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Fused bicyclic pyrrolizinones as new scaffolds for human NK_1 antagonists

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Abstract—Previous work on human NK_1 antagonists in which the core of the structure is a substituted pyrrolidine has been disclosed. These compounds showed good binding affinity and functional IP activity, however, many did not exhibit the necessary brain penetration for good in vivo activity. The discovery and preparation of a novel 5,5-fused pyrrolidine core is presented in this paper. This scaffold maintains the excellent binding affinity and functional IP activity of the previously reported compounds, but also exhibits excellent brain penetration as observed in a gerbil foot-tapping assay. The determination of the core structural stereochemistry, which eventually led to the final synthesis of a single active diastereomer, is described.

1. Introduction

The therapeutic potential of tachykinin receptor antagonists has become a focal point of research in recent years. Animal studies with NK_1 antagonists indicate several prospective disease treatments, such as CNS disorders, pain, emesis, and GI disorders.[1] The ability of human NK_1 (hNK_1) receptor antagonists to inhibit emesis has been documented with the FDA approval of Emend® (aprepitant) as a treatment for chemotherapy induced nausea and vomiting (CINV).[2] Research into a new class of hNK_1 antagonists was driven by the potential of other novel therapies that target the central nervous system (CNS).

The ability of these hNK_1 antagonists to penetrate the brain is a pre-requisite for their potential use for the clinical treatment of various CNS mediated disorders. Therefore, it was important to discover highly potent antagonists with good brain penetration and high selectivity for the hNK_1 receptor. In vitro assessment of new compounds can readily be carried out by determining their binding affinity to the hNK_1 receptor.[3] In vivo activity and the ability of compounds to gain access to NK_1 receptors in the brain was studied in the gerbil, a species whose NK_1 receptors have pharmacology similar to humans. Specifically, the ability of a test compound to inhibit the vigorous hindlimb thumping (foot tapping) elicited by central administration of an NK_1 agonist was measured.[4] This foot-tapping response has been shown to be NK_1 agonist specific since NK_2 and NK_3 receptor agonists do not induce this response and this response is specifically inhibited by peripheral administration of potent, brain-penetrant NK_1 receptor antagonists.[5]

Much research has been done on hNK_1 antagonists with piperidine, morpholine, pyrrolidine, and other heterocyclic and cycloalkyl core structures.[6,7] This paper will present hNK_1 antagonists featuring a novel fused bicyclic pyrrolidine scaffold that have subnanomolar binding affinity and good central activity in the gerbil foot-tapping assay (see Fig. 1).

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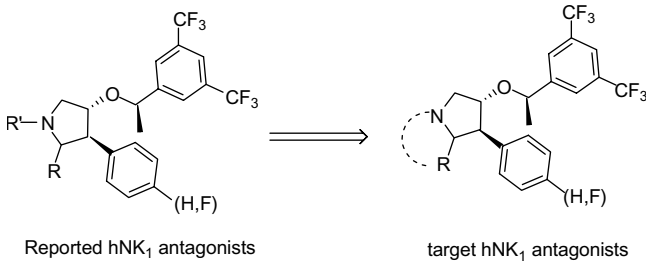


Figure 1. Fused bicyclic idea.

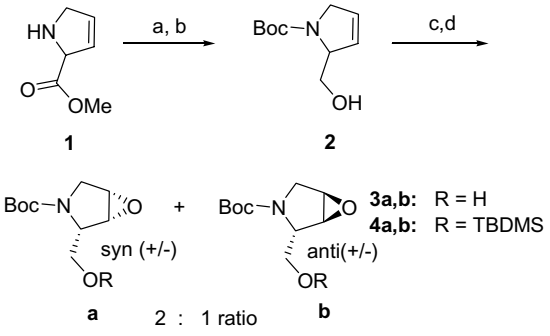
2. Background

1,3,4-Trisubstituted pyrrolidine-based hNK_1 antagonists have been reported to display good bioavailability and efficacy profiles; although, many of these compounds show substantial shifts in binding in the presence of human serum.[7] To improve this property, it was decided that a more rigid structure might be advantageous since substituents at the 2-position of the pyrrolidine were tolerated.[8] In addition, the success of fused bicyclic tetrahydroquinoline hNK_1 antagonists[9] inspired our interest in fused bicyclic pyrrolidines. Thus, the decision was made to cyclize the 2-position substituent of the pyrrolidine to the pyrrolidine nitrogen. The hope was that this modification would retain hNK_1 binding affinity and improve on other physical and pharmacokinetic properties.

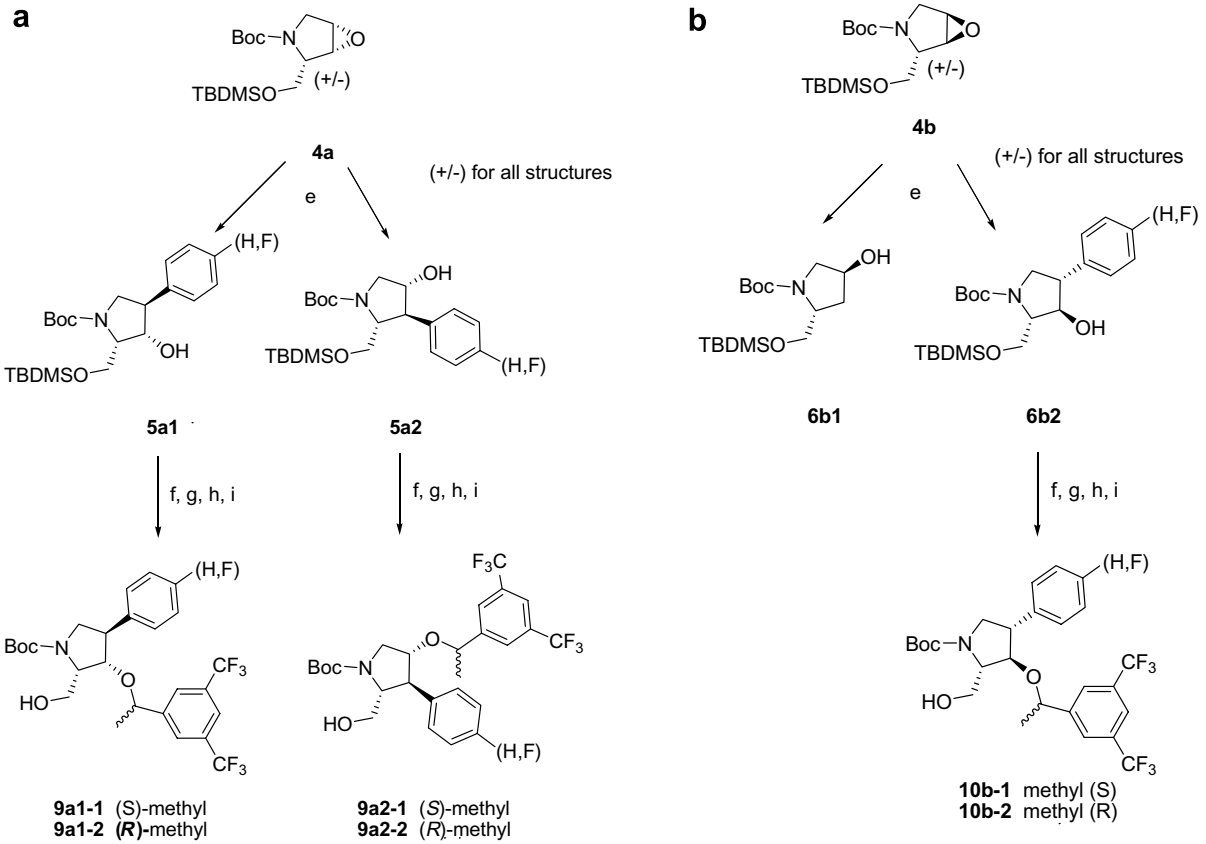
3. Chemistry

3.1. Chemistry of 2,3,4-substituted pyrrolidines

The hydroxymethyl substituent at the pyrrolidine 2-position was envisioned to be a useful intermediate for cyclization to different bicyclic ring systems. Thus, chemistry was first developed using commercially available racemic methyl 3,4-dehydroprolinate (**1**). Schemes 1 and 2 outline the syntheses of the different diastereomers which were assayed to screen for the isomer with highest affinity on the hNK_1 receptor assay (see below).



Scheme 1. Reagents and conditions: (a) Boc_2O, TEA, DCM; (b) DiBAL-H, THF −78 °C; (c) *m*-CPBA, DCM, rt, overnight; (d) *tert*-butyldimethylsilyl chloride, imidazole, DCM.



Scheme 2. Reagents and conditions: (e) phenyl- or 4-fluorophenylmagnesium bromide, copper(I) iodide, THF 0 °C, rt; (f) bis-3,5-trifluoromethylbenzoyl chloride, triethylamine (TEA), DCM, rt; (g) Tebbe® reagent, THF −40 °C to rt; (h) 10% palladium on carbon, H_2 atmosphere, ethanol; (i) 1.0 M TBAF in THF, rt, 1 h.

The commercially available pyrrolidine **1** was protected with *tert*-butylcarboxyl (Boc) via standard conditions and its methyl ester reduced to the alcohol **2** by treatment with DiBAL-H in THF at −78 °C. The double bond was then epoxidized with *m*-CPBA to give racemic *syn* (**3a)** and *anti* (**3b)** isomers, relative to the 2-hydroxymethyl substituent.[10] The epoxides were separated by column chromatography and the hydroxyl group of each isomer was protected as its silyl ether (**4a,b**).

The two epoxides (**4a,b**) were then reacted separately with either phenyl- or 4-fluorophenylmagnesium bromide and copper(I) iodide to produce the 3,4-disubstituted pyrrolidine intermediates **5a1**, **5a2** (Scheme 2a and **6b1**, **6b2**) (Scheme 2b). The reaction products were separated by careful column chromatography. ^{1}HNMR analysis of the intermediates indicated that compound **6b1** was a by-product that did not possess the aryl moiety. The three isolated phenyl substituted products were utilized to produce three of the possible four 2-hydroxymethyl substituted diastereomers. Acylation of the C-3 hydroxyl groups with bis-3,5-trifluoromethylbenzoyl chloride, followed by treatment with μ-chloro-μ-methylene[bis(cyclopentadienyl) titanium]-dimethylalum inum (Tebbe® reagent)[11], produced the corresponding vinyl ethers. Hydrogenation with 10% palladium on carbon in ethanol afforded the desired ethers as stereochemical mixtures at the benzylic ether position.

The ether intermediates were then treated with TBAF in THF to remove the silyl protecting groups to afford the desired alcohols **9a1**, **9a2**, and **10b**. Careful separation of each isomeric pair by Horizon MPLC silica gel chromatography afforded six separate products in racemic form in both the 4-H and 4-fluoro series. The problem of the relative stereochemistry of the 2-substitution needed to be resolved since potentially eight diastereomers and their enantiomers could have been formed by this sequence. The possible isomers obtained are shown in the two figures below (Figs. 2 and 3).

The *R*/*S*-methyl stereochemistry was first determined by hNK_1 binding activity, since the *S*-methyl derivatives

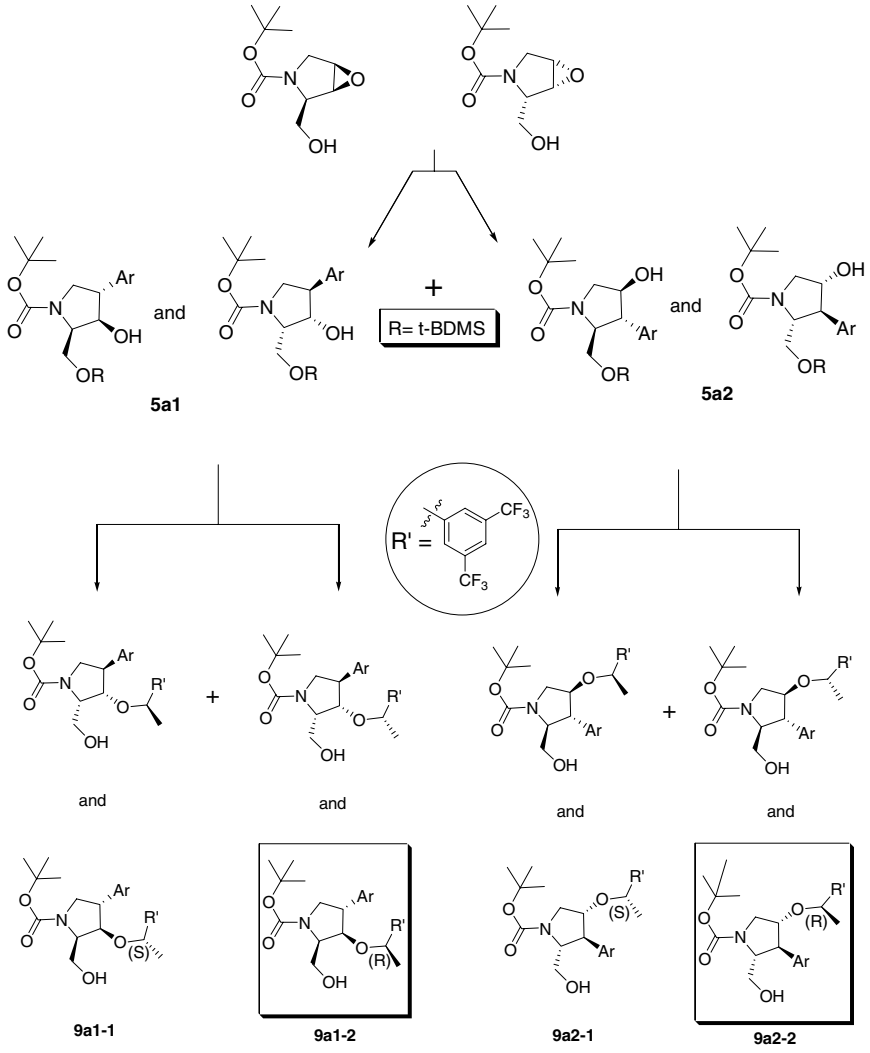


Figure 2. All potential products derived from *syn* epoxide (**3a**).

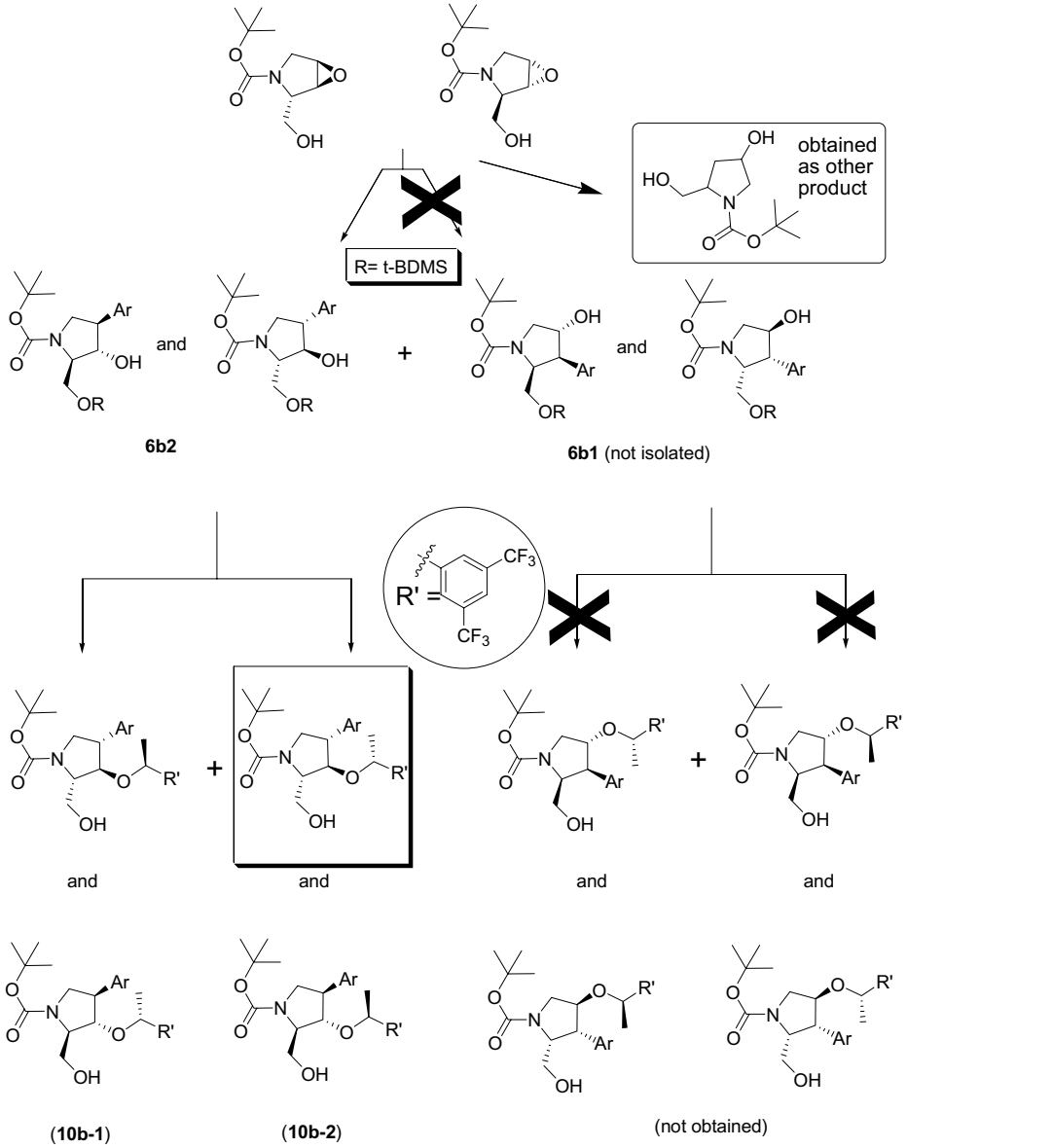
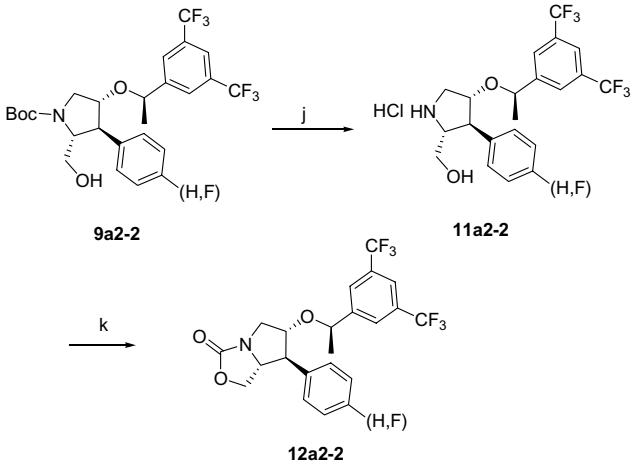


Figure 3. All potential products derived from *anti* epoxide (**3b**).

are known to be much less potent than the *R*-methyl analogs. Then the relative stereochemistry was based on chemical reactivity observations and the regiochemistry was determined by H^1 and 2D TOCSY NMR spectroscopy. The desired active isomers shown in boxes were determined by these methods. However, the fused bicyclic structures, produced by further chemical manipulations, were more rigorously characterized by spectroscopic methods since they exhibited first order spectra (vide infra).

3.2. Chemistry of the fused bicyclic carbamates

The synthesis of the fused bicyclic carbamates was a simple two-step process, as outlined in Scheme 3 for isomer **9a2-2.** The three isomers were treated with 4 N HCl in dioxane to remove the BOC protecting group and the resulting hydroxy methyl pyrrolidines were reacted with phosgene to form the bicyclic carbamate compounds **12a1-2**, **12a2-2**, and **13b-2**.



Scheme 3. Reagents and conditions: (j) 4 N HCl in dioxane, rt, 1 h; (k) phosgene, *N*-ethyl-*N*,*N*-diisopropylamine (DIEA), DCM, rt, overnight.

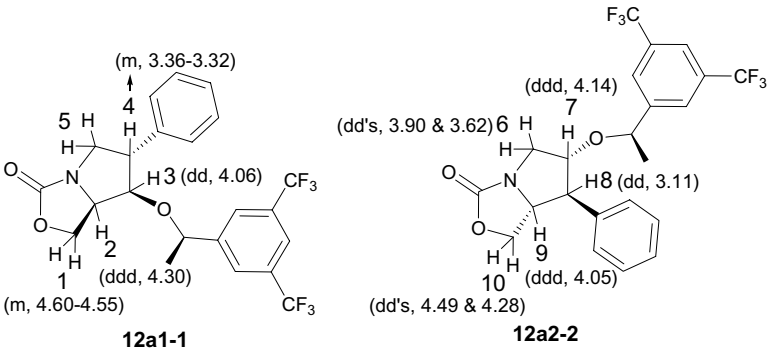


Figure 4. Chemical shifts and coupling constants of bicyclic compounds **12a1-1** and **12a2-2**.

3.3. Stereochemical analysis

The NMR spectra of isomers **12a1-1** and **12a2-2** were first order and allowed more rigorous stereochemical assignments. For the **12a1-1** isomer, one may conclude that the ether was adjacent to the 2-pyrrolidine substituent since H-3 couples to H-2 and H-4 and is further downfield than H-4. Small 'W' coupling of H-3 to the downfield hydrogens H-1 was also observed which supports this assignment. The chemical shifts for H-1 and H-3 hydrogens all appeared in the downfield region, consistent with their assignment to a carbon possessing an oxygen substituent. H-2 couples only to downfield hydrogens (δ = 4.60–4.55 and 4.06), assigned hydrogens H-1 and H-3. To further confirm this, we examined H-4 (the most upfield proton not including the methyl group) and determined that it is coupled to the hydrogens H-5 and downfield proton H-3.

With the structure of isomer **12a1-1** assigned, the only other regioisomer possible for **12a2-2** is that of the phenyl adjacent to the hydroxymethyl substituent. 2D TOCSY spectrum was examined to confirm this and the results agreed with our regiochemical assignment. The hydrogen of the ether (H-7 in this case) is coupled only to the three upfield protons H-6 and H-8. One other important feature was the coupling pattern. In isomer **12a1-1**, the ether hydrogen (H-3) is a clean dd, and therefore, was only coupled to two hydrogens. The one possibility that remains is that the ether must be the substituent between the phenyl and the 2-pyrrolidine substituent. For isomer **12a2-2**, the ether hydrogen (H-7) is a ddd, therefore, it must be coupled with three hydrogens. The one possibility consistent with this structural assignment is that of the ether's location next to the unsubstituted pyrrolidine carbon and the phenyl substituted carbon. Therefore, we were comfortable with the stereochemical assignments of bicyclic analogs **12a1-1** and **12a2-2** (see Fig. 4).

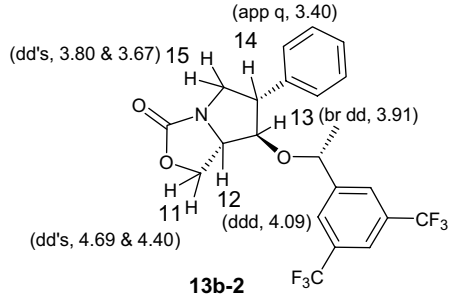


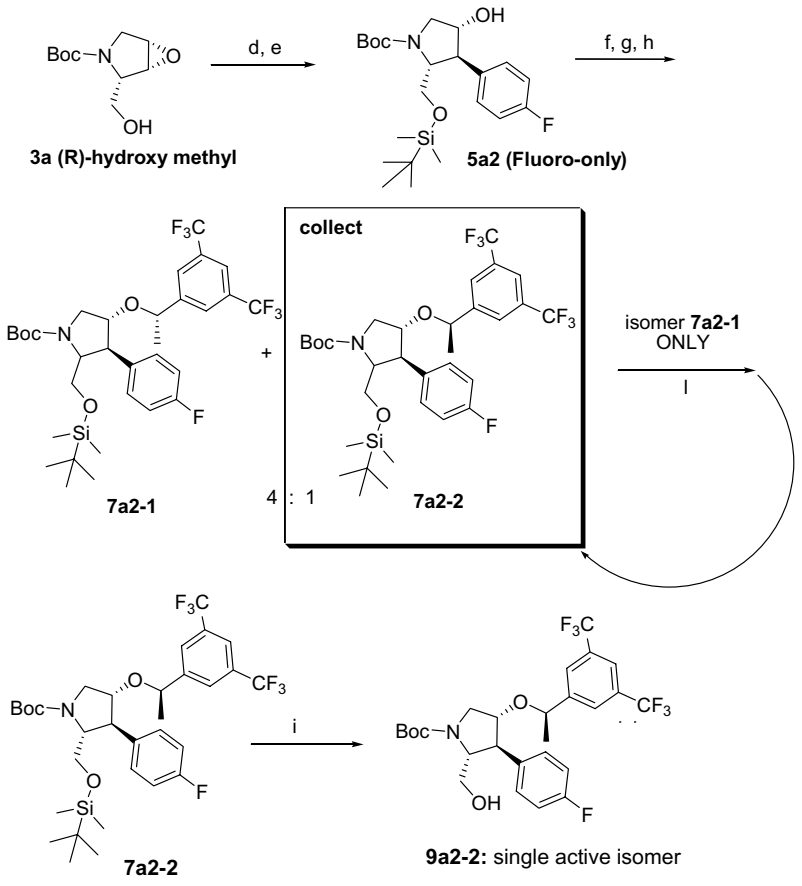
Figure 5. Chemical shifts and coupling constants of bicyclic compound **13b-2**.

For the remaining isomer **13b-2**, the 2D TOCSY readily provided data that allowed the regio-stereochemical assignment. Examining the ether hydrogens H-13, we observed a pronounced coupling to H-12 and H-14, and also small coupling to hydrogens H-11 and H-15. The hydrogen (H-13) appears to couple with all the hydrogens around the two fused rings. We reasoned that H-13 exhibits 'W' coupling to both hydrogens H-11 and H-15. The one possible structure that is consistent with these data possesses an ether at the 3-position adjacent to both the 4-phenyl and 2-pyrrolidine substituent. If one considers the reverse regiochemistry with the phenyl adjacent to both substituents, H-13 would not be able to have any coupling to hydrogens H-11. Therefore, the ether must be adjacent to the two substituents for it to be possible to have 'W' coupling to the hydrogens of H-11 and H-15 consistent with the assigned regio-chemistry of **13b-2**. The relative stereochemistry of each isomer was assigned solely on the basis of which epoxide (**3a**) or (**3b**) it was derived from (see Fig. 5).

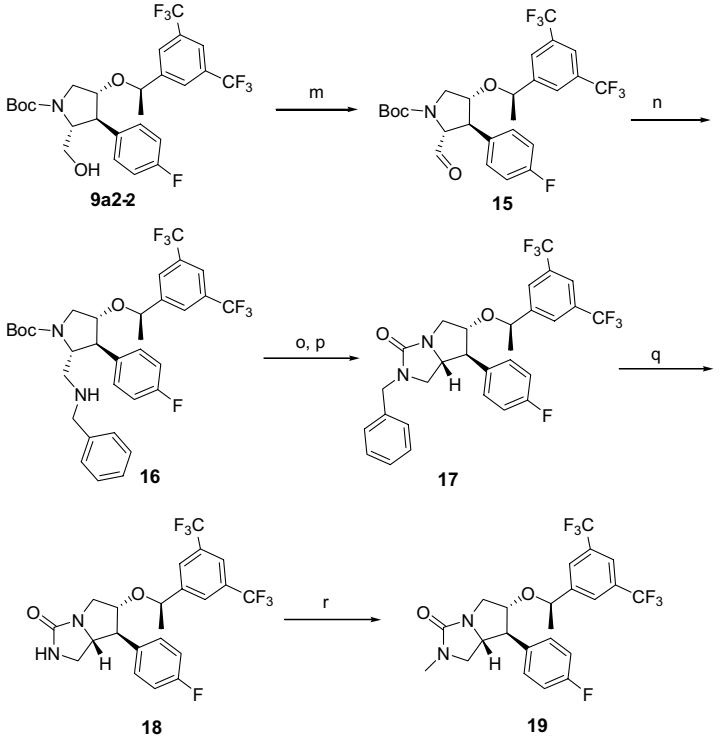
The relative stereochemistry of the most active isomer (**12a2-2**), see section on biological results and discussion, was further supported by 2D NOESY experiments.[12]

3.4. Chemistry discussion: fused bicyclic ureas

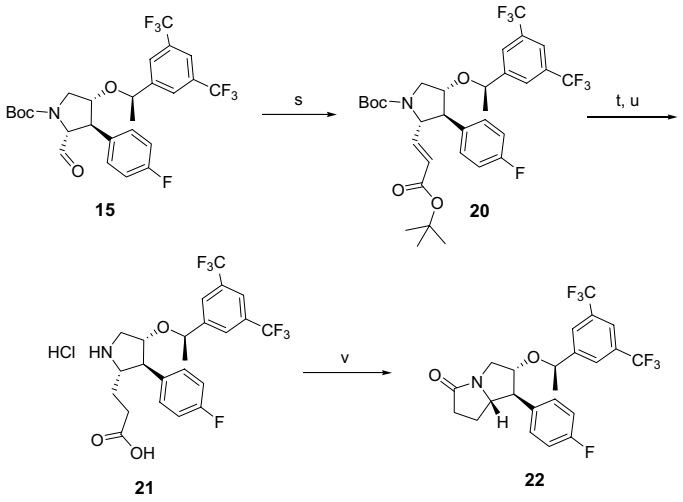
We desired only the active enantiomer of **12a2-2** for further analog synthesis, therefore, an asymmetric synthesis was investigated. To that end, the racemic methyl 3,4-dehydroproline acetate was resolved enzymatically to obtain the desired (*R*)-methyl ester enantiomer as described in the literature.[13] The recovered (*S*)-acid was recycled by re-esterification, then racemization with LHMDS in THF. The recovered racemate could be enzymatically resolved again to obtain more of the desired (*R*)-methyl ester which gave an 82% yield of the desired (*R*)-isomer after three recycles. The (*R*)-ester was reduced by treatment with DIBAL-H in THF to afford the (*R*)-hydroxylmethyl intermediate (**2**). After epoxidation with *m*-CPBA, the stereoisomers were separated by



Scheme 4. Reagent and conditions: (d) *tert*-butyldimethylsilyl chloride, imidazole, DCM; (e) 4-fluorophenylmagnesium bromide, copper(I) iodide, THF 0 °C, rt; (f) bis-3,5-trifluoromethylbenzoyl chloride, triethylamine (TEA), DCM, rt; (g) Tebbe® reagent, THF −40 °C to rt; (h) 10% palladium on carbon, H_2 atmosphere, ethanol; (i) 1.0 M TBAF in THF, rt, 1 h; (l) 1.0 M potassium *tert*-butoxide in THF 40 °C, 4 h.



Scheme 5. Reagents and conditions: (m) oxalyl chloride, DMF; then TEA, THF −78 °C to rt; (n) benzylamine, sodium triacetoxyborohydride, TEA, DCM; (o) 4 N HCl in dioxane, 1 h; (p) phosgene, DIEA, DCM; (q) 10% palladium on carbon, 1 equiv HCl, H_2, methanol; (r) NaH, MeI, THF −40 °C.



Scheme 6. Reagents and conditions: (s) (*tert*-butoxycarbonylmethylene)triphenyl phosphorane, DCM; (t) 10% palladium on carbon, H_2 atmosphere, ethanol; (u) 4 N HCl in dioxane, 1 h; (v) EDC, DMAP, DIEA, DCM, rt, overnight.

column chromatography and the desired higher Rf isomer (**3a**) was used to complete the synthesis. Similarly, the opening of the epoxide with 4-fluorophenylmagnesium bromide produced two diastereomers of which, after separation, the desired less polar isomer (**5a2**) was further utilized. The chemistry described earlier was used to produce the (*R*) and (*S*)-α-methyl benzyl ethers in 1:4 ratio. Separation of the benzylic ether isomers was then performed. Unfortunately, the major isomer was of the undesired (*S*)-ether configuration. However, epimerization of the benzylic methyl was examined and it was found that treatment with *t*-BuOK in THF at 40 °C for 4 h gave complete epimerization of the methyl group to give a 1:1 ratio. The two isomers were then separated via careful column chromatography and the undesired (*S*)-isomer was again epimerized to provide the desired (*R*)-methyl ether in reasonable overall yield (81%). The silyl group was then removed with TBAF in THF to give the desired active single enantiomer, **9a2-2** (see Scheme 4).

Simple chemical manipulations gave the desired fused bicyclic ureas and amide with this enantiomerically pure intermediate in hand. First, the alcohol **9a2-2** was oxidized to the aldehyde **15** via Swern oxidation.[14] This intermediate was then immediately used without purification in a reductive amination with benzylamine to obtain intermediate **16**. Treatment of intermediate **16** with 4 N HCl in dioxane gave the amino pyrrolidine which was then cyclized to the urea **17** with phosgene. Hydrogenation of *N*-benzyl urea **17** gave the unsubstituted cyclic urea **18** which was then converted to the *N*-methyl urea **19** via treatment with sodium hydride and addition of methyl iodide (see Scheme 5).

3.5. Chemistry discussion: fused bicyclic amides

The cyclic amide synthesis began with the same aldehyde intermediate **15** as for the cyclic ureas. A Wittig reaction[15] gave the precursor useful to prepare the cyclized amide analogs. Hydrogenation of this α,β-unsaturated ester **20** was accomplished using H_2 with 10% palladium on carbon, followed by treatment with 4 N HCl in dioxane to simultaneously remove the *tert*-butyl ester and the N-Boc protecting group. The resulting amino acid intermediate **21** was then cyclized via standard EDC coupling procedures[16] to afford the fused bicyclic amide **22** (see Scheme 6).

Table 1. NK_{-1} binding activity for the hydroxymethyl intermediates **9** and **10**

Compound	*p*-Benzyl substituents	hNK_{-1} binding IC_{50}[a] (nM)
9a1-1	H	13% at 0.1 μM
	F	39% at 0.1 μM
9a1-2	H	7.8 nM
	F	4.4 nM
9a2-1	H	26% at 0.1 μM
	F	92% at 0.1 μM
9a2-2	H	0.63 nM
	F	0.28 nM
10b-1	H	26% at 0.1 μM
	F	41% at 0.1 μM
10b-2	H	3.6 nM
	F	1.2 nM

[a] See Ref. 18.

4. Biological results and discussion

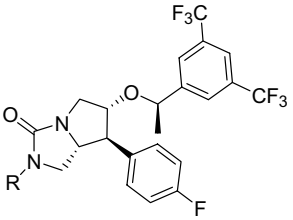
Table 1 contains the hNK_1 binding data[3] for the hydroxymethyl target intermediates; six each from the phenyl or 4-fluorophenyl series. The data show that one isomer (**9a2-2**) in both phenyl and 4-fluorophenyl series clearly possessed the highest binding affinity; therefore, these were chosen as the primary intermedi-

Table 2. NK_1 assay results for bicyclic carbamates

Compound	*p*-Benzyl substituents	hNK_{-1} binding IC_{50}[a] (nM)	Human serum shift + 50% HS[b]	GFT brain % inh[c]
12a1-2	H	1.5	31% at 0.1 μM	na
	F	1.0	na	na
12a2-2	H	0.27	37 nM	2.5%
	F	0.14	37 nM	49%
13b-2	H	1.3	25% at 0.1 μM	na
	F	0.33	57 nM	na

[a,b] See Ref. 18.
[c] GFT: measure of brain penetration analyzed at 0 h at 1 mpk iv; see Refs. 5 and 6d.

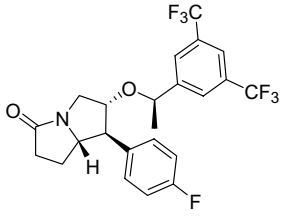
Table 3. NK_1 assay results for bicyclic urea series



Compound	R	hNK_{-1} binding IC_{50}[a] (nM)	Human serum shift + 50%HS[b]	GFT Brain % inh[c]
17	Bn	2.7	na	na
18	CH_3	0.88	32 nM	na
19[d]	H	0.06	2 nM	100%

[a,b] See Ref. 18.
[c] GFT: measure of brain penetration analyzed at 0 h at 1 mpk iv; see Refs. 5 and 6d.
[d] GFT for this compound was also determined at 24 h for a 3 mpk dosage and was found to have ~8% brain penetration.

Table 4. Bicyclic amide assay results



22

hNK_1 binding	0.06 nM
Human serum shift	2.2 nM
Gerbil foot tapping	100 % inh at 0 h, 1 mg/kg
	100 % inh at 24 h 3 mg/kg
Titration (ID_{50})	0.03 mg/kg 0 h

ates to prepare the initial fused bicyclic designs. This result was in clear agreement with the reported results in the previous pyrrolidine and cyclopentane series.[6,7]

Table 2 below contains the hNK_1 binding results, without and in the presence of 50% human serum,[17] and gerbil foot-tapping (GFT) data for the bicyclic carbamates. One isomer, **12a2-2,** had superior binding affinity with a minimal shift in binding in the presence of 50% human serum as compared to the other stereoisomers. The 4-fluorophenyl compounds of this series of hNK_1 antagonists showed two- to threefold improved hNK_1 binding affinity as compared to the parent phenyl analogs. The gerbil foot-tapping data also demonstrate that the 4-fluorophenyl analogs have improved efficacy as compared to the unsubstituted-phenyl compounds of the same relative stereochemistry. As a result of these data, the 4-fluorophenyl series of analogs with the **12a2-2** relative stereochemistry were investigated further with other fused bicyclic systems.

In Table 3, the hNK_1 binding affinity relationship of substituents on the nitrogen of the bicyclic ureas shows that less bulky groups are clearly preferred. The benzyl is not tolerated as compared to the smaller methyl with a threefold decrease in potency. However, the unsubstituted cyclic urea was much more active and also had a decreased human serum shift relative to the N-substituted ureas. Gerbil foot-tapping efficacy was improved for the unsubstituted cyclic urea **19**, 100% inhibition at 0 h at 1 mg/kg iv as compared to 49% inhibition for the 4-fluorophenyl cyclic carbamate, **12a2-2**, in the same assay. However, no activity was observed at 24 h for compound **19**. This compound lacked the duration of central activity we desired to be considered for further evaluation (see Table 4).

The cyclic amide **22** was equipotent in the hNK_1 binding assay with similar human serum shift as compared to both the urea and carbamate analogs. However, central

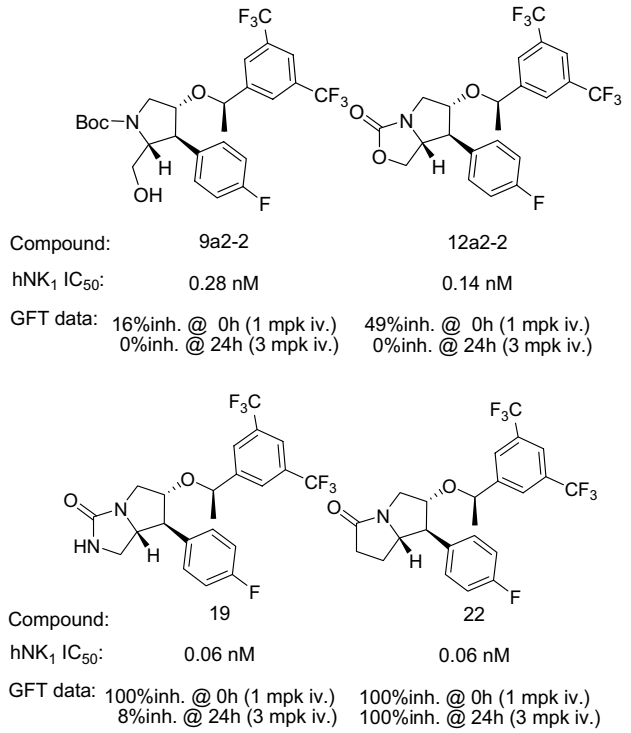


Figure 6. hNK_1 binding and gerbil foot-tapping results for best compounds in each series.

efficacy was improved as determined in the GFT assay: 100% inhibition at both 0 and 24 h time points at our screening dosages (1 mg/kg and 3 mg/kg, respectively). Titration at 0 and 24 h showed that compound **22** had excellent potency and useful duration of action for central antagonist activity in this in vivo model. These results opened a new series of fused bicyclic heterocycles as centrally active hNK_1 antagonists.

5. Conclusion

Figure 6 shows the most interesting analogs of each fused bicyclic pyrrolidine series and the most potent open hydroxymethyl compound (**9a2-2**). The gerbil foot-tapping results revealed that the bicyclic fused carboxamide had the most promising properties for a CNS penetrant hNK_1 antagonist and that the fused core indeed provides the necessary brain penetration needed for an hNK_1 antagonist. The binding affinity was subnanomolar and a low dose of compound **22** completely inhibits the icv agonist induced activity (foot-tapping response) in the gerbil model. Other bicyclic carboxamide analogs will be described in the future.

6. Experimental

6.1. General

Proton nuclear magnetic resonance (^1H NMR) spectra were obtained with a Varian Associates Unity+ 500 or Inova 600 instrument by using deuteriochloroform solutions unless otherwise noted. Chemical shifts (δ) are reported in parts-per-million (ppm) downfield from tetramethylsilane and coupling constants (J values) are given in hertz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 50.103 MHz on the above mentioned Varian Associates Unity+ 500 or Inova 600 instrument in deuteriochloroform solutions unless otherwise noted. Fast-atom bombardment (FAB-MS) and electron spray ionization mass spectra (ESI-MS) were obtained with a Hewlett Packard Series 1100MSD LC-MS. The positive ion peaks are given in units of mass/charge (m/z). High pressure liquid chromatography (HPLC) purifications were performed on the Gilson diode array detector HPLC using a stepwise gradient of 1:9–9:1 acetonitrile/water with 0.1% TFA buffer as the eluant.

Precoated silica gel plates (E. Merck 60) were used for analytical thin-layer chromatography. Pre-coated silica gel preparative plates (E. Merck 500 or 1000 μM) or SupelCo SupelClean™ LC-Si SPE 3 mL tubes were used for small quantity purification. E. Merck silica gel (230–400 mesh) was employed for flash column chromatography. All solvents and reagents were obtained from either Aldrich Chemical Co. or Fisher Scientific Co. All reactions except those in aqueous solutions or otherwise noted were run under nitrogen atmosphere.

6.1.1. Racemic: *tert*-butyl-4-{1-[3,5-bis(trifluoromethyl) phenyl]ethoxy}-2-(hydroxymethyl)-3-phenylpyrrolidine-1-carboxylate

6.1.1.1. *tert*-Butyl-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2). To a solution of 10 g (44 mmol) 1-*tert*-butyl-2-methyl 2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (prepared according to the procedure of Sturmer, R.; Schafer, B.; Wolfart, V.; Stahr, H.; Kazmaier, U.; Helmchen, G. *Synthesis* **2001** (1), 46–48) in 150 mL dry THF under nitrogen atmosphere at −78 °C was added dropwise over 30 min 100 mL (100 mmol) of a 1.0 M solution of DIBAL in cyclohexane. The reaction mixture was stirred at −78 °C for 15 min and then warmed to room temperature. Upon completion of the reaction (as monitored by TLC), the reaction mixture was quenched with excess water and transferred to a separatory funnel. The reaction mixture was extracted with EtOAc (2× 200 mL) and then methylene chloride (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The resulting thick yellow oil was purified by silica gel chromatography eluting with gradient hexanes–EtOAc (9/1) to hexanes–EtOAc (2/8). The product fractions were combined and evaporated under vacuum to give 16.3 g of the title compound. ^1H (500 MHz, $CDCl_3$) δ 5.82 (dd, J = 1.3, 4.6 Hz, 1H); 5.66–5.62 (m, 1H); 4.75 (br s, 1H); 4.20 (dd, J = 1.9, 15.6 Hz, 1H); 4.10 (ddd, J = 2.0, 5.5, 15.6 Hz, 1H); 3.80 (dd, J = 2.1, 11.4 Hz, 1H); 3.58 (dd, J = 7.5, 11.4 Hz, 1H), 1.52 (s, 9H) ppm.

6.1.1.2. *tert*-Butyl-2-(hydroxymethyl)-6-oxa-3-aza bicyclo[3.1.0]hexane-3-carboxylate (3). To a solution 16.3 g (81.9 mmol) **2** in 500 mL methylene chloride was added

163.7 mmol (2 equiv) MCPBA. The reaction mixture was stirred at ambient *T* for 24 h. The reaction mixture was quenched with excess $Ca(OH)_2$ and stirred vigorously for 30 min. The reaction mixture was filtered, washed with methylene chloride, and the solvent of the filtrate removed under vacuum. The residue was purified by chromatography on silica gel eluting with a hexanes–EtOAc (100/0 to 10/90) gradient system to provide two isomeric products; 6.57 g of the major less polar isomer 1 (*syn*-isomer, **3a**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (d, J = 10.8 Hz, 1H); 3.94–3.82 (m, 2H); 3.77 (br s, 1H); 3.74 (d, J = 13 Hz, 1H); 3.62 (s, 1H); 3.42 (d, J = 13 Hz, 1H); 1.46 (s, 9H). ^{13}C (125 MHz, $CDCl_3$) 158.02, 64.19, 61.90, 58.58, 53.75, 49.71, 28.57 ppm. Also obtained 3.44 g of the minor more polar isomer 2 (*anti*-isomer, **3b**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.17 (t, J = 5.2 Hz, 0.5H), 4.03 (t, J = 4.2 Hz, 0.5H), 3.88 (d, J = 13 Hz, 0.5H), 3.86–3.74 (m, 3H), 3.70–3.65 (m, 1H), 3.60 (d, J = 3.0 Hz, 0.5H), 3.37 (dd, J = 1.2, 13 Hz, 1H), 1.45 (br s, 9H). ^{13}C (125 MHz, $CDCl_3$): δ 156.11 (154.96), 80.88 (80.62), 62.86 (62.37), 60.18 (60.07), 58.08 (57.29), 55.35 (54.89), 47.81 (47.75), 28.69 (28.62).

6.1.1.3. *tert*-Butyl-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (4a). To a solution of 6.56 g (30.5 mmol) of major isomer 1(**3a**) in 45 mL dry DMF under nitrogen atmosphere was added 4.17 g (61 mmol) imidazole followed by 4.6 g (30.5 mmol) *tert*-butylchlorodimethylsilane. The reaction mixture was stirred for 16 h and then diluted with water. The mixture was transferred to a separatory funnel and extracted with ether (3× 50 mL). The combined ether extracts were washed with water (2× 25 mL), dried over magnesium sulfate, filtered, and the solvent removed under vacuum. The residue was purified by chromatography on silica gel eluting with a hexanes–EtOAc gradient (95/5 to 40/60) to provide 9.04 g of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.33 (br s, 0.5H); 4.15 (br s, 0.5H); 3.90 (t, J = 2.5 Hz, 1H); 3.88–3.76 (m, 1H); 3.72 (br d, J = 14.2 Hz, 1H); 3.65 (d, J = 12.5 Hz, 1H); 3.60–3.52 (m, 1H); 3.46 (d, J = 12.5 Hz, 1H); 1.46 (br s, 9H); 0.93 (s, 9H); 0.12 (s, 6H) ppm.

6.1.1.4.

6.1.1.4.1. *tert*-Butyl-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-hydroxy-3-phenylpyrrolidine-1-carboxylate (more polar isomer) (isomer *5a2* major)

6.1.1.4.2. *tert*-Butyl-2-({[*tert*-butyl(dimethyl)silyl] oxy} methyl)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate (less polar isomer) (5a1 minor). To a slurry of 25 mg (0.13 mmol) CuI in 2 mL dry THF cooled to 0 °C in an ice/MeOH bath was added dropwise by syringe 1.31 mL (1.31 mmol) of a 1.0 M solution of phenylmagnesium bromide in THF. The resulting mixture was stirred for 10 min. at which time a solution of 250 mg (0.87 mmol) of **4a** in 1 mL THF was added. The resulting reaction mixture was stirred for 5 h at ambient *T*. The mixture was quenched by the addition of 2 mL water and extracted with ether 93× 10 mL. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the solvent removed under vacuum. The resulting oil was purified by preparative TLC eluting with EtOAc–hexanes (25/75) to provide two isomeric products (isomer **5a2** major). More polar isomer by TLC: 130 mg (37%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (app t, J = 7.5 Hz, 2H), 7.28–7.24 (m, 1H), 7.16 (br d dd, J = 7.55, 10.5 Hz, 2H); 4.44 (dd, J = 2.4, 10.6 Hz, 1H); 4.24–4.16 (m, 1H); 4.04 (br s, 1H), 3.76–3.70 (m, 1H); 3.67 (d, J = 10.6 Hz, 1H); 3.48 (dd, J = 12.4, 15.6 Hz, 1H); 3.37 (s, 1H); 1.53 (s, 9H); 0.96 (s, 9H); 0.17 (s, 6H). MS: 408 (M+H), 308 (M+H-Boc) (isomer **5a1** minor). Minor less polar isomer by TLC: 103 mg (34%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.35 (m, 2H); 7.34–7.25 (m, 3H); 4.44 (dd, J = 8.45, 16 Hz, 1H); 4.24 (dd, J = 4.0, 10.9 Hz, 0.5H), 4.10–4.02 (m, 2H); 3.97–3.92 (m, 0.5H); 3.82 (dd, J = 8.5, 16.4 Hz, 1H), 3.52–3.36 (m, 3H), 1.52 (s, 3.5H); 1.48 (s, 5.5H), 0.96 (s, 9H); 0.14 (s, 6H). MS: 408 (M+H), 308 (M+H-Boc).

6.1.1.5. *tert*-Butyl-4-{[3,5-bis(trifluoromethyl)benzoyl]oxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-phenylpyrrolidine-1-carboxylate. To a solution 3.0 g (7.37 mmol) of the more polar isomer (**5a2**) in 60 mL dry methylene chloride under nitrogen atmosphere was added 2.27 mL (16.2 mmol) DIPEA followed by 1.47 mL (8.1 mmol) 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting mixture was stirred at ambient *T* for 16 h and then partitioned between aq 1 N HCl (5 mL). The layers were separated and the organic layer was washed with satd aq sodium bicarbonate (5 mL) then brine (5 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed under vacuum. The residue was purified by chromatography on silica gel eluting with EtOAc/hexanes gradient (0–40% EtOAc) to afford 4.52 g of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 2H); 8.10 (s, 1H); 7.38 (app t, J = 7.4 Hz, 2H); 7.34–7.26 (m, 3H); 5.92–5.45 (br m, 1H); 4.25 (dd, J = 6.4, 12.1 Hz, 1H); 4.10 (br s, 1H); 4.08–4.00 (m, 1H); 3.92 (br d, J = 7.0 Hz, 2H); 3.80 (br s, 1H); 3.58 (d, 10.7 Hz, 0.5H); 3.48–3.42 (m, 0.5H); 1.53 (s, 9H); 0.90 (s, 5H); 0.88 (s, 4H), 0.07 (s, 2.5H); 0.04 (s, 3.5H) ppm. MS: 670 (M+Na), 548 (M+H-Boc).

6.1.1.6. *tert*-Butyl-4-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-phenylpyrrolidine-1-carboxylate. In a pressure tube was placed a solution of 1.0 g (1.55 mmol) of the intermediate *tert*-Butyl-4-{[3,5-bis(trifluoromethyl)benzoyl]oxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-phenylpyrrolidine-1-carboxylate in 30 mL dry toluene. To this solution was added 6.2 mL (6.2 mmol) of a 1.0 M solution of Petasis reagent in toluene. The pressure tube was purged several times with nitrogen, sealed, and heated at 70 °C for 16 h. The reaction vessel was cooled to room temperature and filtered through a plug of silica gel eluting with EtOAc–hexanes (20/80) to afford 500 mg (50%) of the title compound. MS: 668 (M+Na), 547 (M+H-Boc).

6.1.1.7. *tert*-Butyl-4-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-phenylpyrrolidine-1-carboxylate (7a2). To a solution of 50 mg (0.077 mmol) of the intermediate *tert*-butyl-4-

({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-phenylpyrrolidine-1-carboxylate in 3 mL MeOH was added 5 mg (0.1 by wt) 10% Pd–C. The resulting mixture was degassed and then stirred under hydrogen balloon atmosphere for 3 h. The reaction mixture was filtered and the solvent of the filtrate removed under vacuum. The residue was purified by prep TLC eluting with EtOAc–hexanes (1/9). Less polar diastereomer (**7a2-1**): 24 mg (48%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 1H); 7.43 (s, 2H); 7.20–7.15 (m, 3H); 7.07 (d, J = 6.4 Hz, 2H); 4.38 (q, J = 6.2 Hz, 1H); 4.12 (dd, J = 6.8, 10.0 Hz, 1H); 4.04–3.91 (m, 2H); 3.70 (br s, 1H); 3.64 (d, 10.5 Hz, 0.5H); 3.52–3.39 (m, 1.5H); 3.30 (dd, J = 8.0, 10.3 Hz, 1H); 1.52 (s, 2.5 H); 1.48 (s, 6.5 H); 1.38 (d, J = 6.2 Hz, 3H); 0.91 (s, 9H); 0.12 (s, 6H) ppm. More polar diastereomer (**7a2-2**); 26 mg (52%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H); 7.52 (s, 1H); 7.49 (s, 1H); 7.27–7.21 (m, 3H); 7.07 (d, J = 6.4 Hz, 2H); 4.54–4.45 (m, 1H); 4.12 (dd, J = 6.8, 10.0 Hz, 1H); 4.04–3.95 (m, 1H); 3.91 (d, J = 7.0 Hz, 1H); 3.82–3.78 (m, 0.5H); 3.73 (br s, 0.5 H); 3.64 (d, 10.5 Hz, 0.5H); 3.60–3.50 (m, 1.5H); 3.30 (dd, J = 8.0, 10.3 Hz, 1H); 1.52 (s, 3.5 H); 1.48 (s, 5.5 H); 1.40 (d, J = 7.6 Hz, 3H); 0.94 (s, 9H); 0.17 (s, 3H); 0.15 (s, 3H) ppm.

6.1.1.8. *tert*-Butyl-4-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-2-(hydroxymethyl)-3-phenylpyrro-lidine-1-carboxylate (9a2-2). The more polar intermediate Step G, 90 mg (0.14 mmol) was dissolved in ~2 mL (~2 mmol) of a 1.0 M solution of TBAF in THF. The reaction mixture was stirred at room temperature for 2 h and then the solvent was removed under vacuum. The residue was taken up in methylene chloride (~50 mL), washed with water (2× 5 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed under vacuum The residue was purified by prep. TLC eluting with hexanes–EtOAc (4/6) to afford 68 mg of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H); 7.46 (s, 2H); 7.27–7.24 (m, 3H); 7.08 (dd, J = 2.0, 7.2 Hz, 2H); 4.45 (app q, J = 6.3 Hz, 1H); 4.00 (dd, J = 2.3, 11.0 Hz, 2H) 3.99 (overlapping br s, 1H); 3.72 (br s, 2H), 3.38 (app t, J = 11.2 Hz, 1H), 2.92 (br s, 1H); 1.53 (s, 9H); 1.41 (d, J = 6.2 Hz, 3H) ppm. MS: 556 (M+Na), 434 (M+H-Boc).

All other isomers (**9a1-1**, **9a1-2**, **9a2-2**, **10b1**, and **10b2**) were synthesized in the same manner as described above for **9a2-2**.

6.1.2. Single isomer: *tert*-butyl (2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-2-(hydroxymethyl)-3-(4-fluorophenyl)pyrrolidine-1-carboxylate

6.1.2.1. 1-*tert*-Butyl-2-methyl (2*R*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (1, *R*-ester). (Prepared according to the procedure of Sturmer, R.; Schafer, B.; Wolfart, V.; Stahr, H.; Kazmaier, U.; Helmchen, G. *Synthesis* **2001** (1), 46–48). To a mixture of 8 g (35.2 mmol) 1-*tert*-butyl-2-methyl (2*RS*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate in 200 mL distilled water was added 1.6 g (19.3 mmol) sodium bicarbonate followed by 1.6 g Novozyme 435®. The resulting suspension was heated at 50 °C in an oil bath for 18 h. The resulting orange mixture was cooled to room temperature and the solids removed by filtration. The solids were washed with water (2× 20 mL) and ether. The filtrate was extracted with ether (3× 150 mL) and the solvent removed under vacuum to afford the 1-*tert*-butyl-2-methyl (2*R*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate. The 1-*tert*-butyl (2*S*)-2,5-dihydro-1*H*-pyrrole-2-carboxylate could be recovered by acidification of the aqueous layer and extracting with an organic solvent as described in the original reference.

6.1.2.2. *tert*-Butyl-(2*R*)-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2, *R*-hydroxy methyl). The title compound was prepared from 1-*tert*-butyl-2-methyl (2*R*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate according to the procedure in the prior racemic synthesis. ^{1}H (500 MHz, $CDCl_3$) δ 5.82 (dd, J = 1.3, 4.6 Hz, 1H); 5.66–5.62 (m, 1H); 4.75 (br s, 1H); 4.20 (dd, J = 1.9, 15.6 Hz, 1H); 4.10 (ddd, J = 2.0, 5.5, 15.6 Hz, 1H); 3.80 (dd, J = 2.1, 11.4 Hz, 1H); 3.58 (dd, J = 7.5, 11.4 Hz, 1H), 1.52 (s, 9H) ppm.

The same procedures in the prior racemic synthesis were used to give the intermediates needed to synthesize **9a2-2** as the only isomer obtained. A modification in the final procedures was done and is included below.

6.1.2.3. *tert*-Butyl (2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-(4-fluorophenyl)pyrrolidine-1-carboxylate (7a2-2). To a solution of 39 g (58.7 mmol) *tert*-butyl (2*R*,3*S*,4*R*)-4-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-(4-fluorophenyl)pyrrolidine-1-carboxylate in 400 mL EtOH was added 2 g (0.05 by wt) 10% Pd–C. The resulting mixture was hydrogenated in two 500 mL pressure vessels at 40PSI and room temperature for 2 h. The reaction mixture was filtered and the solvent of the filtrate removed under vacuum to give an approximately 4:1 mixture of undesired (**7a1-2**): desired product (**7a2-2**).

The undesired less polar isomer (**7a1-2**) can be isomerized to a 1:1 mixture of isomers in which the desired *tert*-butyl-(2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)-phenyl]ethoxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-(4-fluorophenyl)pyrrolidine-1-carboxylate can be obtained after separation of the isomers by chromatography on silica gel. Several recycles of the undesired less polar isomer afforded the major desired isomer with highly improved yields. The procedure below explains the racemization of the benzylic ether methyl substituent.

To 120 mL (120 mmol) of a 1.0 M solution of potassium *tert*-butoxide in THF under nitrogen atmosphere, cooled to −78 °C, was added a solution of ~39 g of the above crude product in 400 mL dry THF dropwise over 30 min. The reaction mixture was slowly warmed in an ice/water bath then to room temperature. After the temperature reached room temperature, the mixture was heated at 40 °C for 3 h. The reaction mixture was cooled to room temperature,

quenched with saturated aqueous ammonium chloride, and extracted with excess EtOAc. The combined extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and the residue was purified by column chromatography on silica gel eluting with EtOAc/hexanes gradient (0/100 to 20/80) to provide 7.4 g (19%) *tert*-butyl (2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-2-({[*tert*-butyl(dimethyl)-silyl]oxy}methyl)-3-(4-fluorophenyl)pyrrolidine-1-carboxylate, desired more polar **7a2-2**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (s, 1H); 7.52 (s, 2H); 7.02 (dd, J = 6.2, 8.3 Hz, 2H); 7.00–6.94 (m, 2H); 4.45–4.34 (m, 1H); 4.12 (dd, J = 6.8, 10.0 Hz, 1H); 4.04–3.95 (m, 1H); 3.92–3.80 (m, 2H); 3.82–3.78 (m, 1H); 3.70–3.62 (m, 1H); 3.56 (app t, J = 7.2, 1H); 3.50 (d, J = 9 Hz, 1H); 3.24–3.30 (m, 1H); 1.52 (s, 3.5H); 1.48 (s, 4.5H); 1.42 (d, J = 6.6 Hz, 3H), 0.94 (s, 9H); 0.06 (s, 3H); 0.04 (s, 3H) ppm. In addition, mixed fractions containing 4.6 g of >95% pure desired more polar were isolated and 16 g of a mixture containing a majority of undesired less polar diastereomer which could be further recycled to desired product by isomerization. Undesired less polar diastereomer (**7a1-2**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H); 7.58 (s, 2H); 7.24–7.16 (m, 2H); 7.04 (dd, J = 6.2, 8.4 Hz, 2H); 4.50–4.40 (m, 1H); 4.08 (br d, J = 6.0 Hz, 1H); 3.92–3.83 (m, 2H); 3.80–3.76 (m, 1H); 3.72 (br s, 1H); 3.68–3.55 (m, 2H); 3.26–3.20 (m, 1H); 3.15 (br t, J = 9.2 Hz, 1H); 1.46 (s, 3.5H); 1.44 (s, 4.5H); 1.36 (d, J = 6.6 Hz, 3H), 0.94 (s, 9H); 0.07 (s, 3H); 0.05 (s, 3H) ppm.

6.1.3. *tert*-Butyl (2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9a2-2). The title compound was prepared from *tert*-butyl (2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-(4-fluorophenyl)pyrrolidine-1-carboxylate (**7a2-2**) according to the procedure in the prior racemic synthesis. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H); 7.46 (s, 2H); 7.06 (dd, J = 5.2, 8.6 Hz, 2H); 6.97 (dd, J = 8.7, 7.9 Hz, 2H); 4.45 (app q, J = 6.3 Hz, 1H); 4.00 (dd, J = 2.3, 11.0 Hz, 2H) 3.99 (overlapping br s, 1H); 3.72 (br s, 2H), 3.38 (dd, J = 7.7, 10.6 Hz, 1H), 2.92 (br s, 1H); 1.53 (s, 9H); 1.41 (d, J = 6.6 Hz, 3H) ppm. MS: 574 (M+Na), 451 (M+H-Boc).

6.1.4. (2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-2-(hydroxyl methyl)pyrrolidine hydrochloride (11a2-2). The title compound was prepared by treatment of 50 mg of *tert*-butyl (2*S*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl] ethoxy}-3-(4-fluorophenyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**9a2-2**) with 2 mL of 4 N HCl in dioxane for 1 h at room temperature. Concentration in vacuo afforded 42 mg of the title compound; no further purification was necessary. MS: 434 (M+H).

6.1.5. (6*R*,7*S*)-6-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl] ethoxy}-7-phenyltetrahydro-1H-pyrrolo[1,2-*c*] [1,3]oxazol-3-one (12a2-2). To a solution of 40 mg (0.085 mmol) of (**11a2-2**) in dichloromethane (3 mL) was added 0.06 mL (0.340 mmol) of DIEA, followed by 22 mg (0.085 mol) of disuccinimidyl-carbonate (DSC) and the resulting solution stirred at room temperature overnight. The mixture was concentrated in vacuo and purified via preparative TLC plate eluting with 70% ethyl acetate in hexane to afford 17 mg, (48% yield) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H); 7.50 (s, 2H); 7.06 (dd, J = 5.2, 8.6 Hz, 2H); 6.97 (dd, J = 8.7, 7.9 Hz, 2 H); 4.51 (app q, J = 6.3 Hz, 1H); 4.49 (dd, J = 2.3, 9.1 Hz, 1H) 4.28 (dd, J = 3.2, 9.1 Hz, 1H), 4.14 (ddd, J = 4.3, 6.6, 10.9 Hz, 1H), 4.05 (ddd, J = 3.1, 8.0, 11.2 Hz, 1H), 3.90 (dd, J = 4.1, 12.1 Hz, 1H), 3.62 (dd, 6.4, 12.2 Hz, 1H), 3.11 (dd, J = 6.9, 9.0 Hz, 1H), 1.44 (d, J = 6.6 Hz, 3H).

The other two diastereomers, **12a1-2** and **13b-2**, were also prepared in similar fashion as described for **12a2-2**. Below are the ^{1}H NMR results for these compounds.

6.1.5.1. (6*S*,7*R*,7a*R*)-7-{(1*R*)-1-[3,5-Bis(trifluoromethyllphenyl)]ethoxy}-6-phenyltetrahydro-1H-pyrrolo[1,2-*c*][1,3]oxazol-3-one (12a1-2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H); 7.70 (s, 2H); 6.98–6.92 (m, 4H); 4.65 (q, J = 6.4 Hz, 1 H); 4.60–4.55 (m, 2 H) 4.30 (ddd, J = 5.0, 7.3, 9.9 Hz, 1 H), 4.06 (dd, J = 7.3, 11.2 Hz, 1 H), 3.95 (dd, J = 3.0, 4.4 Hz, 1 H), 3.39 (d, J = 5.2 Hz, 1H), 3.36–3.32 (m, 1H), 1.54 (d, J = 6.4 Hz, 3H).

6.1.5.2. (6*S*,7*R*,7a*S*)-7-{(1*R*)-1-[3,5-Bis(trifluoromethyl) phenyl]ethoxy}-6-phenyltetrahydro-1H-pyrrolo[1,2-*c*][1,3] oxazol-3-one (13b-2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H); 7.65 (s, 2H); 7.06 (dd, J = 5.2, 8.6 Hz, 2H); 6.97 (dd, J = 8.7, 7.9 Hz, 2H); 4.69 (dd, J = 2.2, 9.1 Hz, 1H), 4.60 (d, J = 3.2 Hz, 1H), 4.54 (q, J = 6.5 Hz, 1H), 4.40 (dd, J = 6.8, 9.0 Hz, 1H), 4.09 (ddd, J = 5.0, 6.8, 8.6 Hz, 1H), 3.91 (br dd, J = 3.0, 5.4 Hz, 1H), 3.80 (dd, J = 4.1, 5.5 Hz, 1H), 3.67 (dd, J = 6.3, 9.1 Hz, 1H), 3.40 (app q, J = 6.3 Hz, 1H), 1.44 (d, J = 6.7 Hz, 3H).

6.1.6. *tert*-Butyl-4-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-2-formyl-3-phenylpyrrolidine-1-carboxylate (15). To a stirred solution of 0.016 mL (0.19 mmol) oxalyl chloride in 4 mL dry methylene chloride under nitrogen atmosphere at −78 °C was added 0.025 mL (0.372 mmol) DMSO dropwise over 5 min by syringe. After 10 min, to this mixture was added a solution of 50 mg (0.093 mmol) *tert*-butyl-4-{1-[3,5-bis(trifluoromethyl) phenyl]ethoxy}-2-(hydroxymethyl)-3-phenylpyrrolidine-1-carboxylate (**9a2-2**) in 1 mL dry methylene chloride. The reaction mixture was stirred at −78 °C for 1 h, then 0.104 mL (0.744 mmol) TEA was added by syringe. The reaction mixture was stirred at −78 °C for 15 min, then warmed to room temperature and stirred an additional hour. The reaction mixture was quenched with aq 1 N HCL (~5 mL) and transferred to a separatory funnel. The reaction mixture was extracted with EtOAc (2× 5 mL). The combined organic extracts were washed with water (5 mL) then brine (5 mL), dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum to afford 45 mg of the title compound. The resulting crude product (**15**) was used without further purification.

6.1.7. *tert*-Butyl-2-[(benzylamino)methyl]-4-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-phenylpyrrolidine-1-carboxylate hydrochloride (16). To a stirred solution of 45 mg (0.085 mmol) of **15** and 0.010 mL (0.085 mmol) benzylamine in 5 mL dry methylene chloride under nitrogen atmosphere at room temperature were added ~50 mg 4A molecular sieves followed by 90 mg (0.423 mmol) $NaBH(OAc)_3$. The reaction mixture was stirred at room temperature. for 16 h, then quenched with satd aq sodium bicarbonate (~10 mL) and transferred to a separatory funnel. The reaction mixture was extracted with methylene chloride (2× 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The resulting crude product was purified by prep TLC eluting with hexanes–EtOAc (65/45) to afford 30 mg of the free base of the title compound. The isolated free base was converted to the hydrochloride salt by treatment with HCL to afford the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H); 7.62 (s, 2H); 7.40 (br d, J = 7.1 Hz, 3H); 7.34 (d, J = 7.1 Hz, 2H); 7.29–7.26 (m, 3H); 7.15–7.11 (m, 2H); 4.68 (app q, J = 6.2 Hz, 1H); 4.25 (d, J = 13.0 Hz, 1H); 4.13 (t, J = 8.3 Hz, 1H); 4.10–4.05 (m, 1H); 4.04 (d, J = 13.0 Hz, 1H); 3.42–3.35 (m, 1H); 3.33 (dd, J = 1.6, 3.2 Hz, 2H); 3.19 (d, J = 13.3 Hz, 1H); 3.11 (t, J = 7.6 Hz, 1H); 1.54 (s, 9H); 1.37 (d, J = 6.3 Hz, 3H) ppm. MS: 623 (M+H).

6.1.8. 2-(Benzylamino)methyl-4-{1-[3,5-bis(trifluoromethyl)-phenyl]ethoxy}-3-phenylpyrrolidine hydrochloride. The title compound was prepared by treatment of 30 mg of *tert*-Butyl-2-[(benzylamino) methyl]-4-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-phenylpyrrolidine-1-carboxylate hydrochloride (**16**) with 1 mL of 4 N HCl in dioxane for 1 h at room temperature. Concentration in vacuo afforded 14 mg of the title compound; no further purification was necessary. MS: 523 (M+H).

6.1.9. (6*R*,7*S*)-2-Benzyl-6-{(1*R*)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy}-7-phenylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazol-3-one (17). To a solution of 2-(benzylamino)methyl-4-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-phenylpyrrolidine hydrochloride (25 mg, 0.04 mmol) and DIEA (30 mL, 0.16 mmol) in dichloromethane (1 mL) was added phosgene (20% solution, 24 mL, 0.05 mmol) and the resulting solution stirred overnight at room temperature. The solution was transferred directly to a preparative TLC plate and purified by eluting with 30% ethyl acetate in hexane to afford 12 mg of **17**. ^{1}H NMR (500 MHz, CD_3OD): δ 7.77 (s, 1H), 7.54 (s, 2H), 7.43 (br d, J = 7.1 Hz, 3H); 7.33 (d, J = 7.1 Hz, 2H); 7.29–7.24 (m, 3H); 7.15–7.09 (m, 2H); 4.65 (app q, J = 6.2 Hz, 1H), 4.49 (q, J = 6.5 Hz, 1H), 4.14 (ddd, J = 4.6, 7.0, 11.2 Hz, 1H), 3.90 (ddd, J = 2.3, 7.8, 10.0 Hz, 1H), 3.86 (dd, 4.3, 12.1 Hz, 1H), 3.57 (t, J = 8.5 Hz, 1H), 3.52 (dd, J = 6.6, 12.1 Hz, 1H), 3.32 (dd, J = 2.2, 9.2 Hz, 1H), 3.04 (dd, J = 7.1, 9.5 Hz, 1H), 1.41 (d, J = 6.5 Hz, 1H). MS: 566 $(MH)^+$; 588 $(M+Na)^+$.

6.1.10. (6*R*,7*S*)-6-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl] ethoxy}-7-phenylhexahydro-3H-pyrrolo[1,2-*c*]imidazol-3-one (18). To a solution of 10 mg (0.02 mmol) of **17** in 1 mL MeOH and 2 equiv of 2 M HCl/ether was added 2.5 mg (0.25 by wt) 10% Pd–C. The resulting mixture was degassed and then stirred under hydrogen balloon atmosphere for 3 h. The reaction mixture was filtered and the solvent of the filtrate removed under vacuum. The residue was purified by prep TLC eluting with EtOAc–hexanes (1/1) to afford 8 mg of the title compound (**18**). ^{1}H NMR (500 MHz, CD_3OD): δ 7.70 (s, 1H), 7.50 (s, 2H), 7.30–7.22 (m, 2H overlapped by $CDCl_3$ signal), 7.08 (app t, J = 8.7 Hz, 2H), 4.58 (s, 1H), 4.49 (q, J = 6.5 Hz, 1H), 4.14 (ddd, J = 4.6, 7.0, 11.2 Hz, 1H), 3.90 (ddd, J = 2.3, 7.8, 10.0 Hz, 1H), 3.86 (dd, 4.3, 12.1 Hz, 1H), 3.57 (t, J = 8.5 Hz, 1H), 3.52 (dd, J = 6.6, 12.1 Hz, 1H), 3.32 (dd, J = 2.2, 9.2 Hz, 1H), 3.04 (dd, J = 7.1, 9.5 Hz, 1H), 1.41 (d, J = 6.5 Hz, 1H). MS: 477 $(MH)^+$; 499 $(M+Na)^+$.

6.1.11. (6*R*,7*S*)-6-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl] ethoxy}-2-methyl-7-phenylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazol-3-one (19). To a solution of 4 mg (0.01 mmol) of **18** in DMF (0.5 mL) under nitrogen, cooled to 0 °C via ice bath, was added NaH (1 mg, 0.04 mmol) and the resulting solution stirred for 30 min. After aging for 30 min, MeI (1 μL, 0.02 mmol) was added to the reaction mixture and the solution was stirred overnight allowing to warm to room temperature. The reaction mixture was quenched with aqueous NH_4Cl and extracted with ethyl acetate (3× 2 mL). The organics were combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Preparative plate purification (250 μM plate) eluting with ethyl acetate–hexane (1/1) afforded 3.25 mg (80%) of **19** as a clear film. ^{1}H NMR (500 MHz, CD_3OD): δ 7.70 (s, 1H), 7.50 (s, 2H), 7.30–7.22 (m, 2H overlapped by $CDCl_3$ signal), 7.08 (app t, J = 8.7 Hz, 2H), 4.49 (q, J = 6.5 Hz, 1H), 4.14 (ddd, J = 4.6, 7.0, 11.2 Hz, 1H), 3.90 (ddd, J = 2.3, 7.8, 10.0 Hz, 1H), 3.86 (dd, 4.3, 12.1 Hz, 1H), 3.57 (t, J = 8.5 Hz, 1H), 3.52 (dd, J = 6.6, 12.1 Hz, 1H), 3.32 (dd, J = 2.2, 9.2 Hz, 1H), 3.12 (s, 3H), 3.04 (dd, J = 7.1, 9.5 Hz, 1H), 1.41 (d, J = 6.5 Hz, 1H). MS: 491 $(MH)^+$; 513 $(M+Na)^+$.

6.1.12. *tert*-Butyl-(2*S*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-2-[(1*E*)-3-*tert*-butoxy-3-oxoprop-1-en-1-yl]pyrrolidine-1-carboxylate (20). To a solution of 977 mg (1.78 mmol) *tert*-butyl-(2*R*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl] ethoxy}-3-(4-fluorophenyl)-2-formyl pyrrolidine-1-carboxylate (**15**) in 30 mL dry methylene chloride under nitrogen atmosphere was added 670 mg (1.78 mmol) (*tert*-butoxycarbonylmethylene) triphenyl phosphorane. The resulting mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum and the residue purified by Horizon MPLC using a gradient eluting system of 0–20% ethyl acetate in hexane to afford 1.01 g (88%) of the title compound. MS: 648.2 (MH^+).

6.1.13. *tert*-Butyl-(2*S*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-2-(3-*tert*-butoxy-3-oxopropyl)pyrrolidine-1-carboxylate. To a solution of 1.01 g of **20** in 30 mL ethanol under nitrogen atmosphere was added 100 mg 10% Pd–C catalyst. The resulting mixture was stirred under hydrogen balloon

atmosphere at room temperature. After several hours, the catalyst was filtered through filter aid and the solvent was removed under vacuum to afford 945 mg (94%) of the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.78 (s, 1H); 7.66 (s, 2H); 7.12 (dd, J = 5.3, 8.5 Hz, 2H); 6.98 (app t, J = 8.6 Hz, 2H); 4.72 (q, J = 6.4 Hz, 1H); 4.14 (ddd, J = 2.7, 7.3, 12.0 Hz, 1H) 3.90 (dd, J = 7.1, 14.2 Hz, 1H); 3.81 (br s, 1H), 3.28 (br s, 1H), (br m, 1H), 2.20 (br app dd, J = 6.6, 7.5 Hz, 2H); 2.06–1.96 (m, 2H); 1.50 (s, 9H), 1.43 (s, overlapping a d, 9H) 1.43 (d, J = 6.4 Hz, 3H). MS: 650(MH)$^+$, 594 (M-56; M-*tert*-bu)$^+$, 550 (M-100; M-BOC)$^+$.

6.1.14. 3-[(2*S*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-Bis(trifluoromethyl) phenyl]ethoxy}-3-(4-fluorophenyl)pyrrolidin-2-yl]propanoic acid hydrochloride (21). The title compound was prepared by treatment of *tert*-butyl (2*S*,3*S*,4*R*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-2-(3-*tert*-butoxy-3-oxopropyl)pyrrolidine-1-carboxylate with 30 mL of 4 N HCl in dioxane for 1 h at room temperature. Concentration in vacuo afforded 770 mg of the title compound; no further purification was necessary. ^{1}H NMR (500 MHz, CD_3OD): δ 7.78 (s, 1H); 7.64 (s, 2H); 7.21 (dd, J = 5.0, 8.7 Hz, 2H); 7.20 (app t, J = 8.7 Hz, 2H); 4.72 (app q, J = 6.2 Hz, 1H); 4.22 (ddd, J = 2.7, 7.3, 12.0 Hz, 1H) 3.82 (dd, J = 7.3, 12.2 Hz, 1H); 3.66 (ddd, J = 3.2, 4.6, 12.0 Hz, 1H), 3.50 (dd, J = 4.6, 12.3 Hz, 1H), 3.14 (dd, J = 7.4, 12.0 Hz, 1H), 2.35 (app dd, J = 6.8, 12.7 Hz, 2H); 2.06–1.96 (m, 1H); 1.98–1.87 (m, 1H); 1.43 (d, J = 6.7 Hz, 3H). MS: 494 (MH)$^+$; 516 (M+Na)$^+$.

6.1.15. (6*R*,7*S*,7a*S*)-6-{(1*R*)-1-[3,5-Bis(trifluoromethyl) phenyl]ethoxy}-7-(4-fluorophenyl)hexahydro-3*H*-pyrrolizin-3-one (22). To a solution of 768 mg of **21**, 20 mg (0.15 mmol) DMAP, and 253 μL (1.45 mmol) DIEA in 75 mL dichloromethane under nitrogen atmosphere was added 556 mg (2.90 mmol) EDC and the resulting solution stirred overnight at room temperature. The reaction mixture was washed with 1 N HCl solution (20 mL), followed by saturated NaHCO3 solution (20 mL) and then brine (30 mL). The organic solution was dried over sodium sulfate, filtered through a fritted funnel, and concentrated in vacuo. The residue was purified by eight preparative TLC plates eluting with ethyl acetate to afford 600 mg (88%) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.45 (s, 2H), 7.06 (dd, J = 5.3, 8.7 Hz, 2H), 6.98 (app t, J = 8.7 Hz, 2H), 4.46 (q, J = 6.5 Hz, 1H), 4.17 (ddd, J = 5.8, 7.4, 13.8 Hz, 1H), 3.89 (ddd, J = 6.9, 10.1, 13.9 Hz, 1H), 3.70 (dd, J = 6.0, 11.9 Hz, 1H), 3.60 (ddd, J = 1.2, 7.3, 11.9 Hz, 1H), 2.84 (dd, J = 8.4, 9.9 Hz, 1H), 2.67 (dd, J = 9.9, 16.9 Hz, 1H), 2.53 (dddd, J = 2.5, 9.9, 12.4, 16.8 Hz, 1H), 2.25–2.17 (m, 1H), 1.93–1.83 (m, 1H), 1.42 (d, J = 6.7 Hz, 3H). MS: 476 (MH)$^+$; 498 (M+Na)$^+$.

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