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Mimics of Peptide Turn Backbone and Side-Chain Geometry by a General Approach for Modifying Azabicyclo[5.3.0]alkanone Amino Acids

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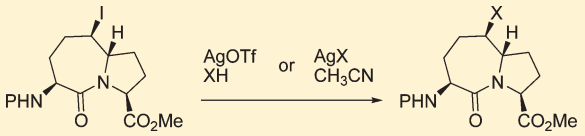
Supporting Information

ABSTRACT: Peptide mimics with constrained backbone and side-chain geometry are important tools for studying structure activity relationships of biologically active candidates. A general method for creating β-turn mimics possessing side-chain diversity has been developed featuring diastereoselective S_N1 displacements of an iodide precursor. In particular, 6-iodo-pyrroloazepin-2-one amino ester **10** has served as a common precursor in reactions with a variety of alcohol, phenol, nitrate, and azide nucleophiles to provide an array of constrained peptide mimics.



Turn motifs reverse the overall direction of a polypeptide chain[1] and play important roles in peptide folding, recognition, and biology. Mimics of peptide turns have thus served as useful tools for studying conformation−activity relationships.[2] In particular, azabicyclo[X.Y.0]alkanone dipeptide surrogates have been commonly employed as β- and γ-turn mimics.[3] For example, the 7,5-fused pyrroloazepinone, as well as analogues possessing an aryl, alkyl, or heteroalkyl ring substituent, have been employed as components of proapoptotic protein second mitochondria-derived activator of caspases (SMAC) mimics (**1**[4] and **2**[5]), bradykinin B2 receptor antagonists (**3**[6]), and $\alpha_v\beta_3/\alpha_v\beta_5$ integrin receptor antagonists[7] (**4**, Figure 1).

The importance of side-chain functionality at the turn sites of bioactive peptides has evoked many syntheses of azabicycloalkanone mimics possessing various functional groups at different ring positions.[8] The methods for generating such scaffolds with side-chain attachments have, however, required multistep processes and often provided stereoisomeric mixtures.[9] Toward a strategy for adding side-chain groups to a common heterocycle scaffold with stereocontrol, an efficient method has now been achieved featuring displacement of an iodide precursor, as illustrated by the stereoselective functionalization of the 6-position of the pyrroloazepinone skeleton.

Several routes exist for synthesizing bicyclic lactams of various ring sizes, stereochemistry, functionality, and substitution pattern.[10,11] Among these methods, a particularly effective entry into substituted azabicyclo[X.3.0]alkanones has involved the stereoselective electrophilic transannular cyclization of their corresponding 9- and 10-membered macrocyclic dipeptides (Scheme 1).[12] Following the procedure for the synthesis of 6-iodo-pyrroloazepin-2-one amino ester **10**, dipeptide **7** was readily assembled by coupling homoallylglycines **5** and **6** using TBTU and HOBt and subjected to ring-closing metathesis using the first generation of Grubbs' catalyst **8** to give the macrocycle **9**.[13] Electrophilic transannular cyclization was optimized to avoid loss of the Boc group, such that bicycle **10** was obtained in improved yields (54−71%) by using excess sodium bicarbonate in acetonitrile to neutralize HI formed during the reaction. The (6*R*)-iodide stereochemistry of both Boc- and Fmoc-**10** was previously established by X-ray analysis.[12]

At first, attempts were made to react (6*R*)-iodides **10a** and **10b** with nucleophiles under S_N2 displacement conditions; however, either starting material was recovered or elimination products were observed. For example, starting material was recovered after treatment of **10** with sodium azide under mild conditions. After heating under more vigorous conditions, LC−MS analysis of crude material indicated no alkyl azide formation; instead, a molecular ion was detected corresponding to product from elimination. Moreover, a vinyl proton signal at 5.23 ppm was observed in the NMR spectrum of the crude product.

Without success in the S_N2 displacement, silver salts were used next to assist the ionization of the iodide[14] and facilitate nucleophilic attack, by way of a secondary carbocation. Under such conditions, elimination was avoided; moreover, diastereoselective nucleophilic attack on the least hindered face of the bicycle gave a product with a net retention of configuration.

Initially, a series of silver salts were tested in methanol to determine optimal activity with iodide **10a**. After 1 h of stirring at room temperature, the products were analyzed by LC−MS, which indicated that silver salts of tosylate, trifluoroacetate, and nitrate gave the desired methyl ether **11** contaminated with products from substitution by the anions of the respective salt. Silver iodide gave 100% recovery of starting material. On the other hand, silver triflate consumed the starting material and delivered the bicyclic methyl ether **11**. Silver triflate became the initial salt of choice for substitution with alcohols and water (Table 1).

By using silver triflate to assist in iodide displacement, alcohols and phenol were used as oxygen nucleophiles to give methyl, ethyl, isopropyl, and phenyl ethers **11**−**14** in 91%, 87%, 77%, and

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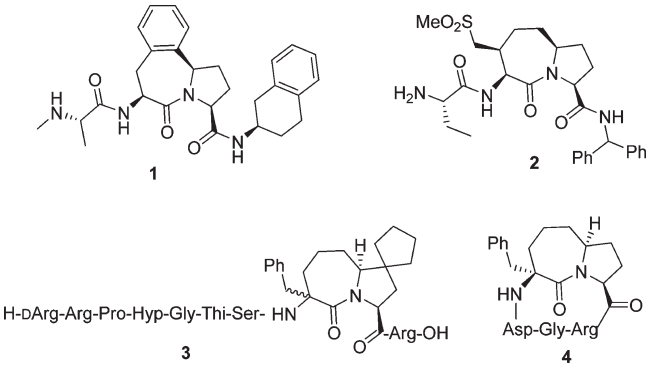


Figure 1. Examples of biologically active substituted pyrroloazepinones.

Scheme 1. Synthesis of 6-Iodo-azabicyclo[5.3.0]alkanone Methyl Ester 10a (*N*-Fmoc) and 10b (*N*-Boc)

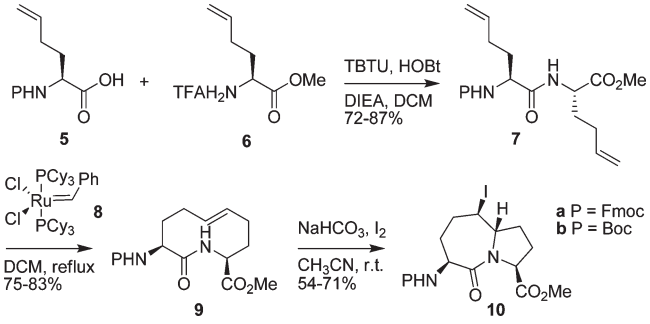
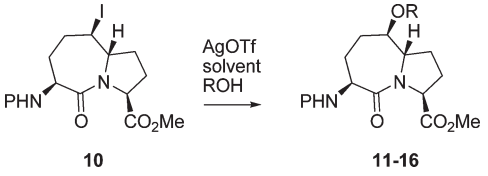


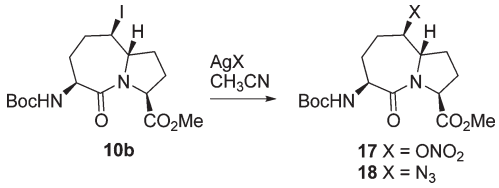
Table 1. Substitution of 10 with AgOTf and Oxygen Nucleophiles



product	P	ROH	solvent	*T* (°C)	yield (%)
11	Fmoc	MeOH		rt	91
12	Fmoc	EtOH		rt	87
13	Boc	*i*-PrOH		rt	77
14	Fmoc	PhOH		50	53
15	Fmoc	H_2O	CH_3CN	rt	67
16	Boc	H_2O	CH_3CN	rt	66

53% yields, respectively. The steric bulk of the nucleophile appears to have influenced the yields of the methyl, ethyl, and isopropyl ethers, which were prepared using their respective alcohols as solvent under homogeneous conditions at room temperature. For the formation of the phenyl ether, the iodide and silver salt were reacted with phenol in the absence of a co-solvent at 50 °C. Both the Fmoc- and the Boc-protected 6-iodoazabicyclo[5.3.0]-alkanones **10a** and **10b** were reacted with water in acetonitrile to obtain alcohols **15** and **16** in 67% and 66% yield, respectively. Acetonitrile was added as co-solvent to help solubilize the starting material, which could not be dissolved in water.

Scheme 2. S_N1 Substitution of 10b with Silver Salts of the Desired Nucleophiles



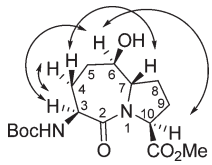


Figure 2. NOESY correlations observed for **16**.

Attempts to use nitrogen nucleophiles such as Et_2NH and $BnNH_2$ caused amine-induced Fmoc-deprotection of **10a**; however, trace amounts of amine were observed by LC−MS, but not isolated using Boc-protected **10b**. Other nucleophiles [PrSH, AcSH, KSCN, KCN, CuCN, NaN_3, $HP(O)(OMe)_2$, and $P(OMe)_3$] failed to provide product in acetonitrile, dioxane, and DMSO. On the other hand, application of the silver salt of certain nucleophiles proved successful (Scheme 2). For example, silver nitrate was soluble in acetonitrile and reacted with iodide **10b** to give alkyl nitrate **17** in 89% yield. Azide **18** was prepared in 45% and 76% yields using silver azide at 40 and 60 °C, respectively. Despite applications of increasing temperature, sonication, microwave irradiation, and the addition of sodium thiosulfate, attempts were unsuccessful using silver salts of cyanide and thiocyanate, likely because of their low dissociation constants (K_{sp}).[15] The displacement reaction is driven to completion by precipitation of the biproduct, silver iodide, which has a K_{sp} of 8.3×10^{-18}.[15] The reactions were inhibited as the dissociation constants of the silver salts approached that of silver iodide.

Only one stereoisomer was detected in the crude product from each displacement reaction. The relative stereochemistry of the new center was assigned to be the same as that of the starting iodide and presumed to arise from attack of the carbocation from the convex face of the bicycle. Assignment of the stereochemistry is based on that for alcohol **16** (Figure 2). In the spectrum of **16**, most of the ring protons appeared at distinct chemical shifts, and their sequential order was assigned using a COSY experiment. For example, the downfield carbamate proton coupled with the proton of the adjacent 3-position carbon, which was used as the starting point for tracing the through-bond connectivities of the various protons around the bicycle. Moreover, the 3-position proton exhibited magnetization transfer with the C4 α-proton at 2.38 ppm in the NOESY spectrum, as well as the proton on the alcohol-bearing 6-position carbon. The latter NOE, as well as the magnetization transfer between the 6- and 10-position protons established the alcohol to have the *R*-stereochemistry. The ring fusion stereochemistry was assigned the *S*-configuration because of the observed NOE between the 4β- and 7-position protons (1.71 and 3.66 ppm, respectively; the β-protons are considered to be on the same face as that on which the amine is located).

A novel approach has been developed for installing side chains onto peptide mimics by way of a common iodide intermediate.

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Eight azabicyclo[5.3.0]alkanone dipeptide mimics were prepared possessing different 6-position ring substituents using silver-assisted iodide displacements. Considering the diversity of alcohols amenable for use in this method as well as the potential for modification of azide **18** by way of chemistry such as Staudinger[16] and 1,3-dipolar cycloaddition reactions,[17,18] this method may find general use for creating libraries of turn mimics for studying the structure−activity relationships of various side chains in biologically active peptides.

EXPERIMENTAL SECTION

General Experimental. Unless otherwise stated, all reactions were performed under argon atmosphere, in oven-dried glassware, using distilled solvents, which were transferred by syringe. Anhydrous CH_3CN and MeOH were obtained from a solvent filtration system and further dried overnight over activated 4 Å molecular sieves; EtOH and *i*-PrOH were distilled from CaH_2. Phenol was recrystallized from petroleum ether, and the crystals were dried by coevaporation with toluene (3×) and stored under vacuum in a desiccator over P_2O_5. Silver trifluoromethanesulfonate was flame-dried under argon atmosphere prior to use. Silver azide, cyanide, and thiocyanate were precipitated from reactions of stoichiometric aqueous silver nitrate with sodium azide, potassium cyanide, and potassium thiocyanate, respectively, collected by filtration, washed with water and ether, coevaporated with toluene, and stored under vacuum in a desiccator over P_2O_5. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield from residual $CHCl_3$ (δ 7.26 and 77.0 ppm). Two dimensional NMR experiments (i.e., COSY, NOESY, and HSQC) for **16** were performed at 500 and 125 MHz. Analytical thin-layer chromatography (TLC) was performed by using glass-backed silica gel plates coated with a 0.25 mm thickness of silica gel, and visualization was achieved by cerium ammonium molybdate (CAM) staining. Flash column chromatography was performed on silica gel of 40−63 μm particle size.[19]

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Fmoc)amino-6-iodo-1-azabicyclo[5.3.0]decane-10-carboxylate (10a). A solution of macrocycle **9a** (134 mg, 0.3 mmol, prepared according to ref 13) in acetonitrile (3 mL) was treated with $NaHCO_3$ (75 mg, 0.9 mmol), followed by iodine (228 mg, 0.9 mmol) in three portions, stirred for 20 min at rt, and treated with 1 M $Na_2S_2O_3$ until the purple solution became clear. The product was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (0 to 35% EtOAc in hexanes as eluant) afforded iodide **10a** as yellow oil (114 mg, 67% yield); spectroscopic data was in accordance with ref 12.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Boc)amino-6-iodo-1-azabicyclo[5.3.0]decane-10-carboxylate (10b). As described for the synthesis of Fmoc-counterpart **10a**, the Boc-protected bicycle **10b** was prepared from **9b** (954 mg, 2.9 mmol, prepared according to ref 13) in acetonitrile (30 mL), using $NaHCO_3$ (737 mg, 8.8 mmol) and iodine (2.2 g, 8.8 mmol). Purification by flash chromatography (0 to 35% EtOAc in hexanes as eluant) afforded iodide **10b** as pale yellow oil (810 mg, 62% yield); spectroscopic data was in accordance with ref 12.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Fmoc)amino-6-methoxy-1-azabicyclo[5.3.0]decane-10-carboxylate (11). Silver trifluoromethanesulfonate (33.6 mg, 0.13 mmol) was flame-dried in a round-bottom flask under argon flow, allowed to cool to room temperature, treated with a solution of iodide **10a** (50.0 mg, 0.09 mmol) in methanol (2.20 mL), stirred at rt overnight, and concentrated to dryness. The mixture was taken up in EtOAc and filtered through a plug of Celite. The filtrate was transferred to a separatory funnel and washed with water and brine, and the organic phase was dried over $MgSO_4$, filtered, and concentrated to a residue, which was purified by flash column chromatography using 25% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave **11** (38.1 mg, 91% yield) as white foam; R_f 0.33 (60% EtOAc in hexanes as eluant); $[\alpha]^{20}_D$ −22.3 (*c* 0.01 g/ml, $CHCl_3$); ^{1}H NMR δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 4.5, 6.7 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 5.83 (broad s, 1H), 4.35−4.33 (m, 2H), 4.20−4.18 (m, 2H), 3.93−3.91 (m, 1H), 3.74 (s, 3H), 3.43−3.42 (m, 1H), 3.36 (s, 3H), 3.25−3.24 (m, 1H), 2.47−2.45 (m, 1H), 2.19−2.08 (m, 3H), 1.88−1.86 (m, 1H), 1.72 (s, 2H), 1.51−1.48 (m, 1H); ^{13}C NMR δ 170.6, 170.3, 156.1, 143.9, 143.8, 141.2, 127.6, 127.0, 125.2, 119.9, 66.9, 59.5, 57.9, 56.7, 52.3, 51.7, 47.0, 26.2, 24.6, 23.0, 22.5; HRMS calcd for $C_{27}H_{31}N_2O_6$ $[M + H]^+$ 479.2177, found 479.2178.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Fmoc)amino-6-ethoxy-1-azabicyclo[5.3.0]decane-10-carboxylate (12). As described for **11**, after reaction of iodide **10a** (30.0 mg, 0.05 mmol), silver trifluoromethanesulfonate (20.1 mg, 0.08 mmol), and EtOH (1.1 mL) and workup, the residue was purified by flash column chromatography using 25% to 75% EtOAc in hexanes as eluant to furnish **12** (22.4 mg, 87% yield) as white foam; R_f 0.51 (60% EtOAc in hexanes as eluant); $[\alpha]^{20}_D$ −21.6 (*c* 0.007 g/mL, $CHCl_3$); ^{1}H NMR δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.4, 2H), 5.80 (broad s, 1H), 4.35 (d, *J* = 6.5 Hz, 2H), 4.25−4.10 (m, 2H), 3.94 (dd, *J* = 3.8, 8.4 Hz, 1H), 3.74 (s, 3H), 3.71−3.59 (m, 1H), 3.48−3.26 (m, 2H), 2.47 (broad s, 1H), 2.25−2.05 (m, 3H), 1.88 (q, *J* = 9.3 Hz, 1H), 1.71 (broad s, 1H), 1.51 (q, *J* = 9.1 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 170.6, 170.3, 144.0, 143.9, 141.3, 127.7, 127.0, 125.2, 119.9, 106.0, 75.7, 64.6, 57.8, 52.3, 51.8, 47.1, 27.0, 24.7, 23.2, 22.7, 15.5; HRMS calcd for $C_{28}H_{33}N_2O_6$ $[M + H]^+$ 493.2331, found 493.2394.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Boc)amino-6-isopropoxy-1-azabicyclo[5.3.0]decane-10-carboxylate (13). As described for **11**, after reaction of iodide **10b** (25.0 mg, 0.06 mmol), silver trifluoromethanesulfonate (17.1 mg, 0.07 mmol), and *i*-PrOH (0.6 mL) and workup, the residue was purified by flash column chromatography using 0 to 45% EtOAc in hexanes as eluant to provide **13** (16.3 mg, 77% yield) as yellow oil; R_f 0.45 (60% EtOAc in hexanes as eluant); $[\alpha]^{20}_D$ −45.4 (*c* 0.014 g/mL, $CHCl_3$); ^{1}H NMR δ 5.46 (broad s, 1H), 4.10 (quintet, *J* = 5.6 Hz, 1H), 3.85 (dd, *J* = 3.9, 8.8 Hz, 1H), 3.72 (s, 3H), 3.71−3.59 (m, 1H), 3.39−3.29 (m, 2H), 2.47−2.34 (m, 1H), 2.19−2.04 (m, 3H), 1.93−1.59 (m, 3H), 1.54−1.43 (m, 1H), 1.42 (s, 9H), 1.13 (overlapping doublets, *J* = 6.3, 6.3 Hz, 6H); ^{13}C NMR δ 170.7, 170.6, 155.8, 79.7, 73.6, 70.5, 60.4, 58.3, 52.3, 51.7, 28.8, 28.5, 25.1, 23.7, 23.5, 22.4, 22.2; HRMS calcd for $C_{19}H_{33}N_2O_6$ $[M + H]^+$ 385.2333 Found: 385.2341.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Fmoc)amino-6-phenoxy-1-azabicyclo[5.3.0]decane-10-carboxylate (14). As described for **11**, after reaction of iodide **10a** (30.0 mg, 0.05 mmol), silver trifluoromethanesulfonate (20.2 mg, 0.08 mmol), and phenol (1.10 mL) at 50 °C and workup, the residue was purified by flash column chromatography using 0 to 40% EtOAc in hexanes as eluant to yield **14** (14.9 mg, 53%) as beige foam; R_f 0.72 (60% EtOAc in hexanes as eluant); $[\alpha]^{20}_D$ −24.8 (*c* 0.004, $CHCl_3$); ^{1}H NMR δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.4, 2H), 7.29 (m, 4H), 6.99 (t, *J* = 7.3, 1H), 6.88 (d, *J* = 8.6, 2H), 5.78 (broad s, 1H), 4.40−4.28 (m, 3H), 4.21 (t, *J* = 7.0, 2H), 4.12−4.05 (m, 1H), 3.77 (s, 3H), 3.73 (broad s, 1H), 2.43 (broad s, 1H), 2.28−2.12 (m, 4H), 2.05−1.89 (m, 1H), 1.79−1.61 (m, 2H); ^{13}C NMR δ 170.6, 170.4, 156.9, 143.9, 143.8, 141.3, 129.8, 127.7, 127.0, 125.2, 121.7, 119.9, 115.8, 91.6, 73.7, 66.9, 58.5, 57.7, 52.4, 51.8, 47.1, 26.7, 24.6, 22.7; HRMS calcd for $C_{32}H_{33}N_2O_6$ $[M + H]^+$ 541.2333, found 541.2337.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Fmoc)amino-6-hydroxy-1-azabicyclo[5.3.0]decane-10-carboxylate (15). Silver trifluoromethanesulfonate (67.1 mg, 0.261 mmol) was flame-dried in a round-bottom flask under argon flow, allowed to cool to room temperature, and treated with a solution of iodide **10a** (50.0 mg, 0.0871 mmol) in

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acetonitrile (4.00 mL), followed by distilled H_2O (1.00 mL). The mixture was stirred at room temperature for 2 h, concentrated to dryness, taken up in EtOAc, and filtered through a plug of Celite. The filtrate was transferred to a separatory funnel and washed with water and brine, and the organic phase was dried over $MgSO_4$, filtered, and concentrated to a residue, which was purified by flash column chromatography using a gradient of 50% to 100% EtOAc in hexanes as eluant and gave **15** (27.1 mg, 67% yield) as white foam; R_f 0.15 (60% EtOAc in hexanes as eluant); $[\alpha]^{20}_D$ −27 (*c* 0.009 g/mL, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3): δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H); 7.39 (t, *J* = 7.2 Hz, 2H); 7.31 (dt, J = 7.4, 1.1 Hz, 2H); 5.81 (broad s, 1H); 4.43−4.30 (m, 2H); 4.24−4.08 (m, 2H); 3.85−3.77 (m, 1H); 3.73 (s, 3H); 3.71−3.62 (m, 1H); 3.33 (bs, 1H); 2.43 (bs, 1H); 2.27−2.08 (m, 4H); 2.01−1.68 (m, 3H); 1.63−1.45 (m, 1H); ^{13}C NMR ($(CD_3)_2CO$) δ; 170.2, 143.9, 141.3, 127.7, 127.0, 125.1, 119.9, 77.2, 68.7, 61.9, 58.4, 52.3, 59.9, 47.1, 31.6, 24.5, 23.9, 22.1; HRMS calcd for $C_{26}H_{29}N_2O_6$ $[M + H]^+$ 465.20201, found 465.20236.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Boc)amino-6-hydroxy-1-azabicyclo[5.3.0]decane-10-carboxylate (16). As described for **15**, iodide **10b** (55.0 mg, 0.12 mmol) in acetonitrile (1.00 mL) was treated with silver trifluoromethanesulfonate (46.9 mg, 0.18 mmol) and distilled H_2O (25.0 μL, 1.22 mmol), and the residue after workup was purified by flash column chromatography using 50% to 100% EtOAc in hexanes as eluant gave **16** (41.6 mg, 66% yield) as white foam; R_f 0.32 (100% EtOAc); $[\alpha]^{20}_D$ −37 (*c* 0.0056 g/ml, $CHCl_3$); ^{1}H NMR δ 5.47 (broad s, 1H), 4.10 (quin, *J* = 4.2, 1H), 3.80 (dd, *J* = 7.1 Hz, 2.8 Hz, 1H), 3.72 (s, 3H), 3.70−3.61 (m, 1H), 3.31 (quin, *J* = 4.6 Hz, 1H), 2.43−2.33 (m, 1H), 2.21−2.07 (m, 4H), 2.02 (broad s, 1H), 1.97−1.85 (m, 1H), 1.77−1.64 (m, 1H), 1.59−1.46 (m, 1H), 1.42 (s, 9H); ^{13}C NMR δ 170.5, 170.4, 155.9, 79.8, 68.9, 62.0, 58.5, 52.4, 51.7, 31.6, 28.5, 24.9, 24.1, 22.3; HRMS calcd for $C_{16}H_{26}N_2NaO_6$ $[M + Na]^+$ 365.16831, found 365.16911.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Boc)amino-6-nitrooxy-1-azabicyclo[5.3.0]decane-10-carboxylate (17). To a solution of **10b** (25.0 mg, 0.06 mmol) in acetonitrile (0.60 mL), silver nitrate (11.3 mg, 0.0663 mmol) was added and the mixture was stirred at room temperature for 2 h and concentrated to dryness. The residue was purified by flash column chromatography using 0 to 40% EtOAc in hexanes as eluant and gave **17** (19.1 mg, 89% yield) as colorless oil; R_f 0.30 (50% EtOAc in hexanes as eluant); $[\alpha]^{20}_D$ −43.9 (*c* 0.014 g/ml, $CHCl_3$); IR ($CDCl_3$) 3407, 2931, 1632, 1550, 1436, 1270, 1165 cm^{-1}; ^{1}H NMR δ 5.41 (broad s, 1H), 5.06 (dt, *J* = 4.8, 7.7, 1H), 4.20−4.07 (m, 2H), 3.74 (s, 3H), 3.66 (dt, *J* = 5.7, 7.8, 1H), 2.47−2.38 (m, 1H), 2.31−1.95 (m, 5H), 1.87−1.60 (m, 2H), 1.43 (s, 9H); ^{13}C NMR δ 171.2, 170.5, 155.7, 80.0, 78.7, 57.0, 56.0, 52.6, 51.4, 28.5, 25.4, 24.8, 23.3, 22.4; HRMS calcd for $C_{16}H_{25}N_3NaO_8$ $[M + Na]^+$ 410.1534, found 410.1538.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-Oxo-3-*N*-(Boc)amino-6-azido-1-azabicyclo[5.3.0]decane-10-carboxylate (18). Similar to the procedure for **17**, iodide **10b** (25.0 mg, 0.06 mmol) was reacted with silver azide (9.9 mg, 0.07 mmol) and acetonitrile (0.6 mL) at 60 °C. After workup, the residue was purified by flash column chromatography using 0 to 40% EtOAc in hexanes as eluant and gave **18** (15.4 mg, 76% yield) as a clear oil; R_f 0.35 (50% EtOAc in hexanes as eluant); $[\alpha]^{20}_D$ −55.7 (*c* 0.013 g/ml, $CHCl_3$); IR ($CDCl_3$) 3414, 2953, 2102, 1672, 1165 cm^{-1}; ^{1}H NMR δ 5.40 (broad s, 1H), 4.09 (q, *J* = 5.7, 1H), 3.78 (dd, *J* = 3.9, 9.5, 1H), 3.73 (s, 3H), 3.52−3.41 (m, 1H), 3.35−3.27 (m, 1H), 2.48−2.36 (m, 1H), 2.36−2.25 (m, 1H), 2.24−2.09 (m, 3H), 2.03−1.86 (m, 1H), 1.79−1.61 (m, 2H), 1.43 (s, 9H); ^{13}C NMR δ 170.5, 170.0, 155.8, 79.9, 60.2, 59.5, 58.5, 52.5, 51.8, 28.5, 28.1, 24.8, 24.1, 23.1; HRMS calcd for $C_{16}H_{25}N_5NaO_5$ $[M + Na]^+$ 390.1748, found 390.1753.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. General experimental methods and spectral data for compounds **11**−**18**; copies of ^{1}H and ^{13}C NMR spectra for compounds **11**−**18**; copies of COSY and NOESY for compound **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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