, *J*=14.1, 11.7, 4.7 Hz, 1 H) 2.41 (dd, *J*=13.7, 6.6 Hz, 1 H) 2.06 - 2.14 (m, 1 H) 1.95 - 1.91 (m, 3 H) 1.91 - 1.81 (m, 2 H) 1.45 (s, 9 H) 1.17 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 152.8, 139.5, 139.0, 117.0, 111.6, 77.6, 52.8, 44.1, 36.7, 33.5, 33.1, 26.6, 16.8, 16.7 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{17}H_{28}N_2NaO_3$ 331.1992; found 331.1991; $[\alpha]_D^{22}$: +53.5 (*c* = 0.515g/100mL; MeOH).

***tert*-Butyl (2*S*,4*R*)-4-(2-methoxyacrylamido)-2-methyl-4-vinylpiperidine-1-carboxylate 18:** O-(2-Oxo-1(2H)pyridyl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TPTU) (1.210 g, 4.08 mmol) was added to a mixture of 2-methoxyacrylic acid (416 mg, 4.08 mmol), and DIPEA (1.78 mL, 10.2mmol) in DMF (10 mL) under nitrogen. The mixture was stirred at rt for 45 minutes prior to addition of *tert*-butyl (2S,4R)-4-amino-2-methyl-4-vinylpiperidine-1-carboxylate (700 mg, 2.91 mmol) dissolved in DMF (1.5 mL). This mixture was stirred at rt for 18 h. The mixture was partitioned between saturated aqueous sodium bicarbonate (25 mL) and MTBE (2 x 40 mL). The pooled MTBE phases were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resultant amber oil was purified by silica gel chromatography (Gradient: 0% to 85% ethyl acetate in heptane) to afford *tert*-butyl (2*S*,4*R*)-4-(2-methoxyacrylamido)-2-methyl-4-vinylpiperidine-1-carboxylate as a colorless oil (871 mg, 2.91 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) : δ 6.51 (s, 1 H) 6.11 (dd, *J*=17.6, 10.7 Hz, 1 H) 5.33 (d, *J*=2.4 Hz, 1 H) 5.21 (d, *J*=8.1 Hz, 1 H) 5.18 (d, *J*=1.2 Hz, 1 H) 4.39 (d, *J*=2.4 Hz, 1 H) 4.22 - 4.14 (m, 1 H) 3.97 - 3.90 (m, 1 H) 3.62 (s, 3 H) 3.04 (ddd, *J*=14.2, 11.7, 4.4 Hz, 1 H) 2.37 (dd, *J*=13.5, 6.5 Hz, 1 H) 2.14 (dt, *J*=14.0, 3.1 Hz, 1 H) 1.91 - 1.82 (m, 2 H) 1.44 (s, 9 H) 1.16 (d, *J*=6.8 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 154.8, 154.3, 141.1, 113.8, 89.3,

79.4, 55.5, 54.5, 46.1, 38.9, 35.6, 34.7, 28.4, 18.7 ppm.; $[\alpha]_D^{21}$: +13.6 (*c* = 0.75g/100mL; MeOH).

***tert*-Butyl (2S,4R)-4-(2-fluoroacrylamido)-2-methyl-4-vinylpiperidine-1-carboxylate 19:** O-(2-Oxo-1(2H)pyridyl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate **(**TPTU) (22.2 g, 74.9 mmol) was added to a mixture of 2-fluoroacrylic acid (6.74 g, 74.9 mmol), and DIPEA (22.8 mL, 131 mmol) in DMF (75 mL) under nitrogen. The mixture was stirred at rt for 35 min prior to addition of *tert*-butyl (2S,4R)-4-amino-2-methyl-4-vinylpiperidine-1-carboxylate (9.00 g, 37.5 mmol) in 10 mL DMF. Reaction mixture was stirred at rt for 18 h, then was diluted with saturated aqueous sodium bicarbonate (100 mL) and water (100 mL), and MTBE (150 mL) forming an emulsion. The mixture was filtered over Celite. The aqueous phase was then separated and washed with another 150 mL of MTBE (filtered over Celite again). The combined MTBE extracts were washed water (150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resultant amber oil was purified by silica gel chromatography (Gradient: 0% to 100% ethyl acetate in heptane) to afford *tert*-butyl (2S,4R)-4-(2-fluoroacrylamido)-2-methyl-4-vinylpiperidine-1-carboxylate as a yellow oil (10.56 g, 33.8 mmol, 90.3 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 - 6.01 (m, 2 H) 5.68 (d, *J*=3.5 Hz, 0.5 H) 5.56 (d, *J*=3.1 Hz, 0.5 H) 5.23 (dd, *J*=13.9, 3.3 Hz, 2 H) 5.09 (d, *J*=3.5 Hz, 0.5 H) 5.05 (d, *J*=3.1 Hz, 0.5 H) 4.21 (dq, *J*=13.0, 6.6 Hz, 1 H) 4.00 - 3.90 (m, 1 H) 3.02 (ddd, *J*=14.1, 11.7, 4.3 Hz, 1 , H) 2.34 (dd, *J*=13.7, 6.7 Hz, 1 H) 2.16 (dt, *J*=13.9, 2.8 Hz, 1 H) 1.94 - 1.81 (m, 2 H) 1.44 (s, 9 H) 1.16 (d, *J*=6.7 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (d, *J* =30 Hz), 156.8 (d, *J* =332 Hz) 154.7, 140.5, 114.5, 98.6 (d, *J* =15 Hz), 79.6, 55.0, 46.0, 38.9, 35.4, 34.6, 28.4, 18.6

ppm.; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{16}H_{25}FN_2NaO_3$ 335.1741; found 335.1737; $[\alpha]_D^{23}$: +98.4 (*c* = 0.485g/100mL; MeOH).

***tert*-Butyl (5*R*,7*S*)-3,7-dimethyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 20:** A solution of tert-butyl (2S,4R)-4-methacrylamido-2-methyl-4-vinylpiperidine-1-carboxylate (38 mg, 0.13 mmol) in toluene (3 mL) was sparged with nitrogen then evacuated with vacuum three times. To this mixture was added (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (Hoveyda-Grubbs 2nd Generation catalyst, 11.9 mg, 0.019 mmol). The mixture was heated at 80 °C under nitrogen for 18 h. The mixture was allowed to cool to near rt and concentrated *in vacuo* yielded brown oil. Purification by silica gel chromatography (Gradient: 50% to 100% ethyl acetate in heptane) afforded *tert*-butyl (5*R,*7*S*)-3,7-dimethyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate as an off-white solid (25.5 mg, 0.091 mmol, 70%).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (br. s., 1 H) 6.99 - 6.95 (m, 1 H) 4.45 (td, *J*=6.7, 2.9 Hz, 1 H) 4.11 - 4.04 (m, 1 H) 3.06 – 2.95 (m, 1 H) 2.05 (dd, *J*=13.5, 6.4 Hz, 1 H) 1.88 (d, *J*=1.6 Hz, 3 H) 1.86 - 1.80 (m, 1 H) 1.68 - 1.61 (m, 1 H) 1.51 (dt, *J*=13.7, 2.3 Hz, 1 H) 1.47 (s, 9 H) 1.23 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 154.5, 145.6, 134.0, 79.9, 59.8, 46.1, 39.6, 36.6, 35.1, 28.5, 18.7, 10.9 ppm.; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{15}H_{25}N_2O_3$ 281.1860; found 281.1859; $[\alpha]_D^{22}$: +35.0 (*c* = 0.535g/100mL; MeOH).

***tert*-Butyl (5*R*,7*S*)-3-methoxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 21:** A solution of tert-butyl (2S,4R)-4-(2-methoxyacrylamido)-2-methyl-4-vinylpiperidine-1-carboxylate (1.47 g, 4.53 mmol) in toluene (15 mL) was sparged with argon for 5 m. To this

mixture was added (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (Hoveyda-Grubbs 2nd Generation catalyst, 426 mg, 0.68 mmol). The mixture was heated at 85 °C under argon for 18 h. Additional Hoveyda-Grubbs II catalyst (150 mg, 0.24 mmol) was added and this mixture was heated 90 °C for 18 h. The mixture was allowed to cool to near rt and concentrated *in vacuo* to a brown oil. Purification by silica gel chromatography (Gradient: 20% to 100% ethyl acetate in heptane) afforded *tert*-butyl (5*R,*7*S*)-3-methoxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate as a tan solid (1.06 g, 3.56 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (br. s., 1 H) 5.93 (s, 1 H) 4.42 (td, *J*=6.8, 2.9 Hz, 1 H) 4.11 – 3.98 (m, 1 H) 3.72 (s, 3 H) 3.04 – 2.92 (m, 1 H) 2.02 (dd, *J*=13.7, 6.4 Hz, 1 H) 1.82 (td, *J*=12.8, 5.0 Hz, 1 H) 1.61 (d, *J*=14.1 Hz, 1 H) 1.50 (d, *J*=13.7 Hz, 1 H) 1.43 (s, 9 H) 1.21 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 154.5, 150.8, 114.0, 80.0, 57.3, 56.9, 46.2, 40.6, 36.5, 36.1, 28.4, 18.5 ppm.; HRMS (ESI-TOF) m/z: [M H]+ Calcd for $C_{15}H_{25}N_2O_4$ 297.1809; found 297.1809; $[\alpha]_D^{21}$: +34.19 (*c* 0.8, MeOH).

***tert*-Butyl (5*R,*7*S*)-3-fluoro-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 22:** A solution of *tert*-butyl (2S,4R)-4-(2-fluoroacrylamido)-2-methyl-4-vinylpiperidine-1-carboxylate (10.13 g, 32.43 mmol), in toluene (125 mL) was sparged with argon for 10 min. To the solution was added (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (Hoveyda-Grubbs 2nd Generation catalyst, 2.00 g, 3.19 mmol) and the mixture heated at 90 °C for 18 h. Additional (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (Hoveyda-Grubbs 2nd Generation catalyst, 1.05 g, 1.67 mmol) was added and this mixture was heated 90 °C for 18 h. The mixture was allowed to cool to near rt and concentrated *in vacuo* to a dark oil. Purification

by silica gel chromatography (Gradient: 10% to 100% ethyl acetate in heptane) afforded *tert*-butyl (5*R,*7*S*)-3-fluoro-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate as a tan solid (5.512 g, 19.4 mmol, 59.8%) and starting material (3.62 g). ^{1}H NMR (400 MHz, CD_3OD) δ 7.06 (s, 1 H) 4.55 - 4.43 (m, 1 H) 4.08 - 4.01 (m, 1 H) 3.11 (ddd, *J*=14.1, 12.9, 2.7 Hz, 1 H) 2.09 (ddd, *J*=13.7, 6.5, 2.9 Hz, 1 H) 1.85 (tdd, *J*=13.1, 13.1, 4.5, 2.9 Hz, 1 H) 1.68 - 1.61 (m, 1 H) 1.57 (dt, *J*=13.6, 2.0 Hz, 1 H) 1.46 (s, 9 H) 1.26 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (d, J =31 Hz), 154.3, 152.3 (d, J =279 Hz), 123.0 (d, J =3 Hz), 80.1, 56.7 (d, J =5 Hz), 45.9, 39.9 (d, J =2 Hz), 36.5, 35.3 (d, J =2 Hz), 28.4, 18.4 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{14}H_{21}FN_2NaO_3$ 307.1428; found 307.1427; $[\alpha]_D^{23}$: +33.8 (*c* 0.510, MeOH).

***tert*-Butyl (5*R,* 7*S*)-1-(3-fluorophenyl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 23:** In an oven dried sealed tube equipped with a stir ba*r,* was added *tert*-butyl (5*R,* 7*S*)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate (0.48 g, 1.80 mmol) and reagents, CuI (0.173 g, 3.60 mmol), K_3PO_4 (1.18 g, 5.40 mmol), DMEDA (1.34 mL, 12.6 mmol) and 3-fluoroiodobenzene (0.423 mL, 3.60 mmol). The tube was sealed under N_2 and the resulting solution was stir at 90 ^{o}C for 24h. The reaction mixture was filter through Celite eluting with EtOAc. Combined filtrates were concentrated under reduced pressure to yield a green oily residue. Flash column chromatography of the organic crude, using a gradient of EtOAc in heptanes (0 to 100%) afforded *tert*-butyl (5*R,* 7*S*)-1-(3-fluorophenyl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate (0.53 g, 1.46 mmol, 81%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J*=6.1 Hz, 1 H), 7.42 (td, *J*=8.2, 6.4 Hz, 1 H), 7.13 (tdd, *J*=8.4, 8.4, 2.5, 0.9 Hz, 1 H), 6.93 - 6.89 (m, 1 H), 6.85 (dt, *J*=9.4, 2.2 Hz, 1 H), 6.32 (d, *J*=6.3 Hz, 1 H), 4.52 (br. s., 1 H), 4.21 - 4.04 (m, 1 H), 3.05 (t, *J*=13.2 Hz, 1 H), 2.09 (dd, *J*=13.4, 6.8 Hz, 1 H), 1.90 (td, *J*=12.9, 4.3 Hz, 1 H), 1.65 (d, *J*=12.1 Hz, 1 H), 1.47 (d, *J*=13.3 Hz, 1 H), 1.42 (s, 9 H), 1.27

(d, *J*=1.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.3, 161.8, 151.2, 136.5 (d, *J* = 9.5 Hz), 130.7 (d, *J* = 9.2 Hz), 126.4 (d, *J* = 3.3 Hz), 126.2, 118.1 (d, *J* = 21.8 Hz), 115.9 (d, *J* = 20.9 Hz), 80.1, 67.5, 45.6, 38.0, 36.3, 33.6, 28.3, 18.7 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{20}H_{25}FN_2NaO_3$ 383.1741; found 383.1741; $[\alpha]_D^{25}$: +25.8 (c = 0.16g/100mL; MeOH).

***tert*-Butyl (5*R*,7*S*)-1-(3-fluorophenyl)-3,7-dimethyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 24:** A mixture of *tert*-butyl (5*R*,7*S*)-3,7-dimethyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate (22.7 mg, 0.081 mmol), 3-fluorobromobenzene (22 μL, 0.20 mmol), cesium carbonate (79 mg, 0.24 mmol), CuI (61.6 mg, 0.32 mmol), and DMEDA (43 μL, 0.40 mmol), in dioxane (1 mL) was sealed under nitrogen and heated at 100 ^{o}C for 18 h. The mixture was removed from heat and allowed to cool back to rt. The mixture was unsealed and partitioned between saturated aqueous sodium bicarbonate (10 mL) and ethyl acetate (3 x 20 mL). The pooled ethyl acetate layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to a brown oil. Purification by silica gel chromatography (Gradient: 0% to 100% ethyl acetate in heptane) afforded *tert*-butyl (5*R*,7*S*)-1-(3-fluorophenyl)-3,7-dimethyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate as an off-white solid (14 mg, 0.037 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (td, *J*=8.1, 6.4 Hz, 1 H) 7.15 (d, *J*=2.0 Hz, 1 H) 7.07 - 7.01 (m, 1 H) 6.85 - 6.81 (m, 1 H) 6.77 (dt, *J*=9.4, 2.2 Hz, 1 H) 4.43 (br. s., 1 H) 4.05 (dd, *J*=5.3, 4.1 Hz, 1 H) 2.97 (t, *J*=13.3 Hz, 1 H) 1.98 (dd, *J*=13.3, 6.6 Hz, 1 H) 1.91 (d, *J*=1.6 Hz, 3 H) 1.80 (td, *J*=13.0, 4.5 Hz, 1 H) 1.52 (d, *J*=9.8 Hz, 1 H) 1.35 (s, 9 H) 1.31-1.36 (m, 1 H) 1.20 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 163.0 (d, J =248 Hz), 154.4, 144.0, 137.0 (d, J =10 Hz), 134.1, 130.5 (d, J =9 Hz), 126.4 (d, J =3 Hz), 118.0 (d, J =22 Hz), 115.7 (d, J =21 Hz),

115.6, 80.0, 65.1, 46.0, 38.1, 36.4, 33.9, 28.4, 18.77, 11.32 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{21}H_{27}FN_2NaO_3$ 397.1898; found 397.1903; $[\alpha]_D^{19}$: +31.58 (*c* 0.4, MeOH).

***tert*-Butyl (5*R*,7*S*)-1-(3-fluorophenyl)-3-methoxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 25:** A mixture of *tert*-butyl (5*R,*7*S*)-3-methoxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate (229 mg, 0.77 mmol), 3-fluoroiodobenzene (272 µL, 2.32 mmol), cesium carbonate (763 mg, 2.32 mmol), CuI (595 mg, 3.09 mmol), and DMEDA (411 µL, 3.86 mmol), in dioxane (15 mL) was sealed under nitrogen and heated at 95 ^oC for 18 h. The mixture was removed from heat and allowed to cool back to rt. The mixture was unsealed and partitioned between saturated aqueous sodium bicarbonate (30 mL) and ethyl acetate (3 x 50 mL). The pooled ethyl acetate layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to brown oil. Purification by silica gel chromatography (Gradient: 10% to 100% ethyl acetate in heptane) afforded *tert*-butyl (5*R,*7*S*)-1-(3-fluorophenyl)-3-methoxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate as a white solid (195 mg, 0.50 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (q, *J*=7.5 Hz, 1 H) 7.12 (t, *J*=7.8 Hz, 1 H) 6.96 - 6.78 (m, 2 H) 6.23 (s, 1 H) 4.61 - 4.41 (m, 1 H) 4.22 - 4.05 (m, 1 H) 3.83 (s, 3 H) 3.11 – 2.97 (m, 1 H) 2.09 (dd, *J*=13.0, 6.5 Hz, 1 H) 1.97 - 1.84 (m, 1 H) 1.59 (d, *J*=13.1 Hz, 1 H) 1.47 - 1.38 (m, 10 H), 1.29 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.0 (d, *J* =248 Hz), 154.3, 151.0, 136.0 (d, *J* = 10 Hz), 130.7 (d, *J* = 9 Hz), 126.4 (d, *J* =3 Hz), 118.0 (d, *J* = 22 Hz) , 116.0 (d, *J* =21 Hz), 112.7, 80.1, 62.5, 57.2, 38.8, 34.6, 28.3, 18.5 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{21}H_{27}FN_2NaO_4$ 413.1847; found 413.1853; $[\alpha]_D^{24}$: +3.67 (*c* 0.3, MeOH).

***tert*-Butyl (5*R*,7*S*)-3-fluoro-1-(3-fluorophenyl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 26:** A mixture of *tert*-butyl (5*R,*7*S*)-3-fluoro-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate (3.22 g, 11.32 mmol), 3-fluoroiodobenzene (2.66 mL, 22.7 mmol), potassium phosphate (7.45 g, 33.95 mmol), CuI (1.09 g, 5.65 mmol), and DMEDA (8.45 mL, 79.0 mmol), in toluene (100 mL) was sealed under nitrogen and heated at 90 ^{o}C for 18 h. The mixture was removed from heat and allowed to cool back to rt. The mixture was unsealed and partitioned between saturated aqueous sodium bicarbonate (75 mL) and ethyl acetate (3 x 100 mL). The pooled ethyl acetate layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to a brown oil. Purification by silica gel chromatography (Gradient: 5% to 90% ethyl acetate in heptane) afforded *tert*-butyl (5*R,*7*S*)-3-fluoro-1-(3-fluorophenyl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate as a white solid (2.03 g, 5.4 mmol, 47%); and recovered starting material (778 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (td, *J*=8.2, 6.2 Hz, 1 H) 7.22 - 7.13 (m, 1 H) 6.94 (dd, *J*=7.8, 0.8 Hz, 1 H) 6.91 - 6.85 (m, 2 H) 4.55 (br. m., 1 H) 4.17 (br. m., 1 H) 3.01 (t, *J*=12.9 Hz, 1 H) 2.14 (ddd, *J*=13.3, 6.8, 2.9 Hz, 1 H) 1.96 (t, *J*=12.7 Hz, 1 H) 1.69 (d, *J*=11.3 Hz, 1 H) 1.52 (d, *J*=13.3 Hz, 1 H) 1.43 (s, 9 H) 1.27 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J =249 Hz), 161.9 (d, J =31 Hz), 154.2, 152.7 (d, J =279 Hz), 135.2 (d, J = 10 Hz), 130.9 (d, J = 9 Hz), 126.3 (d, J = 3 Hz), 121.7 (d, J = 4 Hz), 118.0 (d, J =22 Hz), 116.4 (d, J =21 Hz), 80.3, 62.4 (d, J = 4 Hz), 45.8, 38.2, 36.2, 33.9, 28.3, 18.4 ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{20}H_{24}F_2N_2NaO_3$ 401.1647; found 401.1650; $[\alpha]_D^{23}$: +30.2 (*c* 0.59, MeOH).

***tert*-Butyl (5*R,* 7*S*)-7-methyl-2-thia-1,8-diazaspiro[4.5]decane-8-carboxylate 2,2-dioxide 27:** A methanolic solution (30 mL) of *tert*-butyl (5*R,* 7*S*)-7-methyl-2-thia-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 2,2-dioxide (0.310 g, 1.02 mmol) was placed in a 100 mL Parr Shaker flask.

Then Pd/C (0.090 g) was added to the solution. The resulting black heterogeneous solution was placed under a H_2 Parr Reactor at rt and at 50 PSI under H_2 for 3 h. The reaction mixture was filtered through a Celite pad. The Celite pad was then washed with MeOH (3x) and combined filtrates were concentrated under reduced pressure to yield *tert*-butyl (5*R,* 7*S*)-7-methyl-2-thia-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 2,2-dioxide (0.306 g, 1.01 mmol, 99%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (td, *J*=6.9, 4.2 Hz, 1 H), 4.20 (s, 1 H), 4.03 - 3.95 (m, 1 H), 3.28 - 3.13 (m, 2 H), 3.00 (ddd, *J*=14.4, 11.8, 3.7 Hz, 1 H), 2.51 - 2.35 (m, 2 H), 1.98 (dd, *J*=13.7, 6.5 Hz, 1 H), 1.90 - 1.82 (m, 1 H), 1.79 - 1.68 (m, 2 H), 1.45 (s, 9 H), 1.19 (d, *J*=7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 80.0, 58.1, 47.2, 46.2, 42.3, 37.1, 35.8, 34.2, 28.4, 18.3, ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{13}H_{24}N_2NaO_4S$ 327.1349; found 327.1348; $[\alpha]_D^{25}$: +23.7 (c = 0.18g/100mL; MeOH).

***tert*-Butyl (5*R,* 7*S*)-1-(3-fluorophenyl)-7-methyl-2-thia-1,8-diazaspiro[4.5]decane-8-carboxylate 2,2-dioxide 28:** To a 0.15 M solution of *tert*-butyl (5*R,* 7*S*)-7-methyl-2-thia-1,8-diazaspiro[4.5]decane-8-carboxylate 2,2-dioxide (0.300 g, 0.986 mmol) in dioxane (7 mL; already containing DMEDA: 0.525 mL, 4.93 mmol) was added a mixture of the 1-fluoro-3-iodobenzene (0.65 g, 2.96 mmol), CuI (0.759 g, 3.94 mmol) and K_3PO_4 (0.641 g, 2.96 mmol) in a 16 mL screw cap vial. The resulting suspension was capped and heated at 80 ^{o}C for 72 h. Then the reaction mixture was filtered through Celite and the filter cake was washed with EtOAc (2x50mL). The combined filtrates were concentrated under reduced pressure to yield a white gummy solid. Flash column chromatography of the organic crude, using a gradient of EtOAc in heptanes (0 to 100%) afforded *tert*-Butyl (5*R,*7*S*)-1-(3-fluorophenyl)-7-methyl-2-thia-1,8-diazaspiro[4.5]decane-8-carboxylate 2,2-dioxide (0.070 g, 0.177 mmol, 18%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (td, *J* = 8.2, 6.3 Hz, 1H), 7.31 (qd, *J* = 8.3, 6.9, 3.7 Hz, 1H), 7.20 – 7.09 (m, 2H), 7.04 (dt, *J* = 9.4, 2.3 Hz, 1H), 4.41 (b, 1H), 4.07 (b, 1H), 3.41 – 3.24 (m, 2H), 2.98 (t, *J* = 13.6 Hz, 1H), 2.75 – 2.53 (m, 2H), 1.88 – 1.56 (m, 4H), 1.39 (s, 9H), 1.21 (d, 7.3Hz 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.4, 130.4, 130.3, 128.9, 128.9, 128.5, 120.5, 120.3, 116.8, 116.6, 80.0, 62.2, 45.1, 39.9, 34.0, 31.0, 28.3, ppm; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{19}H_{27}FN_2NaO_4S$ 421.1568; found 421.1574; $[\alpha]_D^{24}$: +23.5 (c = 0.25g/100mL; MeOH).

Experimental for Continuous flow transformation on scale to prepare **6a**:

The flow reactor was primarily built using Isco pumps (316s, PTFE and Kalrez™ check valves), along Hastelloy coils. The reactor system can be divided up into four components. The pumping system consisted of two Isco syringe pumps that operated in tandem, with one pump refilling as the other one discharges. The discharge system, which also sets the system pressure used a Mity Mite™ back pressure regulator. This regulator controls the system pressure by a diaphragm. The top of the diaphragm is loaded with nitrogen from a regulated high pressure (3,000 psi) cylinder. The maximum pressure in the reactor will be the same as the pressure applied by a regulated nitrogen, assuming that the limit of the relief valves is not exceeded. The reaction zone is the thermostatted region of the system, and consists of 1760 mls of coiled stainless steel tubing encased in an enclosed vessel. Oil is supplied to the vessel by a Huber™ circulator and determines the reaction temperature. The system is thus operable from 50 ^{o}C to 250 ^{o}C. One through the reaction zone the fluid is cooled with two 90 mL heat exchangers using house glycol in the jackets. Finally, fore and aft the reaction zone are two relief valves set to open at 1200psi. The vents for these components discharge via a large (2.4 ft^2) heat exchanger to a nitrogen-

purged knockout vessel. This vessel is equipped with its own pressure relief valve set to 100 psi. The discharge of this relief is to the hood.

In a Nalgene container 0.537 kg of (S)-*tert*-Butyl-4-(2-hydroxyethylidene)-2-methylpiperidine-1-carboxylate in 4.5 L of Toluene. To this solution was added 37 g (50 mL) of trimethylamine. The flow reactor was then heated to 180 ^{o}C and each syringe pump was loaded with 1 L of Toluene and the system was purged for 1 h at that temperature between 20-40 mL/min. The system is heated with an external Huber™ circulator. The syringe pumps were then charged each with 1 L of the substrate/trimethylamine solution and the flow reactor was then fed this solution at 44 mL/min at 180 ^{o}C and 500 psi. Finally the reacted solution was fed into a rotovap and the toluene is removed by vacuum distillation to yield an oily heterogenous solution. The product was crystallized with diethyl ether to yield 325 g (60% yield) of *tert*-Butyl (2S, 4R)-2-methyl-4-(2,2,2-trichloroacetamido)-4-vinylpiperidine-1-carboxylate.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

^{1}H NMR and ^{13}C NMR for all synthesized compounds including ^{1}H NOESY NMR of compounds 6a, 6b and 9. X-ray crystallographic data for compound 6a.

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Notes

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References

[1] (a) Brodney, M.A.; Efremov, I. V.; Helal, C.J.; O'Neill, B.T.; PCT Int. Appl. WO 2010/58333, **2010.** (b) Coburn, C. A.; Egbertson, M. S.; Graham, S. L.; Mcgaughey, G.B.; Stauffer, S. R.; Yang, W. L.; Lu, W.; Fahr, B. PCT Int. Appl. WO 2007/011810, **2007**. (c) Barrow, J.C.; Stauffer, S.R.; Rittle, K.E.; Ngo, P.L.; Yang, Z-Q; Selnick, H.G.; Graham, S.L.; Munshi, S.; McGaughey, G.B.; Holloway, M. K.; Simon, A.J.; Price, E.A.; Sankaranarayanan, S.; Colussi, D.; Tugusheva, K.; Lai, M-T.; Espeseth, A.S.; Xu,M.; Huang, Q.; Wolfe, A.; Pietrak, B.; Zuck, P.; Levorse,D.A.; Hazuda,D.; Vacca; J.P. *J. Med. Chem*. **2008**, 51(20), 6259-6262. (d) Egbertson, M.; McGaughey, G.B.; Pitzenberger, S.M.; Stauffer, S.R.; Coburn, C.A.; Stachel, S.J.; Yang, W.; Barrow, J.C.; Neilson, L-A.; McWherter, M.; Perlow, D.; Fahr, B.; Munshi, S.; Allison, T. J.; Holloway, K.; Selnick, H. G.; Yang, Z-Q.; Swestock, J.; Simon, A.J.; Sankaranarayanan, S.; Colussi, D.; Tugusheva, K.; Lai, M-T; Pietrak, B.; Haugabook, S.; Jin, L.; Chen, I.-W.; Holahan, M.; Stranieri-Michener, M.; Cook, J. J.; Vacca, J.; Graham, S. L. *Bioorg. Med. Chem. Lett.* **2015**, 25, 4812–4819. (e) Orexin inhibitors: Breslin, M. J.; Cox, C. D.; Whitman, D. B. WO2007/25069 A2, **2007**. (f) NKI Tachikynin receptor: Alvaro, G.; Castiglioni, E.; Marasco, A. WO 2009/133135 A1, **2009**. (g) Calcium Channel Blockers: Smith, E.M.; Sorota, S.; Kim, H.M.; McKittrick, B.A.; Nechuta, T.L.; Bennett, C.; Knutson, C.; Burnett, D. A.; Kieselgof, J.; Tan, Z.; Rindgen, D.; Bridal, T.; Zhou, X.; Jia, Y-P.; Dong, Z.; Mullins, D.; Zhang, X.; Priestley, T.; Correll, C. C.; Tulshian, D.; Czarniecki, M.; Greenlee, W. J. *Bioorg. Med. Chem. Lett*. **2010**, 20(15), 4602-4606. (h) BACE Inhibitors: Stauffer, S. R.; Hills, I. D.; Nomland, A. WO 2008/054698, **2008.**

[2] (a) Karran, E.; Mercken, M.; De Strooper, B. *Nat. Rev. Drug Discov*. **2011**, 10(9), 698-712. (b) Benilova, I.; Karran, E.; De Strooper, B. *Nat. Neurosci.* **2012**, 15(3), 349-357. (c) Karran, E.; De Strooper, B. *J. Neurochem*. **2016**, 139(S2), 237-252.

3 (a) Wyss, D.F.; Cumming, J.N.; Strickland, C.O.; Stamford, A.W. *Methods and Principles in Med. Chem.* **2016**, 67, 329-353. (b) Scott, J.D.; Li, S.W.; Brunskill, A.P. J.; Chen, X.; Cox, K.; Cumming, J.N.; Forman, M.; Gilbert, E.J.; Hodgson, R.A.; Hyde, L.A.; Jiang, Q.; Iserloh, U.; Kazakevich, I.; Kuvelkar, R.; Mei, H.; Meredith, J.; Misiaszek, J.; Orth, P.; Rossiter, L.M.; Slater, M.; Stone, J.; Strickland, C. O.; Voigt, J. H.; Wang, G.; Wang, H.; Wu, Y.; Greenlee, W.J.; Parker, E.M.; Kennedy, M.E.; Stamford, A.W. *J. Med. Chem*. **2016**, 59(23), 10435-10450. (c) Brodney, M.A.; Beck, E.M.; Butler, C.R.; Barreiro, G.; Johnson, E.F.; Riddell, D.;

Parris, K.; Nolan, C.E.; Fan, Y.; Atchison, K.; Gonzales, C.; Robshaw, A.E.; Doran, S.D.; Bundesmann, M.W.; Buzon, L.; Dutra, J.; Henegar, K.; LaChapelle, E.; Hou, X.; Rogers, B.N.; Pandit, J.; Lira, R.; Martinez-Alsina, L.; Mikochik, P.; Murray, J. C.; Ogilvie, K.; Price, L.; Sakya, S.M.; Yu, A.; Zhang, Y.; O'Neill, B.T. *J. Med. Chem*. **2015**, 58(7), 3223-3252. (d) Butler, C. R.; Brodney, M. A.; Beck, E. M.; Barreiro, G.; Johnson, E. F.; Riddell, D.; Parris, K.; Nolan, C. E.; Fan, Y.; Atchison, K.; Gonzales, C.; Robshaw, A. E.; Doran, S.D.; Bundesmann, M. W.; Buzon, L.; Dutra, J.; Henegar, K.; LaChapelle, E.; Hou, X.; Rogers, B. N.; Pandit, J.; Lira, R.; Martinez-Alsina, L.; Mikochik, P.; Murray, J. C.; Ogilvie, K.; Price, L.; Sakya, S.M.; Yu, A.; Zhang, Y.; O'Neill, B.T. *J. Med. Chem*. **2015**, 58(6), 2678-2702. (e) May, P. C.; Dean, R. A.; Lowe, S. L.; Martènyi, F.; Sheehan, S. M.; Boggs, L.N.; Monk, S.A.; Mathes, B.M.; Mergott, D. J.; Watson, B.M.; Stout, S. L.; Timm, D. E. *J. Neurosci*. **2011**, 31, 16507. (f) May, P. C.; Willis, B. A.; Lowe, S. L.; Dean, R. A.; Monk, S. A.; Cocke, P. J.; Audia, J.E.; Boggs, L. N.; Borders, A. R.; Brier, R. A.; Calligaro, D. O.; Day, T. A.; Ereshefsky, L.; Erickson, J. A.; Gevorkyan, H.; Gonzales, C. R.; James, D. E.; Jhee, S. S.; Komjathy, S. F.; Li, L.; Lindstrom, T. D.; Mathes, B. M.; Martènyi, F.; Sheehan, S.M.; Stout, S. L.; Timm, D. E.; Vaught, G. M.; Watson, B. M.; Winneroski, L. L.; Yang, Z.; Mergott, D. J. *J. Neurosci*. **2015**, 35, 1199.

[4] (a) Jenkins, I. D.; Lacrampe, F.; Ripper, J.; Alcaraz, L.; Van Le, P.; Nikolakopoulos, G.; de Almeida Leone, P.; White, R. H.; Quinn, R. J. *J. Org. Chem*. **2009**, 74(3), 1304-1313. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, 57(14), 5845-5859. (c) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Mueller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, 49(20), 3524-3527. (d) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U-H.; Reider, P. J. *Org. Lett.* **2001**, 3(5), 671-674. (e) Stocks, M. J.; Alcaraz, L.; Bailey, A.; Bowers, K.; Donald, D.; Edwards, H.; Hunt, F.; Kindon, N.; Pairaudeau, G.; Theaker, J.; Warner, D. J. *Bioorg. Med. Chem. Lett.* **2010**, 20(24), 7458-7461. (f) Kung, D. W.; Coffey, S. B.; Jones, R. M.; Cabral, S.; Jiao, W.; Fichtner, M.; Carpino, P. A.; Rose, C. R.; Hank, R. F.; Lopaze, M. G.; Swartz, R.; Chen, H.; Hendsch, Z.; Posner, B.; Wielis, C. F.; Manning, B.; Dubins, J.; Stock, I. A.; Varma, S.; Campbell, M.; DeBartola, D.; Kosa-Maines, R.; Steyn, S. J.; McClure, K. F. *Bioorg. Med. Chem. Lett.* **2012**, 22(13), 4281-4287.

[5] (a) Lee, C.; Lira, R.; Dutra, J.; Ogilvie, K.; O'Neill, B.T.; Brodney, M. A.; Helal, C.J.; Young, J. M.; LaChapelle, E.; Sakya, S.; Murray, J.C. *J. Org. Chem*. **2013**, 78 (6), 2661-2669. (b) Corey, E.J.; Link, J.O. *J. Am. Chem. Soc*. **1992**, 114, 1906-1908.

[6] (a) Overman, L.E. *J. Am. Chem. Soc.* **1976**, 98 (10), 2901–2910. (b) Fernandes, R. A.; Kattanguru, P.; Gholap, S. P.; Chaudhari, D.A. *Org. Biomol. Chem*., **2017**, 15, 2672.

[7] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, 121 (4), 791–799.

[8] (a) Daly, M.; Gill, K.; Sime, M.; Simpson, G. L.; Sutherland, A. *Org. Biomol. Chem.* **2011**,9, 6761-6770. (b) Calder, E. D. D.; Sharif, S. A. I.; McGonagle, F. I.; Sutherland, A. *J. Org. Chem.* **2015**, *80* (9), 4683–4696. (c) Sharif, S.A.I.; Calder, E.D.D.; Delolo, F, G.; Sutherland, A. *J. Org. Chem.* **2016**, *81* (15), 6697–6706.

[9] (a) Strecker, A. *Ann. Chem. Pharm*. **1850**, 75 (1), 27−45. (b) Strecker, A. *Ann. Chem. Pharm*. **1854**, 91 (3), 349−351.(c) Shibasaki, M.; Kanai, M.; Mita, K. *Org. React*. **2008**, 70, 1. (d) Sacripante, G.; Edward, J.T. *Can. J. Chem.*, **1982**, 60, 1982-1987. (e) Edward, J.T.; Jitrangsri, C. *Can. J. Chem*. **1982**, 60, 3339-3350.

[10] (a) Sorensen, M. H.; Nielsen, C.; Nielsen, P. *J. Org. Chem*. **2001**, 66(14), 4878-4886. (b) Dominguez, C.; Ezquerra, J.; Baker, S. R.; Borrelly, S.; Prieto, L.; Espada, M. Pedregal, C. *Tetrahedron Lett.* **1998**, 39, 9305−9308. (c) Scaffidi, A.; Skelton, B. W.; Stick, R. V.; White, A. H. *Aus. J. Chem.* **2004**, 57(8), 723-732. (d) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc*.; **1992**, 114, 1906.

[11] (a) Henegar, K. E.; Lira, R.; Kim, H.; Gonzalez-Hernandez, J. *Org. Process Res. Dev.*, **2013**, *17* (7), 985–990. (b) Henegar, K. E.; Lira, R. *J. Org. Chem*. **2012**, 77, 2999−3004.

[12] (a) For a leading reference see: Watson, P. S.; Jiang, B; Scott, B. *Org. Lett.* **2000**, 2(23), 3679-3681. (b) Paulson, H.; Todt, K. *Angew. Chem., Int. Ed. Engl.* **1966**, 5 (10), 899-900.

[13] Coburn, C. A.; Egbertson, M. S.; Graham, S. L.; Mcgaughey, G. B.; Stauffer, S. R.; Yang, W. L.; Lu, W.; Fahr, B. PCT Int. Appl. WO2007/011810, **2007**

[14] Srikrishna, A.; Kumar, P. P. *J. Indian Chem. Soc*. **1999**, 76, (11-12), 521-526.

[15] (a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412–12413. (b) Berkowitz, D.B.; Wu, B.; Li, H. *Org. Lett.* **2006**, Vol. 8, (5), 971-974.

[16] Overman, L. E.; Carpenter, N. E. *Org. React.* **2005,** 66, 1-107.

[17] Montero, A.; Mann, E. Herradon, B. *Tetrahedron Lett.* **2005**, 46, 401–405.

[18] (a) Hanesian, S.; Sailes, H.; Therrien, E. *Tetrahedron* **2003**, 59, 7047-7056. (b) Hanson, P.R; Probst, D.A; Robinson, R.E; Yau, M. *Tetrahedron Lett.* **1999**, 40, 4761-4764.

[19] Trnka, T.M.; Grubbs, R.H. *Acc. Chem. Res.* **2001**, 34, 18-29.

[20] (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett*, **2003**, 15, 2428. (b) Ley, S.; Thomas, A.; *Angew. Chem., Int. Ed*., **2003**, 42 (44), 5400. (c) Buchwald, S.L.; Streiter, E.; Blackmond, D. *J. Am. Chem. Soc.* **2005**, 127, 4120−4127. (d) see also reference 5a.